ESSENTIALS IN OPHTHALMOLOGY

G. K. KRIEGLSTEIN · R. N. WEINREB

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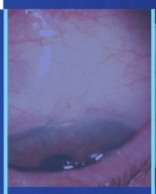

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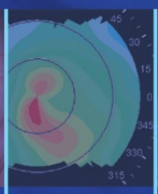

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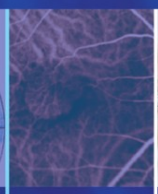

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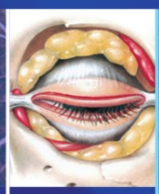

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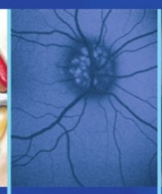

Pediatric Ophthalmology, Neuro-Ophthalmology, Genetics

Cornea and External Eye Disease

Oculoplastics and Orbit

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Foreword

The series *Essentials in Ophthalmology* was initiated two years ago to expedite the timely transfer of new information in vision science and evidence-based medicine into clinical practice. We thought that this prospicient idea would be moved and guided by a resolute commitment to excellence. It is reasonable to now update our readers with what has been achieved.

The immediate goal was to transfer information through a high quality quarterly publication in which ophthalmology would be represented by eight subspecialties. In this regard, each issue has had a subspecialty theme and has been overseen by two internationally recognized volume editors, who in turn have invited a bevy of experts to discuss clinically relevant and appropriate topics. Summaries of clinically relevant information have been provided throughout each chapter.

Each subspecialty area now has been covered once, and the response to the first eight volumes in the series has been enthusiastically positive. With the start of the second cycle of subspecialty coverage, the dissemination of practical information will be continued as we learn more about the emerging advances in various ophthalmic subspecialties that can be applied to obtain the best possible care of our patients. Moreover, we will continue to highlight clinically relevant information and maintain our commitment to excellence.

G. K. Krieglstein
R. N. Weinreb
Series Editors

Preface

Ophthalmic plastic and reconstructive surgery continues to evolve as an important subspecialty dealing with a large variety of complex challenges. Despite close relationships and overlap with other surgical and nonsurgical disciplines, it has developed into a distinct identity, while also achieving a high level of patient satisfaction.

The second volume of *Oculoplastics and Orbit* in the *Essentials of Ophthalmology* series addresses a wide spectrum of disorders including oncology, ophthalmic manifestations of systemic diseases, as well as functional and aesthetic concerns involving orbital, periorbital, and facial structures.

In order to achieve optimal results, a full understanding of the surgical anatomy, as described in Chapter 5, should be combined with recent surgical advances, including microsurgical approaches. Newer techniques using various alloplastic and autologous materials have also been developed to provide or replace orbital volume.

Various clinical applications that are dependent upon the stage of each disorder and the experience of the surgeon have significantly improved patient outcomes.

Another area of development has been the use of minimally invasive approaches for the surgical repair of lid, lacrimal, and orbital problems, including the use of filler materials and injectable self-inflating pellets for augmenting orbital volume.

Chapters dealing with complications such as orbital implant exposure or problems with salivary gland transposition surgery are openly discussed and will hopefully stimulate efforts to find better techniques for further reducing surgical side effects and complications.

The editors have selected specific topics for this volume in an effort to provide an up-to-date review of various eyelid, lacrimal, and orbital problems including aesthetic concerns regarding the aging face. This volume is intended not only for subspecialists, but also for comprehensive ophthalmologists and other healthcare professionals with an interest in oculoplastic disorders. It is our hope that the information presented may be useful in improving the understanding and management of these complex problems.

R. F. Guthoff
J. A. Katowitz
Editors

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Chapter 1

Repair of Involutional Ectropion and Entropion: Transconjunctival Surgery of the Lower Lid Retractors

1

Markus J. Pfeiffer

Core Messages

- Vertical deviation of the orbicularis muscle plays the most important role in entropion and ectropion formation.
- The orbicularis muscle is controlled by translamellar connections between the lower lid retractors and the anterior lamella.
- In ectropion, retractor laxity causes an absence of the angle at the lacrimal punctum.
- In entropion, retractor laxity produces a loss of the lid crease.
- Ectropion and entropion can be corrected by transconjunctival advancement of the retractors without excision of tissue.
- Horizontal lid laxity also requires correction.

1.1 Introduction

The opposite conditions of ectropion and entropion are caused by a similar pathogenesis and can be treated with similar principles. Therefore, they are presented in this chapter as two variations of the same entity. The traditional concept of inverting surgery for ectropion or everting surgery for entropion does not take into account that the most adequate procedure should simply aim to repair involutional pathology and try to restore normal anatomy. Both ectropion and entropion can be treated by transposition of the lower lid retractors, without excision of tissue or rotating sutures. Retractor surgery has been introduced more widely over the last 20 years [2, 4, 6, 7]. This chapter is an attempt to analyze why the backward-directed vector of the retractors can effectively correct vertical deviations, even though this may appear paradoxical at first sight. Many modifications of retractor manipulations are possible. The modified techniques described in this chapter have proved their value over 20 years in a great number of patients.

1.2 Surgical Anatomy of the Lower Lid

Lower lid surgery requires a profound knowledge of palpebral and orbital anatomy. A basic knowledge can be obtained from anatomical studies of anatomical drawings and from anatomical specimens. As the tissues look very different during surgery, it is necessary to give names to some peroperative observations that are not listed in anatomical textbooks. Bloodless surgery achieved with the carbon dioxide laser provides a far better differentiation of the structures. The laser is combined with hydrodissection by injecting an anesthetic solution under the layer and thus making the structures more visible below. The following anatomical observations have been selected according to their surgical relevance to lower lid surgery.

1.2.1 Lower Lid Position and the Intercanthal Line

The lower lid position has to be evaluated in association with the spherical surface of the globe. The lower lid tends to follow the intercanthal line, the shortest line that can be drawn on the globe surface from the medial to the lateral canthal attachments. Note that medially at the lacrimal punctum, the intercanthal line is directed backward close to the globe's surface to join the posterior limb of the medial canthal tendon, while the lid margin forms an angle parallel to the anterior limb (Fig. 1.1). Medial ectropion is equivalent to the loss of the medial angle (Fig. 1.2). In ideal and stable conditions, the intercanthal line of the lower lid is identical to an equatorial line drawn through the medial and lateral canthus. In this case, the tension of the pretarsal orbicularis muscle will keep the lid margin in this position. In cases of a low lateral canthus, the intercanthal line is lower than the equatorial line, creating a tendency toward an even more inferior position of the lower lid and developing scleral show or even a lateral ectropion (Fig. 1.3). The effect of the low lateral canthus can be demonstrated using the model of a rubber band around a ping-pong ball. If the rubber band is moved away downward from the equator, it tends to slip off. In cases of a low lateral canthus or of exophthalmos, the intercanthal line is lower than the equatorial line and the lid cannot be raised by any tightening procedures. In these cases, the position of the lateral canthus has to be moved upward or the exophthalmos has to be corrected before any further surgery can be considered.

1.2.2 Posterior Lamella of the Lower Lid

The posterior lid lamella is an essential structure, because it provides a mucous interface, the fornix. The conjunctival lining of the fornix allows independent movements of the eyeball and the eyelid. Vertical incisions into the fornix should be avoided because scarring may produce an inhibition of the movement of the tarsal and bulbar conjunctiva. We recommend horizontal incisions to expose the tarsal muscle and the lower lid retractors. The lower lid retractors (fascia capsulopalpebralis) are formed by a shell shaped fascia that covers the inferior hemisphere of the globe. Medially and laterally the fibers continue into the canthal tendons. The lateral fusion with the canthal tendon is obvious when we perform a lateral tarsal strip procedure and have to dissect the lateral retractors to be able to elevate the lid laterally. The medial fusion of the retractors and the posterior limb of the medial canthal tendon is found between the inferior lacrimal punctum and the caruncle. The vector of these fibers is directed posteriorly and is essential for the proper position of the lacrimal punctum.

1.2.3 Anterior Lamella of the Lower Lid

The pretarsal and preseptal skin is the thinnest of the body. Chronic epiphora induces skin irritation and shrinking. Any loss of skin surface must be ruled out. A certain skin redundancy is not only normal, but necessary to permit an elevation of the lower lid above the level of the intercanthal line. This extra elevation can be observed in forced closure, when the contracted preseptal orbicularis muscle slides below the inferior edge of the tarsus and lifts the tarsus over the intercanthal line. The orbicularis muscle plays an important role in the pathogenesis of ectropion and entropion. In both conditions the orbicularis muscle loses its control over the position of the posterior lamella by an upward dislocation in entropion or a downward dislocation in ectropion.

1.2.4 Relationship Between the Anterior and Posterior Lamellae

The relationship between the two lower lid lamellae is most important for the pathomechanism of involutional ectropion and entropion. In the tarsal area, the layers of the anterior and the pos-

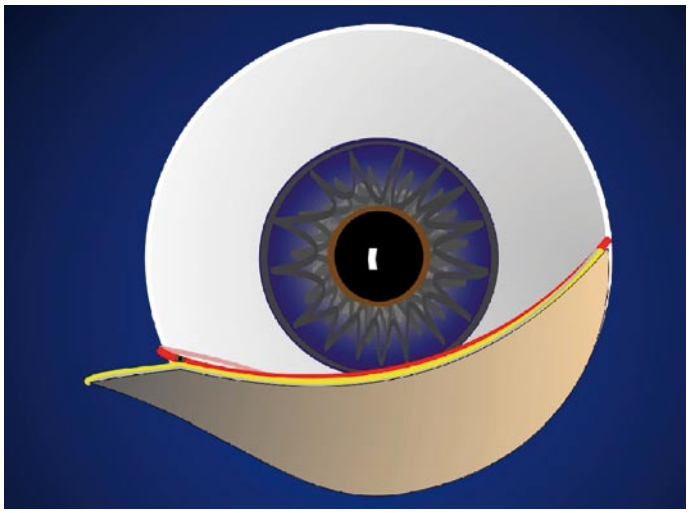


Fig. 1.1 The intercanthal line (*red line*) runs close to the globe's surface from the lateral canthus to the lacrimal punctum, where it continues into the posterior limb of the medial canthal tendon creating an angle with the lid margin (*yellow line*)

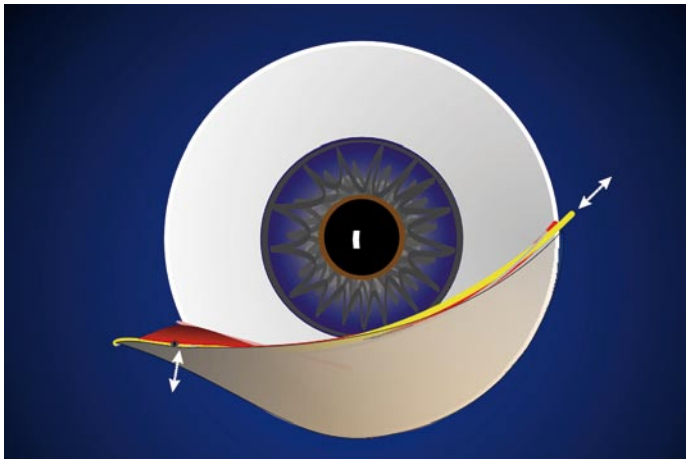


Fig. 1.2 Medial ectropion is equivalent to the loss of the angle at the lacrimal punctum caused by the laxity of the posterior medial fixation

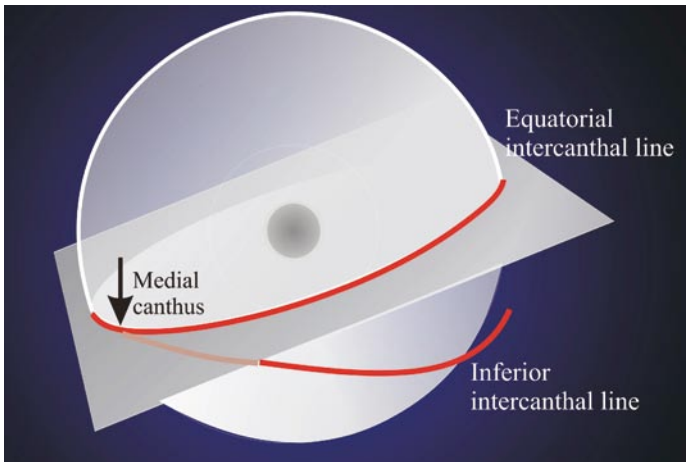


Fig. 1.3 In ideal and stable conditions, the intercanthal line of the lower lid is identical to an equatorial line drawn through the medial and lateral canthus. In this case, the tension of the pretarsal orbicularis muscle will keep the lid margin in this position. In cases of a low lateral canthus, the intercanthal line is lower than the equatorial line. Increasing horizontal tension will cause lower lid retraction.

terior lamellae are united by close attachments. Thus, the pretarsal orbicularis muscle acts like a belt on the tarsus. Involutional changes induce a laxity of these attachments and enable the muscle to become detached. In the septal area both lamellae are separated. If both lamellae are disected by a transconjunctival approach, the pre-retractor space, where reticular adhesions connect to the anterior lamella, is exposed. These translamellar fibrous insertions are important for the control of the preseptal muscle and the formation of the lower lid crease. An involutional laxity of these translamellar fibers will allow the pretarsal muscle to glide upward and is considered to be the main mechanism of entropion formation.

1.2.5 Lower Lid Crease

The lower lid crease forms between the tarsal und the septal area. It is present in the majority of younger individuals and tends to disappear in the aging eyelid. Unlike the upper lid crease, the lower lid crease is aesthetically less appreciated. The formation of a lower lid crease is, however, an important sign of a functioning posterior attachment of the orbicularis muscle and offers the best protection from entropion. The translamellar fibers of the lower lid retractors insert into the preseptal orbicularis muscle. Entropion repair is much more effective and lasting if this translamellar connection is restored.

1.2.6 Orbital Septum and the Orbitomalar Septum

Involutional changes not only cause lid laxity in horizontal, vertical, and anteroposterior directions, but also induce a weakening of the orbital septum and a displacement of orbital fat anteriorly. Orbital fat protrusion contributes to a further separation of the lamellae and detachment of the orbicularis muscle from the posterior lamella [1] creating an additional factor of ectropion or entropion formation. The malar area of the midface is suspended by the orbitomalar septum connecting the inferior orbital rim with the malar fat pad. The laxity of the orbitomalar septum causes drooping of the malar fat pad and downward traction of the anterior lamella of the lower lid. For this reason, we always take advantage of the lateral canthoplasty incision for a simultaneous section and superolateral transposition of the orbitomalar septum.

1.2.7 Lid Margin Shape and the Lid Margin Angle at the Lacrimal Punctum

Lower lid function is closely related to the correct position of the lid margin. Deviations of only 1 mm can cause functional problems such as punctal eversion or trichiasis. The stability of the tarsus determines the position of the mucocutaneous junction at the interior edge and the lash line at the exterior edge of the lid margin. Deformities of the lid margin's shape are signs of complicated entropion and ectropion and have to be addressed with additional procedures.

Summary for the Clinician

- The lower lid position depends on the intercanthal line.
- Translamellar connections between the anterior and posterior lamellae are responsible for the control of the orbicularis fibers.
- The presence of a lower lid crease is a sign of a functioning retractor attachment to the anterior lamella.
- Medially and laterally the retractor fibers continue into the canthal tendons.

1.3 Preoperative Evaluation and Surgical Planning

This is the most important step of the treatment, because an incomplete evaluation or inadequate planning cannot be compensated by the best surgical performance. The following important details should be checked before planning the procedure.

1.3.1 Evaluation of the Intercanthal Line

Check the shortest line between the medial and the lateral canthus on the globe and compare this line with the equatorial line between the two canthi. Take into account that a horizontal shortening of the lower lid by a tarsal strip procedure or full thickness excision will lower the lid if the equatorial line is higher than the intercanthal line. An elevation of the lateral canthus should be planned to raise the intercanthal line up to the level of the equatorial line (Fig. 1.4).

1.3.2 Evaluation of the anterior and posterior Surface

Check the conjunctival surface and the skin surface carefully. A minimal deficit of only 1 mm may be sufficient for surgical failure. Plan the replacement of skin or mucous membrane by grafts and do not rely on the less obvious skin deficit when the patient is in a supine position on the operating table.

1.3.3 Evaluation of the Three Vectors Influencing Lid Function

Check the lid motility for laxity or restriction in three directions (vertical, horizontal, and sagittal). The simple snap-back test is only the first step in checking lid laxity. The lower lid should be examined by pushing it upward over the limbus to rule out vertical retraction and by lateral and medial stretching to test the condition of the canthal fixations. The sagittal vector (antero-posterior or translamellar attachments) can be evaluated by checking whether or not the lid crease is present.

1.3.4 Evaluation of the Lid Margin and the Punctum

Check the shape of the lid margin with the slit lamp. Deformation of the lid margin tends to occur in longstanding chronic ectropion and entropion. The "classic" rectangular shape of the margin is deformed to a "gothic" arch in entropion or to a "roman" arch in ectropion. Lid margin deformities contribute to complicated ectropion or entropion. They can be corrected with additional "shaping" procedures or lamellar repositioning surgery.

Summary for the Clinician

- Exclude the following signs of complicated ectropion and entropion, because they require additional surgery:
- Inferior position of the lateral canthus or a low intercanthal line.
- Deficit of skin surface or conjunctival surface.
- Deformity of the lid margin.

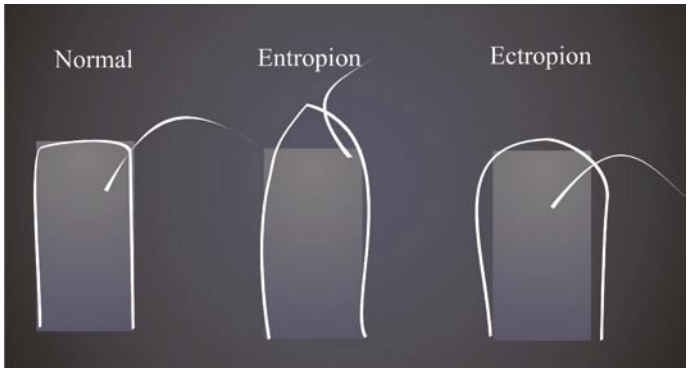


Fig. 1.4 Section of the lid margin. The normal "classic" rectangular shape of the margin is deformed into a "gothic" arch in complicated entropion or into a "roman" arch in complicated ectropion. Lid margin deformities can be corrected with additional "shaping" procedures or lamellar repositioning surgery

1

1.4 Surgical Technique for Ectropion Repair

The following technique avoids excision of tissue. The correction is obtained by separation, transposition, and fixation of the lid lamellae.

1.4.1 Principle of Retractor Fixation

The action of the retractors is composed of a "backward" and a "downward" vector. In the center of the lower lid both vectors are equivalent. Near the lacrimal punctum, the backward vector is dominant and is useful for correcting medial ectropion by pulling the lid margin backward in the direction of the posterior limb of the medial canthal tendon. The advancement of the retractors forms the posterior component. Alone it would be insufficient, because it only approximates the lower border of the tarsal plate to the globe. Therefore, a second anterior component is needed to lift the anterior lamella (orbicularis muscle) upward in an inverting manner (Fig. 1.5).

1.4.2 Access to the Medial Retractors

The conjunctival incision begins close to the caruncle and ends laterally 3–4 mm below the lacrimal punctum, near the medial edge of the tarsal plate. This incision will expose some fibers of the tarsal muscle. If the inferior lip of the conjunctival incision is pushed downward, the whitish layer of the retractors is exposed underneath. The retractors are transsected horizontally parallel to the conjunctival incision. Thus, the preretractor space is opened and the orbital septum can be seen. The retractors are mobilized bluntly backward and downward with a cotton tip (Fig. 1.6).

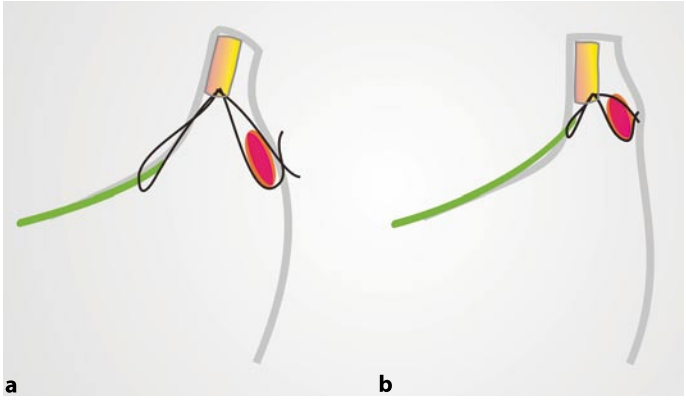


Fig. 1.5 **a** The posterior component of the retractor fixation advances the retractors (*green*) to the tarsus (*yellow*). **b** The anterior component lifts the anterior lamella (orbicularis muscle, *red*) upward, and the two components have an inverting effect

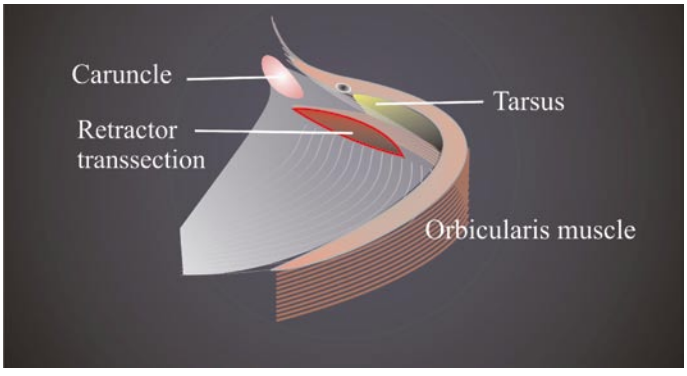


Fig. 1.6 The conjunctival incision begins close to the caruncle and ends laterally 3–4 mm below the lacrimal punctum, near the medial edge of the tarsal plate. The retractors are transsected horizontally parallel to the conjunctival incision

1.4.3 Access to the Central Retractors

In cases of pronounced medial and central ectropion, the retractor exposure has to be extended horizontally over the entire lower lid. The conjunctival incision runs from the caruncle laterally, parallel to the tarsus, and 2 mm below the inferior border. The inferior lip of the conjunctival incision is pushed bluntly downward together with the tarsal muscle to expose the retractors, which are transsected horizontally. Thus, the pre-retractor space is exposed, showing the typical reticular adhesions between the posterior and anterior lamella. These reticular adhesions can be separated by blunt dissection down to the orbital septum.

1.4.4 Exposure of the Inferior Tarsal Border

In order to place the retractor advancement sutures, the inferior tarsal border has to be exposed at the site where the bite is planned. In medial ectropion a single suture is placed at the medial and inferior border of the tarsus, approximately 2 mm lateral from the lacrimal punctum. In pronounced central ectropion two additional sutures are placed at the borders of the central third of the lid. Some caution is needed not to injure the vascular arcade at the lower tarsal border.

1.4.5 Suture Technique

The posterior component of the suture advances the retractors to the medial inferior border of the tarsal plate. A double-armed 6-0 nylon suture with a small half circle needle is used to grasp first the retractors and then the inferior tarsal border (Fig. 1.7). Medially, the retractors can be caught just below the punctum if the posterior limb of the medial canthal tendon is intact. If the medial canthal fixation is insufficient, the retractors are grasped half way between the punctum and the caruncle to improve the medial posterior attachment (Fig. 1.8). According to the laxity of the retractors, the suture has to be passed in at the appropriate level to create sufficient support of the posterior component and to avoid excessive tightness. The adjustment of retractor advancement is much less difficult than the advancement of the aponeurosis in ptosis surgery. It is recommended to begin with minimal or moderate advancement and only change to further advancement if the effect is insufficient. The anterior component of the suture is equally as important as the posterior component. After having been passed through the inferior border of the tarsus (Fig. 1.9), the suture runs downward to lift the preseptal orbicularis muscle fibers. Small horizontal skin incisions are necessary to grasp the needles over the anterior surface of the preseptal orbicularis muscle, where the suture is tied and the knot buried under the skin. This crane-like

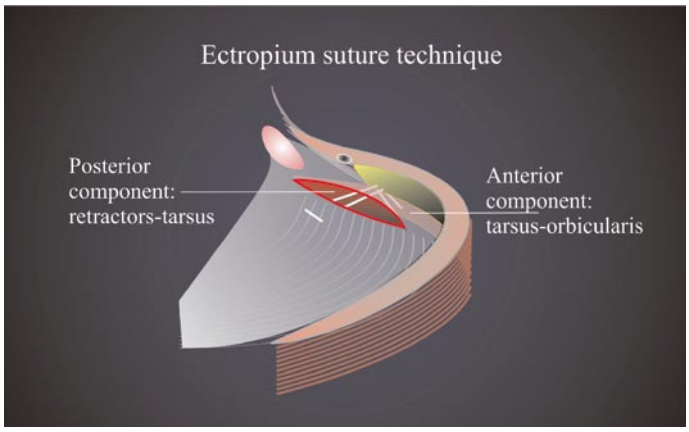


Fig. 1.7 The posterior component of the suture advances the retractors to the medial inferior border of the tarsal plate. The anterior component lifts the orbicularis muscle upward

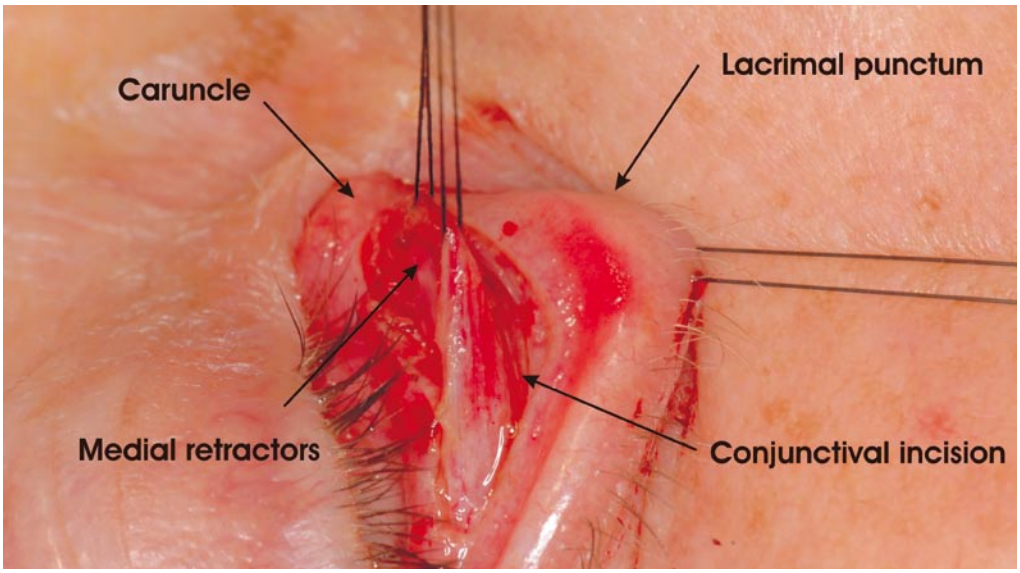


Fig. 1.8 The conjunctival incision runs from the caruncle to the medial inferior border of the tarsus. The medial lower lid retractors are exposed and grasped half way between the caruncle and the lacrimal punctum with a 6-0 non resorbable suture.

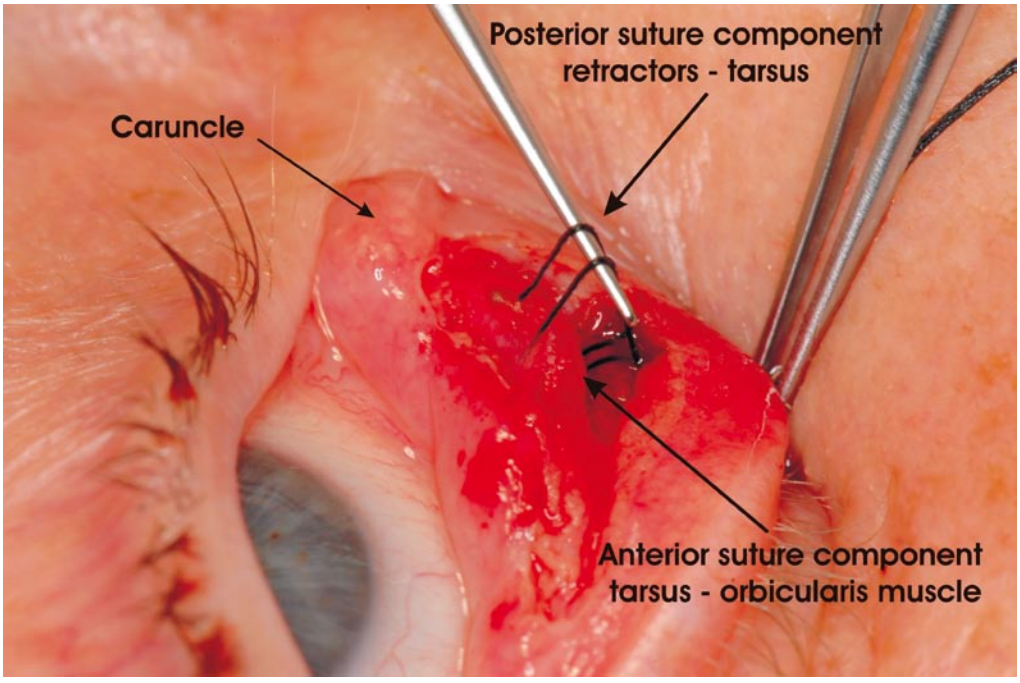


Fig. 1.9 The thin forceps lifts up the posterior component of the suture, that runs from the retractors to the inferior edge of the tarsal plate. The anterior component of the same suture is passed downward to perforate the orbicularis muscle before it is tied on its anterior surface (shown by the thicker forceps).

mechanism of the suture provides an upward directed vector and a lifting of the anterior lamella toward the lid margin with vertical effect. The sutures are not removed (Figs. 1.10, 1.11).

1.4.6 Correction of Horizontal Laxity

Most cases of involutional ectropion will also require a horizontal tightening procedure to correct lid laxity. In patients with a low lateral canthus and a low intercanthal line, the lateral tarsal strip procedure can be combined with repositioning of the lateral canthus at a higher level and a lifting of the entire anterior lamella. The standard lateral tarsal strip procedure can be performed directly after retractor surgery without producing any tissue loss [2, 3].

Summary for the Clinician

- The posterior component of the suture approximates the tarsus to the globe.
- The anterior component of the suture lifts the orbicularis muscle upward.
- The medial fixation near the lacrimal punctum is the most important step, because it provides medial canthal fixation.
- In pronounced ectropion additional sutures are placed lateral to the punctum.

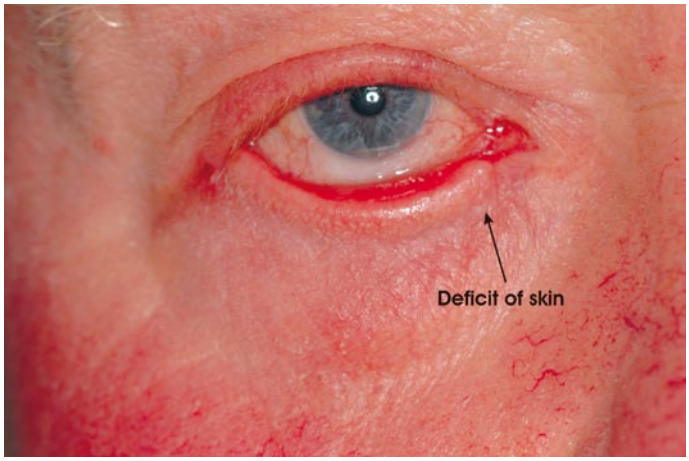


Fig. 1.10 Preoperative ectropion with a moderate deficit of medial eyelid skin and moderate lid margin deformity.

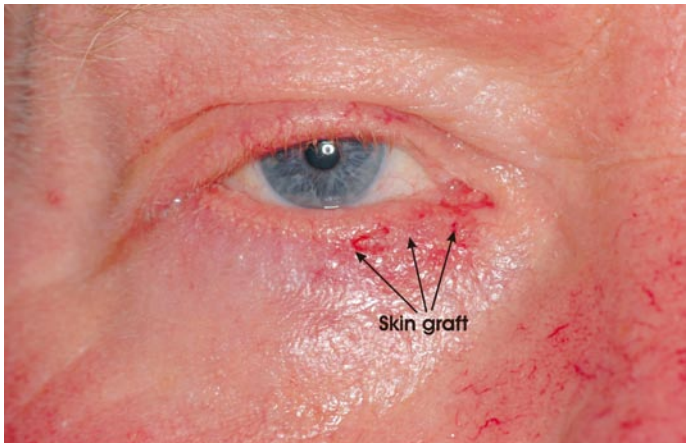


Fig. 1.11 Ten days postoperatively, after medial retractor fixation and a lateral tarsal strip procedure. The medial skin deficit had to be corrected by a free skin graft.

1.5 Surgical Technique for Entropion Repair

As in the ectropion repair procedure described above, the following technique for treating entropion avoids excision of tissue. The correction is obtained by separation, transposition, and fixation of the lid lamellae.

1.5.1 Principle of Retractor Fixation

The "backward" and "downward" vector of the retractor action can be used to attach and control overriding orbicularis muscle fibers in involutional entropion. A sagittal translamellar connection of the posterior and anterior lid lamellae is created. The principle was described by Wies 50 years ago. His technique created a translamellar scar by a simple, horizontal, full-thickness transsection in the lid crease level [9]. The translamellar connection reforms the natural attachments of the retractor fibers into the orbicularis muscle to form the lower lid skin crease (Fig. 1.12).

1.5.2 Access to the Lower Lid Retractors

The horizontal conjunctival incision is placed 2 mm below the inferior border of the tarsus. The inferior lip of the conjunctival incision is pushed bluntly downward, together with the tarsal muscle, to expose the retractors, which are transsected horizontally. Thus, the preretractor space is exposed, showing the typical reticular adhesions between the posterior and anterior lamellae. The posterior aspect of the preseptal orbicularis muscle is exposed. If a blepharoplasty is planned in the same session, the reticular adhesions can be separated by blunt dissection downward to open the orbital septum.

1.5.3 Suture Technique

Two braided 5-0 nylon sutures with a 3/5 circle needle are passed through the retractors at the medial and the central third of the lid. Two small horizontal skin incisions are placed over the upper preseptal muscle, where the new lid crease is to be created. The sutures are passed directly from the posterior position through the orbicularis muscle and appear anteriorly in the skin incisions where they are tied and buried under the skin. The sutures are not removed (Figs. 1.13, 1.14).

Summary for the Clinician

- Translamellar retractor advancement restores physiologic attachments between the anterior and the posterior lamellae.
- Lid crease formation after suture placement is a sign that the preseptal orbicularis muscle is prevented from sliding upward.
- Horizontal shortening can be performed in the same session.

1.6 Repair of Complicated Cases and Complications of Retractor Surgery

1.6.1 Complicated Involutional Ectropion

Complicated involutional ectropion develops after longstanding chronic ectropion with secondary deformation of eyelid tissue. Chronic epiphora causes chronic skin eczema and shrinking of the skin. It can best be corrected by free skin grafting in the subciliary area. Longstanding eversion of the lid also causes keratinization of the tarsoconjunctiva with deformation of the lid margin. These cases will need additional "shaping" procedures or complete separation and repositioning of the anterior and posterior lamellae.

1.6.2 Complicated Involutional Entropion

After longstanding chronic involutional entropion, the lid margin can suffer a "gothic arch"

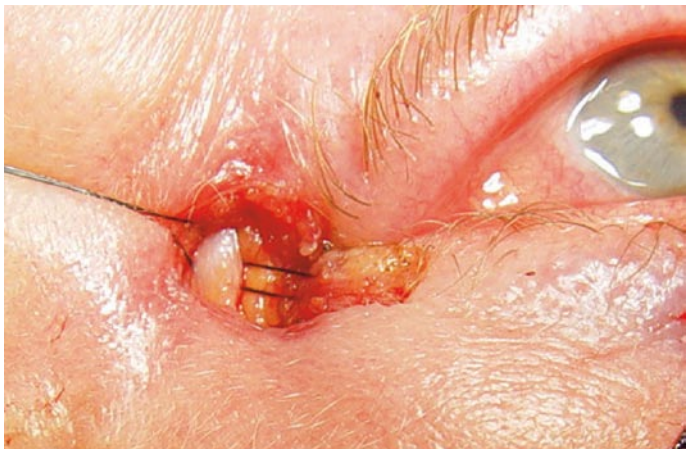


Fig 1.12 Most cases of involutional ectropion and entropion will also need a horizontal tightening procedure to correct lid laxity. In cases of low lateral canthus and low intercanthal line, the lateral tarsal strip procedure can be combined with repositioning of the lateral canthus to a higher level

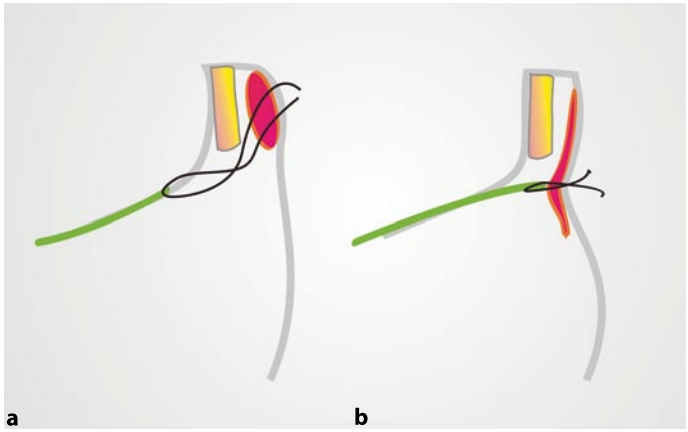


Fig 1.13 **a** The "backward" and "downward" vector of the retractor action (*green*) can be used to attach overriding orbicularis muscle fibers (*red*) in involutional entropion. **b** A sagittal translamellar connection of the posterior and anterior lid lamellae is created to attach the orbicularis muscle and to restore the lower lid crease

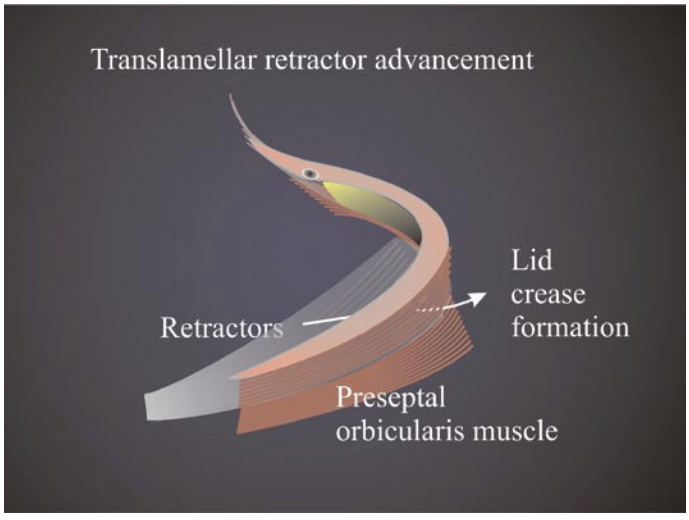


Fig. 1.14 The horizontal conjunctival incision is placed 2 mm below the inferior border of the tarsus. The inferior lip of the conjunctival incision is pushed bluntly downward together with the tarsal muscle to expose the retractors, which are transsected horizontally and advanced toward the anterior lamella with penetrating sutures that are tied subcutaneously over the preseptal orbicularis muscle

deformity where the lash line is displaced to the apex and the inner and outer edges of the margin are absent. In mild cases, the condition can be corrected by additional shaping of the lid margin. With the high frequency needle, a sulcus can be created posterior to the lash line in the area of conjunctivalization. If the retractor sutures are placed at a higher pretarsal level of the orbicularis muscle, they act in a more pronounced everting manner and can be used to open the sulcus. In severe cases, complete separation and repositioning of the anterior and posterior lamellae are necessary.

1.6.3 Complications of Retractor Surgery

Under-correction of entropion or ectropion is probable after retractor surgery without correction of the horizontal laxity. The lateral tarsal strip procedure can, however, be performed at a later stage. Under-correction can also occur after incorrect placement of the retractor sutures. In these cases, repeat suturing should be planned as early as possible. Results after ectropion surgery can appear over-corrected when the lash line is directed upward or even inward, due the deformity of the lid margin. We have often observed a spontaneous normalization of the lash line orientation after a few weeks. If this does not occur, we can split the lid margin at the gray line in order to evert the lash line. In entropion surgery excessive tightening of the retractors can cause a retraction or eversion. To avoid severe lid retraction, the retractors have to be released as early as possible.

Summary for the Clinician

- Identify complicated cases because they will need additional surgery.
- Try to avoid excision of tissue.
- Do not exaggerate the tightening or advancement.
- Try to restore a normal flexible tone to the three vectors of fixation.

References

1. Beigi B (2001) Orbicularis oculi muscle stripping and tarsal fixation for recurrent entropion. Orbit 20(2):101–105
2. Collin JRO (2005) Manual of systematic eyelid surgery. Butterworth Heinemann/Elsevier, Amsterdam
3. Corin S, Veloudios A, Harvey JT (1991) A modification of the lateral tarsal strip procedure with resection of orbicularis muscle for entropion repair. Ophthalmic Surg 22:606–608
4. Dresner SC, Karesh JW (1993) Transconjunctival entropion repair. Arch Ophthalmol 111:1144–1148
5. Khan SJ, Meyer DR (2002) Transconjunctival lower eyelid involutional entropion repair: long-term follow-up and efficacy. Ophthalmology 109:2112–2117
6. Pfeiffer MJ (2004) Involutives Unterlidektropium: Chirurgische Therapie. Ophthalmochirurgie 16:89–96
7. Pfeiffer MJ (2005) Involutives Unterlidentropion: Chirurgische Therapie. Ophthalmochirurgie 17:23–28
8. Quickert MH, Rathburn JE (1971) Suture repair of entropion. Arch Ophthalmol 85:304–305
9. Wies FA (1954) Surgical treatment of entropion. J Int Coll Surg 21:758–760

Chapter 2

Update on Mohs Micrographic Surgery Techniques for Excision and Reconstruction of Periocular Tumors: A Multidisciplinary Approach

2

Christopher J. Miller, William R. Katowitz

Core Messages

- The successful treatment of periocular tumors depends on the accomplishment of three goals:
  - Cure of the tumor
  - Preservation of function
  - Cosmetic reconstruction
- Periocular tumors exhibit a high incidence of subclinical spread. Physical examination does not reliably predict the full extent of periocular tumors.
- Excision with standard surgical margins and common methods of pathologic margin evaluation frequently result in tumor recurrence and unnecessary loss of healthy tissue.
- Mohs micrographic surgery offers the highest published cure rates for the most common periocular tumors.
- Mohs micrographic surgery results in maximal preservation of healthy tissue, leading to optimal cosmetic and functional outcomes.
- The success of the Mohs technique derives from 100% microscopic margin evaluation of the cut surgical edge and meticulous tissue mapping.
- The Mohs micrographic surgeon serves dual roles as surgeon and pathologist.
- Excision with intraoperative frozen sections can achieve cure rates nearly comparable to those of Mohs micrographic surgery, but may not allow maximal tissue sparing.
- The reconstructive surgeon who uses intraoperative frozen sections will benefit from close communication with the pathologist to ensure maximal microscopic evaluation of the surgical cut edge and to maintain orientation of the surgical specimen relative to the patient.
- Strong data support the use of Mohs micrographic surgery for periocular basal cell and squamous cell cancers.
- Strong data support the use of Mohs micrographic surgery for periocular sebaceous carcinoma combined with conjunctival map biopsies.
- Growing evidence supports the use of Mohs micrographic surgery to treat lentigo maligna and melanoma in situ.
- Mohs micrographic surgery is a valuable addition to a multidisciplinary approach to treating patients with periocular tumors.

2.1 Introduction

2.1.1 Role of Mohs Micrographic Surgery in Treating the Patient with Periocular Malignancy

The successful treatment of periocular tumors depends on the accomplishment of three primary goals:

- Cure of the tumor
- Preservation of function
- Cosmetic reconstruction

Balancing efforts to achieve these three goals can challenge the reconstructive surgeon. Whereas generous surgical margins enhance cure rates, they can lead to extensive cosmetic and functional morbidity. By contrast, modest surgical margins may simplify reconstruction, improve cosmetic outcomes, and preserve function of critical periorbital anatomy only to increase the risk of tumor recurrence. Strong evidence supports the use of Mohs micrographic surgery to treat periorbital malignancies, due to its reliably high cure rates and maximal preservation of healthy tissue [22]. The term "micrographic" describes two inherent aspects of the technique:

- Microscopic margin control ("micro")
- Detailed tissue mapping ("graphic")

This chapter discusses Mohs micrographic surgery and its role in the treatment of the most common periorbital malignancies.

2.1.2 History of Mohs Micrographic Surgery in the Treatment of Periocular Malignancies

The use of Mohs micrographic surgery for periocular tumors began in the 1930s, when Dr. Frederic Mohs first conceived and developed the idea of excising cancers under complete microscopic margin control [46]. As a research assistant at the University of Wisconsin, Dr. Mohs discovered that a paste containing zinc chloride could fix tissue in situ without altering its detailed histology. In 1936, he began treating patients with skin cancer using the fixed tissue technique. He chemically fixed the cancer and surrounding tissue with zinc chloride paste, performed saucerized surgical excision, and microscopically evaluated the complete surgical margin with an intricate system of mapping and inking the excised specimen. This complete method of microscopic margin control allowed Dr. Mohs to locate "silent" (i.e., subclinical) tumor extensions, to indicate the precise location of residual tumor on his tissue map, and to perform successive targeted excisions until the tumor was cleared. By 1941, he had published the results of his seminal series of 414 patients treated by the technique, 48 of whom had eyelid cancers [45]. Although the fixed tissue technique achieved excellent cure rates, the zinc chloride fixative caused patients significant pain and edema and prevented immediate reconstruction of most wounds, necessitating second intention healing or delayed reconstruction.

In 1953, while treating a tumor of the eyelid, Dr. Mohs first omitted the use of the fixative and began using the fresh-tissue technique that is commonly used today. The omission of the fixative and conversion to the fresh-tissue technique decreased patient discomfort, increased the speed of the procedure, and allowed immediate reconstruction of the surgical defect [46]. By the 1970s, the fresh-tissue technique of micrographic surgery had gained wider acceptance and was applied to treat skin cancers in all regions of the body. The procedure has since evolved to gain continued recognition as a method of treating skin cancers that produces high cure rates, conserves tissue, and optimizes cosmetic and functional outcomes.

2.1.3 Clarification of the Meaning of Clinical, Surgical, and Pathologic Margins

First, it is necessary to clarify the meaning of clinical, surgical, and pathologic margins, since these terms will be used throughout the chapter. Clinical margin refers to the dimensions of the tumor as determined by visualization and palpation during physical examination. Surgical margin refers to the amount of normal-appearing tissue that the surgeon removes around the clinical margins of the tumor. The surgeon must decide an appropriate surgical margin in two dimensions, namely, width and depth. The cut

surgical margin refers to the edge of the excised tissue where it was separated by the scalpel from the tissue that remained on the patient. Pathologic margin refers to the edges of the cut surgical margin that the pathologist examines under the microscope. Techniques used to determine pathologic margins vary widely in the extent to which they examine the cut surgical margin [1, 9, 59]. The accuracy of pathologic margins improves proportionately to the amount of the cut surgical margin evaluated under the microscope. Pathologic margins can be determined postoperatively (e.g., standard excision) or intraoperatively (e.g., Mohs micrographic surgery or frozen section biopsies). Mohs micrographic surgery offers the most complete method of intraoperative pathologic margin evaluation, a critical factor leading to its high cure rates.

2.2 Steps of Mohs Micrographic Surgery

2.2.1 Step 1: Determination of Clinical Margins

The precision of Mohs micrographic surgery (Fig. 2.1) begins with a careful physical examination of the tumor. In a position comfortable for both patient and surgeon, the Mohs surgeon assesses the clinical margins by visualizing and palpating the tumor under high quality lights. Stretching the skin around the tumor and using tangential light highlight color and texture differences between the tumor and surrounding skin and improve accuracy of the clinical margins.

Periocular tumors frequently have indistinct margins that make determination of clinical margins by physical examination unreliable [26]. When the clinical margins of the tumor are poorly defined, the Mohs surgeon delineates areas with definite versus possible tumor extension. The surgical margin during the initial Mohs layer removes those areas where the surgeon has a high degree of confidence that the tumor is present. In order to avoid unnecessary removal of potentially healthy skin, the surgeon avoids extending the surgical margin around areas where tumor extension is dubious. Complete examination of the pathologic margin will reveal whether excision of clinically suspect areas is necessary.

2.2.2 Step 2: Debulking of the Tumor

After achieving adequate local anesthesia, the surgeon debulks the tumor at the definite clinical margins (i.e., the visible and palpable borders of the tumor). The primary purpose of removing the bulk of the tumor is to facilitate excising a Mohs layer (see Sect. 2.2.3) that will allow the entire three-dimensional cut surgical margin to lie in a single, flat, two-dimensional plane.

Debulking the tumor also provides secondary benefits. For example, debulking by curettage can delineate areas of subclinical extension and better define the clinical margins of a tumor [20]. A curette is a surgical instrument with a distal, round or oval ring that has a sharp edge on only one side. The surgeon scrapes the cutting edge of the curette's distal ring against the tumor, which feels friable and has an oatmeal consistency compared with the firm and gritty underlying healthy dermis. By distinguishing a difference in feel between the friable tumor and healthy dermis, the Mohs surgeon can uncover areas of subclinical spread and more accurately delineate the clinical margins of the tumor.

Debulking by curettage is appropriate primarily for basal cell and squamous cell cancers and is best reserved for tumors where the biopsy suggests superficial invasion. Confirmation of superficial invasion of the tumor by curettage allows the Mohs surgeon to take a conservative deep margin that provides the maximal number of options available for reconstruction. For example, if curettage of a superficial basal cell cancer in the medial canthus does not extend through the dermis, the surgeon can be more confident that a surgical margin extending to the superficial subcutaneous fat will clear the tumor. A superficial wound in this location extends the range of reconstruction options available, such as second intention healing or a full-thickness skin graft.

Debulking by scalpel excision is the method of choice in the following instances:

- Melanocytic lesions
- Less common nonmelanoma tumors (e.g., sebaceous cell carcinoma)
- Basal cell and squamous cell cancers in which the surrounding skin does not provide a firm enough background against which to press a curette

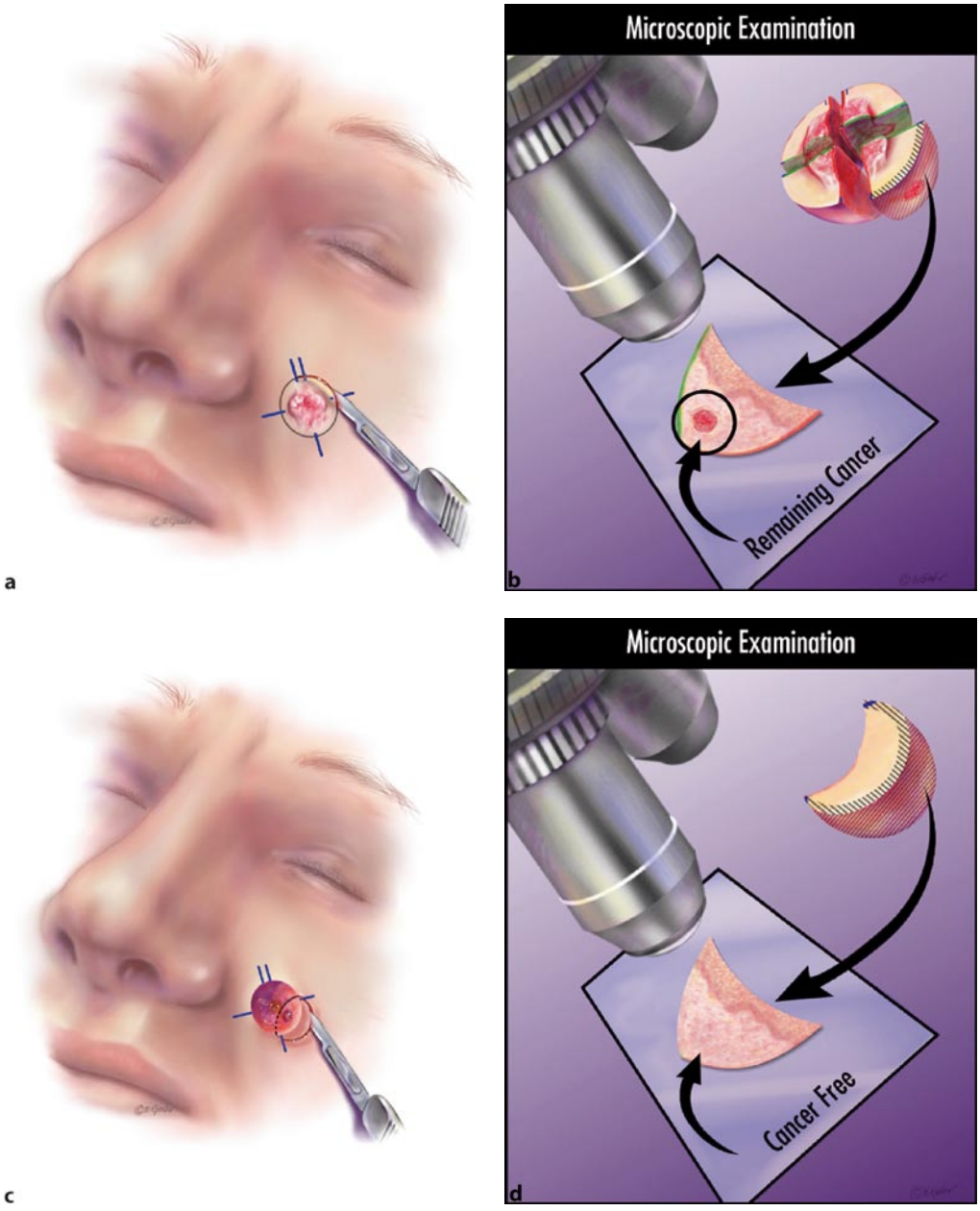
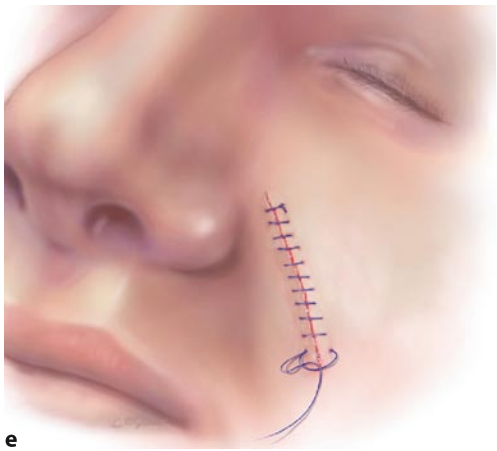


Fig. 2.1 Steps of Mohs micrographic surgery. Basal cell carcinoma of the left maxillary cheek. **a** Clinically visible tumor is debulked and a Mohs excision with 1–2 mm of clinically normal tissue is excised. **b** The specimen is grossly sectioned into four pieces along hash marks, and the cut edges are inked with green and red dyes. Frozen section slides for each piece reveal subclinical tumor spread in the right lower quadrant. **c** Selective excision of the remaining focus of tumor. **d** Another tissue map is created. This time, the frozen section slide shows that no tumor remains. **e** *(see next page)*



e

Fig. 2.1 *(continued)* Steps of Mohs micrographic surgery. Basal cell carcinoma of the left maxillary cheek. **e** Reconstruction of the tumor-free wound

- Basal cell and squamous cell cancers for which clinical examination suggests invasion beyond the dermis

In these instances, the lateral margins of the debulking excision correspond exactly with the clinical margins of the tumor. The depth of the debulking excision requires careful judgment by the Mohs surgeon, based on information obtained from the diagnostic biopsy and clinical examination of the tumor. For thin tumors that involve primarily epidermis (e.g., superficial basal cell carcinoma or squamous cell carcinoma in situ), the debulk specimen may extend only to the dermis and resemble a shave biopsy. For bulkier tumors, the debulk excision may extend to the superficial subcutaneous fat or deeper, depending on the extent of the tumor.

In contrast to curettage, scalpel debulking affords intact tissue that the Mohs surgeon can examine microscopically. Serial vertical frozen sections (breadloaf technique) through the sharp debulk specimen offer distinct advantages. First, the vertical sections serve as a positive control that assists the surgeon in the interpretation of the Mohs margins, especially if the tumor has subtle histologic features. Second, the vertical sections can reveal high-risk histologic factors, such as perineural invasion, which may not have been detected on the diagnostic biopsy and may affect prognosis and decisions regarding adjuvant therapy. This advantage benefits patients most frequently when treating high-risk squamous cell cancer or broad melanocytic lesions for which detection of invasion has significant prognostic significance.

2.2.3 Step 3: Excising the Initial Mohs Specimen

The surgeon excises a thin surgical margin around the lateral and deep edges of the defect from the debulking procedure. This initial Mohs excision intends to achieve complete removal of the tumor, typically with a surgical margin of 1–2 mm of clinically normal-appearing tissue. Large or deeply invasive tumors in areas of pliable skin (e.g., areas with thick subcutaneous fat) may require wider margins to ensure integrity of the margin and to facilitate tissue processing. The Mohs surgeon maintains orientation of the specimen relative to the patient using a variety of techniques that mark corresponding areas on the patient and specimen, including nicking with a scalpel, ink marking, and photographs. After achieving hemostasis of the Mohs defect, a temporary bandage is placed over the wound as the patient waits for the Mohs surgeon to evaluate the adequacy of the margins under the microscope.

Review of the literature regarding the angle of excision of the Mohs specimen can confuse a surgeon unfamiliar with the Mohs technique. Classic review articles on Mohs micrographic surgery describe excision of the Mohs layer with a 45° angle and include illustrations of "bowl-

shaped" tissue specimens [65]. In actuality, Mohs surgeons excise the specimen with a wide variety of angles according to the characteristics of both the tissue and the tumor [24]. Above all, the Mohs surgeon keeps in mind that the entire cut surgical margin of the Mohs specimen must be able to lie in a single flat plane that allows complete histologic evaluation of the cut surgical margin. In general, the angle of the excision will approximately parallel the lateral and deep margins of the defect from the debulking procedure.

2.2.4 Step 4: Gross Sectioning and Inking the Fresh Tissue Mohs Specimen

As already mentioned, the surgeon or Mohs histotechnologist immediately grosses the fresh tissue Mohs specimen so that the three-dimensional cut surgical margin lies in a single, flat plane. In order to evaluate 100% of the pathologic margin, the entire three-dimensional cut surgical margin must ultimately conform to the two dimensions of a glass slide.

To maintain precise orientation relative to the patient and to facilitate tumor mapping, gross sectioning of the Mohs specimen should correspond whenever possible to the orienting nicks or ink marks that the surgeon made during the initial Mohs excision. The number of pieces into which the specimen is grossly sectioned depends on multiple factors, including the size of the Mohs specimen and the ease with which the outer surgical margin conforms to a two-dimensional plane. Colored tissue dyes are used to ink the epidermal and deep edges created during the grossing. These colored dyes maintain orientation of each piece, help to localize residual tumor with precision, and serve as a marker that allows the surgeon to determine that the microscopic sections represent the complete pathologic margin.

2.2.5 Step 5: Mapping the Mohs Specimen

The surgeon or histotechnologist creates a map of the Mohs specimen that reflects the grossing and inking of the fresh tissue Mohs specimen and allows the surgeon to keep the tissue oriented relative to the patient. Most frequently, surgeons draw the map by hand. However, digital or Polaroid photographs may be used for large or convoluted specimens to maintain precise orientation. In general, the map approximates the scale of the actual Mohs specimen and documents the position of the orienting marks, the placement of the colored dyes, and the numbers assigned to each of the pieces of the grossed Mohs specimen.

2.2.6 Step 6: Embedding, Sectioning, and Staining the Pieces of the Mohs Specimen

A histotechnologist freezes each grossed piece of the Mohs specimen in an embedding medium so that the true surgical margin of each piece lies in a single flat plane. The histotechnologist uses a cryostat to cut 4- to 8-μm frozen sections at the complete cut surgical margin of each piece. These microscopic sections are placed on a slide, then fixed and stained with appropriate tissue dyes (e.g., hematoxylin and eosin). This step can take as few as 15 min for small Mohs specimens. Larger or more technically challenging specimens may require increased time.

Confusion may arise based on the multiple descriptors ascribed to the Mohs histologic sections, such as "horizontal," "tangential," and "oblique" sections. In reality, none of these terms describes the Mohs histologic sections with complete accuracy. Fundamentally, the Mohs histologic section must include the complete cut surgical margin in a single, flat plane. Multiple techniques of grossly sectioning the surgical specimen and relaxing incisions help the Mohs surgeon to force the cut surgical margin to conform to a single flat plane. The histologic Mohs sections correspond to the complete cut surgical margin.

2.2.7 Step 7: Interpretation of the Pathologic Margins by the Mohs Surgeon

In contrast to standard excision techniques, which require consultation with a pathologist, the Mohs surgeon interprets the frozen section

pathologic margins to determine the presence or absence of tumor. If no tumor is detected on frozen microscopic sections, then the patient is ready for reconstruction. If any tumor is detected on microscopic sections then the Mohs surgeon indicates the precise location of the tumor on the Mohs tissue map. The colored dyes and hash marks allow the surgeon to pinpoint the exact location of the residual tumor on the tissue map and the corresponding areas on the patient. The patient returns to the operating suite and the Mohs surgeon excises those precise areas where tumor still remains. The surgeon repeats steps 3 through 7 until the entire tumor has been removed, at which time the patient is ready for reconstruction.

Summary for the Clinician

- A food analogy helps to conceptualize the technique of Mohs micrographic surgery. One can consider the skin cancer to be analogous to a pie.
- The central tumor represents the filling, and the surgical margin (usually 1–2 mm of normal-appearing tissue around the visible tumor) represents the pie-crust.
- The debulking procedure removes most or all of the tumor ("pie filling").
- The Mohs excision cuts a thin surgical margin, analogous to a pie-crust, around the defect from the debulking procedure.
- The excised Mohs specimen (pie-crust) is grossly sectioned so that its outer edges (which correspond to the true cut surgical margin) lie in a single plane.
- After proper embedding technique, the Mohs histotechnician uses a microtome to section the tissue along the cut surgical margin (outer edge of the pie-crust) of the entire specimen.
- If any tumor is detected on the microscopic sections (i.e., filling popping through the pie-crust), then the surgeon notes the exact location of the residual tumor on the tissue map and excises those precise areas where tumor still remains.

2.3 Advantages of Mohs Micrographic Surgery

2.3.1 High Cure Rates

The surgeon's first goal is to cure the tumor. For the four most common periocular tumors, standard margins are frequently recommended. For basal cell and squamous cell cancers, the recommended margin of excision is at least 4 mm [12, 74]. For periocular sebaceous carcinoma without obvious orbital involvement, standard margins of excision include 5- to 6-mm margins of normal-appearing tissue around the tumor [69]. Recommended surgical margins are 5 mm for melanoma in situ and 1 cm for invasive melanoma with a Breslow depth <1 cm.

These recommended margins are frequently insufficient to achieve complete excision, due to the high incidence of subclinical spread of periocular tumors [40, 41, 69]. Subclinical spread refers to extensions of tumor beyond the dimensions that can be appreciated by clinical examination. The supposed mechanisms for subclinical spread in the periocular region include tracking of tumor along embryonic fusion planes, perineural spread, extension along nearby periosteum and tarsal plates, or infiltration among the dense sebaceous glands that populate the eyelid [8]. The inability to detect extensions of tumor along these subclinical planes, renders standard surgical excision in the periocular region unreliable and may result in incomplete excision in 23–64% of cases [26, 46, 58]. Surgical defects can measure 4.2 to 4.6 times the preoperative clinical margins of periocular basal cell carcinoma and 2.6 times the preoperative clinical margins for periocular squamous cell carcinoma [18]. Residual tumor after incomplete excision with standard margins can result in a high rate of recurrence [27, 66]. Recurrent tumors become increasingly recalcitrant to treatment, causing extensive morbidity and mortality [60, 63]. Medial canthal tumors pose a particular threat to the patient's life, due to the possibility of deep intracranial invasion [3].

Due to its ability to detect subclinical tumor extension intraoperatively, strong evidence supports treating periocular tumors with Mohs micrographic surgery [22]. Mohs micrographic surgery offers complete microscopic margin evaluation of the cut surgical margin, facilitating

reliable detection of subclinical extension. By detecting and targeting all areas of the cancer, collaboration with the Mohs surgeon can help the oculoplastic surgeon achieve a high rate of cure, the paramount goal of surgical excision [62, 63].

2.3.2 Tissue Conservation

Mohs micrographic surgery also spares maximal amounts of healthy tissue. In the periocular region, tissue conservation yields considerable benefits, including simpler reconstructive options and preservation of critical anatomic structures. Defects after Mohs micrographic surgery frequently provide the unexpected benefits of preserving the posterior lamella and lacrimal system and may avoid the need for more invasive orbital surgery and even exenteration [3, 26, 32, 48]. Ultimately, the patient benefits from preservation of function and cosmetic reconstruction, the two remaining primary goals of the reconstructive surgeon. Tissue conservation associated with Mohs micrographic surgery derives from the precise orientation of the surgical specimen relative to the patient and meticulous system of tissue mapping used to document the presence or absence of tumor at the surgical margin. If evaluation of the initial Mohs margin detects areas of subclinical microscopic tumor extension, the Mohs surgeon pinpoints the exact location of residual tumor on the tissue map and then removes the corresponding areas on the patient in subsequent stages. Healthy skin unaffected by tumor remains untouched. This ability to target and remove the precise areas affected by tumor forces the Mohs defect to conform to the tumor's asymmetric subclinical growth pattern, which the surgeon cannot reliably predict by clinical examination alone [18, 74].

2.3.3 Optimal Division of Labor

Collaboration between the Mohs surgeon and the oculoplastic surgeon has the potential to optimize patient outcomes. When the reconstructive surgeon excises the tumor, mindfulness of the preferred reconstructive plan may tempt the surgeon to compromise margins. In a multidisciplinary approach, the Mohs micrographic surgeon can objectively remove the tumor, and the reconstructive surgeon can schedule the procedure electively with ample opportunity to estimate the necessary operating time.

Summary for the Clinician

The advantages of Mohs surgery are:

- High cure rates
- Tissue conservation
- Optimal division of labour

2.4 Differences Between Mohs Micrographic Surgery and Common Standard Excision Techniques

2.4.1 Determining Appropriate Surgical Margins: How Does One Decide Where to Cut?

The differences between Mohs micrographic surgery and methods of standard excision begin with determination of an appropriate initial surgical margin. With any method of excision, the surgeon must determine an appropriate surgical margin around all clinically apparent tumors in two dimensions, width and depth. Due to the high incidence of subclinical tumor extension in the periocular region, surgical margins based on clinical examination alone are unreliable [26, 58]. Standard surgical margins for periocular tumors are frequently insufficient to remove the entire tumor [40, 41, 46, 69], and tumors can have subclinical extension that involves clinically normal-appearing skin in more than 85% of cases [5, 35]. Since tumors extend subclinically in an asymmetric pattern [74], wider or deeper surgical margins may be required in one direction, while narrower margins will be sufficient in others. Wide and deep surgical margins that extend uniformly around all clinically apparent tumor risk unnecessary removal of excessive amounts of healthy tissue.

Mohs micrographic surgery respects the principle of asymmetric subclinical extension and

spares healthy tissue by creating a surgical defect that extends just beyond the true extent of the tumor. Rather than removing a wide initial surgical margin, the Mohs technique allows the surgeon to start with a more conservative surgical margin of 1–2 mm. Complete microscopic margin evaluation of the cut surgical margin and meticulous tissue mapping allow the surgeon to detect and successively remove precise areas of the subclinical tumor extension. All successive Mohs excisions conform to the pattern of subclinical tumor spread, as opposed to removing additional tissue around the entire surgical defect.

2.4.2 Comparing and Contrasting Methods of Microscopic Margin Evaluation

The method of microscopic margin evaluation in Mohs surgery is significantly more thorough compared with the most common methods of pathologic margin evaluation. Excellent review articles characterize different methods of grossly sectioning surgical specimens and illustrate that some methods offer a much more complete evaluation of the cut surgical margin than others [1, 9, 59]. The most common method of grossly sectioning excision specimens only samples a small percentage of the cut surgical margin, thereby increasing the likelihood of missing small foci of subclinical extension [1, 9, 59]. Although explanation of these grossing methods lies beyond the scope of this chapter, a few points deserve mention.

In standard excision methods, the surgeon excises a margin of clinically normal tissue around the visible and palpable tumor, and the surgical specimen is sent to a pathologist for margin evaluation. A technician or a pathologist grossly cuts random step sections through the tissue with a scalpel blade. The grossly sectioned pieces are embedded and cut on a microtome into very thin sections that are mounted on a glass slide, stained, and examined histopathologically. The pathologist notes whether the centrally located tumor extends to the deep or lateral margins of the sections on the slide. If the tumor does not extend to the deep or lateral margin in the sections examined, then the pathologist determines that the tumor has been removed.

It is critical to note that these sections only represent a small sample of the entire surgical margin. If the random gross sections failed to cut through a small focus of subclinical microscopic tumor that extends to the cut surgical margin, the standard methods of microscopic evaluation will not detect it. To reduce this risk of a false negative margin, Mohs surgery examines 100% of the cut surgical margin under the microscope. The tissue sections on the microscopic slides represent the entire three-dimensional cut surgical margin of any tissue removed.

2.4.3 Dual Vs. Separate Roles of Surgeon and Pathologist

Another critical difference between Mohs micrographic surgery and standard excision techniques is the fact that the Mohs surgeon also functions as the pathologist. Logistical and communication challenges arise when the surgeon does not serve as the pathologist. For example, when performing standard excision with frozen section evaluation, the pathologist ideally witnesses the removal of the tumor in the operating room in order to maintain orientation of the specimen and to determine the most appropriate method of grossly sectioning the tissue to obtain frozen sections [75]. By contrast, the Mohs surgeon's dual role as surgeon and pathologist helps solve logistical and communication challenges associated with standard excision and intraoperative frozen section analysis. With immediate clinicopathologic correlation, the Mohs surgeon can pinpoint the exact location of any microscopically positive tumor margins and remove the precise areas of residual tumor in subsequent Mohs layers. Since the Mohs surgeon excises only those areas where tumor remains (versus around the entire defect), subsequent excisions can spare critical anatomic structures and help simplify reconstruction.

Although excision with intraoperative frozen-section control increases confidence that the tumor has been completely removed and can obtain excellent cure rates for periocular tumors [22], it may result in greater loss of healthy tissue and higher recurrence rates compared with Mohs surgery [28, 54]. Without meticulous mapping of the excised tissue relative to the patient,

conventional frozen sections rely on random tissue samples that do not allow the surgeon to pinpoint the precise location of a positive surgical margin [54]. Unless the surgeon communicates closely with the pathologist, a positive margin may obligate the surgeon to excise an additional margin around the entire defect, even if tumor is only focally present at the margin [28]. Since subclinical spread does not extend evenly in all directions, these additional uniform margins may lead to excessive tissue removal in several dimensions. To ensure adequacy of evaluation of the surgical margin and to spare healthy tissue, the oculoplastic surgeon who utilizes excision with intraoperative frozen section control benefits from close communication with the pathologist and a thorough understanding of the method used to grossly section the excised tissue specimen [75]. Excision with frozen section control may be more applicable to smaller tumors of the lid margin. If the pathologist can maintain orientation of the specimen and carefully freeze the entire surgical cut margin, then the results may be satisfactory and comparable to those achieved with Mohs surgery.

2.5 Potential Pitfalls of Mohs Micrographic Surgery

Errors can occur at any step in the process of Mohs micrographic surgery. Some key errors deserve mention. The success of Mohs micrographic surgery depends on a contiguous growth pattern of the tumor. Discontiguous or multifocal tumor growth defies the accuracy of microscopic margin control. The Mohs surgeon may obtain clear margins through intervening areas of normal tissue without ever recognizing that other tumor foci were left behind. Discontiguous tumor growth is common in recurrent tumors. Since one cannot guarantee that the tumor has recurred at several places within the scar, the Mohs surgeon must excise the entire scar along with all visibly recurrent tumors to maximize the likelihood of complete cure.

Several errors can result in falsely negative margins, thereby leading to a higher rate of tumor recurrence. Incomplete surgical margins may occur if the Mohs surgeon fails to recognize a rent or buttonhole in the deep margin of the Mohs excision specimen. Inaccurate mapping technique can mislead the surgeon to remove tissue at subsequent stages that does not include the residual tumor. Errors in grossing technique or tissue processing can result in incomplete pathologic margins. Dense inflammation on Mohs microscopic sections can mask small foci of tumor. Additionally, the Mohs surgeon may fail to detect small foci of tumor on the Mohs microscopic sections.

Certain errors can decrease the tissue-sparing benefits expected of the Mohs procedure. Inaccurate preoperative assessment of the clinical margins of the tumor can lead to excessive surgical margins. Epithelial structures mimicking tumor may mislead the Mohs surgeon to carry out unnecessary additional stages.

Finally, Mohs micrographic surgery is typically performed with the patient under local anesthesia. Since the Mohs surgeon only learns the true extent of the tumor intraoperatively, periocular tumors may be found to involve deeper structures that the surgeon cannot resect under local anesthesia [38]. Tumors located in the medial canthus may be at particularly high risk of intraorbital or bony invasion undetected preoperatively [38]. If preoperative assessment reveals restriction of the extraocular muscles or proptosis, or if bony or intraorbital invasion is suspected, then preoperative imaging studies, including computed tomography and magnetic resonance imaging, are mandatory. Mohs micrographic surgery may not be the most suitable treatment option in such instances [32].

Since many shortcomings of the technique can result from human error, the success of Mohs micrographic surgery depends highly on the skill of the Mohs surgeon and the Mohs histotechnologists. Referring doctors should ensure that the Mohs surgeon they utilize has had appropriate training to maximize the likelihood of competency. Since 1983, the American College of Mohs Micrographic Surgery and Cutaneous Oncology (ACMMSCO) has mandated official requirements for a Mohs surgery fellowship with a minimal duration of 1 year. Currently, more than 50 standardized fellowships are accredited by the ACMMSCO. These fellowships include intensive training in frozen section dermatopa-

thology, cutaneous oncology, and reconstructive surgery [15]. To maximize quality control and patient care, fellowship training sponsored by the ACMMSCO is advisable, though not mandatory, for any physician practicing Mohs micrographic surgery [15].

Summary for the Clinician

The disadvantages of Mohs surgery are:

- Discontiguous or multifocal tumor growth defies the accuracy of microscopic margin control.
- Falsely negative margins result in higher rate of tumor recurrence.
- Inaccurate preoperative assessment of the clinical margins of the tumor can lead to excessive surgical margins.
- Since the Mohs surgeon only learns the true extent of the tumor intraoperatively, periocular tumors may be found to involve deeper structures that the surgeon cannot resect under local anesthesia.

2.6 Periocular Tumors: Indications for Mohs Micrographic Surgery

2.6.1 Choosing a Management Plan Based on Risk Assessment of the Periocular Malignancy

While substantial data support the efficacy of Mohs micrographic surgery to achieve excellent cure rates and maximize tissue sparing, multiple treatment modalities can be used to treat periocular malignancies, including cryotherapy, curettage, topical chemotherapy, radiation, or standard excision with intra- or postoperative margin evaluation. Review of these therapeutic options lies beyond the scope of this chapter.

In general, if the tumor characteristics carry a low risk of recurrence or metastasis, the use of medical or ablative treatment modalities may be considered. Ablative treatments do not allow assessment of pathologic margins. Therefore, the only confirmation of efficacy is absence of tumor recurrence. When high-risk tumor factors predominate, excisional modalities with either post- or intraoperative margin assessment are recommended. Excision with intraoperative frozen sections or Mohs micrographic surgery has become the standard of care for treating periocular tumors [22].

In general, Mohs micrographic surgery is indicated primarily for high-risk periocular malignancies. "Risk" refers to the likelihood of recurrence or metastasis. Risk factors that predict a higher likelihood of recurrence or metastasis derive from the clinical history, physical exam, and tumor pathology. Excellent resources review treatment algorithms based on the assessment of the risk of recurrence or metastasis of a tumor [52]. This section will summarize common indications for Mohs micrographic surgery, including high-risk basal and squamous cell cancers, sebaceous carcinoma, and lentigo maligna.

2.6.2 Mohs Micrographic Surgery for Basal Cell and Squamous Cell Cancers

Basal cell carcinoma is the most common malignant periocular tumor, accounting for 80–90% of eyelid malignancies [21]. The tumor most frequently causes morbidity due to local growth and invasion; however, metastasis rarely occurs [29, 68]. Some authors cite mortality rates from basal cell carcinomas ranging from 2 to 11% [75]. Overall, 5-year cure rates exceeding 89.9% have been reported for surgical excision, curettage and electrodesiccation, radiation therapy, and cryotherapy of basal cell carcinomas [61]. However, these high cure rates may not apply to periocular tumors. Recurrence rates for periocular tumors treated by unmonitored surgical excision and destructive modalities are high, ranging from 5 to 100% [40]. Mohs micrographic surgery offers cure rates of 99% for primary basal cell cancers and 94% for recurrent basal cell cancers, and is recommended by some authors as the treatment of choice for periocular basal cell carcinoma [42, 61, 62].

Squamous cell carcinoma is the second most common malignant periocular tumor [41]. Squamous cell carcinoma causes morbidity due to local growth and invasion and may cause mor-

tality from metastasis. Overall, the rate of metastasis for squamous cell carcinoma of the skin is 2–6% [64]. Mohs micrographic surgery can offer a 5-year cure rate exceeding 98% for periocular squamous cell carcinoma [47]. Some authors have recommended Mohs micrographic surgery as the treatment of choice for periocular squamous cell carcinoma [22, 41].

For both basal cell and squamous cell carcinomas, certain risk factors predict the likelihood of recurrence or metastasis. This section reviews these risk factors, which may also serve as indications for Mohs micrographic surgery.

2.6.2.1 Recurrent Versus Primary Tumors

Cure rates achieved by any treatment modality, including Mohs micrographic surgery, decline when treating recurrent versus primary tumors [61–63]. In general, Mohs micrographic surgery of primary basal cell carcinoma achieves a 5-year cure rate of 99% [61], compared with a 5-year cure rate of 94.4% when treating recurrent basal cell carcinoma [62]. Mohs micrographic surgery of primary squamous cell carcinoma achieves a 5-year cure rate of 96.9%, compared with a 5-year cure rate of 90% when treating recurrent squamous cell carcinoma [63]. Compared with all other treatment modalities, Mohs micrographic surgery produces statistically higher cure rates when treating recurrent tumors [62, 63].

2.6.2.2 History of Prior Irradiation

Tumors arising within a field of prior radiotherapy carry a higher risk of recurrence or metastasis [52]. Ablative therapies are not recommended.

2.6.2.3 Immunosuppressed Patient

Squamous cell carcinoma has a significantly greater incidence of metastasis in immunosuppressed versus immunocompetent hosts [52]. Only anecdotal reports support an increased risk of recurrence or metastasis of basal cell carcinomas arising in an immunosuppressed host [52]. The increased risk of recurrence and metastasis is an indication for Mohs micrographic surgery.

2.6.2.4 Additional Historical Risk Factors

Mohs micrographic surgery is indicated if tumors arise within a site of chronic scarring, if they exhibit preoperative symptoms and signs suggestive of perineural spread (e.g., pain, burning, stinging, anesthesia, paresthesia, facial paralysis, diplopia, and blurred vision), or if they exhibit rapid growth [52].

2.6.2.5 Size and Location

Location and size are well-established risk factors for recurrence and metastasis [52]. The mask area, or "H-zone," of the face is considered a high-risk location [52]. Arising in part of this mask area, periocular tumors predictably demonstrate a high risk of recurrence or metastasis [8]. Within the periocular region, tumors located in the medial canthus tend to carry the highest risk of recurrence [5]. Determination of risk by size is arbitrary; however, periocular tumors measuring 6 mm or more in diameter are considered high-risk [52]. Regardless of the size and exact location within the periocular region, ill-defined clinical margins increase the likelihood of recurrence or metastasis.

2.6.2.6 Histologic Subtypes

In certain histologic subtypes of basal cell and squamous cell cancer there is a greater likelihood of recurrence or metastasis. In general, high-risk histologic subtypes of basal cell and squamous cell cancers exhibit small infiltrative islands, strands, or single cells of tumor that may not have a sufficient burden in the dermis to manifest visible changes at the skin surface. Consequently, for these tumors there is a greater likelihood of extensive subclinical spread.

High-risk histologic subtypes for basal cell carcinoma include micronodular, infiltrative,

sclerosing, and morpheaform (or desmosplastic) patterns [52]. Nodular and superficial basal cell carcinomas are considered to carry a lower risk of recurrence or metastasis. In the periocular region, however, nodular and superficial basal cell carcinomas may also be considered high-risk, since they tend to have substantial subclinical spread. Up to 85% of basal cell carcinomas of any histologic subtype tend to have subclinical spread requiring wider excisions than expected by clinical examination [19].

With regard to squamous cell cancer, moderately and poorly differentiated cancers carry a higher risk of recurrence or metastasis compared with well-differentiated tumors [19, 52, 55, 63]. Squamous cell carcinomas with an adenoid (or acantholytic), adenosquamous (or mucin-producing), basosquamous, or desmoplastic pattern also carry an increased risk of recurrence or metastasis [43, 52, 55]. Finally, squamous cell cancers that invade deeply are more likely to recur [52, 55].

2.6.2.7 Perineural Involvement

Perineural involvement poses an increased risk of recurrence of both basal cell and squamous cell cancers, and an increased risk of metastasis in cases of squamous cell cancer.

2.6.3 Mohs Micrographic Surgery for Sebaceous Carcinoma

Periocular sebaceous carcinoma is a potentially aggressive malignancy that arises from the abundant sebaceous glands of the periocular region, including the meibomian glands of the tarsus, the Zeis glands of the eyelashes, and the sebaceous glands of the caruncle. The sebaceous carcinoma has various clinical and pathologic presentations and can be mistaken for basal cell or squamous cell carcinoma, both clinically and histologically [22]. Delayed diagnosis may increase the risk of orbital invasion, which occurs in 6–45% of cases, and the likelihood of metastasis to regional lymph nodes, which can occur in 17–28% of cases [22]. Clinical and pathologic features that indicate a poor prognosis include:

- Involvement of both the upper and lower eyelids
- Tumor diameter exceeding 10 mm
- Duration of symptoms of longer than 6 months
- Previous treatment with radiation
- Vascular, lymphatic, or orbital invasion
- Multicentric origin
- Highly infiltrative pattern
- Pagetoid invasion of the conjunctival epithelium of the globe or eyelids [17]

Although radiation therapy and cryotherapy have been advocated in the treatment of sebaceous carcinoma, surgery remains the primary treatment modality [69]. Historically, standard excision with recommended surgical margins of 5–6 mm results in local recurrence rates approaching 30% [69]. Due to high recurrence rates with standard therapies, Mohs micrographic surgery, or excision with frozen section control combined with conjunctival map biopsies, is the treatment of choice [22]. With any excision modality, conjunctival map biopsies are recommended to help detect intraepithelial (pagetoid) spread, to help determine appropriate surgical margins, and to identify patients who may require exenteration [22, 57].

In contrast to the wealth of data supporting the use of Mohs micrographic surgery for basal cell and squamous cell cancer, only small retrospective case reports support the use of Mohs micrographic surgery for sebaceous carcinoma. In the largest case series, Spencer et al. used Mohs micrographic surgery with the fresh tissue technique to treat 18 patients with sebaceous carcinoma of the eyelid [69]. All patients underwent four quadrant conjunctival biopsies before Mohs surgery. In all cases, Mohs micrographic surgery achieved tumor-free margins, and the defect was immediately repaired by an oculoplastic surgeon. After an average follow-up of 37 months (range 6–142 months), 16 patients remained tumor-free with no evidence of local recurrence or metastasis. The tumor recurred in 2 patients (11.1%), 1 with orbital extension and parotid gland metastasis at 9 months and 1 with local recurrence at 19 months. Although their recurrence rate of 11% is favorable compared to 30% recurrence rates associated with wide excision, longer fol-

low-up may lead to an increase in the number of recurrences.

Snow et al. reported 9 cases of periocular sebaceous carcinoma treated with Mohs micrographic surgery and the frozen tissue technique [67]. One patient had a local recurrence at 1.5 years after Mohs micrographic surgery. The remaining 8 patients were free of recurrence with a follow-up period ranging from 1 to 14 years (mean 3.2 years). Snow et al. also reviewed the literature to compile 40 additional cases of periocular sebaceous carcinoma treated with Mohs micrographic surgery. Including their own series of 9 patients, the overall local cure rate following Mohs surgery was 87.8% [6, 17, 19, 43, 53, 57, 67] with a mean follow-up of 3.1 years.

In summary, due to the high recurrence rates associated with wide excision, either Mohs micrographic surgery or wide excision with intraoperative frozen sections combined with conjunctival map biopsies is recommended to treat periocular sebaceous carcinoma [22].

2.6.4 Mohs Micrographic Surgery for Melanoma

Primary malignant melanoma of the skin near the eye constitutes 1% or less of all malignant eyelid tumors [22]. Although melanoma comprises only a small percentage of cancers of all regions of the skin, it accounts for more deaths than any other skin cancer. Multiple studies have investigated prognostic factors associated with melanoma. For localized melanoma, tumor thickness and ulceration are the two most powerful prognostic indicators [6]. Since there are no effective treatments for metastatic melanoma, complete surgical excision of localized melanoma remains the treatment of choice.

Recommended surgical margins vary according the thickness of the melanoma [53]. For in situ melanoma, recommended surgical margins are 0.5 cm; for melanomas with a Breslow depth of ≤1.0 mm, recommended surgical margins are 1.0 cm; for melanomas with a Breslow depth ranging from 1.01–2.0 mm, recommended surgical margins are 1–2 cm; and for melanomas with a Breslow depth >2.0 mm, recommended surgical margins are 2.0 cm [53]. The routine use of 1- to 2-cm margins on the eyelid would yield large surgical defects. Consequently, the customary approach is to conserve tissue by using either Mohs micrographic surgery or narrow (4–5 mm) margins examined by a well-trained and experienced pathologist [22]. Although debate continues about the best method of treating periocular melanoma [22], growing evidence supports the use of Mohs micrographic surgery [2, 10, 13, 51, 76]. This section will focus briefly on lentigo maligna, an in situ form of melanoma most commonly treated with Mohs micrographic surgery.

Lentigo maligna is an in situ form of melanoma that occurs primarily on the head and neck of middle-aged to elderly individuals with heavily sun-damaged skin. The lesion typically presents as an irregular, ill-defined macule with variegated colors ranging from tan to black. The background sun-damage makes it very challenging to determine the adequacy of both the clinical and pathologic margins.

Because lentigo maligna can evolve into lentigo maligna melanoma, an invasive subtype of melanoma, surgical excision is the standard treatment [53]. A standard surgical margin with 0.5 cm of clinically normal skin results in recurrence rates of 8–20% [37]. To improve cure rates, multiple investigators have treated lentigo maligna with Mohs micrographic surgery or variations of staged excisional techniques employing rigorous intra- or postoperative margin evaluation prior to repair [2, 4, 10, 13, 16, 37, 76]. These techniques, whose explanation lies beyond the scope of this chapter, have been summarized in excellent review articles [37]. Although there is debate about the accuracy of interpreting melanocytes on frozen sections [7, 79], rapid immunostains for frozen sections substantially enhance the reliability of Mohs micrographic surgery to treat melanoma [2, 10, 12, 13, 76]. Multiple authors show cure rates superior to excision with standard margins using frozen section Mohs micrographic surgery with and without rapid immunostains [10, 80].

A uniform theme among the various techniques employing rigorous pathologic margin evaluation is that standard excision with 0.5-cm margins is insufficient in more than 50% of cases of sizeable lentigo maligna [10]. Bricca et al. demonstrated that excision with 6-mm margins is insufficient for complete tumor removal in 17% of cases [13]. Due to the high incidence of

subclinical spread, Mohs micrographic surgery or mapped serial excision with rigorous intra- or postoperative margin evaluation should be employed to treat periocular lentigo maligna [39]. Application of these techniques to lentigo maligna of the eyelid can improve cure rates compared with standard excision.

2.7 Reconstruction of Periocular Defects after Mohs Micrographic Surgery

2.7.1 Preoperative Considerations

Careful preoperative assessment of the patient and meticulous inventory of intact anatomy optimizes the reconstructive plan. For tumors and defects at or near the eyelid margin, the oculoplastic surgeon can preoperatively identify patients at greatest risk of lid malposition. With the patient seated and in primary gaze (i.e., looking straight ahead with the head in a normal horizontal position), the lower eyelid should overlie the inferior limbus by about 1 mm. Exposed sclera inferior to the limbus signals an increased risk of eyelid laxity and potential lid malposition [11]. A "snap-back test" or lid retraction test can further assess the degree of lower lid laxity [11]. With the patient in a seated position, the surgeon grasps the skin of the lower eyelid between the thumb and forefinger and pulls the eyelid inferiorly away from the globe. An ability to stretch the lid 8 mm or more away from the surface of the globe signals excessive lid laxity [11]. Slow recoil after release of the lid or a return to the globe surface only after blinking or manipulation also indicates an increased risk of lid malposition. Intraoperatively, the surgeon can have the patient perform maneuvers in either the supine or seated position to determine the effect of the reconstruction on lid position. To place maximal downward tension on the lower lid, the patient should open the eyes widely, gaze superiorly, and simultaneously open the mouth widely [11]. If the lid does not remain snug against the globe, ectropion may result.

In the medial canthus, the reconstructive surgeon must inspect the surgical defect to assess the integrity of the medial canthal tendon and lacrimal drainage system prior to reconstruction. Similarly, the surgeon must inspect lateral canthal defects to assess integrity of the lateral canthal tendon.

2.7.2 Periocular Reconstruction

Reconstruction of periocular defects requires thorough knowledge of the region's complex anatomy, normal eyelid function, and the lacrimal production and drainage systems. Excellent references study these topics more extensively [77, 78]. Whenever possible, the reconstructive surgeon should preserve intact periorbital anatomy, restore defective structures, and optimize cosmesis. In the periocular region, functional and cosmetic outcomes frequently correlate. For example, sound reconstruction of the eyelid margin not only restores a normal appearance, but also preserves tear flow and protects the globe from injury. As the periocular region serves as a focal point for the visual perception of an individual's face, the aesthetic implications of the periocular reconstruction cannot be overstated [44]. Malposition of the free margins of the eyelids or bulky flaps and tight-webbed closures that ablate the subtle concavities around the eye impart a markedly abnormal appearance.

A complete review of reconstructive techniques for periocular tumors lies beyond the scope of this chapter. Several review articles address periocular reconstruction more extensively [11, 30, 50, 70]. Some general points deserve mention. Goals of periocular reconstruction include protection of the globe, specifically the cornea, preservation of eyelid function, maintenance of lacrimal drainage system patency, and optimization of cosmesis. Local flaps provide reliable survivability, due to their rich intrinsic vascular supply, and superior cosmetic results, due to excellent matching of skin color and texture. Although the lack of intrinsic blood supply may make them less reliable, careful application of full-thickness skin grafts can produce satisfactory cosmetic outcomes and low complication rates [34].

Table 2.1 lists common reconstructive options and salient references for the reader desiring further study. Figures 2.2–2.13 illustrate a number of reconstructive options for repairing periocular defects after Mohs micrographic surgery.

Table 2.1. Common reconstruction options for periocular defects

Region and defect	Closure option	Indication
Eyelids		
Partial thickness (anterior lamellar)	Second intention [36]	
	Primary closure	
	Local skin and myocutaneous flap [11]	
	Full-thickness skin graft [34]	
Full-thickness	Second intention [25, 36]	
	Primary closure	Defects <15 mm or <25% of lid margin
	Primary closure + lateral canthotomy + cantholysis	Defects 25–50% of lid margin
	Tenzel semicircular flap [72]	Defects of 50–75% of lid margin
	Hughes tarsoconjunctival flap + full-thickness skin graft or local flap [33]	Lower eyelid defects >75% of lid margin
	Cutler-Beard technique [23]	Upper eyelid defects >75% of lid margin
	Free graft for posterior lamella + local flap for anterior lamella	Defects >75% of lid margin
	Mustarde rotating cheek and opposing lid flaps	Large lid defects >75%
	Composite lid grafts [73]	Defects <8 mm of lid margin
Medial canthus	Second intention [36, 49]	
	Local flaps (e.g., nasoglabellar transposition flap)	
	Paramedian forehead flap [56]	
	Full-thickness skin grafts	
	Combination of above	
Lateral canthus	Second intention	
	Local flaps	
	Full-thickness skin grafts	

2.7.3 Eyelid Reconstruction

2.7.3.1 General Principles of Eyelid Reconstruction

For defects of the eyelid, reconstructive options vary according to the thickness of the defect (i.e., partial or anterior lamellar defects versus full-thickness defects) and the breadth of the defect. Full-thickness defects involving the lid margin may pose a greater reconstructive challenge compared with anterior lamellar defects. Similarly, surgical wounds involving the loose skin of the preseptal eyelid frequently prove less challenging than defects of the pretarsal lid and lid margin. In general, full-thickness eyelid defects require reconstruction of both the anterior and posterior lamellae, at least one of which must have an intrinsic vascular supply. Tension vectors should be oriented parallel to the lid margin to avoid distraction of the lid from the globe.

2.7.3.2 Upper Eyelid Reconstruction

2.7.3.2.1 Primary Wound Closure for Small to Moderate Defects of the Upper Lid Margin

Defects involving less than 25% of the upper lid margin can be closed primarily, usually without cantholysis (Fig. 2.2) For larger defects involving up to 50% of the upper lid margin, primary closure with use of a canthotomy and cantholysis will usually suffice, particularly in older patients with lax tissue (Fig. 2.3). Defects involving more than 50% of the upper lid margin usually require some form of sliding or rotating flap. The Tenzel semicircular flap works well with moderate defects [25].

As demonstrated in Fig. 2.4, the Mohs resection has permitted preservation of a significantly greater amount of normal tissue than would have resulted from a routine resection taking wide margins. Resection of this defect may appear less challenging at first. It is important to recognize, however, that despite the preservation of tarsus, a small marginal defect is present that will mandate a wedge resection. Use of a cantholysis and a small Tenzel type of semicircular flap provides an aesthetic and functional result.

An A to T design (bilateral advancement flap) to reconstruct the anterior lamellar portion of this type of defect avoids formation of a "dog ear" and preserves the contour of the skin of the upper lid. After repair of the posterior lamella, the surgeon makes a horizontal incision at the position of the normal lid crease and advances the cut edges of the skin medially. Conservative horizontal resection of any excess skin overlapping the lid crease restores the normal contour of the preseptal lid and allows the surgeon to hide the horizontal scar in the lid crease. The "dog ear" on the pretarsal lid can be excised and repaired with a vertical scar equal to the height of the tarsal plate.

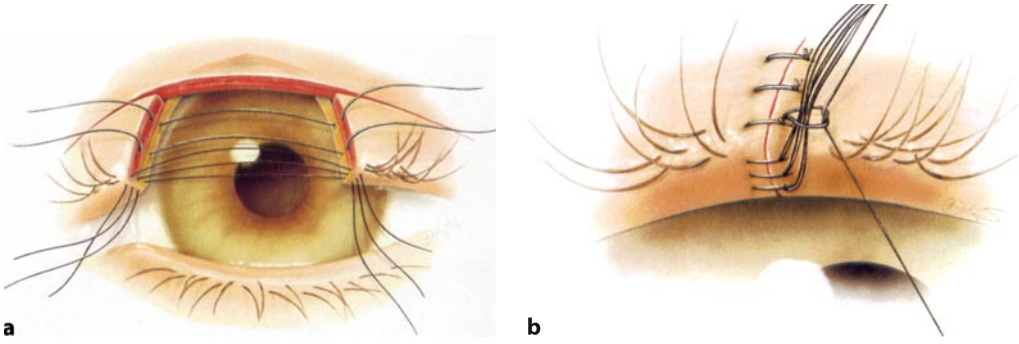


Fig. 2.2 Repair of upper lid marginal defect: 3-suture technique. **a** A 6-0 silk is placed in the Gray line for stability with 7-0 silks placed anterior in the lash line and posterior in the meibomian gland orifices. 5-0 vicryl interrupted sutures are used to reapproximate the tarsus. **b** The ends of the margin sutures are tied into one of the vertical 6-0 silk skin sutures

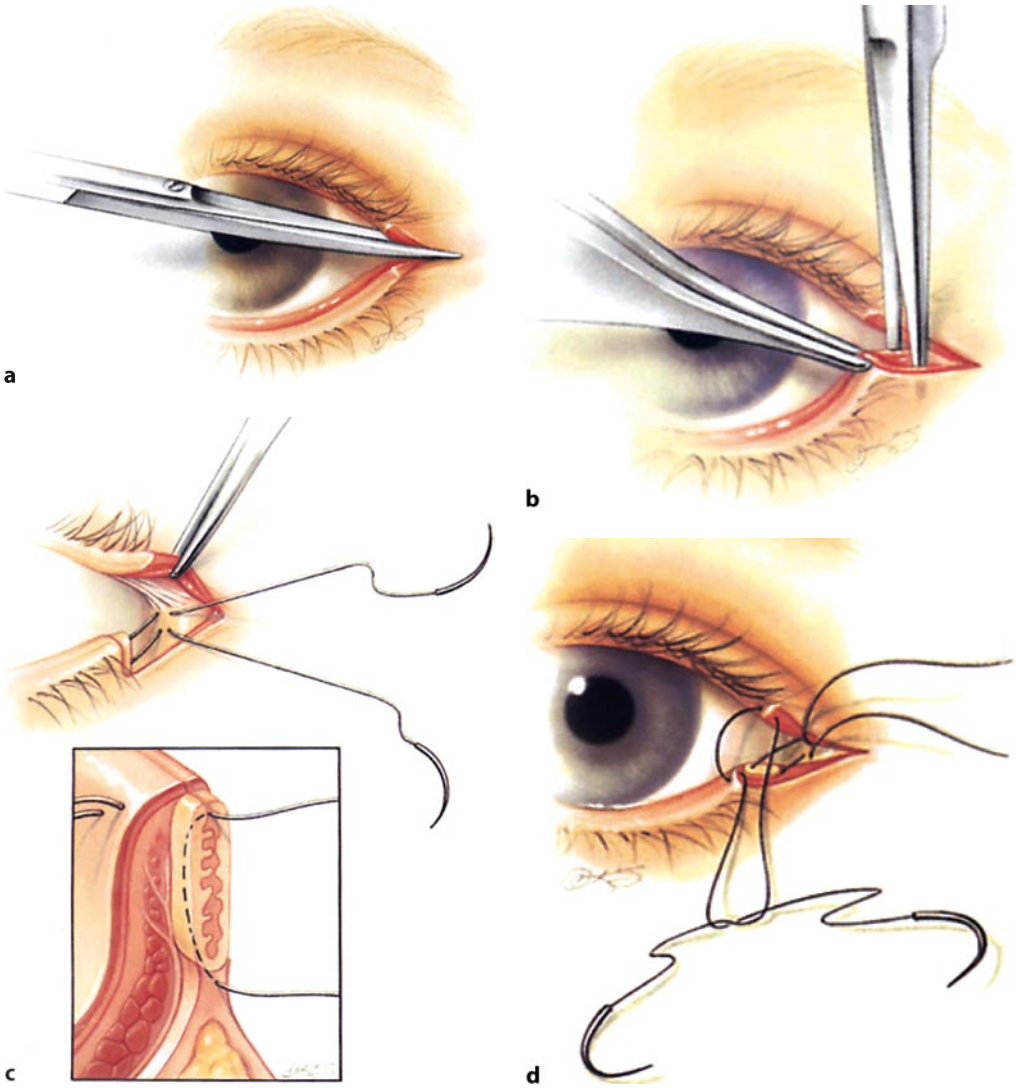


Fig. 2.3 Canthotomy and cantholysis. **a** Canthotomy incision with scalpel or sharp scissors. **b** Cantholysis completed by releasing the lower arm of the canthal tendon from its periosteal attachment to Whitnall's tubercle. **c** The cut margin of the lower eyelid is secured with a 4-0 vicryl suture that passes vertically through the tarsus and both arms are passed through the periosteum at the lateral orbital tubercle. **d** The lateral canthal angle is reformed with a 5-0 suture passed from gray line to gray line in a buried fashion. The skin wound is closed with interrupted 6-0 sutures

2.7.3.2.2 Sliding or Rotating Flaps for Large Defects of the Upper Lid Margin

For defects involving 75% or more of the upper lid margin a Cutler-Beard bridge flap (Fig. 2.5) [72] or a Mustarde lid-sharing flap rotated from the opposing lid (Fig. 2.6) [49] proves useful. The advantage of the latter is the possibility of transferring lower lid lashes to the reconstructed upper lid. Both flaps have the disadvantage of occluding the visual axis for several postoperative weeks to ensure adequate vascularization of the flap prior to separation of the pedicle. The surgeon must

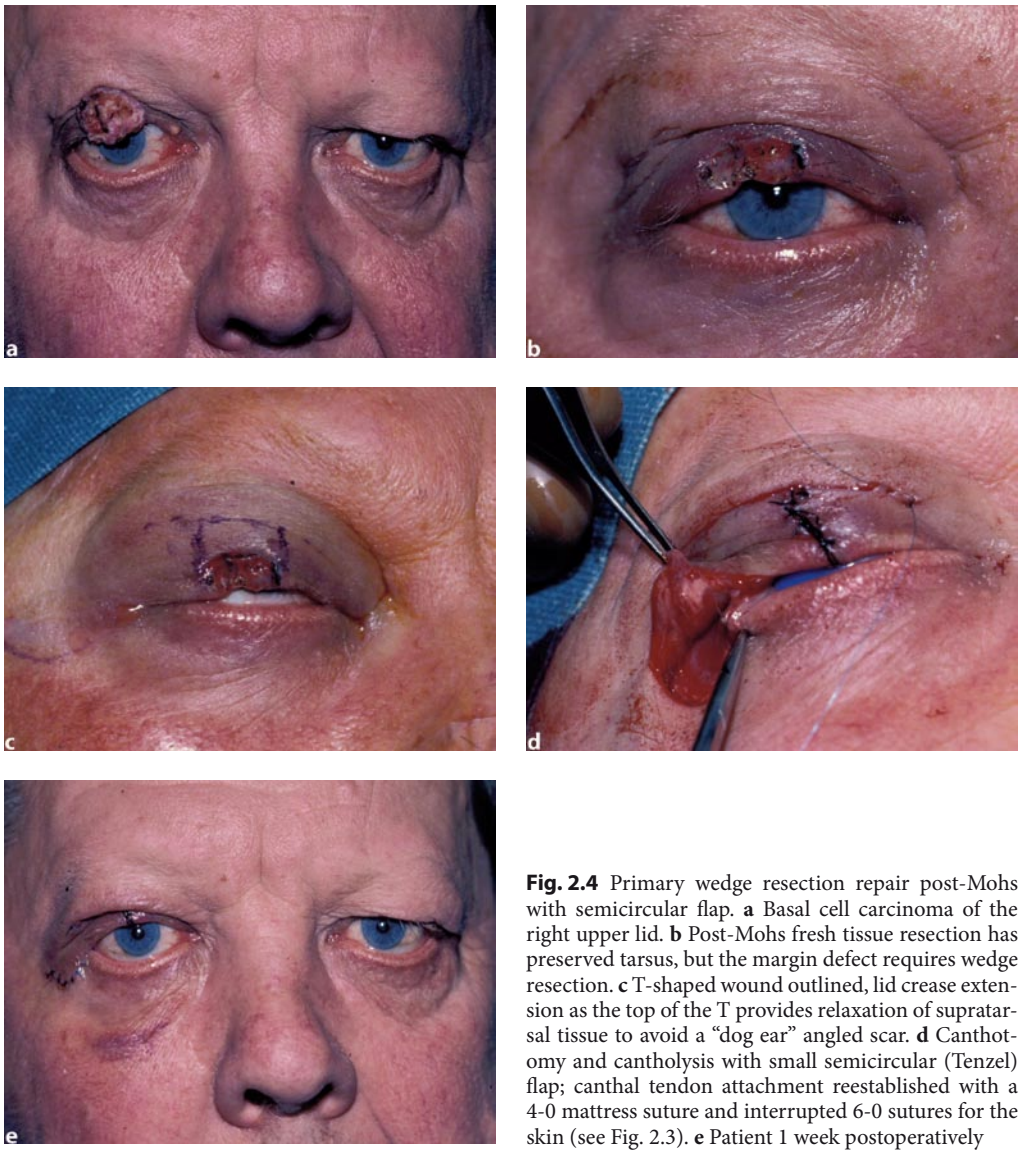


Fig. 2.4 Primary wedge resection repair post-Mohs with semicircular flap. **a** Basal cell carcinoma of the right upper lid. **b** Post-Mohs fresh tissue resection has preserved tarsus, but the margin defect requires wedge resection. **c** T-shaped wound outlined, lid crease extension as the top of the T provides relaxation of supratarsal tissue to avoid a "dog ear" angled scar. **d** Canthotomy and cantholysis with small semicircular (Tenzel) flap; canthal tendon attachment reestablished with a 4-0 mattress suture and interrupted 6-0 sutures for the skin (see Fig. 2.3). **e** Patient 1 week postoperatively

take care to maximize the vascular supply at the base of the Cutler-Beard or Mustarde lid-sharing flap. In either case, the surgeon should allow at least 4 mm of vertical height from the lid margin to the horizontal lid incision with either technique in order to minimize the risk of lid margin necrosis. The surgeon usually divides the pedicle of the Cutler-Beard bridge flap at 4 weeks. With this type of flap, separation requires careful estimation of the amount of tissue necessary to prevent lid retraction. There must be sufficient tissue for both the upper and lower lid. The lower lid bridge is replaced after freshening the lateral and medial edges and then closing all three exposed sides in three layers: tarsus, orbicularis, and skin. In the upper lid, some debulking may be necessary. Care must also be taken to advance the conjunctiva slightly with a running suture, such as 7-0 catgut, in order to avoid corneal irritation from the fine hairs at the keratinized skin margin (Fig. 2.5).

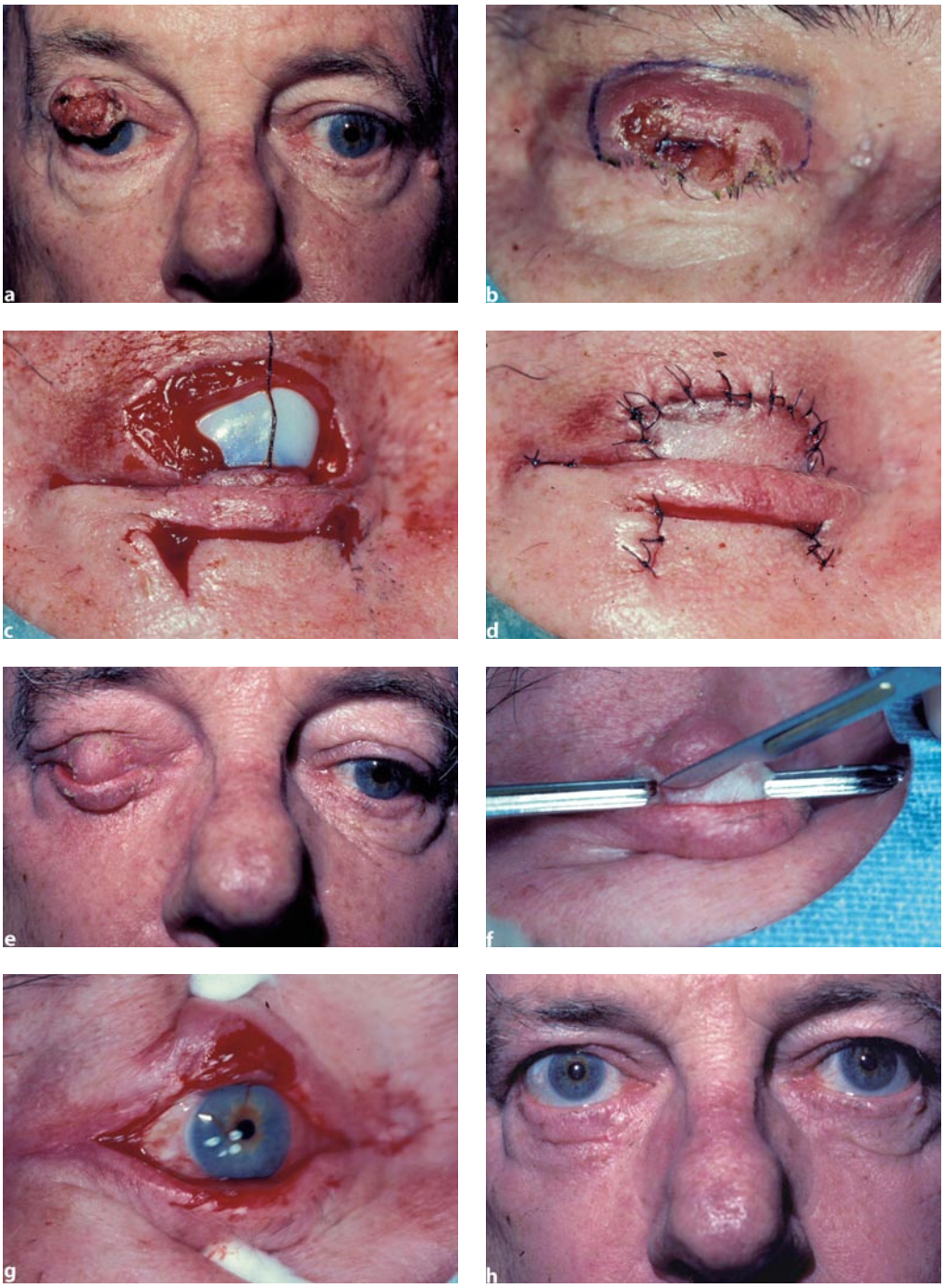


Fig. 2.5 Sliding bridge flap repair (Cutler-Beard). **a** Patient with lesion of the right upper lid pre-biopsy. **b** After in-office shave biopsy. **c** Post-MOHS defect >50%; Cutler-Beard sliding flap is prepared. **d** Flap is secured with layered closure. **e** Six weeks post-first-stage bridge flap repair. **f** Bridge flap separated. **g** Reconstructed upper lid is debulked as needed; care is taken to advance the conjunctiva slightly using a 7-0 catgut running suture in order to provide a smooth surface for the cornea. **h** Patient 1 year postoperatively

The surgeon usually divides the rotating Mustarde lid-sharing flap at 4–6 weeks. When the base is separated from the rotated flap, each lid margin must be repaired in standard fashion to avoid a notch. Some form of ptosis repair is often required and can be performed at a later stage when function and contour can be more adequately assessed (Fig. 2.6).

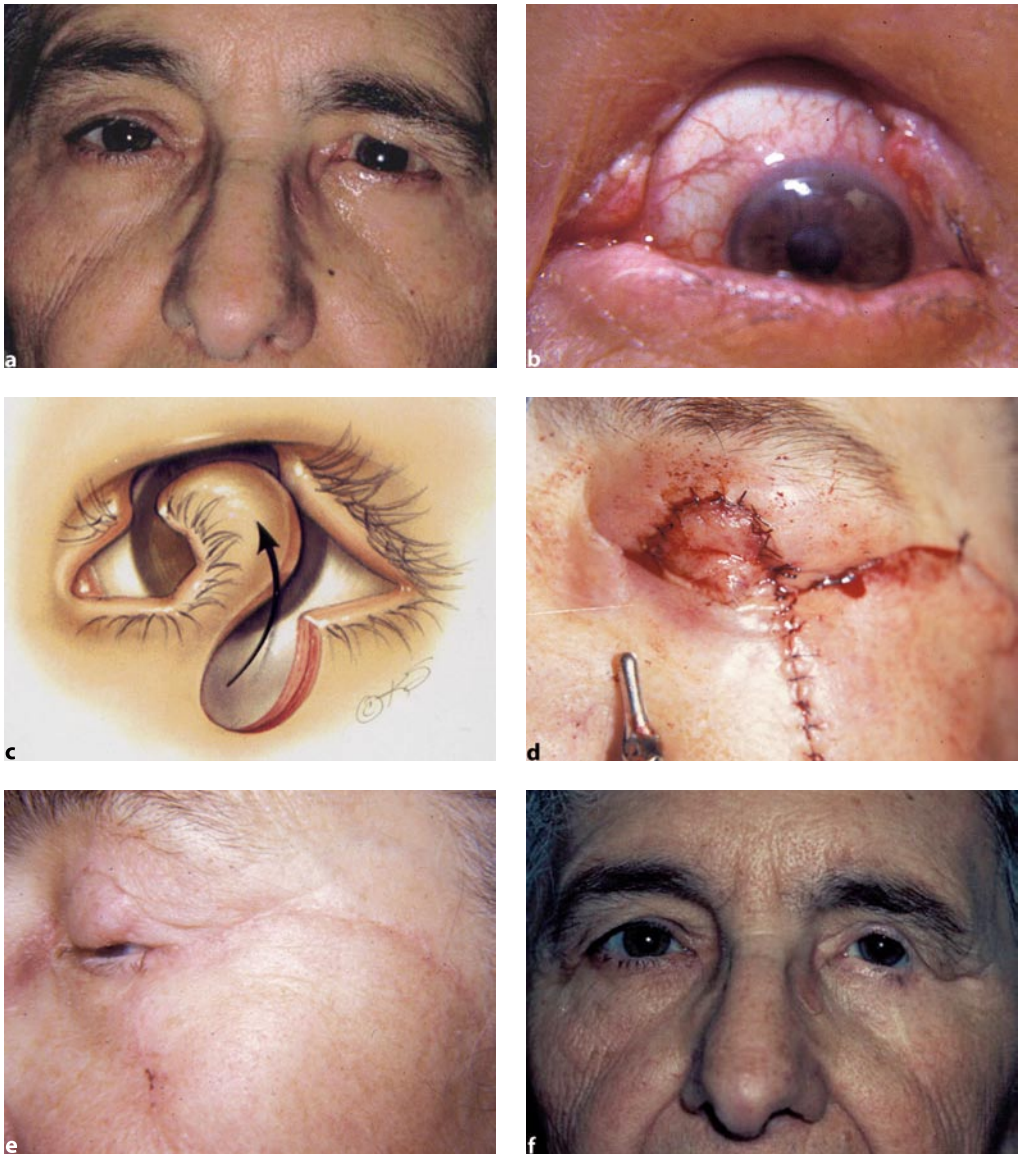


Fig. 2.6 Mustarde lid-sharing rotation flap. **a** Alternative technique for a large upper lid defect in this patient with a defect secondary to radiation therapy for a basal cell carcinoma. **b** Close-up of the defect in the left upper lid. **c** Schematic illustration of the procedure. **d** Rotated flap in position. **e** One month post-separation of the lids. **f** One-year after rotation flap and ptosis repair with frontalis suspension

2.7.3.3 Reconstruction of Lower Lid Defects After Mohs Micrographic Surgery

2.7.3.3.1 General Principles of Reconstruction of Defects of the Lower Lid

In the lower lid, extramarginal defects are most frequently repaired by sliding or rotating myocutaneous flaps or by use of full-thickness skin grafts harvested from the upper lid or retroauricular skin. Full-thickness skin grafts of the eyelid do not usually require bolster dressings. A pressure dressing for several days will usually suffice, as long as the surgeon has achieved meticulous hemostasis. Small pie-crust perforations in the graft can also be used to permit any drainage from elevating the graft. In general, the surgeon can approach marginal defects of the lower lid with reconstructions analogous to those discussed in the section on upper lid reconstruction (see Sect. 2.7.3.2). Table 2.1 highlights common reconstruction techniques, based on the breadth of the marginal defect.

2.7.3.3.2 Alternatives to Reconstruction of the Posterior Lamella of the Lower Eyelid

Large full-thickness defects in the lower lid require reconstruction of the posterior lamella to prevent entropion and lower lid retraction. Two common options include a lid-sharing procedure, such as the Hughes flap, or a free tarsal graft harvested from the upper lid. We have found that a free tarsal graft with a hinge of attached conjunctiva can be safely harvested from the upper lid and used to provide stability as a new posterior lamella, as well as to create an inferior cul de sac and even to line the inferior globe if status-post bulbar conjunctival excision (Fig. 2.7). This technique reliably achieves excellent cosmetic and functional outcomes without occlusion of the visual axis, as is required with either the Hughes or Mustarde lid-sharing technique. If adequate tarsus is not available, other grafts such as nasoseptal cartilage with nasal mucosal lining can be used as alternatives. If preserved donor dermis is used, however, a conjunctival flap is usually difficult to mobilize. Vascular supply for these free grafts is mainly provided by the overlying skin or skin/muscle flap.

2.7.3.3.3 Anterior Lamellar Replacement

Larger skin/muscle defects can also be repaired with a semicircular flap, although if the lower lid defect is much greater than 50%, a larger rotating cheek flap as described by Mustarde is preferable [49]. Although temporalis-based sliding flaps or mid-forehead flaps can also be utilized for large lower lid defects, we prefer the Mustarde rotating cheek flap, which can cover the lid and even extend to the medial canthus, if necessary. To avoid paralysis of the superior branches of the facial nerve, the rotating cheek flap in the subcutaneous plane lateral to the orbital rim must be lifted. Undermining below the orbicularis muscle inside the orbital rim presents little risk of paralysis, since its extensive nerve supply usually preserves enough sphincter action to close the eyelids.

2.7.3.4 Reconstruction of Medial Canthal Defects After Mohs Micrographic Surgery

2.7.3.4.1 General Principles of Medial Canthal Reconstruction

The concave surface and complex anatomy of the medial canthus present multiple challenges. Ablating the concave medial canthus with bulky flaps or webbed closures that impart marked contour deformities should be avoided. The reconstructive surgeon must carefully inspect the surgical defect to assess integrity of the medial canthal tendon and lacrimal excretory apparatus. If severed, the medial canthal tendon may be resuspended in order to recreate the proper curvature of the eyelid against the globe and to prevent

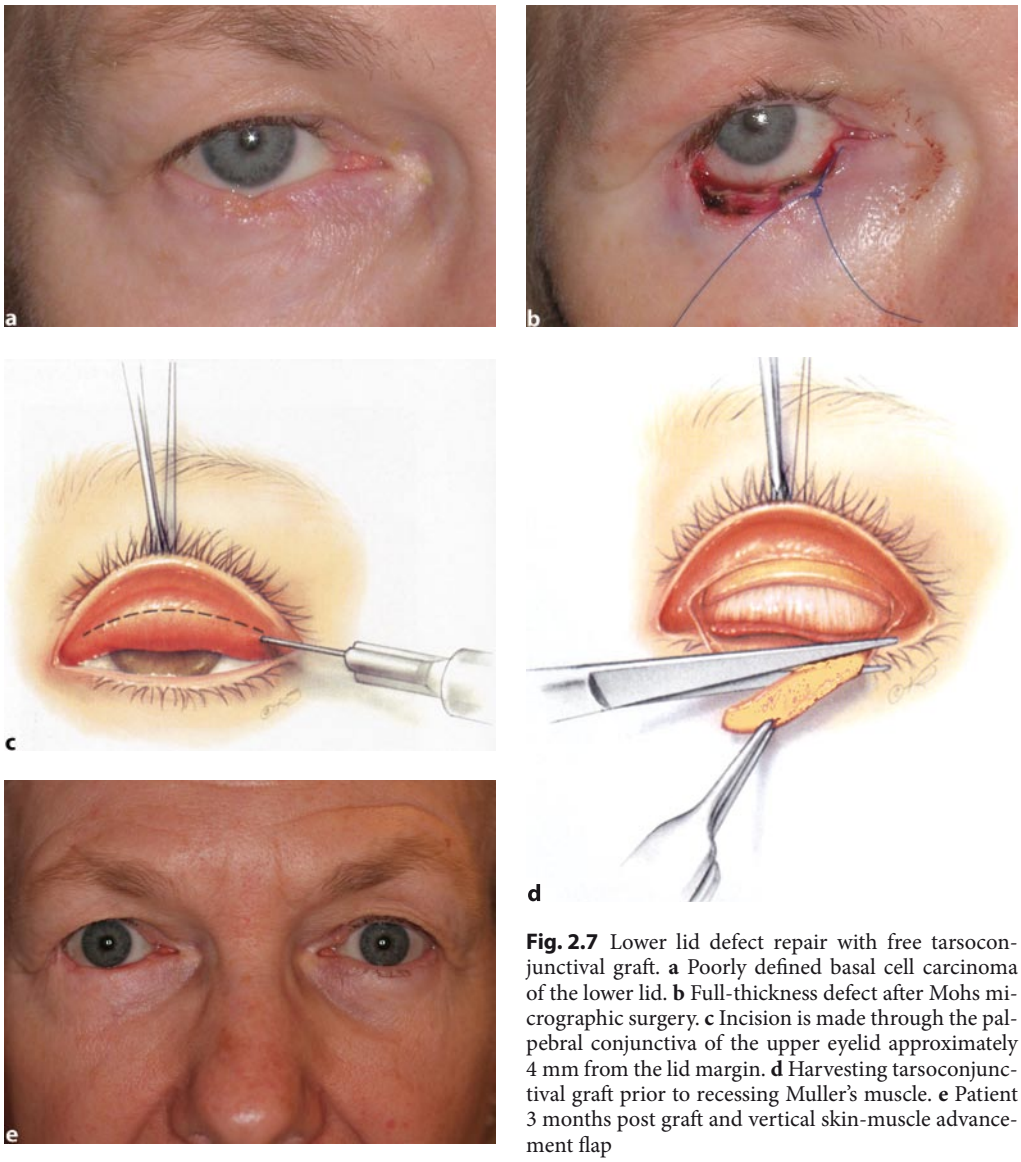


Fig. 2.7 Lower lid defect repair with free tarsoconjunctival graft. **a** Poorly defined basal cell carcinoma of the lower lid. **b** Full-thickness defect after Mohs micrographic surgery. **c** Incision is made through the palpebral conjunctiva of the upper eyelid approximately 4 mm from the lid margin. **d** Harvesting tarsoconjunctival graft prior to recessing Muller's muscle. **e** Patient 3 months post graft and vertical skin-muscle advancement flap

epiphora [31]. If tumor resection disrupts the lacrimal excretory apparatus, nasolacrimal intubation can prevent persistent epiphora and recurrent conjunctival irritation [71]. Although some surgeons prefer to delay reconstruction of the lacrimal drainage system for fear of disseminating tumor cells, reliable margins obtained after Mohs micrographic surgery encourage many surgeons to reconstruct the lacrimal drainage system immediately after tumor resection [3].

2.7.3.4.2 Common Reconstruction Options for Medial Canthal Defects

Medial canthal defects, if small, circular, and relatively shallow, can heal by secondary intention. Asymmetric defects can create unsightly contractions, however (Fig. 2.8). Full-thickness skin grafts harvested from the upper lid or retroauricular skin can provide an excellent reconstruc-

tion option for moderate-sized defects (Fig. 2.9). The glabella serves as an excellent tissue reservoir for local flaps to repair small to moderate defects in the medial canthus, particularly for defects superior to the level of the medial canthal tendon (Fig. 2.10). For defects that lie mostly inferior to the level of the medial canthal tendon, a bilobed flap can be an effective solution (Fig. 2.11). For larger defects, a combination of multiple flaps from the glabella, nasolabial fold, upper

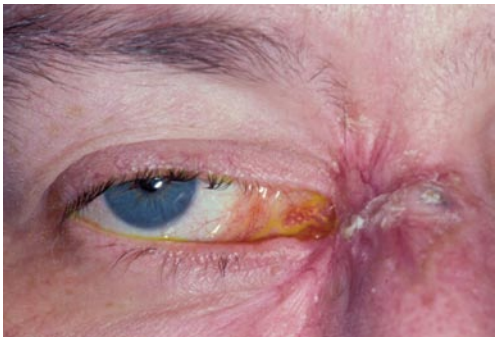


Fig. 2.8 Secondary intention healing in medial canthal defects. Acceptable result dependent on the size and symmetry of the wound. Disparity of the vertical to horizontal dimensions can result in severe contraction, as observed in this patient referred 6 months post-Mohs resection because of tearing due to poor lid closure and lacrimal outflow problems

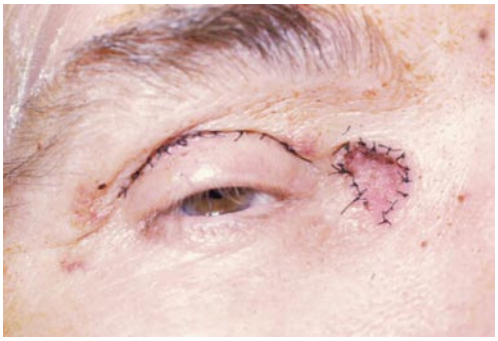


Fig. 2.9 Skin graft repair of a medial canthal defect. Free full-thickness skin graft from the upper lid donor site. If the defect is deeper, thicker retro-auricular skin may be used

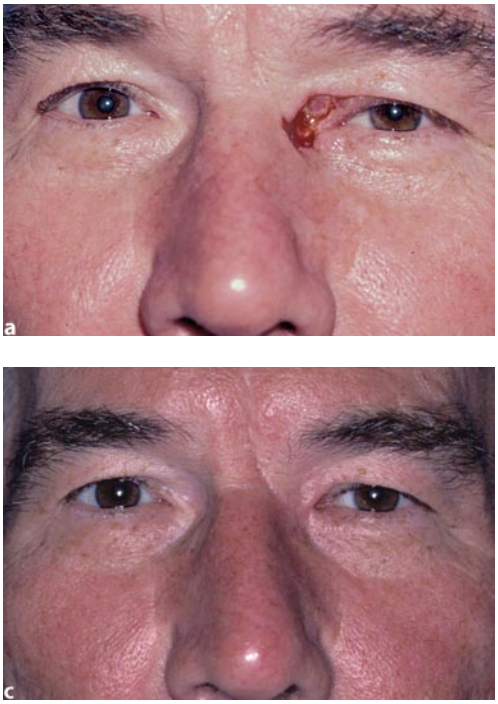


Fig. 2.10 Sliding glabellar flap for a medial canthal defect. **a** Post-Mohs defect in a basal cell carcinoma lesion. **b** Glabellar frown line is extended and a myocutaneous flap created. **c** Patient 1 year postoperatively

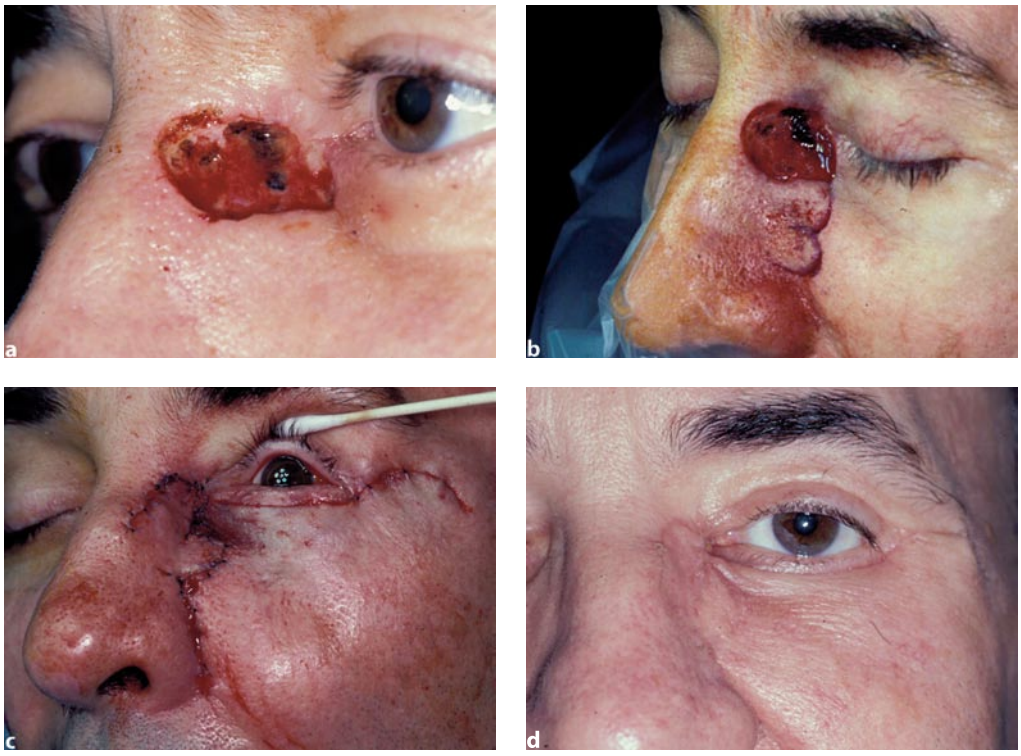


Fig. 2.11 Bilobed flap repair for medial canthal defect. **a** Post-Mohs excision for basal cell carcinoma. **a** Bilobed flap outlined. **b** Flaps rotated into defect and incisions closed. **c** Patient 4 months postoperatively

lid crease, and lateral cheek may be necessary to cover the defect. If the nasolacrimal system has been compromised, reconstruction with silastic intubation may be utilized (Fig. 2.12). Without confirmation of clear margins by Mohs micrographic surgery of medial canthal lesions, any invasive surgery into the nose should be deferred for at least 1 year to minimize the risk of seeding residual tumor into the nasopharynx.

2.7.3.4.3 Reconstruction of Combined Medial Canthal and Lower Lid Defects

Some extensive defects may require an extremely large flap that is both rotating and sliding. This type of problem is more commonly encountered in patients who have a history of numerous skin malignancies. The patient in Fig. 2.13 had extensive malignant skin disease affecting the face with multiple areas of basal cell carcinoma and a history of squamous cell carcinoma resected from the leg. She had undergone a recent repair following Mohs resection for a right cheek basal cell carcinoma and had obvious tumor involving the left lower lid, cheek, and medial canthus. The Mohs defect measured 40×40 mm with 85% lower lid loss; the glabellar, nasolabial fold, and the rotating cheek flaps are outlined. Note the circled areas of suspected additional tumors. The sliding and rotating cheek flap is mobilized, the upper lid everted in preparation for harvesting the tarsoconjunctival graft for the posterior lamella of the reconstructed lower lid, silastic tubing is inserted through the upper punctum and canaliculus and through the distal remnant of the lower canaliculus, and both ends are then passed down the nasolacrimal duct (see Fig. 2.7d). Free

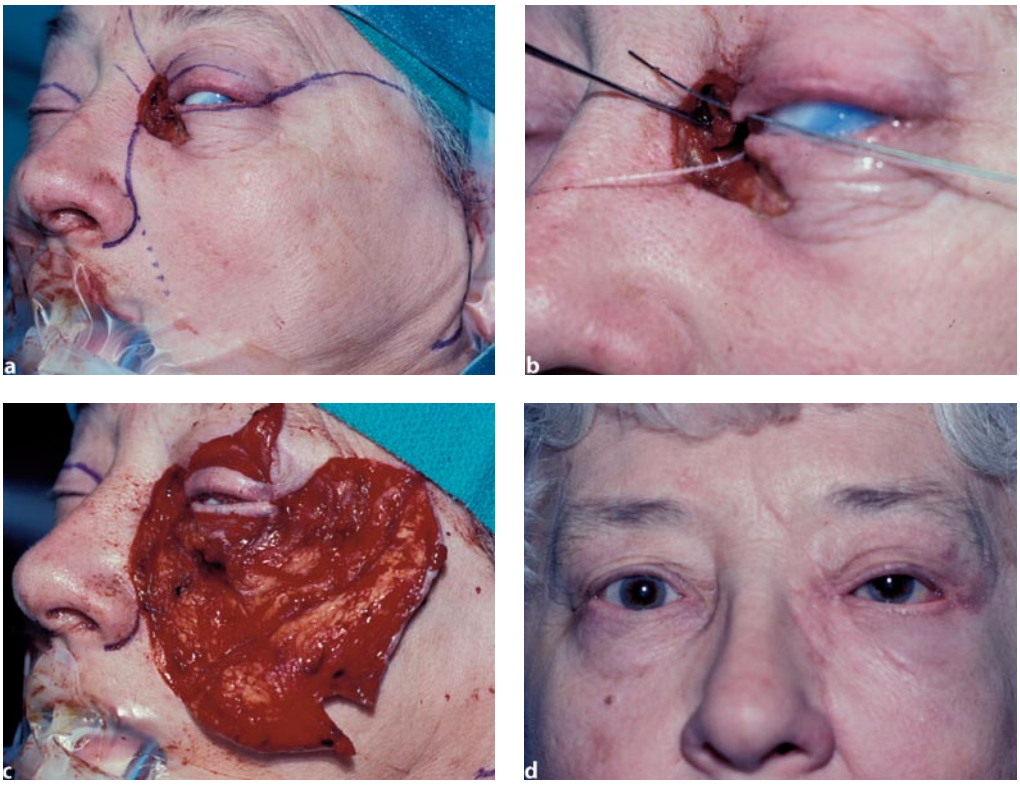


Fig. 2.12 Multiple flap and nasolacrimal repair for medial canthal defect. **a** Multiple flap technique, outlining sliding glabellar, nasolabial fold, upper lid crease, and rotating cheek flaps for repair. **b** Intubation of canaliculi with silastic tubing to be passed down the nasolacrimal duct. **c** Rotating cheek flap reflected; dissection beyond the orbital rim must be subcutaneous to avoid seventh nerve paresis. **d** Patient 1 year postoperatively; no epiphora noted after removal of the silastic tubing 6 months postoperatively

tarsal graft is harvested from the everted upper lid. The tarsal graft is sutured in place and the sliding portion of the rotated flap is secured over the medial canthal and lateral defect.

This scenario can make excision extremely difficult for the Mohs surgeon to decide where to stop excising and when to pursue other management strategies. Balancing cure with function and appearance can be extremely difficult in these cases. In truth, control of progression may be the only recourse. A multidisciplinary approach involving dermatology, oculoplastic surgery, and oncology should be pursued in an effort to offer such patients the best chance of survival, of preserving visual function, and of minimizing discomfort and unnecessary expenses.

2.7.3.4.4 Reconstruction of Lateral Canthal Defects after Mohs Micrographic Surgery

Post-Mohs defects in the lateral canthal region are most often extensions of lower lid tumors. Repair of these defects follows the same principles discussed in the previous sections. The major reconstructive concern, beyond cure and protection of the globe, is to create a sharp lateral canthal angle with sufficient support in the reconstructed lower lid to avoid retraction and/or ectropion. In severe instances, transposition flaps from upper to lower lid can be helpful for canthal defects or resultant dystopias, but are usually left

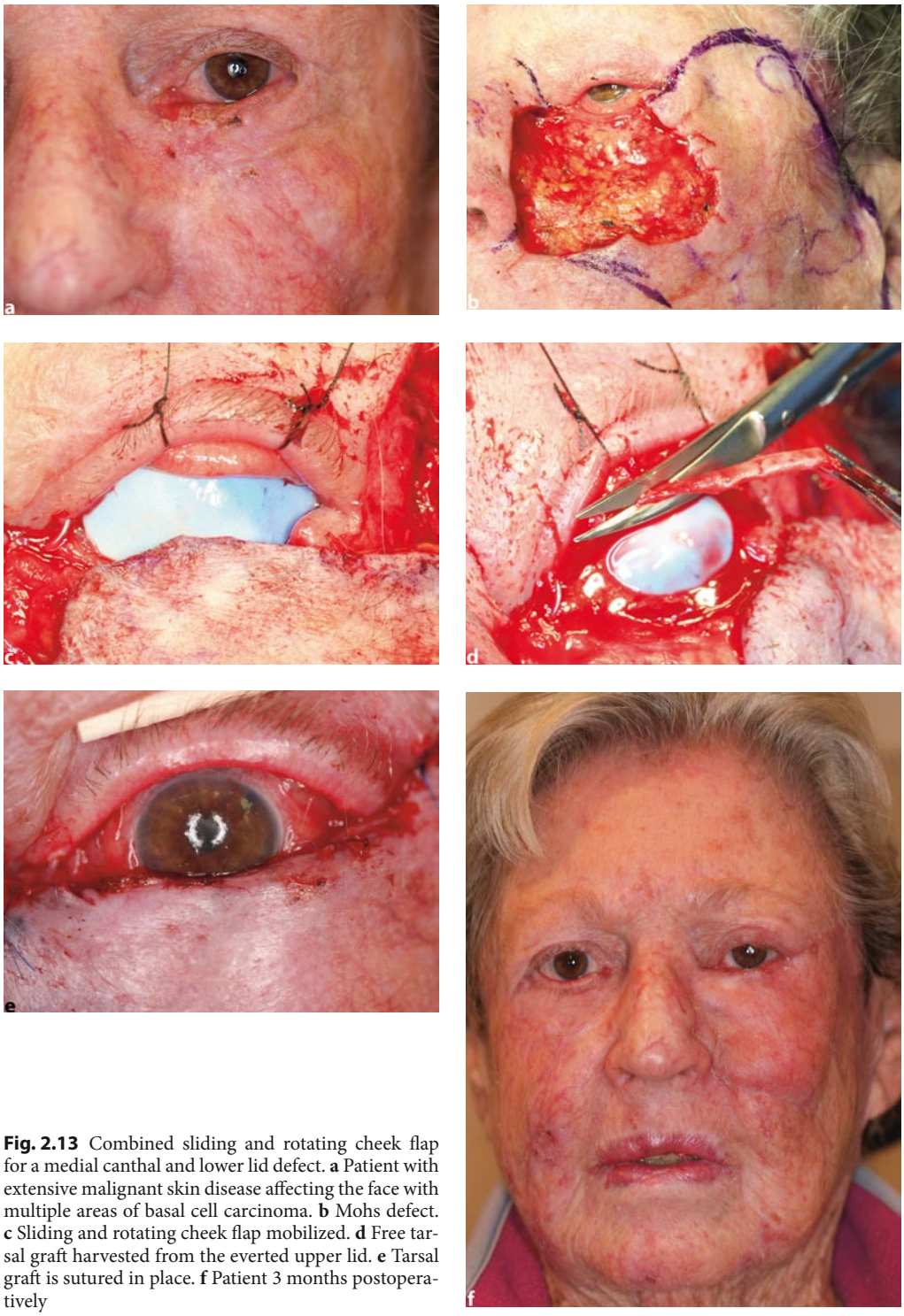


Fig. 2.13 Combined sliding and rotating cheek flap for a medial canthal and lower lid defect. **a** Patient with extensive malignant skin disease affecting the face with multiple areas of basal cell carcinoma. **b** Mohs defect. **c** Sliding and rotating cheek flap mobilized. **d** Free tarsal graft harvested from the everted upper lid. **e** Tarsal graft is sutured in place. **f** Patient 3 months postoperatively

for secondary stage repair in severe cases of tissue loss or destruction. Many types of flaps have been described for lateral canthal defects, but variations of the rotating Mustarde cheek flap often provide the most effective and aesthetically pleasing results.

2.8 Conclusion

Due to a high incidence of subclinical tumor spread, standard excision of periocular malignancies and common techniques of pathologic margin evaluation result in high rates of incomplete excision and tumor recurrence. Mohs micrographic surgery respects the principle of subclinical tumor spread and uses 100% microscopic margin evaluation and meticulous tissue mapping to detect and target all parts of the tumor and spare healthy tissue. The complete method of margin evaluation maximizes cure, and the tissue-sparing benefits enhance patient function and cosmesis. Strong evidence supports the use of Mohs micrographic surgery to treat periocular basal cell and squamous cell cancers and sebaceous carcinoma. Increasing amounts of data support the use of Mohs micrographic surgery or variations of the technique to treat lentigo maligna. In the multidisciplinary care of patients with periocular malignancies, Mohs micrographic surgery increases the likelihood of achieving the three primary goals of treating patients with cancer:

- Cure of the tumor
- Preservation of function
- Cosmetic reconstruction

The reconstructive surgeon can employ a variety of options to repair periocular defects after Mohs micrographic surgery.

References

1. Abide JM, Nahai F, Bennett RG (1984) The meaning of surgical margins. Plast Reconstr Surg 73(3):492–497
2. Albertini JG, et al. (2002) Mohs micrographic surgery for melanoma: a case series, a comparative study of immunostains, an informative case report, and a unique mapping technique. Dermatol Surg 28(8):656–665
3. Aliseda D, Vazquez J, Munuera JM (1997) Medial canthus tumor surgery: a prospective study of microscopically controlled excision. Eur J Ophthalmol 7(3):216–222
4. Anderson KW, et al. (2001) Treatment of head and neck melanoma, lentigo maligna subtype: a practical surgical technique. Arch Facial Plast Surg 3(3):202–206
5. Arlette JP et al. (1998) Basal cell carcinoma of the periocular region. J Cutan Med Surg 2(4):205–208
6. Balch CM, et al. (2001) Prognostic factors analysis of 17,600 melanoma patients: validation of the American Joint Committee on Cancer melanoma staging system. J Clin Oncol 19(16):3622–3634
7. Barlow RJ, White CR, Swanson NA (2002) Mohs' micrographic surgery using frozen sections alone may be unsuitable for detecting single atypical melanocytes at the margins of melanoma in situ. Br J Dermatol 146(2):290–294
8. Batra RS, Kelley LC (2002) Predictors of extensive subclinical spread in nonmelanoma skin cancer treated with Mohs micrographic surgery. Arch Dermatol 138(8):1043–1051
9. Bennett RG (1989) The meaning and significance of tissue margins. Adv Dermatol 4:343–355; discussion 356–357
10. Bhardwaj SS, Tope WD, Lee PK (2006) Mohs micrographic surgery for lentigo maligna and lentigo maligna melanoma using Mel-5 immunostaining: University of Minnesota experience. Dermatol Surg 32(5):690–696; discussion 696–697
11. Bowman PH, Fosko SW, Hartstein ME (2003) Periocular reconstruction. Semin Cutan Med Surg 22(4):263–272
12. Bricca GM, Brodland DG, Zitelli JA (2004) Immunostaining melanoma frozen sections: the 1-hour protocol. Dermatol Surg 30(3):403–408
13. Bricca GM, et al. (2005) Cutaneous head and neck melanoma treated with Mohs micrographic surgery. J Am Acad Dermatol 52(1):92–100
14. Brodland DG, Zitelli JA (1992) Surgical margins for excision of primary cutaneous squamous cell carcinoma. J Am Acad Dermatol 27(2 Pt 1):241–248

15. Brodland DG, et al. (2000) The history and evolution of Mohs micrographic surgery. Dermatol Surg 26(4):303–307
16. Bub JL, et al. Management of lentigo maligna and lentigo maligna melanoma with staged excision: a 5-year follow-up. Arch Dermatol 140(5):552–558
17. Callahan EF, et al. (2004) Sebaceous carcinoma of the eyelid: a review of 14 cases. Dermatol Surg 30(8):1164–1168
18. Carter KD, Nerad JA, Whitaker DC (1999) Clinical factors influencing periocular surgical defects after Mohs micrographic surgery. Ophthal Plast Reconstr Surg 15(2):83–91
19. Cherpelis BS, Marcusen C, Lang PG (2002) Prognostic factors for metastasis in squamous cell carcinoma of the skin. Dermatol Surg 28(3):268–273
20. Chung VQ, Bernardo L, Jiang SB (2005) Presurgical curettage appropriately reduces the number of Mohs stages by better delineating the subclinical extensions of tumor margins. Dermatol Surg 31(9 Pt 1):1094–1099; discussion 1100
21. Cook BE Jr, Bartley GB (1999) Epidemiologic characteristics and clinical course of patients with malignant eyelid tumors in an incidence cohort in Olmsted County, Minnesota. Ophthalmology 106(4):746–750
22. Cook BE Jr, Bartley GB (2001) Treatment options and future prospects for the management of eyelid malignancies: an evidence-based update. Ophthalmology 108(11):2088–2098; quiz 2099–2100, 2121
23. Cutler NL, Beard C (1955) A method for partial and total upper lid reconstruction. Am J Ophthalmol 39(1):1–7
24. Davis DA, Pellowski DM, William Hanke C (2004) Preparation of frozen sections. Dermatol Surg 30(12 Pt 1):1479–1485
25. Deutsch BD, Becker FF (1997) Secondary healing of Mohs defects of the forehead, temple, and lower eyelid. Arch Otolaryngol Head Neck Surg 123(5):529–534
26. Downes RN, Walker NNP, Collin JR (1990) Micrographic (MOHS') surgery in the management of periocular basal cell epitheliomas. Eye 4 (Pt 1):160–168
27. Friedman HI, et al. (1997) Recurrent basal cell carcinoma in margin-positive tumors. Ann Plast Surg 38(3):232–235
28. Glatt HJ, Olson JJ, Putterman AM (1992) Conventional frozen sections in periocular basal-cell carcinoma: a review of 236 cases. Ophthalmic Surg 23(1):6–8; discussion 9
29. Ionescu DN, Arida M, Jukic DM (2006) Metastatic basal cell carcinoma: four case reports, review of literature, and immunohistochemical evaluation. Arch Pathol Lab Med 130(1):45–51
30. Jewett BS, Shockley WW (2001) Reconstructive options for periocular defects. Otolaryngol Clin North Am 34(3):601–625
31. Kelly CP, et al. (2004) Medial canthopexy: a proven technique. Ophthal Plast Reconstr Surg 20(5):337–341
32. Kumar B, et al. (1997) A review of 24 cases of Mohs surgery and ophthalmic plastic reconstruction. Aust N Z J Ophthalmol 25(4):289–293
33. Leibovitch I, Selva D (2004) Modified Hughes flap: division at 7 days. Ophthalmology 111(12):2164–2167
34. Leibovitch I, et al. (2005) Incidence of host site complications in periocular full thickness skin grafts. Br J Ophthalmol 89(2):219–222
35. Lindgren G, et al. Mohs' micrographic surgery for basal cell carcinomas on the eyelids and medial canthal area. I. Characteristics of the tumours and details of the procedure. Acta Ophthalmol Scand 78(4):425–429
36. Lowry JC, Bartley GB, Garrity JA (1997) The role of second-intention healing in periocular reconstruction. Ophthal Plast Reconstr Surg 13(3):174–188
37. McKenna JK, et al. (2006) Lentigo maligna/lentigo maligna melanoma: current state of diagnosis and treatment. Dermatol Surg 32(4):493–504
38. Madani S, Huilgol SC, Carruthers A (2000) Unplanned incomplete Mohs micrographic surgery. J Am Acad Dermatol 42(5 Pt 1):814–819
39. Malhotra R, et al. (2003) Mapped serial excision for periocular lentigo maligna and lentigo maligna melanoma. Ophthalmology 110(10):2011–2018
40. Malhotra R, et al. (2004) The Australian Mohs database. I. Periocular basal cell carcinoma experience over 7 years. Ophthalmology 111(4):624–630
41. Malhotra R, et al. (2004) The Australian Mohs database: periocular squamous cell carcinoma. Ophthalmology 111(4):617–623

42. Malhotra R, et al. (2004) The Australian Mohs database. II. Periocular basal cell carcinoma outcome at 5-year follow-up. Ophthalmology 111(4):631–636
43. Martin RC II, et al. (2000) Basosquamous carcinoma: analysis of prognostic factors influencing recurrence. Cancer 88(6):1365–1369
44. Menick FJ (1987) Artistry in aesthetic surgery. Aesthetic perception and the subunit principle. Clin Plast Surg 14(4):723–735
45. Mohs FE (1941) Chemosurgery. A microscopically controlled method of cancer excision. Arch Surg 41:279–295
46. Mohs FE (1986) Micrographic surgery for the microscopically controlled excision of eyelid cancer: history and development. Adv Ophthalmic Plast Reconstr Surg 5:381–408
47. Mohs FE (1986) Micrographic surgery for the microscopically controlled excision of eyelid cancers. Arch Ophthalmol 104(6):901–909
48. Monheit GD, Callahan MA, Callahan A (1989) Mohs micrographic surgery for periorbital skin cancer. Dermatol Clin 7(4):677–697
49. Mott KJ, Clark DP, Stelljes LS (2003) Regional variation in wound contraction of Mohs surgery defects allowed to heal by second intention. Dermatol Surg 29(7):712–722
50. Moy RL, Ashjian AA (1991) Periorbital reconstruction. J Dermatol Surg Oncol 17(2):153–159
51. Nagi C, O'Grady TC, Izadpanah A (2002) Mohs micrographically controlled surgery and the treatment of malignant melanoma. Semin Oncol 29(4):336–340
52. National Comprehensive Cancer Network (2006) Basal cell and squamous cell skin cancers. Clinical Practice Guidelines in Oncology. National Comprehensive Cancer Network
53. National Comprehensive Cancer Network (2006) Melanoma. Clinical Practice Guidelines in Oncology. National Comprehensive Cancer Network
54. Nemet AY, et al. (2006) Management of periocular basal and squamous cell carcinoma: a series of 485 cases. Am J Ophthalmol 142(2):293–297
55. Petter G, Haustein UF (2000) Histologic subtyping and malignancy assessment of cutaneous squamous cell carcinoma. Dermatol Surg 26(6):521–530
56. Price DL, et al. (2004) Forehead flap periorbital reconstruction. Arch Facial Plast Surg 6(4):222–227
57. Putterman AM (1986) Conjunctival map biopsy to determine pagetoid spread. Am J Ophthalmol 102(1):87–90
58. Rakofsky SI (1973) The adequacy of the surgical excision of basal cell carcinoma. Ann Ophthalmol 5(5):596–600
59. Rapini RP (1990) Comparison of methods for checking surgical margins. J Am Acad Dermatol 23(2 Pt 1):288–294
60. Rowe DE (1995) Comparison of treatment modalities for basal cell carcinoma. Clin Dermatol 13(6):617–620
61. Rowe DE, Carroll RJ, Day CL Jr (1989) Long-term recurrence rates in previously untreated (primary) basal cell carcinoma: implications for patient follow-up. J Dermatol Surg Oncol 15(3):315–328
62. Rowe DE, Carroll RJ, Day CL Jr (1989) Mohs surgery is the treatment of choice for recurrent (previously treated) basal cell carcinoma. J Dermatol Surg Oncol 15(4):424–431
63. Rowe DE, Carroll RJ, Day CL Jr (1992) Prognostic factors for local recurrence, metastasis, and survival rates in squamous cell carcinoma of the skin, ear, and lip. Implications for treatment modality selection. J Am Acad Dermatol 26(6):976–990
64. Rudolph R, Zelac DE (2004) Squamous cell carcinoma of the skin. Plast Reconstr Surg 114(6):82e–94e
65. Shriner DL, et al. (1998) Mohs micrographic surgery. J Am Acad Dermatol 39(1):79–97
66. Sigurdsson H, Agnarsson BA (1998) Basal cell carcinoma of the eyelid. Risk of recurrence according to adequacy of surgical margins. Acta Ophthalmol Scand 76(4):477–480
67. Snow SN, et al. (2001) Sebaceous carcinoma of the eyelids treated by Mohs micrographic surgery: report of nine cases with review of the literature. Dermatol Surg 28(7):623–631
68. Spates ST, Mellette JR Jr, Fitzpatrick J (2003) Metastatic basal cell carcinoma. Dermatol Surg 29(6):650–652
69. Spencer JM, et al. Sebaceous carcinoma of the eyelid treated with Mohs micrographic surgery. J Am Acad Dermatol 44(6):1004–1009
70. Spinelli HM, Jelks GW (1993) Periocular reconstruction: a systematic approach. Plast Reconstr Surg 91(6):1017–1024; discussion 1025–1026
71. Spinelli HM, et al. (2005) The role of lacrimal intubation in the management of facial trauma and tumor resection. Plast Reconstr Surg 115(7):1871–1876

72. Tenzel RR, Stewart WB (1978) Eyelid reconstruction by the semicircle flap technique. Ophthalmology 85(11):1164–1169
73. Werner MS, Olson JJ, Putterman AM (1993) Composite grafting for eyelid reconstruction. Am J Ophthalmol 116(1):11–16
74. Wolf DJ, Zitelli JA (1987) Surgical margins for basal cell carcinoma. Arch Dermatol 123(3):340–344
75. Wong VA, et al. (2002) Management of periocular basal cell carcinoma with modified en face frozen section controlled excision. Ophthal Plast Reconstr Surg 18(6):430–435
76. Zalla MJ, et al. Mohs micrographic excision of melanoma using immunostains. Dermatol Surg 26(8):771–784
77. Zide BM (2005) Surgical anatomy around the orbit: the system of zones. Lippincott Williams & Wilkins, Philadelphia, pp 1–130
78. Zide BM, Jelks GW (1985) Surgical anatomy of the orbit. Raven, New York, pp 1–75
79. Zitelli JA, Moy RL, Abell A (1991) The reliability of frozen sections in the evaluation of surgical margins for melanoma. J Am Acad Dermatol 24(1):102–106
80. Zitelli JA, Brown C, Hanusa BH (1997) Mohs micrographic surgery for the treatment of primary cutaneous melanoma. J Am Acad Dermatol 37(2 Pt 1):236–245

Chapter 3

Upper Eyelid Retraction: Current Concepts in Management

3

James Kirszrot, Peter A.D. Rubin

Core Messages

- Upper eyelid retraction is best classified as neurogenic, myogenic, and mechanistic.
- Neurogenic eyelid retraction can be acquired or present at birth.
- The acquired form can be due to a dorsal midbrain problem or secondary to aberrant regeneration.
- Myogenic retraction is most commonly due to thyroid eye disease: myasthenia gravis and congenital eye muscle fibrosis.
- Severe upper eyelid retraction can cause mild to severe corneal exposure.
- Surgical approaches can be anterior or posterior.
- Excision of Muller's muscle with aponeurosis recession can be performed via a posterior approach.
- The posterior approach is preferred for mild retraction (1–2mm) and for the A-scan eyelid.
- The anterior approach for upper lid retraction is reserved for moderately severe problems and involves levator aponeurosis disinsertion with Muller's muscle excision.
- A full-thickness blepharotomy is reserved for severe cases of retraction that have not responded to prior surgical efforts.

3.1 Introduction

The treatment of upper eyelid retraction represents one of the most challenging aspects of ophthalmic plastic surgery. This entity produces an unnatural physical appearance, often referred to as the "stare," which can give the illusion of exophthalmos (Fig. 3.1). In addition, retraction can lead to lagophthalmos and exposure keratopathy with sequelae that are potentially sight-threatening. Numerous surgical procedures have been described regarding the correction of upper lid retraction, with varying results, further complicating the treatment of this condition. For the purposes of this review the authors will focus on the surgical correction of thyroid-related retraction.

3.2. Differential Diagnosis of Upper Lid Retraction

The differential diagnosis of upper lid retraction is quite extensive. In clinical practice, thyroid eye disease is the most common underlying cause, and the finding of retraction alone upon physical examination warrants work-up for thyroid disease. Once this condition is ruled out, the differential becomes quite diverse. Bartley has proposed a classification scheme composed of three categories of retraction: neurogenic, myogenic, and mechanistic [1, 2].

Neurogenic eyelid retraction can be acquired or present at birth. A benign conjugate downward gaze with upper eyelid retraction has been described in preterm infants [9]. Furthermore,

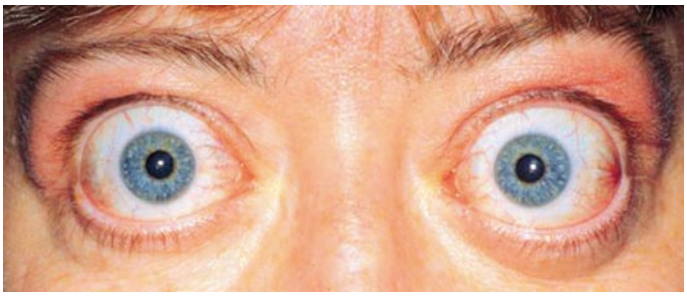


Fig. 3.1 Eyelid retraction

normal infants may elicit an "eye popping" reflex when ambient light levels are suddenly reduced [12]. Acquired causes include the dorsal midbrain syndrome and aberrant regeneration, among others. Unilateral ptosis is commonly observed to cause a "pseudoretraction" of the contralateral upper lid [11], presumably via Hering's law of equal innervation.

Myogenic eyelid retraction is commonly caused by thyroid eye disease. In fact, retraction is the most common finding in patients with thyroid orbitopathy, present in approximately 90% of such patients at some point in the clinical course of their disease [1]. Other causes of myogenic retraction include congenital muscle fibrosis and myasthenia gravis, among others.

Mechanistic retraction can be due to a plethora of underlying abnormalities. Globe prominence, as seen in thyroid eye disease, buphthalmos, severe myopia, and orbital tumors, can result in eyelid retraction. Cicatricial processes including scarring from infection, radiation therapy or aggressive lid surgery, eyelid tumors or burns, can also cause secondary retraction.

Summary for the Clinician

- The etiology of upper eyelid retraction is quite diverse; however, it is most commonly the result of thyroid-related eye disease.
- Functionally, upper eyelid retraction can lead to exposure keratopathy, which in its severe form can lead to infection and permanent vision loss.

3.3 Etiology of Thyroid-related Upper Lid Retraction

While the exact etiology of upper eyelid retraction due to thyroid eye disease has not been elucidated, several theories have been proposed to explain this common clinical finding. Exophthalmos may lead to eyelid retraction, as the eyelids may not be able to lengthen sufficiently to maintain coverage of the globe. This may explain the "lateral flare" often seen in thyroid patients, since in the primary position the globes are directed away from the orbital axis, thereby exposing more sclera temporally [10]. Alternatively, fibrosis of the lacrimal gland and lateral levator aponeurosis has been described [7], which potentially accentuates lateral eyelid retraction. Histological examination of the levator muscle has shown enlargement of muscle fibers in patients with thyroid eye disease [16]. Alternatively, primary hyperactivity of the levator [8] and excessive stimulation of the sympathetically innervated Muller's muscle have been postulated as mechanisms. Finally, fibrosis and retraction of the inferior rectus may cause over-action of the levator–superior rectus complex, causing upper eyelid retraction.

3.4 Physical Examination

A thorough physical examination is required prior to deciding upon a treatment algorithm for upper eyelid retraction due to thyroid eye disease. This requires intimate knowledge of eyelid and orbital anatomy. Variables such as age, level of alertness, and direction of gaze can alter measurements. Examinations should be repeated as

necessary to ensure reliable, reproducible results. Photographs should be obtained to document eyelid positions and confirm stability.

In adults, the average palpebral fissure measures 10 mm in height. Normally, there is no visible sclera between the edges of the cornea and the eyelid margin. The upper lid contacts the cornea approximately 2 mm below the upper limbus in primary gaze. The lower lid contacts the cornea at the level of the lower limbus. The distance from the limbus at the 12 o'clock position to the eyelid margin should be measured with a ruler while having the patient look in primary gaze. It is important to understand that this measurement may be quite variable. Occasionally, the upper lid may change position during the actual process of taking a measurement. This may be due to squinting in response to the proximity of the ruler, or due to further retraction of the eyelid. The authors have found the use of a transparent ruler useful in decreasing the squinting response of the patient [13].

In patients with thyroid eye disease, additional critical components of the physical examination include visual acuity, extraocular motility, pupillary examination, color vision, confrontational visual fields, Hertel exophthalmometry, presence of lagophthalmos and Bell's phenomenon, and slit lamp and fundus examination. Finally, while blepharoptosis is relatively uncommon in patients with thyroid eye disease, it is important to rule out the "pseudoretraction" phenomenon that may be present with unilateral ptosis.

3.5 Sequelae of Upper Lid Retraction

Thyroid-related upper lid retraction can cause both functional and cosmetic problems. The most severe consequence involves exposure keratopathy, which is related to the degree of lagophthalmos. In its mildest form, this can lead to symptoms of ocular irritation and blurred vision. This can be worsened in the setting of a poor Bell's phenomenon and poor reflex tearing, and in extreme situations can lead to corneal ulceration, potential perforation, and permanent loss of vision. Additionally, special clinical situations warrant particular mention. Glaucoma patients with filtering blebs are predisposed to desiccation and infection of the blebs secondary to exposure. Also, patients with peripheral iridotomies may report monocular diplopia if the retracted upper lid exposes the iridotomy site. Finally, patients with exophthalmos *and* retraction may be more prone to spontaneous globe subluxation, particularly patients with the lipogenic variant of thyroid orbitopathy [14].

Cosmetically, upper lid retraction gives the appearance of prominent globes, sometimes referred to as a "stare." In patients with thyroid eye disease, this is often compounded by pre-existing globe proptosis, producing a very abnormal appearance.

Summary for the Clinician

- Cosmetically, it can cause an unnatural appearance, which is often worsened by underlying exophthalmos.

3.6 Medical Management of Thyroid-related Upper Lid Retraction

Whenever possible, symptomatic upper lid retraction should initially be treated medically. This is especially true for patients newly diagnosed with thyroid disease, and those who demonstrate a high degree of variability in lid measurements. Typically, the authors advocate at least 6 months of documented examination stability prior to considering surgical intervention. In the interim, various medical treatments are available to treat the ocular irritation and exposure keratopathy.

Artificial tears and tear gels or ointments should be used aggressively to prevent exposure keratopathy. During sleep, patients should be counseled on taping the upper lids closed to address nocturnal lagophthalmos. Alternatively, moisture chambers such a swim goggles may be worn while asleep to prevent excessive evaporation of tears. These can be used in combination with tear gel or ointment.

Other medications have been used to treat retraction. Use of topical guanethidine, an alpha-

adrenergic blocker, has been described in patients with thyroid-related retraction [4]. However, this medication has many side effects, including miosis, conjunctival injection, punctate keratitis, and ocular pain upon instillation. Use of botulinum toxin (Botox) injections into the upper lid has also been described in several prospective series, with promising results [15, 17]. Side effects of this treatment include possible ptosis and diplopia. In addition, the temporary nature of botulinum toxin makes it less ideal for long-term treatment of eyelid retraction. In our experience, we have found this modality to be of little benefit.

If exposure keratopathy and ocular irritation are severe or refractory to medical management, temporary eyelid closure via a suture tarsorrhaphy may be undertaken. This procedure is quickly and easily performed, and is also reversible. The authors prefer a double armed 5-0 nylon suture passed in mattress fashion from the lateral third of the lower lid to the corresponding position of the upper lid and tied over foam bolsters. It is critical to place the sutures through the tarsus, to achieve greater stability and minimize "cheese-wiring" the suture. This procedure may also be useful for temporary prevention of globe subluxation. In general, permanent tarsorrhaphies are cosmetically unappealing and when used in our practice are small (<5 mm) and as an adjunct to lateral canthoplasty or more rarely, upper lid recession.

3.7 Important Considerations Before Addressing Surgery for Upper Lid Retraction

In general, the authors advocate documenting at least 6 months of clinical stability before entertaining any surgical intervention in patients with thyroid eye disease. In addition, any patient who is being considered for repair of eyelid retraction should first be evaluated for orbital decompression. Significant proptosis often exacerbates eyelid retraction, and recession alone in such patients can yield a cosmetically unappealing result (Fig. 3.2). The authors have previously reported that bony decompression alone may significantly reduce lid retraction, lateral flare, and ocular surface exposure (Fig. 3.3) [5]. With lesser degrees of proptosis, recession alone may mask the appearance of prominent globes. There is no rigid cut-off value for the amount of exophthalmos that warrants decompression first. Rather, the clinical appearance of the patient, the changes in patient appearance relative to their baseline, prethyroid state, and surgical experience of the clinician should dictate management. We advocate consideration of bony decompression when Hertel measurements surpass approximately 24 mm. If possible, old photographs should be obtained prior to surgery in order to assess the baseline appearance of the patient and discuss realistic expectations. Obviously, close consultation with the patient, taking into consideration each of these factors, permits a customized, collaborative treatment plan.

Simultaneous orbital decompression and correction of upper lid retraction has also been described, as it may decrease the total number of surgical procedures for the patient [3]. We feel that the introduction of an additional variable such as decompression surgery increases the degree of difficulty of obtaining a satisfactory result. In our hands, the best results of upper lid recession surgery are achieved when performed in a cooperative, awake patient to permit intraoperative adjustment. The authors feel that there is little advantage to be gained from this combination surgery, especially if patients are undergoing sizeable bony decompressions simultaneously.

3.8 Basic Principles for Surgical Correction of Retraction

Recession of the upper eyelid is a very challenging oculoplastic procedure. A spectrum of constantly evolving techniques has been described, each with individual pros and cons. In our experience, this procedure has a relatively high rate of re-operation (i.e., "enhancements") necessary to achieve satisfactory eyelid height and contour. The patient should be properly educated regarding this fact prior to entertaining surgery. Realistic goals should also be set regarding surgery, namely decreasing symptoms of exposure, maintaining symmetry between both eyes, and

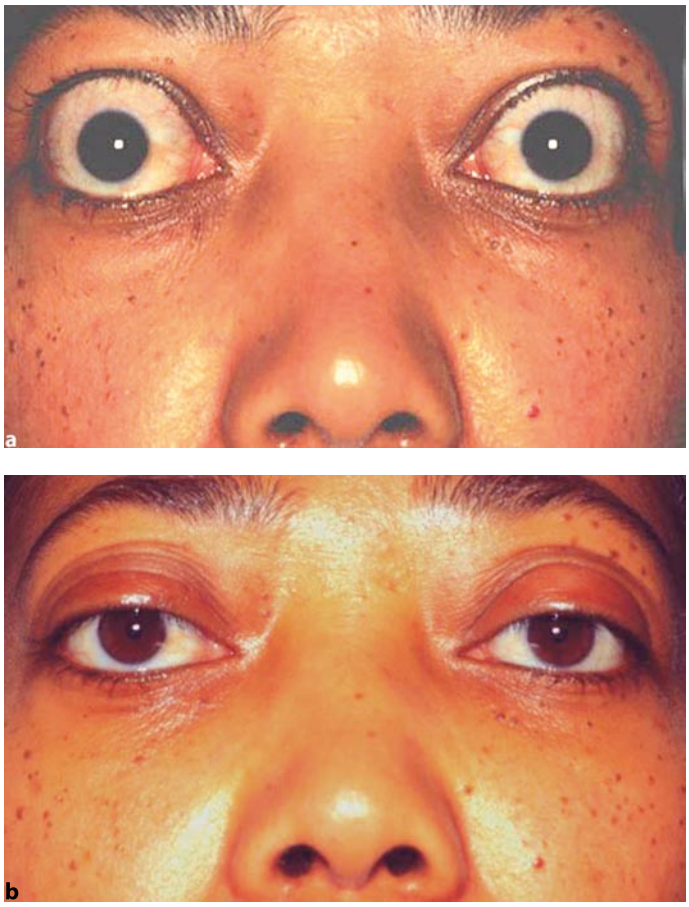


Fig. 3.2 **a** Significant retraction exacerbated by exophthalmos. **b** Following recession alone, the cosmetic results are suboptimal despite normalization of the palpebral fissure heights, as the proptotic globes still result in prominent pre-tarsal platform that is not consistent with the patient's pre-morbid appearance. In such cases, we advocate strong consideration of orbital decompression in advance of eyelid surgery.

improvement of the cosmetic appearance of retraction. Returning a patient completely to their pre-disease appearance is unrealistic and will undoubtedly lead to patient dissatisfaction.

In general, correction of upper lid retraction can be performed via an anterior approach through the skin, or via a posterior approach through the conjunctiva. The anterior approach allows superior visualization of anatomic structures and better control of eyelid contour, while the posterior approach has the benefit of no visible skin scar.

We advocate several general principles regarding surgery for upper lid retraction. First, when operating via the anterior approach, skin excision should be avoided. Any removal of skin could shorten the anterior lamella, potentially counteracting the lid lengthening goal of surgery. Second, pre-aponeurotic fat that is typically encountered in the anterior approach should not be excised. Postoperatively, this fat may act as a barrier between the orbicularis and the levator–Muller's complex preventing adhesions and producing unsatisfactory results. If fullness of the upper lid persists, this fat can be removed later in a staged fashion, and some conservative skin excision is possible. Third, spacer grafts do not play a role in the repair of upper lid retraction. Grafts such as donor sclera, fascia lata, and acellular dermis have been used to lengthen the upper lid and separate the levator–Muller's complex from the upper border of tarsus. Unlike lower lid surgical recession gravity assists the surgical recession of the upper lids. The authors have not found grafts

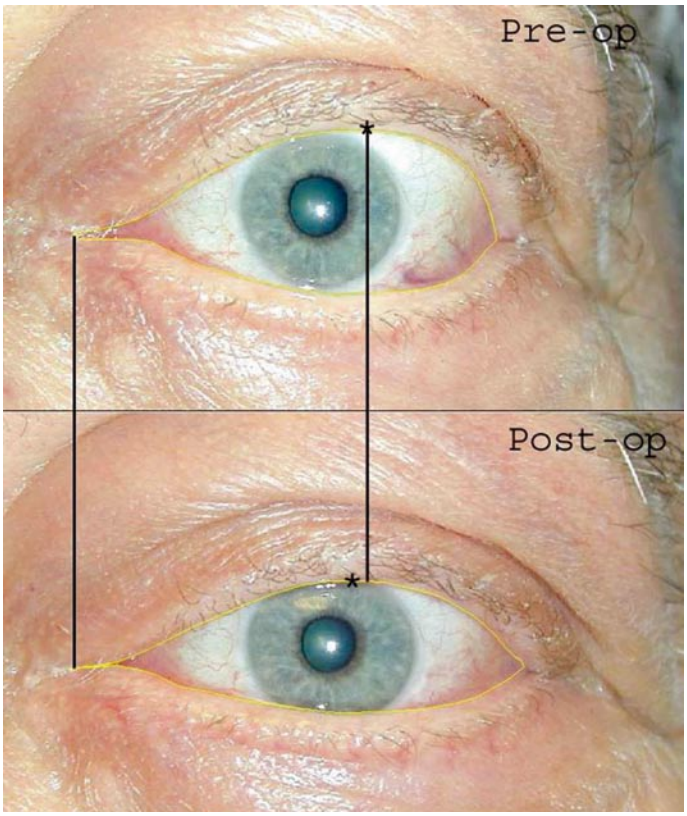


Fig. 3.3 Bony orbital decompression alone can reduce upper lid retraction and lateral flare, as the lid peak is shifted nasally (reproduced from Chang et al. [5])

to be necessary in upper lid surgery. Finally, we have evolved to avoid the use of traction sutures postoperatively. In rare cases, where the upper lid does not lower as much as anticipated intraoperatively, we have used a pressure patch to place the upper lid in a fully closed position for 24–48 h to establish the desired anatomic alignment of the upper lid retractors.

Summary for the Clinician

- The treatment of thyroid eye disease encompasses both medical management and surgical repair.
- Repair of upper lid retraction represents an evolving process, with many techniques available to achieve the same results.

3.9 Preoperative Medication

Surgery for eyelid retraction is typically performed in an ambulatory setting under local anesthesia. As such, patients can often be quite anxious. Following appropriate patient counseling, we advocate the use of a low-dose, short-acting anxiolytic medication preoperatively (alprazolam 0.25 mg; 1–2 tablets po 30 min prior to surgery).

Blood pressure should also be checked routinely before surgery. Patients may have a transient increase in pressure prior to surgery, likely due to anxiety. Also, patients with a history of hypertension may not be well controlled or may forget to take their medication on the day of surgery. Proper control of perioperative blood pressure can reduce the risk of both intraoperative and postoperative hemorrhage. We advocate the use of antihypertensive medication when systolic blood pressure exceeds 115 mmHg (clonidine 0.1 mg po 30 min prior to surgery).

Finally, proper patient counseling should be performed regarding cessation of blood thinning medications. We provide a complete list of drugs, including vitamins and supplements, to be avoided. These should be stopped 10 days prior to surgery and may be restarted 4–5 days postoperatively. Appropriate medical evaluation should be performed for patients on long-term anticoagulation, including acquisition of coagulation profiles.

3.10 Surgical Recession: Posterior Approach

The posterior (transconjunctival) approach to lid recession is generally preferred for mild degrees of retraction, typically measuring 1–2 mm. Also, Asian patients benefit from this technique since the anterior anatomy of the eyelid crease is not altered. In this patient population, the final cosmetic appearance is superior via the transconjunctival technique (Fig. 3.4).

The upper lid and eyelid margin is anesthetized with local 2% lidocaine containing epinephrine 1:100,000 and a corneal shield is placed on the eye. Next, a 4-0 silk traction suture is placed through the lid margin and the lid is everted over a Desmarres retractor. Additional anesthetic can now be injected under the palpebral conjunctiva. With the use of toothed forceps and Westcott scissors, the conjunctiva is incised just superior to the upper border of tarsus and a plane is identified between Muller's muscle and the levator aponeurosis. Another 4-0 silk traction suture is placed through the cut edge of the conjunctiva–Muller's complex. Gentle downward pressure is placed on this suture and complete dissection of Muller's muscle from the underside of the levator is performed. This can be accomplished with a combination of blunt dissection with cotton-tipped applicators and sharp dissection with Westcott scissors. Light bipolar cautery may be used for hemostasis.

Next, Muller's muscle must be dissected away from the conjunctiva. With continued gentle downward pressure on the traction suture, local anesthetic is injected into Muller's muscle, thereby hydrodissecting it away from the underlying conjunctiva. Fine-toothed forceps are used to pull Muller's muscle away from the conjunctiva, and Stevens scissors are used to initiate a plane between the two structures. Through a combination of both sharp and blunt dissection starting at the superior border of Muller's muscle, the conjunctiva and Muller's muscle are separated, and the latter is completely excised. In selected cases just the lateral portion of Muller's muscle is ex-

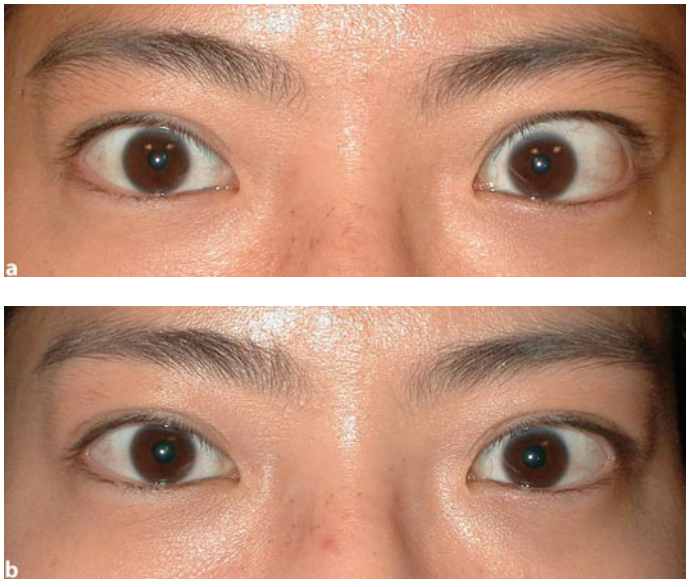


Fig. 3.4 **a** Preoperative and **b** postoperative photos of internal recession surgery on an Asian patient. The anatomy of the lid crease is not altered and the cosmetic results are satisfactory

cised. Care should be taken to minimize buttonholing or damage to the conjunctiva. Again, light bipolar cautery can be used for hemostasis. It is important to remove as much Muller's muscle as possible.

Intraoperatively, the patient should be placed in the sitting position in primary gaze to assess the eyelid height and contour. Some finesse is required, as the presence of anesthetic in the lid at the time of surgery may alter its final position. The conjunctival incision need not be sutured, and patients are prescribed a topical antibiotic/steroid such as Tobradex four times per day for 1 week, at which time eyelid height and contour are evaluated. Generally, if revision is required it should be performed within 3 weeks. Typically, under-corrections do not improve greatly in the postoperative period, while over-corrections may improve as swelling and ecchymosis subside (Fig. 3.5).

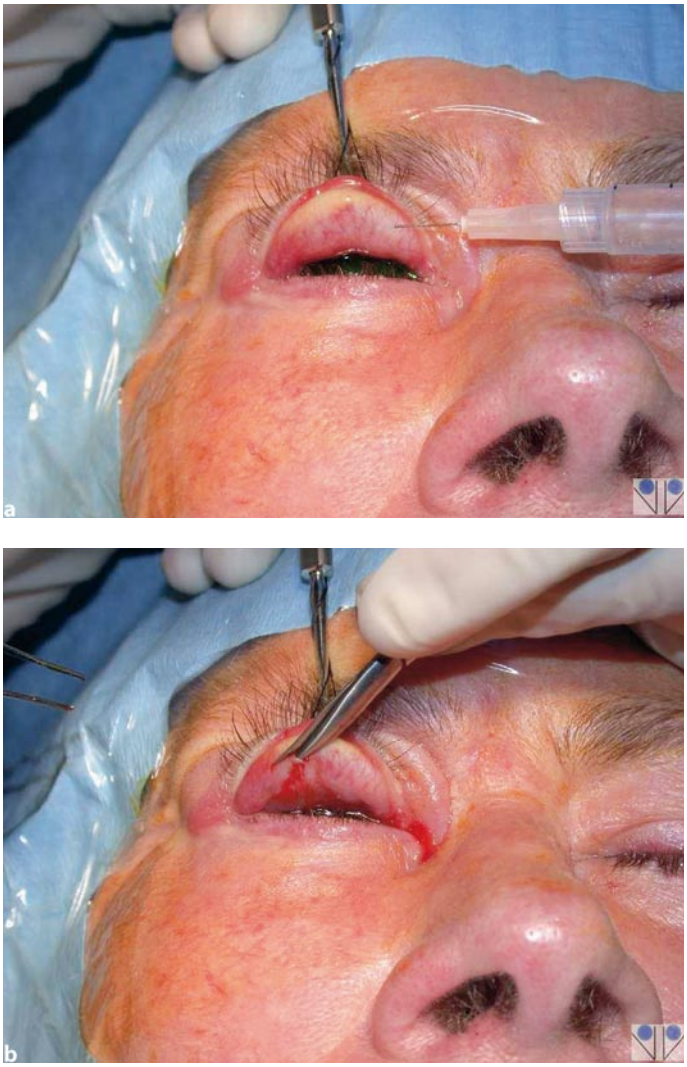
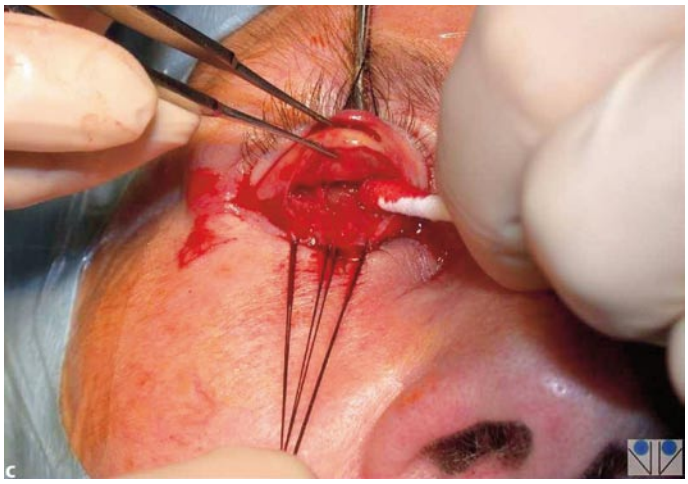
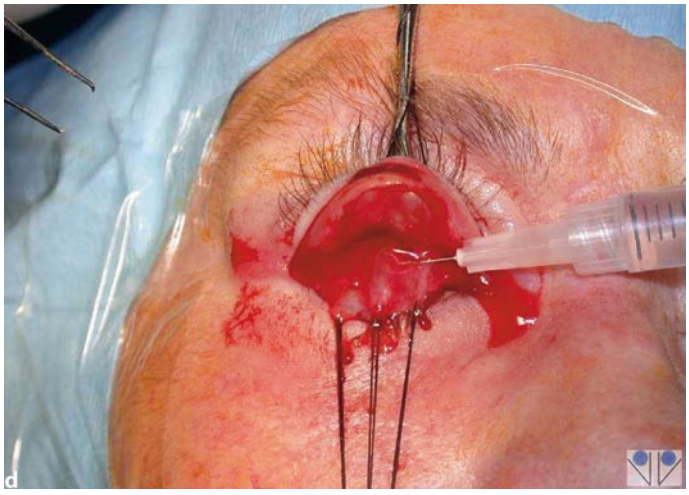


Fig. 3.5 The posterior (transconjunctival) approach to upper eyelid recession. **a** A 4-0 silk traction suture is placed in the upper lid, which is everted over a Desmarres retractor; additional anesthesia is then given. **b** The conjunctiva–Muller's complex is incised superior to the upper border of tarsus. **c** *(see next page)*





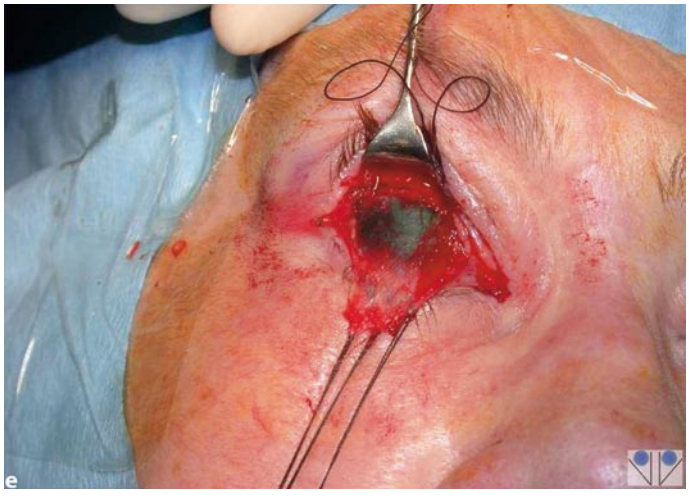


Fig. 3.5 *(continued)* The posterior (transconjunctival) approach to upper eyelid recession. **c** A 4-0 silk traction suture is placed through the conjunctiva/Muller's complex. **d** Hydrodissection of Muller's muscle from the conjunctiva with local anesthetic. **e** Muller's muscle is excised, leaving the conjunctiva

3.11 Surgical Recession: Anterior Approach

Correction of retraction via the anterior approach is reserved for patients with moderate to severe degrees of retraction (typically, greater than 2 mm) that mullerectomy alone would not correct. A skin incision *is* required, but is well hidden within the eyelid crease, yielding acceptable cosmetic results. We discuss two surgical techniques: levator disinsertion/mullerectomy and full-thickness blepharotomy. We routinely perform the former as the initial procedure, whereas the latter is reserved for severe cases that are refractory to prior surgery.

3.11.1 Levator Disinsertion/ Mullerectomy

The upper eyelid crease is marked with a surgical marking pen and the lid is injected locally with 2% lidocaine with epinephrine 1:100,000. Next, a skin incision is made along the marked area with a No. 15 Bard-Parker blade. The orbicularis is tented up with two fine-toothed forceps and dissection is carried down to the orbital septum with Westcott scissors. The septum is then opened wide with the Westcott scissors for the entire length of the incision. Hemostasis is achieved with bipolar cautery.

Having opened the septum, the pre-aponeurotic fat can be identified overlying the levator aponeurosis. As previously mentioned, excision of this fat should be avoided in order to prevent potential adhesions of the anterior and posterior lamellae. A Desmarres retractor can be used to retract this fat superiorly. Westcott scissors are then used to sharply dissect the levator aponeurosis from the anterior superior portion of tarsus. This sharp dissection is continued so that the levator is separated from the underlying Muller's muscle.

Muller's muscle must then be separated from the conjunctiva. With the aid of an assistant placing downward traction on the eyelid, local anesthetic is injected under Muller's muscle, thereby hydrodissecting it from the conjunctiva. Fine-toothed forceps can then be used to lift the muscle fibers away from the conjunctiva and Steven scissors can be used to bluntly dissect in this plane. Muller's muscle is then excised as completely as possible, as described for the anterior approach. Examination of the patient in the sitting position and primary gaze can be performed at this time in order to gauge the amount of recession induced thus far.

Next, the lateral horn of the levator is identified and cut in a lateral to medial direction with Westcott scissors. Care should be taken not to damage the lacrimal ductules during this step. This maneuver helps reduce the prominent lateral flare often associated with thyroid-related retraction. The distal edge of the lateral levator is then transposed medially and sutured in mattress fashion to the remnants of Muller's muscle centrally with a double armed 6-0 Vicryl suture. The suture is tied temporarily and the patient is placed in the sitting position to evaluate lid height and contour. When these are judged to be satisfactory, the suture is tied permanently, and supporting sutures are placed both medial and lateral to the initial suture.

The skin incision is closed with interrupted 6-0 nylon sutures. As previously mentioned, spacer grafts and traction sutures are not necessary, and skin excision should be avoided. Patients are re-evaluated in 1 week for eyelid height and contour and for suture removal. Erythromycin ophthalmic ointment is placed over the incision three times per day. If re-operation for over- or under-correction is anticipated it should be performed during the early postoperative period, typically within 3 weeks of the initial surgery. At this stage, the wound can be easily teased open and the levator repositioned without much difficulty (Fig. 3.6).

3.11.2 Graded Full-Thickness Anterior Blepharotomy

This technique has been attributed to Koornneef and well described by Elner [6]. Although some advocate its use as the primary treatment for upper lid retraction, in our experience it is reserved for severe upper lid retraction that is refractory to previous recession surgery. The upper eyelid crease is marked with a surgical marking pen, and 2% lidocaine with epinephrine 1:100,000 is injected locally into the lid. The mark should be centered over the lid peak.

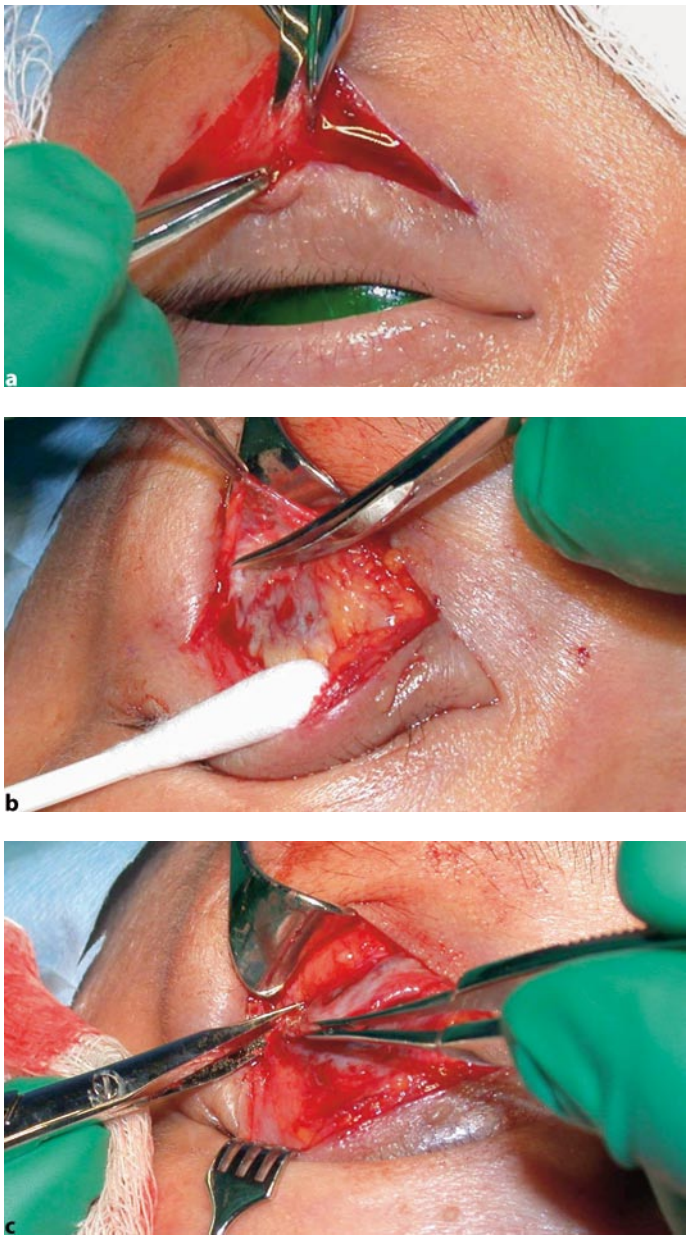
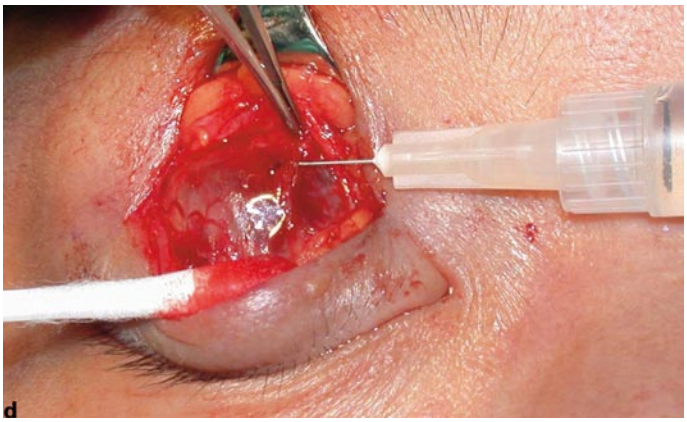
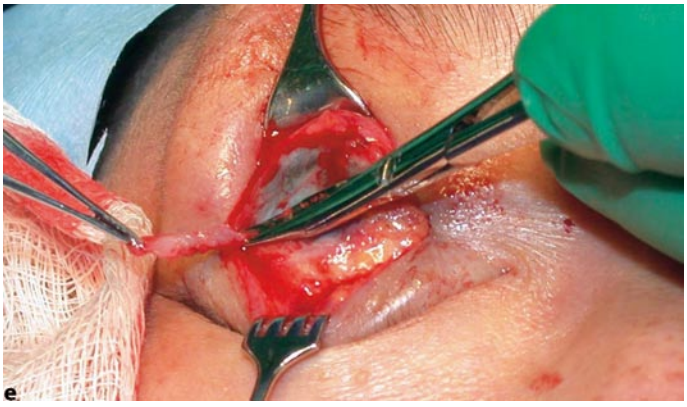


Fig. 3.6 Levator disinsertion/mullerectomy for correction of upper eyelid retraction. **a** A lid crease incision is made and the orbital septum is opened wide. **b** The levator is exposed, disinserted from tarsus and separated from the underlying Muller's muscle. **c** The lateral horn of the levator is cut. **d** *(see next page)*

A 4-0 silk traction suture is placed in the margin of the upper lid. Next, a No. 15 Bard-Parker blade is used to make an incision over the marked area through skin and orbicularis. This incision should be made over the relevant portion (central, medial, lateral) of the marked crease. Dissection with Westcott scissors and fine-toothed forceps is performed in order to expose the levator aponeurosis near the superior border of the tarsal plate. Downward traction on the marginal suture should be performed to facilitate this step. The levator, Muller's muscle and the underlying conjunctiva are incised with Stevens scissors at the upper tarsal border, completing the blepharotomy. This is performed in the region of greatest retraction. Hemostasis can be maintained with the use of bi-





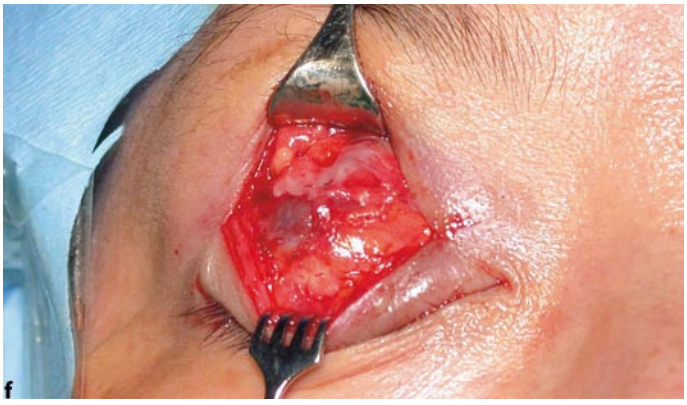


Fig. 3.6 *(continued)* Levator disinsertion/mullerectomy for correction of upper eyelid retraction. **d** Muller's muscle is hydrodissected away from the conjunctiva with local anesthetic. **e** Muller's muscle is excised as completely as possible. **f** The cut edge of the levator is transposed medially and sutured to the remnants of Muller's muscle

polar cautery. The patient is then examined in the sitting position in primary gaze to assess lid height and contour. The incision can be extended medially or laterally as needed in order to control these parameters. In cases of prominent temporal flare, dissection can be carried out laterally and the lateral horn of the levator can be cut. This maneuver should be performed carefully so as to avoid damage to the lacrimal gland ductules. If over-correction or contour flattening is encountered, the distal edge of the levator aponeurosis can be sutured to the upper border of tarsus with a 6-0 Vicryl suture in mattress fashion. Skin is then closed with interrupted 6-0 nylon sutures (Fig. 3.7).

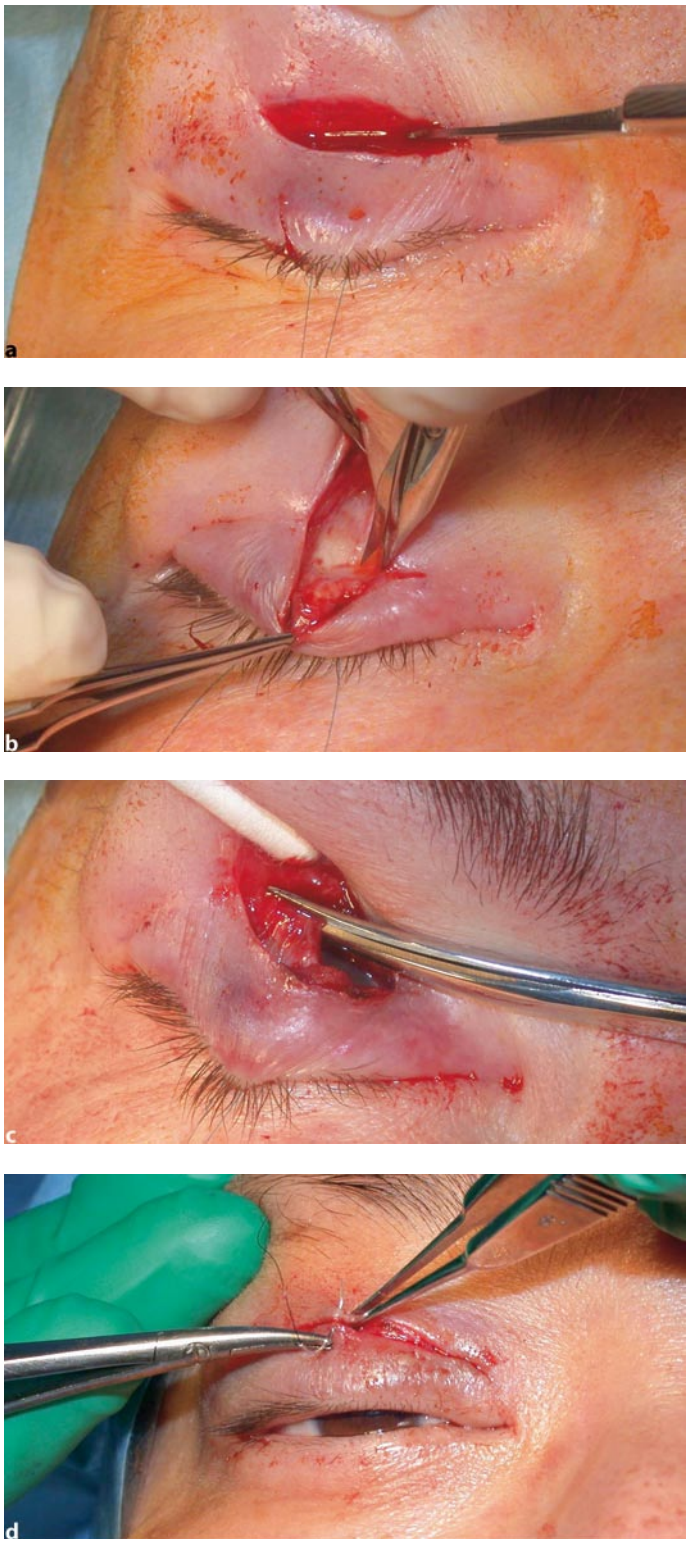


Fig. 3.7 Graded anterior full-thickness blepharotomy for correction of upper lid retraction. **a** A skin incision is made over the relevant portion of the upper lid crease. **b** The levator aponeurosis is exposed near its insertion at the superior border of tarsus. **c** The levator, Muller's muscle, and conjunctiva are cut. This can be extended medially or laterally as needed. **d** Skin alone is closed with interrupted 6-0 nylon sutures when sufficient recession is achieved

Erythromycin ointment is placed over the incision three times per day and sutures are removed at 1 week. As before, assessment of height and contour are made at this time and if re-operation is necessary this should be performed within 3 weeks of surgery. Again, spacer grafts and traction sutures are not necessary and skin excision should be avoided.

3.12 Conclusion

The etiology of upper eyelid retraction is quite diverse; however, it is most commonly the result of thyroid-related eye disease. Functionally, retraction can lead to exposure keratopathy, which in its severe form can lead to infection and permanent vision loss. Cosmetically, it can cause an unnatural appearance, which is often worsened by underlying exophthalmos. The treatment of this entity encompasses both medical management and surgical repair, the latter representing an extremely challenging task for the oculoplastic surgeon. Intimate knowledge of eyelid anatomy is necessary prior to undertaking this task. Even so, repair of upper lid retraction is an evolving process, with many techniques available to achieve the same results. Each of the described procedures as well as others may be effective; however, it is important for each surgeon to customize and evolve their own treatment algorithm to achieve increasingly better results. Nevertheless, even in the most experienced hands, there is a relatively high re-operation rate inherent to this process. As a result, proper patient counseling is essential to establish realistic goals and to set patient expectations at the appropriate level.

Summary for the Clinician

- It is important for each surgeon to evolve their own treatment algorithm to achieve increasingly better results.
- A relatively high re-operation rate is inherent to this process.
- Proper patient counseling is essential to establish realistic goals.

References

1. Bartley GB (1994) The epidemiologic characteristics and clinical course of ophthalmopathy associated with autoimmune thyroid disease in Olmsted County, Minnesota. Trans Am Ophthalmol Soc 92:477–588
2. Bartley GB (1995) The differential diagnosis and classification of eyelid retraction. Trans Am Ophthalmol Soc 93:371–387; discussion 387–389
3. Ben Simon GJ, Mansury AM, et al. (2005) Simultaneous orbital decompression and correction of upper eyelid retraction versus staged procedures in thyroid-related orbitopathy. Ophthalmology 112(5):923–932
4. Cant JS, Lewis DR, et al. (1969) Treatment of dysthyroid ophthalmopathy with local guanethidine. Br J Ophthalmol 53(4):233–238
5. Chang EL, Bernardino CR, Rubin PA (2004) Normalization of upper eyelid height and contour after bony decompression in thyroid-related ophthalmopathy: a digital image analysis. Arch Ophthalmol 122(12):1882–1885
6. Elner VM, Hassan AS, et al. (2004) Graded full-thickness anterior blepharotomy for upper eyelid retraction. Arch Ophthalmol 122(1):55–60
7. Grove AS Jr (1981) Upper eyelid retraction and Graves' disease. Ophthalmology 88(6):499–506
8. Guimaraes FC, Cruz AA (1995) Palpebral fissure height and downgaze in patients with Graves upper eyelid retraction and congenital blepharoptosis. Ophthalmology 102(8):1218–1222
9. Kleiman MD, DiMario FJ Jr, et al. (1994) Benign transient downward gaze in preterm infants. Pediatr Neurol 10(4):313–316
10. Lemke BN (1991) Anatomic considerations in upper eyelid retraction. Ophthal Plast Reconstr Surg 7(3):158–166
11. Meyer DR, Wobig JL (1992) Detection of contralateral eyelid retraction associated with blepharoptosis. Ophthalmology 99(3):366–375
12. Perez RB (1972) The eye-popping reflex of infants. J Pediatr 81(1):87–89
13. Rubin PA (2005) Eyelid position measurement. Ophthalmology 112(3):524; author reply 524–525
14. Rubin PA, Watkins LM, et al. (1998) Orbital computed tomographic characteristics of globe subluxation in thyroid orbitopathy. Ophthalmology 105(11):2061–2064

15. Shih MJ, Liao SL, et al. (2004) A single transcutaneous injection with Botox for dysthyroid lid retraction. Eye 18(5):466–469
16. Small RG (1989) Enlargement of levator palpebrae superioris muscle fibers in Graves' ophthalmopathy. Ophthalmology 96(4):424–430
17. Uddin JM, Davies RD (2002) Treatment of upper eyelid retraction associated with thyroid eye disease with subconjunctival botulinum toxin injection. Ophthalmology 109(6):1183–1187

Chapter 4

Lower Eyelid Retraction: Current Concepts in Management

4

Scott M. Goldstein

Core Messages

- Eyelid retraction is a multifactorial problem.
- A thorough history and examination are needed to best define the underlying pathophysiology.
- Be sure to evaluate all three lamellae of the lower eyelid in localizing the etiology.
- Surgery should be tailored toward the disease process in a graded fashion depending on the severity of the lid retraction.
- The goal of surgery is to restore the balance between the horizontal and vertical forces acting on the eyelid.

4.1 Introduction

The eyelids are a critical structure, paramount in maintaining the health of the eye and ocular surface. Malpositioning of the eyelid leads to a variety of problems that leaves the patient uncomfortable and often seeking intervention. When addressing lid malpositioning, there are two primary goals: first, to maintain or restore function, and second, to achieve this in an aesthetically pleasing manner. The two are intertwined as surgery is approached for functional or for cosmetic purposes.

The etiology of lid retraction is multifactorial (Table 4.1) and can occur for a variety of reasons [1]. The most common reasons include thyroid-related ophthalmopathy, facial nerve paralysis and cicatricial scarring, either from trauma or surgery (Fig. 4.1). In addition, inflammatory disease of the skin or conjunctiva may lead to contraction, retraction, and frank ectropion or entropion. Pseudoretraction can also be seen in cases of proptosis or pseudoproptosis.

The approach to patients with lid retraction requires a good history, a thorough examination, and proper surgical planning. Certainly, patients should be questioned about any systemic diseases like Graves disease, and further, a review of symptoms that might point toward undiagnosed thyroid issues. Thyroid disease mainly causes upper lid retraction, but lower lid changes are encountered as well. Any history of facial trauma and prior surgery is also important and should be explored. Recent and remote problems that may be linked to facial nerve palsy should be sought. In addition, chronic ocular diseases and topical eye drop usage should be queried. When questioning patients, the duration of the problem, along with its severity or other associated factors, can be helpful.

4.2 Over-action of the Upper Lid Retractors

The upper eyelid has three retractors: the levator palpebrae, Muller's muscle, and the frontalis muscle (see Chapter 3). Over-action of these retractors may induce lid retraction. This can be seen in unilateral ptosis where the frontalis muscle is recruited to open the eyelids. This may help the ptotic side; however, the nonptotic side will demonstrate some degree of lid retraction. The treatment in this situation is to treat the eyelid ptosis. Sometimes, patients with recruitment

of the frontalis muscle will continue to subconsciously utilize this mechanism postoperatively. If this persists, botulinum toxin injections can be used [2].

Thyroid-related eye disease is a significant cause of upper lid retraction. A combination of increased sympathetic tone along with levator inflammation and fibrosis and proptosis will all cause the upper eyelid to retract. Patients will often note prominent eyes and may develop exposure issues from the retraction. There may be a lateral flare to the lid retraction as well as lid lag of the upper lid on down gaze (Dalrymple's sign, von Graefe's sign). The inability to distract the upper lid inferiorly (Grove's sign) is helpful in demonstrating fibrosis in the upper lid when planning surgery. In addition to the upper eyelid changes, significant proptosis can also cause lower lid retraction. When treating thyroid-related eye disease, it is optimal for the condition to be stable for 6 months before intervening with surgery. In cases of proptosis, the orbital disease should be treated before planning treatment of the lid position. However, a recent study out of UCLA found that upper eyelid retractor surgery can usually be successfully added at the end of an orbital decompression procedure and speed up the timetable to restoring the normal eye appearance [3].

In treating thyroid-related upper eyelid retraction the goal is bring the lid back in to a more natural position. This is done in a graded approach depending on the extent of retraction. Multiple procedures have been described over the years that are geared toward weakening the retracting forces of the levator or Muller's muscle, or both [4–6]. In cases with 3 mm of retraction or less, often Muller's muscle excision alone or with a levator tenotomy can be performed. In more significant cases, a levator recession is added to Muller's excision. Either an external or an internal approach to Muller's muscle or the levator muscle can be utilized. In the external surgery, a standard lid crease incision is made and the dissection is taken through the septum to the levator aponeurosis. The aponeurosis is disinserted from the tarsal plate, exposing Muller's muscle. Muller's muscle should be sufficiently weakened via excision. Depending on the extent of retraction, the levator aponeurosis is weakened and recessed at the time of surgery as well. It is important to thoroughly release the levator and surrounding fibrotic tissue to obtain a good result. An internal incision can accomplish the same thing in reverse order, especially if surgery is geared only toward weakening Muller's muscle. The lower lid will be covered below.

Table 4.1. Causes of lid retraction

Neuropathic	Facial nerve palsy
	Supranuclear (e.g., dorsal midbrain syndrome)
	Midbrain tumor
Myopathic	Thyroid-related orbitopathy
	Iatrogenic surgical scarring of upper or lower lid
	Trauma with cicatrix
	Hepatic cirrhosis
Inflammatory	Pemphigoid
	Chronic dermatitis/ cutaneous disease
Pseudoretraction	Orbital tumor with proptosis
	High myopia
	Shallow orbit

4.3 Facial Palsy and Lid Retraction

Facial nerve paralysis secondary to idiopathic Bell's palsy is the most common cause of facial weakness; however, this is a diagnosis of exclusion [7]. The thorough clinician will consider other causes like infection, neoplasia, or trauma. Herpes zoster infection of the ear, Ramsay Hunt syndrome, can cause facial nerve paralysis as can Lyme's disease. Cutaneous malignancies, especially squamous cell carcinoma with perineural spread, as well as mass lesions along the course of the nerve may cause compression, which will lead to nerve dysfunction. Obviously, the un-

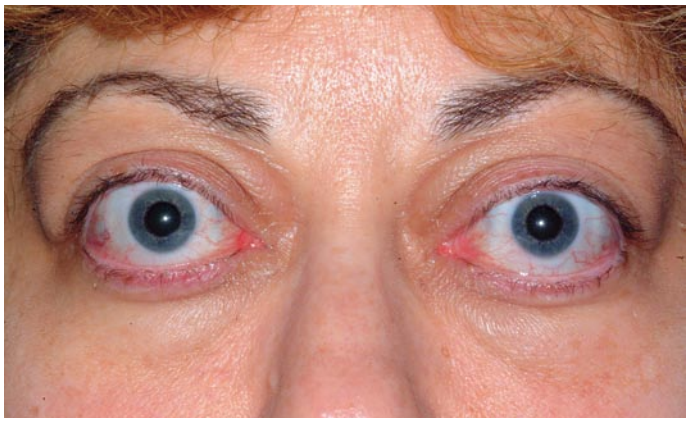


Fig. 4.1 Thyroid-related lid retraction

derlying cause of the facial weakness should be addressed. However, the secondary problems associated with the paralysis must also be considered.

The ophthalmologist is most concerned with protecting the ocular surface, which will be compromised by upper and lower lid retraction, especially in older patients with soft tissue laxity. In the upper eyelid the eyelid–brow continuum should be examined. Weakness of the orbicularis muscle will cause uninhibited action of the lid retractors and thus lid retraction. However, brow ptosis from paralysis of the frontalis muscle will also be present. In older patients with redundant tissue this mechanical weight on the eyelid may minimize the lid retraction. Paralytic upper lid retraction is best treated with a loading procedure to weigh down the eyelid and aid in closure.

At this time, gold weight implants constitute the standard treatment of upper lid retraction from paralysis [8]. External lid weights can be applied to treat patients early in the paralysis, especially those with the potential for reversal. In irreversible paralysis, gold weights can be utilized earlier. An external weight is applied to the eyelid to estimate the appropriate size needed. A balance should be created in reducing the lid retraction and lagophthalmos without being so heavy as to induce mechanical ptosis. The weight is placed through a small central lid crease incision. The pretarsal orbicularis is dissected off the tarsus to create a pocket just large enough for positioning of the weight. Once in the pocket, there should be no tension on the wound. If there is, the pocket should be expanded. Once in position, the weight is fixated to the tarsus with three sutures. Either absorbable or nonabsorbable sutures may be used. If a nonabsorbing suture is utilized, the knots should be rotated to the posterior/deep side of the gold weight to prevent the knot from eroding the superficial tissue anterior to the weight. After the weight is secured, the lid crease incision is secured in two layers. As for the lower lid, a graded approach is utilized to correct the position of the eyelid.

4.4 Lower Lid Retraction

The lower lid is much less forgiving than the upper eyelid. There are multiple vertical and horizontal forces that determine the position of the lower lid, which normally sits just above the lower limbus. When lid malpositioning is present, it is because these forces are out of balance. In particular, there are four areas for concern: the horizontal strength of the eyelid, the vertical pull of the anterior lamella, the vertical forces on the orbital septum, and the vertical pull of the posterior lamella. Eyelid retraction of the lower lid is most commonly a cicatricial process in the septum that tethers the eyelid to the orbital rim. Anterior lamellar shortening will often result in ectropion and posterior lamellar shortening in entropion.

The approach to the lower lid starts with a thorough examination as previously stated. It is important to note lid position, lid mobility or tethering, cutaneous or conjunctival scarring, and orbital and facial skeletal changes so that

the severity of the problem can be ascertained and surgery appropriately planned. When the lower eyelid is retracted inferiorly, patients will develop dry eye symptoms from exposure of the ocular surface. In some instances, this can lead to chronic breakdown of the cornea (Fig. 4.2). Lower lid retraction can often have a component of ectropion or entropion if there is a length discrepancy between the anterior and the posterior lamella, or in addition, there is scarring in either lamella. In the end, the goal is to improve function and cosmesis such that exposure symptoms resolve and facial symmetry and harmony can be achieved.

As mentioned with the upper eyelid, lower lid retraction can occur from thyroid-related ophthalmopathy, facial palsy, and scarring from trauma or previous eyelid surgery. These conditions should be considered when planning surgery. For thyroid patients it may be the proptosis itself that causes lower lid retraction.

4.5 Nonsurgical Approaches

Cicatricial disease is a leading cause of lid retraction. In this situation, the pathology occurs in the anterior, middle or posterior lamella. Anterior and posterior disease from inflammatory processes or scarring as well as middle lamella disease from trauma or surgery can often be treated with topical medications or injections of steroids.

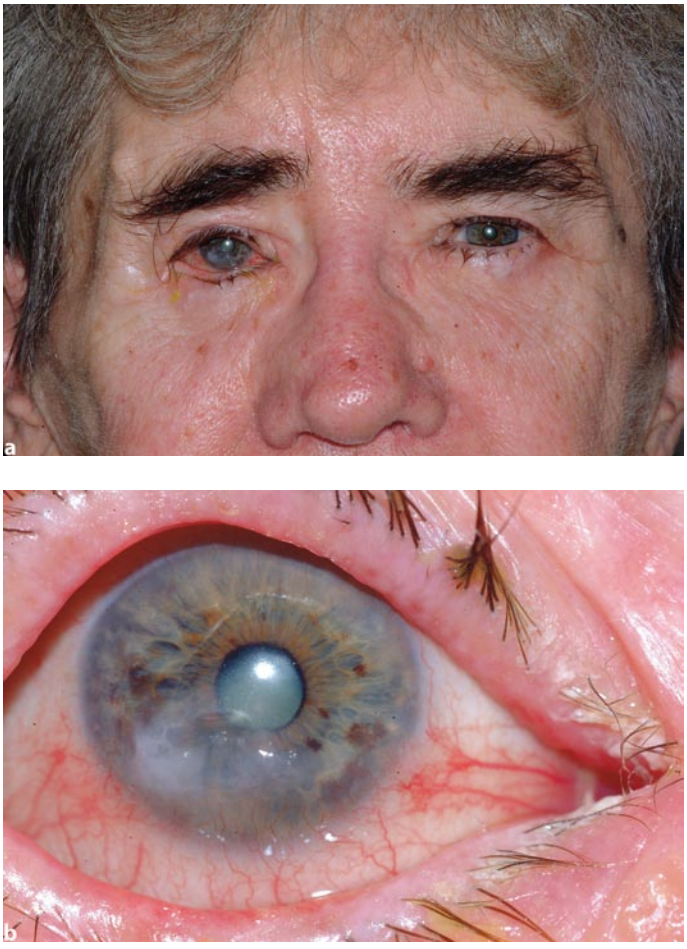


Fig. 4.2 Patient shown 20 years after right facial fractures and lid injury sustained in a car accident. **a** Cicatricial upper and lower lid retraction with lagophthalmos. **b** Despite multiple surgeries over the years and chronic lubrication, she has chronic exposure issues and intermittent keratitis that has left her with a right corneal scar

Cutaneous disease such as atopic dermatitis or conjunctival diseases like pemphigoid should first be treated topically. For cutaneous disease topical steroid cream or ointment, or possibly tacrolimus, can be applied two to four times daily, which will quieten down the inflammation [9]. This often allows the lid to relax and settle back to its normal position and function. The same is true of conjunctival disease. Usage of any inciting medication like glaucoma medications should be stopped, and the use of anti-inflammatory medications, mainly steroids, should be instituted. Finally, for internal scarring, a combination of massaging, time, and intralesional steroid injections are helpful in relaxing scar tissue, especially in the first 1–2 months after the injury or surgery (Fig. 4.3).

Summary for the Clinician

- Treat chronic dermatitis or conjunctival disease medically before moving on to surgery.
- Topical steroids such as fluoromethalone should be applied to the skin two to four times per day.
- Topical tarcolimus can be used for chronic eczema.
- Stop any eye medications inducing conjunctival disease and treat with topical steroid solutions.

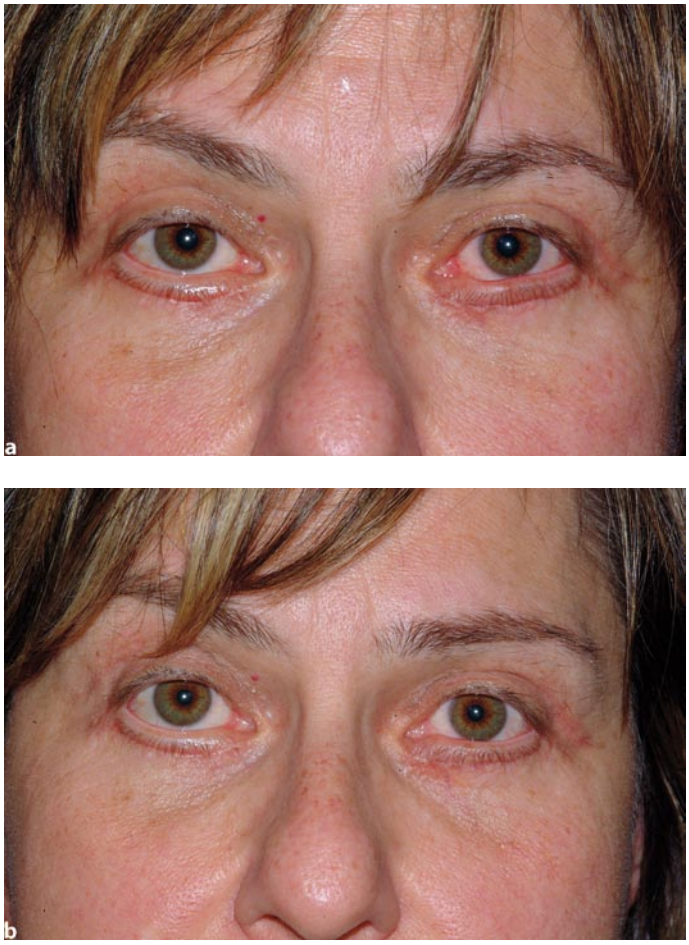


Fig. 4.3 Patient referred 2 weeks after lower lid blepharoplasty for left lower lid retraction. **a** Bilateral subciliary scars noted with the medial portion of the left lid tethered. **b** The combination of lid massage and a 20-mg Kenalog injection into the left lower lid seen 2 weeks later with the left eyelid cicatrix resolved

4.6 Surgical Approaches

Regardless of the etiology, the approach to correcting lower lid retraction is a similar and graded algorithm used in each case. The goal is to restore the harmony and balance between the anterior and the posterior lamella, while releasing any scarring in the orbital septum, is required [10]. In addition, the continuum between the lid and cheek should be addressed in the surgical planning. As mentioned, a stepwise, graded approach should be utilized depending on the extent of the retraction. On the conservative end, mild cases can be treated with recession of the lower lid retractors, similar to the procedures performed on the upper lid. In more extensive cases, a complex reconstruction is required to release the scar tissue in the middle lamella of the lid and anterior orbit around the lower lid retractors combined with a subperiosteal cheek lift and spacer graft to restore balance between the anterior and the posterior portion of the eyelid. Note, that in the setting of true retraction, horizontal tightening alone will be inadequate to treat the eyelid. That stated, any horizontal laxity or scarring that is contributing to the retraction should be addressed during surgery.

4.7 Recession of Retractors

In mild cases of retraction, a simple approach from the conjunctival side of the eyelid can be utilized to recess the lower lid retractors to treat the retraction. Recessing the lower lid retractors 3–5 mm will allow elevation of the lid margin about 1–2 mm, which can make a subtle but important difference. The surgery is performed as follows: a transconjunctival incision is made 1–2 mm below the inferior border of the tarsus and the posterior lamella is dissected and freed. This horizontal incision runs medially from the edge of the caruncle out to the lateral canthus. If there is a component of horizontal laxity, a lateral tarsal strip procedure is incorporated (Fig. 4.4). A few interrupted sutures can be utilized to tack

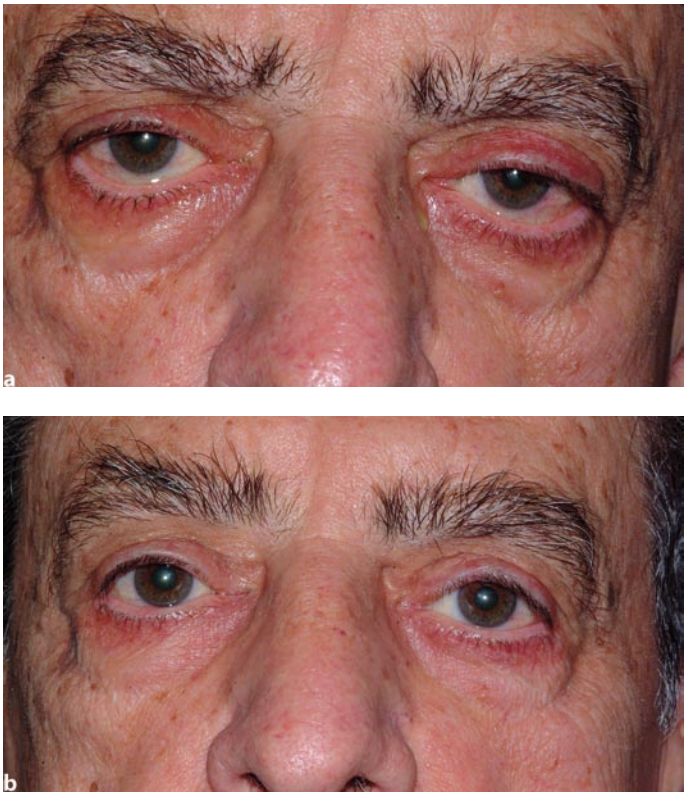


Fig. 4.4 **a** Patient with involutional lower lid retraction secondary to laxity, as well as upper lid ptosis, complained of chronic tearing. **b** An upper lid levator resection and lower lid retractor recession combined with a lateral tarsal strip allowed for repositioning of all four lids and resolution of the epiphora

down the conjunctiva–retractor flap in the desired location. Since the natural tendency of the eyelid is to move downward, a frost suture can be incorporated to help keep the lid in the desired position and splint the eyelid, but is not usually necessary in mild cases.

4.8 Spacer Graft

When the retraction becomes more severe, a spacer graft is inserted to lengthen the posterior lamella and further stabilize the eyelid. A variety of materials have been utilized, including hard palate, AlloDerm, nasal or ear cartilage, and porous polyethylene [11–14]. Each of the materials utilized has its own advantages. The gold standard is a hard palate graft. The use of a graft is especially helpful for patients with poor lid tone, such as those with facial palsy and paralytic retraction or ectropion. Bear in mind that the lower lid is very delicate and that every millimeter counts. Just 1–2 mm of under-correction will leave the patient with chronic exposure issues. On the other hand, over-correction can potentially block vision, especially on down gaze.

Typically a 1×2-cm ellipse or rectangular graft is harvested from the roof of the mouth (Fig. 4.5). Before the lid is dissected, attention is given to the mouth where an oral gag is utilized to keep the mouth open. A marking pen is used to demarcate where the graft will be harvested. Remember to stay to one side of the midline on the flat and smooth part of the palate. In addition, the posterior soft palate must be avoided to prevent a palatal fistula and incompetence. The posterior edge of the graft should be palpated to ensure the graft does not include part of the soft palate. After the area is marked, local anesthetic is injected into the roof of the mouth. While vasoconstriction is setting in, the eyelid dissection is performed. Once the lid is freed up as described previously, the palatal graft is harvested. It is important to make the incision from posterior to anterior, so blood does not obscure your view. After the hard palate graft is harvested, it can be sewn in by first anchoring it at the two ends of the ellipse and then running absorbable sutures along the superior and inferior border. The vertical height of the graft should ultimately be about 1 mm greater than the space between the edge of the tarsus and the posterior lamellar flap so that the lid heals in the appropriate position.

As mentioned, other autogenous and alloplastic implants are available. AlloDerm (Lifecell, Branchburg, NJ, USA), processed acellular cadaveric skin, has been utilized, mostly with success [11, 12]. Its use obviates the need for adding a second surgical site to the procedure and thus increasing patient morbidity. This stated, there is some concern that over time AlloDerm graft loses some rigidity and support. Recent research shows that the thick AlloDerm (1×2-cm size) has had similar success compared with hard palate grafting [15].

Cartilage grafts are best placed through a skin incision. Again, these grafts harvested from ear or nose require a second operative site, although the morbidity is not as bothersome as that with hard palate harvesting [13]. These grafts are also

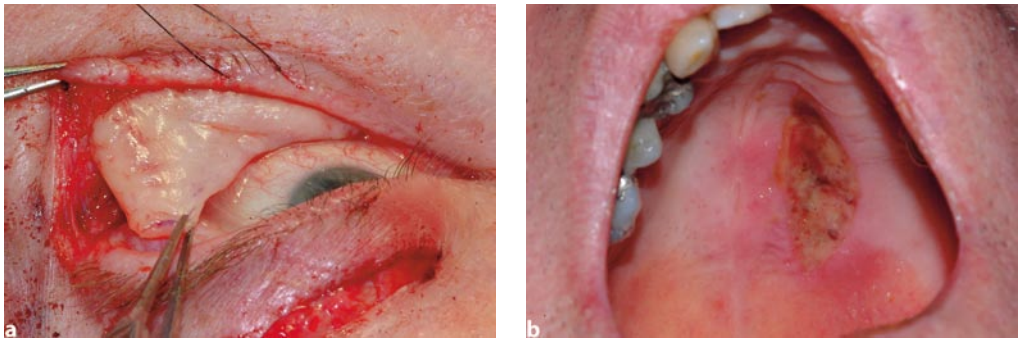


Fig. 4.5 **a** A hard palate graft is positioned for placement in the lower lid before being trimmed to size. **b** The palate is shown 1 week after harvest and is healing nicely

more rigid and therefore must be sculpted. In addition, this thicker, more rigid tissue can be palpated and seen inside the lid. As for the porous polyethylene graft, it is a 0.4-mm porous implant that can be sewn into the eyelid through an anterior, subciliary incision [14]. The inferior portion of the implant can be fixated to the orbital rim. Caution must be exercised with this, as a solid, rigid implant will prop up the lid, but almost fix in place and block the visual axis on down gaze.

4.9 Midface Surgery

It is important to recognize that the lower eyelid and the cheek are a continuous structure. The soft tissues in the lid–cheek continuum are separated by the orbitomalar ligament adjacent to the arcus marginalis. Elevation of the anterior myocutaneous cheek tissue will effectively lengthen the lower lid and remove any anterior vertical traction. Often, when evaluating treatment options for lower lid retraction, consideration must be given to simultaneous cheek elevation, especially in cases where there is cicatricial shortening of the eyelid. The same transconjunctival incision is made, freeing up the posterior lamella. When significant cicatricial disease is present, the scar tissue must be released completely. This often entails dissecting into the anterior–inferior portion of the orbit to release the scarring. Steroids or 5-FU can be applied to the internal wound to help minimize recurrence. Once everything is freed up and mobile, attention is given to the cheek. By lifting the cheek, it directly takes weight and retracting forces off the eyelid.

The dissection proceeds to the level of the arcus marginalis, where either the preperiosteal or the subperiosteal plane can be entered. In a preperiosteal dissection, the suborbicularis oculi fat (SOOF) is mobilized and suspended to the arcus [16]. Since the SOOF is continuous with the superficial musculoaponeurotic system (SMAS), this will help lift a portion of the cheek and is good for aesthetic surgery when contouring the cheek–lid continuum. However, SOOF lifting is less helpful in severe cases of retraction where the lower lid needs significant lengthening.

The most aggressive lifting procedure entails a subperiosteal lifting procedure combined with some of the aforementioned lower lid procedures. When performing a full midface lift, vertical height is added to the lower lid and the underlying weight pulling on the eyelid is lessened. Midface lifts can be performed from a variety of approaches [17]. In planning the lid retraction surgery it makes most sense to proceed with the midface surgery via the lower lid incision used for releasing the retractors and scar tissue (Fig. 4.6). The arcus marginalis is identified and incised on the anterior face of the inferior orbital rim. A sufficient cuff of tissue must be left behind to allow for suturing. The subperiosteal plane is entered and the dissection is brought laterally toward the masseter muscle, medially toward the nose, taking care not to injure the infraorbital nerve, and inferiorly toward the gingival sulcus (Fig. 4.7). The periosteum is incised and the whole cheek is lifted superiorly as one myocutaneous unit. This wide dissection allows for a more powerful lift. The tissue is then secured at the arcus marginalis with a series of interrupted horizontal mattress

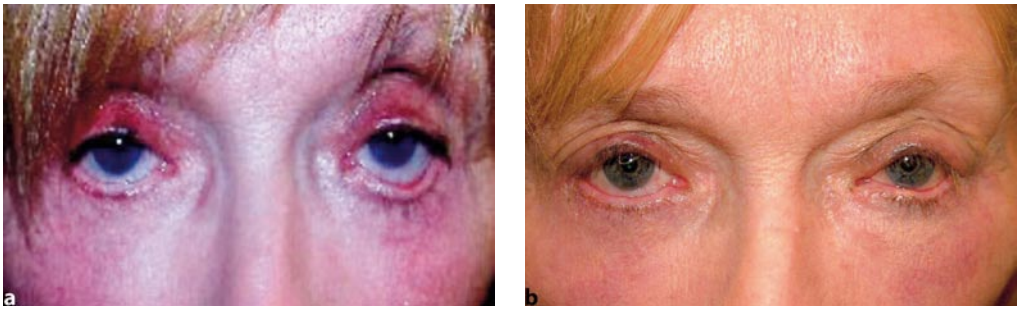


Fig. 4.6. a A patient referred with post-blepharoplasty lower lid retraction unresponsive to tarsal strip procedures and hard palate grafting. **b** Two months following subperiosteal midface lift

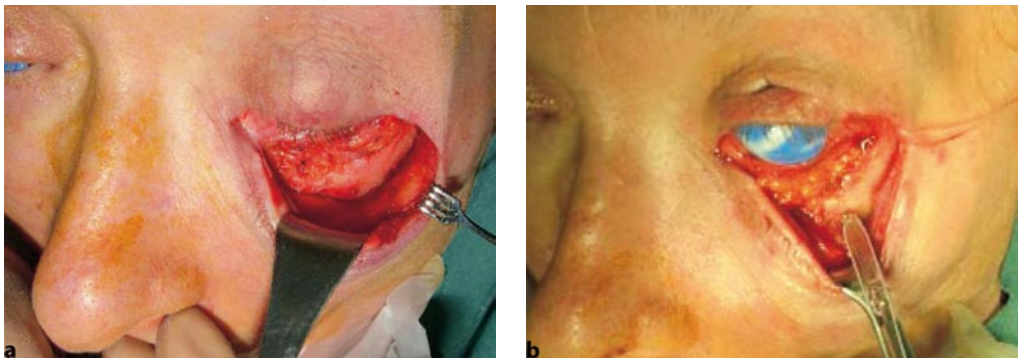


Fig. 4.7. a Subperiosteal dissection over the malar bone through a transconjunctival incision in the patient in Fig. 4.6. **b** Insertion of Mitek anchors after drilling holes in the malar rim. Sutures from anchors used to secure periosteum and lower lid in an elevated position following relaxing inferior periosteal incision. Canthal angle is then reformed with lateral canthopexy and canthoplasty

sutures. By obtaining a full release and elevation of the midface, the anterior lamella of the lid is effectively lengthened, obviating the need for a skin graft. In addition, reducing the weight pulling the lid inferiorly reduces the risk of recurrent cicatrix formation. After the midface has been lifted and secured, the spacer graft is placed to support and buttress the middle and posterior lamella. Finally, the lower lid is tightened and secured laterally in an appropriate position.

Figure 4.8 demonstrates a case of left facial palsy in which all of these factors are in play and

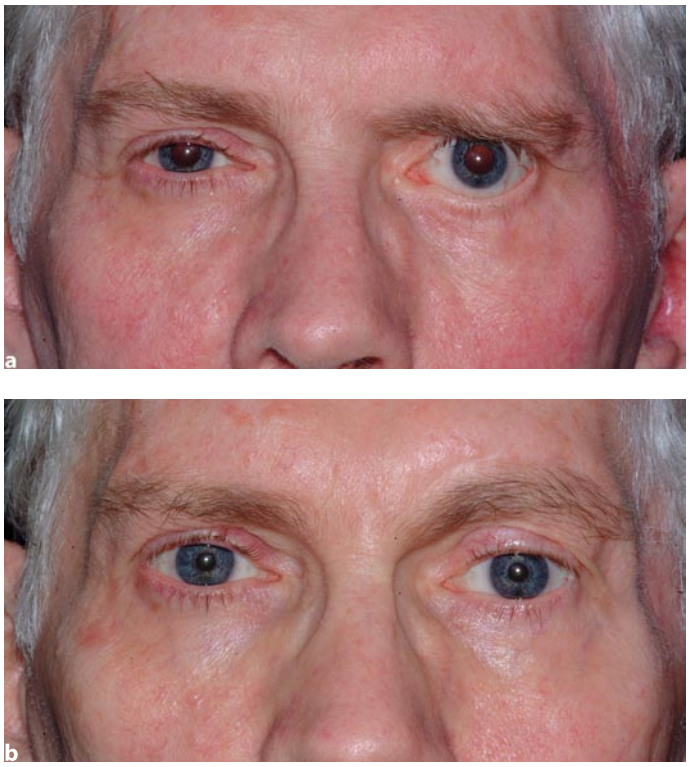


Fig. 4.8. a Patient suffering from left facial nerve palsy with upper and lower lid retraction as well as brow ptosis and midface descent. **b** Patient shown 2 years after direct brow lift, upper lid gold weight, lower lid retraction repair with suborbicularis oculi fat lift, hard palate graft, and lateral tarsal strip

a combination of brow, upper eyelid, lower eyelid, and cheek surgery have been utilized to restore the left upper face brow–eyelid continuum and the lower eyelid–cheek continuum. Frost traction sutures between the lower lid and brow help splint the lower lid during the first postoperative week and further contribute to a successful outcome.

4.10 Lateral Tarsal Strip

Lower eyelid retraction surgery is typically directed at stabilizing or lengthening the vertical vectors of the eyelid. However, the horizontal forces should not be overlooked. In fact, horizontal laxity is often a contributing factor to the retraction itself. It is also imperative to realize that simply shortening and tightening the lower eyelid can often exacerbate the retraction. Since the globe is a sphere, shortening the eyelid will force the lid to slide under the globe and thus potentially accentuate the retraction rather than improve it. This is especially true in patients with shallow, negative vector orbits. In these cases, any lower lid horizontal tightening should be conservative and often the lid should be tacked on a more superior rather than posterior vector.

The lateral tarsal strip is the most versatile procedure utilized for tightening the lower lid. This essential oculoplastic surgery technique is performed in a variety of surgical situations, and thus should be mastered by all who perform lid surgery [18]. A lateral canthotomy and inferior cantholysis are performed to release the eyelid. The lateral edge of the eyelid is distracted laterally to the appropriate tension to reposition the eyelid. The point where the lower lid meets the lateral edge of the superior lid is noted and marked. Next, the superior mucosa and anterior lamella are dissected off the tarsus with Westcott scissors. The conjunctival surface posterior can be cauterized. The strip of tarsus is trimmed to minimize redundancy and then a small half-circle canthopexy needle is used to secure the tarsal strip to the lateral orbital tubercle. Typically, a 4-0 or 5-0 Vicryl on a P-2 needle (Ethicon, Somerville, NJ, USA) is the suture of choice. Two interrupted stitches are placed to ensure stability.

Summary for the Clinician

- Lower lid retraction surgery should be graded depending on the severity of the retraction.
- The goal is to restore the balance between the vertical and horizontal forces in the lid.
- Mild cases can often be treated with recession of the retractors.
- Moderate cases need a spacer graft.
- Severe cases require more aggressive surgery incorporating midface repositioning.
- A tarsal strip procedure should be incorporated in any of the above procedures if there is any laxity.
- A frost traction suture should be used in moderate to severe cases to help splint the eyelid and allow appropriate healing.

References

1. Karesh JW (2000) Eyelid retraction: evaluation, management, and treatment. In: Mauriello JA (ed) Unfavorable results of eyelid and lacrimal surgery. Butterworth-Heinemann, Boston, pp 275–300
2. Ben Simon GJ, Blaydon SM, Schwarcz RM, Nakra T, Goldberg RA, McCann JD (2005) Paradoxical use of frontalis muscle and the possible role of botulinum a toxin in permanent motor relearning. Ophthalmology 112(5):918–922
3. Ben Simon GJ, Mansury AM, Schwarcz RM, Lee S, McCann JD, Goldberg RA (2005) Simultaneous orbital decompression and correction of upper eyelid retraction versus staged procedures in thyroid-related orbitopathy. Ophthalmology 112(5):923–932
4. Ben Simon GJ, Mansury AM, Schwarcz RM, Modjtahedi S, McCann JD, Goldberg RA (2005) Transconjunctival Muller muscle recession with levator disinsertion for correction of eyelid retraction associated with thyroid-related orbitopathy. Am J Ophthalmol 140(1):94–99

5. Putterman AM (1981) Surgical treatment of thyroid related upper eyelid retraction: a graded Muller's muscle excision and levator recession. Ophthalmology 88:507
6. Elner VM, Hassan AS, Frueh BR (2003) Graded full-thickness anterior blepharotomy for upper eyelid retraction. Trans Am Ophthalmol Soc 101:67–73
7. Papazian MR, Campbell JH, Nabi S (1993) Management of Bell's Palsy. J Oral Maxillofac Surg 51:661–665
8. Caeser RH, Freibel J, McNab AA (2004) Upper lid loading with gold weights in paralytic lagophthalmos: a modified technique to maximize the long term functional and cosmetic success. Orbit 23:27–32
9. Nivenius E, van der Ploeg I, Jung K, Chryssanthou E, van Hage M, Montan PG (2006) Tacrolimus ointment vs steroid ointment for eyelid dermatitis in patients with atopic keratoconjunctivitis. Eye, doi: 10.1038/sj.eye.6702367
10. Pak J, Putterman AM (2005) Revisional eyelid surgery: treatment of severe postblepharoplasty lower eyelid retraction. Facial Plast Surg Clin North Am 13(4):561–569
11. Leibovitch I, Malhotra R, Selva D (2006) Hard palate and free tarsal grafts as posterior lamella substitutes in upper lid surgery. Ophthalmology 113(3):489–496
12. Li TG, Shorr N, Goldberg RA (2005) Comparison of the efficacy of hard palate grafts with acellular human dermis grafts in lower eyelid surgery. Plast Reconstr Surg 116(3):873–878
13. Marks MW, Argenta LC, Friedman RJ, Hall JD (1989) Conchal cartilage and composite grafts for correction of lower lid retraction. Plast Reconstr Surg 83:629
14. Wong JF, Soparkar CN, Patrinely JR (2001) Correction of lower eyelid retraction with high density porous polyethylene: the Medpor((R)) Lower Eyelid Spacer. Orbit 20:217–225
15. Taban M, Douglas R, Li T, Goldberg RA, Shorr N (2005) Efficacy of "thick" acellular human dermis (AlloDerm) for lower eyelid reconstruction: comparison with hard palate and thin AlloDerm grafts. Arch Facial Plast Surg 7(1):38–44
16. Hoenig JA, Shorr N, Shorr J (1997) The suborbicularis oculi fat in aesthetic and reconstructive surgery. Int Ophthalmol Clin 37:179–191
17. Shorr N (1995) Madame Butterfly procedure: total eyelid reconstruction in three layers utilizing a hard palate graft: management of the unhappy postblepharoplasty patient with round eye and scleral show. Int J Aesthetic Restorative Surg 3:3–26
18. Anderson RL, Gordy DD (1979) The tarsal strip procedure. Arch Ophthalmol 97:2192–2196

Chapter 5

Surgical Orbital Anatomy

5

A. Ducasse

Core Messages

- Knowledge of regular orbital anatomy and its variations is important in performing orbital surgery.
- Variations are frequent, especially for arteries and veins.
- The orbit is at the junction of the skull and the face .
- Three orbital walls are very thin and in contact with the sinuses: the inferior, medial, and superior walls.
- The lateral wall is the strongest orbital wall .
- The four rectus muscles with their fascias and their intermuscular connections limit a conical space, the fasciomuscular cone.
- Inside the cone we find the optic nerve and the ophthalmic artery; intraconal surgery has more complications than extraconal surgery.
- The lacrimal gland has three types of innervation and three types of vascularization and may depend on the external carotid system.
- The eyeball is located at the anterior part of the orbit. In the case of enlargement of orbital structures (fat and ocular muscles) as in Graves ophthalmopathy, proptosis is the first symptom.
- Orbital fat fills all the spaces between the orbital structures with intraconal fat and extraconal fat.
- The ethmoidal foramina represent the limit between the cranial fossa and the ethmoid sinuses and are the upper limit for orbital decompression without risk of a leakage of cerebrospinal fluid.

5.1 Introduction

A perfect knowledge of orbital anatomy is indispensable for accurately diagnosing orbital diseases and for performing safe orbital surgery. During the 19th and 20th centuries, many studies and many dissections were done in an effort to produce the actual conception of orbital anatomy. One characteristic of the human orbit is the great variability of the anatomical structures found, especially the arteries, which gives to each orbit its particularities. Before the routine use of CT scanning or MRI, it was very difficult for an ophthalmologist or an orbital surgeon to appreciate the arrangement of structures within the orbit. However, it is possible to give a general view of the organization of orbital anatomy, describing the main, well-known variations. In his book *Clinical and surgical orbital anatomy* Dutton said: "few areas in ophthalmology have proven to be as elusive or difficult to teach as orbital anatomy" [21].

Situated between the skull and the face, the orbits contain the visual apparatus, especially the eyeball, and the vessels are at the junction between both the internal and the external carotid system. It is useful to separate the container (bony orbit) from the contents (several visual structures: eyeball, ocular muscles, lacrimal gland, fat, orbital arteries, veins, and nerves).

5.2 Bony Orbit

The bony orbit is a large cavity directed forward and laterally with a 90° angle between the two lateral orbital walls.

Its shape is roughly pyramidal and there are describe four walls united by four margins (or angles). In fact, there are four walls in the anterior

orbital part; in the posterior part there are only three walls, with the absence of the inferior one.

5.2.1 Embryology

Bones of the skull and face develop in two ways: membranous ossification and endochondral ossification. In the first case, there are no cartilaginous precursors and bone ossifies directly from the connective tissue, and in the second case, there is cartilage, which develops first, and secondarily bone develops into this cartilage.

The orbit, sphenoid, and ethmoid bones arise from four ossification areas on the median line and laterally the wings of the sphenoid develop in two cartilages. The facial part of the orbit, the maxillary, lacrimal, and zygomatic bones, develops by membranous ossification. The endochondral ossification starts at about 7 or 8 weeks, while membranous ossification is slower and occurs between the 6th and the 7th months of gestation.

5.2.2 Dimensions of the Orbit

The great orbital axis is directed forward and laterally creates an angle of 23° with the visual axis, which is strictly anteroposterior. This is a characteristic of human orbits, and probably evolved to improve the visual field of erect man. The orbital depth is variable, usually ranging from 42 to 50 mm and its volume is about 26–29 cm^3 [32]. The anterior orbital rim measures on average 40 mm wide and 35 mm high.

5.2.3 Description

Seven bones contribute to the construction of the orbit: the frontal, zygomatic, sphenoid, ethmoid, maxillary, lacrimal, and palatine bones. Each wall connects to a sinus cavity except the lateral wall.

5.2.3.1 Upper Orbital Wall

Also called the orbital roof, this wall is triangular with a posterior top. It consists of two bones: the orbital nasal plate of the frontal bone anteriorly and the lesser wing of the sphenoid bone posteriorly. The frontal plate forms the orbital fossa with a double concavity: anteroposterior and coronal. In the anterior corners of this bone, we can see laterally the lacrimal gland fossa and medially the area for the trochlea of the superior oblique muscle.

This wall separates the orbital contents and the anterior cranial fossa with the frontal lobe of the brain; forward and medially it separates the orbit from the frontal sinus, which varies in size according to the age of the individual. This wall is very thin, and may present spontaneous dehiscence and be easily perforated during orbital surgery.

5.2.3.2 Lateral Orbital Wall

Triangular with a posterior top, the lateral wall is directed obliquely forward and laterally. It consists of three bones . Anteriorly the frontal bone is above and the zygomatic bone is below. The zygomatic bone is located close to the anterior rim, the Whitnall's orbital tubercle (lateral orbital tubercle). Posteriorly, the lateral orbital wall is consists of the greater wing of the sphenoid.

The lateral wall separates the orbit and the temporal fossa anteriorly with the temporal muscle, the orbit, and the middle cranial fossa posteriorly with the temporal lobe of the brain. It is the thickest and strongest orbital wall, especially at the front.

The zygomatico-orbital foramen is a Y-shaped foramen containing the zygomatico-orbital nerve, branche of the zygomatic nerve, and the zygomatico-orbital vessels.

5.2.3.3 Inferior Orbital Wall

Also called the orbital floor, the inferior orbital wall exists only in the anterior orbital part and is triangular with an anterior base. It is directed downward, forward, and laterally. Three bones participate in its formation: the orbital face of the zygomatic bone at the front and laterally, the orbital face of the maxillary bone at the front and medially, and posteriorly a very small bony area consisting of the orbital process of the palatine bone.

The infraorbital sulcus, directed toward the front and medially, runs over the posterior part of this wall. It arises from the anterior part of the inferior orbital fissure, goes forward, and penetrates the bone to form the infraorbital canal, which opens 5–6 mm under the infraorbital rim as the infraorbital foramen. These structures contain the infraorbital nerve, the terminal branch of the maxillary nerve, and the infraorbital vessels. The infraorbital nerve provides branches for the teeth and the upper lip and it may be injured during orbital decompression with secondary anesthesia of the cheek and the upper lip.

The inferior wall separates the orbit from the maxillary sinus; this floor is very thin, which explains the frequency of floor fractures in cases of facial trauma.

5.2.3.4 Medial Orbital Wall

In an anteroposterior direction, the medial wall measures about 45–50 mm in length and is formed with four bones: the maxillary, lacrimal, ethmoid, and sphenoid bones. Anteriorly, there is the lateral face of the frontal process of the maxillary with the anterior lacrimal crest. The lacrimal bone presents on its lateral face a vertical crest, the posterior lacrimal crest, and between the two lacrimal crests, anterior and posterior, is the lacrimal sac fossa. The orbital septum is fixed on the posterior lacrimal crest and the orbit starts from this crest (the lacrimal sac is located in front of the orbit). The lacrimal sac fossa opens below in the nasolacrimal duct. Posteriorly, the lateral face of the ethmoid constitutes the major part of the medial wall and behind the lateral face of the body of the sphenoid bone at the orbital apex.

This wall is very thin and separates the orbit from the nasal cavity at the front and the ethmoidal cells and the sphenoidal sinus posteriorly. Trauma to the face may create a dehiscence of this wall, and surgically, the two walls, which are easy to destroy when performing orbital decompression, are the inferior and the medial walls. During a dacryocystorhinostomy, we create an aperture between the lacrimal sac and the nose, through the maxillary and lacrimal bones.

5.2.4 Orbital Margins or Angles

5.2.4.1 Superior and Medial Margin

Between the medial and upper walls is an angle consisting of the fronto-maxillary, fronto-lacrimal, and fronto-ethmoidal sutures. The anterior and posterior ethmoidal foramina are situated on this margin. Knowledge of their location is very important surgically when performing exenteration or ligation of the anterior ethmoidal artery, in case of nasal bleeding.

The anterior ethmoidal artery and nerve are in the anterior ethmoidal foramen and the posterior ethmoidal artery and nerve in the posterior ethmoidal foramen. Furthermore, the ethmoidal foramina represent the limit between the cranial fossa and the orbit and we must not go beyond this limit during orbital decompression.

In cases of trauma to the anterior ethmoidal artery, an orbital periosteal hematoma may occur and must be treated. According to Kirchner et al. [33] the anterior foramen is located 14–18 mm behind the orbital rim; according to Caliot et al. [6] 11–32 mm behind this rim; and according to the author's previous research [19] 9–34 mm behind the trochlea of the superior oblique muscle. The range is usually between 18 and 22 mm with an average of 19.8 mm. The posterior foramen is located 10 mm behind the anterior foramen with great variation, from 16 to 42 mm behind the orbital bony rim [6] and in our study, 15 mm behind the anterior foramen [19]. The posterior foramen is located 4–7 mm in front of the orbital opening of the optic canal.

According to Kurihashi and Yamashita [36] the distance between the superomedial margin and the anterior cranial fossa is variable and may be 3 mm or less, which explains the possibility of cerebrospinal fluid leakage during a dacryocystorhinostomy.

5.2.4.2 Inferior and Medial Margin

Between the inferior and medial walls, from the front to the back is an area formed by the lacrimomaxillary, ethmoidomaxillary, and sphenopalatine sutures; anteriorly, we can see the upper aperture of the nasolacrimal duct. Usually, this margin is called the orbital strut, and for some

orbital surgeons, it is necessary to preserve this strut during orbital decompression. When we have performed endonasal decompression we can destroy this strut, giving a more effective passage of fat into the maxillary and ethmoid sinuses.

5.2.4.3 Superior and Lateral Margin

Between the upper and lateral walls is an area consisting of the superior orbital fissure posteriorly. This fissure varies considerably in size and shape; usually, it comma-shaped and is directed forward, laterally and superiorly. It is situated between the inferior face of the lesser wing of the sphenoid and the upper edge of the orbital face of the greater wing of the sphenoid, and limited medially by the lateral face of the body of this bone. Sharma [46] describes nine types of fissures. Located between the middle cranial fossa and the orbit, the fissure permits the transit of numerous nerves and vessels from the middle cranial fossa into the orbit. The fissure is divided by the annulus of Zinn, which is located on the body of the sphenoid bone and serves as the tendinous origin of the rectus muscles. The central opening of this annulus permits the passage of nerves and vessels into the intraconal orbital space, as the oculomotor nerve (III) with its two parts, the superior and inferior divisions, the abducens nerve (VI), and the nasociliary nerve, a branch of the ophthalmic nerve. The other structures, which pass through the superior fissure, but outside this central opening, reach the extraconal orbital space as the trochlear nerve (IV), the frontal and the lacrimal nerves, branches of the ophthalmic nerve, branches of the trigeminal nerve (V), and the ophthalmic veins. This fissure is in fact the anterior wall of the cavernous sinus.

5.2.4.4 Inferior and Lateral Margin

Between the inferior and lateral walls is an area consisting at the back of the inferior orbital fissure directed forward and laterally, limited by the orbital face of the maxillary bone, and the inferior edge of the greater wing of the sphenoid bone. This fissure is closed by the orbital periosteum and separates the orbit and the pterygopalatine fossa.

5.2.5 Orbital Rim

Quadrilateral and open at its medial part, the rim consists of the anterior edge of the frontal bone with the supraorbital foramen at the junction between its medial third and its lateral two-thirds. In this foramen, we find the supraorbital artery and nerve. A bony bridge can close this foramen and according to Webster [53], reporting 108 bony skulls, a bilateral closed foramen was found in 20.93% of the cases, and an unilateral closed foramen in 25% of the cases. Laterally, the orbital rim consists of the edges of the zygomatic process of the frontal bone, of the zygomatic bone laterally with the lateral orbital tubercle, of the maxillary bone inferiorly, and medially by the posterior lacrimal crest on the lacrimal bone. The orbital rim is very thick and serves to protect the eyeball during facial trauma.

5.2.6 Orbital Apex

The orbital apex is located at the posterior part of the superior orbital fissure (Fig. 5.1). Close to it, we find the optic canal.

The optic canal, measuring 6–12 mm in length and 5–6 mm in diameter, cuts into the lesser wing of the sphenoid bone, and is limited by the body of this bone medially. The canal is directed downward, forward, and laterally. It presents a posterior endocranial orifice with a horizontal oval shape and an anterior orbital orifice with a vertical oval shape. It lies between the orbit and the anterior cranial fossa and allows the optic nerve with its sheets and the ophthalmic artery, which usually crosses the inferior part of the nerve into the canal, to pass. The medial wall of this canal is in touch with the sphenoidal sinus and is very thin [22] and sometimes absent (4%). So it is possible to decompress the optic nerve using an endonasal approach, in the case of canal fractures with visual loss. The indications for this decompression vary according to the surgeon and it appears to give better results in cases of a hematoma in the canal or in cases of bony compression of the nerve.

The orbital apex is near the cavernous sinus with the internal carotid artery, which gives off the ophthalmic artery over the roof of the cavernous sinus and then gives off its four terminal branches for the brain.

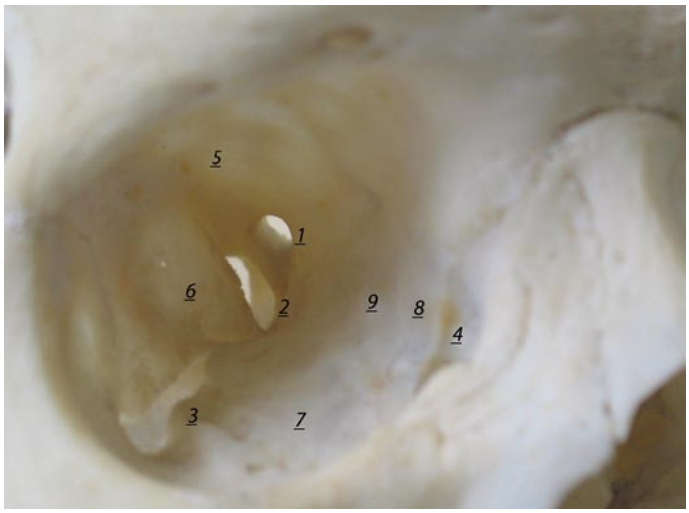


Fig. 5.1 Bony orbit with the orbital apex: *1* optic canal, *2* superior orbital fissure, *3* inferior orbital fissure, *4* fossa of the lacrimal sac, *5* frontal bone, *6* greater wing of the sphenoid bone, *7* maxillary bone, *8* lacrimal bone, *9* ethmoidal bone

In cases of Graves ophthalmopathy, compression of the optic nerve or of the ophthalmic artery may produce optic neuropathy with visual loss and visual field diminution due to an increase in the muscular mass at the apex where the structures are very close to each other.

Summary for the Clinician

- Three orbital walls are in contact with facial sinuses: the upper with the frontal sinus, just about developed, the inferior with the maxillary sinus, and the medial with the ethmoid and sphenoidal sinuses.
- All these walls are very thin and a trauma, however small, may cause an orbital fracture with the possibility of muscular incarceration (especially in the case of inferior orbital wall fracture) and/or emphysema of the orbit with risk of infection.

5.3 Orbital Periosteum

Around the orbital structures and close to the orbital bones, the periosteum is a thin fibrous membrane that is quite easily separable from the bones except at the optic canal and the superior orbital fissure where it continues with the dura mater of the optic nerve and the cavernous sinus. It forms a real periosteal sac around the orbital contents, perforated by the neurovascular structures such as the ethmoidal arteries. It encloses the inferior orbital fissure with a smooth muscle, Muller's muscle. In a forward direction, it continues with the periosteum of the bones of the orbital rim.

5.4 Orbital Contents

The orbital space limited by the bony orbit with the orbital periosteum is closed at the front by the orbital septum, which runs from the edges of the tarsal plates to the orbital rim. Medially, it runs along the posterior orbital crest, which

represents the anterior limit of the orbit; laterally it is fixed on the lateral palpebral ligament. The orbital septum separates the intraorbital fat and the orbicularis muscle [5]. It is perforated in its upper part by the levator palpebrae superior muscle, which leaves the orbit to reach the eyelid [39].

5.4.1 Eyeball

With a diameter of 24 mm, the eyeball is located at the anterior part of the orbit. It goes beyond the anterior orbital rim and it occupies about 7.5 cm^3 in volume. The eyeball is nearer the lateral wall (6 mm) and the upper wall (9 mm) than the inferior and medial walls (11 mm). After enucleation, a spherical implant is usually placed into the orbit, to replace the lost volume. Most orbital surgeons prefer a large implant from 18 to 22 mm, which replaces about 3–4 cm^3 [21]. Because of its orientation (forward and lateral), the lateral orbital wall does not adequately protect the eyeball and in cases of lateral trauma, a severe contusion is possible.

5.4.2 Optic Nerve

Leaving the eyeball at its posterior part, the optic nerve (second cranial nerve) is not really a nerve, but an expansion of the central nervous system. Each optic nerve reaches the optic canal after an intraorbital pathway crossing the ophthalmic artery and penetrating the canal where it may be injured. One optic nerve then reaches the other to form the optic chiasm, situated over the hypophysis. In the endocranial part, the optic nerve crosses the anterior cerebral artery and it may be compressed by a vascular aneurysm or by a tumor of the hypophysis.

In the orbit, the optic nerve starts from the optic disc, which is a canal, and cuts into the sclera. The optic disc has three parts: prelaminar, laminar, and retro-laminar.

Behind the optic disc, the optic nerve forms the axis of the fasciomuscular cone. Its orbital length is about 2.5 cm with a pathway in an S-shape with two curves, a first convex laterally and a second convex medially.

In the optic canal, the nerve is covered by sheets of fibrous tissue, which are the prolongation of the cranial meninges: the pia mater, the arachnoid, and the dura mater.

The arterial blood supply of the optic nerve is variable. It is provided at the optic disc by the arterial circle of Zinn-Haller and more posteriorly by the central retinal artery when this artery is into the optic nerve and more posteriorly by the arteries of the optic nerve, which number 2 or 3 [24]. The intracanalicular part of the optic nerve has a poor vascularization and that explains the fragility of the nerve into the canal.

Summary for the Clinician

- The optic nerve is a large nerve in the orbit, but its vascularization is very poor, especially in the intracanalicular part, which may be damaged during orbital trauma or orbital compression.

5.4.3 Orbital Muscles

In each orbit we can find seven striated muscles: six are oculomotor and fixed directly onto the eyeball and one is the levator muscle of the upper eyelid.

5.4.3.1 Levator Muscle of the Upper Eyelid (Levator Palpebrae Superioris Muscle)

Innervated by the upper branch of the oculomotor nerve, the levator muscle permits the elevation of the upper eyelid. It begins at the orbital apex, directly on the orbital periosteum, above and extends a little medially to the optic canal (Fig. 5.2). The muscle goes forward under the orbital roof, just above the superior rectus; at the anterior part of the orbit the muscle is divided into two parts, an anterior aponeurotic part, which perforates the orbital septum, the levator aponeurosis, and a posterior part, which forms the superior tarsal Muller's muscle. Muller's muscle consists of smooth muscular fibers and sympathetic inner-

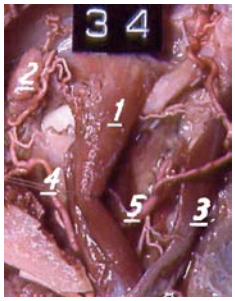


Fig. 5.2 Superior view of a left orbit: *1* levator muscle of the upper eyelid, *2* main lacrimal gland, *3* superior oblique muscle, *4* lacrimal artery, *5* ophthalmic artery

vation, which responds to epinephrine. This part is 10 mm long. The aponeurotic part begins at the level of a white area, the upper transverse ligament or Whitnall's ligament [38]. The aponeurosis goes forward and terminates below the upper eyelid, either at the posterior part of the skin or at the anterior part of the upper tarsal plate; a few fibers reach the bone laterally and medially. The lateral horn, more importantly, reaches the orbital tubercle and divides the lacrimal gland into its two lobes, orbital and palpebral. The total length of the levator muscle is about 56 mm, the length of the aponeurotic part is 15–20 mm with a width of 30 mm. Muller's muscle is innervated by the autonomic nervous system (sympathetic) and its injury may cause minor ptosis, which responds to epinephrine. At the inferior part of the levator muscle, Codère [7] describes white condensation just under Whitnall's ligament, calling it the inferior ligament of Whitnall.

In cases of ptosis, some surgical possibilities may be performed on the aponeurotic part or on Muller's muscle. In some cases the only possibility is to suspend the upper eyelid from the frontal muscle.

5.4.3.2 Oculomotor Muscles

Among the six oculomotor muscles, we can distinguish between four rectus muscles, superior, inferior, medial, and lateral, all of which reach the eyeball in front of the equator, and two oblique muscles, superior and inferior, which reach the eyeball behind the equator. All except the inferior oblique muscle begin at the orbital apex. They are innervated by three oculomotor nerves, the trochlear nerve (IV) for the superior oblique muscle, the abducens nerve (VI) for the lateral rectus muscle, and the oculomotor nerve (III) for the other muscles.

5.4.3.2.1 Rectus Muscles

Measuring an average 4 cm in length, the four rectus muscles extend from the orbital apex to the sclera. These muscles, with their connective fascias and their intermuscular septa, define the orbital cone where the optic nerve and the ophthalmic artery are located.

The four rectus muscles arise from Zinn's tendon. This tendon originates in the greater wing of the sphenoid bone and in the body of the sphenoid bone. This tendon is divided into four small bands of connective tissue and each rectus muscle originates in two contiguous bands. The medial rectus from the superomedial and inferomedial bands, the superior rectus from the superolateral and superomedial bands, the inferior rectus from the inferomedial and inferolateral bands, and the lateral rectus from the inferolateral and superolateral bands.

From this posterior insertion the muscular body, triangular, goes forward following its orbital wall, the superior rectus, the superior wall under the levator palpebrae, the medial rectus, the medial wall, and so on. Thus, three rectus muscles (superior, inferior, and lateral) have the same axis as the orbit, which is different from the visual axis, while the medial rectus goes in an anteroposterior direction.

Anteriorly, the four rectus muscles are fixed into the sclera by a tendon with a width of 10 mm. The distance between the insertion and the limbus is, according to Porter and Berard [2, 42], 5.5 mm for the medial rectus, 6.5 mm for the inferior rectus, 7 mm for the lateral rectus, and 7.75 mm for the superior rectus, making a line called the spiral of Tillaux.

Physiologically, the horizontal rectus has one action, abduction for the lateral rectus and adduction for the medial rectus. The vertical recti have an action with three components: the superior rectus produces elevation, adduction, and

inner rotation; the inferior rectus permits depression, adduction, and outward rotation.

5.4.3.2.2 Oblique Muscles

Superior Oblique Muscle

Originating in the orbital apex and the orbital periosteum, above and medial to the optic canal, the muscle goes forward along the medial wall of the orbit, to reach its trochlea. The trochlea is a fibrocartilaginous ring situated in the trochlear fossa [29] of the frontal bone, at the anteromedial part of the orbital roof. It is easy to separate the trochlea from the bony orbit by ungluing the periosteum. After the trochlea, the oblique superior muscle becomes a tendon that goes obliquely backward, downward, and laterally, making an angle with the muscular part of 50–54° [42]. It crosses under the superior rectus and inserts directly into the sclera behind the equator of the eyeball. The total length of the muscle is about 50 mm: 30 mm for the muscular body and 20 mm for the tendon. Its action is depression, abduction, and inward rotation.

Inferior Oblique Muscle

A single orbital muscle that does not arise from the orbital apex, but from the anteromedial part of the orbital floor, near the superior foramen of the nasolacrimal duct. It measures 30–35 mm in length and its muscular part goes backward, laterally and upward. It crosses over the inferior rectus muscle and inserts into the sclera behind the equator of the eyeball. Its action consists of elevation, abduction, and outer rotation.

5.4.3.3 Supernumerary Muscles

Sometimes, there are supernumerary muscles leading into the orbit. The most frequent is the levator muscle of the trochlea, which is between the levator muscle of the superior eyelid and the trochlea (Sacks found it in 7 out of 98 orbits [45]) In some animals (bovids), there is a retractor of the eyeball, a muscle rarely found in humans.

5.4.4 Muscular Fascias

Around the eyeball, the Tenon's capsule is a fibroelastic membrane that covers the sclera from the limbus to the optic nerve [10]. It consists of two laminas.

The six oculomotor muscles perforate this membrane to penetrate the sclera. Each muscle has its own fascia and each rectus muscle fascia is connected to the other fascias by an intermuscular fascia. All these fascias permit movement of the eyeball and delimit a conical space behind the eyeball with its top at the orbital apex, called the fasciomuscular cone (Fig. 5.3). Membranous expansions link the rectus muscle fascias to the other muscles, the levator muscle of the upper eyelid and oblique muscles. The fascias of the superior rectus and the levator muscle of the upper eyelid in particular are connected to permit the elevation of the upper eyelid during upward gaze. In the same way the fascias of the inferior rectus muscle and the inferior oblique muscle are connected, forming a strong adherence, known as Lockwood's ligament.

Each muscular fascia provides aponeurotic expansion for the conjunctiva, the eyelids, and the orbital walls, the most important coming from the horizontal rectus muscles, from the lateral rectus to the lateral wall of the orbit and from the medial rectus to the posterior lacrimal crest. The inferior rectus fascia also provides expansion for the inferior orbital wall and for the inferior edge of the tarsal plate–arcuate expansion.

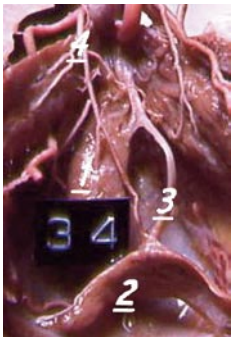


Fig. 5.3 Fasciomuscular cone, inside: *1* inferior rectus muscle, *2* inferior oblique muscle, *3* inferior branch of the oculomotor nerve, *4* inferior muscular artery

Previously, Koornneef [34, 35] has described these fascias as "a locomotor eyeball system." According to him, these fascias consist of collagen fibers containing vessels, nerves, and smooth muscle fibers. At the anterior part of the orbit, these fascias are principally circumferential and at the posterior part, they are radiate.

Summary for the Clinician

- The four rectus muscles limit, with their intermuscular fascias, the fasciomuscular cone in which we find the optic nerve and the ophthalmic artery.
- In orbital pathology, especially in the case of orbital tumors, it is very important to localize the tumor as being inside or outside this cone.
- The surgical approach is more complicated and more dangerous in cases of intraconal orbital tumors. The major complication of this surgery is the definitive blindness.

5.4.5 Main Lacrimal Gland

Tears are secreted daily by the main and accessory lacrimal glands. The accessory glands are located mainly in the conjunctiva whereas the main lacrimal gland is situated at the superolateral part of the orbit. Firm, yellowy red, with a lobular aspect, easily separated from the surrounding orbital fat, each main lacrimal gland measures an average of 20 mm in length, 15 mm in width, and 5 mm in depth.

In fact, the gland consists of two parts, a palpebral lobe and a more voluminous orbital lobe. These two lobes are in contact with each other, separated by the lateral horn of the levator muscle of the upper eyelid.

The orbital lobe is located in the lacrimal gland fossa, a hollow in the horizontal part of the frontal bone. The lacrimal gland has two sides and two edges, a superolateral side in contact with the bone and an inferomedial one that is in contact with the anterior part of the lateral rectus and the lateral part of the levator muscle, its lateral horn, and the lateral orbital expansion of the superior rectus. The anterior edge of the gland touches the orbital septum and the posterior edge the orbital fat. At the back, the gland receives a neurovascular pedicle consisting of the lacrimal nerve and arteries. The main excretory ducts (3 to 5) open in the upper conjunctival fornix.

Histologically, the gland consists of acini, which form lobes; in each acinus we can find a basal membrane, a layer of myoepithelial cells, and a medial layer of secretory cells.

5.4.6 Orbital Arteries

The arterial supply of the orbit comes mainly from the internal carotid system and partly via the branches of the external carotid system. Thus, we can find in the orbit anastomosis between these two carotid systems. Variations are extremely frequent – variations in the origin of the arterial branches, of their caliber, of their pathway, of their distribution – and orbital arterial systematization is very difficult.

5.4.6.1 Ophthalmic Artery

The ophthalmic artery originates in the cranial fossa from the internal carotid, leads to the optic canal, and provides numerous collateral branches for the eyeball, the muscles, and the nasal cavities (Fig. 5.4). It leads out of the orbit at an anterosuperomedial angle.

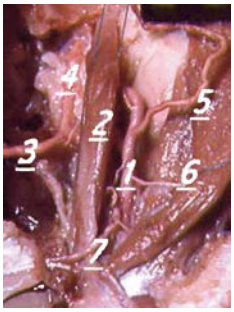


Fig. 5.4 Ophthalmic artery: *1* ophthalmic artery, *2* superior oblique muscle, *3* anterior ethmoidal artery, *4* extraconal part of the ophthalmic artery, *5* supraorbital artery, *6* superior rectus under the levator muscle of the upper eyelid, *7* posterior ethmoidal artery

5.4.6.1.1 Embryology

Embryology of the ophthalmic artery was described by Padget [41]. Before the embryo reaches 18 mm, there are two primitive ophthalmic arteries, one dorsal and one ventral. These two branches arise from the future internal carotid artery. These two primitive ophthalmic arteries unite to form one primitive ophthalmic artery.

After the embryo has reached 18 mm, the supraorbital branch of the stapedial artery goes into the orbit and supplies two branches: a lateral, future lacrimal artery and a medial artery, which anastomoses with the primitive ophthalmic artery. This medial branch supplies the supraorbital and ethmoidal arteries. The stapedial artery is a branch of the external carotid system and usually the proximal part of the supraorbital branch of the stapedial artery becomes the middle meningeal artery, and the part that goes through the lateral wall of the orbit disappears into the orbit. This embryology explains the multiple arterial variations found and the possibility of greater participation of the middle meningeal artery in orbital vascularization.

5.4.6.1.2 Origin

Usually, the ophthalmic artery is a collateral branch of the cerebral part of the internal carotid artery. When the internal carotid goes out of the cavernous sinus, it supplies the ophthalmic artery and then goes backward to terminate in these four cerebral branches. The ophthalmic artery starts on the anteromedial side of the internal carotid artery under the anterior clinoid process.

Numerous variations of this origin have been described, e.g., the artery arising from the internal carotid, but going into the cavernous sinus, or having two branches. Sometimes the ophthalmic artery arises from the middle meningeal artery. According to Hayreh [25], out of 170 orbits, the origin was in the internal carotid in 164 cases and in the middle meningeal artery in 6. In Lang and Kageyama's report [37] the origin was in the internal carotid with location in the cavernous sinus in 18%. In our experience, out of more than 100 orbital dissections, we have always found the origin to be in the internal carotid artery.

The arterial diameter at its origin is between 1 and 2 mm: 0.7 to 1.4 mm according to Hayreh [25], 1.5±0.27 mm according to Jimenez-Castellanos [31], and 1.54±0.4 mm in men and 1.31±0.5 in women according to Lang and Kageyama [37].

5.4.6.1.3 Course

The ophthalmic artery has three parts, the intracranial, intracanicular, and intraorbital parts.

Intracranial

The intracranial part is in the subdural space; this part measures an average of 9 mm, ranging from 4.8 to 15.1 according to Hayreh [27]. The artery reaches the optic canal in contact with the inferior part of the optic nerve, located as it is in the anterior cranial fossa.

Intracanicular

The intracanicular part of the artery goes through the optic canal under the optic nerve and usually crosses the nerve from the inside to the outside. This part measures 7–14 mm according to the length of the optic canal. At the anterior part of the canal, the artery is usually inferolateral at the inferolateral part of the nerve [37].

Intraorbital

The intraorbital part, which can measure up to 32.6 mm [31], is divided into three parts.

Latero-optic

A latero-optic part is at the back; the artery is on the lateral side of the optic nerve, a little oblique, above and forward. With the nerve it penetrates into the fasciomuscular cone where it crosses the inferior ophthalmic vein, the inferior division of the oculomotor nerve, the nasociliary nerve, and the superior division of the oculomotor nerve.

Optic

The artery crosses the optic nerve from outside to inside, above or below. Usually, the artery crosses over with two angulations, one called "angle" by Hayreh [28]. The crossing is usually 13–29 mm behind the eyeball (Fig. 5.5) [13].

Under-crossings vary from 5.4 to 28% in different studies, with an average of 17 to 20%. The lower rates are found in the Japanese literature: Taguchi 5.4% [50], Adachi 6.5% [1]. In other parts of the world, the frequency of under-crossing is greater: Zuckerland 15% [54], Sudakevitch 13.6% [49], Hayreh 17.4% [28], Lang and Kageyama 18.6% [37], Henry 20% [30], Hamard et al. 18.6% [23], Desantis 28% [11], and in our report of a hundred orbits, 23% [13].

At the crossing, the artery is in contact with the nasociliary nerve, which is usually above the artery, with the upper ophthalmic vein above the artery and the ciliary ganglion located on the lateral part of the optic nerve just ahead of the crossing.

Medio-optic

After crossing, the ophthalmic artery reaches the medial wall of the orbit, usually with a large loop. In this part of its course, it is crossed once, twice or several times by the nasociliary nerve.

After this loop, the artery usually leads out of the cone passing between the medial rectus muscle and the superior oblique muscle, an average of 16.5 mm behind the trochlea. This is the case in 76% of orbits [14]. After crossing under the superior oblique muscle, the artery reaches the anterior ethmoidal foramen where it supplies the anterior ethmoidal artery and then forward along the medial orbital wall, passing under the trochlea of the superior oblique muscle and terminating its course at the superomedial angle of the orbit. In a few cases, the artery stays in the cone, outside the medial rectus and oblique superior muscles (24% in our study). In some cases, the artery, after passing out of the cone, again reaches the intraconal space, crossing under the superior oblique muscle for a second time.

With the artery, we find the nasociliary nerve, which supplies its two terminal branches: the ethmoidal anterior nerve, which reaches the anterior ethmoidal foramen, and the infratrochlear nerve, which runs along the terminal part of the ophthalmic artery.

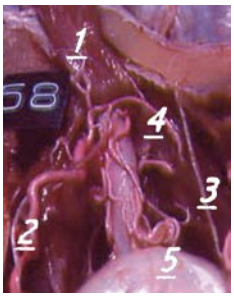


Fig. 5.5 Superior view of the orbital cone in cases of crossing under the ophthalmic artery. *1* superior rectus muscle, *2* ophthalmic artery, *3* lacrimal nerve, *4* lateral muscular artery, *5* lateral ciliary trunk. It can be seen that there is no lacrimal artery arising from the ophthalmic artery

5.4.6.1.4 End

At the superior and medial part of the orbit, the artery perforates the orbital septum 10 mm above the medial canthal tendon and terminates in one or more frontal branches (usually two, one medial and one lateral) for the frontal skin and an angular artery, which usually anastomoses with the nasal artery, terminal branch of the facial artery, a branch of the external carotid system. At its end, the artery has a diameter measuring between 0.5 and 1.5 mm.

5.4.6.1.5 Collateral Branches of the Ophthalmic Artery

The ophthalmic artery supplies numerous collateral branches; only arteries with a diameter of up to 0.3 mm are relatively invariable. The number of collateral branches varies from 10 to 19 per orbit. They arise mainly from the intraorbital part of the artery and from its optic and medio-optic parts in particular. Variations are very frequent and depend in part on the type of crossing between the artery and the optic nerve. Branches

are sometimes absent or arise from another artery. Most frequently, the first branch is the central retinal artery or a ciliary artery.

We can divide these arteries into two groups, those for the optic structures (central retinal artery, ciliary arteries, arteries for the optic nerve), and those for the annexes (supraorbital, ethmoidal, lacrimal, muscular, and palpebral arteries).

Arteries of the Optic Nerve

Not numerous and small in size, these arteries originate in the intracanicular part of the artery or in its intraorbital part.

Central Retinal Artery

Invariable, the central retinal artery is a branch of the ophthalmic artery in 50% of orbits and in the other 50% it comes from another artery. Out of 100 orbits [13] we found 49 cases of the central retinal artery originating in the ophthalmic artery, 37 in the medial ciliary artery, 8 in the inferior muscular artery, and 6 in the lateral ciliary artery. The central retinal artery is small, usually with a diameter measuring less than 0.5 mm, range 0.2 to 0.4 mm [37].

Often beginning above and outside the optic nerve, it reaches the inferior part of the nerve and runs along this part for between 3 to 20 mm. Then it penetrates the optic nerve 6 to 15 mm behind the eyeball, goes into the nerve to the papilla, where it divides into its terminal branches [26].

Posterior Ciliary Arteries

Classically, long posterior ciliary arteries and short posterior ciliary arteries have been described. The first participate in the great arterial circle of the iris and the second do not. In fact, these arteries arise usually from two or three trunks of the ophthalmic artery and divide behind the optic nerve before penetrating the sclera. It becomes impossible to differentiate the length of the small branches after penetration. Therefore, the number of the long ciliary arteries varies according to different authors; most of them describe two or three arteries [24], a few more, two to five arteries. Most authors report 15 to 20 short ciliary arteries.

In fact, it would be more logical to talk about posterior ciliary trunks that supply numerous branches: two long ciliary arteries, medial and lateral, and many short posterior ciliary arteries.

There are usually two posterior ciliary trunks, a medial and a lateral trunk, which is always the largest. When there is a third trunk, it is often superior; rarely, there may be a fourth trunk, which is lateral or inferior [16].

The lateral posterior ciliary trunk is fixed and arises from the ophthalmic artery (in 92% of cases), from its latero-optic part, before the crossing with the optic nerve, or from the optic part. Sometimes, it arises from the lacrimal artery. Located at its origin on the lateral side of the optic nerve, it goes along this side to the eyeball, divided into numerous branches: short ciliary arteries and one long lateral posterior ciliary artery, which perforates the sclera 4 mm away from the papilla. The diameter of the trunk measures between 0.3 and 1 mm, with an average of 0.56 mm.

The medial ciliary trunk is more variable; it takes its origin from the ophthalmic artery in 82% of cases. In 17% of cases, its origin is in the inferior muscular artery. Its course is dependent on the location of its origin. If it starts inside the optic nerve (55%) it goes along the medial side of the nerve as the lateral artery, but if it starts outside the optic nerve (45%; in that case, it is often the first branch of the ophthalmic artery), it crosses the nerve, usually underneath (87%). Its diameter is often smaller than that of the lateral trunk (0.3 to 1 mm with an average of 0.51 mm) [37].

The short posterior ciliary arteries arise from the posterior ciliary trunks and penetrate the sclera around the optic nerve. Ducournau [20] separates these arteries in two groups: those near the optic nerve (paraoptic group) consisting of four to five arteries, and those that perforate the sclera at a distance from the papilla (distal group) consisting of five to ten arteries.

All these arteries, the short ciliary arteries, long posterior ciliary arteries, and central retinal

artery form around the optic nerve, behind the papilla, a great neurovascular bundle.

Lacrimal Artery

There are two types of lacrimal artery: classical lacrimal arteries coming from the ophthalmic artery and meningolacrimal arteries coming from the external carotid system (Fig. 5.6).

When it originates in the ophthalmic artery, the lacrimal artery is a voluminous arterial trunk measuring 0.3–1.8 mm in diameter (average 0.99 mm) [37]. Out of 100 orbits, we found 83 lacrimal arteries arising in the ophthalmic artery [17]; Lang and Kageyama found the same origin in 82.5% of their cases [37]. Usually, the lacrimal artery starts from the optic segment at the crossing between the ophthalmic artery and the optic nerve (more rarely from the latero-optic part).

From its origin, above and outside the optic nerve, the lacrimal artery goes forward and laterally and leaves the cone to reach the lateral wall of the orbit; sometimes (in 54% of orbits) an anastomosis arises from the middle meningeal artery where the sphenoidal artery joins the lacrimal artery. On the lateral wall of the orbit, the artery goes along the superolateral margin, over the superior edge of the lateral rectus to the lacrimal gland. The lacrimal nerve, which penetrates the orbit more laterally, crosses over the artery to join it. During its course the artery supplies muscular branches for the lateral rectus muscle (80%), the superior rectus (69%), and the levator muscle of the upper eyelid (41%). The artery and the nerve arrive at the posterior part of the gland where they supply numerous branches, and after the gland, they supply arterial branches for the skin of the temporal area and the two lateral palpebral arteries, superior and inferior, and one or two zygomatic branches, which go through the zygomatic bone [24].

The meningolacrimal arteries arise from the external carotid system: nearly always from the middle meningeal artery, occasionally from the deep anterior temporal artery. We found 27 meningolacrimal arteries in 100 orbits. They penetrate the orbit through an isolated bony aperture, Hyrtl's canal, and so are more anterior and lateral than the classical arteries. These arteries are found more frequently when the ophthalmic artery crosses under the optic nerve. Their diameter is smaller, ranging from 0.3 to 1.5 mm with an average of 0.73 mm. They supply fewer muscular branches for the lateral rectus (in 4 out of 27 orbits), the superior rectus (2 out of 27), and the levator (8 out of 27). They are outside the lacrimal nerve from their origin to the lacrimal gland and do not usually cross it.

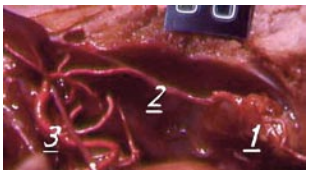


Fig. 5.6 Classical lacrimal artery: *1* lacrimal gland, *2* lacrimal artery and lacrimal nerve, *3* ophthalmic artery

We can divide the vascularization of the lacrimal gland into three types: type 1 with only one classical lacrimal artery, from the ophthalmic artery (73%); type 2 with only one lacrimal artery, but with a meningolacrimal artery (17%); and type 3 with two lacrimal arteries, one classical and one meningolacrimal (17%). In those cases, the gland is the location of an intraorbital anastomosis between the two carotid systems.

Supraorbital Artery

Absent in 12% of the orbits, it originates most frequently in the ophthalmic artery on its medio-optic part, more rarely from the posterior ethmoidal artery or the lacrimal artery. Its diameter ranges from 0.2 to 1.2 mm with an average of 0.57 mm [25]. Lang and Kageyama [37] report an average of 0.71 mm for men and 0.55 for women. Starting in the cone, the artery goes up and forward, out of the cone, passing between the superior oblique muscle and the levator of the upper eyelid, and then runs along the superior face of the levator under the orbital roof. It runs along the medial edge of the frontal nerve and reaches the supraorbital foramen with the supraorbital branch of the frontal nerve. It supplies branches for the skin of the forehead, and

muscular branches for the levator muscle (80%), the superior oblique muscle (30%), and more rarely for the superior rectus muscle.

Ethmoidal Arteries

The ethmoidal arteries have a very short intraorbital course and reach the nose where they provide an important part of the blood supply.

Posterior Ethmoidal Artery

Absent in 23% of orbits [19] it is a small artery with an average diameter of 0.4 mm. It originates most frequently in the ophthalmic artery in its medio-optic part (75%), sometimes in the supraorbital artery (17%), or in the anterior ethmoidal artery (7%). Located at its origin in the cone, it goes up and medially to come out of this cone, passing between the superior oblique muscle and the levator muscle of the upper eyelid and then reaches the posterior ethmoidal foramen, usually crossing over the superior oblique muscle (94%). When it crosses the muscle, it crosses the trochlear nerve too, usually above it. In the posterior ethmoidal foramen, we find with the artery the posterior ethmoidal nerve (sphenoethmoidal nerve of Luschka), a variable branch of the nasociliary nerve. The artery leaves the orbit to reach the dura mater and the posterior part of the nasal fossa.

In the orbit, it supplies collateral branches for the superior oblique muscle (59%), the levator muscle (37%), and more rarely for the superior and medial rectus muscles.

Anterior Ethmoidal Artery

More invariable and more voluminous than the posterior artery, the anterior ethmoidal artery is also fixed (Fig. 5.7). According to Hayreh, it was absent [23] in 9% of cases of over-crossing ophthalmic artery/optic nerve, and 20% in cases of under-crossing. In our experience it was absent in only 2% of orbits [19]. Its diameter ranges from 0.2 to 1.5 mm, with an average of 0.76 mm.

It always begins in the medio-optic part of the ophthalmic artery, in the anterior part of the orbit, and it is possible to distinguish two types of anterior ethmoidal arteries, according to the course of the ophthalmic artery. When the ophthalmic artery goes out of the fasciomuscular cone, the anterior ethmoidal artery always starts outside the cone, directly in the anterior ethmoidal foramen and has practically no intraorbital course (76%). When the ophthalmic artery stays in the cone, the anterior ethmoidal artery originates in the cone and reaches the anterior ethmoidal foramen by a short course, passing under the superior oblique muscle.

With the anterior ethmoidal artery, we always find the anterior ethmoidal nerve, the terminal branch of the nasociliary nerve. Both go through the anterior ethmoidal foramen and reach the upper part of the ethmoid. The artery supplies the anterior part of the nasal fossa with two terminal branches, a medial branch for the nasal septum and a lateral branch for the lateral wall of the nasal cavity. The anterior ethmoidal artery supplies the anterior meningeal artery.

In the orbit, the anterior ethmoidal artery rarely supplies the muscular branches, but rather the superior oblique muscle (in 49% of orbits), or less often, the medial or superior rectus, or the levator muscles.

Muscular Arteries

The muscular arteries are very numerous: there are muscular trunks that often supply several muscles and smaller branches arising from the ophthalmic artery or another branch that supply only one muscle.

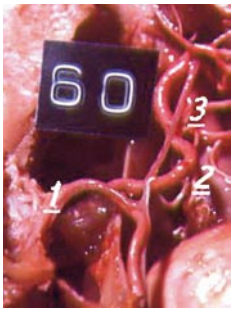


Fig. 5.7 Anterior ethmoidal artery: *1* anterior ethmoidal artery, *2* ophthalmic artery, *3* nasociliary nerve

Muscular Trunks or Arteries

One artery is invariable, the inferior muscular artery, whereas the others are vary, i.e., the lateral, superior and medial muscular arteries.

The inferior muscular artery is a constant and fixed artery. With the lacrimal artery, it is one of the two more voluminous branches of the ophthalmic artery. Its diameter ranges from 0.8 to 1.2 mm. It originates from the inferior part of the ophthalmic artery in its medio-optic part just after the crossing with the optic nerve. It dips toward the orbital floor, often crossing the medial side of the optic nerve, and rapidly supplies two or three terminal trunks: medial, lateral, and sometimes posterior. Each trunk supplies between 6 and 25 collateral branches for the muscles. There are always branches for the medial rectus (for its lateral side and its inferior edge), branches for the lateral rectus (to its inferior edge), branches to the inferior rectus and forward to the inferior oblique muscle when the inferior muscular artery terminates at the posterior edge of this muscle. With the artery the inferior branch of the oculomotor nerve reaches the oblique inferior muscle. More rarely, the muscular inferior artery supplies branches to the superior rectus and rarely to the levator muscle of the upper eyelid.

The superior muscular artery is rarely found (9%) [13]. When it exists, it is a small and short branch that supplies the superior rectus, the superior oblique, and the levator muscle of the upper eyelid. A medial muscular artery is seldom found (3%). More frequently we can find a lateral muscular artery (in 23% of orbits). Most often, we find it when the ophthalmic artery crosses under the optic nerve and when the lacrimal gland is supplied by a meningolacrimal artery. In fact, this lateral muscular artery is a lacrimal artery that does not reach the gland. It supplies the lateral rectus and sometimes the superior rectus muscles.

Small Muscular Branches

Very numerous, these short arteries directly reach one muscle from the ophthalmic artery or one of its branches. They are more frequent for the medial rectus, the oblique superior rectus, and sometimes for the lateral rectus muscles.

Muscular Vascularization

Each muscle receives several arteries, which nearly always reach it by its ocular side and often behind.

Superior Rectus Muscle

The superior rectus muscle receives muscular branches from the ophthalmic artery, the lacrimal artery, and less frequently from the supraorbital, posterior ethmoidal, superior muscular, or lateral muscular arteries. These pedicles, between one and five for each muscle, were also found by Cordier et al. [8]. The arteries usually penetrate the muscle on its inferior side, in its posterior third (70%). Frequently, these arteries leave the ophthalmic artery or the lacrimal artery when they cross over the optic nerve, just under the superior rectus.

Medial Rectus Muscle

The medial rectus muscle receives branches from the ophthalmic artery (85%) for its lateral side and its superior edge, at their medial and posterior thirds. In a constant manner, it also receives by its inferior edge at its posterior third a branch supplied by the inferior muscular artery. Rarely, it receives branches from the anterior ethmoidal or posterior ethmoidal arteries, superior muscular or medial muscular, and sometimes from the supraorbital arteries. There are usually five to nine branches.

Inferior Rectus Muscle

Four to six branches of the inferior muscular artery penetrate the superior side of the inferior rectus muscle, at its posterior third, and its medial edge at its medial third. There are usually four pedicles for each muscle.

Lateral Rectus Muscle

In 83% of cases, the lacrimal artery or the lateral muscular artery provide the blood supply

of the lateral rectus muscle; the branches reach the muscle via its medial side and its superior edge at the medial and posterior thirds [8]. In 70% of cases, the inferior muscular artery supplies one or more branches to the inferior edge of the muscle. In summary, it receives three to six branches.

Superior Oblique Muscle

The superior oblique muscle receives 2–4 branches from the posterior ethmoidal artery (63%), the anterior ethmoidal artery (46%), or the ophthalmic artery (61%) [18], generally via its superior edge or its lateral side.

Inferior Oblique Muscle

The inferior oblique muscle usually receives two main branches. The inferior muscular artery terminates in the lateral third of the posterior edge in 98% of orbits, described by Henry [30] as the "Artery of the petit oblique"; it forms with the terminal part of the inferior branch of the third cranial nerve an invariable neurovascular pedicle. The infraorbital artery supplies a branch at the bony insertion of the muscle in 88% of orbits; the infraorbital artery is a branch of the external carotid system. We found the two arteries together in 86% of orbits, a single branch of the inferior muscular artery in 12%, and a single branch of the infraorbital artery in 2%.

Cordier et al. [8] has demonstrated that these muscular branches penetrate the muscles from behind and go ahead to supply the anterior ciliary arteries at the anterior part of the rectus muscle (one to two per muscle). These anterior ciliary arteries perforate the sclera in front of the muscular rectus insertions and participate in the structure of the great arterial circle of the iris.

The knowledge of this arterial disposition is important during orbital surgery; we can remember that the muscular branches are nearly all situated on the intraconal side of the muscles, principally at their posterior part.

Levator Muscle of the Upper Eyelid

The levator muscle of the upper eyelid receives branches from the ophthalmic and supra orbital arteries, and more rarely from the lacrimal, posterior ethmoidal, or superior muscular arteries.

Palpebral Arteries

The last collateral branches of the ophthalmic artery are two palpebral arteries, a superior one and an inferior one. They can be separated at their origin or have a common trunk. The diameter is small 0.1 to 0.5 mm. The inferior palpebral artery is often larger than the superior one. The short superior palpebral artery, perforates the orbital septum and supplies two branches, which participate in the superior palpebral arcades.

The inferior palpebral artery crosses behind the medial canthal tendon and supplies two branches going into the inferior eyelid that participate in the inferior palpebral arcades. These arcades are formed by the anastomosis between the palpebral arteries of the ophthalmic artery and the palpebral branches of the lacrimal artery.

5.4.6.2 Infraorbital Artery

A branch of the maxillary artery, itself a terminal branch of the external carotid artery, the infraorbital artery originates in the pterygopalatine fossa and penetrates into the orbit via the inferior orbital fissure. With the infraorbital nerve it goes into the infraorbital canal to the infraorbital foramen [9]. It supplies branches on the orbital floor that supply the superior aperture of the nasolacrimal duct and very often (in 88% of orbits) a branch for the inferior oblique muscle.

5.4.6.3 Anastomosis Between the Two Carotid Systems

The ophthalmic artery is a branch of the internal carotid system. The infraorbital artery and the meningolacrimal artery are branches of the external carotid system, so it is possible for anas-

tomosis to exist between the two carotid systems in the orbit [15]:

5.4.6.3.1 Intraorbital Anastomosis

We found intraorbital anastomosis at the inferior oblique muscle in 86% of orbits and in the main lacrimal gland: in 10% of orbits there are two lacrimal arteries arising from the two carotid systems.

5.4.6.3.2 Extraorbital Anastomosis

Extraorbital anastomosis is more frequent. In the nasal cavities and in the cranial dura mater via the ethmoidal arteries, which anastomose with branches of the sphenopalatine artery, a branch of the maxillary artery, and in the periorbital area with frequent anastomosis between the angular artery and the terminal branch of the facial artery [4]. In the eyelids, anastomosis exists between the palpebral arcades and the facial arteries.

5.4.7 Orbital Veins

The venous drainage of the orbit is carried out by three veins: the superior ophthalmic vein, and two small and variable veins: the medial and the inferior ophthalmic veins. These three veins take the blood toward the cavernous sinus. The special organization of the veins is different from that of the arteries [3]. Veins are mainly dependent on the septum and fascias, which really form a "hammock" for the superior ophthalmic vein.

The venous orbital blood comes from the different structures of the orbit. The drainage of the eyeball is carried out by the central retinal vein and by the four vortex veins. The orbital muscles and the lacrimal gland have their own veins that join one of the three ophthalmic veins.

5.4.7.1 Superior Ophthalmic Vein

The superior ophthalmic vein is the main vein of the orbit and is invariable; its maximal diameter is estimated to be 6.2 mm [40]. Its origin is in the superomedial angle of the orbit and then the vein goes laterally and backward to reach the superior orbital fissure.

Its origin, located under the trochlea of the superior oblique muscle, is made by two roots that join 5–6 mm behind the trochlea. Its course has three parts: extraconal at the anterosuperomedial part of the orbit, between the medial rectus and the levator muscle of the upper eyelid; a second part that is intraconal under the superior rectus muscle, above the optic nerve and the ophthalmic artery; and a third part is again extraconal and reaches the orbital superior fissure.

5.4.7.1.1 Collateral Branches of the Superior Ophthalmic Vein

The superior root receives the veins from the levator muscle of the upper eyelid and the oblique superior muscle, and the inferior root receives the medial palpebral vein, the anterior ethmoidal vein, and the lacrimal sac vein; when the trunk is constructed, it receives the veins of the different muscles and the voluminous lacrimal vein and the episcleral veins.

5.4.7.2 Inferior Ophthalmic Vein

Located at the inferior part of the orbit, the inferior ophthalmic vein is also variable; it usually consists of veins from the superior oblique muscle, inferior and lateral rectus muscles, and joins or does not join the superior ophthalmic vein to reach the cavernous sinus.

5.4.7.3 Medial Ophthalmic Vein

A medial ophthalmic vein is present in 40% of normal individuals [21], even though a middle ophthalmic vein described by Henry [30], which is variable, usually arises from the medial, inferior, and lateral rectus muscles. It is intraconal above the optic nerve and reaches the superior orbital fissure and joins or does not join the superior ophthalmic vein before terminating in the cavernous sinus.

5.4.7.4 Organization of Orbital Venous Drainage

The three ophthalmic veins take the blood toward the cavernous sinus; periorbital drainage toward the facial system is also present via the angular vein, which receives the orbitolacrimofacial vein. The angular vein joins the facial vein and the orbit is thus located in the organization of the veins as well as in the organization of the arteries at the junction between the endocranial drainage by the cavernous sinus and the facial drainage.

5.4.8 Orbital Lymphatics

The lymphatic vascularization of the eyelid, conjunctiva, and lacrimal system is well known, with a lateral path for the upper eyelid and the lateral part of the inferior eyelid that reaches the parotid knots, a medial way for the medial part of the inferior eyelid, and the medial canthal area to the submandibular knots.

The presence of lymphatic vessels in the orbit has been discussed; classically, there have been no reports [12], but recent studies [47] have found in the monkey lymphatic structures in the lacrimal gland, at the orbital apex, and in orbital muscles.

5.4.9 Orbital Nerves

In the orbit we can find motor nerves for the oculomotor muscles and sensory nerves, branches of the trigeminal nerve.

Three cranial nerves give motor innervation to the seven orbital muscles The oculomotor nerve, or third cranial nerve, innervates five muscles, the superior, medial, and inferior rectus muscles, the oblique inferior, and the levator muscle of the upper eyelid; moreover it contains parasympathetic fibers that innervate the ciliary muscle and the sphincter of the iris. The trochlear nerve or fourth cranial nerve innervates the superior oblique muscle and the abducens nerve or sixth cranial nerve innervates the lateral rectus muscle. Only one nerve, the trigeminal nerve, or fifth cranial nerve, provides sensory innervation.

As with each cranial nerve, the orbital nerves have a real origin (nucleus), a visible origin, and a course before they penetrate the orbit.

The oculomotor nerve has its nucleus in the mesencephalon in front of the superior colliculus, its visible origin at the anterior face of the mesencephalon near the posterior perforated space, and it perforates the roof of the cavernous sinus and goes forward into its lateral wall and divides before penetrating the orbit in two branches, superior and inferior.

The trochlear nerve also has its nucleus in the mesencephalon near the inferior colliculus, its visible origin in the posterior part of the mesencephalon (it is one characteristic of the trochlear nerve), and it runs around the mesencephalon, reaches the cavernous sinus, where it goes in the lateral wall, crossing the two branches of the oculomotor nerve.

The abducens nerve has its nucleus in the pons in front of the fourth ventricle, its visible origin at the anterior side of the pons, and it penetrates the cavernous sinus and there it crosses the lateral side of the internal carotid artery.

The trigeminal nerve divides into three terminal branches at the trigeminal ganglion, i.e., the mandibular, maxillary, and ophthalmic nerves. The ophthalmic nerve is the sensory branch for the orbit, which reaches the lateral wall of the cavernous sinus and divides into its three terminal branches: the frontal, lacrimal, and nasociliary nerves.

All these nerves penetrate the orbit via the superior orbital fissure and at the anterior part of the lateral wall of the cavernous sinus we find from the top to the bottom the lacrimal, frontal, trochlear, superior branch of the oculomotor, and the nasociliary and inferior branche of the oculomotor nerve. The abducens nerve leads into the cavernous sinus. In the orbit, some nerves reach the intraconal space, the two branches of the oculomotor nerve, the abducens, and the nasociliary nerves, and some are extraconical, the lacrimal, frontal, and trochlear nerves.

5.4.9.1 Intraorbital Oculomotor Nerves

5.4.9.1.1 Superior Branch of the Oculomotor Nerve

Very small, the superior branch of the oculomotor nerve reaches the superior rectus and supplies a branch to the levator muscle of the upper eyelid.

5.4.9.1.2 Inferior Branch of the Oculomotor Nerve

Longer and larger, the inferior branch of the oculomotor nerve rapidly supplies one branch for the medial rectus after one branch to the inferior rectus, and with the terminal part of the inferior muscular artery it reaches the posterior edge of the inferior oblique muscle where it terminates [44]. Before ending, this inferior branch supplies the motor root of the ciliary ganglion (short root), which contains the preganglionic, parasympathetic fibers from the third cranial nerve.

5.4.9.1.3 Trochlear Nerve

The trochlear nerve crosses the levator muscle of the upper eyelid and terminates in the superior oblique muscle at its posterior third of its superior edge; it measures 25.1 mm in length and penetrates the muscle at 17.25 mm of its posterior insertion [52]. Usually, it also crosses the posterior ethmoidal artery.

5.4.9.1.4 Abducens Nerve

Very short, the abducens nerve terminates right away in the posterior third of the medial face of the lateral rectus.

5.4.9.2 Intraorbital Branches of the Trigeminal Nerve

5.4.9.2.1 Frontal Nerve

The frontal nerve is a voluminous, flat nerve that runs along the superior part of the levator muscle of the upper eyelid under the orbital roof (Fig. 5.8). It joins the supraorbital artery and about 5 mm behind the superior orbital margin, it divides into two branches, the supraorbital nerve, which reaches the supraorbital foramen, and the supratrochlear nerve, which reaches the supratrochlear foramen medially. In 10% of cases, the frontal nerve does not divide [51].

These two branches supply the sensory innervation of the forehead, the frontal sinus, the medial two-thirds of the conjunctiva, and the upper eyelid.

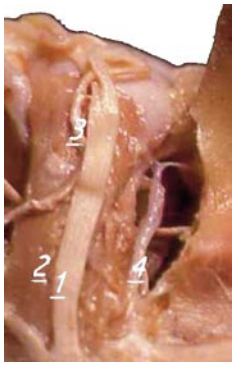


Fig. 5.8 Superior view of the orbit: *1* frontal nerve, *2* levator muscle of the upper eyelid, *3* supraorbital artery, *4* lacrimal vein

5.4.9.2.2 Lacrimal Nerve

The lacrimal nerve is the thinnest nerve of the orbit (Fig. 5.9). Extraconical (0.5–0.8 mm) [17], it runs along the superolateral margin of the or-

Fig. 5.9 Lacrimal handle: *1* lacrimal nerve, *2* zygomatic branch

bit over the superior edge of the lateral rectus. It joins the lacrimal artery and with it, reaches the lacrimal gland. It may divide into two branches before the gland in 59.5% of the cases [51]. After the gland, nervous branches reach the lateral third of the upper eyelid and conjunctiva and the temporal skin. The secretory innervation is supplied by parasympathetic fibers arising from the superior salivary nucleus in the pons. These preganglionic fibers accompany the facial nerve to reach the pterygopalatine ganglion. The postganglionic fibers leave the facial nerve and reach the maxillary nerve, then the zygomatic nerve, which perforates the lateral wall of the orbit and reaches the lacrimal gland. This zygomatic branch is constant; in 15% of the cases, there are two of them. It reaches the inferior part of the gland in 92.5%. Classically, this branch anastomoses with the lacrimal nerve before the gland; this anastomosis is called the lacrimal handle and is rarely found. Lacrimal innervation can be divided into three types [17], a type 1 with a lacrimal handle before the gland, joining the zygomatic branch and the lacrimal nerve (7.5%), a type 2 where the two nerves reach the gland separately with an anastomosis macroscopically visible in the gland (in 37.5%), and a type 3 without anastomosis into the gland (55%). According to Trauzettel and Jo [51] secretory fibers reach the gland without joining the lacrimal nerve in 80.7% of cases. Ruskell reports the same observations in the monkey [43].

In the gland, there are also sympathetic fibers that probably arise in the sympathetic plexus along the lacrimal artery.

Summary for the Clinician

- The excretory nerve for the lacrimal gland is not the lacrimal nerve, but the zygomatic nerve, which reaches the gland through the lateral wall of the orbit, arising from the pterygopalatine ganglion.
- In order to stop lacrimal secretion, it is necessary to cut this nerve, as is performed during Whitwell surgery.

5.4.9.2.3 Nasociliary Nerve

A single intraconal branch of the ophthalmic nerve, the nasociliary nerve runs forward and medially, crossing over the optic nerve and usually the ophthalmic artery. More anteriorly, it crosses the ophthalmic artery several times in its medio-optic part. At the anterior third of the orbit, it supplies its two terminal branches, the anterior ethmoidal nerve, which crosses under the oblique superior muscle, joins the anterior ethmoidal artery, goes through the anterior ethmoidal foramen, and reaches the nasal cavity, and the infratrochlear nerve, which runs along the terminal part of the ophthalmic artery and goes out of the orbit with it and innervates the medial canthal area, particularly the lacrimal sac, the canaliculus, and the caruncle.

During its course, the nasociliary nerve supplies several branches: the posterior ethmoidal nerve (variably), which joins the posterior ethmoidal artery, the two long ciliary nerves, medial and lateral, which join the posterior ciliary trunks, and the sensory root (long) of the ciliary ganglion.

5.4.9.3 Ciliary Ganglion

The ciliary ganglion is located at the posterior part of the orbit, about 1 cm in front of the optic canal on the lateral side of the optic nerve. It is separated from the lateral rectus by orbital fat and measures 2.5 mm in length.

The ciliary ganglion receives three branches or roots [48], the motor root (short) arising from the inferior branch of the oculomotor nerve, containing parasympathetic fibers arising from the parasympathetic nucleus of cranial nerve III (the Edinger-Westphal nucleus). These fibers terminate in the ganglion and form a synapse with the postganglionic fibers. The sensory root (long) is a collateral branch of the nasociliary nerve; the sensory fibers go through the ganglion without stopping. The third root is the sympathetic root; it contains postganglionic sympathetic fibers, the preganglionic, arising from the medulla (C7 to T2). From the anterior part of the ganglion, 9–14 short ciliary nerves emerge, which join the

short ciliary arteries and the long ciliary arteries and nerves. These short ciliary nerves contain the innervation for the ciliary muscle, the sphincter muscle of the iris, the dilator muscle of the iris, and sensory fibers for the cornea.

5.4.10 Orbital Fat

The whole space located between the various structures described is filled with orbital fat. This fat consists of small lobes limited by a capsule; these lobes are separated by the different septum and orbital fascias. We can separate the central fat, intraconal fat around the optic nerve, and the peripheral extraconal fat between the rectus muscles and the orbital periosteum. It is particularly abundant in the inferior part of the orbit. In the anterior part it reaches the orbital septum and is organized behind the septum in fat pockets, three inferior (lateral, medial, and median with the passage of the inferior oblique muscle between the median and medial pockets) and two superior (median and medial). The septum is located between this orbital fat and the preseptal fat.

Summary for the Clinician

- In case of Grave's ophthalmopathy, to decrease the proptosis, it is possible to take out extraconal and intraconal orbital fat.
- It is in the inferior part of the extraconal space that we find the largest amount of the fat.

5.5 Anatomical Orbital Topography

The orbital surgeon needs to be familiar with the regular anatomy and variations in the orbital anatomy. We can divide the orbit into two main areas: the fasciomuscular cone and the extraconal area. The fasciomuscular cone is delimited by the four rectus muscles and their fascias, the intermuscular fascias, and the eyeball at the front. The top of the cone is at the orbital apex. The extraconal space can also be divided into four areas, one for each orbital wall: superior, lateral, inferior, and medial. Some anatomical structures are fixed, i.e., the eyeball, the optic nerve, the orbital muscles, the nerves, and the periosteum on the orbital walls. Others are more variable, i.e., the veins, the fat, and mainly the arteries. These variations are rarely symmetrical and do not have predominance according to gender or side.

5.5.1 Intraconal Space

The intraconal space contains:

- The optic nerve
- The ophthalmic artery, which in the posterior part of the orbit is on the lateral side of the nerve, then crosses over it and runs toward the medial wall. Crossing over is found in 77% of orbits and crossing under in 23%. The kind of crossing determines the arterial organization of the orbit, the absence of some arterial branches, variations in origin, course, and distribution of the arterial branches. One very common association is crossing under the optic nerve and the presence of a meningolacrimal artery and a lateral muscular artery. At the anterior part of the cone, the ophthalmic artery has two possibilities, either staying in the cone (24%) or going out of the cone, passing under the superior oblique muscle (76%)
- The intraconal branches of the ophthalmic artery consist mainly of the central retinal artery at the inferior side of the optic nerve and the long and short posterior ciliary arteries. The posterior ethmoidal and supraorbital arteries, which originate in the cone, leave it quickly; more rarely, the anterior ethmoidal artery arises in the cone (in cases when the ophthalmic artery stays in the intraconal part). The lacrimal artery also leaves the intraconal space quickly to reach the lateral orbital wall. Finally, the muscular inferior muscular artery supplies two or three trunks in the inferior part of the orbit. Most of the muscular arterial branches are in the intraconal space before penetrating the different muscles. Nearly all these muscular arteries are located in the posterior part of the orbit

- The nasociliary nerve runs through the cone, medially and forward; it crosses over the optic nerve and often the ophthalmic artery (58%). More anteriorly, it crosses this artery a second, sometimes a third time and supplies two terminal branches, the anterior ethmoidal nerve, which joins the anterior ethmoidal artery, and the infratrochlear nerve, which always stays in the cone. This nerve provides the cone with the posterior ethmoidal nerve, the long ciliary nerves, and the sensory root of the ciliary ganglion
- Other nerves in the cone are the short abducens nerve and the two branches of the oculomotor nerve, the superior short branch, which reaches the superior rectus, and the longer inferior branch, which joins the inferior muscular artery and supplies the motor root of the ciliary ganglion
- The superior ophthalmic vein is in the cone; it goes backward and laterally over the optic nerve, under the superior rectus

Thus, we find in the cone:

- Above the optic nerve, from bottom to top:
  - Ophthalmic artery
  - Nasociliary nerve
  - Superior ophthalmic vein
  - Superior branch of the oculomotor nerve
  - Variable superior muscular artery
  - Superior rectus
- Outside the optic nerve:
  - Ophthalmic artery behind
  - Ciliary ganglion
  - Lateral long and short ciliary arteries and nerves
  - Often the origin of the lacrimal artery
  - Abducens nerve behind
  - Lateral rectus
- Under the optic nerve:
  - Central retinal artery
  - Inferior muscular artery and its branches
  - Inferior branch of the oculomotor nerve
  - Inferior rectus
- Inside the optic nerve:
  - Origin of the posterior ethmoidal and supraorbital arteries behind
  - Medial long and short ciliary arteries and nerves
  - Origin of the inferior muscular artery
  - Nasociliary nerve
  - Medio-optic part of the ophthalmic artery
  - Medial rectus

Surrounding these anatomical structures, we find the intraconal fat.

5.5.2 Superior Extraconal Space

Between the superior rectus and the orbital roof there is a narrow space. It contains the levator muscle of the upper eyelid along with its superior face, the trochlear nerve behind, the frontal nerve with its two branches: the supraorbital and the supratrochlear nerves at the front. The supraorbital artery joins the frontal nerve, but it is absent in 12% of cases. The superior branch of the oculomotor nerve innervates the superior rectus and the levator.

5.5.3 Lateral Extraconal Space

Between the lateral wall and the lateral rectus, the lateral extraconal space contains in its anterosuperior part the lacrimal gland with its pedicle, the lacrimal artery, vein, and nerve. In some cases (27%) a meningolacrimal artery goes into the orbit via the Hyrtl's canal and sometimes there are two lacrimal arteries, one arising from the ophthalmic artery, the other from the middle meningeal artery. At the front, on the lateral wall of the orbit, we find the zygomatic branch for the inferior part of the gland, which exceptionally joins the lacrimal nerve before the gland. It is this branch we must cut to perform Whitwell surgery in the case of tearing due to an excess of tears.

In the inferior part of this lateral extraconal space, there is much fat.

5.5.4 Inferior Extraconal Space

Between the inferior rectus and the inferior wall, there is a wide area, crossed by the inferior oblique muscle and filled with an abundance of fat. On the orbital floor, the infraorbital artery usually supplies a branch for the inferior oblique

muscle. At the lateral third of the posterior edge of this muscle, the inferior muscular artery and the inferior branch of the oculomotor nerve terminate. In this area it is easier to perform retrobulbar anesthesia. Above the orbital floor, laterally, we find a wide area filled with fat, which we can remove to perform orbital decompression in cases of Grave's ophthalmopathy.

5.5.5 Medial Extraconal Space

Between the medial rectus and the superior oblique muscles and the medial wall of the orbit, this limited space contains many vascular and nervous structures. Behind is the posterior ethmoidal artery with the variable posterior ethmoidal nerve, which reaches the posterior ethmoidal foramen located 5–7 mm in front of the optic canal and 10–15 mm behind the anterior ethmoidal foramen. The artery is absent in 20% of the cases and when it is present it crosses the superior edge of the oblique muscle and the trochlear nerve.

More anteriorly, the ophthalmic artery, when it becomes extraconal, passing under the superior oblique muscle, comes into contact with the medial wall of the orbit, near the anterior ethmoidal foramen and supplies the anterior ethmoidal artery there. This artery is joined by the anterior ethmoidal nerve, the terminal branch of the nasociliary nerve, which is always outside the superior oblique muscle and crosses underneath it. The anterior ethmoidal foramen is located an average of 20 mm behind the orbital rim.

5.6 Conclusions

Orbital anatomy is quite complicated, with many components that cross each other at different levels. The frequent variations in such structures as arteries, veins, etc., demonstrate the difficulty in giving a simple and easy-to-learn view of this anatomy. However, it is possible to recognize some constant aspects and some of the frequent variations that are often associated, such as crossing under ophthalmic artery-optic nerve with a lateral muscular and a meningolacrimal artery. The recent developments in image-making now permit, and will permit more and more in the future, the depiction of the location of the orbital components and the possibility of surgical difficulties. All dissections were realised in Laboratoire d'Anatomie du CHR de Reims (Pr JF DELATTRE, JB FLAMENT).

References

1. Adachi B (1928) Das Arteriensystem der Japaner, vol 1. Verlag der Kaiserlich-Japanischen Universität, Kyoto, pp 103–111
2. Bérard PV, Quéré MA, Roth A, et al. (1984) Chirurgie des strabismes. Masson, Paris, pp 106–130
3. Bergen MP (1982) A spatial reconstruction of the orbital vascular pattern in relation with the connective tissue system. Acta Morphol Neerl Scand 20:117–137
4. Berthelot JL, Hureau J (1982) Clinical anatomical study of the macroscopic anastomoses of the ophthalmic artery in the periorbital region. Anat Clin 3:271–278
5. Bremond-Gignac DS, Deplus S, Cussenot O, et al. (1994) Anatomic study of the orbital septum. Surg Radiol Anat 16:121–124
6. Caliot P, Plessis JL, Poirier M, et al. (1995) The intraorbital arrangement of the anterior and posterior ethmoidal foramina. Surg Radiol Anat 17:29–33
7. Codère F, Tucker NA, Renaldi B (1995) The anatomy of Whitnall ligament. Ophthalmology 102:2016–2019
8. Cordier J, Rauber G, Raspiller A, et al. (1980) Vascularisation artérielle des muscles droits, interne et externe. J Fr Ophtalmol 3:731–736
9. Coulter VL, Holds JB, Anderson RL (1990) Avoiding complications of orbital surgery: the orbital branches of the infraorbital artery. Ophthalmic Surg 21:141–143
10. De Gottrau P, Gajisin S, Roth A (1993) L'insertion de la capsule de Tenon sur les muscles droits. J Fr Ophthalmol 16:436–441
11. Desantis M, Anderson KJ, King DW, et al. (1984) Variability in relationships of arteries and nerves in the human orbit. Anat Anz 157:227–231
12. Doxanas MT, Anderson RL (1984) Clinical orbital anatomy. Williams and Wilkins, Baltimore

13. Ducasse A, Segal A (1992) Le contenu orbitaire. Etude anatomique des différents compartiments et de leur contenu. Ophtalmologie 6:180–185
14. Ducasse A, Delattre JF, Segal A, et al. (1985) Anatomical basis of the surgical approach to the medial wall of the orbit. Anat Clin 7:15–21
15. Ducasse A, Segal A, Delattre JF, et al. (1985) La participation de l'artère carotide externe à la vascularisation orbitaire. J Fr Ophtalmol 8:333–339
16. Ducasse A, Segal A, Delattre JF (1986) Aspects macroscopiques des artères ciliaires longues postérieures. Bull Soc Ophtalmol Fr 86:845–848
17. Ducasse A, Segal A, El Ladki S, et al. (1990) Vascularisation artérielle et innervation de la glande lacrymale. A propos de 100 dissections. Ophtalmologie 4:129–133
18. Ducasse A, Flament JB, Segal A (1991) Etude anatomique de la vascularisation et de l'innervation des muscles obliques de l'œil. Ophtalmologie 5:5–8
19. Ducasse A, Segal A, Flament JB (1993) Les artères ethmoïdales. Situation, variations. Ophtalmologie 7:361–363
20. Ducournau D (1980) La systématisation vasculaire de la choroïde. J Fr Ophtalmol 3:5–16
21. Dutton JD (1994) Atlas of clinical and surgical orbital anatomy. Saunders, Philadelphia
22. Goldberg RA, Hannani K, Toga AW (1992) Microanatomy of the orbital apex. Computed tomography and microcryoplaning of soft and hard tissue. Ophthalmology 99:1447–1452
23. Hamard H, Saraux H, Bonnet M (1977) Ischémie aigue de la tête du nerf optique. Bull Soc Ophtalmol Fr Rapport Annuel
24. Hayreh SS (1962) The ophthalmic artery: branches. Br J Ophthalmol 46:212–247
25. Hayreh SS (1963) Arteries of the orbit in the human being. Br J Surg 50:938–953
26. Hayreh SS (1996) Blood supply of the optic nerve head. Ophthalmologica 210:285–295
27. Hayreh SS, Dass R (1962) The ophthalmic artery: origin and intracranial and intracanalicular course. Br J Ophthalmol 46:65–98
28. Hayrey SS, Dass R (1962) The ophthalmic artery: intraorbital course. Br J Ophthalmol 46:165–185
29. Helveston EM, Merriam WW, Ellis FD, et al. (1982) The trochlea. A study of the anatomy and physiology. Ophthalmology 89:124–133
30. Henry J (1959) Contribution à l'étude de l'anatomie des vaisseaux de l'orbite et de la loge caverneuse par injection de matières plastiques, du tendon de Zinn et de la capsule de Tenon. Thèse Med Paris 638
31. Jimenez-Castellanos J, Carmona A, Castellanos I, et al. (1995) Microsurgical anatomy of the human ophthalmic artery: a mesoscopic study of its origin, course and collateral branches. Surg Radiol Anat 17:139–143
32. Jo A, Rizen V, Niolic V, et al. (1989) The role of orbital wall morphological properties and their supporting structures in the etiology of blow-out fractures. Surg Radiol Anat 11:241–248
33. Kirchner JA, Yanagisawa E, Crelin ES (1961) Surgical anatomy of the ethmoidal arteries. A laboratory study of 150 orbits. Arch Otolaryngol 74:382–386
34. Koornneef L (1977) New insights in the human orbital connective tissue. Result of a new anatomical approach. Arch Ophthalmol 95:1269–1273
35. Koornneef L (1979) Orbital septa: anatomy and function. Ophthalmology 86:876–880
36. Kurihashi K, Yamashita A (1991) Anatomical consideration for dacryocystorhinostomy. Ophthalmologica 203:1–7
37. Lang J, Kageyama I (1990) The ophthalmic artery and its branches; measurements and clinical importance. Surg Radiol Anat 12:83–90
38. Maes-Castellarin S, Adenis JP, Robert PY (1995) Relationship between Whitnall's ligament and the position of the superior eyelid. Anatomical study in man. Orbit 14:43–51
39. Meyer DR, Linberg JV, Wobig JL, et al. (1991) Anatomy of the orbital septum and associated eyelid connective tissues. Implications for ptosis surgery. Ophthalmic Plast Reconstr Surg 7:104–113
40. Murakami K, Murakami G, Komatsu A, et al. (1991) Gross anatomical study of veins in the orbit. Acta Soc Ophthalmol Jpn 95:31–38
41. Padget DH (1948) The development of the cranial arteries in the human embryo. Carnegie Institution of Washington Contrib Embryol 32:205–261
42. Porter JD, Baker RS, Ragusa RJ, et al. (1995) Extraocular muscles: basic and clinical aspects of structure and function. Surv Ophthalmol 39:451–484
43. Ruskell GL (1971) The distribution of autonomic postganglionic nerve fibres to the lacrimal gland in monkeys. J Anat 109:229–242

44. Sacks JG (1983) Peripheral innervation of extraocular muscles. Am J Ophthalmol 95:520–527
45. Sacks JG (1985) The levator trochlear muscle. A supernumerary orbital structure. Arch Ophthalmol 103:540–541
46. Sharma PK, Malhotra VK, Tenari SP (1988) Variations in the shape of the superior orbital fissure. Anat Anz 165:55–56
47. Sherman DD, Gonnering RS, Wallon IH, et al. (1993) Identification of orbital lymphatics: enzyme histochemical light microscopic and electron microscopic studies. Ophthalmic Plast Reconstr Surg 9:153–169
48. Sinnreich Z, Nathan H (1981) The ciliary ganglion in man (anatomical observations) Anat Anz 150:287–297
49. Sudakevitch T (1947) The variations in system of trunks of the posterior ciliary arteries. Br J Ophthalmol 31:738–760
50. Taguchi K (1898) Über das Foramen Clinoideoophthalmicum mit Berücksichtigung der Arteria Ophthalmica beim Menschen. Tokyo Igakkwai Zasshi 12:33–55
51. Trauzettel H, Jo A (1971) Die Topographie der Nerven in der Orbita. Verh Anat Ges 66:633–645
52. Villain M, Segnarbieux F, Bonnel F, et al. (1993) The trochlear nerve: anatomy by microdissection. Surg Radiol Anat 15:169–173
53. Webster RC, Gaunt JM, Hamdan US, et al. (1986) Supraorbital and supratrochlear notches and foramina: anatomical variations and surgical relevance. Laryngoscope 96:311–315
54. Zuckerkandle E, Meyer F (1887) Zur Anatomie der Orbitalarterien. Morph Jahrb 12:414–458

Chapter 6

Periocular Capillary Hemangioma: New Concepts in Natural History and Response to Glucocorticoids

6

David H. Verity, Geoffrey E. Rose

Core Messages

- Capillary hemangioma is the commonest orbital vascular anomaly in childhood.
- The etiology remains unknown, although studies identifying placenta-associated vascular antigens in hemangiomas implicate placenta-to-embryo embolization or aberrant placental differentiation within the embryo.
- Amblyopia, due to astigmatism, visual deprivation, or ocular imbalance, may occur in up to half of all children despite intervention.
- The period of greatest risk is during the first 2 years of life, when the lesion typically enlarges, leading to a disproportionate volume effect within the orbit.
- Characteristic features on Doppler ultrasonography, which differentiates capillary hemangioma from rhabdomyosarcoma, include acoustic heterogeneity (multiple internal acoustic reflections), high spatial vessel density, and high internal blood velocity – sometimes as high as 100 cm/s.
- The decay profile of capillary hemangioma is characterized by early proliferation, followed by cycles of decay and proliferation.
- Erratic decay profiles of both volume and maximum internal velocity in many children indicate a complex interplay between factors influencing both proliferation and involution.
- Intralesional steroid treatment is followed by an attenuation of the cyclical decay profiles compared with lesions among untreated children.
- Among treated patients, delayed proliferative cycles persist after steroid therapy, with a "rebound" rise in volume and velocity occurring approximately 5–20 months after treatment.
- Regression is incomplete in many cases, final decay leading to a fibro-fatty residuum.
- These periodic fluctuations in hemangioma volume and internal velocity should be anticipated, with intervention reserved for the minority of patients either with evidence of amblyopia, or where the size or position of the lesion is considered to pose a significant risk to visual development.

6.1 Introduction

Capillary hemangioma is the commonest childhood orbital vascular anomaly, usually presents as a painless swelling or vascular marking of the eyelids, and typically enlarges in infancy before undergoing spontaneous regression during childhood [8, 24]. Most periorbital hemangiomas pose no threat to visual development, but larger lesions may result in amblyopia due to mechanical ptosis, induced astigmatism, or displacement of the globe (Figs. 6.1, 6.2).

6.1.1 Etiology

The origin – and the mechanisms controlling growth and regression – of capillary hemangiomas is uncertain, although several theories exist (Table 6.1). Circumstantial evidence suggests that they might be of placental origin and that cellular growth and atrophy, or possibly apoptosis, may be controlled by maternal vascular growth factors that have crossed the placenta [4, 7, 11, 33]. The early growth of clinically manifest lesions may reflect a withdrawal of maternal inhibitory factors that were able to cross the placenta before birth and it is probable that locally-derived growth factors affect the lesion's growth and regression in the first few years of life.

6.1.2 Investigation

Whilst capillary hemangiomas have characteristic features on CT or MRI, Doppler ultrasonography provides an ideal investigation for these lesions, giving a readily available and repeatable estimate of tumor volume and also providing characteristics of internal vascularity [30, 40]. Three main characteristics are demonstrable on ultrasound examination:

- Acoustic heterogeneity within the lesion
- High spatial density of vessels throughout the tumor (typically more than 5/cm^2)
- High velocity of blood flow (as high as 100 cm/s) [42]

The large number of high-flow vessels differentiates capillary hemangiomas from the other rapidly-growing childhood lesion, namely, rhabdomyosarcoma.

Several ultrasonographic methods are of value in examining capillary hemangiomas [42], and include estimates of tumor size, blood velocity and flow direction that can be elicited by B-Mode imaging, color flow mapping, and spectral Doppler techniques.

B-Mode imaging will confirm the presence of an orbital hemangioma. The lesion is assumed to be ovoid in shape and the volume calculated as previously described, employing the radius in each of the three orthogonal axes ("x," "y," and "z" axes) [37].

Color flow mapping converts echo displacements into velocity measurements, thus allowing blood flow to be imaged in color and the resultant image superimposed on a B-Mode image; by convention, flow toward the probe is coded in red, and blue is used for flow away from the ultrasound probe. Using similar principles to color flow mapping, Color Doppler

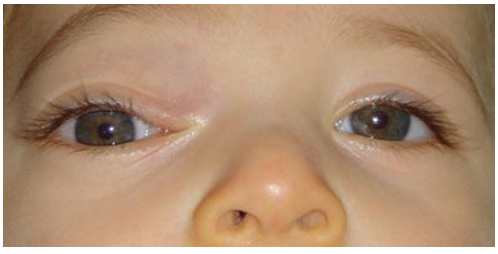


Fig. 6.1 Capillary hemangioma in the superotemporal quadrant of the orbit causing displacement of the globe

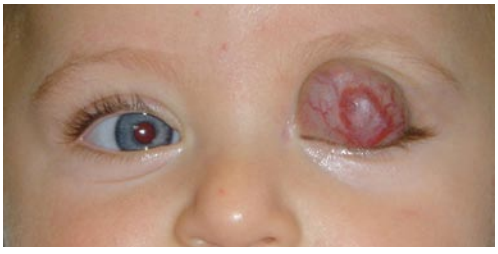


Fig. 6.2 Mechanical ptosis secondary to capillary hemangioma in the upper eyelid resulting in deprivation amblyopia

Table 6.1. Proposed etiology for capillary hemangioma (adapted from Bauland et al. [3], and others)

Theory	Proposed pathophysiology
Placental origin	Shared expression of the erythrocyte-type glucose transporter molecule GLUT-1 (found only on the placental trophoblast, blood tissue barriers, and capillary endothelium of hemangiomata), and the expression of other placenta-associated vascular antigens (e.g., Lewis Y antigen) in hemangiomas, implicates either placenta-to-embryo embolization or aberrant placental differentiation within the embryo [4, 7, 11, 32, 33]
Angioblast theory	It has been proposed that hemangiomas develop from sequestrations of omnipotent angioblasts since surface markers present on both normal vascular endothelium *and* lymphatic vessels are also encountered on the endothelium of hemangiomas. This suggests that capillary hemangiomas are formed of immature vascular tissue [14]
Abnormal angiogenesis	Folkman has suggested that hemangiomas result from an imbalance between angiogenic and angiostatic influences, with altered expression in hemangiomas of VEGF, basic fibroblastic growth factor (bFGF), E-selectin and other angiogenic molecules including TIE2, angiopoietin 2 and insulin-like growth factor 2 [9, 21, 28, 38, 47]

Energy (CDE) renders color intensity as a function of blood flow. A red color scale is used, by convention, with color intensity being approximately proportional to the number of moving cells and the technique may be used to estimate the density of blood vessels in hemangiomas (Fig. 6.3a). Spectral Doppler examination results in a real-time graphical output, known as a "spectrogram" or "spectrograph," which presents the real-time velocity of blood flow at a particular point within a chosen vessel, flow toward the probe being displayed above the time axis, and vice-versa (Fig. 6.3b).

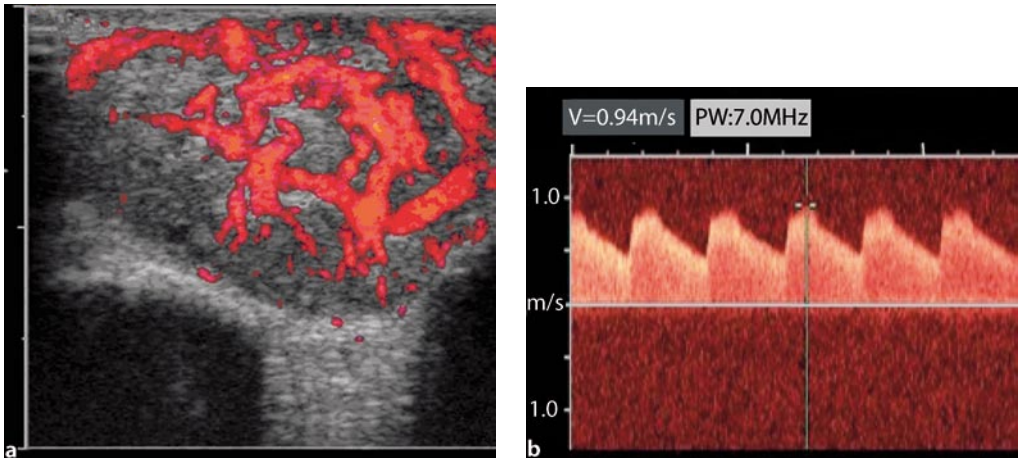


Fig. 6.3 Doppler ultrasonography methods to investigate capillary hemangioma. **a** Color Doppler echo image in the horizontal plane (velocity range +3 to –3 cm/s). Note multiple vessels identified in this range. **b** Spectrogram derived from color flow mapping, in this case employing high velocity gates, identifying a vessel with a systolic velocity of 94 cm/s

6.1.3 Management

The threat to visual development from periocular hemangiomas is greatest in the first year or two of life, this threat being due to induced astigmatism, visual deprivation due to ptosis, or ocular imbalance [35]. Even if objective measures of vision are unobtainable in an infant, medical or surgical intervention is indicated where a lesion is considered to pose a risk to visual development (Table 6.2). Despite prompt intervention, however, over half of affected children may become amblyopic [34]. Whilst glucocorticoids form the mainstay of treatment, other therapies include surgical excision, systemic interferon or intralesional laser ablation (Table 6.2) [6, 39].

Glucocorticoids have long been known to hasten the regression of superficial capillary hemangiomas [15, 36, 43, 46] and, with ultrasonographic guidance, have also been used for deeper lesions within the orbit [31]. A common regime for treating periocular hemangiomas combines intralesional and perilesional injections of steroids, typically 40 mg of depot methylprednisolone slowly injected into the center of the lesion and 4 mg of soluble dexamethasone around the lesion; if the hemangioma shows evidence of regression, the injections may be repeated another two or three times, at 6-weekly intervals. Despite the accepted value of steroid therapy, however, there is a small risk of both local [13, 17, 18, 41] and systemic complications [23].

Adverse side effects of intralesional steroid injections include:

- Eyelid necrosis [37]
- Subcutaneous fat atrophy [16]
- Central retinal artery spasm and occlusion (presumed secondary to retrograde flow of the drug, under high injection pressures, into the ophthalmic artery) [17, 18]
- Adrenal suppression [22]

Compared with other tissues, there is a high density of glucocorticoid receptor expression on cutaneous hemangiomas, and this is even greater in proliferating lesions [27], possibly accounting for their sensitivity to steroid therapy. Although the intracellular effects of glucocorticoid receptor activation are well understood [44], the mechanism by which the growth of capillary hemangiomas is suppressed – and the duration of this effect – remains uncertain. Candidate pathways include the production of α-fibroblast growth factor, vascular endothelial growth factor (VEGF), and proliferating cell nuclear antigen [2, 25, 29]. Recent in vitro work indicates that steroids reduce the transcription of three specific genes in capillaries, namely, the clusterin/apolioprotein (an apoptotic gene), mitochondrial cytochrome b, and interleukin 6 [25]. These effects are greatest in the case of triamcinolone and dexamethasone, and least with hydrocortisone.

Table 6.2. Treatment options for capillary hemangiomas

Intervention	Treatment modality
Glucocorticoids	Intralesional injections [34, 36]
	Topical (clobetasol propionate) [19]
	Sub-Tenon's injections [12]
	Systemic steroids (oral, pulsed parenteral) [15, 45]
Interferon α-2b	Daily subcutaneous injections (3 months) [20, 26]
Surgical resection	Early surgical resection in selected cases [1, 35, 38]
Intralesional laser	Nd:YAG, KTP or CO_2 [6]

Summary for the Clinician

- Capillary hemangioma:
  - Is the most common orbital vascular anomaly in childhood.
  - Typically enlarges before spontaneously regressing.
  - May be complicated by amblyopia in up to half of cases, this being caused by astigmatism, visual deprivation, or ocular imbalance, typically occurring within the first 2 years of life.
- Doppler ultrasonography identifies lesions with acoustic heterogeneity, high spatial density of vessels, and high internal blood velocity.
- The etiology remains unknown, although circumstantial evidence implicates either placenta-to-embryo embolization or aberrant placental differentiation within the embryo.
- Treatment options include glucocorticoids and/or surgical excision.

6.2 New Insights into the Natural History of Periorbital Capillary Hemangiomas

Pediatric capillary hemangiomas are characterized by an early growth period and a later involutional phase [24]. The proliferative phase is due to a rapid division of both immature vascular endothelium [14] (this division is thought to be influenced by an abnormal proliferation of mast cells [22]) and adjacent pericytes, which continue to proliferate in the postpartum period. Involution of the hemangioma leads to a fibro-fatty residuum, with recent evidence implicating a persistence of mesenchymal stem cells within the hemangioma, these later forming adipocytes [45].

Although the literature frequently describes periocular capillary hemangiomas as lesions that gradually regress following an initial period of growth, new evidence suggests that their proliferation, involution, and variations in internal blood velocity may be more complex than once thought.

6.2.1 How Long and How Significant is the Growth Phase of Capillary Hemangiomas?

Using more objective measures, the natural history for a large cohort of pediatric periorbital capillary hemangiomas has recently been reported for the first time [42]. A series of repeated ultrasonographic assessments (a median of seven assessments) was made in a group of infants in whom neither medical nor surgical intervention was required. Using Doppler ultrasonography (Sect. 6.1.2), the estimated volume and maximum internal blood velocity was followed in a cohort of 24 children, of whom exactly one half were boys. Although involvement of the upper and lower eyelids was the same, there was a left-sided predominance (17 out of 24 lesions).

The lesion became clinically apparent at the age of 2.1 months (range 0–14 months), and the average age at last visit (when the lesion had markedly regressed, so as to pose no threat to visual development) was 44.4 months (range 10–100 months). The maximum estimated size of the capillary hemangioma in this group varied between 0.92 ml and 8.98 ml (mean 4.12 ml) and was, therefore, larger than the developing globe in many cases.

Periocular capillary hemangiomas have been historically described as undergoing involution after an early period of growth, and this study confirmed that there is, indeed, an initial rise in volume in most children (20 out of 24). The phase of expansion would, however, appear longer than the traditionally accepted period of 12–18 months, with the age of *greatest* volume being as late as 60 months in one child and occurring at an average of 20 months. Over three-quarters of hemangiomas assessed within the first year of life had increased in size after the first measurement (Fig. 6.4a). On average, a doubling of volume in the first year of life occurred, with the greatest change observed being a four-fold increase. During the first 18 months after birth, the hemangiomas increased by up to nine times the initial volume (4–930%).

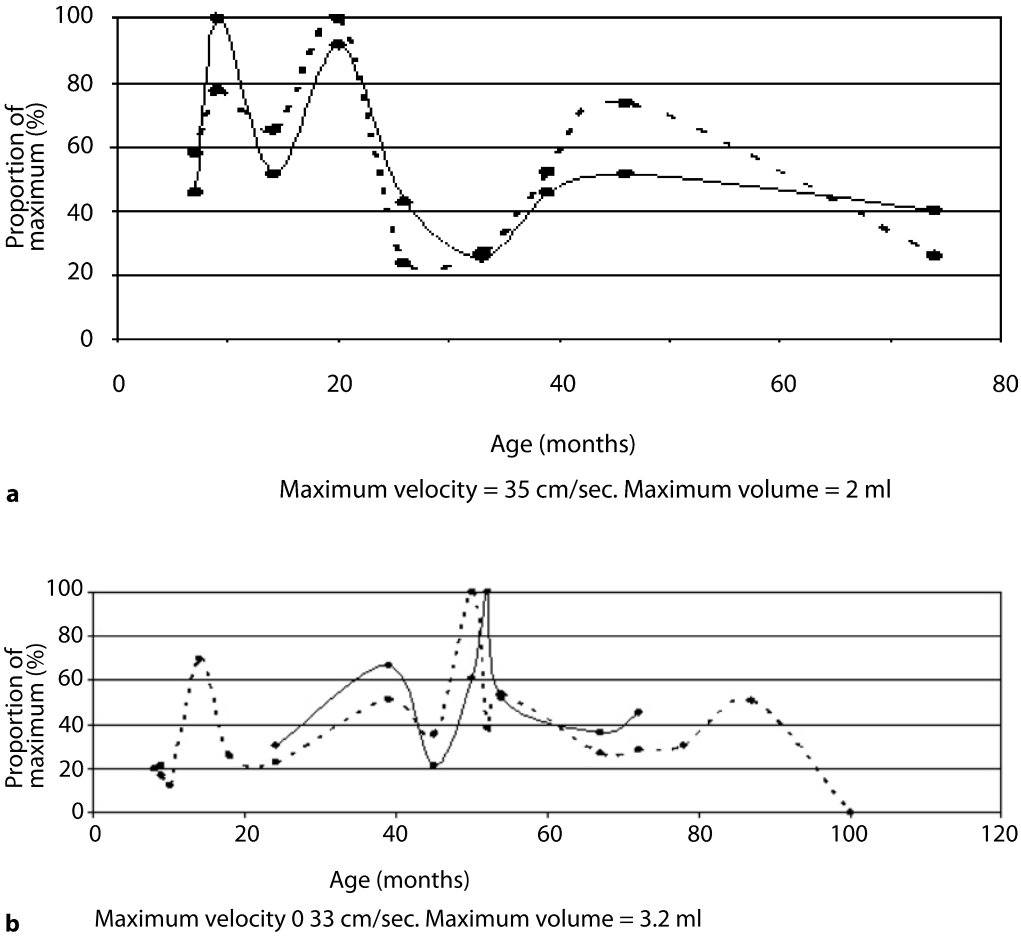
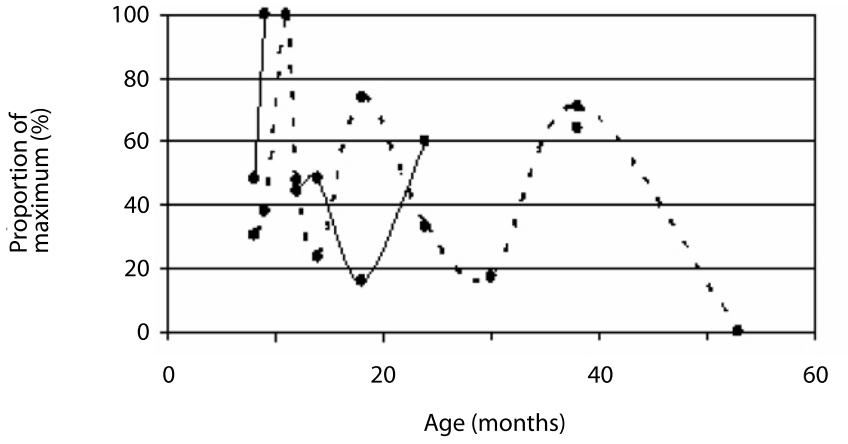


Fig. 6.4 Ultrasonographic studies of volume (B-mode scan) and internal blood velocity (color flow mapping, color Doppler energy, and spectral Doppler techniques). Profiles of velocity (*solid line*) and volume (*dotted line*) are given as a proportion (%) of the maximum value recorded for each child. **a** Cyclical rises occur in both volume and velocity profiles, there being a close correlation between the two parameters in many children. **b** Capillary hemangiomas do not decay exponentially. In certain patients, there may even be a late rise in volume: in this child, relatively late proliferative phases were detected at 50 and 85 months of age. **c** *(see next page)*

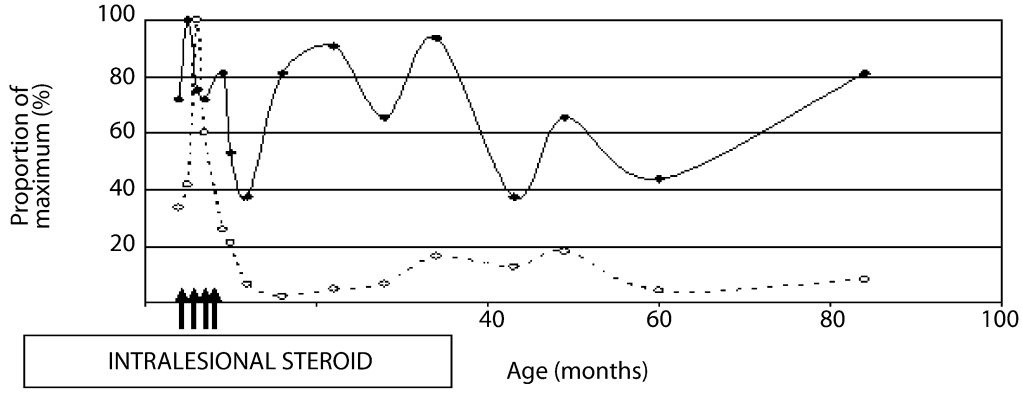
In practical terms, most children will show a marked expansion of periocular hemangiomas and this will typically continue for up to 2 years, but may be ultrasonographically detectable beyond the child's 7th birthday (Fig. 6.4b). The relative volume effect of such late expansion(s) is, however, reduced by growth of the orbital cavity during the same period.

6.2.2 What is the Nature of Involution for Capillary Hemangiomas?

Longitudinal studies in an untreated group of children have, for the first time, allowed a description of the decay patterns, or profiles, for these lesions [42]. In contrast to the traditionally held view that capillary hemangiomas undergo a gradual involution, it would appear that many



c Maximum velocity = 25 cm/sec. Maximum volume = 2.5 ml

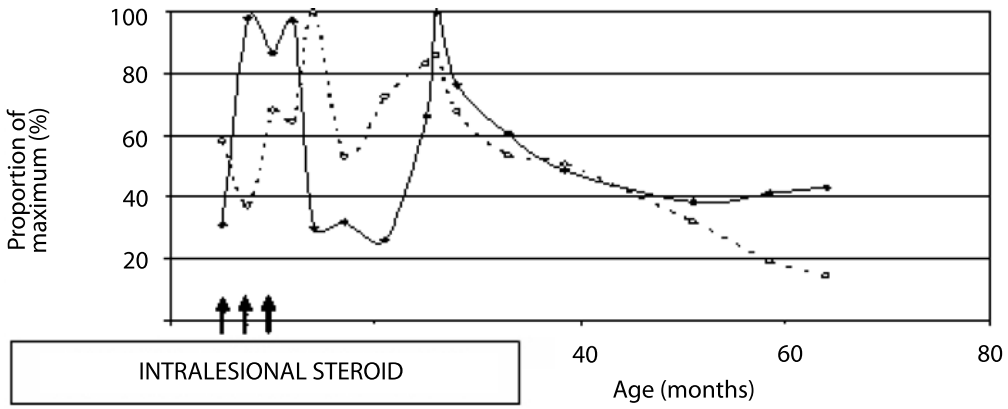


d Maximum velocity = 32 cm/sec. Maximum volume = 20.7.ml

Fig. 6.4 *(continued)* Ultrasonographic studies of volume (B-mode scan) and internal blood velocity (color flow mapping, color Doppler energy, and spectral Doppler techniques). Profiles of velocity (*solid line*) and volume (*dotted line*) are given as a proportion (%) of the maximum value recorded for each child. **c** A marked volume loss is seen following the proliferative phase. **d** Steroid therapy may cause a significant "damping" of the cyclical changes, with a disproportionate effect on the volume. (Note the comparatively large volumes in **d** and **e**). **e** *(see next page)*

of these lesions demonstrate a series of cyclical changes in volume and blood velocity, these taking the form of damping oscillations around an exponential pattern of decay (Fig. 6.4a).

In children with 5 or more datasets, three-quarters showed two or more volume "peaks," half had three or more volume peaks, and two children showed four clearly defined oscillations during their follow-up. Two features of these volume oscillations were described. First, there appeared to be a sequential decrease in size ("damping") of the peaks and, second, for each child the interval between peaks increased. For the whole group, the average first interval (between the first



e Maximum velocity = 107 cm/sec. Maximum volume = 9.7 ml

Fig. 6.4 *(continued)* Ultrasonographic studies of volume (B-mode scan) and internal blood velocity (color flow mapping, color Doppler energy, and spectral Doppler techniques). Profiles of velocity (*solid line*) and volume (*dotted line*) are given as a proportion (%) of the maximum value recorded for each child. **e** A "rebound" increase in both parameters may occur approximately 15 months after steroid injections

and second volume peaks) was 8 months, this being significantly shorter than the second interval (18 months) and the third interval (15.5 months; occurring in just 2 patients). One interpretation of these findings is that natural involution, resulting in an exponential profile, is masked by periods of episodic growth, these growth phases being pronounced early in life, with the "height" of subsequent peaks being a function both of residual tissue volume in the preceding trough, and the intensity and duration of the proliferative phase. Whether involution – possibly by apoptosis – increases in response to the proliferative phase (the volume loss after proliferation being marked in some children; Fig. 6.4c) is uncertain, but it is interesting to note that these volume peaks were never sustained for more than two or three consecutive measurements.

Several children in this "natural history" group show, however, an erratic decay profile – some with a final volume measurement (as late as 3 years of age) similar to, *or even higher than*, the initial measurement. These observations further support the concept of a complex and dynamic balance between proliferation and involution, which – not being limited to the early postpartum period – may continue beyond the 5th year of life.

Less is known about time-related changes in blood velocity within pediatric hemangiomas: peak velocities as high as 100 cm/s have been recorded, greater than that within the aorta (~50 cm/s) or normal capillary beds (~0.1 cm/s) [42]. In many cases the periodicity, and overall pattern, of the velocities correlates closely with that of the volume profiles – suggesting that the proliferation and involution of mesenchymal and endothelial tissues may run in parallel (Fig. 6.4a). The ages at which these peak velocities were recorded reflect that of volume measurements, ranging from 3 to 52 months. Finally, late velocity spikes were observed in over a third of patients – further evidence that the natural behavior of capillary hemangiomata remains dynamic for several years after birth (Fig. 6.4b, c).

6.2.3 Do Capillary Hemangiomas Undergo Complete Involution?

In contradistinction to the traditional view that capillary hemangiomas undergo *complete* regression, ultrasonographic studies by the current authors suggest that capillary hemangiomas

may not regress completely, with persistent tissue identifiable ultrasonographically in many patients after clinical resolution of the lesion [42], this tissue being in the form of a fibro-fatty residuum [48]. Indeed, in the natural history group, a final volume of less than 10% of the maximum was recorded in only a quarter of children and in only one-sixth of children was the lesion undetectable on ultrasound examination – this being at an average of 72 months (range 53–100 months) [42]. In 8 children in whom there was complete *clinical* regression of the hemangioma – all at more than 4 years' follow-up – the lesion could still be detected ultrasonographically in 4 children [42].

Summary for the Clinician

- Recent Doppler ultrasonography studies indicate that:
  - The natural history of capillary hemangiomas is one of early postpartum growth followed by *cycles* of decay and proliferation.
  - A doubling of hemangioma size may occur within the first year of life.
  - The peaks and frequency of volume expansions typically decrease over time.
  - Lesions may not regress completely, final decay leading to a fibro-fatty residuum.
- Several children showed erratic decay profiles, suggesting a complex biological equilibrium between proliferation and involution, which may persist beyond the seventh year of life.

6.3 Changes in Capillary Hemangiomas After Local Steroid Therapy

The natural history group of children with hemangiomas has, for the first time, recorded the ultrasonographic characteristics for these lesions and this has facilitated a comparison with those of children who required local steroid therapy for maintenance of visual development. A group of 9 children were followed after using a regime of intralesional and perilesional steroid injection (Sect. 6.1.3).

6.3.1 Hemangioma Characteristics Associated with Need for Intervention

Nine children received local steroid therapy and one of the children also had surgical resection of the hemangioma. Infants requiring treatment presented at a significantly earlier age than the natural history group, all attending within a month of birth, and the mean duration of follow-up was significantly longer in the treated group (mean 65 months; range 26–105) than in the natural history group.

Unlike the equal sex distribution in the natural history group [42], 8 of the 9 treated children were girls – this reflecting the 1.5 female predominance reported elsewhere [5, 24], and the 3.2:2 ratio for all patients managed by the current author (GER). The cause of this female preponderance within the treated group remains uncertain, but might reflect the influence of different hormones or local cytokines on the vascular endothelium, pericytes or mesenchyme of these childhood hemangiomas.

The average maximum size in the treated children was 8.9 ml, over twice the size of that in the untreated group, and the maximum internal velocity in these larger lesions (mean 63.8 cm/s) tended to be greater than that in the untreated hemangiomas (mean 52 cm/s).

6.3.2 Involutional Changes in Volume and Velocity After Steroid Therapy

The changes in volume and velocity during involution of steroid-treated hemangiomas show a similar cyclical pattern to that in the natural history group, but with some notable differences. At the time when steroid therapy was given, early variations in size and velocity were typically less extreme compared with those in untreated children. Steroid therapy causes a significant, and sometimes prolonged, "damping" of the cyclical

changes (Fig. 6.4d) – often with the effect on volume estimates being more marked than that on flow. There is a tendency for a "rebound" increase in both volume and flow at about 5–20 months after steroid injections – a relative *delay* compared to the cyclical changes of the untreated hemangioma. Subsequent "oscillations" of volume and flow appear to be similar to those of untreated lesions and, contrary to expectation, most treated hemangiomas attained their greatest volume, or showed subsequent volume rises, *after* steroid therapy (Fig. 6.4e).

All 9 children had persistent hemangiomas, detectable on ultrasonography, after steroid therapy, with 8 children followed beyond 5 years of age. One child, followed up until 8 years of age, had a residual lesion with an estimated volume of 1.6 ml.

Summary for the Clinician

- Lesions in female patients tend to be larger than those in male patients.
- Treatment with intralesional steroid is followed by attenuation of the cyclical variations in size and velocity, compared with lesions among untreated children.
- This effect is often more marked on volume estimates than on velocity.
- Approximately 5–20 months following treatment, a "rebound" increase in volume and velocity may occur.
- Most treated hemangiomas had significant proliferative phases *after* steroid therapy.

6.4 Conclusion

Serial ultrasonographic examination has allowed a better definition of the growth and involutional phases of periocular capillary hemangiomas, with most children showing an early rise in volume and remarkably high internal blood velocities in many lesions. The cyclic changes in volume and flow estimates suggest that – unlike the clearly defined "proliferative" and "involutional" phases described in the previous literature – these two processes might occur as a dynamic equilibrium, with a slowly damping oscillation in volume and blood flow. The influences responsible for this behavior remain unknown; although maternal growth factors have been proposed as a driving stimulus for hemangioma growth [31], they are unlikely to persist for any significant time and would not explain our observation of increasing size up to 4 years of age. The typical oscillatory profile in most lesions (both treated and untreated) suggests that neonatal endothelium and pericytes may persist in these tumors, with episodic proliferation occurring against a background of on-going involution (or apoptosis). The frequent occurrence of ultrasonographically detectable lesions at beyond 5 years of age concurs with the suggestion that involution is incomplete in many of these lesions [46].

The significance of the velocity profiles, whilst similar to volume profiles, are interpreted less readily because velocity is a function both of vessel caliber and perfusion pressure – neither of which are measured using the current techniques. Nevertheless, the cyclical behavior of maximal internal velocity also suggests a dynamic relationship between the lesion and its feeder (or shunt) vessels, which might persist well into the first decade of life. Whether changes in blood velocity precede changes in volume – or whether the metabolic demands of an actively growing lesion influence the vessels that supply the mass – cannot be determined from these observations.

With rapid growth of the bony orbit during the first 3 years [10], the volume of the hemangioma – compared with the total orbital volume – becomes relatively less significant. The ultrasound profiles for steroid-treated lesions suggest that this drug exerts a moderately prolonged suppression of the cyclical changes in volume, this suppression being, therefore, of particular value early in childhood, when a child is also at greatest risk of amblyopia.

From a clinical perspective, these new insights into periocular capillary hemangiomas indicate that about three-quarters of lesions will more than double in size during the first year of life. A similar proportion will show cyclical changes in size that, with time, become less marked and occur at greater intervals. Parents can be reas-

sured that periodic changes in size and internal velocity are normal and do not, per se, form an indication for clinical intervention – the latter being restricted to reducing any factors leading to impairment of visual development.

Summary for the Clinician

- Serial ultrasonographic studies have identified a complex profile of proliferation and decay in pediatric capillary hemangioma, these two processes occurring as a dynamic equilibrium.
- The correlation in many cases between volume and velocity indicates a dynamic relationship between the hemangioma and its vascular supply, persisting for a number of years.
- About three-quarters of hemangiomas will increase in size during the first year of life, this change being up to four-fold in magnitude.
- The clinician may reassure the parents that, while visual development is normal, periodic changes in size and velocity are to be expected, and are not a reason for clinical intervention.

References

1. Aldave AJ, Shields CL, Shields JA (1999) Surgical excision of selected amblyogenic periorbital capillary hemangiomas. Ophthalmic Surg Lasers 30:754–757
2. Antaya RJ (2002) Infantile hemangioma. In: Ortone JP, et al. (eds) eMedicine dermatology. eMedicine Corp, St. Petersburg. Available at: http://www.emedicine.com/derm/topic201.htm
3. Bauland CG, van Steensel MA, Steijlen PM, et al. (2006) The pathogenesis of hemangiomas: a review. Plast Reconstr Surg 117:29e–35e
4. Bree AF, Siegfreid E, Sotelo-Avila C, et al. (2001) Infantile haemangiomas: speculation on placental trophoblastic origin. Arch Dermatol 137:573–577
5. Bruckner AL, Frieden IJ (2003) Hemangiomas of infancy. J Am Acad Dermatol 48:477–493
6. Burstein FD, Simms C, Cohen SR, et al. (2000) Intralesional laser therapy of extensive hemangiomas in 100 consecutive pediatric patients. Ann Plast Surg 44:188–194
7. Burton BK, Schulz CJ, Angle B, et al. (1995) An increased incidence of hemangiomas in infants born following chorionic villus sampling (CVS). Prenat Diagn 15:209–214
8. Castillo BV Jr, Kaufman L (2003) Pediatric tumors of the eye and orbit. Pediatr Clin North Am 50:149–172
9. Chang J, Most D, Bresnick S, et al. (1999) Proliferative haemangiomas: analysis of cytokine gene expression and angiogenesis. Plast Reconstr Surg 103:1–9
10. Chau A, Fung K, Yip L, et al. (2004) Orbital development in Hong Kong Chinese subjects. Ophthalmic Physiol Opt 24:436–439
11. Clark DE, Smith SK, He Y, et al. (1998) A vascular endothelial growth factor antagonist is produced by the human placenta and released into the maternal circulation. Biol Reprod 59:1540–1548
12. Coats DK, O'Neil JW, D'Elia VJ, et al. (2003) Sub-Tenon's infusion of steroids for treatment of orbital hemangiomas. Ophthalmology 110:1255–1259
13. Cogen MS, Elsas FJ (1989) Eyelid depigmentation following corticosteroid injection for infantile ocular adnexal hemangioma. J Pediatr Ophthalmol Strabismus 26:35–38
14. Dadras SS, North PE, Bertoncini J, et al. (2004) Infantile haemangiomas are arrested in an early developmental vascular differentiation state. Mod Pathol 17:1068–1079
15. Delesalle F, Staumont D, Houmany MA, et al. (2006) Pulse methylprednisolone therapy for threatening periocular haemangiomas of infancy. Acta Derm Venereol 86:429–432
16. Droste PJ, Ellis FD, Sondhi N, et al. (1988) Linear subcutaneous fat atrophy after corticosteroid injection of periocular hemangiomas. Am J Ophthalmol 105:56–59
17. Egbert JE, Schwartz GS, Walsh AW (1996) Diagnosis and treatment of an ophthalmic artery occlusion during an intralesional injection of corticosteroid into an eyelid capillary hemangioma. Am J Ophthalmol 121:638–642
18. Egbert JE, Paul S, Engel WK, et al. (2001) High injection pressure during intralesional injection of corticosteroids into capillary hemangiomas. Arch Ophthalmol 119:677–683

19. Elsas FJ, Lewis AR (1994) Topical treatment of periocular capillary hemangioma. J Pediatr Ophthalmol Strabismus 31:153–156
20. Fledelius HC, Illum N, Jensen H, et al. (2001) Interferon-alfa treatment of facial infantile haemangiomas: with emphasis on the sight-threatening varieties. A clinical series. Acta Ophthalmol Scand 79:370–373
21. Folkman J (1995) Clinical application of research on angiogenesis. N Engl J Med 333:1757–1763
22. Glowacki J, Mulliken JB (1982) Mast cells in hemangiomas and vascular malformations. Pediatrics 70:48–51
23. Goyal R, Watts P, Lane CM, et al. (2004) Adrenal suppression and failure to thrive after steroid injections for periocular hemangioma. Ophthalmology 111:389–395
24. Haik BG, Karcioglu ZA, Gordon RA, et al. (1994) Capillary haemangioma (infantile periocular haemangioma). Surv Ophthalmol 38:399–426
25. Hasan Q, Tan ST, Xu B, Davis PF (2003) Effects of five commonly used glucocorticoids on haemangioma in vitro. Clin Exp Pharmacol Physiol 30:140–144
26. Hastings MM, Milot J, Barsoum-Homsy M, et al. (1997) Recombinant interferon alfa-2b in the treatment of vision-threatening capillary hemangiomas in childhood. J AAPOS 1:226–230
27. Jiang XW, Wang GH, Li JH, et al. (2005) Expression of glucocorticoid receptor isoforms in cutaneous hemangiomas and vascular malformations. Chin Med J (Engl) 118:977–981
28. Kräling BM, Razon MJ, Boon L, et al. (1996) E-selectin is present in proliferating endothelial cells in human hemangiomas. Am J Pathol 148:1181–1191
29. Nauck M, Karakiulakis G, Perruchoud AP, et al. (1998) Corticosteroids inhibit the expression of the vascular endothelial growth factor gene in human vascular smooth muscle cells. Eur J Pharmacol 341:309–315
30. Neudorfer M, Leibovitch I, Stolovitch C, et al. (2004) Intraorbital and periorbital tumors in children – value of ultrasound and color Doppler imaging in the differential diagnosis. Am J Ophthalmol 137:1065–1072
31. Neumann D, Isenberg SJ, Rosenbaum AL, et al. (1997) Ultrasonographically guided injection of corticosteroids for the treatment of retroseptal capillary hemangiomas in infants. J AAPOS 1:34–40
32. North PE, Waner M, Mizeracki A, et al. (2000) GLUT1: a newly discovered immunohistochemical marker for juvenile hemangiomas. Hum Pathol 31:11–22
33. North PE, Waner M, Mizeracki A, et al. (2001) A unique microvascular phenotype shared by juvenile hemangiomas and human placenta. Arch Dermatol 137:559–570
34. O'Keefe M, Lanigan B, Byrne SA (2003) Capillary haemangioma of the eyelids and orbit: a clinical review of the safety and efficacy of intralesional steroid. Acta Ophthalmol Scand 81:294–298
35. Plager DA, Snyder SK (1997) Resolution of astigmatism after surgical resection of capillary haemangiomas in infants. Ophthalmology 104:1102–1106
36. Ranchod TM, Frieden IJ, Fredrick DR (2005) Corticosteroid treatment of periorbital haemangioma of infancy: a review of the evidence. Br J Ophthalmol 89:1134–1138
37. Richtig E, Langmann G, Mullner K, et al. (2004) Calculated tumour volume as a prognostic parameter for survival in choroidal melanomas. Eye 18:619–623
38. Ritter MR, Dorrell MI, Edmonds J, et al. (2002) Insulin-like growth factor 2 and potential regulators of hemangioma growth and involution identified by large-scale expression analysis. Proc Natl Acad Sci USA 99:7455–7460
39. Slaughter K, Sullivan T, Boulton J, et al. (2003) Early surgical intervention as definitive treatment for ocular adnexal capillary haemangioma. Clin Exp Ophthalmol 31:418–423
40. Sleep TJ, Fairhurst JJ, Manners RM, et al. (2002) Doppler ultrasonography to aid diagnosis of orbital capillary haemangioma in neonates. Eye 16:316–319
41. Sutula FC, Glover AT (1987) Eyelid necrosis following intralesional corticosteroid injection for capillary hemangioma. Ophthalmic Surg 18:103–105
42. Verity DH, Restori M, Rose GE (2006) The natural history of periocular capillary haemangiomas: changes in internal blood velocity and lesion volume. Eye 20:1228–1237
43. Verma K, Verma KK (2001) Infantile periocular haemangioma treated with two days in a week betamethasone oral mini pulse therapy. Indian J Pediatr 68:355–356

44. Walker RS, Custer PL, Nerad JA (1994) Surgical excision of periorbital capillary hemangiomas. Ophthalmology 101:1333–1340
45. Waner M, Suen JY (1999) Treatment options for the management of hemangiomas. In: Waner M, Suen JY (eds) Hemangiomas and vascular malformations of the head and neck. Wiley-Liss, New York, pp 233–261
46. Wasserman BN, Medow NB, Homa-Palladino M, et al. (2004) Treatment of periocular capillary hemangiomas. J AAPOS 8:175–181
47. Yu Y, Varghese J, Brown LF, et al. (2001) Increased TIE2 expression, enhanced response to angiopoietin-1, and dysregulated angiopoietin-2 expression in hemangioma-derived endothelial cells. Am J Pathol 159:2271–2280
48. Yu Y, Fuhr J, Boye E, Gyorffy S, et al. (2006) Mesenchymal stem cells and adipogenesis in hemangioma involution. Stem Cells 24:1605–1612

Chapter 7

Venous-lymphatic Malformations (Lymphangioma) of the Orbit: Diagnostic and Therapeutic Challenges

7

William R. Katowitz, Michael Kazim

Core Messages

- Lymphangiomas are more accurately called venous-lymphatic malformations (VLM).
- VLM are congenital malformations.
- They may be mostly solid or have large cystic components.
- MRI is best for VLM.
- Solid VLM can mimic hemangiomas.
- Solid VLM are more amenable to resection whereas cystic VLM are more easily drained.
- Sclerotherapy remains an alternative to surgery.

7.1 Introduction

Vascular anomalies of the orbit include venous-lymphatic malformations (VLM). These lesions, often referred to as lymphangioma, are considered congenital and most commonly present in childhood. Approximately one-third are identified in the first weeks of life [17]. VLM represented 4% of 1,264 orbital tumors in Shields' series [35] and 3% of 600 in Iliff and Green's series [20]. The most common presenting sign is painful unilateral proptosis resulting from spontaneous hemorrhage (Fig. 7.1a). Less commonly, VLM may enlarge slowly (Fig. 7.2a, b). Anterior lesions can be visible as a red, fleshy mass below the conjunctiva that can bleed spontaneously (Fig. 7.3). The lack of distention of VLM with valsalva distinguishes this entity from orbital varix. VLM can enlarge in association with upper respiratory tract or facial infections. The lesions are unencapsulated and do not obey tissue planes, thereby presenting particular challenges when surgical resection is considered. They can occur anywhere in the orbit and associated adnexa. Intracranial extension has been documented rarely. The more extensive, posterior-based lesions are also likely to extend to the palate, a helpful diagnostic feature if present.

There is disagreement as to whether the lesions are isolated lymphatic anomalies or part of a continuum of venous malformations with orbital varices at one end of the spectrum and lymphatic malformations with or without venous tissue at the other [27].

The purpose of this chapter is to review more recent advances in the diagnosis and treatment of venous-lymphatic malformations.

7.2 Classification

The classification of orbital vascular anomalies has undergone numerous revisions. Redenbacher first described lymphatic malformations in 1828. In 1982 Mulliken and Glowacki distinguished

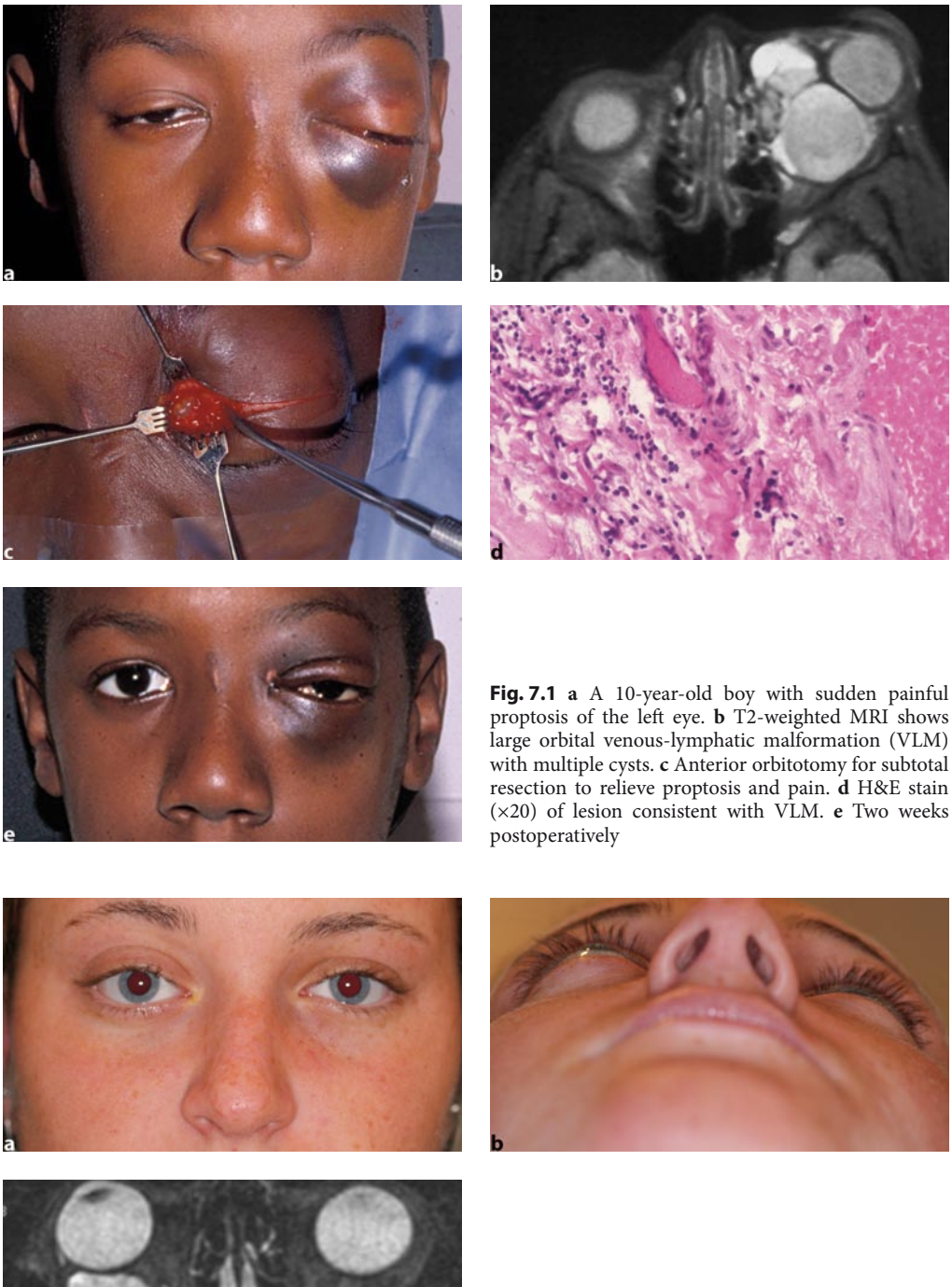


Fig. 7.1 **a** A 10-year-old boy with sudden painful proptosis of the left eye. **b** T2-weighted MRI shows large orbital venous-lymphatic malformation (VLM) with multiple cysts. **c** Anterior orbitotomy for subtotal resection to relieve proptosis and pain. **d** H&E stain (×20) of lesion consistent with VLM. **e** Two weeks postoperatively

Fig. 7.2 **a** A 16-year-old girl with gradual proptosis of the right eye. **b** Right-sided proptosis. **c** T2-weighted MRI shows a large VLM extending to the orbital apex that is mainly solid (a small cyst is visible posteriorly)

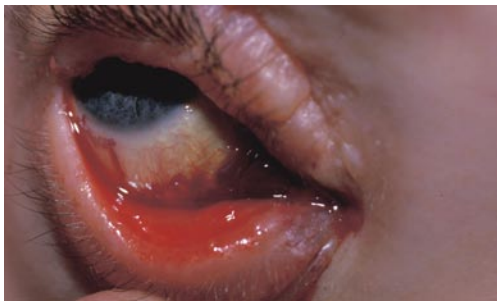


Fig. 7.3 A 6-year-old boy with recurrent hemorrhage of orbital VLM (this patient had already undergone subtotal resection)

infantile hemangiomas, which are typically small and absent at birth and ultimately involute, from vascular malformations which are present at birth and do not involute [28]. This classification, however, does not recognize the more recently described non-involuting form of congenital hemangioma [4].

The International Society for the Study of Vascular Anomalies (ISSVA) has subdivided vascular anomalies into tumors and malformations (Table 7.1) [10]. VLM fall into the latter category. Rootman et al. described orbital VLM clinically by their location in the orbit. They were categorized as superficial, deep, combined [32], and complex (associated with intracranial malformations) [22], and later as part of a hemodynamic spectrum of vascular malformations [31]. In 1999 the Orbital Society adopted this latter classification system in which VLM are typically associated with type 1 (no flow) [16].

There is support in the radiology literature for use of the term venous-lymphatic malformation, as opposed to lymphangioma [5]. This is really an extension of the classification by Wright et al. in which these lesions are considered to represent an abnormality of the orbital venous system [48]. Whether or not VLM and varices represent a spectrum of venous malformations, or are really separate entities has not as yet been settled [16]. VLM most commonly have distinctive cystic elements that predominate or are exclusive of any apparent solid components. However, there is a small sub-group of VLM that are predominantly solid and well-circumscribed. The latter group can be mistaken on both clinical and radiographic examination for capillary hemangio-

Table 7.1. The current classification set by the International Society for the Study of Vascular Anomalies [1, 10]

Tumors	Malformations			
	Simple		Combined	
	Slow flow	High flow	Slow flow	High flow
Infantile hemangiomas (Glut-1+)	Capillary	Arterial	VLM	AVM
Congenital hemangiomas (NICH, RICH)	Venous		CVLM	CAVM
Pyogenic granuloma	Lymphatic			
Tufted angioma				
Kaposiform hemangioendothelioma				
Hemangiopericytoma				

AVM arteriovenous malformation, *CAVM* capillary arteriovenous malformation, *CVLM* capillary venous lymphatic malformation, *VLM* venous lymphatic malformation, *NICH* noninvoluting congenital hemangioma, *RICH* rapidly involuting congenital hemangioma

mas in children, and as cavernous hemangiomas in adults, but can be distinguished histopathologically.

7.3 Imaging

7.3.1 Magnetic resonance imaging

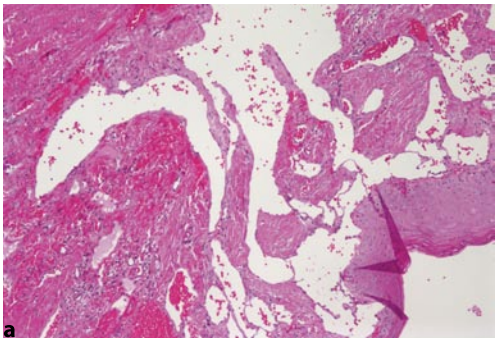
Magnetic resonance imaging is the standard method of studying vascular abnormalities. When combined with MR angiography, it is also possible to define the hemodynamic characteristics of these lesions. MR images of VLM can show large blood-containing cysts or tiny serpiginous channels (Fig. 7.1b) [25]. They show partial contrast enhancement with the most vivid enhancement corresponding to intralesional venous channels, which most likely represent the source of hemorrhage [6]. When combined with MRA, MRI can be used to differentiate slow-flow from high-flow vascular malformations, which demonstrate a characteristic flow void on MR pulse sequences [44].

7.3.2 Computed Tomography

When imaged using CT, VLM typically appear as irregular heterogeneous tumors that are not confined by fascial planes. It can occasionally be difficult to distinguish VLM from hemangiomas, particularly when they are more solid and posteriorly located in the orbit. Rootman et al. described 5 cases in a series of 85 that mimicked cavernous hemangioma on CT [36]. CT angiography can identify feeding vessels in orbital tumors and should be considered if orbital sclerotherapy is being contemplated as a therapeutic option [18]. However, it has been our experience that the vascular supply to even the most hemorrhagic VLM fails to be identified by even the higher resolution trans-arterial angiography.

7.4 Histology

Microscopic inspection of lymphangioma usually demonstrates an unencapsulated mass with ectatic vascular channels separated by connective tissue septae (Fig. 7.1d). There is often evidence of both new and old hemorrhage as well as accumulations of lymphocytes. Some histologic studies have supported the concept that VLM are of venous origin. Wright et al. examined 57 lymphangioma specimens and found two-thirds to have venous connections [48]. Previously, intralesional hemorrhage made it difficult to distinguish lymphatic malformations and venous-lymphatic malformations [13]. The new monoclonal antibody D2-40 is a highly sensitive and specific marker of lymphatic endothelium, which can now aid in identifying VLM and distinguish these tumors from hemangioma (Fig. 7.4) [1].



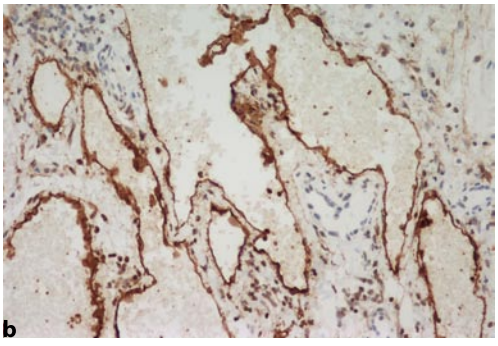


Fig. 7.4 **a** Same patient as in Fig. 7.3. Low power micrograph demonstrating gaping vascular spaces in the superficial dermis, separated by fibrous septae and lined by flattened endothelium. Scattered red cells are present within these spaces, consistent with previous hemorrhage (H&E, ×100). **b** Immunohistochemistry for D2-40 reveals strong positivity (brown staining) within the cytoplasm of the endothelial cells lining the dilated vascular spaces, a finding consistent with lymphatic endothelium (D2-40, ×200).

7.5 Treatment

7.5.1 Treatment Overview

Given the risk of hemorrhage and the challenges to surgical resection, the majority of authors recommend supportive, non-surgical management for most orbital and adnexal venous-lymphatic malformations [17].

7.5.2 Systemic Steroids

Systemic steroids have mixed results in the management of orbital VLM. A brief course of oral corticosteroids can be helpful in cases of acute hemorrhage or when a URI results in lesion expansion due to lymphoid hypertrophy. Corticosteroids can also be used prior to surgery in an effort to shrink the mass. However, no study has suggested that steroids alone can more completely reverse the proptosis resulting from enlargement of VLM than that occurring spontaneously [39, 42].

7.5.3 Surgery

Surgical resection of orbital VLM is challenging due to the lack of encapsulation, transgression of tissue planes, and propensity to hemorrhage both intraoperatively and in the postoperative period. Indications for surgery include compressive optic neuropathy, exposure keratopathy, and untreatable amblyopia. Surgical planning has to include a consideration of the location and the nature of the lesion. Cystic VLM are typically drained through an open orbitotomy to relieve the mass effect of the lesion (Fig. 7.1). One author has used intralesional fibrin glue (Tisseel) to aid dissection and achieve more complete tumor resection [7]. Since recurrence, regardless of the extent of the resection, is the norm, care should be given to avoid injury to vital structures in an effort to complete the resection. Alternatively, decompression of the hemorrhagic cyst may in some cases be achieved by image-guided needle aspiration. Orbital bone decompression, either alone or combined with tumor debulking, has also been used for proptosis reduction [19].

Venous-lymphatic malformations that are radiographically more solid, featuring smaller channels, and producing compressive optic neuropathy as a consequence of apical location or large bulk are more amenable to surgical resection. These lesions are typically more adherent to the surrounding tissues and have a greater propensity to hemorrhage than the cystic variant. As a consequence complete removal may be impractical when attempting to preserve vision [23].

Subtotal resection to accomplish the surgical goals may be aided by use of the carbon dioxide laser [21]. Recently, Gündüz et al. reported 18 patients who underwent total or subtotal resection of orbital VLM. These authors found that the surgically well-delineated extraconal lymphangiomas can be resected totally without recurrence at short-term follow-up (average of 20.4 months). In this series, recurrence was noted in 2 out of 13 cases, with subtotal resection at a mean follow-up of 29.4 months. Both of these lesions had cystic components [15]. These findings are in contrast to Tunç et al., who reported a higher recurrence rate of 58.3% at a mean follow-up of 9.2 years in their series of 26 patients. These findings highlight the need to follow patients over an extended period of time and the potentially significant chance of recurrence [43].

7.5.4 Laser Treatment

The CO_2 laser has been used for subtotal excision of VLM. Advantages of this instrument include good hemostasis from tissue vaporization and less surgical trauma to surrounding tissue. This laser has also been anecdotally effective with anterior lesions, specifically with conjunctival involvement. Complications from the CO_2 laser include corneal anesthesia, papillary dilation from ciliary nerve damage, and symblepharon formation [21, 24, 45].

7.5.5 Sclerotherapy

The goal of any sclerosing agent is to close a vessel lumen, either through direct vessel embolization or through incited inflammatory reactions, which lead to gross vessel wall destruction and

subsequent lesion shrinkage. Many agents have been used outside of the orbit. Few have been used intraorbitally, however, due to the risk of vision loss resulting from vascular compromise of the optic nerve and globe.

7.5.5.1 OK-432

OK-432 is a newer agent that has shown some promise in the treatment of lymphangioma. Picibanil (OK-432) was introduced in Japan in 1975 as an anticancer agent. This drug, isolated from *Streptococcus pyogenes* culture, has been shown to augment anticancer immunity through the induction of cytokine release and activation of immunologic cell activity [33]. This agent was first used to treat VLM via intralesional injection in 1986 by Ogita et al. [30]. It has since been used in numerous studies to treat lymphangioma with success rates showing 50% or more reduction in 67% of the patients reported [26, 30].

Although there are no long-term follow-up data, a report on the intralesional injection of OK-432 in a 14-year-old boy with proptosis resulted in a 5-mm reduction of the proptosis and complete visual recovery [41]. Greene et al. also reported the successful use of OK-432 in a cohort of patients (17 were treated with sclerotherapy, but the number treated with OK-432 was not specified) [14]. One theory of the mechanism of OK-432 in sclerotherapy is through induced inflammation from the destruction of lymph duct endothelial cells [29]. Some evidence indicates that OK-432 has a greater application in macrocystic VLM, but is less promising with microcystic disease [2].

Side effects of this medication include temporary fever and local inflammation [29], as well as increased intraocular pressure [41]. Given the limited use of OK-432 in the orbit to date, more clinical trials are suggested to more fully evaluate its safety and effectiveness in the management of orbital VLM.

7.5.5.2 Sodium Morrhuate

Sodium morrhuate has been used extensively as a sclerosing agent for esophageal varices. This agent has been shown to directly damage vessel endothelium and red cells [40]. Recently, Schwarcz et al. reported intralesional sodium morrhuate injection in 6 patients with orbital VLM. Three of the 6 patients had poor vision. An average of 2.6 injections were used for anterior presenting lesions, either under direct visualization or under radiographic guidance. Complications in this series ranged from intralesional hemorrhage (which resolved spontaneously) to mild pain. There was no incidence of further vision loss (Fig. 7.5) [34].

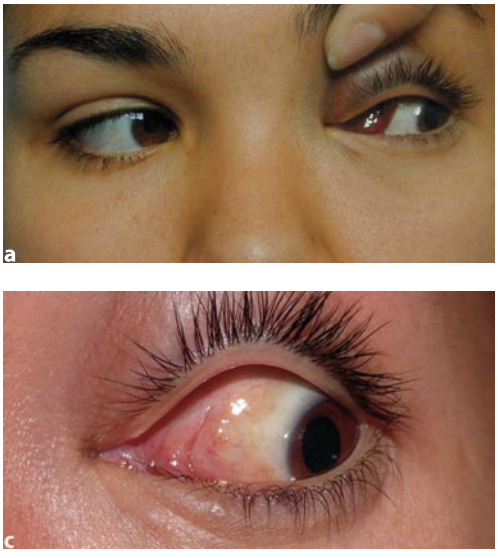


Fig. 7.5 **a** Preoperative photo of a patient with a left orbital VLM extending into the subconjunctival space. **b** Intraoperative injection of sodium morrhuate. **c** Four weeks post-injection. (Courtesy of Raymond Douglas, Jules Stein Eye Institute)

Another concern with any sclerosing agent injected into the orbit is the risk of distant embolization. While this has not been reported as a complication in the small series of patients treated with orbital injections reported thus far, there have been, however, reports of this problem occurring in animal models following injection for esophageal varices [8, 12, 40]. Such concerns should raise a red flag of caution, particularly for the patient with a posterior tumor, and further underscores the need for better radiographic studies to identify feeder vessels with this type of VLM.

7.5.5.3 Other Agents

Alcohol, in varying concentrations, has long been established as a sclerosant in VLM. Ethanol causes endothelial denudation and leads to immediate thrombosis at the site of the injection. If used in the orbit, this carries a significant risk of thrombosis for the ophthalmic vein [38]. Ethibloc contains 60% alcohol and when in contact with blood creates an embolism that induces thrombosis and fibrosis [9]. Sodium tetradecyl sulfate (Sotradecol) containing 2% alcohol has also been used in orbital lymphangioma, but with only moderate success [47]. Other available agents, though not reported for orbital injection of lymphangioma, have included bleomycin [3] and acetic acid [46].

7.5.5.4 Image-guided Sclerotherapy

One of the greatest risks to orbital sclerotherapy is ophthalmic vein thrombosis, which can lead to an orbital compartment syndrome, vision loss, and cavernous sinus thrombosis. To properly treat orbital VLM, it is critical to first establish a pre-procedural characterization of the lesion, both to plan the approach and to identify venous drainage pathways. Next, needle guidance with X-ray fluoroscopy, MRI, or CT is an important aid to achieving a more accurate injection technique. Lastly, real-time monitoring of the sclerosing agent is useful for identifying the rate and the distribution of the agent in the orbit [11, 25].

Summary for the Clinician

- Venous-lymphatic malformations are congenital anomalies of the orbit that should be differentiated from tumors such as hemangioma.
- VLM are often referred to as lymphangioma; however, the term VLM more accurately describes the origin and natural history of this type of lesion.
- VLM can be mostly solid, and thus more amenable to surgical resection, or have large cystic components, which can be drained.
- Given the high rate of recurrence and spontaneous hemorrhage any intervention must be carefully plotted.
- Sclerotherapy remains a viable treatment modality that needs further investigation.

7.6 Future Treatment Modalities

Recent histologic evidence obtained from the examination of persistent VLM lesions suggests a possible role in future treatment [37]. Sidle et al. report higher expression of angiogenic factors in what they defined as recurrent tumors compared with nonrecurrent specimens. Specifically, specimens identified as recurrent lymphangioma stained more avidly with pigment epithelium-derived factor (PEDF) and vascular endothelial growth factor (VEGF) [37]. This study suggests the potential for the use of anti-VEGF agents as an alternative to sclerotherapy in surgically debulked VLM.

References

1. Al-Adnani M, Williams S, Rampling D, et al. (2006) Histopathological reporting of paediatric cutaneous vascular anomalies in relation to proposed multidisciplinary classification system. J Clin Pathol 59:1278–1282
2. Banieghbal B, Davies MR (2003) Guidelines for the successful treatment of lymphangioma with OK-432. Eur J Pediatr Surg 13:103–107

3. Baskin D, Tander B, Bankaoglu M (2005) Local bleomycin injection in the treatment of lymphangioma. Eur J Pediatr Surg 15:383–386
4. Berenguer B, Mulliken JB, Enjolras O, et al. (2003) Rapidly involuting congenital hemangioma: clinical and histopathologic features. Pediatr Dev Pathol 6:495–510
5. Bilaniuk LT (1999) Orbital vascular lesions: role of imaging. Radiol Clin North Am 37:169–183
6. Bilaniuk LT (2002) Imaging the pediatric orbit. In: Katowitz JA (ed) Pediatric oculoplastic surgery. Springer, New York, pp 365–405
7. Boulos PR, Harissi-Dagher M, Codere F, et al. (2005) Intralesional injection of Tisseel fibrin glue for resection of lymphangioma and other thin-walled orbital cysts. Ophthal Plast Reconstr Surg 21:171–176
8. DePuey EG, Richards WO, Millikan WJ, et al. (1988) Scintigraphic detection of pulmonary embolization of esophageal variceal sclerosant. Endoscopy 20:91–94
9. Emran MA, Dubois J, Laberge L, et al. (2006) Alcoholic solution of zein (Ethibloc) sclerotherapy for treatment of lymphangiomas in children. J Pediatr Surg 41:975–979
10. Enjolras O (1997) Classification and management of the various superficial vascular anomalies: hemangiomas and vascular malformations. J Dermatol 24:701–710
11. Ernemann U, Westendorff C, Troitzsch D, et al. (2004) Navigation-assisted sclerotherapy of orbital venolymphatic malformation: a new guidance technique for percutaneous treatment of low-flow vascular malformations. Am J Neuroradiol 25:1792–1795
12. Frisbie JH (2005) An animal model for venous thrombosis and spontaneous pulmonary embolism. Spinal Cord 43:635–639
13. Galambos C, Nodit L (2005) Identification of lymphatic endothelium in pediatric vascular tumors and malformations. Pediatr Dev Pathol 8:181–189
14. Greene AK, Burrows PE, Mulliken JB, et al. (2005) Periorbital lymphatic malformation: clinical course and management in 42 patients. Plast Reconstr Surg 115:22–30
15. Gunduz K, Demirel S, Yagmurlu B, et al. (2006) Correlation of surgical outcome with neuroimaging findings in periocular lymphangiomas. Ophthalmology 113:1236
16. Harris GJ (1999) Orbital vascular malformations: a consensus statement on terminology and its clinical implications. Am J Ophthalmol 127:453–455
17. Harris GJ, Sakol PJ, Bonavolonta G, et al. (1990) An analysis of thirty cases of orbital lymphangioma. Pathphysiologic considerations and management recommendations. Ophthalmology 97:1583–1592
18. Hasegawa M, Fulisawa H, Hayshi Y, et al. (2005) CT arteriography for orbital tumors: diagnostic and surgical value. J Clin Neurosci 12:548–552
19. Hsuan J, Malhotra R, Davis G, et al. (2004) Orbital decompression for gross proptosis associated with orbital lymphangioma. Ophthal Plast Reconstr Surg 20:463–465
20. Iliff WJ, Green WR (1979) Orbital lymphangiomas. Ophthalmology 86:914–929
21. Jordan DR, Anderson RL (1987) Carbon dioxide (CO2) laser for conjunctival lymphangioma. Ophthalmic Surg 18:728–730
22. Katz SE, Rootman J, Vangveeravong S, et al. (1998) Combined venous lymphatic malformations of the orbit (so-called lymphangiomas). Association with noncontiguous intracranial vascular anomalies. Ophthalmology 105:176–184
23. Kazim M, Kennerdell JS, et al. (1992) Orbital lymphangioma. Correlation of magnetic resonance images and intraoperative findings. Ophthalmology 99:1588–1594
24. Kennerdell JS, Maroon JC, Garrity JA, et al. (1986) Surgical management of orbital lymphangioma with the carbon dioxide laser. Am J Ophthalmol 102:308–314
25. Lewin JS (2004) Low-flow vascular malformations of the orbit: a new approach to a therapeutic dilemma. Am J Neuroradiol AJNR 25:1633–1634
26. Luzzatto C, Lo Piccolo R, Fascetti LF, et al. (2005) Further experience with OK-432 for lymphangiomas. Pediatr Surg Int 21:969–972
27. Lyons C, Rootman (2005) Vascular disease. In: Taylor D, Hoyt C (eds) Pediatric ophthalmology and strabismus. Elsevier, New York, pp 385–396
28. Mulliken JB, Glowacki J (1982) Hemangiomas and vascular malformations in infants and children: a classification based on endothelial characteristics. Plast Reconstr Surg 69:412–422
29. Ogita S, Tsuto T, Takahasi T (1987) A case report of sclerosing therapy with OK-432 for cystic hygroma in children. Geka (Surgery) 49:421–423

30. Ogita S, Tsuto T, Nakamura K, et al. (1993) OK-432 therapy for cystic hygroma and cavernous lymphangioma. Jpn J Pediatr Surg 25:371–376
31. Rootman J (2003) Vascular malformations of the orbit: hemodynamic concepts. Orbit 22:103–120
32. Rootman J, Hay E, Graeb D, et al. (1986) Orbital-adnexal lymphangiomas. A spectrum of hemodynamically isolated vascular hamartomas. Ophthalmology 93:1558–1570
33. Ryoma Y, Moriya Y, Okamoto M, et al. (2004) Biological effect of OK-432 (picibanil) and possible application to dendritic cell therapy. Anticancer Res 24:3295–3301
34. Schwarcz RM, Ben Simon GJ, Cook T, et al. (2006) Sclerosing therapy as first line treatment for low flow vascular lesions of the orbit. Am J Ophthalmol 141:333–339
35. Shields JA, Shields CL, Scartozzi S (2004) Survey of 1264 patients with orbital tumors and simulating lesions; the 2002 Montgomery lecture, part 1. Ophthalmology 111:997–1008
36. Selva D, Strianese D, Rootman J, et al. (2001) Orbital venous-lymphatic malformations (lymphangiomas) mimicking cavernous hemangiomas. Am J Ophthalmol 131:364–370
37. Sidle DM, Maddalozzo J, Meier JD, et al. (2005) Altered pigment epithelium-derived factor and vascular endothelial growth factor levels in lymphangioma pathogenesis and clinical recurrence. Arch Otolaryngol Head Neck Surg 131:990–995
38. Siniluoto TM, Svendsen PA, Wikholm GM, et al. (1997) Percutaneous sclerotherapy of venous malformations of the head and neck using sodium tetradecyl sulphate (sotradecol). Scand J Plast Reconstr Surg Hand Surg 31:145–150
39. Sires BS, Goins CR, Anderson RL, et al. (2001) Systemic corticosteroid use in orbital lymphangioma. Ophthal Plast Reconstr Surg 17:85–90
40. Stroncek DF, Hutton SW, Silvis SE, et al. (1985) Sodium morrhuate stimulates granulocytes and damages erythrocytes and endothelial cells: probable mechanism of an adverse reaction during sclerotherapy. J Lab Clin Med 106:498–504
41. Suzuki Y, Obana A, Gohto Y, et al. (2000) Management of orbital lymphangioma using intralesional injection of OK-432. Br J Ophthalmol 84:614–617
42. Tawfik HA, Budin H, Dutton JJ (2005) Lack of response to systemic corticosteroids in patients with lymphangioma. Ophthal Plast Reconstr Surg 21:302–305
43. Tunç M, Sadri E, Char DH (1999) Orbital lymphangioma: an analysis of 26 patients. Br J Ophthalmol 83:76–80
44. Vilanova JC, Barcelò J, Villalòn M (2004) MR and MR angiography characterization of soft tissue vascular malformations. Curr Probl Diagn Radiol 33:161–170
45. Wesley RE, Bond JB (1985) Carbon dioxide laser in ophthalmic plastic and orbital surgery. Ophthalmic Surg 16:631–633
46. Won JH, Kim BM, Kim CH, et al. (2004) Percutaneous sclerotherapy of lymphangiomas with acetic acid. J Vasc Interv Radiol 15:595–600
47. Wojno T (1999) Sotradecol (sodium tetradecyl sulfate) injection of orbital lymphangioma. Ophthal Plast Reconstr Surg 15:432–437
48. Wright JE, Sullivan TJ, Garner A, et al. (1997) Orbital venous anomalies. Ophthalmology 104:905–913

Chapter 8

Thyroid-related Orbitopathy: New Immunologic Concepts and Future Implications

8

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Core Messages

- The potential for immune response to thyrotropin (TSHR) and insulin-like growth factor-1 receptor (IGF-1R) participating in disease pathogenesis of thyroid associated orbitopathy (TAO).
- The unique biosynthetic and proinflammatory properties of orbital fibroblasts are central to TAO.
- TAO is characterized by distinct clinical stages that may reflect site-specific immune mechanisms.
- Adipogenic and infiltrative disease may reflect the unique properties of orbital fibroblasts.

8.1 Introduction

Graves' disease (GD) is a systemic autoimmune disease that targets the thyroid, orbit, and skin. Thyroid-associated orbitopathy (TAO) describes the orbital and periorbital manifestations of the disease [33, 34, 159]. Several important concepts have emerged in the pathogenesis of TAO that potentially explain the manifestations of the disease. Immune recognition of "foreign" and "self" is predicated upon molecular recognition of target structures. The mechanisms of immune recognition and discrimination of self and nonself is beyond the scope of this chapter, but several important epitopes or molecular targets have emerged that may prove relevant to the pathogenesis of TAO and GD. It is increasingly clear that a single target may not fully explain the diverse systemic- and anatomic-specific disease manifestations. Rather analogous to other autoimmune diseases, immune recognition of multiple disease epitopes may be fundamental to the development of TAO and GD [57, 107, 117, 134].

Another emerging concept is recognition that orbital fibroblasts are unique and mediate site-selective manifestations of GD [177, 180, 181]. The unique properties of these sentinel cells may underlie the predilection of the orbit to disease and explain the inflammation, fibrosis, and hyaluronan accumulation that are hallmarks of TAO [99, 180]. Finally, genetic and environmental factors appear to represent determinants of immune responses. Identification of these factors may lead to the development of practical, broad-based treatment and prevention strategies.

8.2 Immunologic Characterization of Disease Stages

8.2.1 Inflammation and Hyaluronan Accumulation

The initial phase of TAO is marked by robust orbital and periorbital inflammation, including the extraocular muscles, and orbital and periorbital fat (Fig. 8.1) [152, 154]. An intense infiltrate of T cells, mast cells and other mononuclear cells is localized in the interstitium between extraocular muscle fibers and in connective adipose tissue with relative paucity near adipocytes [199, 200]. Immunohistochemical studies demonstrate the presence of cytokines including IFN-γ, TNF-α,

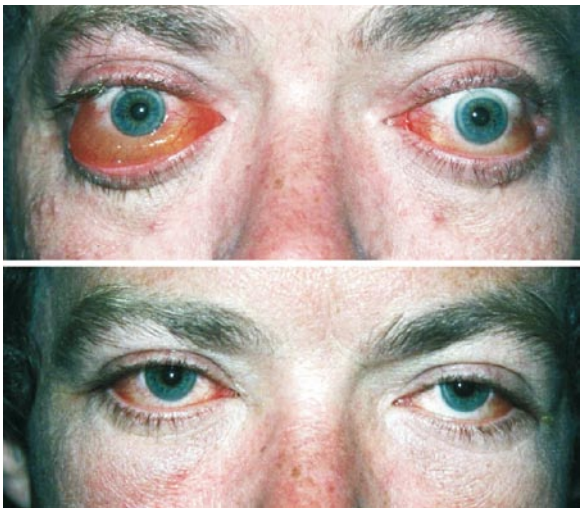

Fig. 8.1. *Top*: patient with characteristic findings of severe inflammatory thyroid-associated orbitopathy (TAO), including soft tissue inflammation, congestion, exophthalmos, and visual loss caused by optic neuropathy. *Bottom*: patient after a course of oral steroid therapy

and IL-1α in the connective tissues associated with T cell infiltration [82]. The T cell infiltrate is predominantly $CD4^+$ and expresses an activated, memory phenotype [83]. It is unclear whether these cytokines are produced by infiltrating mononuclear cells or by fibroblasts. Notably IL-1α, a proinflammatory cytokine, is produced by several cell types, including monocytes, macrophages, and fibroblasts. Cytokines have also been detected in areas devoid of mononuclear infiltration, suggesting the possibility that they derive from fibroblasts [82].

Edema of the orbital structures derives from hyaluronan, a complex carbohydrate with rheologic properties, including extraordinary hydrophilicity [94, 190]. Its accumulation in the interstitial tissues can lead to muscle cell dysfunction and correlates with clinical orbital expansion, congestion, and edema. Hyaluronan accumulation is a hallmark of TAO and is present throughout the disease course [92, 124, 141, 173].

8.2.2 Resolution of Inflammation

The second phase involves the resolution of active inflammation with lessening of clinical disease manifestations [32, 34, 35]. The self-limited resolution of inflammation is peculiar to TAO among autoimmune diseases and the basis for it is critical to our understanding of the disease. Gradual decline of autoantigen abundance, production or presentation may explain these phenomena. Another factor may relate to the absence of orbital lymphoid neogenesis [11, 58]. In many autoimmune diseases, novel lymphoid structures form in target tissues [95, 123, 161]. In rheumatoid arthritis, highly specialized lymphoid tissue develops in the synovial tissue, which sustains antigen presentation, lymphocyte maturation, and homing [50, 115, 122, 189]. In GD, the thyroid gland undergoes lymphoid neogenesis and intense immune-provoked disruption of follicular thyrocytes [18, 19, 87, 206]. While the mechanism for a self-limited immune process in TAO remains unclear, it is a critical component of the immunopathogenesis.

8.3 Autoimmune Target Epitopes

8.3.1 Thyrotropin Receptor

The autoantigen epitope(s) targeted in TAO remain(s) an open question. For decades the thyrotropin receptor (TSHR) has been firmly established as an autoantigen responsible for the hyperthyroidism associated with GD. Formation of autoantibodies to the receptor is nearly universal and results in endocrinologic consequences [54, 116, 138, 155]. However, emerging evidence indicates that a single autoimmune target such as the TSHR fails to explain the pathogenesis of TAO. In other autoimmune diseases, multiple

molecular targets have been identified, each of which may play a distinct pathogenic role.

Autoantibodies are generated to the TSHR, which leads to receptor activation [138, 149, 163, 198]. The role of TSHR in TAO is less clear. It is expressed at low levels in most normal tissues thus far examined and no convincing evidence exists for meaningfully higher expression in TAO [39]. Almost all GD patients express antibodies to the TSHR, but only 40% have TAO. A small group of patients present with clinically obvious TAO before the emergence of endocrine manifestations. Autoantibody formation has also been inconsistently linked to orbital disease severity [69, 72, 101, 103, 118]. Any role of TSH or TSHR autoantibodies in orbital fibroblast activation also remains to be demonstrated. Treatment of orbital fibroblasts with anti-TSHR antibodies or TSH results in vanishingly little response [25]. Thus, TSHR activation of fibroblasts fails to explain localized orbital involvement in TAO, including inflammation and production of hyaluronan.

While there is currently no animal model of GD or TAO, various transgenic mouse models have been developed. These included the overexpression of TSHR in all tissues to generate an immune response characterized by anti-TSHR autoantibodies and variable hyperthyroidism [113, 135, 148, 172]. However, these models have failed to produce TAO. Thus, the role of TSHR in the pathogenesis of TAO remains an open question.

Summary for the Clinician

- The TSHR as a single target of autoimmune activation fails to explain the manifestations of TAO, including inflammation and the production of hyaluronan.

8.3.2 Insulin-like Growth Factor-1 Receptor

Fibroblasts from patients with GD have been examined extensively in culture for their potential to respond to specific IgGs generated in the disease [158]. Sera and IgGs from patients with GD can provoke the expression of IL-16 and RANTES by GD orbital fibroblasts, but not those from control donors [150]. IL-16 has been implicated in a number of human autoimmune diseases, including rheumatoid arthritis [42, 93, 98, 109, 201], inflammatory bowel disease [128, 165, 166], and lupus erythematosis [108, 110, 167]. It binds to CD4 T cells and induces T cell migration, while RANTES is a potent chemokine with more generalized proinflammatory properties. RANTES has also been implicated in autoimmunity. Moreover, it has been detected in the thyroid gland of patients with GD [70, 71, 100]. The specificity of this IgG in GD patients (GD-IgG) is to the insulin-like growth factor-1 receptor (IGF-1R), which is overexpressed on the surface of fibroblasts from patients with the disease. The GD-IgG/IGF-1R interaction mediates the proinflammatory response [181]. In addition, these autoantibodies to the IGF-1R also promote production of hyaluronan by GD orbital fibroblasts [150, 151, 182]. It is as yet unclear what role autoimmune reactivity to the IGF-1R will play in TAO, but autoantibodies promote proinflammatory cytokine production in addition to hyaluronan production.

Summary for the Clinician

- IGF-1R is overexpressed in fibroblasts from GD patients.
- Autoantibodies to this receptor mediate production of proinflammatory cytokines (IL-16 and RANTES) and accumulation of hyaluronan.

8.3.3 Additional Autoantigens

Additional autoantigens have been proposed largely based upon detection of serum autoantibodies, but the vast majority display few pathogenic properties [1, 2, 4–9, 17, 20, 38, 45, 74–76]. Caution must be heeded when interpreting autoantibody and/or T cell autoimmune reactivity, which appears to play little mechanistic role in the disease. An immune response often generates antibody and T cell specificities that are not directed to a self- or a relevant antigen [112, 164]. For example, in vivo data demonstrate that

an immune response is primed and generated to a specific antigen will also generate T cell specificities to various nonpathogenic viral and environmental antigens [57, 192]. This can occur through several mechanisms including epitope spread. This has been noted extensively in diabetes and multiple sclerosis, where diverse antibodies and T cell clones are generated in a predictable fashion [63, 117, 134, 139]. These clones may play little role in disease initiation, but may provide a marker or even promote subsequent inflammation.

Summary for the Clinician

- The role of other autoantigens is unclear since most are nonpathogenic.

8.4 Central Role of Orbital Fibroblasts

The unique properties of orbital fibroblasts appear to underlie the site-specific immune infiltration and volume expansion of TAO. Many of the pathologic features of TAO are mediated by multiple cytokines and small molecule mediators, as is evident in the immunohistochemical analysis of affected orbital tissues.

8.4.1 Inflammation

The response to several inflammatory mediators is characteristic of orbital fibroblasts, especially those from TAO-derived tissues (Fig. 8.2). IL-1β, leukoregulin, and CD154 lead to increased production of the proinflammatory cyclo-oxygenase, prostaglandin endoperoxide H synthase-2 (PGHS-2), also known as COX-2 [47, 49, 197, 207]. The increased activity is due to both increased mRNA synthesis and enhanced transcript stability [47]. Through the activity of PGHS-2, these cytokines preferentially induce prostaglandin E_2 (PGE_2) production in orbital fibroblasts [105, 179, 181]. PGE_2 in turn can bias naïve T cell development toward the Th2 phenotype [40]. These are potent immunoregulatory T cells, which when activated produce IL-4, IL-10, and IL-13, but not IFN-γ. Several autoimmune diseases with prominent fibrotic characteristics generate a Th2-dominant immune response

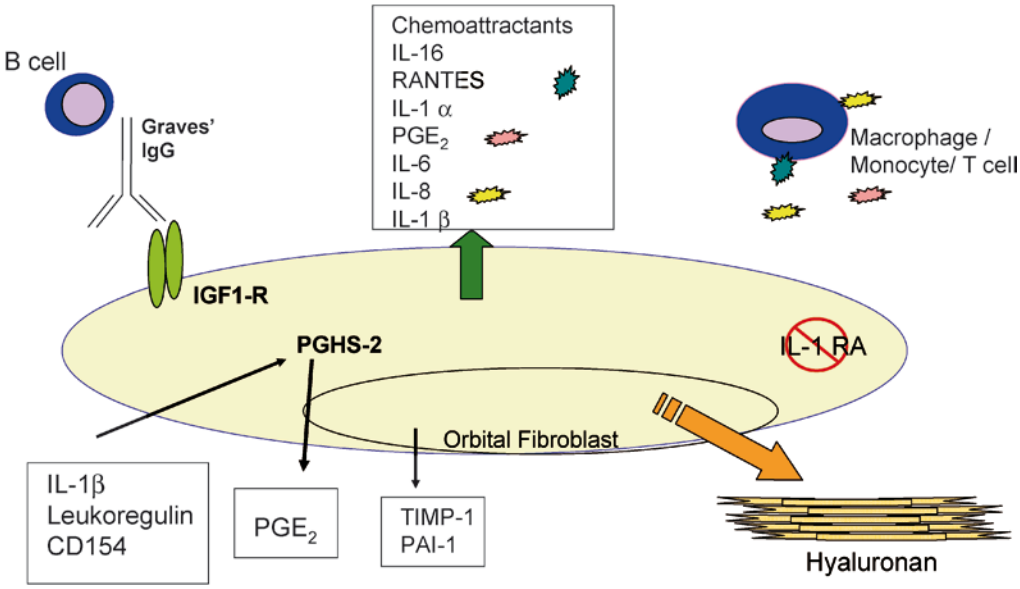

Fig. 8.2. Schematic of the complex interaction between bone marrow-derived cells and orbital fibroblasts

[78, 147, 157]. T cells isolated from orbital tissue in TAO demonstrate a Th2 predominance in advanced disease stages, in contrast to a Th1 or IFN-γ-dominant response early in the disease [14]. The transformation of a cytokine response during a disease stage may be critical to the regulation of inflammation, fibrosis, and disease resolution. In fact, shifting Th1-dominant immune responses toward Th2 can abrogate disease pathogenesis [3, 111, 126, 140, 178, 191]. Thus, responses of fibroblasts to proinflammatory molecules may be critical for T cell activation and bias the immunity occurring in the orbit.

Orbital fibroblasts may condition proinflammatory responses by their low-level expression of the IL-1 receptor antagonist (IL-1ra) [132, 133]. IL-1ra represents a natural inhibitor of IL-1α and IL-1β activity. Since IL-1 can be detected in TAO and appears to exert several proinflammatory actions in orbital fibroblasts, failure to express IL-1ra could amplify the actions of this cytokine family. In addition, the effects of other proinflammatory molecules, such as leukoregulin and CD154, are mediated through IL-1 expression [47, 49, 170].

Summary for the Clinician

- The response to proinflammatory mediators by orbital fibroblast is exaggerated. These properties may be critical for proinflammatory responses and the orbital predilection toward TAO.

8.4.2 Extracellular Matrix and Volume Expansion

Orbital fibroblast cultures demonstrate marked differences in accumulation of extracellular matrix (ECM) in response to proinflammatory cytokines. This attribute may underlie increased orbital volume in TAO. Orbital fibroblasts produce basal levels of hyaluronan that can be increased in response to IL-1β and leukoregulin more dramatically than similarly treated dermal fibroblasts [92, 185]. In addition, hyaluronan synthesis rates are increased by GD-IgGs through binding and activation of the IGF-1R [182]. In both circumstances increased hyaluronan synthesis by orbital fibroblasts can be inhibited with steroids, but basal levels are steroid-insensitive, unlike hyaluronan production in dermal cultures [183, 185, 188].

Maintenance of the extracellular matrix results from a delicate balance between production of macromolecules and remodeling by proteolytic processes. While orbital fibroblasts generate increased levels of hyaluronan, they also produce antagonists to proteolytic processes, thus enhancing the net accumulation of protein constituents of the ECM. When activated by IFN-γ, IL-1β, and TGF-β, they express increased levels of plasminogen activator inhibitor type 1 (PAI-1) and tissue inhibitors of metalloproteinases (TIMPs), resulting in retardation of ECM degradation [48, 88, 184]. These findings suggest that in response to inflammatory mediators, orbital fibroblasts might promote ECM accumulation.

Summary for the Clinician

- The unique responses of orbital fibroblasts to proinflammatory mediators may promote accumulation of hyaluronan.

8.4.3 Surface Molecule Expression

IL-1β and TNF-α increase orbital fibroblast expression of surface molecules such as intercellular adhesion molecules (ICAMs), thereby enhancing cellular interactions [81]. Serum levels of several adhesion molecules are elevated in GD and these levels may be mudulated by steroid therapy [84]. Orbital fibroblasts also display an ability to directly interact with T cells through expression of CD40 and CD154, members of the TNF-α and the TNF-β receptor families [96, 97]. CD40 is expressed by B cells and antigen-presenting cells, while its ligand, CD154 is typically expressed by activated T cells [142]. The CD40–CD154 molecular bridge promotes coordinate costimulation between T and B cells [160]. In an analogous manner, this molecular interaction may promote

effective costimulation between T and B cells with orbital fibroblasts [168, 169]. Engagement of CD40 on orbital fibroblasts increases PGHS-2 expression and PGE_2 synthesis, and involves intermediate production of IL-1α [211]. Engagement of CD40 also enhances hyaluronan production and the synthesis of IL-6 and IL-8 by orbital fibroblasts [170]. The unique expression and functional attributes of CD40–CD154 interactions in TAO may promote site-selective manifestations of the disease.

Summary for the Clinician

- Surface molecules expressed by orbital fibroblasts may promote T and B cell costimulation and the site-selective manifestations of the disease.

8.4.4 Unique Capacity to Differentiate

Orbital fibroblasts also exhibit a distinct capacity to differentiate and this may contribute to the clinical presentation of TAO. The clinical course of TAO diverges from adipogenic predominance to infiltration of extraocular muscle leading to their expansion and fibrosis (Figs. 8.3, 8.4) [13, 136, 143]. In the former, fat expands, but whether increased number and/or volume of adipocytes occur(s) is unresolved. The mechanisms of these extremes in presentation remain speculative.

Thy-1 is a surface marker expressed by most human fibroblasts. In the orbit, Thy-1 display among fibroblasts appears heterogeneous. While the function of Thy-1 is not known, its expression defines functionally distinct fibroblast populations [105, 106]. Thy-1^+ orbital fibroblasts can differentiate into myofibroblasts expressing smooth muscle actin after treatment with TGF-β. Myofibroblasts are critical participants in wound repair and fibrosis. In contrast, Thy-1^- fibroblasts can differentiate into adipocytes under conditions that elevate intracellular cAMP [187, 193]. The expression of Thy-1 by orbital fibroblasts also defines fibroblasts with distinct profiles of cytokine production [146, 175, 186].

Summary for the Clinician

- Orbital fibroblasts exhibit a distinct capacity to differentiate into adipocytes or myofibroblasts.

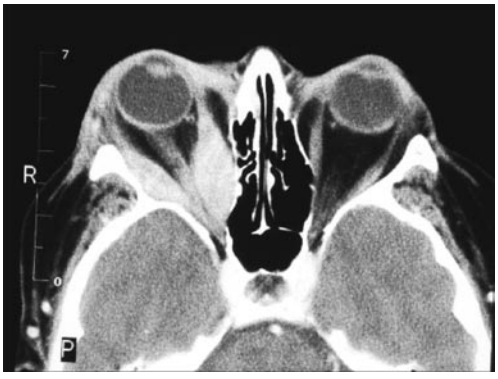

Fig. 8.3. Patient with infiltrative disease of the nontendinous portion of the extraocular muscles. Axial CT image demonstrates unilateral infiltration and the equator of the globe is anterior to the lateral orbital rim, indicating proptosis. Muscle expansion and infiltration can be secondary to hyaluronan accumulation, edema, and fibrosis

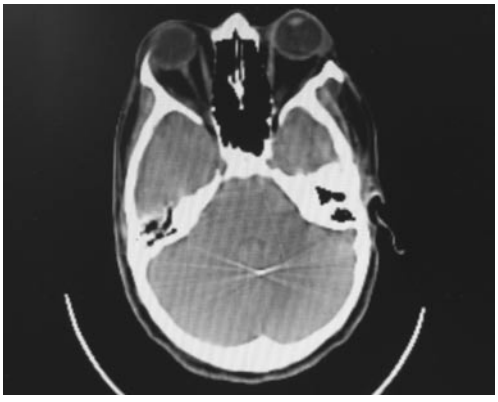

Fig. 8.4. Patient with adipogenic predominant TAO exhibiting exophthalmos with increased orbital fat volume and minimal extraocular muscle expansion. Axial CT scan of a patient with 7 mm of proptosis. The equator of the globe is anterior to the lateral orbital rim

8.5 Impact of Environmental and Genetic Factors

Evidenced factors including genetic background, age, and gender contribute to disease susceptibility. As is the case with other autoimmune disorders and evidenced by the relatively low concordance rates among monozygotic twins, environmental factors play a key role.

8.5.1 Genetics

Increased incidence of GD among family members suggests that genetic factors might contribute to susceptibility [51, 68, 89]. Monozygotic twin studies demonstrate concordance of 30–60% when the other twin is affected [156, 176]. Several studies have demonstrated that altered expression of specific HLA haplotypes is associated with disease [26, 90, 209, 210]. In addition, orbital fibroblasts dramatically upregulate HLA expression in response to proinflammatory signals such as IFN-γ [85]. It remains unclear how these gene products may enhance disease susceptibility.

A number of reports have suggested that polymorphisms of the cytotoxic T lymphocyte antigen (CTLA-4) may be associated with GD [10, 24, 52, 61, 104]. CTLA-4 is expressed by activated T cells and can act to dampen immune responses, by direct signaling and/or interactions with other co-stimulatory molecules expressed by antigen-presenting cells [52]. CTLA-4 competes for binding to CD80 and CD86, which are costimulatory molecules expressed by antigen-presenting cells. Binding of these molecules by CTLA-4 prevents further costimulation and dampens an immune response. It remains unclear how the polymorphisms associated with GD may alter immune response.

Summary for the Clinician

- Several immunologic genetic markers are important in TAO including HLA and CTLA-4; however, the mechanisms are unclear.

8.5.2 Environment

Cigarette smoking has been considered by some the strongest environmental risk factor for developing TAO [27–30, 119, 153,]. The odds ratio relative to controls has been reported to be as high as 20.2 for current smokers and 8.9 for current and ex-smokers, suggesting both a direct and immediate effect of smoking [77, 144]. In addition, among patients with TAO, smokers have more severe eye disease [30, 60]. Smoking can also worsen other autoimmune diseases, including rheumatoid arthritis and Crohn's disease, but the mechanisms remain unclear [46, 79, 80, 174]. Serum cytokine levels are not substantially different in smokers and nonsmokers with TAO [31, 162, 194, 196]. However, hypoxia and constituents of tobacco may increase production of glycosaminoglycans, adhesion molecules, IL-1 and HLA-DR display by orbital fibroblasts [119, 127, 130, 195]. These in vitro findings suggest potential local mechanisms for increasing susceptibility to TAO.

Infectious factors remain suspects since onset of disease exhibits seasonal and geographic variations [12, 129, 205]. Infectious agents may influence the breakdown of tolerance or promotion of autoimmunity in GD [55, 145]. Most notably, *Yersinia enterocolitica* may play a role in the induction of GD, potentially by molecular mimicry [36, 37, 53, 114]. A high proportion of GD patients express measurable antibodies to *Y. enterocolitica* [21, 171]. The organism binds TSH and antibodies isolated from patients with GD can inhibit this binding [86, 171, 202–204, 208]. To date, a causal relationship between *Yersinia* infection and the development of GD or TAO has not been established.

Summary for the Clinician

- By far the most important environmental factor contributing to disease development and severity is cigarette smoking.
- While the mechanism is unclear, smoking appears to enhance local cytokine and surface molecule production.

8.6 Therapeutic Implications

Many hurdles confound drug discovery and the introduction of new therapies to the clinic. Implementation of a standardized clinical and laboratory assessment of TAO that reflects disease activity could greatly facilitate the evaluation of therapies [131]. Despite these limitations, therapies that specifically target the immune mechanisms of the disease, could make a significant impact (Fig. 8.5).

8.6.1 Immune Subset Depletion

Approaches using cell depletion have proven successful in the treatment of autoimmune disease [41, 59, 73, 102]. Given the diverse functions of T and B cells, depleting these populations significantly dampens the immune response [23, 43]. Recent observations suggest that normal immune regulation is dependent upon a highly specialized group of T lymphocytes or regulatory T cells [44, 137]. In murine models, regulatory T cells comprise 1–4% of the T cell population and can limit immune responses [125]. If the regulatory T cell population is diminished or functionally impaired, an aberrant immune response can develop. Conversely, when this population is sufficient, autoimmune responses are modulated [59, 91]. T cell depletion therapies may enhance the function and frequency of regulatory T cells. In several human diseases, decreased regulatory T cells are associated with increased

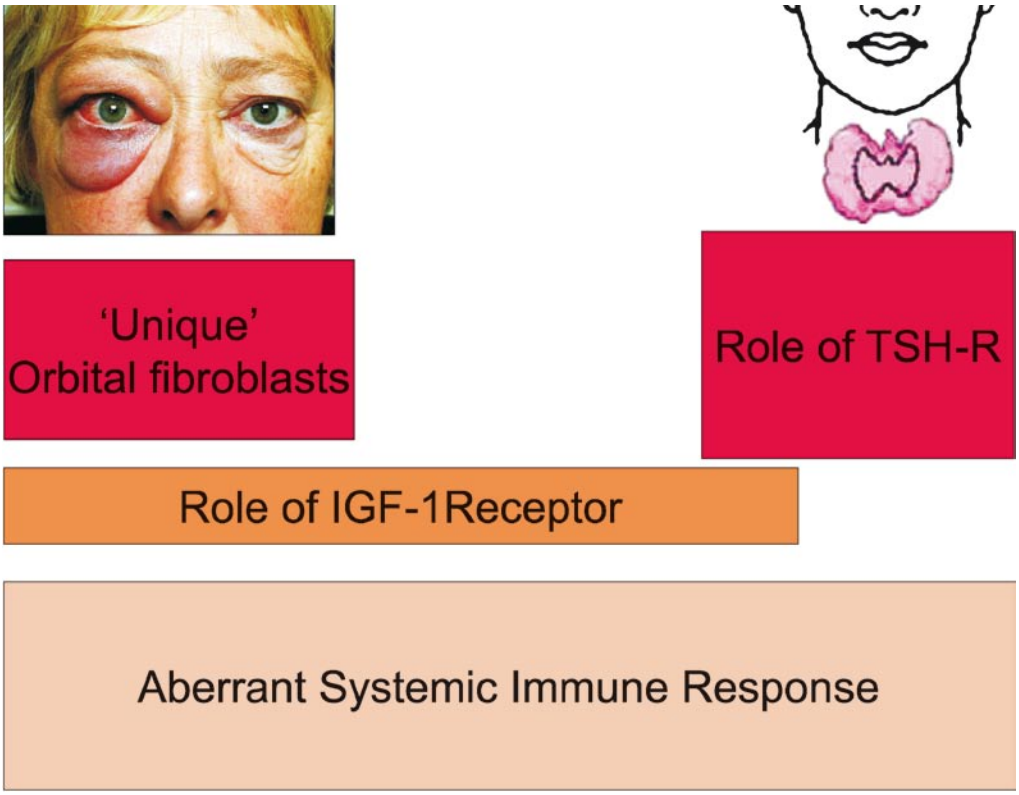

Fig. 8.5. The etiology of thyroid and orbit involvement in Graves' disease is complex and likely interdependent upon several factors. TAO may be dependent upon an aberrant systemic immune response and unique orbital fibroblast responses to several inflammatory mediators. Targeting the specific mediators of TAO may offer novel and specific treatment alternatives

severity. After treatment, the regulatory cell population expands and the disease remits [102]. Studies on the complexity of regulatory T cells continue to unfold and have generated promising results.

8.6.2 Cytokine Therapies

Several classes of drugs are currently available for treatment of autoimmune disorders. These interfere with immune cell activation at various levels [22, 56, 62, 65, 66, 120, 121]. Some inhibit the production or action of cytokines.

Investigation into the applicability of these agents in TAO hinges on an effective method of clinical evaluation. For example, investigation of rheumatoid arthritis has demonstrated that TNF-α plays an important role in disease pathogenesis [15, 16, 64, 67, 212]. Therapies were developed using neutralizing monoclonal antibodies that specifically limit the immune response [213].

Summary for the Clinician

- Specific treatment approaches include immune subset depletion, and neutralizing cytokine actions

References

1. Adler G, Pacuszka T, Targonska I, Lewartowska A, Nauman J (1994) Incidental presence of antibodies against gangliosides in Graves' disease. Autoimmunity 18:149–152
2. Adler G, Pacuszka T, Strugalska M, Targonska I, Panasiewicz M, Lewartowska A (1996) Anti-fucosyl-GM1 ganglioside IgG and IgM autoantibodies in human serum: no link to pathology. Immunol Lett 52:89–93
3. Adorini L, Trembleau S (1997) Immune deviation towards Th2 inhibits Th-1-mediated autoimmune diabetes. Biochem Soc Trans 25:625–629
4. Ahmann A, Baker JR Jr, Weetman AP, Wartofsky L, Nutman TB, Burman KD (1987) Antibodies to porcine eye muscle in patients with Graves' ophthalmopathy: identification of serum immunoglobulins directed against unique determinants by immunoblotting and enzyme-linked immunosorbent assay. J Clin Endocrinol Metab 64:454–460
5. Ahn IM, Izumi M, Nagataki S (1988) Islet cell surface antibodies in Graves' disease; as organ non-specific antibodies. Korean J Intern Med 3:38–44
6. Ajjan RA, Kemp EH, Waterman EA, Watson PF, Endo T, Onaya T, Weetman AP (2000) Detection of binding and blocking autoantibodies to the human sodium-iodide symporter in patients with autoimmune thyroid disease. J Clin Endocrinol Metab 85:2020–2027
7. Akamizu T (2003) Monoclonal antibodies to thyroid specific autoantigens. Autoimmunity 36:361–366
8. Akawaza S, Kawasaki E, Yano M, Abiru N, Yamaguchi Y, Nagataki S (1994) Autoantibodies to glutamic acid decarboxylase (GAD), 64,000-Mr islet cell protein (64K) antibodies and islet cell antibodies (ICA) in insulin-dependent diabetes mellitus with and without autoimmune diseases in Japan. Diabetes Res Clin Pract 24 [Suppl]: S89–S93
9. Akcay MN, Akcay G (2003) Liver function tests during antithyroid therapy in hyperthyroidism. Hepatogastroenterology 50 [Suppl 2]: cclxxxi–cclxxxii
10. Allahabadia A, Heward JM, Nithiyananthan R, Gibson SM, Reuser TT, Dodson PM, Franklyn JA, Gough SC (2001) MHC class II region, CTLA4 gene, and ophthalmopathy in patients with Graves' disease. Lancet 358:984–985
11. Aloisi F, Pujol-Borrell R (2006) Lymphoid neogenesis in chronic inflammatory diseases. Nat Rev Immunol 6:205–217
12. Amino N, Hidaka Y, Takano T, Izumi Y, Tatsumi KI, Nakata Y (2003) Association of seasonal allergic rhinitis is high in Graves' disease and low in painless thyroiditis. Thyroid 13:811–814
13. Anderson RL, Tweeten JP, Patrinely JR, Garland PE, Thiese SM (1989) Dysthyroid optic neuropathy without extraocular muscle involvement. Ophthalmic Surg 20:568–574

14. Aniszewski JP, Valyasevi RW, Bahn RS (2000) Relationship between disease duration and predominant orbital T cell subset in Graves' ophthalmopathy. J Clin Endocrinol Metab 85:776–780
15. Arend WP, Dayer JM (1990) Cytokines and cytokine inhibitors or antagonists in rheumatoid arthritis. Arthritis Rheum 33:305–315
16. Arenzana-Seisdedos F, Teyton L, Virelizier JL (1987) Immunoregulatory mediators in the pathogenesis of rheumatoid arthritis. Scand J Rheumatol Suppl 66:13–17
17. Ariga T, Yoshida T, Mimori T, Yu RK (1991) Autoantibodies against Forssman glycolipids in Graves' disease and Hashimoto's thyroiditis. Clin Exp Immunol 86:483–488
18. Armengol MP, Juan M, Lucas-Martin A, Fernandez-Figueras MT, Jaraquemada D, Gallart T, Pujol-Borrell R (2001) Thyroid autoimmune disease: demonstration of thyroid antigen-specific B cells and recombination-activating gene expression in chemokine-containing active intrathyroidal germinal centers. Am J Pathol 159:861–873
19. Armengol MP, Cardoso-Schmidt CB, Fernandez M, Ferrer X, Pujol-Borrell R, Juan M (2003) Chemokines determine local lymphoneogenesis and a reduction of circulating CXCR4+ T and CCR7 B and T lymphocytes in thyroid autoimmune diseases. J Immunol 170:6320–6328
20. Armitage M, Franklyn J, Scott-Morgan L, Parr J, Borsey DQ, Sheppard M, Wilkin TJ (1990) Insulin autoantibodies in Graves' disease – before and after carbimazole therapy. Diabetes Res Clin Pract 8:169–176
21. Asari S, Amino N, Horikawa M, Miyai K (1989) Incidences of antibodies to Yersinia enterocolitica: high incidence of serotype O5 in autoimmune thyroid diseases in Japan. Endocrinol Jpn 36:381–386
22. Atzeni F, Turiel M, Capsoni F, Doria A, Meroni P, Sarzi-Puttini P (2005) Autoimmunity and anti-TNF-alpha agents. Ann N Y Acad Sci 1051:559–569
23. Bacchetta R, Gregori S, Roncarolo MG (2005) CD4+ regulatory T cells: mechanisms of induction and effector function. Autoimmun Rev 4:491–496
24. Badenhoop K, Donner H, Braun J, Siegmund T, Rau H, Usadel KH (1996) Genetic markers in diagnosis and prediction of relapse in Graves' disease. Exp Clin Endocrinol Diabetes 4:98–100
25. Bahn RS, Dutton CM, Natt N, Joba W, Spitzweg C, Heufelder AE (1998) Thyrotropin receptor expression in Graves' orbital adipose/connective tissues: potential autoantigen in Graves' ophthalmopathy. J Clin Endocrinol Metab 83:998–1002
26. Ban Y, Concepcion ES, Villanueva R, Greenberg DA, Davies TF, Tomer Y (2004) Analysis of immune regulatory genes in familial and sporadic Graves' disease. J Clin Endocrinol Metab 89:4562–4568
27. Bartalena L (2002) Smoking and Graves' disease. J Endocrinol Invest 25:402
28. Bartalena L, Martino E, Marcocci C, Bogazzi F, Panicucci M, Velluzzi F, Loviselli A, Pinchera A (1989) More on smoking habits and Graves' ophthalmopathy. J Endocrinol Invest 12:733–737
29. Bartalena L, Bogazzi F, Tanda ML, Manetti L, Dell'Unto E, Martino E (1995) Cigarette smoking and the thyroid. Eur J Endocrinol 133:507–512
30. Bartalena L, Marcocci C, Tanda ML, Manetti L, Dell'Unto E, Bartolomei MP, Nardi M, Martino E, Pinchera A (1998) Cigarette smoking and treatment outcomes in Graves ophthalmopathy. Ann Intern Med 129:632–635
31. Bartalena L, Manetti L, Tanda ML, Dell'Unto E, Mazzi B, Rocchi R, Barbesino G, Pinchera A, Marcocci C (2000) Soluble interleukin-1 receptor antagonist concentration in patients with Graves' ophthalmopathy is neither related to cigarette smoking nor predictive of subsequent response to glucocorticoids. Clin Endocrinol (Oxf) 52:647–651
32. Bartley GB (1994) The epidemiologic characteristics and clinical course of ophthalmopathy associated with autoimmune thyroid disease in Olmsted County, Minnesota. Trans Am Ophthalmol Soc 92:477–588
33. Bartley GB (1995) The differential diagnosis and classification of eyelid retraction. Trans Am Ophthalmol Soc 93:371–387
34. Bartley GB, Fatourechi V, Kadrmas EF, Jacobsen SJ, Ilstrup DM, Garrity JA, Gorman CA (1996) Clinical features of Graves' ophthalmopathy in an incidence cohort. Am J Ophthalmol 121:284–290
35. Bartley GB, Fatourechi V, Kadrmas EF, Jacobsen SJ, Ilstrup DM, Garrity JA, Gorman CA (1996) Chronology of Graves' ophthalmopathy in an incidence cohort. Am J Ophthalmol 121:426–434
36. Bech K (1990) Yersinia enterocolitica and thyroid autoimmunity. Autoimmunity 7:291–294

37. Bech K, Lumholtz B, Nerup J, Thomsen M, Platz P, Ryder LP, Svejgaard A, Siersbaek-Nielsen K, Hansen JM, Larsen JH (1977) HLA antigens in Graves' disease. Acta Endocrinol 86:510–516
38. Bednarczuk T, Stolarski C, Pawlik E, Slon M, Rowinski M, Kubota S, Hiromatsu Y, Bartoszewicz Z, Wall JR, Nauman J (1999) Autoantibodies reactive with extracellular matrix proteins in patients with thyroid-associated ophthalmopathy. Thyroid 9:289–295
39. Bell A, Gagnon A, Grunder L, Parikh SJ, Smith TJ, Sorisky A (2000) Functional TSH receptor in human abdominal preadipocytes and orbital fibroblasts. Am J Physiol Cell Physiol 279: C335–C340
40. Betz M, Fox BS (1991) Prostaglandin E2 inhibits production of Th1 lymphokines but not of Th2 lymphokines. J Immunol 146:108–113
41. Bisikirska B, Colgan J, Luban J, Bluestone JA, Herold KC (2005) TCR stimulation with modified anti-CD3 mAb expands CD8+ T cell population and induces CD8+CD25+ Tregs. J Clin Invest 115:2904–2913
42. Blaschke S, Schulz H, Schwarz G, Blaschke V, Muller GA, Reuss-Borst M (2001) Interleukin 16 expression in relation to disease activity in rheumatoid arthritis. J Rheumatol 28:12–21
43. Bluestone JA (2005) Regulatory T-cell therapy: is it ready for the clinic? Nat Rev Immunol 5:343–349
44. Bluestone JA, Tang Q (2005) How do CD4+CD25+ regulatory T cells control autoimmunity? Curr Opin Immunol 17:638–642
45. Boucher A, Bernard N, Zhang ZG, Rodien P, Salvi M, Wall JR (1993) Nature of 64 kDa eye muscle and thyroid membrane proteins and their significance in thyroid-associated ophthalmopathy – an hypothesis. Autoimmunity 16:79–82
46. Calkins BM (1989) A meta-analysis of the role of smoking in inflammatory bowel disease. Dig Dis Sci 34:1841–1854
47. Cao HJ, Smith TJ (1999) Leukoregulin upregulation of prostaglandin endoperoxide H synthase-2 expression in human orbital fibroblasts. Am J Physiol 277:C1075–C1085
48. Cao HJ, Hogg MG, Martino LJ, Smith. TJ (1995) Transforming growth factor-beta induces plasminogen activator inhibitor type-1 in cultured human orbital fibroblasts. Invest Ophthalmol Vis Sci 36:1411–1419
49. Cao HJ, Wang HS, Zhang Y, Lin HY, Phipps RP, Smith TJ (1998) Activation of human orbital fibroblasts through CD40 engagement results in a dramatic induction of hyaluronan synthesis and prostaglandin endoperoxide H synthase-2 expression. Insights into potential pathogenic mechanisms of thyroid-associated ophthalmopathy. J Biol Chem 273:29615–29625
50. Carlsen HS, Baekkevold ES, Morton HC, Haraldsen G, Brandtzaeg P (2004) Monocyte-like and mature macrophages produce CXCL13 (B cell-attracting chemokine 1) in inflammatory lesions with lymphoid neogenesis. Blood 104:3021–3027
51. Chabchoub I, Makni H, Boulila-el Gaied A, Maalej A, Abid M, Jouida J, Ayadi H (1996) Expression of the autoreactive Ig repertoire in a large family, with high prevalence of thyroid autoimmune diseases. Arch Inst Pasteur Tunis 73:163–166
52. Chistiakov DA, Turakulov RI (2003) CTLA-4 and its role in autoimmune thyroid disease. J Mol Endocrinol 31:21–36
53. Corapcioglu D, Tonyukuk V, Kiyan M, Yilmaz AE, Emral R, Kamel N, Erdogan G (2002) Relationship between thyroid autoimmunity and Yersinia enterocolitica antibodies. Thyroid 12:613–617
54. Cho BY (2002) Clinical applications of TSH receptor antibodies in thyroid diseases. J Korean Med Sci 17:293–301
55. Cox SP, Phillips DI, Osmond C (1989) Does infection initiate Graves disease? A population based 10 year study. Autoimmunity 4:43–49
56. Criscione LG, St Clair EW (2002) Tumor necrosis factor-alpha antagonists for the treatment of rheumatic diseases. Curr Opin Rheumatol 14:204–211
57. Davies S, Nicholson T, Laura M, Giovannoni G, Altmann DM (2005) Spread of T lymphocyte immune responses to myelin epitopes with duration of multiple sclerosis. J Neuropathol Exp Neurol 64:371–377
58. Drayton DL, Liao S, Mounzer RH, Ruddle NH (2006) Lymphoid organ development: from ontogeny to neogenesis. Nat Immunol 7:344–353
59. Earle KE, Tang Q, Zhou X, Liu W, Zhu S, Bonyhadi ML, Bluestone JA (2005) In vitro expanded human CD4+CD25+ regulatory T cells suppress effector T cell proliferation. Clin Immunol 115:3–9

60. Eckstein A, Quadbeck B, Mueller G, Rettenmeier AW, Hoermann R, Mann K, Steuhl P, Esser J (2003) Impact of smoking on the response to treatment of thyroid associated ophthalmopathy. Br J Ophthalmol 87:773–776
61. Einarsdottir E, Soderstrom I, Lofgren-Burstrom A, Haraldsson S, Nilsson-Ardnor S, Penha-Goncalves C, Lind L, Holmgren G, Holmberg M, Asplund K, Holmberg D (2003) The CTLA4 region as a general autoimmunity factor: an extended pedigree provides evidence for synergy with the HLA locus in the etiology of type 1 diabetes mellitus, Hashimoto's thyroiditis and Graves' disease. Eur J Hum Genet 11:81–84
62. Elliott MJ, Maini RN (1995) Anti-cytokine therapy in rheumatoid arthritis. Baillieres Clin Rheumatol 9:633–652
63. Ellmerich S, Takacs K, Mycko M, Waldner H, Wahid F, Boyton RJ, Smith PA, Amor S, Baker D, Hafler DA, Kuchroo VK, Altmann DM (2004) Disease-related epitope spread in a humanized T cell receptor transgenic model of multiple sclerosis. Eur J Immunol 34:1839–1848
64. Elson CJ, Thompson SJ, Westacott CI, Bhoola KD (1992) Mediators of joint swelling and damage in rheumatoid arthritis and pristane induced arthritis. Autoimmunity 13:327–331
65. Emery P (2001) Infliximab: a new treatment for rheumatoid arthritis. Hosp Med 62:150–152
66. Emery P (2003) Role of adalimumab, a novel TNF antagonist in advancing rheumatoid arthritis control. Drugs Today (Barc) 39 Suppl B:17–23
67. Feldmann M, Brennan FM, Williams RO, Elliott MJ, Maini RN (1995) Cytokine expression and networks in rheumatoid arthritis: rationale for anti-TNF alpha antibody therapy and its mechanism of action. J Inflamm 47:90–96
68. Friedman JM, Fialkow PJ (1978) The genetics of Graves' disease. Clin Endocrinol Metab 7:47–65
69. Gerding MN, van der Meer JW, Broenink M, Bakker O, Wiersinga WM, Prummel MF (2000) Association of thyrotrophin receptor antibodies with the clinical features of Graves' ophthalmopathy. Clin Endocrinol 52:267–271
70. Gianoukakis AG, Martino LJ, Horst N, Cruikshank WW, Smith TJ (2003) Cytokine-induced lymphocyte chemoattraction from cultured human thyrocytes: evidence for interleukin-16 and regulated upon activation, normal T cell expressed, and secreted expression. Endocrinology 144:2856–2864
71. Gianoukakis AG, Douglas RS, King CS, Cruikshank WW, Smith TJ (2006) Immunoglobulin G from patients with Graves' disease induces interleukin-16 and RANTES expression in cultured human thyrocytes: a putative mechanism for T-cell infiltration of the thyroid in autoimmune disease. Endocrinology 147:1941–1949
72. Goh SY, Ho SC, Seah LL, Fong KS, Khoo DH (2004) Thyroid autoantibody profiles in ophthalmic dominant and thyroid dominant Graves' disease differ and suggest ophthalmopathy is a multiantigenic disease. Clin Endocrinol 60:600–607
73. Gottlieb A, Krueger JG, Bright R, Ling M, Lebwohl M, Kang S, Feldman S, Spellman M, Wittkowski K, Ochs HD, Jardieu P, Bauer R, White M, Dedrick R, Garovoy M (2000) Effects of administration of a single dose of a humanized monoclonal antibody to CD11a on the immunobiology and clinical activity of psoriasis. J Am Acad Dermatol 42:428–435
74. Grus FH, Augustin AJ, Toth-Sagi K (1998) Diagnostic classification of autoantibody repertoires in endocrine ophthalmopathy using an artificial neural network. Ocul Immunol Inflamm 6:43–50
75. Guma M, Salinas I, Reverter JL, Roca J, Valls-Roc M, Juan M, Olive A (2003) Frequency of antineutrophil cytoplasmic antibody in Graves' disease patients treated with methimazole. J Clin Endocrinol Metab 88:2141–2146
76. Gunji K, Kubota S, Stolarski C, Wengrowicz S, Kennerdell JS, Wall JR (1999) A 63 kDa skeletal muscle protein associated with eye muscle inflammation in Graves' disease is identified as the calcium binding protein calsequestrin. Autoimmunity 29:1–9
77. Hagg E, Asplund K (1987) Is endocrine ophthalmopathy related to smoking? Br Med J (Clin Res Ed) 295:634–635
78. Harris SG, Padilla J, Koumas L, Ray D, Phipps RP (2002) Prostaglandins as modulators of immunity. Trends Immunol 23:144–150
79. Harrison BJ, Silman AJ (2000) Does smoking influence disease outcome in patients with rheumatoid arthritis? J Rheumatol 27:569–570
80. Harrison BJ, Silman AJ, Wiles NJ, Scott DG, Symmons DP (2001) The association of cigarette smoking with disease outcome in patients with early inflammatory polyarthritis. Arthritis Rheum 44:323–330

81. Heufelder AE, Bahn RS (1992) Graves' immunoglobulins and cytokines stimulate the expression of intercellular adhesion molecule-1 (ICAM-1) in cultured Graves' orbital fibroblasts. Eur J Clin Invest 22:529–537
82. Heufelder AE, Bahn RS (1993) Detection and localization of cytokine immunoreactivity in retroocular connective tissue in Graves' ophthalmopathy. Eur J Clin Invest 23:10–17
83. Heufelder AE, Bahn RS (1993) Elevated expression in situ of selectin and immunoglobulin superfamily type adhesion molecules in retroocular connective tissues from patients with Graves' ophthalmopathy. Clin Exp Immunol 91:381–389
84. Heufelder AE, Bahn RS (1993) Soluble intercellular adhesion molecule-1 (sICAM-1) in sera of patients with Graves' ophthalmopathy and thyroid diseases. Clin Exp Immunol 92:296–302
85. Heufelder AE, Bahn RS, Smith TJ (1992) Regulation by glucocorticoids of interferon gamma-induced HLA-DR antigen expression in cultured human orbital fibroblasts. Clin Endocrinol (Oxf) 37:59–63
86. Heyma P, Harrison LC, Robins-Browne R (1986) Thyrotrophin (TSH) binding sites on Yersinia enterocolitica recognized by immunoglobulins from humans with Graves' disease. Clin Exp Immunol 64:249–254
87. Hiromatsu Y, Kaku H, Mukai T, Miyake I, Fukutani T, Koga M, Shoji S, Toda S, Koike N (2004) Immunohistochemical analysis of bcl-2, Bax and Bak expression in thyroid glands from patients with Graves' disease. Endocr J 51:399–405
88. Hogg MG, Evans CH, Smith TJ (1995) Leukoregulin induces plasminogen activator inhibitor type 1 in human orbital fibroblasts. Am J Physiol 269: C359–C366
89. Holland FJ, McConnon JK, Volpe R, Saunders EF (1991) Concordant Graves' disease after bone marrow transplantation: implications for pathogenesis. J Clin Endocrinol Metab 72:837–840
90. Hu R, Beck C, Chang YB, DeGroot LJ (1992) HLA class II genes in Graves' disease. Autoimmunity 12:103–106
91. Huang X, Zhu J, Yang Y (2005) Protection against autoimmunity in nonlymphopenic hosts by CD4+ CD25+ regulatory T cells is antigen-specific and requires IL-10 and TGF-beta. J Immunol 175:4283–4291
92. Kaback LA, Smith TJ (1999) Expression of hyaluronan synthase messenger ribonucleic acids and their induction by interleukin-1beta in human orbital fibroblasts: potential insight into the molecular pathogenesis of thyroid-associated ophthalmopathy. J Clin Endocrinol Metab 84:4079–4084
93. Kageyama Y, Ozeki T, Suzuki M, Ichikawa T, Miura T, Miyamoto S, Machida A, Nagano A (2000) Interleukin-16 in synovial fluids from cases of various types of arthritis. Joint Bone Spine 67:188–193
94. Kahaly G, Forster G, Hansen C (1998) Glycosaminoglycans in thyroid eye disease. Thyroid 8:429–432
95. Kaiserling E (2001) Newly-formed lymph nodes in the submucosa in chronic inflammatory bowel disease. Lymphology 34:22–29
96. Kaufman J, Graf BA, Leung EC, Pollock SJ, Koumas L, Reddy SY, Blieden TM, Smith TJ, Phipps RP (2001) Fibroblasts as sentinel cells: role of the CDcd40-CDcd40 ligand system in fibroblast activation and lung inflammation and fibrosis. Chest 120:53S–55S
97. Kaufman J, Sime PJ, Phipps RP (2004) Expression of CD154 (CD40 ligand) by human lung fibroblasts: differential regulation by IFN-gamma and IL-13, and implications for fibrosis. J Immunol 172:1862–1871
98. Kaufmann J, Franke S, Kientsch-Engel R, Oelzner P, Hein G, Stein G (2001) Correlation of circulating interleukin 16 with proinflammatory cytokines in patients with rheumatoid arthritis. Rheumatology (Oxford) 40:474–475
99. Kazim M, Goldberg RA, Smith TJ (2002) Insights into the pathogenesis of thyroid-associated orbitopathy: evolving rationale for therapy. Arch Ophthalmol 120:380–386
100. Kemp EH, Metcalfe RA, Smith KA, Woodroofe MN, Watson PF, Weetman AP (2003) Detection and localization of chemokine gene expression in autoimmune thyroid disease. Clin Endocrinol (Oxf) 59:207–213
101. Kim WB, Chung HK, Park YJ, Park DJ, Lee HK, Cho BY (2001) Clinical significance of classification of Graves' disease according to the characteristics of TSH receptor antibodies. Korean J Intern Med 16:187–200

102. Kohm AP, Williams JS, Bickford AL, McMahon JS, Chatenoud L, Bach JF, Bluestone JA, Miller SD (2005) Treatment with nonmitogenic anti-CD3 monoclonal antibody induces CD4+ T cell unresponsiveness and functional reversal of established experimental autoimmune encephalomyelitis. J Immunol 174:4525–4534
103. Kosugi S, Inoue D, Sugawa H, Enomoto T, Mori T, Imura H (1990) Similarity and dissimilarity between clinical and laboratory findings, especially anti-thyrotropin receptor antibody in ophthalmic Graves' disease without persistent hyperthyroidism and hyperthyroid Graves' disease. Endocrinol Jpn 37:343–354
104. Kouki T, Sawai Y, Gardine CA, Fisfalen ME, Alegre ML, DeGroot LJ (2000) CTLA-4 gene polymorphism at position 49 in exon 1 reduces the inhibitory function of CTLA-4 and contributes to the pathogenesis of Graves' disease. J Immunol 165:6606–6611
105. Koumas L, Smith TJ, Phipps RP (2002) Fibroblast subsets in the human orbit: Thy-1+ and Thy-1- subpopulations exhibit distinct phenotypes. Eur J Immunol 32:477–485
106. Koumas L, Smith TJ, Feldon S, Blumberg N, Phipps RP (2003) Thy-1 expression in human fibroblast subsets defines myofibroblastic or lipofibroblastic phenotypes. Am J Pathol 163:1291–1300
107. Lalive PH, Menge T, Delarasse C, Della Gaspera B, Pham-Dinh D, Villoslada P, von Budingen HC, Genain CP (2006) Antibodies to native myelin oligodendrocyte glycoprotein are serologic markers of early inflammation in multiple sclerosis. Proc Natl Acad Sci USA 103:2280–2285
108. Lard LR, Roep BO, Verburgh CA, Zwinderman AH, Huizinga TW (2002) Elevated IL-16 levels in patients with systemic lupus erythematosus are associated with disease severity but not with genetic susceptibility to lupus. Lupus 11:181–185
109. Lard LR, Roep BO, Toes RE, Huizinga TW (2004) Enhanced concentrations of interleukin 16 are associated with joint destruction in patients with rheumatoid arthritis. J Rheumatol 31:35–39
110. Lee S, Kaneko H, Sekigawa I, Tokano Y, Takasaki Y, Hashimoto H (1998) Circulating interleukin-16 in systemic lupus erythematosus. Br J Rheumatol 37:1334–1337
111. Leonard JP, Waldburger KE, Schaub RG, Smith T, Hewson AK, Cuzner ML, Goldman SJ (1997) Regulation of the inflammatory response in animal models of multiple sclerosis by interleukin-12. Crit Rev Immunol 17:545–553
112. Ludewig B, Odermatt B, Landmann S, Hengartner H, Zinkernagel RM (1998) Dendritic cells induce autoimmune diabetes and maintain disease via de novo formation of local lymphoid tissue. J Exp Med 188:1493–1501
113. Ludgate M (2000) Animal models of Graves' disease. Eur J Endocrinol 142:1–8
114. Luo G, Seetharamaiah GS, Niesel DW, Zhang H, Peterson JW, Prabhakar BS, Klimpel GR (1994) Purification and characterization of Yersinia enterocolitica envelope proteins which induce antibodies that react with human thyrotropin receptor. J Immunol 152:2555–2561
115. Luther SA, Bidgol A, Hargreaves DC, Schmidt A, Xu Y, Paniyadi J, Matloubian M, Cyster JG (2002) Differing activities of homeostatic chemokines CCL19, CCL21, and CXCL12 in lymphocyte and dendritic cell recruitment and lymphoid neogenesis. J Immunol 169:424–433
116. McGregor AM (1990) Autoantibodies to the TSH receptor in patients with autoimmune thyroid disease. Clin Endocrinol (Oxf) 33:683–685
117. McMahon EJ, Bailey SL, Castenada CV, Waldner H, Miller SD (2005) Epitope spreading initiates in the CNS in two mouse models of multiple sclerosis. Nat Med 11:335–339
118. Macchia E, Concetti R, Borgoni F, Cetani F, Fenzi GF, Pinchera A (1989) Assays of TSH-receptor antibodies in 576 patients with various thyroid disorders: their incidence, significance and clinical usefulness. Autoimmunity 3:103–112
119. Mack WP, Stasior GO, Cao HJ, Stasior OG, Smith TJ (1999) The effect of cigarette smoke constituents on the expression of HLA-DR in orbital fibroblasts derived from patients with Graves ophthalmopathy. Ophthalmic Plast Reconstr Surg 15:260–271
120. Maini RN, Elliott M, Brennan FM, Williams RO, Feldmann M (1994) Targeting TNF alpha for the therapy of rheumatoid arthritis. Clin Exp Rheumatol 12 [Suppl 11]:S63–S66
121. Maini RN, Elliott MJ, Brennan FM, Feldmann M (1995) Beneficial effects of tumour necrosis factor-alpha (TNF-alpha) blockade in rheumatoid arthritis (RA). Clin Exp Immunol 101:207–212

122. Manzo A, Paoletti S, Carulli M, Blades MC, Barone F, Yanni G, Fitzgerald O, Bresnihan B, Caporali R, Montecucco C, Uguccioni M, Pitzalis C (2005) Systematic microanatomical analysis of CXCL13 and CCL21 in situ production and progressive lymphoid organization in rheumatoid synovitis. Eur J Immunol 35:1347–1359
123. Marchal-Somme J, Uzunhan Y, Marchand-Adam S, Valeyre D, Soumelis V, Crestani B, Soler P (2006) Cutting edge: nonproliferating mature immune cells form a novel type of organized lymphoid structure in idiopathic pulmonary fibrosis. J Immunol 176:5735–5739
124. Martins JR, Furlanetto RP, Oliveira LM, Mendes A, Passerotti CC, Chiamolera MI, Rocha AJ, Manso PG, Nader HB, Dietrich CP, Maciel RM (2004) Comparison of practical methods for urinary glycosaminoglycans and serum hyaluronan with clinical activity scores in patients with Graves' ophthalmopathy. Clin Endocrinol (Oxf) 60:726–733
125. Masteller EL, Warner MR, Tang Q, Tarbell KV, McDevitt H, Bluestone JA (2005) Expansion of functional endogenous antigen-specific CD4+CD25+ regulatory T cells from nonobese diabetic mice. J Immunol 175:3053–3059
126. Mattner F, Smiroldo S, Galbiati F, Muller M, Di Lucia P, Poliani PL, Martino G, Panina-Bordignon P, Adorini L (2000) Inhibition of Th1 development and treatment of chronic-relapsing experimental allergic encephalomyelitis by a non-hypercalcemic analogue of 1,25-dihydroxyvitamin D(3). Eur J Immunol 30:498–508
127. Metcalfe RA, Weetman AP (1994) Stimulation of extraocular muscle fibroblasts by cytokines and hypoxia: possible role in thyroid-associated ophthalmopathy. Clin Endocrinol (Oxf) 40:67–72
128. Middel P, Reich K, Polzien F, Blaschke V, Hemmerlein B, Herms J, Korabiowska M, Radzun HJ (2001) Interleukin 16 expression and phenotype of interleukin 16 producing cells in Crohn's disease. Gut 49:795–803
129. Misaki T, Iida Y, Kasagi K, Konishi J (2003) Seasonal variation in relapse rate of Graves' disease after thionamide drug treatment. Endocr J 50:669–672
130. Miyauchi S, Matsuura B, Onji M (2000) Increased levels of serum interleukin-18 in Graves' disease. Thyroid 10:815–819
131. Mourits MP, Prummel MF, Wiersinga WM, Koornneef L (1997) Clinical activity score as a guide in the management of patients with Graves' ophthalmopathy. Clin Endocrinol 47:9–14
132. Muhlberg T, Heberling HJ, Joba W, Schworm HD, Heufelder AE (1997) Detection and modulation of interleukin-1 receptor antagonist messenger ribonucleic acid and immunoreactivity in Graves' orbital fibroblasts. Invest Ophthalmol Vis Sci 38:1018–1028
133. Muhlberg T, Joba W, Spitzweg C, Schworm HD, Heberling HJ, Heufelder AE (2000) Interleukin-1 receptor antagonist ribonucleic acid and protein expression by cultured Graves' and normal orbital fibroblasts is differentially modulated by dexamethasone and irradiation. J Clin Endocrinol Metab 85:734–742
134. Musse AA, Boggs JM, Harauz G (2006) Deimination of membrane-bound myelin basic protein in multiple sclerosis exposes an immunodominant epitope. Proc Natl Acad Sci USA 103:4422–4427
135. Nagayama Y, Kita-Furuyama M, Ando T, Nakao K, Mizuguchi H, Hayakawa T, Eguchi K, Niwa M (2002) A novel murine model of Graves' hyperthyroidism with intramuscular injection of adenovirus expressing the thyrotropin receptor. J Immunol 168:2789–2794
136. Nunery WR, Martin RT, Heinz GW, Gavin TJ (1993) The association of cigarette smoking with clinical subtypes of ophthalmic Graves' disease. Ophthalmic Plast Reconstr Surg 9:77–82
137. O'Garra A, Vieira P (2004) Regulatory T cells and mechanisms of immune system control. Nat Med 10:801–805
138. Orgiazzi J (2000) Anti-TSH receptor antibodies in clinical practice. Endocrinol Metab Clin N Am 29:339–355
139. Pal R, Deshmukh US, Ohyama Y, Fang Q, Kannapell CC, Gaskin F, Fu SM (2005) Evidence for multiple shared antigenic determinants within Ro60 and other lupus-related ribonucleoprotein autoantigens in human autoimmune responses. J Immunol 175:7669–7677
140. Panina-Bordignon P, Mazzeo D, Lucia PD, D'Ambrosio D, Lang R, Fabbri L, Self C, Sinigaglia F (1997) Beta2-agonists prevent Th1 development by selective inhibition of interleukin 12. J Clin Invest 100:1513–1519

141. Pappa A, Jackson P, Stone J, Munro P, Fells P, Pennock C, Lightman S (1998) An ultrastructural and systemic analysis of glycosaminoglycans in thyroid-associated ophthalmopathy. Eye 12:237–244
142. Paul W (2003) Fundamental Immunology, 5th edn. Lippincott Williams and Wilkins, Philadelphia
143. Peyster RG, Ginsberg F, Silber JH, Adler LP (1986) Exophthalmos caused by excessive fat: CT volumetric analysis and differential diagnosis. AJR Am J Roentgenol 146:459–464
144. Pfeilschifter J, Ziegler R (1996) Smoking and endocrine ophthalmopathy: impact of smoking severity and current vs lifetime cigarette consumption. Clin Endocrinol (Oxf) 45:477–481
145. Phillips DI, Barker DJ, Rees Smith B, Didcote S, Morgan D (1985) The geographical distribution of thyrotoxicosis in England according to the presence or absence of TSH-receptor antibodies. Clin Endocrinol (Oxf) 23:283–287
146. Phipps RP, Baecher C, Frelinger JG, Penney DP, Keng P, Brown D (1990) Differential expression of interleukin 1 alpha by Thy-1+ and Thy-1– lung fibroblast subpopulations: enhancement of interleukin 1 alpha production by tumor necrosis factor-alpha. Eur J Immunol 20:1723–1727
147. Phipps RP, Stein SH, Roper RL (1991) A new view of prostaglandin E regulation of the immune response. Immunol Today 12:349–352
148. Pichurin P, Chen CR, Pichurina O, David C, Rapoport B, McLachlan SM (2003) Thyrotropin receptor-DNA vaccination of transgenic mice expressing HLA-DR3 or HLA-DQ6b. Thyroid 13:911–917
149. Prabhakar BS, Bahn RS, Smith TJ (2003) Current perspective on the pathogenesis of Graves' disease and ophthalmopathy. Endocr Rev 24:802–835
150. Pritchard J, Horst N, Cruikshank W, Smith TJ (2002) Igs from patients with Graves' disease induce the expression of T cell chemoattractants in their fibroblasts. J Immunol 168:942–950
151. Pritchard J, Han R, Horst N, Cruikshank WW, Smith TJ (2003) Immunoglobulin activation of T cell chemoattractant expression in fibroblasts from patients with Graves' disease is mediated through the insulin-like growth factor I receptor pathway. J Immunol 170:6348–6354
152. Prummel MF (1999) Pathogenetic and clinical aspects of endocrine ophthalmopathy. Exp Clin Endocrinol Diabetes 107 [Suppl 3]:S75–S78
153. Prummel MF, Wiersinga WM (1993) Smoking and risk of Graves' disease. JAMA 269:479–482
154. Prummel MF, Bakker A, Wiersinga WM, Baldeschi L, Mourits MP, Kendall-Taylor P, Perros P, Neoh C, Dickinson AJ, Lazarus JH, Lane CM, Heufelder AE, Kahaly GJ, Pitz S, Orgiazzi J, Hullo A, Pinchera A, Marcocci C, Sartini MS, Rocchi R, Nardi M, Krassas GE, Halkias A (2003) Multicenter study on the characteristics and treatment strategies of patients with Graves' orbitopathy: the first European Group on Graves' Orbitopathy experience. Eur J Endocrinol 148:491–495
155. Rees Smith B, McLachlan SM, Furmaniak J (1988) Autoantibodies to the thyrotropin receptor. Endocr Rev 9:106–121
156. Ringold DA, Nicoloff JT, Kesler M, Davis H, Hamilton A, Mack T (2002) Further evidence for a strong genetic influence on the development of autoimmune thyroid disease: the California twin study. Thyroid 12:647–653
157. Roper RL, Phipps RP (1994) Prostaglandin E2 regulation of the immune response. Adv Prostaglandin Thromboxane Leukot Res 22:101–111
158. Rotella CM, Zonefrati R, Toccafondi R, Valente WA, Kohn LD (1986) Ability of monoclonal antibodies to the thyrotropin receptor to increase collagen synthesis in human fibroblasts: an assay which appears to measure exophthalmogenic immunoglobulins in Graves' sera. J Clin Endocrinol Metab 62:357–367
159. Rundle F, Wilson C (1944) Bulging of the eyelids with exophthalmos. Clin Sci 5:31–45
160. Salmaso C, Olive D, Pesce G, Bagnasco M (2002) Costimulatory molecules and autoimmune thyroid diseases. Autoimmunity 35:159–167
161. Salomonsson S, Jonsson MV, Skarstein K, Brokstad KA, Hjelmstrom P, Wahren-Herlenius M, Jonsson R (2003) Cellular basis of ectopic germinal center formation and autoantibody production in the target organ of patients with Sjogren's syndrome. Arthritis Rheum 48:3187–3201
162. Salvi M, Girasole G, Pedrazzoni M, Passeri M, Giuliani N, Minelli R, Braverman LE, Roti E (1996) Increased serum concentrations of interleukin-6 (IL-6) and soluble IL-6 receptor in patients with Graves' disease. J Clin Endocrinol Metab 81:2976–2979
163. Saravanan P, Dayan CM (2001) Thyroid autoantibodies. Endocrinol Metab Clin N Am 30:315–337

164. Scotet E, Peyrat MA, Saulquin X, Retiere C, Couedel C, Davodeau F, Dulphy N, Toubert A, Bignon JD, Lim A, Vie H, Hallet MM, Liblau R, Weber M, Berthelot JM, Houssaint E, Bonneville M (1999) Frequent enrichment for CD8 T cells reactive against common herpes viruses in chronic inflammatory lesions: towards a reassessment of the physiopathological significance of T cell clonal expansions found in autoimmune inflammatory processes. Eur J Immunol 29:973–985
165. Seegert D, Schreiber S (2002) Overview: interleukin-16 and its role in inflammatory bowel disease. Curr Opin Investig Drugs 3:562–564
166. Seegert D, Rosenstiel P, Pfahler H, Pfefferkorn P, Nikolaus S, Schreiber S (2001) Increased expression of IL-16 in inflammatory bowel disease. Gut 48:326–332
167. Sekigawa I, Matsushita M, Lee S, Maeda N, Ogasawara H, Kaneko H, Iida N, Hashimoto H (2000) A possible pathogenic role of CD8+ T cells and their derived cytokine, IL-16, in SLE. Autoimmunity 33:37–44
168. Sempowski GD, Chess PR, Moretti AJ, Padilla J, Phipps RP, Blieden TM (1997) CD40 mediated activation of gingival and periodontal ligament fibroblasts. J Periodontol 68:284–292
169. Sempowski GD, Chess PR, Phipps RP (1997) CD40 is a functional activation antigen and B7-independent T cell costimulatory molecule on normal human lung fibroblasts. J Immunol 158:4670–4677
170. Sempowski GD, Rozenblit J, Smith TJ, Phipps RP (1998) Human orbital fibroblasts are activated through CD40 to induce proinflammatory cytokine production. Am J Physiol 274:C707–C714
171. Shenkman L, Bottone EJ (1976) Antibodies to Yersinia enterocolitica in thyroid disease. Ann Intern Med 85:735–739
172. Shimojo N, Arima T, Yamaguchi K, Kikuoka S, Kohn LD, Kohno Y (2000) A novel mouse model of Graves' disease: implications for a role of aberrant MHC class II expression in its pathogenesis. Int Rev Immunol 19:619–631
173. Shishido M, Kuroda K, Tsukifuji R, Fujita M, Shinkai H (1995) A case of pretibial myxedema associated with Graves' disease: an immunohistochemical study of serum-derived hyaluronan-associated protein. J Dermatol 22:948–952
174. Silman AJ, Newman J, MacGregor AJ (1996) Cigarette smoking increases the risk of rheumatoid arthritis. Results from a nationwide study of disease-discordant twins. Arthritis Rheum 39:732–735
175. Silvera MR, Phipps RP (1995) Synthesis of interleukin-1 receptor antagonist by Thy-1+ and Thy-1– murine lung fibroblast subsets. J Interferon Cytokine Res 15:63–70
176. Skillern PG (1972) Genetics of Graves' disease. Mayo Clin Proc 47:848–849
177. Smith RS, Smith TJ, Blieden TM, Phipps RP (1997) Fibroblasts as sentinel cells. Synthesis of chemokines and regulation of inflammation. Am J Pathol 151:317–322
178. Smith T, Hewson AK, Kingsley CI, Leonard JP, Cuzner ML (1997) Interleukin-12 induces relapse in experimental allergic encephalomyelitis in the Lewis rat. Am J Pathol 150:1909–1917
179. Smith TJ (1999) The putative role of prostaglandin endoperoxide H synthase-2 in the pathogenesis of thyroid-associated orbitopathy. Exp Clin Endocrinol Diabetes 107 [Suppl 5]:S160–S163
180. Smith TJ (2002) Orbital fibroblasts exhibit a novel pattern of responses to proinflammatory cytokines: potential basis for the pathogenesis of thyroid-associated ophthalmopathy. Thyroid 12:197–203
181. Smith TJ (2003) The putative role of fibroblasts in the pathogenesis of Graves' disease: evidence for the involvement of the insulin-like growth factor-1 receptor in fibroblast activation. Autoimmunity 36:409–415
182. Smith TJ, Hoa N (2004) Immunoglobulins from patients with Graves' disease induce hyaluronan synthesis in their orbital fibroblasts through the self-antigen, insulin-like growth factor-I receptor. J Clin Endocrinol Metab 89:5076–5080
183. Smith TJ, Bahn RS, Gorman CA, Cheavens M (1991) Stimulation of glycosaminoglycan accumulation by interferon gamma in cultured human retroocular fibroblasts. J Clin Endocrinol Metab 72:1169–1171
184. Smith TJ, Ahmed A, Hogg MG, Higgins PJ (1992) Interferon-γ is an inducer of plasminogen activator inhibitor type 1 in human orbital fibroblasts. Am J Physiol 263:C24–C29

185. Smith TJ, Wang HS, Evans CH (1995) Leukoregulin is a potent inducer of hyaluronan synthesis in cultured human orbital fibroblsts. Am J Physiol 268:C382–C388
186. Smith TJ, Sempowski GD, Berenson CS, Cao HJ, Wang HS, Phipps RP (1997) Human thyroid fibroblasts exhibit a distinctive phenotype in culture: characteristic ganglioside profile and functional CD40 expression. Endocrinology 138:5576–5588
187. Sorisky A, Pardasani D, Gagnon A, Smith TJ (1996) Evidence of adipocyte differentiation in human orbital fibroblasts in primary culture. J Clin Endocrinol Metab 81:3428–3431
188. Spicer AP, Kaback LA, Smith TJ, Seldin MF (1998) Molecular cloning and characterization of the human and mouse UDP-glucose dehydrogenase genes. J Biol Chem 273:25117–25124
189. Takemura S, Braun A, Crowson C, Kurtin PJ, Cofield RH, O'Fallon WM, Goronzy JJ, Weyand CM (2001) Lymphoid neogenesis in rheumatoid synovitis. J Immunol 167:1072–1080
190. Tallstedt L, Norberg R (1988) Immunohistochemical staining of normal and Graves' extraocular muscle. Invest Ophthalmol Vis Sci 29:175–184
191. Trembleau S, Penna G, Gregori S, Gately MK, Adorini L (1997) Deviation of pancreas-infiltrating cells to Th2 by interleukin-12 antagonist administration inhibits autoimmune diabetes. Eur J Immunol 27:2330–2339
192. Unutmaz D, Pileri P, Abrignani S (1994) Antigen-independent activation of naive and memory resting T cells by a cytokine combination. J Exp Med 180:1159–1164
193. Valyasevi RW, Harteneck DA, Dutton CM, Bahn RS (2002) Stimulation of adipogenesis, peroxisome proliferator-activated receptor-gamma (PPARgamma), and thyrotropin receptor by PPARgamma agonist in human orbital preadipocyte fibroblasts. J Clin Endocrinol Metab 87:2352–2358
194. Wakelkamp IM, Gerding MN, Van Der Meer JW, Prummel MF, Wiersinga WM (2000) Both Th1- and Th2-derived cytokines in serum are elevated in Graves' ophthalmopathy. Clin Exp Immunol 121:453–457
195. Wakelkamp IM, Gerding MN, van der Meer JW, Prummel MF, WiersingaWM (2002) Smoking and disease severity are independent determinants of serum adhesion molecule levels in Graves' ophthalmopathy. Clin Exp Immunol 127:316–320
196. Wakelkamp IM, Prummel MF, Wiersinga WM (2004) Serum IL-18 levels are not increased in patients with untreated Graves' ophthalmopathy. Hormone Metab Res 36:44–47
197. Wang HS, Cao HJ, Winn VD, Rezanka LJ, Frobert Y, Evans CH, Sciaky D, Young DA, Smith TJ (1996) Leukoregulin induction of prostaglandin-endoperoxide H synthase-2 in human orbital fibroblasts. An in vitro model for connective tissue inflammation. J Biol Chem 271:22718–22728
198. Weetman AP, McGregor AM (1984) Autoimmune thyroid disease: developments in our understanding. Endocr Rev 5:309–355
199. Weetman AP, Cohen S, Gatter KC, Fells P, Shine B (1989) Immunohistochemical analysis of the retrobulbar tissues in Graves' ophthalmopathy. Clin Exp Immunol 75:222–227
200. Wegelius O, Asboe-Hansen G, Lamberg BA (1957) Retrobulbar connective tissue changes in malignant exophthalmos. Acta Endocrinol (Copenh) 25:452–456
201. Weis-Klemm M, Alexander D, Pap T, Schutzle H, Reyer D, Franz JK, Aicher WK (2004) Synovial fibroblasts from rheumatoid arthritis patients differ in their regulation of IL-16 gene activity in comparison to osteoarthritis fibroblasts. Cell Physiol Biochem 14:293–300
202. Wenzel BE, Heesemann J, Wenzel KW, Scriba PC (1988) Patients with autoimmune thyroid diseases have antibodies to plasmid encoded proteins of enteropathogenic Yersinia. J Endocrinol Invest 11:139–140
203. Wenzel BE, Heesemann J, Wenzel KW, Scriba PC (1988) Antibodies to plasmid-encoded proteins of enteropathogenic Yersinia in patients with autoimmune thyroid disease. Lancet 1:56
204. Wenzel BE, Heesemann J, Heufelder A, Franke TF, Grammerstorf S, Stemerowicz R, Hopf U (1991) Enteropathogenic Yersinia enterocolitica and organ-specific autoimmune diseases in man. Contrib Microbiol Immunol 12:80–88
205. Westphal SA (1994) Seasonal variation in the diagnosis of Graves' disease. Clin Endocrinol (Oxf) 41:27–30
206. Weyand CM, Kurtin PJ, Goronzy JJ (2001) Ectopic lymphoid organogenesis: a fast track for autoimmunity. Am J Pathol 159:787–793
207. Wilson R, Buchanan L, Fraser WD, Jenkins C, Smith WE, Reglinski J, Thomson JA, McKillop JH (1998) Evidence for carbimazole as an antioxidant? Autoimmunity 27:149–153

208. Wolf MW, Misaki T, Bech K, Tvede M, Silva JE, Ingbar SH (1991) Immunoglobulins of patients recovering from Yersinia enterocolitica infections exhibit Graves' disease-like activity in human thyroid membranes. Thyroid 1:315–320
209. Wong GW, Cheng SH, Dorman JS (1999) The HLA-DQ associations with Graves' disease in Chinese children. Clin Endocrinol (Oxf) 50:493–495
210. Zantut-Wittmann DE, Boechat LH, Pinto GA, da Silva Trevisan MA, Vassallo J (1999) Autoimmune and non-autoimmune thyroid diseases have different patterns of cellular HLA class II expression. Sao Paulo Med J 117:161–164
211. Zhang Y, Cao HJ, Graf B, Meekins H, Smith TJ, Phipps RP (1998) CD40 engagement up-regulates cyclooxygenase-2 expression and prostaglandin E2 production in human lung fibroblasts. J Immunol 160:1053–1057
212. Ziff M (1989) Pathways of mononuclear cell infiltration in rheumatoid synovitis. Rheumatol Int 9:97–103
213. Zwerina J, Redlich K, Schett G, Smolen JS (2005) Pathogenesis of rheumatoid arthritis: targeting cytokines. Ann N Y Acad Sci 1051:716–729

Chapter 9

Decompression Surgery for Thyroid-Related Orbitopathy: Status of the Art and Unresolved Issues

9

Lelio Baldeschi

Core Messages

- In thyroid-related orbitopathy (TRO) disfigurement and functional deficits depend on raised intraorbital pressure.
- Decompression surgery is aimed at reducing raised intraorbital pressure by means of enlargement of the bony orbit and/or orbital fat removal.
- Decompression surgery can be used to address dysthyroid optic neuropathy and is the mainstay therapy for the treatment of stable typical disfiguring alterations, and/or symptoms of the disease. Recently, however, it has been linked to reactivation of stable orbitopathy.
- The multifaceted nature of the disease, the different indications for decompression surgery, surgeon preferences and expertise, variations in orbital osteology, and patients' expectations and attitude toward intervention and possible complications, imply the use of many different surgical techniques.
- Most of the techniques currently used seem to be effective in reversing or restoring optic nerve dysfunction, eye position, and/or congestive symptomatology and disfigurement; nevertheless, an unbiased analysis of the current literature in terms of effectiveness versus safety is extremely difficult due to the great heterogeneity of the patients included in the published studies and variations applied to surgical techniques.
- Fibrosis due to long-lasting orbital disease or possible consequence of retrobulbar irradiation administered in the early phase of TRO has been questioned as being a possible cause of poor distensibility and plasticity of the orbital soft tissues leading to diminished effectiveness of orbital expansion surgery. Recent investigations do not confirm this.
- Consecutive strabismus may complicate any decompression procedure. The pathogenesis of this complication is multifaceted and not completely understood.

9.1 Introduction

The autoimmune process at the root of thyroid orbitopathy (TRO) leads to accumulation of complex carbohydrates called glycosaminoglycans and collagen within the extraocular muscles and orbital fat. The consequent edema and fibrosis lead to marked swelling of the soft tissues confined within the boundary of the bony orbit with an increase in intraorbital pressure. Rarely, the increased intraorbital pressure is a cause of potentially sight-threatening conditions such as optic neuropathy or exposure keratopathy, but more frequently it leads to different degrees of venous congestion, strabismus, eyelid swelling, retraction, and exophthalmos. The latter four are principally responsible for the major aesthetic changes affecting patients with TRO.

In current clinical practice, besides strong recommendations to give up direct smoking, or to avoid passive smoking, prompt restoration of stable euthyroidism and immunosuppression, when necessary, are used as a first-line treatment. This aids in decreasing the duration of the early dynamic, active, inflammatory phase of the orbitopathy and in reversing its tendency to progress toward more severe symptomatology [7, 43, 44, 52]. In such a phase, when medical therapy fails, sight-threatening complications can benefit from functional orbital decompression, which is commonly performed by means of enlargement of the bony orbit [52].

Decompression surgery, by means of enlargement of the bony orbit or by orbital fat removal, is also the mainstay therapy for the rehabilitation of patients with TRO affected by stable disfiguring alterations, and/or symptoms such as retro-ocular pressure and/or grittiness due to mild corneal exposure that can typify the inactive postinflammatory phase of the disease. In addition, or as an alternative to orbital decompression, surgical rehabilitation of patients with TRO may need other interventions namely strabismus and functional and aesthetic eyelid surgery, which should be performed in this order, since each preceding step can influence the step that follows. What is to be expected from functional and rehabilitative orbital decompressions and various unresolved issues related to this type of surgery will be discussed in this chapter.

9.2 Orbital Decompression: No Technique Fits All

Since the beginning of the last century, orbital decompression has been used for the treatment of patients with TRO [12, 34]. Through the years there have been many proposed techniques and many variations. This has been largely due to the multifaceted nature of the disease, the different indications for decompression surgery, surgeon preferences and expertise, variations in orbital osteology, and patients' expectations and attitudes toward intervention. Furthermore, the constant attempt to implement the beneficial effects of this type of surgery, while simultaneously decreasing the aesthetic impact of surgical scars, the convalescence periods and risks of iatrogenic complications in general, and of consecutive strabismus in particular, has further extended the case scenario.

Independent of the specific technique, the basic principle underlying all decompression surgeries remains to reduce the contribution of mechanical factors to the development of the disease in the active phase, and to minimize their effects in the subsequent inactive phase. Mechanical factors play a crucial role in both active and inactive TRO. In the active phase, together with immunological and cellular processes, mechanical factors contribute to the positive feedback circle, which results in the progression of orbitopathy [2]. Later, during the post-inflammatory phase, these factors become the cause of the typical signs and symptoms of the disease.

Despite years of study, the exact mechanism causing the autoimmunity alterations of TRO still remains obscure. Specific medical therapy does not yet exist and the effect of nonspecific immunosuppressive treatments on stable disease dependent alterations is minimal [7, 42, 54]. As a consequence, raised intraorbital pressure, depending on expansion of the fat and/or the extraocular muscle compartments, together with the infiltration of the lacrimal gland, continues to be surgically addressed by expansion of the bony orbital boundary and/or by fat removal. These two possibilities, although developed separately, should no longer be considered alternatives, but rather complementary approaches to tailoring the most adequate treatment to the specific patient's needs [30].

Summary for the Clinician

- In thyroid-related orbitopathy, orbital decompression attained by means of enlargement of the bony orbit or of fat removal is an accepted method of addressing sight-threatening conditions or disfigurement.
- Surgery should be tailored to the specific patient's needs.

9.3 State of the Art and Unresolved Issues

9.3.1 Decompression for Functional Reasons

For optic neuropathy or for exposure keratopathy refractory to local measures and/or minor eyelid surgeries, orbital decompression has been widely used. Eyeball subluxation, which may be a possible cause of acute optic neuropathy and exposure keratopathy [46], and choroidal folds due to deformation of the eyeball secondary to extraocular muscle swelling, can also be addressed by means of orbital decompression. However, the true effectiveness of this surgical intervention as a first-line treatment for the severe functional implications of TRO remains uncertain.

In a recent large retrospective study, 84 patients with dysthyroid optic neuropathy (DON) treated with transantral orbital decompression as primary treatment showed an improvement in visual acuity and visual field defects in 74% and 71% of the cases respectively at follow-up examination after ≤182 days. A follow-up questionnaire mailed to the patients a median of 17.4 years after decompression, however, revealed that among those who responded to the questionnaire, after the first decompression, 21% required further decompression surgery, 7% radiotherapy, 7% glucocorticoids, and 58% squint surgery. The authors concluded that decompression surgery can offer a rapid solution to dysthyroid optic neuropathy with an acceptable list of adverse effects. They also advocate, however, the necessity of further investigations, to determine whether surgery or medical treatment is preferable [48].

Recently, we compared surgical and medical decompression as a first-line treatment for dysthyroid optic neuropathy by means of a randomized controlled clinical trial. We concluded that immediate decompression surgery did not result in a better outcome in terms of increased visual acuity, and therefore intravenous, followed by oral glucocorticoids appeared to be the first-choice therapy [52].

In line with our conclusions it resulted the trend of clinicians from three European professional organizations involved in the treatment of patients with TRO, namely the European Thyroid Association, the European Society of Ophthalmic Plastic and Reconstructive Surgery and the European Association of Nuclear Medicine, who answered a questionnaire sent by the European Group on Graves' Orbitopathy (EUGOGO) [14, 41]. In the case of DON, steroids in some form (oral, IV, subconjunctival/retrobulbar) were recommended by the vast majority (90.5%) of the responders, while surgical decompression (alone or in combination with other treatments) by only 20.9% [41].

Compression and stretching, vasculopathy, and inflammation have been quoted as being possible causes of optic nerve dysfunction in TRO [30], although the latter remains purely theoretical speculation that has never been confirmed by post-mortem histopathological studies [24]. Independently, if optic nerve dysfunction is caused by enlargement of the extraocular muscles or of the orbital fat compartment or by enlargement of both, it has been hypothesized that, when the volume of the soft tissues is reduced by means of fat removal or the volume of the bony orbit is expanded by any type of osteotomy, critical relief of pressure at the apex may be achieved. Data are available to support this idea [12, 24]. The predominant trend for addressing surgically dysthyroid optic neuropathy is, however, to remove the medial orbital wall [30]. In particularly severe cases, the removal of the lateral wall including its rim may result convenient in order to provide more room for reaching the orbital apex. Forces exerted by retractors in the attempt to reach the deepest part of the medial orbit can increase the already high retrobulbar pressure up to critical levels for optic nerve fibers and vasculature. The preventive removal of the lateral orbital wall per-

mits better access to the orbital apex, reducing, in fact, the risk of adding an iatrogenic component to the pathologically high orbital pressure associated with dysthyroid optic neuropathy. Of the various options for removing the medial orbital wall, the transconjunctival routes via either a transcaruncular or transinferior fornix approach, which offer an adequate exposure of the surgical site and leave no scars, are currently preferred [27, 31]. The endoscopic transnasal approach, described first and relatively recently by Kennedy [25], addressing the orbital apex without any substantial increase in the intraorbital pressure, can also be a valid alternative.

In TRO exophthalmos, increased palpebral fissure width, blink rate alterations, lid lag, lagophthalmos, deficit of elevation, and poor Bell's phenomenon can all be potentially associated with drying of the ocular surface. In the case of active TRO, ocular surface damage correlates significantly with reduced tear secretion, but not with increased ocular surface or impaired up gaze [13]. The lacrimal gland physiologically expresses the TSH receptor (TSHR), which, in active TRO, can bind with circulating anti-TSHR autoantibodies, contributing in fact to lacrimal gland impairment [13].

In contrast with these findings, Gilbard and Farris [15] reported that the damage to the ocular surface depends principally on a widened palpebral fissure that leads to increased ocular surface evaporation resulting in an elevated tear film osmolarity similar to that of kerato-conjunctivitis sicca. In their series of TRO patients, exophthalmos, lid lag, and lagophthalmos did not correlate with ocular surface damage, and tear secretion measured by the Schirmer test was normal. It is interesting to note that although the patients studied had TRO for only a short duration, it was not clear whether they were or not in the phase of the disease.

We recently reported the influence of decompression rehabilitative surgery on increased eyelid aperture. We found a decrease in eyelid aperture based equally on decreased upper and lower lid displacement in about 50% of our patients who presented preoperatively with increased eyelid aperture. All of these patients underwent decompression by means of a three-wall coronal approach, which left the upper and lower lid retractors undisturbed [4].

The literature concerning ocular surface alteration occurring in TRO is not extensive, and the effect of decompression surgery on severe corneal damages has never been specifically addressed. To date, no technique has been advocated primarily for correction of dysthyroid corneal exposure, and although most of the studies dealing with orbital decompression do indeed report a reduction in symptoms associated with exposure keratopathy, at least one case of a severe corneal ulcer refractory to decompression surgery in TRO has also been published [21].

Eyeball subluxation is another complication of TRO that requires urgent referral to a specialist center [55]. This complication, however, has not gained much attention in the ophthalmic literature, probably due to its rarity (0.1%) [46]. In affected patients, however, it is a recurrent complication that represents a potential cause of visual loss. Eyeball subluxation occurs in the type I "lipogenic" variant of TRO as described by Nunery, and never in the type II "myopathic" variant. Globe subluxation requires, in fact, extensibility of the extraocular muscles [38, 46]. It would appear that definitive treatment for globe subluxation would be achieved by either bony and/or orbital fat decompression. Studies addressing this specific issue, however, have not been reported.

Organized choroidal folds due to eyeball indentation secondary to enlarged extraocular muscles had been thought to be refractory to any orbital decompression, regardless of surgical technique [36]. Recently, however, a positive response of this complication to bony decompression surgery has been reported [23].

Summary for the Clinician

- The current trend for addressing surgically dysthyroid optic neuropathy is to remove the medial orbital wall, although critical relief of pressure at the apex can also be achieved with any type of osteotomy or fat removal.

9.3.2 Decompression for Rehabilitative Cosmetic/Psychosocial, and Symptomatic Reasons

9.3.2.1 Why Rehabilitative Surgery?

More than 800 years ago, before Caleb Parry (1786), Giuseppe Flajani (1802), Antonio Giuseppe Testa (1810), Robert James Graves (1835), and Karl Adolph von Basedow (1840), the Persian physician Sayyid Ismail Al-Jurjani, described the association of goiter and exophthalmos in the *Thesaurus of the Shah of Khwarazm*, the most famous of his five books, and the major medical dictionary of his time [28]. Long before this first description of TRO in the medical literature, however, the typical constellation of signs that characterize the staring expression of patients with TRO, its association with goiter, and psychotic behavior which may be related with hyperthyroidism should no doubt have been a source of criticism and prejudices resulting in social isolation for the affected patients. Traces of this can be detected as early as in the fourth century BC in Etruscan civilization where demonic creatures were given the appearance of patients affected by TRO [29].

Visible deformity, particularly involving the face, has always induced society's aversion. Patients with facial disfigurement suffer from intrusions such as staring or comments. At the root of the patient's distress lies social pressure to conform to an idealized appearance. The obsession regarding appearance devalues those who do not match the perceived ideal and stigmatizes those with visible disfigurement [50].

Despite the long-lasting social implications and medical recognition of TRO, its exact pathogenesis remains unknown. While waiting for a more specific and elegant medical approach, decompression surgery still remains an essential cornerstone in the treatment of this functionally and often aesthetically disabling disease.

9.3.2.2 Rehabilitative Decompression Surgery

For almost one century, decompression surgery has been used to treat TRO, first only to address functional problems, and, more recently, for the treatment of disfiguring exophthalmos, which affects as many as 62% of patients with TRO [8].

Orbital fat decompression was first described by Moore in 1920 [34]. A mean exophthalmos reduction of 6 mm and an improvement in extraocular eye motility have been reported by Olivari in a large series of patients, but similar results have not been confirmed by other authors [39, 51]. Orbital fat decompression has never achieved the popularity of bone decompression due to the possibility of complications (more theoretical than real) regarding this approach and which can include damage to the oculomotor, ciliary and lacrimal nerves, orbital vasculature, extraocular eye muscles, optic nerve, and the eyeball itself [1].

The history of orbital bone decompression surgery dates back to 1911, when Dollinger first proposed orbital enlargement by removing the lateral wall for the cure of exophthalmos [12]. Since then, various types of osteotomies, performed via different routes, have been proposed and continue to be debated. Historically, Hirsh (1930), Naffzinger (1931), Sewell (1936), and Walsh and Ogura (1957) who respectively proposed the removal of the orbital floor, roof, medial wall, and floor and medial wall are quoted as the pioneers of bony decompression surgery [22, 37, 47, 53].

In the 1980s, when the number of rehabilitative orbital decompressions started to rise [32], it became of primary importance to balance a given technique in terms not only of effectiveness in reducing exophthalmos, but also in terms of safety and morbidity. At that time antral–ethmoidal decompression via a transantral approach, as described by Walsh and Ogura in 1957, was the mainstay technique [35, 53]. The major disadvantage reported with transantral surgery was a subsequent motility imbalance as high as 52% [11], and therefore alternative procedures were sought in an attempt to decrease the risk of decompression-induced diplopia. In

cases of mild exophthalmos, trans-lid antral–ethmoidal decompression appeared to be a valid alternative, with a risk of iatrogenic diplopia in only 4.6% of patients [53]. For more severe exophthalmos, infero-medial decompression was used in combination with lateral decompression. Such procedures were also related to a low incidence of secondary diplopia [35]. In 1989, Leone and co-authors, in an attempt to further reduce post-decompression strabismus, proposed balancing the decompression by removing the medial and lateral orbital walls while sparing the floor [26]. This technique, which theoretically should have minimized the risk of iatrogenic diplopia, later appeared to be associated with a higher risk of this complication compared with removal of the lateral orbital wall alone, or with infero-medial and three-wall techniques [20, 40].

Recently, the lateral orbital wall, and in particular its deep portion, has been promoted as being the region of first choice for orbital decompression. Its removal, which is connected with a low risk of consecutive diplopia or severe complications, such as cerebrospinal fluid leak, perfectly fits the needs of an increasingly demanding patient population [16]. The effect of pure lateral wall decompression on exophthalmos reduction is, however, modest if not associated with fat or medial wall removal. Recently, we reported that the removal of the deep lateral wall as part of a rehabilitative coronal-approach three-wall decompression, enhances reduction of exophthalmos from 4.9 mm (SD = 1.1) to 7.2 mm (SD = 2.3) without increasing the risk of secondary diplopia [3]. Interestingly, the standard deviation of the exophthalmos reduction in the group of patients treated with removal of the deep lateral wall was approximately twice that of the group of patients who did not. We interpreted this finding as a manifestation of the known [54] inter-individual variability of the volume of the deep lateral wall. Overall, our findings suggest regarding to the deep lateral wall is an effective, although not always available, zone of possible orbital volume expansion [3, 19].

Rehabilitative decompression surgery is also aimed at addressing the uncomfortable retroocular tension that may characterize the post-inflammatory stage of TRO. When used for this purpose decompression surgery may be performed with minimally invasive techniques leading to minimal, if any, impact on extraocular motility or complications in general [9].

Most of the techniques currently used seem to be effective in restoring eye position and/or congestive symptomatology and disfigurement of the periorbital region. Nevertheless, an unbiased analysis of the current literature in terms of effectiveness versus safety is extremely difficult due to the great heterogeneity of the patients included in the published studies and variations applied to surgical techniques. Furthermore, it should be noted that the evidence in the literature concerning rehabilitative decompression surgery is modest, being based mainly on retrospective case series. In order to estimate the effectiveness of various surgical techniques, a prospective comparison of different treatment modalities along with different decompression surgeries, using a powerful tool such as the TRO quality of life questionnaire [49], has been advocated [9], and the EUGOGO [46] consortium, which represents a natural forum for this type of study, has recently embarked on this survey.

Fibrosis due to long-lasting orbital disease or as a possible consequence of retrobulbar irradiation administered in the early phase of TRO has been questioned as being a possible cause of reduced compliance, or rather poor distensibility and plasticity of the soft orbital tissues [56]. Reduced orbital compliance may diminish the effectiveness of orbital expansion surgery due to the fact that orbital soft tissues can fail to prolapse maximally into the newly created spaces [18].

In this respect, we recently found that orbital irradiation does not adversely interfere with the effects of decompression surgery and that early rehabilitative orbital decompression does not improve surgical outcome, but is associated with a higher risk of post-decompression diplopia [4, 6]. However, on the basis of these latter results, and being aware of the elevated emotional distress of patients disfigured by TRO, we had never thought to recommend delaying decompression surgery. Our results are supportive of proposing surgery in patients seeking rehabilitative decompression late after the onset of TRO [4].

Regarding bony decompression, it should also be pointed out that, in spite of theoretical expectations, severe complications are actually rare in clinical practice. Common complications of this surgical approach are secondary strabismus, infraorbital hypoesthesia and sinusitis [10], lower lid entropion [17], and eyeball dystopia [45]. Leakage of cerebrospinal fluid, infections involving the central nervous system, damage to the optic nerve or its vasculature, cerebral vasospasm, ischemia, and infarction are rare events [33]. Recently, we described an apparent reactivation of TRO after rehabilitative bony orbital decompression in 3 out of 239 patients not treated with perioperative glucocorticoids. This phenomenon occurs in the onset of typical signs and symptoms of active TRO with radiologic evidence of extraocular muscle enlargement a few weeks after surgery and following a normal convalescence period. Based on its clinical characteristics, we proposed naming our observation delayed decompression-related reactivation or DDRR. Although the incidence of DDRR appeared to be to the order of 1.3%, and could be controlled with systemic immunosuppression or retrobulbar irradiation, it is a complication that deserves to be recognized by physicians and should be mentioned to those patients undergoing rehabilitative decompression surgery [5].

Diplopia has a considerable impact on the quality of life of patients with TRO and is a feared complication that often causes patients and physicians to refrain from undertaking decompression rehabilitative surgery. In light of the current literature, strabismus subsequent to decompression surgery has been linked to mechanical and neurological implications connected with the "lipogenic or myopathic" types of TRO [38]. The surgical route, the extension and location of the osteotomy, and respecting structures such as the maxillary ethmoidal strut or the anterior periorbita can all play a role in reducing this complication. Differing types of motor and/or sensory capacities for compensating for induced muscle imbalance may also be contributing factors [4]

Summary for the Clinician

- Deep lateral wall decompression has recently been promoted as an elective, safe area for rehabilitative orbital decompression. However, due to anatomical variations, it is not always available as a zone of possible orbital volume expansion. Associated fat removal from the inferior lateral orbital quadrant can enhance the rehabilitative effect of lateral bone decompression.
- Secondary strabismus has been a more frequent complication of decompression surgery.
- Until a more specific and elegant medical therapy becomes available, orbital decompression remains a very valuable tool in improving impaired visual function, comfort, and appearance of patients with TRO.
- A better understanding of the pathogenesis of strabismus secondary to orbital decompression would be desirable.

References

1. Adenis JP, Rober PY, Lasudry JGH, Dalloul Z (1998) Treatment of proptosis with fat removal orbital decompression in Graves' ophthalmopathy. Eur J Ophthalmol 8:246–252
2. Bahn RS (2003) Pathophysiology of Graves' ophthalmopathy: the cycle of disease. J Clin Endocrinol Metab 88:1939–1946
3. Baldeschi L, MacAndie K, Hintschich C, et al. (2005) The removal of the deep lateral wall in decompression surgery: its contribution to exophthalmos reduction and influence on consecutive diplopia. Am J Ophthalmol 140:642–647
4. Baldeschi L, Wakelkamp IMMJ, Lindeboom R, et al. (2006) Early versus late orbital decompression in Graves' orbitopathy: a retrospective study in 125 patients. Ophthalmology 113:874–878
5. Baldeschi L, Lupetti A, Vu P, et al. (2007) Reactivation of Graves' orbitopathy after rehabilitative orbital decompression. Ophthalmology 114:1395–402

6. Baldeschi L, MacAndie K, Koetsier E, Blank LE, Wiersinga WM (2007) The influence of previous orbital irradiation on the outcome of rehabilitative decompression surgery in Graves orbitopathy. Am J Ophthalmol, submitted
7. Bartalena L, Pinchera A, Marcocci C (2000) Management of Graves' ophthalmopathy: reality and perspectives. Endocr Rev 21:168–199
8. Bartley GB, Fatourechi V, Kadrmas EF, et al. (1996) Clinical features of Graves' ophthalmopathy in an incidence cohort. Am J Ophthalmol 121:284–290
9. Ben Simon GJ, Schwarcz RM, Mansury AM, et al. (2005) Minimally invasive orbital decompression: local anesthesia and hand-carved bone. Arch Ophthalmol 123:1671–1675
10. Carrasco JR, Castillo I, Bilyk JR, et al. (2005) Incidence of infraorbital hypesthesia and sinusitis after orbital decompression for thyroid-related orbitopathy: a comparison of surgical techniques. Ophthal Plast Reconstr Surg 21:188–191
11. De Santo LW (1984) Transantral orbital decompression. In: Gorman CA, Waller RR, Dyer JA (eds) The eye and orbit in thyroid disease. Raven, New York, pp 231–251
12. Dollinger J (1911) Die Druckentlastung der Augenhöhle durch Entfernung der äußeren Orbitawand bei hochgradigem Exophthalmos (Morbus Basedowii) und konsekutiver Hauterkrankung. Dtsch Med Wochenschr 37:1888–1890
13. Eckstein AK, Finkenrath A, Heiligenhaus A, et al. (2004) Dry eye syndrome in thyroid-associated ophthalmopathy: lacrimal expression of TSH receptor suggests involvement of TSHR-specific autoantibodies. Acta Ophthalmol Scand 82:291–297
14. European Group on Graves' Orbitopathy consortium www.eugogo.org
15. Gilbard JP, Farris RL (1983) Ocular surface drying and ocular tear film osmolarity in thyroid eye disease. Acta Ophthalmol (Copenh) 61:108–116
16. Goldberg RA (1998) The evolving paradigm of orbital decompression surgery. Arch Ophthalmol 116:95–96
17. Goldberg RA, Christenbury JD, Shorr N (1988) Medial entropion following orbital decompression for dysthyroid ophthalmopathy. Ophthal Plast Reconstr Surg 4:81–85
18. Goldberg RA, Weinberg DA, Shorr N, Wirta D (1997) Maximal three-wall orbital decompression through a coronal approach. Ophthalmic Surg Lasers 28:832–843
19. Goldberg RA, Kim AJ, Kerivan KM (1998) The lacrimal keyhole, orbital door jamb, and basin of the inferior orbital fissure. Three areas of deep bone in the lateral orbit. Arch Ophthalmol 116:1618–1624
20. Goldberg RA, Perry JD, Hortoleza V, Tong JT (2000) Strabismus after balanced medial plus lateral wall versus lateral wall only orbital decompression for dysthyroid orbitopathy. Ophthal Plast Reconstr Surg 16:271–277
21. Heinz C, Eckstein A, Steuhl KP, Meller D (2004) Amniotic membrane transplantation for reconstruction of corneal ulcer in Graves' ophthalmopathy. Cornea 23:524–526
22. Hirsch VO, Urbanek I (1930) Behandlung eines excessiven Exophthalmus (Basedow) durch Entfernung von Orbitafett von der Kieferhöhle aus. Monatsschr Ohrenheilk Laryngorhinol 64:212–213
23. Jorge R, Scott IU, Akaishi PM, et al. (2003) Resolution of choroidal folds and improvement in visual acuity after orbital decompression for graves orbitopathy. Retina 23:563–565
24. Kazim M, Trokel SL, Acaroglu G, Elliot A (2000) Reversal of dysthyroid optic neuropathy following orbital fat decompression. Br J Ophthalmol 84:600–605
25. Kennedy DW, Goldstein ML, Miller NR, Zinreich SJ (1990) Endoscopic transnasal orbital decompression. Arch Otolaryngol Head Neck Surg 116:275–282
26. Leone CR, Piest KL, Newman RJ (1989) Medial and lateral wall decompression for thyroid ophthalmopathy. Am J Ophthalmol 108:160–166
27. Liao SL, Chang TC, Lin LL (2006) Transcaruncular orbital decompression: an alternate procedure for Graves ophthalmopathy with compressive optic neuropathy. Am J Ophthalmol 141:810–818
28. Ljunggren JG (1983) Who was the man behind the syndrome: Ismail al-Jurjani, Testa, Flagani, Parry, Graves or Basedow? Use the term hyperthyreosis instead. Lakartidningen 80:2902
29. Martinelli M (2005) Demone di Sarteano. Una Patologia? (Demon of Sarteno. Was it a disease?). Archeologia Viva. Giunti, Florence
30. McCann JD, Goldberg RA, Anderson RL, et al. (2006) Medial wall decompression for optic neuropathy but lateral wall decompression with fat removal for non vision-threatening indications. Am J Ophthalmol 141:916–917

31. McCord CD (1981) Orbital decompression for Graves' disease: exposure through lateral canthal and inferior fornix incision. Ophthalmology 88:533–541
32. McCord CD (1985) Current trends in orbital decompression. Ophthalmology 92:21–33
33. McCormick CD, Bearden WH, Hunts JH, Anderson RL (2004) Cerebral vasospasm and ischemia after orbital decompression for Graves ophthalmopathy. Ophthal Plast Reconstr Surg 20:347–351
34. Moore RF (1920) Exophthalmos and limitation of eye movements of Graves' disease. Lancet 2:701
35. Mourits MP, Koornneef L, Wiersinga WM, et al. (1990) Orbital decompression for Graves' ophthalmopathy by inferomedial, by inferomedial plus lateral, and by coronal approach. Ophthalmology 97:636–641
36. Mourits MP, Rose GE, Garrity JA, et al. (2000) Surgical management of Graves' ophthalmopathy. In: Prummel MF (ed) Recent developments in Graves' ophthalmopathy. Kluwer, Dordrecht, pp 133–169
37. Naffziger HC (1931) Progressive exophthalmos following thyroidectomy; its pathology and treatment. Ann Surg 94:582–586
38. Nunery WR (1991) Ophthalmic Graves' disease: a dual theory of pathogenesis. Ophthalmol Clin North Am 4:73–87
39. Olivari N (1988) [Transpalpebral decompression operation in endocrine orbitopathy (exophthalmos)]. Wien Med Wochenschr 18:138–142
40. Paridaens D, Hans K, van Buiten S, Mourits MP (1998) The incidence of diplopia following coronal and trans lid orbital decompression in Graves' orbitopathy. Eye 12:800–805
41. Perros P, Baldeschi L, Boboridis K, et al. (2006) A questionnaire survey on the management of Graves' orbitopathy in Europe. Eur J Endocrinol 155:207–211
42. Prummel MF (1999) Medical treatment of thyroid-associated orbitopathy. Exp Clin Endocrinol Diabetes 107:198–200
43. Prummel MF, Mourits MP, Koornneef L, et al. (1989) Prednisone and cyclosporine in the treatment of severe Graves' ophthalmopathy. N Engl J Med 321:1353–1359
44. Prummel MF, Wiersinga WM, Mourits MP, et al. (1990) Effect of abnormal thyroid function on the severity of Graves' ophthalmopathy. Arch Intern Med 150:1098–1101
45. Rose GE, Lund VJ (2003) Clinical features and treatment of late enophthalmos after orbital decompression: a condition suggesting cause for idiopathic "imploding antrum" (silent sinus) syndrome. Ophthalmology 110:819–826
46. Rubin PAD, Watkins LM, Rumelt S, et al. (1998) Orbital computed tomographic characteristics of globe subluxation in thyroid orbitopathy. Ophthalmology 105:2061–2064
47. Sewall EC (1936) Operative control of progressive exophthalmos. Arch Otolaryngol 24:621–624
48. Soares-Welch CV, Fatourechi V, Bartley GB, et al. (2003) Optic neuropathy of Graves disease: results of transantral orbital decompression and long-term follow-up in 215 patients. Am J Ophthalmol 136:433–441
49. Terwee CB, Dekker FW, Mourits MP, et al. (2001) Interpretation and validity of changes in scores on the Graves' ophthalmopathy quality of life questionnaire (GO-QOL) after different treatments. Clin Endocrinol (Oxf) 54:391–398
50. Terwee CB, Dekker FW, Bonsel GJ, et al. (2003) Facial disfigurement: is it in the eye of the beholder? A study in patients with Graves' ophthalmopathy. Clin Endocrinol (Oxf) 58:192–198
51. Trokel S, Kazim M, Moore S (1993) Orbital fat removal, decompression for Graves ophthalmopathy. Ophthalmology 100:674–682
52. Wakelkamp IMMJ, Baldeschi L, Saeed P, et al. (2005) Surgical or medical decompression as a first line treatment of optic neuropathy in Graves' ophthalmopathy? A randomized controlled trial. Clin Endocrinol (Oxf) 63:323–328
53. Walsch TE, Ogura JH (1957) Transantral orbital decompression for malignant exophthalmos. Laryngoscope 67:544–568
54. Wiersinga WM, Prummel MF (2000) An evidence-based approach to the treatment of Graves' ophthalmopathy. Endocrinol Metab Clin North Am 29:297–319
55. Wiersinga WM, Perros P, Kahaly GJ, et al. (2006) Clinical assessment of patients with Graves' orbitopathy: the European group for Graves' orbitopathy recommendations to generalists, specialists and clinical researchers. Eur J Endocrinol 155:387–389
56. Wilson WB, Manke WF (1991) Orbital decompression in Graves' disease: the predictability of reduction of proptosis. Arch Ophthalmol 109:343–345

Chapter 10

Orbital Volume Augmentation with Injectable Self-inflating Hydrogel Pellet Expanders: A Minimally Invasive Approach

10

Michael P. Schittkowski, Rudolf F. Guthoff

Core Messages

- Children suffering from congenital clinical anophthalmos or microphthalmos require prolonged and complicated socket management.
- Since 1997 a novel therapeutic concept with highly hydrophilic self-expanding hydrogel expanders has been available.
- Injectable self-inflating hydrogel pellet expanders are suitable for minimally invasive volume augmentation in congenital and aquired orbital volume deficiency.

10.1 Introduction

Children suffering from congenital clinical anophthalmos or microphthalmos require prolonged and complicated socket management, and this is more difficult when the globe is not clinically apparent [19]. Therapeutic options include the use of rigid conformers [6, 7], low hydrophilic [8] or, more recently, highly hydrophilic self-expanding hydrogel expanders [23, 28].

Since 1997 our team in Rostock has been developing a therapeutic concept with highly hydrophilic self-expanding hydrogel expanders for use in patients with congenital anophthalmos [23, 28]. To date, 60 children have been treated with this type of expander.

The expander is made of a highly hydrophilic hydrogel consisting of N-vinyl pyrrolidone and methyl methacrylate [30]. It automatically takes up water by osmosis and is therefore self-inflating. The amount of expansion (swelling capacity) can be engineered up to 50-fold. In the dry state the expander is hard and can be produced in any desired shape. In the hydrated state after about 1–2 days, the dimensions increase to the final volume and the expander becomes softer. Consistency is dependent on swelling capacity; the greater the swelling, the softer the implant. The recommended swelling capacity ranges from 6.7- to a maximum of 12.8-fold.

This technique has recently been reviewed by Mazzoli et al. [23] and now appears to be well accepted. Offering the benefit of predictable and controllable self-expansion, hydrogel expanders has become an alternative therapy to the early rehabilitation of the contracted socket.

At the congress of the American Society of Ophthalmic Plastic and Reconstructive Surgery (ASOPRS) in 2003, Li et al. [20] suggested using injectable hydrogel implants made of the same material as a technical modification to achieve volume augmentation in adults with acquired anophthalmic enophthalmos. We have reported this method for congenital microphthalmos and preliminary results were promising [27].

Dermatologists, craniofacial surgeons, ENT, and plastic surgeons also use this technology to fill volume defects, usually a temporary measure before removing the expanders and replacing them with other materials (P. Lohse [osmed GmbH, Ilmenau, Germany], personal communication). Mischkowski and Kübler [24] recently reported inserting eight pellets into the nasal tip and supratip region to prepare for successful correction with cartilage 4 weeks later in congenital nasal hypoplasia associated with Kallmann syndrome in a 20-year-old patient.

This chapter describes the aspects of orbital volume augmentation with injectable self-inflating hydrogel pellet in congenital and aquired orbital volume deficiency and our own practical approach to the technique. We have reviewed the notes of all patients who have been treated in our department to date.

10.2 Compensation for Orbital Volume Deficiency in Congenital Disease

10.2.1 Congenital Blind Microphthalmos

10.2.1.1 Symptoms

Congenital microphthalmos is said to be more common than congenital anophthalmos and has a prevalence rate of between 1.2 and 1.8 per 10,000 births in white populations [35]. It is assessed as being present if the age-adjusted axial diameter is below the 95th percentile [39]. According to the classification proposed by Warburg, the condition described in this chapter is simple total microphthalmos – a visible globe when opening the lid fissure [39]. All patients included in this series were without light perception in the microphthalmic eye. We do not recommend expandable implants in an orbit containing a seeing eye.

When the eyeball is reduced in volume it is deeply set in a small orbit. The palpebral fissure is usually narrowed, and in most cases there may be a fairly deep socket present with proper fornices (Fig. 10.1). In such circumstances it is much easier to fit an artificial eye compared with congenital anophthalmos where the lid fissure is much shorter and fornices are usually missed.

In the case of a small microphthalmos with an axial length that differs significantly from the healthy side or from normal values, an orbital volume deficit results [19, 29]. The smaller the presentation of the microphthalmic eye, the more significant this becomes. While such an orbital volume deficit can be partially compensated for with a prosthesis, the degree of adjustment from the patient's perspective is determined by the lid fissure width, which limits the size and shape of any prosthesis that can be placed in the conjunctival sac. Therefore, even with the best fitting artificial eye, there may be some residual volume deficit that appears as enophthalmos. Consequently, there is often a need to supplement orbital volume.

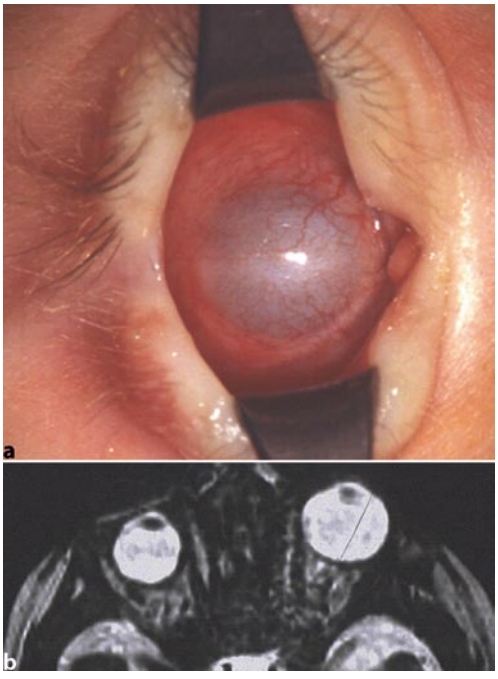

Fig. 10.1 **a** Tight blind microphthalmos: the fornices are well developed; therefore, a prosthesis may be inserted. **b** MRI of the same patient

10.2.1.2 Method

10.2.1.2.1 Ophthalmic Evaluation

Ophthalmic evaluation must initially determine the presence or absence of any visual potential. Depending on the patient's age and degree of pathology, tests were used to assess for fixation, ability to follow moving objects or preferential looking. Visual evoked potentials (VEP) were additionally determined in all patients. Oculoplastic rehabilitation was only started once it was established that there was no visual potential in the microphthalmic eye.

Specific concerns for oculoplastic evaluation were first directed toward the microphthalmic socket in unilateral cases, but the status of the contralateral, hopefully healthy side was examined very precisely to exclude any accompanying pathology.

10.2.1.2.2 Expander Data

The pellet expander (Fig. 10.2) is made of the same highly hydrophilic hydrogel. In the dry state the pellet expander is 8 mm in length and 2 mm in diameter with a volume of 0.025 ml. In vitro, in the hydrated state after about 1 day, these dimensions increase to 15 mm in length and 4 mm in diameter, with a final volume of 0.24 ml. The swelling capacity is therefore 9.6-fold.

10.2.1.2.3 Expander Implantation

The first step was to insert a custom-made, usually double-walled glass prosthesis (Fig. 10.3). The size of the volume deficit was calculated by injecting sterile saline solution or local anesthetic (Fig. 10.4). The fluid was injected through a standard retrobulbar needle until symmetry with the healthy side was achieved, as monitored using

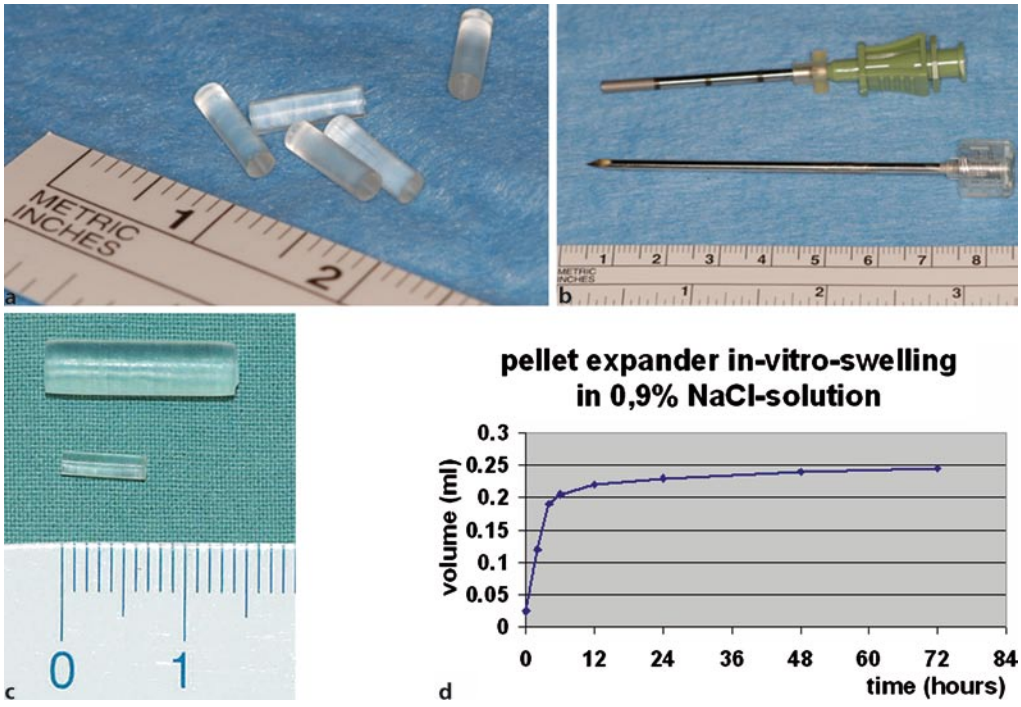

Fig. 10.2 **a** Pellet expanders. **b** Trocar needle system for implantation. **c** Pellet expanders, before (*bottom*) and after (*top*) in vitro swelling in 0.9% sodium chloride**. d** In vitro swelling curve in 0.9% NaCl solution

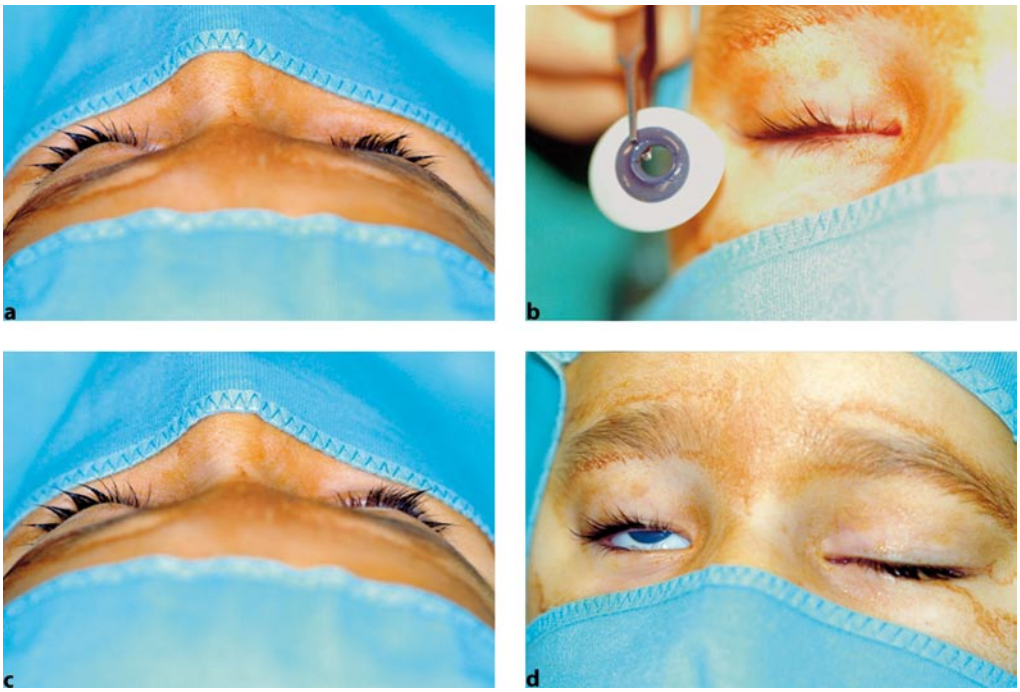

Fig. 10.3 **a** Right-sided enophthalmos due to congenital microphthalmos. **b** First prosthesis before insertion. **c** Prosthesis is fitted, enophthalmos with the prosthesis is reduced, but still significant. **d** No symmetry with the prosthesis alone

intraoperative Hertel measurements. The volume injected was divided by the potential final expander volume of 0.24 ml to yield the number of pellets needed for injection. The pellets were injected via the same cutaneous approach using a customized trocar and were placed behind the microphthalmic globe directed into the intraconal space (Fig. 10.5). The skin was closed with a single suture only.

10.2.1.3 Results

To date, 13 patients with unilateral microphthalmos have been treated with injectable pellet expanders made from self-inflating hydrogel (Figs. 10.6–10.8, Table 10.1). Eleven had unilateral anophthalmos and a healthy seeing fellow eye. Two had unilateral microphthalmos and anophthalmos in the fellow orbit, which was treated with regular hydrophilic expanders [30]. All patients were otherwise healthy and there was no family history of malformations.

All patients experienced improved orbital volume after injection. The main volume increase was noticeable within the first 24 h and was completed within 2 days. This finding was confirmed by ultrasonography and MRI (Figs. 10.6–10.8).

As far as we have been able to judge, these young patients experienced no significant pain during the expansion period. Three patients needed no specific medication for pain relief, 8 patients received one paracetamol suppository on the evening after implantation, and 2 patients received one paracetamol suppository daily for 3 days.

Preoperatively, all microphthalmic eyes showed some motility in all directions of gaze. Pellet implantation did not appear to affect motility in any of the cases.

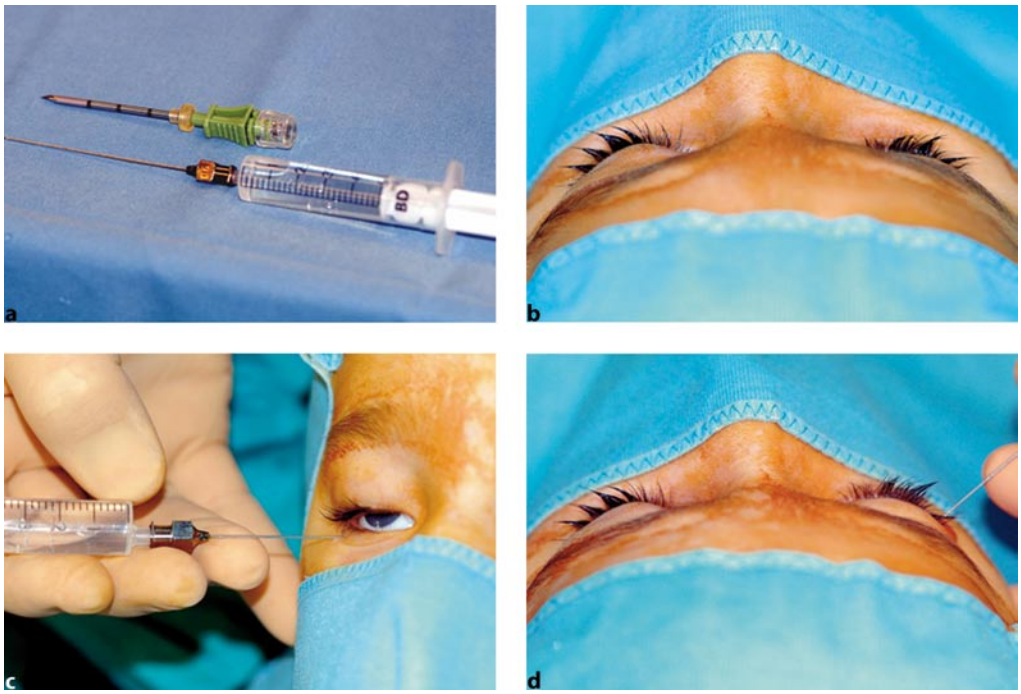

Fig. 10.4 **a** Local anesthetic with a regular retrobulbar needle for injection for volume calculation. **b** Patient from Fig. 10.3 with a prosthesis inserted. **c** Volume injection starts. **d** Volume deficit calculation, symmetry is achieved after 3.5-ml local anesthetic injection

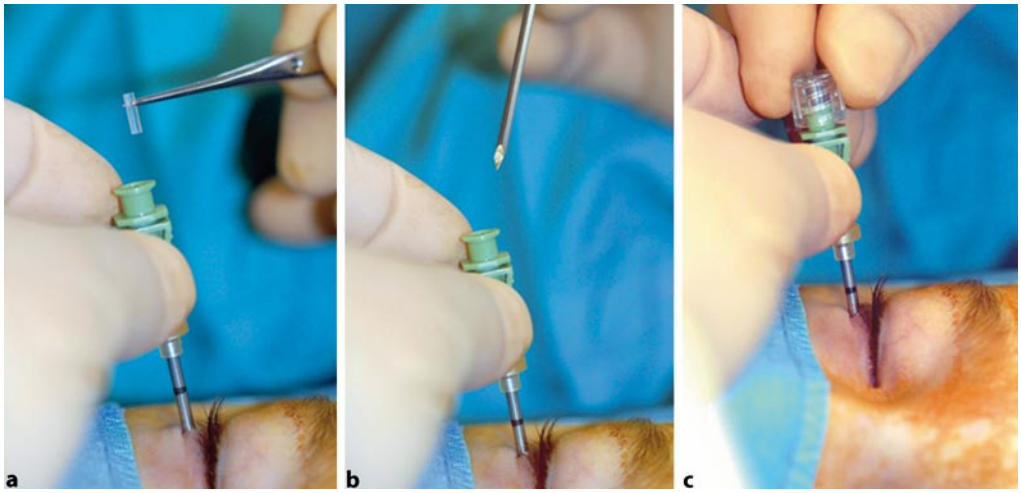

Fig. 10.5 Expander injection. Trocar needle is placed into the retrobulbar tissue in the intraconal space, the pellet expander is inserted and pushed into the tissue

Table 10.1. Microphthalmic patients treated with pellet expanders. *RE* right eye, *LE* left eye

Number	Sex	Side	Age at 1st expander (months)	Axial length (mm) RE/LE	Number of pellets	Prosthesis	Further pellets implanted	Further enlargement prosthesis	Follow-up (months)	Remarks
Unilateral microphthalmos										
1	Male	LE	5	19/11	4	Yes	At age 7 months 10 more pellets	Yes	32	First patient ever treated, for safety reasons fewer expanders used
2	Male	RE	7	10/22	7	Yes		Yes	26	Lost to follow-up
3	Male	RE	8	8/21	8	Yes	Planned	Yes	24	
4	Male	LE	8	21/12	10	Yes		Yes	22	
5	Male	RE	4	8/22	10	Yes		Yes	21	
6	Female	RE	42	14/23	14	Yes		Yes	21	
7	Male	LE	6	19.5/10	10	Yes		Yes	14	
8	Male	LE	5	20/9	10	Yes		Yes	5	
9	Male	LE	4	19/9	8	Yes		Yes	4	
10	Male	RE	20	14/22	10	Yes		Planned	3	
11	Female	LE	90	22/12	9	Yes		Planned	3	
Unilateral microphthalmos, other side anophthalmos										
12	Female	LE	6	Not measured	5	Yes		Yes	5	
13	Male	LE	16	Not measured	11	Yes		Yes	3	
Average	Male 10 Female 3	RE 5 LE 8	Ø 17 4–90	Ø 10.6 8–14	Ø 8.9 4–14	All	1 performed 1 planned	All	Ø 14.1 3–32	

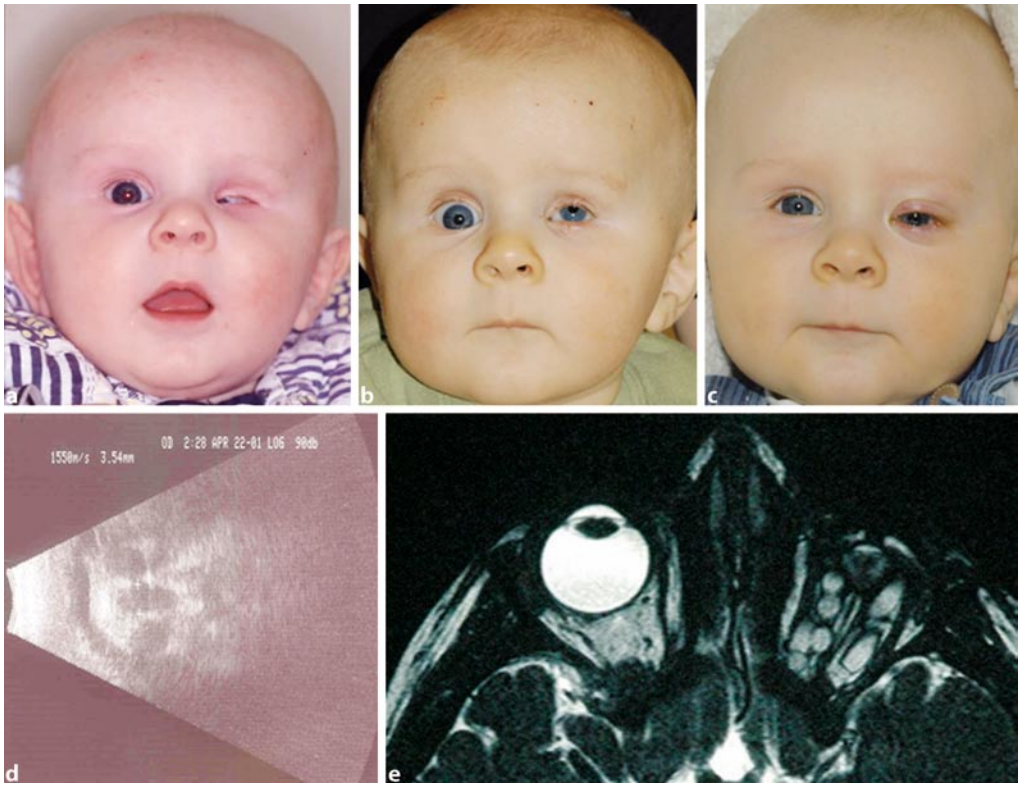

Fig. 10.6 Five-month-old boy with congenital microphthalmos. **a** Left-sided microphthalmos, axial length 11 mm. **b** After injection of four pellets (2.5 ml), a prosthesis could be fitted, but significant enophthalmos remains. **c** Three months later another 10 pellets were injected, and enophthalmos was fully compensated. **d** Postoperative ultrasound demonstrates retrobulbar expander placement. **e** MRI

In each case the prosthesis was subsequently replaced with a larger size, as dictated by the clinical impression. So far no re-injection has been necessary, except in the very first patient who received an injection of less than the calculated volume for safety reasons. To date, none of the patients has experienced expander prolapse or extrusion. No inflammatory signs or other side effects have been observed.

10.2.2 Congenital Clinical Anophthalmos

Thus far, two patients have been treated:

A 6-year old boy with unilateral anophthalmos and a healthy fellow eye was treated with the regular socket and orbital expanders [30] until a 3-ml spherical orbital expander was inserted in July 2002, which is still in place. To treat an orbital volume deficit five pellet expanders were injected transconjunctivally behind the orbital expander in August 2004. This technique was preferred to increasing the 3-ml spherical expander to 4 ml because of the very short anesthesia, which was needed due to the severe general medical problems he had developed in between.

A second patient is a 4-year old girl with unilateral anophthalmos. The fellow eye had sclerocornea with light perception only. On the anophthalmic side, after initial implantation of a hemisphere conjunctival sac expander, an orbital 2-ml expander was later used, which was

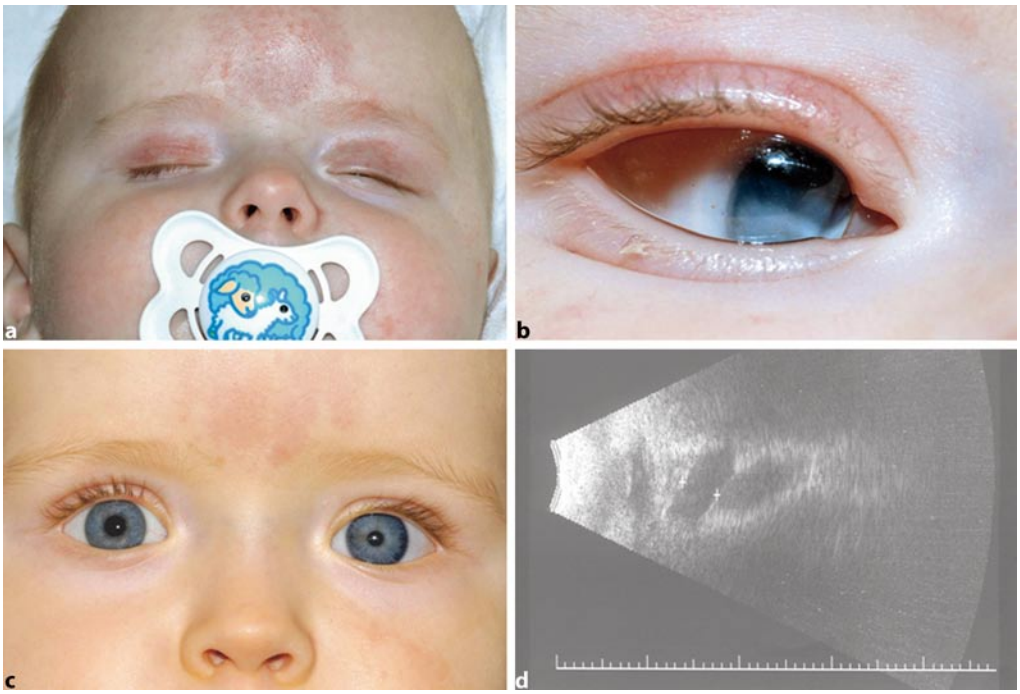

Fig. 10.7 Four-month-old boy – congenital microphthalmos. **a** Right-sided microphthalmos, axial length 8 mm. **b** Patient had been treated with conformers before, but no prosthesis could be fitted. **c** Symmetric situation with ten pellets (2.5 ml) injected and a prosthesis. **d** Postoperative ultrasound

lost 4 weeks postoperatively after extrusion. For re-implantation a 0.9-ml hemisphere expander (1-ml spheres were not yet available) was used. Because of the fear of loss of another expander, pellet expander were implanted twice (five pellets each time).

The technique of implantation was similar to that for microphthalmos as described above, and the expander injection was directed behind the orbital expander in place.

10.2.3 Side Effects

No side effects occurred in congenital anophthalmic or microphthalmic patients, despite the fact that, for safety reasons, in the very first patient ever treated, fewer expanders were injected than planned, and therefore this is the only one who has had two injections so far (Fig. 10.6).

10.3 Compensation for Orbital Volume Deficiency in Acquired Disease

10.3.1 Acquired Anophthalmic Enophthalmos

10.3.1.1 Patients

So far 8 orbits in 7 patients have been treated (see Table 10.2 for details).

10.3.1.2 Method

The 3 children were treated under general and the 4 adults under local anesthesia. The technique was similar to the one used in microphthalmos described above, with the following difference. For volume calculation a local anesthetic

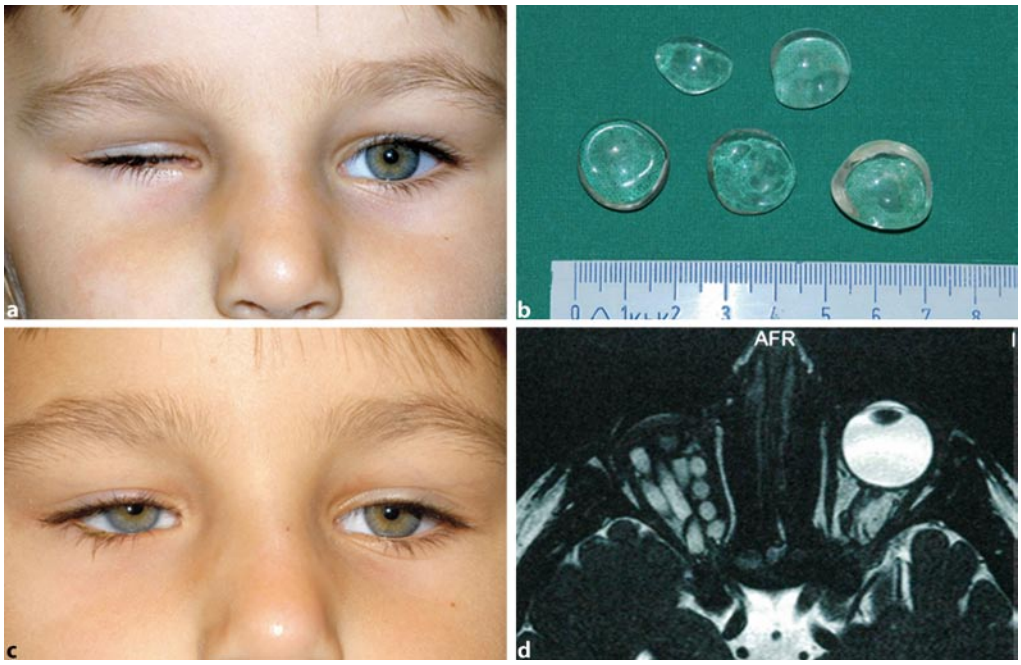

Fig. 10.8 Forty-two-month-old girl with congenital microphthalmos. **a** Right-sided microphthalmos (axial length 14 mm) with facial asymmetry. **b** Some of the conformers had been fitted before. **c** After injection of 14 pellets (3.5 ml) there was a good prosthetic situation. **d** Postoperative MRI demonstrates expanders filling the orbit

was always used. In the case of a previously inserted implant the injection was placed behind that volume to aim for a forward shift of the implant and to avoid expander extrusion. In the two orbits with a dermis fat graft (1 patient) and the two orbits without implant, the expander injection was performed as deep as possible in the soft orbital tissue.

10.3.1.3 Results

All the injections resulted in sufficient treatment of the enophthalmos as clinical impressions dictated (Figs. 10.9, 10.10). This was confirmed by postoperative Hertel readings after the final custom-made artificial eye was inserted. Maximum undercorrection was 1 mm. There was no noticeable overcorrection.

10.3.2 Acquired Enophthalmos Due to Phthisis of the Globe

One orbit has been treated so far with injection of pellet expanders behind a phthisical globe. The technique was similar to that for anophthalmos with implant (see Table 10.2 for details).

10.3.3 Side Effects

In acquired anophthalmos without implant the first orbit (which showed enophthalmos after dermis fat graft) was treated transconjunctivally. Two days later some discharge from the incision side was seen with no severe signs of infection. Microbiological testing was positive for staphylococci as it is for the regular skin flora. It remains unclear whether the discharge resulted from a true infection or from fat necrosis due to the

Table 10.2. Acquired anophthalmic patients treated with pellet expanders. *DFG* dermis fat graft, *HA* hydroxyapatite

Number	Sex	Side	Age at enucleation (years)	Orbital implant Size/type	Age at 1st expander (years)	Time interval to enucleation	Number of pellets	Prosthesis	Follow-up (month)	Remarks
Unilateral acquired anophthalmos/phthisis										
1	Female	LE	21	Size unknown/ plastic	32	11	10	Yes	32	
2	Female	Both	45	Bangerter implant removed, secondary DFG	RE: 62	17	12	Yes	8	Postoperative ptosis needed frontal sling
					LE: 60	15	15	Yes	19	1 week later 3 expanders removed due to infection or fat necrosis (DFG)
3	Female	LE	1	16 mm/HA	7	6	5	Yes	16	
4	Female	LE	4 months	Size unknown/HA	1	1	5	Yes	9	RE clinical anophthalmos, with spherical expander implanted and prosthesis
5	Male	LE	22	No implant	71	49	10	Yes	4	
6	Female	RE	4	No implant	23	19	5	Yes	3	
7	Male	RE	Phthisis bulbi since injury 10 years ago		30	–	5	Yes	3	
8	Male	LE	41	Size unknown/HA	58	17	15	Yes	1	
Average	Male 3 Female 5	RE 3 LE 6	Ø 19.3 0.3–45	4 alloplastic 2 DFG 2 without 1 phthisis	Ø 38.2 1–71	Ø 13.1 1–49	Ø 9.1 5–15	All	Ø 10.5 1–32	

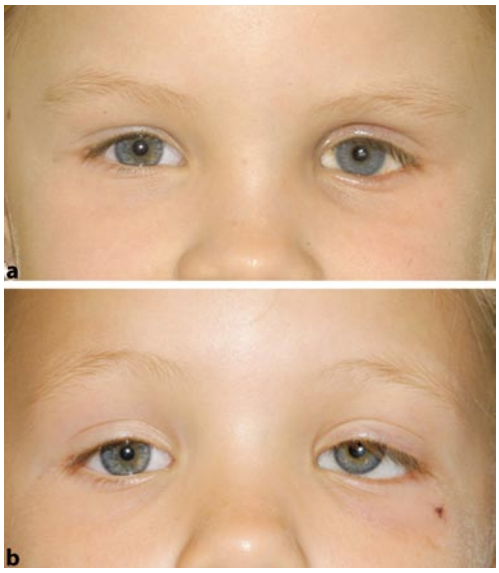

Fig. 10.9 Seven-year-old girl with acquired anophthalmos. **a** Left orbit: at the age of 1 year enucleation (due to retinoblastoma) with 16-mm hydroxyapatite implant was necessary; 6 years later enophthalmos and deep superior sulcus were obvious. **b** Symmetry 3 days after injecting five pellets (1.25 ml), and a new prosthesis was needed

high pressure delivered by the expanders. All the following patients were treated transcutaneously and no similar second reaction was seen, even in the case of a former dermis fat graft.

The same patient also experienced the second side effect after treating the fellow orbit 9 months later: after uneventfully injecting 12 pellets a complete ptosis remained. In accordance with the patient's wish, a frontal sling operation was chosen 7 weeks later to compensate for this and instead of waiting for possible resolution.

None of the other 7 patients experienced any side effects.

Summary for the Clinician

- Results with the patients treated so far suggest that injectable hydrogel expanders are a promising way to compensate for enophthalmos due to orbital volume deficiency in cases in which the condition itself or previous surgery has resulted in disturbing asymmetry.

10.4 Discussion

10.4.1 Congenital Microphthalmos

The degree of globe deformity determines which oculoplastic rehabilitating technique is appropriate for use. The critical first step is to rule out any visual potential in the microphthalmic globe. To cover an eye that has significant visual potential with an opaque prosthesis would obviously produce deprivational amblyopia. Endangering the globe with high pressures delivered by an expanding device is also contraindicated, even where visual acuity is limited to light perception.

The acceptable approach to prosthetic management of microphthalmic cases remains controversial, and no uniform strategy exists. Treatment may consist of observation only or in severe cases may involve surgical removal of the blind globe. In cases with an accompanying orbital cyst (not observed in the patients reported here) therapy is characterized by the surgical approach [5].

Mustardé [25] suggested complete excision of the rudimentary microphthalmic eye and the existing socket lining as a prelude to replacement with a skin-lined cavity of suitable size. For this purpose he advocated using a skin

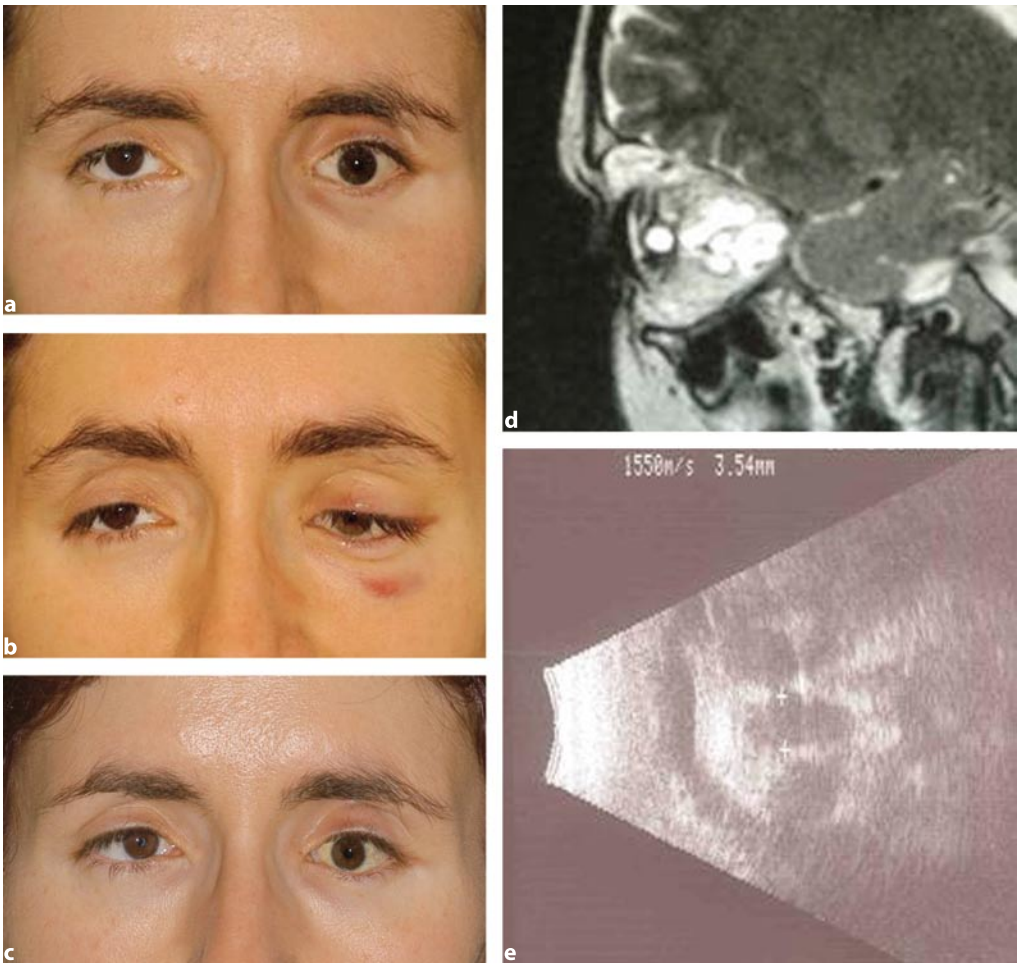

Fig. 10.10 Thirty-two-year-old woman with acquired anophthalmos. **a** Left-sided postenucleation socket syndrome (PESS) after enucleation 11 years ago with a very small implant (exact material not known). **b** Two days after injection of ten pellets (2.5 ml). **c** Three months later with a new prosthesis, some deep superior sulcus is left, but the patient was satisfied with the situation achieved. **d** Postoperative MRI and **e** ultrasound demonstrate the ideal expander placement

graft, with the epithelial surface inside, wrapped around a conformer, which was fixed with external pins for several weeks. Despite the need for a complex surgical procedure, touching the conjunctiva often leads to significant shrinkage and may make it difficult or even impossible to fit a prosthesis.

Several clinical and experimental studies have confirmed that enucleation in childhood compromises orbital growth [2, 17]. The earlier enucleation is performed, the greater the reduction in orbital bone growth, especially if no orbital implant is used [2]. It is believed that the growth of even a microphthalmic globe might stimulate orbital growth much more effectively than an artificial implant. Therefore, preference should be given to therapy that avoids enucleation.

Most authors suggest treatment using increasingly larger conformers [21], but this method necessitates very intensive, sometimes weekly, treatment to gauge progress. The width of the lid fissure determines the size of the conformer or prosthesis, thus limiting the amount of volume that can be adjusted with a hard implant.

Dermis fat grafts have been proposed, as these have the advantage of being autologous and are able to enlarge as the child grows [13]. Again removal of the microphthalmic globe would be necessary.

The concept of self-inflating, highly hydrophilic hydrogels for use in patients with congenital anophthalmos originated in Rostock/Germany in 1997 [3, 41]. Experience with this method has now been gained in almost 60 treated children [10, 30].

At the Congress of the American Society of Ophthalmic Plastic and Reconstructive Surgery (ASOPRS) in 2003, Li et al. [20] presented a modification of the shape, leaving the material itself unchanged, thus allowing expander injection for volume augmentation in adults with acquired anophthalmic enophthalmos. The first application of this approach in congenital microphthalmos was presented by our team at the Congress of the European Society of Ophthalmic Plastic and Reconstructive Surgery (ESOPRS) in 2004 [26].

In this chapter we describe a series of 13 patients who have been followed for up to 32 months after injection. Orbital volume augmentation with injectable self-inflating hydrogel expander pellets is a safe technique for the treatment of an enophthalmic appearance in congenital microphthalmos. The volume required ranged from 1 to 3.5 ml, with an average of 2.2 ml. The technique is minimally invasive and quick to perform. In the first patient ever treated a repeat injection was necessary due to under-correction. From the second patient onward the volume required has been calculated precisely. No complications have been observed to date, although longer follow-up is necessary to assess the effect on orbital growth.

Pellet implantation did not appear to affect motility in the microphthalmic patients reported here. Although highly likely, it is not yet known whether the microphthalmic globe fitted with a thin prosthesis will be able to transmit some of this movement to the artificial eye in the long term.

In this regard, the situation differs considerably from that in congenital anophthalmic sockets where parents have to be informed that even when the socket is well supported in volume terms, there will be virtually no prosthesis motility and in most cases no lid motility [13].

The patients described in this paper were, with two exceptions, very young; and from a methodological standpoint, precise motility measurements were, therefore, almost impossible to obtain. In addition to the age factor, the significantly reduced size of the globe makes it far more difficult to quantify motility.

Summary for the Clinician

- The guiding principle for congenital microphthalmic (blind) eyes is conservative management with solid conformers/prostheses, avoiding surgery if at all possible.

10.4.2 Acquired Anophthalmos

If function is irreversibly lost and organ preservation is impossible aesthetic demands are still high. Numerous methods and techniques for enucleation or evisceration have been described in the past few decades [12].

If no implant is inserted – which should be avoided if possible [31] – or when the implant is too small, a noticeable volume deficit might result. Distress over the visual loss is then accompanied by impaired facial appearance.

Tyers and Collin described, therefore, the term "postenucleation socket syndrome" (PESS) [36], which is characterized by a deepened upper lid sulcus, ptosis, lid laxity, enophthalmos, and backward movement of the prosthesis. This was further investigated later on by Smit et al. using CT scans [33]. Pathogenetically, the phenomena are not only caused by the deficit in volume. Furthermore, a downward displacement of the levator complex, atrophy of orbital fat, retraction of muscles and Tenon's capsule, and last but not least, the effect of gravity to the prosthesis, play an important role [32].

For compensation of a volume deficit after enucleation without an implant, different techniques are available, such as a secondary baseball implant [9], secondary hydroxyapatite implant [22], secondary hydroxylapatite silicone implant [11], secondary dermis fat graft as an orbital implant [15] or to fill the superior sulcus [37], and

different approaches to placing a subperiosteal orbital floor implant [1, 34, 38]. Silicone tissue expanders, which are surgically implanted, and filled multiple times with saline can later be used. These are eventually removed and replaced by graft material as described recently by Honda et al. [16], but appear not as effective, as stated by Bernardino [4] in a letter to the editor.

All the techniques mentioned above include a somewhat more extensive amount of surgery, which is usually performed under general anesthesia. Depending on the kind of procedure there is some hospitalization time (which is also dependent on the patient's health and insurance system) and also involves a variable degree of pain for the patient. Using a dermis fat graft some amount of donor side morbidity is added. Last but not least, there is a significant risk of extrusion of an allogen implant, especially when used as an implant in a second procedure.

Summarizing all the facts mentioned above there is no wonder that there is a still ongoing search for alternative approaches. It was Li et al. [20] who first mentioned the use of the material developed by Wiese [40] for volume augmentation in acquired anophthalmos. This was originally developed for clinical use in our institution for treating congenital anophthalmos [28, 30]. Li et al. developed a modification of the expander shape leaving the chemical and physical qualities unchanged to allow implantation through a trocar needle with a diameter of the inner lumen of 2 mm much like an injection. After testing the technique in two rabbits it was used to treat PESS in 6 adults. Treatment was reported to be successful in 4 out of the 6 patients; 2 patients were seen with expander dislocation into the lower lid.

With our experience of 9 orbits in 8 patients with acquired anophthalmos as reported here, no such side effects were noticed. From the orbits reported here, 4 had an alloplastic implant, 2 a dermis fat graft, 2 were without any implant, and 1 had a phthisical globe. One case of infection and/or fat necrosis occurred following use of a dermis fat graft orbital implant, resulting in some discharge. After giving intravenous antibiotics and removing some of the expanders, the discharge stopped immediately.

A second complication was induction of a complete ptosis in a patient with a dermis fat graft as well. It seems impossible to differentiate whether this was due to direct injury to the nerve or pressure-related.

Despite the specific application in congenital disease reported in the former chapter, the technique may also be useful for a variety of indications in orbital reconstructive surgery due to acquired anophthalmos. In particular, if a secondary procedure is needed, it is far easier to place pellet expanders than to insert an implant and there is no donor site morbidity as with a dermis fat graft, which is even more difficult to harvest and insert. If not used in children all the procedures were performed under local anesthesia, and none took longer than 10 min.

Postoperative pain is minimal, even in a patient with an implant embedded in scars where expander expansion might have been reasoned to cause severe pain.

Summary for the Clinician

- In enucleation surgery, an adequate implant is important to prevent post-enucleation socket syndrome.

10.4.3 Volume Calculation

The calculation of the volume needed for achieving symmetry was done individually for each patient. The number of patients treated so far seems to be too small for applying statistical methods or mathematical models to judge the influence of age, gender, time interval to enucleation (if performed), orbital volume, axial length (in microphthalmos or phthisis).

The amount of pellets required is interestingly quite similar in both the anophthalmos and in the microphthalmos groups; it does not differ either in the range or in the mean number of expanders. This is more surprising when comparing the age (average 1.5 years in microphthalmos and 19.3 years in anophthalmos) and keeping in mind the well-known differences in orbital vol-

ume and orbital growth between the two groups [14, 29].

All patients reported in this chapter were treated successfully in terms of enophthalmos correction. This is not certain compared with other approaches, but it is likely because of the intraoperative calculation. Longer term follow-up will reveal how many patients will need secondary injections, which may be due to growth of the child as in the very young microphthalmic patients or due to fat atrophy or other general reasons.

In a paper by Koo et al. [18] enophthalmos is reported to become significant if it presents greater than 2 mm. Patients within this range are observed as normal when judged by independent observers.

10.4.4 Possible Risks

Admittedly, experience with this material does not extend beyond 9 years – a circumstance regarded by Mazzoli et al. [23] as "the fly in this particular soup." Those authors reviewed reported complications due to the lack of long-term stability with MIRAGel, a material used in retinal surgery in the late 1970s, but is, as far as is known, entirely unconnected with the hydrogel used in our patients. Our material differs chemically from MIRAGel in having a considerably more cross-linked structure that renders it far more stable mechanically. In a material with a swelling capacity of 10-fold, such as was used in our patients, it should also be remembered that only 10% of the implant expander consists of hydrogel – in our patients this corresponded only to 0.1–0.35 ml (average: 0.26 ml) – while 90% is simple water. Nevertheless, careful follow-up is mandatory to monitor for any side effects.

Potential complications may result from not being able to remove all the expander material implanted before. This would most likely be the case with pellets injected behind a microphthalmic or a phthitic eye. Patients are informed that we plan to use the pellet expanders as a permanent implant. In the unlikely event of side effects occurring later on and making removal of the material necessary we would then recommend enucleation of the globe, thus allowing better access to the expanders and replacement by a regular and possibly muscle-fixed orbital implant. But again this seems very unlikely, although it should be discussed as a possibility with the patient before surgery.

In acquired anophthalmos, with use of a dermis fat graft after transconjunctival injection some discharge from the incision side was seen. It remains unclear whether the discharge resulted from a true infection or from fat necrosis. All other patients were treated transcutaneously without any negative consequences. The transcutaneous approach appears safer compared with the transconjunctival one despite the small skin incision, which in any event does not cause a significant scar. We did not observe any pellet extrusion, although this has been reported by Li et al. [20].

Summary for the Clinician

- The advantages of injectable pellet expanders are:
  - The technique is minimally invasive.
  - They are virtually custom made which means that the surgeon has the ability to:
    - Calculate the volume desired
    - Determine the place for expansion
  - They are reliable: a dry hydrogel that comes into contact with water will swell and there is no fear of technical expander failure.

References

1. Adenis JP, Bertin P, Lasudry JG, Boncoeur-Martel MP, Leboutet MJ, Robert PY (1999) Treatment of the postenucleation socket syndrome with a new hydroxyapatite tricalcium phosphate ceramic implant. Ophthal Plast Reconstr Surg 15(4):277–283
2. Apt L, Isenber S (1973) Changes in orbital dimensions following enucleation. Arch Ophthalmol 90(5):393–395

3. Backskulin A, Vogel M, Wiese KG, Gundlach K, Hingst V, Guthoff R (2000) New osmotically active hydrogel expander for enlargement of the contracted anophthalmic socket. Graefes Arch Clin Exp Ophthalmol 238(1):24–27
4. Bernardino CR (2006) Correction of late post-traumatic enophthalmos using a tissue expander. Ann Plast Surg 57(4):477
5. Chaudry IA, Arat YO, Shamsi FA, Boniuk M (2004) Congenital microphthalmos with orbital cysts: distinct diagnostic features and management. Ophthal Plast Reconstr Surg 20(6):452–457
6. Collin JR, Moriarty PA (1982) Management of the contracted socket. Trans Ophthalmol Soc UK 102(1):93–97
7. Dootz GL (1992) The ocularists' management of congenital microphthalmos and anophthalmos. Adv Ophthalmic Plast Reconstr Surg 9:41–56
8. Downes R, Lavin M, Collin R (1992) Hydrophilic expanders for the congenital anophthalmic socket. Adv Ophthalmic Plast Reconstr Surg 9:57–61
9. Frueh BR, Felker BR, Felker GV (1976) Baseball implant. A method of secondary insertion of an intraorbital implant. Arch Ophthalmol 94(3):429–430
10. Gundlach KKH, Guthoff RF, Hingst V, Schittkowski MP, Bier UC (2005) Expansion of the socket and the orbit for congenital clinical anophthalmia. Plast Reconstr Surg 116(5):1214–1222
11. Guthoff R, Vick HP, Schaudig U (1995) [Prevention of postenucleation syndrome: the hydroxylapatite silicone implant. Preliminary experimental studies and initial clinical experiences]. Ophthalmologe 92(2):198–205
12. Guthoff RF, Schittkowski MP, Klett A (2005) Methods to improve prosthesis motility in enucleation surgery without pegging and with emphasis on muscle pedunculated flaps. In: Guthoff R, Katowitz JA (ed) Essentials in ophthalmology. Oculoplastics and Orbit, 1st edn. Springer, Berlin, pp 223–235
13. Handler LF, Heher KL, Katowitz JA (1994) Congenital and acquired anophthalmia. Curr Opin Ophthalmol 5(5):84–90
14. Hintschich C, Zonneveld F, Baldeschi L, Bunce C, Koornneef L (2001) Bony orbital development after early enucleation in humans. Br J Ophthalmol 85(2):205–208
15. Hintschich CR, Beyer-Machule CK (1996) [Dermal fatty tissue transplant as primary and secondary orbital implant. Complications and results]. Ophthalmologe 93(5):617–622
16. Honda T, Sakurai H, Nakazawa H, Isago T, Nozaki M (2006) Correction of late post-traumatic enophthalmos using a tissue expander. Ann Plast Surg 56(6):686–688
17. Kennedy RE (1992) The effect of early enucleation on the orbit in animals and humans. Adv Ophthalmic Plast Reconstr Surg 9:1–39
18. Koo L, Hatton MP, Rubin PA (2006) When is enophthalmos "significant"? Ophthal Plast Reconstr Surg 22(4):274–277
19. Krastinova D, Kelly MB, Mihaylova M (2001) Surgical management of the anophthalmic orbit. I. Congenital. Plast Reconstr Surg 108(4):817–826
20. Li TG, McCann JD, Goldberg RA (2003) Orbital volume augmentation in anophthalmic patients using injectable hydrogel implants. In: Abstracts of the American Society of Ophthalmic Plastic and Reconstructive Surgery 2003 Fall Scientific Symposium 14–15 November 2003, Anaheim, California, p 91
21. McLean CJ, Ragge NK, Jones RB, Collin JR (2003) The management of orbital cysts associated with congenital microphthalmos and anophthalmos. Br J Ophthalmol 87(7):860–863
22. Massry GG, Golds JB (1995) Coralline hydroxyapatite spheres as secondary orbital implants in anophthalmos. Ophthalmology 102(1):161–166
23. Mazzoli RA, Raymond WR IV, Ainbinder DJ, Hansen EA (2004) Use of self-expanding, hydrophilic osmotic expanders (hydrogel) in the reconstruction of congenital clinical anophthalmos. Curr Opin Ophthalmol 15(5):426–431
24. Mischkowski RA, Kübler AC (2006) Correction of congenital nasal hypoplasia associated with Kallmann syndrome using self-inflating injectable tissue expander pellets. Plast Reconstr Surg 118(6):1447–1452
25. Mustardé JC (1980) The eye socket. In: Mustardé JC (ed) Repair and reconstruction in the orbital region, 2nd edn. Churchill Livingstone, Edinburgh, pp 215–244

26. Schittkowski MP, Guthoff RF (2004) Injectable self-inflating hydrogel pellet expanders for treatment of orbital volume deficiency in congenital microphthalmos – first experiences with a new technique. In: Abstracts of the 22nd Meeting of the European Society of Ophthalmic Plastic and Reconstructive Surgery 17–19 June 2004, Leuven, Belgium
27. Schittkowski MP, Guthoff RF (2006) Injectable self inflating hydrogel pellet expanders for the treatment of orbital volume deficiency in congenital microphthalmos: preliminary results with a new therapeutic approach. Br J Ophthalmol 90(9):1173–1177
28. Schittkowski MP, Gundlach KK, Guthoff RF (2003) [Treatment of congenital clinical anophthalmos with high hydrophilic hydrogel expanders]. Ophthalmologe 100(7):525–534
29. Schittkowski M, Hingst V, Knaape A, Gundlach K, Fichter N, Guthoff R (2004) [Orbital volume in congenital clinical anophthalmos]. Klin Monatsbl Augenheilkd 221(11):898–903
30. Schittkowski MP, Katowitz JA, Gundlach KKH, Guthoff RF (2005) Self-inflating hydrogel expanders for the treatment of congenital anophthalmos. In: Guthoff RF, Katowitz JA (eds) Essentials in ophthalmology. Oculoplastics and Orbit. Springer, Berlin, pp 205–222
31. Smit T, Koornneef L (1990) [Is an implant always necessary after enucleation?]. Fortschr Ophthalmol 87(5):533–536
32. Smit T, Koornneef L, Groet E, Otto AJ (1990) [100 years of intra-orbital implants following enucleation]. Ned Tijdschr Geneeskd 134(6):274–277
33. Smit TJ, Koornneef L, Zonneveld FW, Groet E, Otto AJ (1990) Computed tomography in the assessment of the postenucleation socket syndrome. Ophthalmology 97(10):1347–1351
34. Spivey BE, Allen L, Stewart WB (1976) Surgical correction of superior sulcus deformity occurring after enucleation. Am J Ophthalmol 82(3):365–370
35. Stoll C, Alembik Y, Dott B, Roth MP (1992) Epidemiology of congenital eye malformations in 131,760 consecutive births. Ophthalmic Paediatr Genet 13(3):179–186
36. Tyers AG , Collin JR (1982) Orbital implants and post enucleation socket syndrome. Trans Ophthalmol Soc UK 102(1):90–92
37. Van Gemert JV, Leone CR Jr (1986) Correction of a deep superior sulcus with dermis-fat implantation. Arch Ophthalmol 104(4):604–607
38. Villarreal PM, Monje F, Morillo AJ, Junquera LM, Gonzalez C, Barbon JJ (2002) Porous polyethylene implants in orbital floor reconstruction. Plast Reconstr Surg 109(3):877–885; discussion 886–887
39. Warburg M (1993) Classification of microphthalmos and coloboma. J Med Genet 30(8):664–669
40. Wiese KG (1993) Osmotically induced tissue expansion with hydrogels: a new dimension in tissue expansion? A preliminary report. J Craniomaxillofac Surg 21(7):309–313
41. Wiese KG, Vogel M, Guthoff R, Gundlach KK (1999) Treatment of congenital anophthalmos with self-inflating polymer expanders: a new method. J Craniomaxillofac Surg 27(2):72–76

Chapter 11

Hydroxyapatite Orbital Implant Exposure: Symptoms, Physiopathology, Treatment

11

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Core Messages

- Exposure is the most frequent complication of hydroxyapatite orbital implants.
- Several surgical approaches can be utilized to repair exposure of hydroxyapatite implants, either with autologous grafts or with a conjunctiva–Muller's muscle pedicle flap.
- Various autologous grafts can be used after an unsuccessful flap procedure: upper tarsal plate from the other side, temporalis fascia, and fascia lata are first choice.
- Oral mucous membrane, hard palate mucosa, and ear cartilage are used as second choice.
- In cases of conjunctival fornix deficiencies, amniotic membrane grafting can be added to the previous list of grafts.
- A Muller's muscle flap can be used in three different ways: in the first technique, the conjunctiva–Muller's muscle flap is divided at the superior fornix; in the second technique, the Muller's muscle flap is divided at the superior edge of the tarsal plate; in the third technique, part of the superior tarsus is included with Muller's muscle in the flap.
- A second surgical procedure is necessary to divide the pedicle.
- The addition of vascularized tissue improves fibrovascular ingrowth in the implant and favors the treatment of recurrent infection often associated with orbital implant exposure.

11.1 Introduction

Hydroxyapatite (HA) orbital implants are made from the porous skeleton of a coral species allowing fibrovascular ingrowth, which favors tissue integration. HA (coral or synthetic) became one of the most commonly used materials for implants in anophthalmic patients in the 1990s and at the beginning of this century [9]. Synthetic HA is made of the same material, with predetermined size pores, and has become widely used in the past few years in the western countries. In addition to their numerous advantages, HA implants have significant complication rates involving exposure, infection, extrusion, and various peg problems [10, 19]. Implant exposure is the most common complication, occurring in up to 22% of cases [7, 22].

Many surgical techniques have been described to manage such exposure.

To our knowledge, Carle [2, 16] was the first to describe the use of Muller's muscle to repair a conjunctival defect in preference to a HA implant. We report our experience with autologous grafts and

with three different types of conjunctival Muller's muscle pedicle flap techniques used for secondary repair following failure of autologous grafts.

11.2 Diagnosis and Physiopathology

The diagnosis and management of orbital implant exposure is frequently difficult.

The first step is the diagnosis: epiphora and purulent discharge in a patient with a prosthesis should be an alert. Orbital pain is a less frequent symptom. It is then recommended to remove the prosthetic shell and carefully observe the surface of the implant; the exposed area can be seen directly when the defect is large, with exposure of HA spicules, but frequently, the exposed area is covered by exophytic conjunctiva. A broth-moistened swab placed at the level of the exposed area, or a conjunctival biopsy, is inoculated onto various culture media: blood agar, chocolate agar, Sabouraud agar, and thioglycolate broth.

The second step is to attempt to identify the cause of the exposed area. Potential causes include:

- Soft-tissue destruction, as might occur with either infection or chronic inflammation from poor biocompatibility of the implant material with the patient
- The degree of vascularization of the implant (Figs. 11.1–11.4): poorly vascularized implant (Figs. 11.5–11.7) or poor soft-tissue viability surrounding the implant resulting from post-traumatic ischemia or crush injury or any other cause favors implant exposure
- Decreased effective orbital volume secondary to intraorbital hemorrhage, epithelial inclusion cyst
- Systemic conditions that may delay wound healing, such as diabetes or collagen vascular disorders
- Use of medications, such as steroids, that delay wound healing
- Excessive wound tension from an anteriorly positioned implant, an implant too large for the soft tissue available, or substantial soft tissue edema
- Postsurgical trauma, which may be due to a poorly fitting prosthetic shell [6]

Hydroxyapatite exposure is characterized by an insufficient amount of vascularized anterior orbital tissues. Consequently, simple closure is unlikely to be successful unless the defect is small (less than 3 or 4 mm) and there is enough vascularized tissue to be mobilized [13]. All three current pedicled patch techniques provide new vascular tissue, which optimizes conditions for repair of exposed HA orbital implants.

Nonetheless, these novel approaches to HA implant revision have some drawbacks. A secondary surgical procedure is necessary to divide the pedicle in the first two techniques, the tarsorrhaphy used in the tarsoconjunctival pedicle approach is technically demanding, and all three techniques may be complicated by ptosis. In view of these difficulties, the surgical indication is reserved for larger exposed areas (greater than 3–4 mm in diameter).

Summary for the Clinician

- Small areas of hydroxyapatite exposure (less than 4 mm) may occasionally close spontaneously, but larger defects require correction.

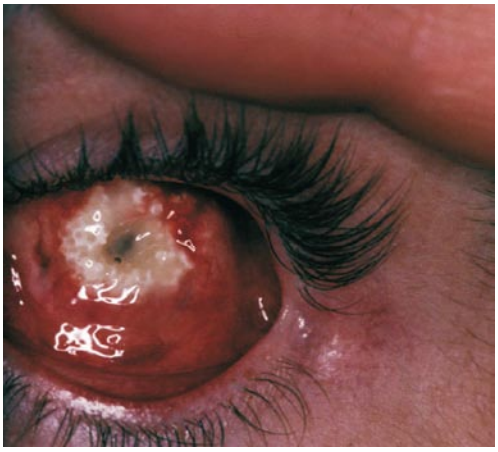

Fig. 11.1 Central and large exposed area over a hydroxyapatite implant

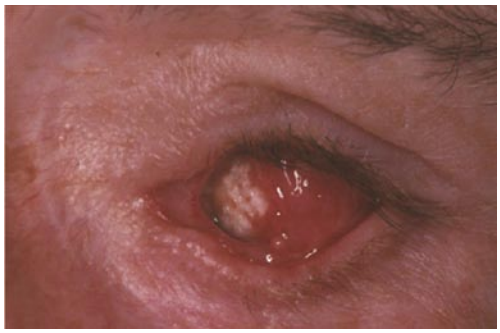

Fig. 11.2 Medial and large exposed area over a hydroxyapatite implant

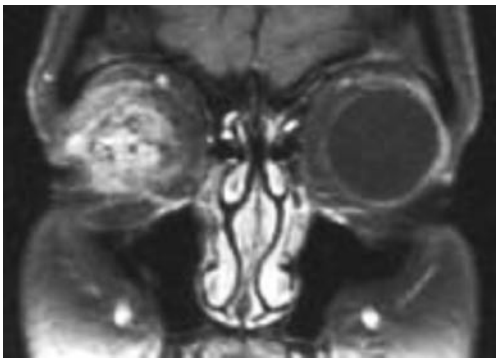

Fig. 11.3 Magnetic resonance imaging, coronal section, T1 sequence with gadolinium demonstrating a nearly complete vascularized implant

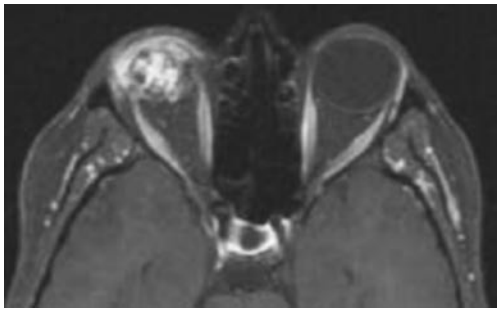

Fig. 11.4 Magnetic resonance imaging, horizontal section, T1 sequence with gadolinium: example of a nearly complete vascularized implant

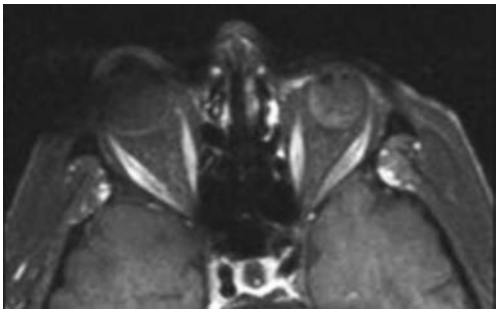

Fig. 11.5 Magnetic resonance imaging, axial section, T1 sequence with gadolinium: example of a poorly vascularized implant

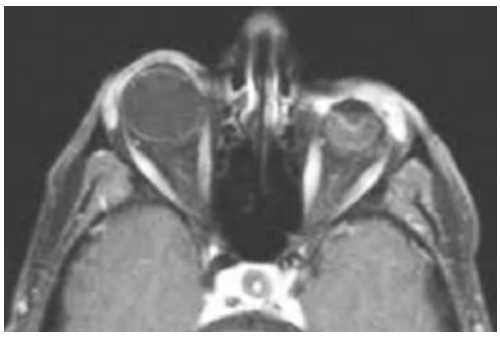

Fig. 11.6 Magnetic resonance imaging, axial section, T1 sequence with gadolinium: example of a poorly vascularized implant

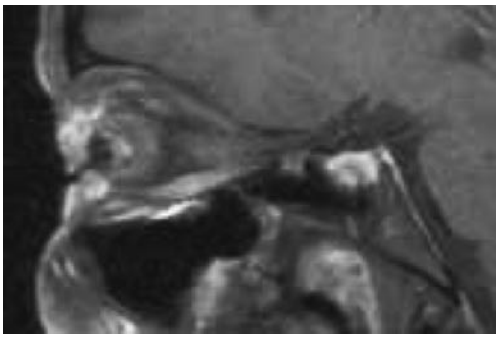

Fig. 11.7 Magnetic resonance imaging, sagittal section, T1 sequence with gadolinium: example of a poorly vascularized implant

11.3 Treatment

11.3.1 Surgical Techniques for Repair of Hydroxyapatite Implant Exposure

11.3.1.1 Autologous Grafts

After freshening the edges of the conjunctiva at the level of the exposure various autologous grafts can be sutured with 6-0 Vicryl sutures. The different grafts are listed in the order of most frequent personal choice of use:

- Tarsal plate from the controlateral eyelid, temporalis fascia [18, 21] or fascia lata harvested from the lateral part of the leg are first choice
- Second choice would be oral mucous membrane, hard palate mucosa (Fig. 11.8), ear cartilage (Fig. 11.9), or various other materials, such as retroauricular muscle [14, 17] or thin dermis fat graft [13]
- Finally, amniotic membrane graft can be used in association for the correction of cul de sac or fornices deficiencies

11.3.2 Surgical Techniques for Muller's Muscle Flap

11.3.2.1 Conjunctiva–Muller's Muscle Flap Technique 1

This first surgical technique is permitted by the double source of Muller's muscle vascularization and is based upon dissecting Muller's muscle from its insertion in the levator aponeurosis (Figs. 11.10–11.12) [2, 16]. The exposed coralline HA implant is thinned on its anterior exposed part with a diamond burr on a hand drill.

The Muller's muscle flap is incised at the level of the superior fornix 10 to 12 mm up from the superior tarsal border. Two vertical sections create a flap that can be rotated downward and sutured to the inferior edge of the defect. In a second procedure, 4–5 weeks later, the flap is divided from its origin and a simple translation is made to finally close the defect .The pedicle is then applied over the implant exposure, where it can be sutured in a straightforward manner. Antibiotic dexamethasone ointment is applied, the prosthesis is replaced if there is not too much tension, and a patch is applied.

11.3.2.2 Conjunctiva–Muller's Muscle Flap Technique 2

Under local or general anesthesia, a 6-0 silk traction suture is placed through the central upper eyelid margin, and the eyelid is everted over a Desmarres retractor (Fig. 11.13). The superior tarsal border is identified and injection of approximately 0.3 ml of 1% lidocaine with epinephrine is used to separate conjunctiva and Muller's muscle from the aponeurosis and to accelerate hemostasis. With Wescott scissors and blunt dissection, the conjunctiva is dissected from the superior tarsal border and overlying Muller's muscle. With calipers, the amount of Muller's muscle needed to fill the defect is measured in its greatest horizontal dimension. Muller's muscle is then dissected from the superior border of the tarsal plate, and care is taken to lyse the overlying loose adhesions to the levator aponeurosis.

The dissection is extended superiorly for approximately 10 or 12 mm. Muller's muscle remains attached to its levator aponeurosis origin. Hemostasis is obtained with careful monopolar cautery. Traction sutures with 6-0 silk are used to separate the conjunctiva and Muller muscle, which is then carefully slid under the existing conjunctiva, its proper orientation being maintained in such a way that it covers the defect without tension. Muller's muscle placed over the exposed HA implant is sewn to the surrounding conjunctiva with 5-0 Vicryl sutures. An antibiotic dexamethasone ointment is applied to the area, and the prosthesis is not replaced to avoid tension on the sutures. A patch is applied.

In a second step, the conjunctiva is cut at the level of the superior fornix and the flap is finally closed over the defect The remaining conjunctiva is returned to its original position above the superior tarsal border with running 6-0 fast-absorbing Vicryl suture passed through the skin surface to avoid eyelid malpositioning.

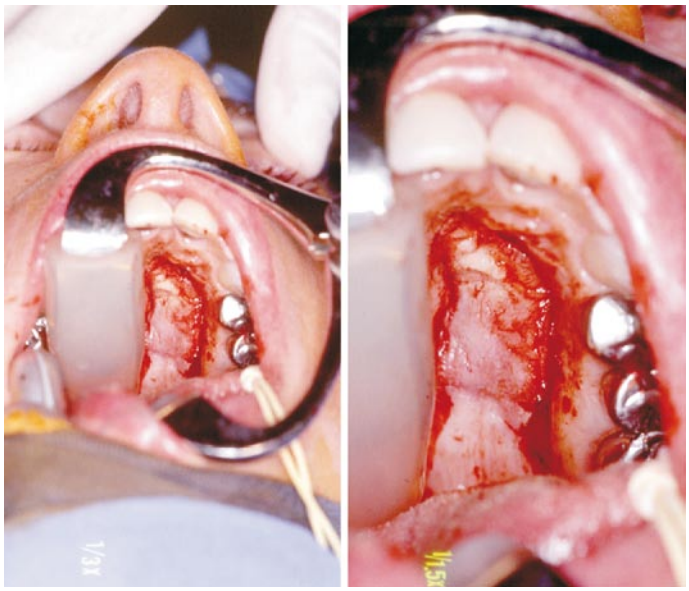

Fig. 11.8 Surgical example of the harvesting of hard palate mucosa

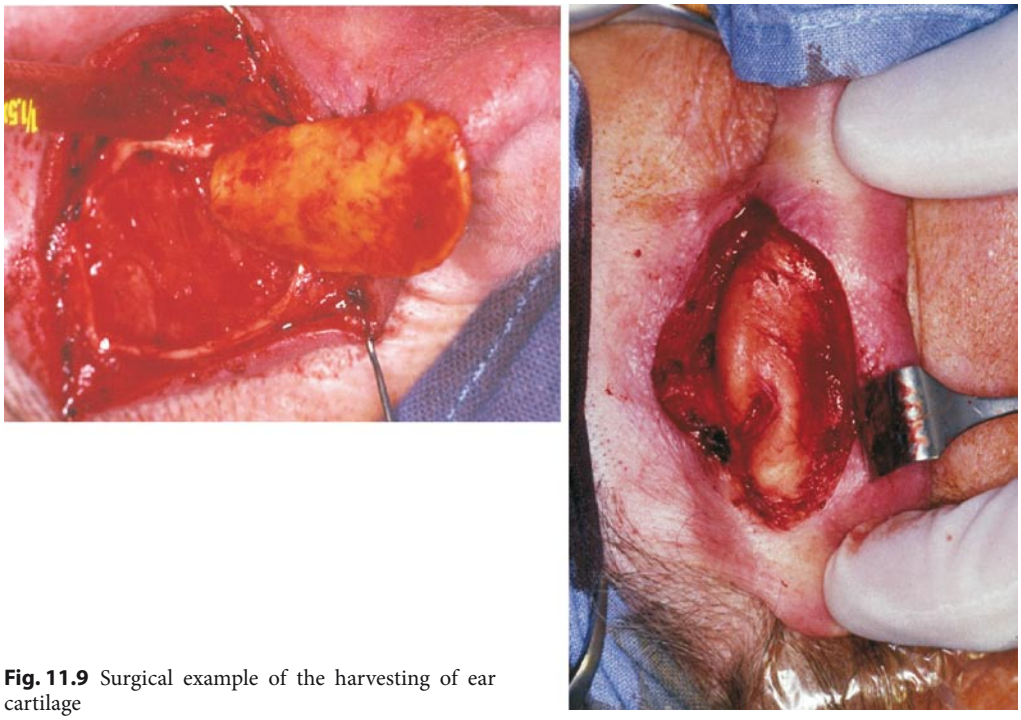

Fig. 11.9 Surgical example of the harvesting of ear cartilage

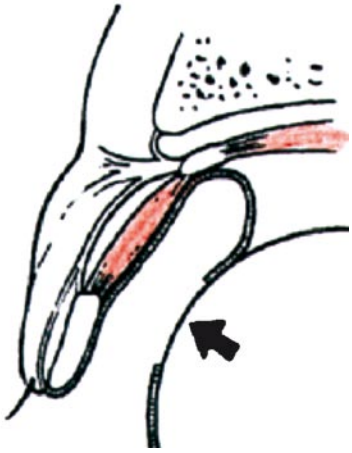

Fig. 11.10 Sagittal section through the exposed orbital implant and upper eyelid (Muller's muscle and striate fibers of the levator are colored in *red*)

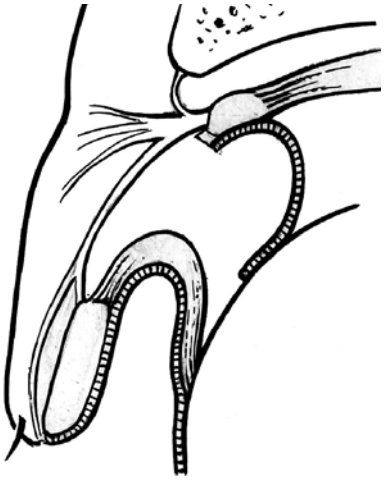

Fig. 11.11 Cross-sectional diagram showing the placement of the Muller's muscle flap over the hydroxyapatite orbital implant defect after the flap is dissected from its origin in the superior fornix and behind the levator aponeurosis

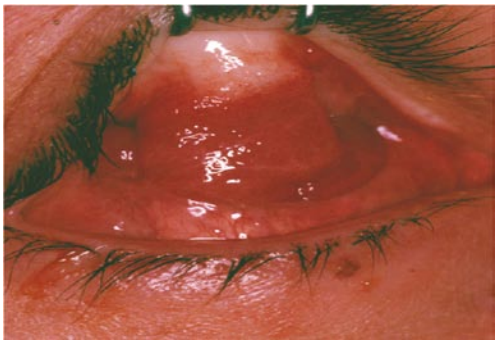

Fig. 11.12 Surgical example showing the placement of the Muller's muscle flap over the hydroxyapatite orbital implant defect after the flap is dissected from its origin in the superior fornix and behind the levator aponeurosis

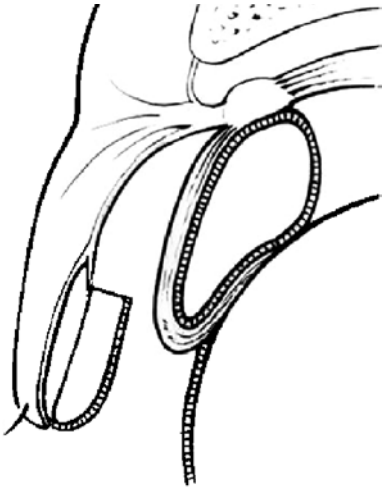

Fig. 11.13 Cross-sectional diagram showing the placement of the Muller's muscle flap over the hydroxyapatite orbital implant defect after the flap is dissected from the superior tarsal border

11.3.2.3 The Tarsoconjunctival Pedicle Flap

The edges of the conjunctiva are freshened and undermined. The exposed coralline HA implant is thinned on its anterior exposed part with a diamond burr on a hand drill [3, 15].

A tarsoconjunctival pedicle flap is fashioned as follows (Fig. 11.14). The upper eyelid is everted and the area required is measured and drawn on the conjunctival surface of the upper eyelid. The tarsus is incised horizontally at the appropriate level and a pedicle of the tarsal conjunctiva is undermined superiorly (toward the superior fornix) to include the conjunctiva and underlying Muller's muscle. The pedicle is inverted such that the deep side faces the defect, and the epithelial conjunctival lining faces anteriorly. The flap is secured with 6-0 polyglactin suture in the upper part of the defect. The flap is divided under local anesthesia 4–5 weeks after the intervention. The upper part of the sectioned flap is sutured to the upper border of the tarsus with 6-0 Vicryl sutures and the end of the sutures are passed through the orbicularis and the skin and tightened at the level of the upper lid crease.

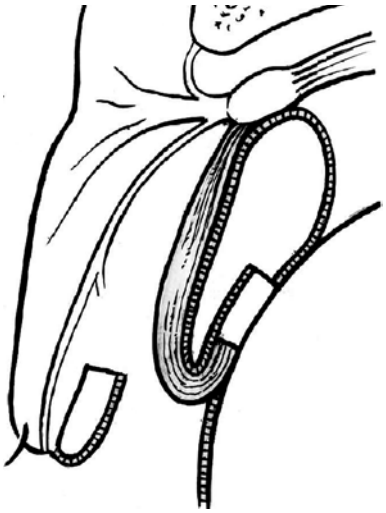

Fig. 11.14 Cross-sectional diagram showing the placement of the Muller's muscle flap over the hydroxyapatite orbital implant defect after the flap is dissected in the middle of the upper tarsus. The flap is divided later on and sutured over the defect. Note the inversion of the tarsus and conjunctiva

Summary for the Clinician

- Three surgical approaches to covering hydroxyapatite exposure are presented:
  - Various autologous grafts
  - A vascularized Muller's muscle pedicle flap, with or without part of the tarsus contributing to the patch
  - Removal and replacement of the implant in the worst cases
- The choice among the three surgical approaches depends in part on the surface and position of the orbital conjunctival exposure, and in part on the status of the implant with regard to the degree of infection, the rate of vascularization, and the number of previous surgical procedures.

11.3.3 Removal and Replacement of the Implant

When previous surgery has failed, the best solution is to remove the implant and its attachments to the ocular muscles. The first step is to dissect the conjunctiva and Tenon's capsule from the sclera, then to pass 6-0 Vicryl sutures around each rectus muscle. Next, the implant and the sclera are removed. Five percent povidone iodine solution is applied to the cavity. A new implant is covered with either fascia lata or temporalis fascia and securely attached with Vicryl sutures. The covered implant is implanted in the orbit and the rectus muscles are attached with Vicryl sutures to its anterior portion.

11.4 Indications

Various factors can influence the choice of the technique:

- The absence or presence of infection: this can be demonstrated by several samples and cultures, or by the issue through the pores of the

implant of mucopurulent debris after pressure on the eyelids or during surgery when burying the implant deeply
- The rate of vascularization of the implant: a poorly vascularized implant can be covered by a vascularized flap as a first step and is an argument in favor of the removal and replacement of the implant as the last step. Therefore, MRI should be performed in the preoperative assessment (Figs. 11.1–11.5)
- The surface of the exposure: a large surface of exposure extending to the upper and lower fornices will lead to poor results of grafts
- Pegging has been reported to increase the rate of exposure and deep infection in the implant, especially in cases of unstable pegging [5, 12]
- The number of operations: an autologous graft can easily be indicated as a first-step procedure as it is a one-step procedure. Muller's muscle flap is rather indicated as a second-step procedure, but the patient should be warned that two surgical procedures will be necessary, and finally, failure of multiple operations indicates removal and replacement of the implant

How should these factors be managed? Autologous graft can be the first line of treatment if the infection and the surface of the exposed area are limited, and if the rate of vascularization of the implant is satisfactory.

Muller's muscle flap can be used in more severe cases.

In the most severe cases with very poor vascularization, severe infection, and failure of previous surgery, the best choice is to remove and replace the implant.

11.5 Discussion

Since the introduction of porous hydroxyapatite implants in the late 1980s, numerous materials have been used for patch grafting including fresh or preserved sclera, temporalis fascia or fascia lata, pedicled conjunctival flaps, hard palate mucosa, conjunctiva, and dermis fat grafts [13].

Regarding the two Muller's muscle flap techniques, the dissection of Muller's muscle from the superior tarsal border in the second technique is more straightforward than in the first. However, the first Muller's muscle flap technique typically provides a little larger, more mobile pedicle, and is therefore more suitable for severe implant exposure. Furthermore, the latter technique can cover very inferior implant exposures by eyelid closure because the Muller's muscle pedicle hinges in the superior part of the tarsus.

These novel procedures for covering HA implant exposures may also be indicated in another severe problem, conjunctival defect in the orbital cavity previously treated with antimetabolite or radiation therapy, considering that the pedicle provides new vascularized tissue.

In order to improve the rate of vascularization and fibrovascular ingrowth in the porous orbital implants, multiple studies have been performed that differ mainly with regard to material composition, size of the pores, and coating.

Bigham [1] demonstrated that 200-μm pores were better than 500-μm ones. For the coating the following additional substances improve the rate of vascularization: recombinant human basic fibroblast growth factor (Rh-bFGF) [1], osteogenin [23], sucralfate, and basic fibroblast growth factor [20]. Insulin-like growth factor 1 (IGF1) [24] and hepatocyte growth factor (HGF) [25] stimulate human fibroblast activity in vitro. Plasma and rTGF-beta2 did not significantly alter the rate of vascularization of HA implants during the first 2 to 3 weeks [8] and calcium metaphosphate coatings did not appear to facilitate fibrovascular ingrowth [11].

To date, poor vascularization of the implant can still be a problem and remains a major factor of implant exposure.

Based on a randomized clinical trial [4], spherical alloplastic nonporous and nonpegged porous enucleation implants provide similar implant and prosthetic motility when they are implanted using similar surgical techniques. According to Custer et al., there is a widely variable incidence of porous implant exposure, but surgical techniques and the type of wrapping material used can reduce the exposure rate [4].

11.6 Conclusion

Although small areas of HA exposure (less than 4 mm) may occasionally close spontaneously,

larger defects cannot, and should be actively managed. Based on our experience, we propose three surgical approaches to covering HA exposure: various autologous grafts, a vascularized Muller's muscle pedicle flap, with or without addition of the tarsus contributing to the patch, and removal and replacement of implant in the worst cases

Which of the three surgical approaches to use depends in part on the surface and position of the orbital conjunctival exposure, and in part on the aspect of the implant (the degree of infection, the rate of vascularization), and finally on the number of previous surgical procedures.

References

1. Bigham WJ, Stanley P, Cahill JM, Curran RW, Perry AC (1999) Fibrovascular ingrowth in porous ocular implants : effect of the material composition, porosity, growth factors, and coating. Ophthal Plast Reconstr Surg 15:317–325
2. Carle E, Rosen CE (1998) The Muller muscle flap for repair of an exposed hydroxyapatite orbital implant. Ophthal Plast Reconstr Surg 14:204–207
3. Charles NS, Soparkar CN, Patrinely JR (1998) Tarsal patch flap for orbital exposure. Ophthal Plast Reconstr Surg 14:391–397
4. Custer PL, Kennedy RH, Woog JJ, Kaltreider SA, Meyer DR (2003) Orbital implants in enucleation surgery. A report by the American Academy of Ophthalmology. Ophthalmology 110:2054–2061
5. De Potter P, Shields CL, Shields JA, Flanders AE, Rao VM (1992) Role of magnetic resonance imaging in the evaluation of the hydroxyapatite implant. Ophthalmology 99:824–829
6. El-Shahed Fak Sherif MM, Ahmed AT (1995) Management of tissue breakdown and exposure associated with orbital hydroxyapatite implants. Ophthal Plast Reconstr Surg 11:91–94
7. Goldberg RA, Holds JB, Ebrahimpour J (1992) Exposed hydroxyapatite implants. Report of six cases. Ophthalmology 99:831–836
8. Holck DEE, Dutton JJ, Proia A, Khawly J, Mittra R, Dev S, Nauman I (1988) Rate of vascularisation of coralline hydroxyapatite spherical implants pretreated with saline gentamicin, rTGF-beta 2 and autogenous plasma. Ophthalmic Plast Reconstr Surg 14:73–80
9. Jordan DR (2001) Problems associated with porous orbital implants. Oper Techn Oculoplast Orbital Reconstr Surg 4:39–47
10. Jordan DR, Chan S, Mawn L, Gilberg S, Dean T, Brownstein S, Hill VE (1999) Complications associated with pegging hydroxyapatite orbital implants. Ophthalmology 106:505–512
11. Jordan DR, Brownstein S, Gilberg S, Coupal D, Kim S, Mawn L (2002) Hydroxyapatite and calcium phosphate coatings on aluminium oxide orbital implants. Can J Ophthalmol 37:7–13
12. Kaltreider SA, Newman SA (1996) Prevention and management of complications associated with the hydroxyapatite implant. Ophthal Plast Reconstr Surg 12:18–31
13. Kim Y-D, Goldberg RA, Shorr N, Kenneth D, Steinsapir VD (1994) Management of exposed hydroxyapatite orbital implants. Ophthalmology 101:1709–1715
14. Liao SL, Kao SC, Tseng JH, Lin LL (2005)Surgical coverage of exposed hydroxyapatite implant with retroauricular myoperiosteal graft. Br J Ophthalmol 89:92–95
15. Martin P, Ghabrial R (1998) Repair of exposed hydroxyapatite orbital implant by a tarsoconjunctival pedicle flap. Ophthalmology 105:1694–1697
16. Mourgues T, Adenis JP (2001) Repair of hydroxyapatite orbital implant exposure with a conjunctival Muller muscle flap. Oper Techn Oculoplast Orbit Reconstr Surg 4:36–38
17. Naugle TC Jr, Lee AM, Haik BG, Callahan MA (1999) Wrapping hydroxyapatite orbital implants with posterior auricular muscle complex grafts. Am J Ophthalmol 128:495–501
18. Pelletier CR, Jordan DR, Gilberg SM (1998) Use of temporalis fascia for exposed hydroxyapatite orbital implants. Ophthal Plast Reconstr Surg 14:198–203
19. Remulla HD, Rubin PA, Shore JW, Sutula FC, Townsend DJ, Woog JJ, Jahrling KV (1995) Complications of porous spherical orbital implants. Ophthalmology 102:586–593
20. Rubin PAD, Nicaeus TE, Warner MA, Remulla HD (1997) Effect of sucralfate and basic fibroblast growth factor on fibrovascular ingrowth into hydroxyapatite and porous polyethylene alloplastic implants using a novel rabbit model. Ophthal Plast Reconstr Surg 13:8–17

21. Sagoo MS, Olver JM (2004) Autogenous temporalis fascia patch graft for porous polyethylene (Medpor) sphere orbital implant exposure. Br J Ophthalmol 88:942–946
22. Shields CL, Shields JA, De Potter P, Singh AD (1994) Problems with hydroxyapatite orbital implant: experience with 250 consecutive cases. Br J Ophthalmol 78:702–706
23. Sires BS, Holds JB, Kincaid MC, Reddi AH (1997) Osteogenin-enhanced bone-specific differentiation in hydroxyapatite orbital implants. Ophthal Plast Reconstr Surg 13:244–251
24. Zambonin G, Grano M, Greco G, Oreffo RO, Triffit JT (1999) Hydroxyapatite coated with insulin-like growth factor 1 (IGF1) stimulates human osteoblast activity in vitro. Acta Orthop Scand 70:217–220
25. Zambonin G, Camerino C, Greco G, Patella V, Moretti B, Grano M (2000) Hydroxyapatite coated with heaptocyte growth factor (HGF) stimulates human osteoblasts in vitro. J Bone Joint Surg Br 82:457–460

Chapter 12

Dermis Fat Implants

12

Christoph R. Hintschich

Core Messages

- Dermis fat grafts can be used as primary or secondary orbital implants.
- They can provide volume replacement, restitution of the orbital soft tissue architecture, and additional lining of the socket.
- Primary implantation is indicated after enucleation, particularly in young patients and under difficult conditions, such as inflammatory "hot" sockets after trauma and significant conjunctival scarring.
- Secondary dermis fat implantation is indicated in chronically exposed orbital implants, empty sockets after extrusion of an orbital implant, and for other forms of contracted socket. It is an excellent and often the only way to rehabilitate difficult sockets.
- Dermofat-grafted sockets can be augmented with further procedures such as secondary alloplastic orbital implantation or mucous membrane grafting, if necessary.
- Volume stability is better in primary than in secondary implants.
- Significant complications and loss of the implant are rare.
- Minor complications such as hair growth and granuloma formation can be easily managed.
- The dermis fat grafted socket with its flat surface is very suitable for accepting a prosthesis and is preferred by many ocularists.
- Disadvantages of dermofat grafts are the inevitable scar formation at the donor site with possible secondary problems and an often longer rehabilitative period. There is also a tendency toward mild volume atrophy, particularly in secondary implants.

12.1 Introduction

A dermis fat implant (dermofat graft, DFG) is an autologous transplant consisting of de-epithelialized epidermis with its adjacent subcutaneous fat tissue. It can be used as an alternative orbital implant to alloplastic implants. Currently, it is the only autologous transplant used for this purpose in ophthalmic plastic and reconstructive surgery.

This chapter will provide some information about the history and development of this surgical method, describe the technique of dermofat grafting and present common indications for this technique. The author's results after primary and secondary dermis fat transplantation will also be presented, including complications and their treatment. Finally, the advantages and disadvantages of dermofat grafting will be discussed.

12.2 History

The idea of using free fat transplants in surgery goes back to the end of the 19th century [22, 30]. At the beginning of the 20th century, free

fat grafting for the maintenance of the acquired anophthalmic socket was introduced. Barraquer from Mexico first described autologous fat transplantation as an implant following evisceration [2], before it was used following enucleation [3, 21, 27]. Free fat was inserted into the extraocular muscle cone and covered with conjunctiva. Later the rectus muscles were sutured across the transplanted tissue [3, 27]. Significant postoperative atrophy, however, made this technique unacceptable [37].

According to Neubauer [29], the first dermis fat transplant including fat in conjunction with de-epithelialized skin, was introduced by Loewe [25] and was extensively utilized by Lexer [23]. In Europe, free dermofat grafting was widely used in the first decades of the 20th century [8, 26, 35, 38, 46–48]. Following the development of modern alloplastic orbital implants during and after the Second World War, dermofat grafting fell into oblivion. It was not until 1978 that dermis fat implants were resurrected by Smith and Petrelli [43] and further propagated by Smith et al. in 1982 [45]. Smith originally used the dermis fat implant as a secondary orbital implant, but then began using it more and more as a primary orbital implant [17, 44]. This short excursion into medical history demonstrates that dermofat grafting is by no means a recent development, but, rather, has been used quite successfully for more than 100 years.

12.3 Principle

Autologous tissue consisting of de-epithelialized skin with its adjacent subcutaneous fat is used as a primary or secondary orbital implant. The graft is usually taken from the gluteal region and transplanted into the socket with the external dermis facing outward. The extraocular rectus muscles or adequate orbital soft tissues are sutured to the margin of the dermis. The conjunctiva of the recipient is fixed onto the surface of the dermis, leaving part of it bare for spontaneous re-epithelialization (Fig. 12.1).

12.4 Surgical Procedure

12.4.1 Primary DFG

As for any other autologous transplantation, the surgical procedure involves two steps: first, harvesting the transplant, and second, preparation of the recipient site with implantation of the graft. The procedure is performed under general anesthesia. The first step is usually the harvesting

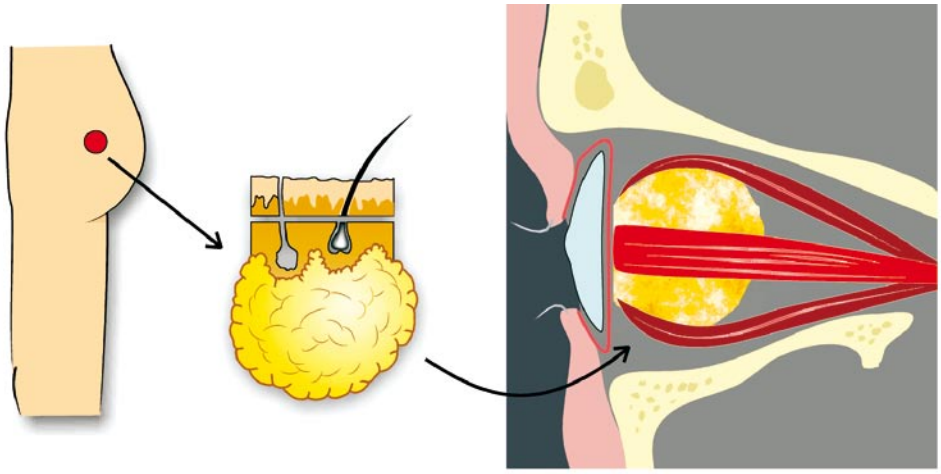

Fig. 12.1 Principle of dermis fat transplant (schematic). De-epithelialized skin with adjacent subcutaneous fatty tissue is transplanted from the gluteal region into the socket

of the dermofat graft. The favorite donor site is the upper outer quadrant of the gluteal region. This is not a weight-bearing area; there is no risk of damaging the sciatic nerve, and even a bikini will hide the scar. Furthermore, the skin itself in this area is thicker compared with other areas, and this is advantageous for graft stability. For harvesting the graft, it is necessary to place the patient in a lateral position on the contralateral hip. Any damage to one of the extremities or the neck has to be avoided by meticulous use of padding, which is usually performed with the help of the anesthesiologist. After disinfection of the region, the dermis fat graft is harvested from an area 5 cm below the middle point of a line that joins the anterior iliac crest and the sciatic tuberosity. Before performing the incision, a circle with a maximum diameter of 25 mm is marked on the skin. The skin is incised superficially with a no. 15 blade, the incision not extending into the dermis. Intradermal injection of saline solution into the demarcated area facilitates the de-epithelialization of the skin. Using a no. 20 blade, which is positioned nearly parallel to the skin surface and moved in a rotational manner, helps with removing the epidermis (Fig. 12.2a). A deep incision is then made perpendicular to the surface, through the dermis and into the subcutaneous fat. The graft is severed from the donor, paying attention not to damage the muscle fascia (Fig. 12.2b). The graft is preserved in a gauze pad moistened with isotonic saline solution, while the donor site is closed with multiple (usually three or four) interrupted 2-0 absorbable sutures (Vicryl™ 2-0) placed through the fatty and subcutaneous tissue. Skin closure is performed with 2-0 black silk horizontal mattress sutures. Steri-strips™ are placed across the wound, and a pressure dressing with eudermic elastic plaster is applied. Harvesting of the graft may take about 15 min.

After moving the patient into a supine position, the operation can be continued. In a primary procedure, enucleation is performed in a standard fashion. Applying additional retrobulbar local anesthesia with long-acting local anesthetics with adrenalin is advisable (bupivacaine, 1% with adrenaline 1:200,000, 4–5 ml). The conjunctiva is opened along the limbus. As much conjunctiva as possible should be saved. The rectus muscles are isolated and tagged with double-armed 5-0 Vicryl™ sutures. The sutures are left long with their needles attached, before the muscles are severed. The oblique muscles can be severed using bipolar diathermy. The globe is mobilized and any adhesions, if present, are transsected. Enucleation is performed using heavy, but only slightly curved, enucleation scissors. The optic nerve is usually severed about 10 mm behind the globe. After enucleation of the entire globe any hemorrhage is controlled by applying pressure for several minutes with a moist swab, which is firmly held in a clamp. The posterior Tenon's capsule can be spread further with blunt scissors. The graft is then implanted within the extraocular muscle cone, using malleable retractors and cotton swabs (Fig. 12.2c). The dermofat transplant should always be treated carefully to minimize damage to the tissue. If necessary, the graft can be trimmed to remove excess fat to allow the tissue to be transferred into the anophthalmic socket bed without undue pressure. The muscles are then sutured to the transplant. The first suture is passed from below, through the dermis about 2 mm from its margin at the 12 o'clock position, and the remaining sutures at the 3, 6, and 9 o'clock positions are placed sequentially. At all times gentle pressure is maintained on the graft, keeping the fat within the orbit. Two additional 5-0 Vicryl™ sutures in each quadrant are then attached to Tenon's fascia and passed through the dermal margin of the graft. Finally, the margin of the conjunctiva is re-approximated to the surface of the dermis with multiple interrupted 6-0 Vicryl™ sutures.

To maintain deep fornices it is essential not to cause undue tension on the conjunctiva. If there is sufficient conjunctival lining available, it is possible to cover the surface of the graft completely. Otherwise the conjunctiva can be sutured to the margin or onto the surface, leaving a bare part of dermis for spontaneous re-epithelialization.

At the end of the procedure a clear plastic shell (conformer) with a rather shallow curvature of appropriate size is inserted into the socket behind the eyelids (Fig. 12.2d). Antibiotic eye drops with some steroids can be employed before a firm dressing of moist and dry pads is applied and left for 2–3 days.

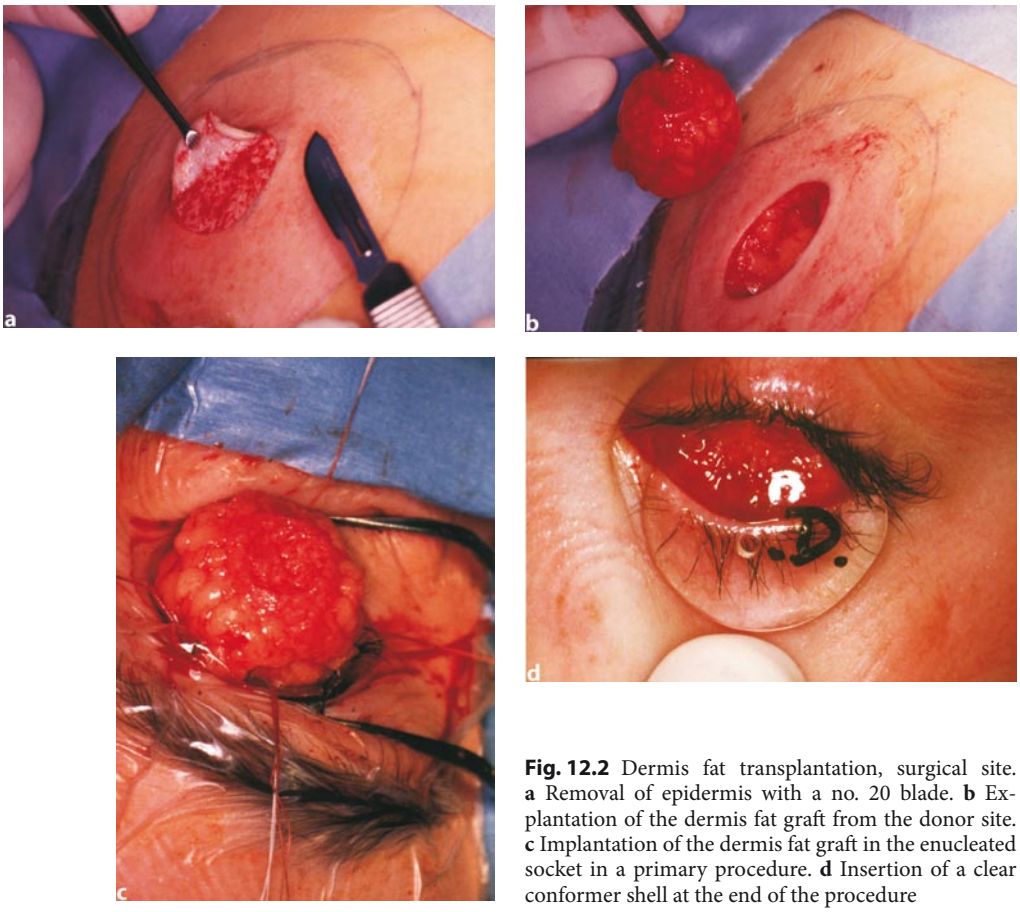

Fig. 12.2 Dermis fat transplantation, surgical site. **a** Removal of epidermis with a no. 20 blade. **b** Explantation of the dermis fat graft from the donor site. **c** Implantation of the dermis fat graft in the enucleated socket in a primary procedure. **d** Insertion of a clear conformer shell at the end of the procedure

Summary for the Clinician

- Be careful while positioning the patient to avoid damage to joints or nerves.
- Ablate the epidermis layer completely (otherwise there is a risk of a smelly socket).
- Use strong suture material for closing the donor site.
- Do not stuff the graft with pressure into the socket.
- Always use a conformer shell postoperatively.

12.4.2 Secondary DFG

In the case of secondary transplantation, the graft is harvested in the same manner. The socket is then prepared for the graft. The next steps of the procedure are now dependent on the condition of the socket. In the case of an eroding or extruding orbital implant, the conjunctiva is transsected in a circle around the extruding part of the alloplastic implant. It is mandatory to avoid leaving any conjunctival tissue posterior in the orbit in order to prevent the development of a conjunctival implantation cyst. The orbital implant is then mobilized and finally explanted.

Usually, bleeding is less than that observed in primary procedures and can be controlled by

applying pressure. If necessary, greater space to accommodate the dermofat graft is produced by blunt dissection and with gentle spreading of the scissors. Any attempt to perform further dissection in order to expose remnants of the extraocular muscles should be avoided. Preparation and dissection in the orbital soft tissues should be as atraumatic as possible. Four double-armed absorbable 5-0 Vicryl™ sutures are placed superiorly, inferiorly, medially, and laterally (at the 12, 3, 6, and 9 o'clock positions) into any available deeper tissue in the socket strong enough to hold the sutures.

In the case of a contracted socket, traction sutures into the upper and lower eyelid may be necessary, because retractors cannot be inserted due to inadequate fornices. A conjunctival incision is usually performed from the caruncle horizontally through the centre to the lateral canthus. A few millimeters of the conjunctiva is mobilized in a circular fashion by subconjunctival dissection. Then a space to accommodate the graft is created, again, mainly by blunt dissection with spreading of the tissues. However, bands of scarred tissue sometimes have to be separated. If there is sufficient space to accept the graft, sutures are then placed in the same fashion as that described above. The dermofat graft is then inserted into the socket, applying only slight pressure. If there is a discrepancy between the available space and the size of the graft, undue pressure on the graft must be avoided. Either the space in the socket can be enlarged or the graft must be trimmed. The sutures are then passed from below through the dermis about 2 mm from its margin at the 12 o'clock position. The remaining sutures at 3, 6, and 9 o'clock positions are placed sequentially as in primary grafting. In the case of a contracted socket, the conjunctiva is sutured just to the margin of the dermis without overlapping to increase the conjunctival lining in order to create adequate fornices.

Again, at the end of the procedure, it is mandatory to insert a conformer with a rather shallow curvature of appropriate size into the socket behind the eyelids. This stabilizes the graft and helps to maintain the fornices. A pressure dressing is applied for 2–3 days.

Summary for the Clinician

- Never insert a dermofat graft onto an alloplastic implant.
- Avoid gratuitous dissecting inside the socket. Do not attempt to search for the extraocular muscles.
- Attach the conjunctival layer without tension onto the dermis, leaving a raw surface as necessary.
- Always use a conformer shell postoperatively.

12.5 Results

At the University Eye Hospital in Munich, 271 dermis fat transplantations were performed between 1991 and 2004. One hundred and ninety-one were primary procedures (I° DFG), and 80 were secondary dermofat grafts (II° DFG). In 2005 the results of 255 dermis fat transplantations were reported (188 primary DFG, 67 secondary DFG) [39].

Indications for enucleation were painful blind eyes (102), choroidal melanoma (60), and for other reasons, such as buphthalmos, retinoblastoma, etc. (26). In patients undergoing secondary dermis fat transplantation, the largest group had a "contracted socket" (39), 17 had an extruded alloplastic orbital implant, and 11 had a post-enucleation socket syndrome. Patients' age ranged from 5 to 89 years (mean 44.4 years). The mean follow-up in the I° DFG group was 14.7 months (range 2–123 months) and 10.9 months (range 2–82 months) in the II° DFG group.

The results were judged clinically, with regard to the relative enophthalmos of the prosthesis, the eyelid aperture, motility of the artificial eye, and prosthesis fitting. In the I° DFG group, motility was graded "excellent" in 74%, "reasonable" in 25%, and "poor" in 1%, whereas in the II° DFG patients motility was significantly worse ("excellent" 34%, "reasonable" 44%, "poor" 18%). There was also a difference between the I° DFG and II° DFG groups regarding artificial eye fitting ("excellent": 81% I° DFG, 49% II° DFG, "reasonable": 15% I° DFG, 40% II° DFG, "poor": 4% I° DFG,

10% II° DFG). In the I° DFG group, patients rated their satisfaction as "excellent" in 82%, "reasonable" in 17%, and "poor" in 1%. In the II° DFG group, the corresponding figures were 58%, 40%, and 2%.

In the group of patients treated for the correction of a contracted socket, 90% of these sockets could be reconstructed with a single secondary dermis fat DFG procedure alone.

12.6 Complications

There are numerous complications that can possibly occur following implantation of an orbital DFG (Table 12.1). The surgeon should carefully discuss these possibilities with the patient. The majority of these complications, however, are minor. They are usually of no consequence for the final result and either resolve spontaneously or can be managed easily. There are, however, some major complications that can truly jeopardize the result or even destroy the surgical efforts.

One of the major complications is loss of the transplant due to necrosis, either from infection or from an unknown cause. This serious complication is not common [1, 41]; in our large series 2.7% occurred in the primary DFG group and 4.5% in the secondary DFG group. The risk of losing a dermofat graft rises dramatically if it is inserted onto a pre-existing alloplastic orbital implant. This can be avoided by carefully evaluating the indication for a specific circumstance.

Long-term maintenance of dermofat grafts is a topic of major concern. Atrophy of dermofat grafts can occur, but it is less common than generally assumed. Primary implants do better than secondary. Smith et al. [44] reported in their series of 118 DFG, that 3 out of 9 patients who had received the graft for the correction of a contracted socket developed significant atrophy of more than 40%. Only 1 out of 51 patients with a primary graft developed a comparably significant atrophy.

Five to 10% loss of volume is assumed to be normal [44]. However, this is difficult to assess. Guberina et al. found that 10 out of 52 DFGs atrophied, one of them significantly [10]. They also showed the best results in primary implants [10]. In our series we found significant and clinically evident atrophy in 3.5% of the primary and 6% of the secondary implants.

The development of deep subconjunctival cysts is a serious complication that can occur after secondary dermofat grafting [32]. In reality, however, it is a complication caused by long-standing exposure or chronic erosion of alloplastic implants with subsequent invasion of conjunctival epithelium, which then cannot be excised completely. The problem arises from the fact that the slow-growing inclusion cyst replaces orbital soft tissue including the transplanted fat tissue. As the cyst enlarges, the patient (or ocularist) notices a proptosis of the prosthesis. Complete surgical removal of the cyst is then indicated. Usually, a significant volume deficit remains, which can only be restored with further surgery, including another dermofat transplant or a tertiary alloplastic orbital implant.

Postoperative hemorrhage can cause significant pressure behind the transplant, which can be a reason for loss of the transplant. In our series the hemorrhage was completely resorbed without any negative sequelae.

Minor complications include pyogenic granulomas, which may develop on the surface of the graft around the suture material. They can be simply ablated in an office procedure.

Single growing hairs are mainly seen in adult male patients. They can be treated by argon laser epilation with a very good success rate.

Rarely, central ulcerations can develop in the graft [1, 18, 41]. These small pits will usually granulate spontaneously without intervention after several weeks.

Growth of fatty tissue can induce a proptosis of the artificial eye. Usually, it is observed in patients who have undergone transplantation in childhood and later gained significant body weight. This is a clear indication of successful integration of the free dermofat graft. Surplus tissue can easily be trimmed under local anesthesia.

It is noteworthy that subjective disturbances of the patient caused by the donor site are rare. Problems can arise from wound dehiscence, prolonged or secondary healing, scar formation, and contour deformity. To avoid wound dehiscence, it is important to use strong suture materials, which on the one hand should grip enough firm subcutaneous tissue, but on the other hand

Table 12.1. Complications occurring following implantation of an orbital dermofat graft (*DFG*)

	I° DFG (%)	II° DFG (%)
Minor complications		
Hair growth	6.9	7.5
Subconjunctival cyst (superficial)	3.5	1.5
Pyogenic granuloma	4.9	2.9
Fat growth	1.4	0
Donor site dehiscence	0.5	0
Major complications		
Necrosis (complete)	2.7%	4.5%
Spontaneous atrophy	3.5%	6.0%
Postoperative hemorrhage	0.7%	0%
Subconjunctival cyst	0%	1.5%

should be buried completely. Early postoperative exercise and sitz baths should be avoided.

Summary for the Clinician

- Small areas of central necrosis in the dermis are left for spontaneous granulation.
- Avoid secondary surgery in the first 6 months postoperatively.

12.6.1 DFG Placement in the Upper Eyelid

Dermofat grafts can be implanted into the upper eyelid for the correction of upper eyelid sulcus deformity [36]. Usually, the graft is then inserted upside down, which means the dermis is fixed onto the periosteum of the upper bony orbital margin. However, the aesthetic results can be rather disappointing, since the implanted fatty tissue is not smooth enough to allow a natural contour with a regular skin crease. There is also a tendency toward excess bulk. While it can be a problematic technique for upper sulcus reformation, it may still be worth a try in selected cases.

12.7 Indications

12.7.1 Primary Dermis Fat Transplantation

Indications for using any primary orbital implant after enucleation are the creation of a healthy socket suitable for wearing a custom-made artificial eye and to prevent a post-enucleation socket syndrome with a marked volume deficit. This is also true of the primary dermis fat transplant.

The indication for primary dermofat grafting is enucleation in general. In these cases it can be used as an alternative to alloplastic orbital implants. However, there are some conditions in which dermofat grafting seems to be advantageous to other forms of implants. This is true in young patients with a long life expectancy (Fig. 12.3) and patients with difficult local preoperative conditions. These conditions include eyes after multiple ocular surgery procedures or severe trauma with marked conjunctival scars and shortened fornices, but also patients with congenital or acquired buphthalmic eyes (Fig. 12.4). The condition of an inflammatory "hot socket," describing a severely traumatized and blind eye with soft tissue damage to eyelids, conjunctiva, Tenon's capsule, and extraocular muscles is also

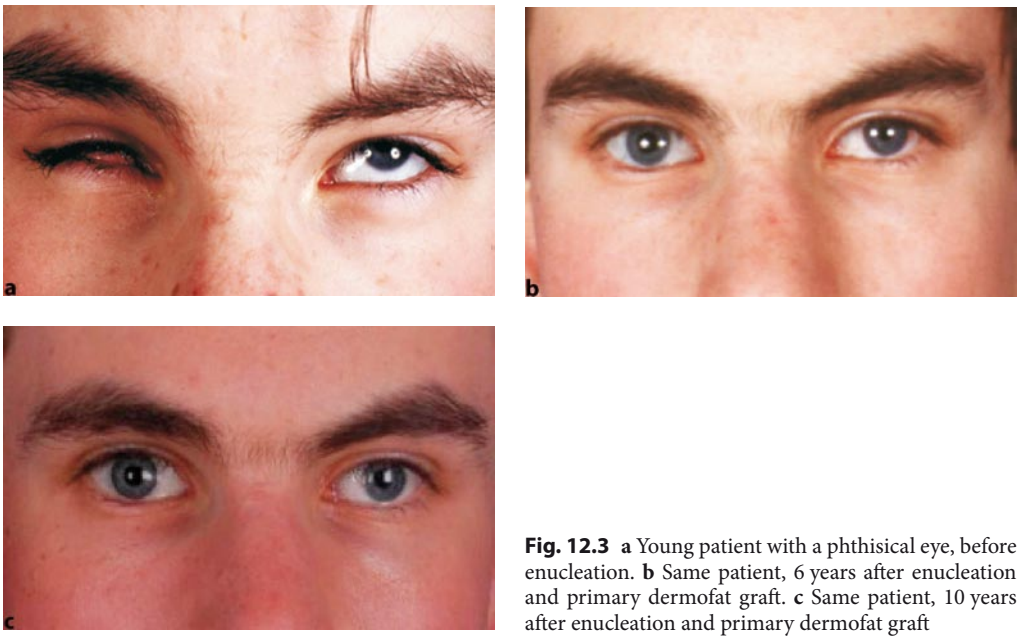

Fig. 12.3 **a** Young patient with a phthisical eye, before enucleation. **b** Same patient, 6 years after enucleation and primary dermofat graft. **c** Same patient, 10 years after enucleation and primary dermofat graft

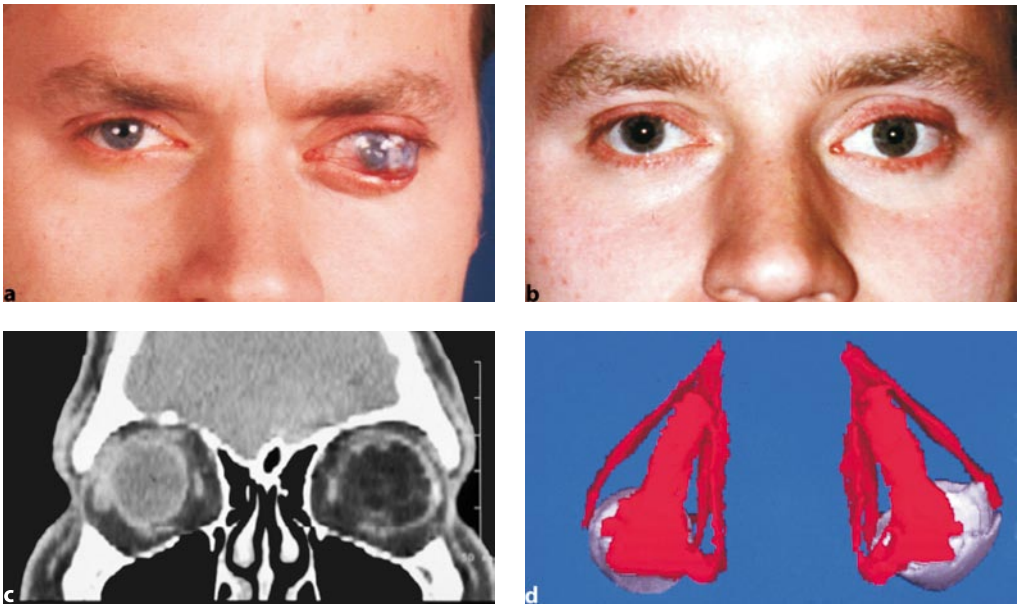

Fig. 12.4 **a** A 22-year-old man with secondary buphthalmos after trauma. **b** Patient 3 years after enucleation and primary dermofat graft. **c** CT (coronal), 3 years after enucleation and primary dermofat graft. Note viable intraconal fatty tissue. **d** 3D reconstruction of the extraocular muscles, the globe (*right*) and the dermofat graft with artificial eye (*left*). Note the regular architecture of the extraocular muscle cone and adequate size of the dermofat graft

an important indication for a primary dermofat graft, if an enucleation is at all indicated.

Congenital anophthalmos represents a rare, but extremely complex entity that is very difficult to manage. Different approaches have been advocated to deal with this condition. This includes more conservative strategies with early conformer fitting as well as surgically aggressive concepts [20, 28, 34] and more recently the implementation of a combined approach with expandable implants and conformers [11] or injectable self-inflating expanders [40]. Implantation of an autogenous dermis fat transplant is an alternative that can provide volume to fill up the deep V-shaped socket and can assist in creating good fornices for better conformer fitting. The DFG will grow in tandem with the child's overall growth, and bony orbital growth can be stimulated with the combination of a DFG and a prosthetic shell [13, 15, 19].

12.7.2 Secondary Dermis Fat Transplantation

Indications for secondary procedures in general include the treatment of post-enucleation socket syndrome with predominantly volume deficits, the management of dislocated, chronically exposed or extruded orbital implants (Fig. 12.5), and all forms of a contracted socket, particularly if the stability of the artificial eye is impaired (Fig. 12.6). Secondary dermofat grafts can be very helpful for the management of these conditions. They can be used for the therapy of pure volume deficit alone. However, in an uncomplicated socket with good fornices, volume may be replaced more easily and securely by inserting an adequate alloplastic spherical implant. Secondary dermofat grafts do tend to atrophy to a certain degree and carry a risk of more significant volume atrophy. Ideally, however, this can be used as the

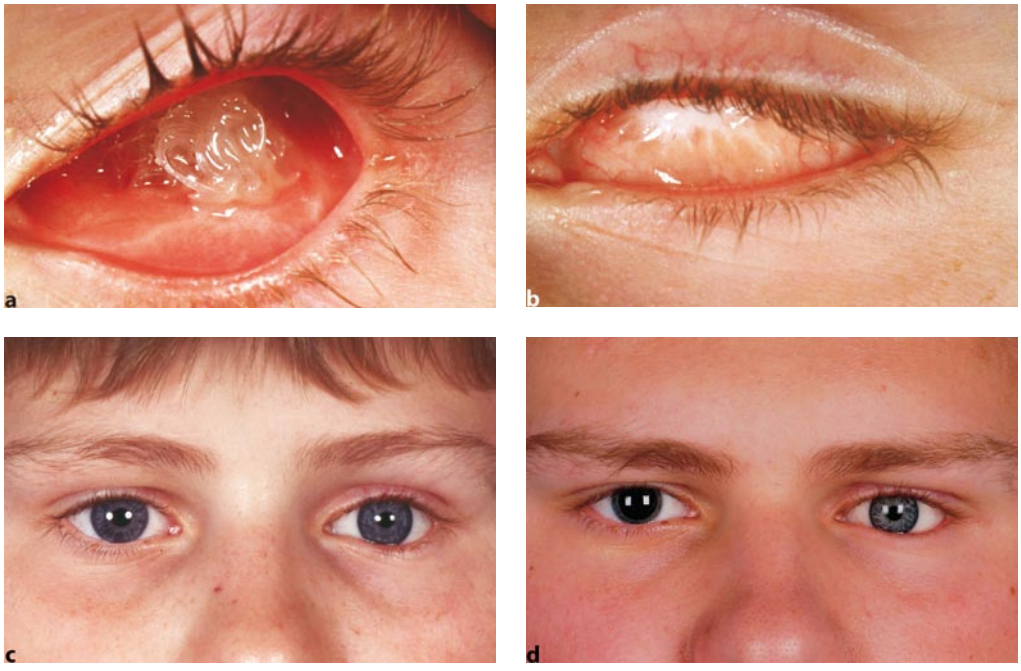

Fig. 12.5 **a** Socket of a young boy with chronically eroded conjunctiva and partially extruded alloplastic orbital implant. **b** Quiet and stabile socket after implant removal and secondary dermis fat transplantation. **c** Patient with artificial eye (*left*) 2 years after implant removal and secondary dermis fat transplantation. **d** Same patient 7 years after surgery

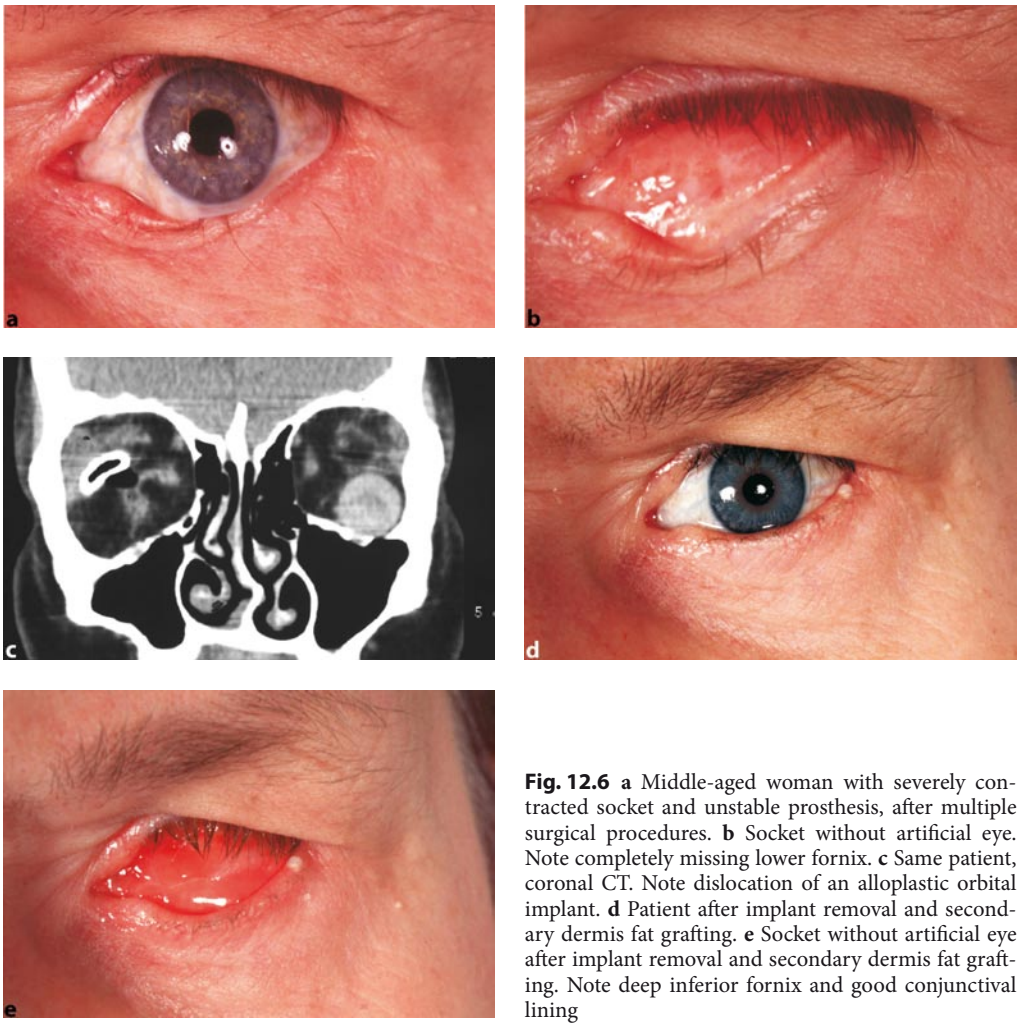

Fig. 12.6 **a** Middle-aged woman with severely contracted socket and unstable prosthesis, after multiple surgical procedures. **b** Socket without artificial eye. Note completely missing lower fornix. **c** Same patient, coronal CT. Note dislocation of an alloplastic orbital implant. **d** Patient after implant removal and secondary dermis fat grafting. **e** Socket without artificial eye after implant removal and secondary dermis fat grafting. Note deep inferior fornix and good conjunctival lining

procedure of choice to improve the socket condition in cases of combined pathology. For sockets with a chronically eroded surface and in cases of recurrent implant erosion or extrusion, dermofat grafting is the only promising procedure currently available. This includes sockets with signs of contraction and reduced conjunctival lining combined with a volume deficit. These difficult sockets can particularly benefit from dermofat grafting. In moderately contracted sockets with some volume deficit, dermofat grafting can replace mucous membrane grafting and alloplastic orbital implant insertion by this single procedure in up to 90%. However, if a considerable volume deficit persists after a dermofat graft under these conditions, either a second dermofat graft or an alloplastic orbital implant behind the dermofat graft can be inserted after complete healing.

Summary for the Clinician

- In patients with chronically eroded and extruding alloplastic orbital implants, implant removal with replacement by a secondary dermis fat transplant is recommended

12.8 Essential Concepts

12.8.1 Size of the Dermofat Graft

The correct and adequate size of the dermis fat transplant does depend on the implantation site. However, there are certain rules that should be kept in mind. Published reports vary. They range from "as much fat as possible" [24], to a "surface of 15×18 mm and a depth from 30 to 40 mm" [1], to a "spherical implant of 35 mm diameter" [31] or "25×25 mm and an adequate depth" [4, 9]. A depth of 10 mm for the fatty part of the graft was shown to be insufficient [42].

In Munich, we have been using circular grafts measuring 25 mm in diameter and about the same in depth. This is a suitable size for any primary procedure involving removal of an average eyeball. However, this has to be modified depending on the size of the orbital implantation site. In secondary procedures, the graft often needs to be smaller, and in congenital anophthalmos our smallest implant measured only 12 mm in diameter. Again, it is essential, not to push the graft into the socket with force.

12.8.2 Shape of the Dermofat Graft

The discoid shape is a stable form with a low risk of central ulcerations. Alternatively, narrower transplants shaped like a banana have been described [7]. Their donor site is easier to close, however, since they have to be sutured in order to get a discoid shape, they are much more at risk of developing central breakdown and ulcerations.

12.8.3 Donor Site

The gluteal region is advantageous as the preferred donor site, because the dermis is stronger and the subcutaneous fatty tissue is, according to Guberina [9], more robust than in other regions. Underwear usually hides the scar. Alternatively, tissue can be harvested from the periumbilical area [5].

12.8.4 Avoid Placement of DFG onto Alloplastic Implants

Inserting a free dermofat graft onto a pre-existing alloplastic orbital implant carries a considerably high risk of transplant failure. In situations in which a dermis fat transplant would appear advantageous for the restoration of a difficult socket with an alloplastic orbital implant already in place, this should be removed and replaced by a dermofat graft. If necessary, for greater volume, an alloplastic implant can later be inserted behind the DFG.

12.8.5 Avoid Compressing the DFG with Orbital Insertion

Any dermofat graft should be handled with care. Unnecessary manipulation with instruments has to be avoided. In particular, the insertion of the graft into the socket should be handled carefully. It should not be squeezed into the space, and any undue pressure should be avoided; otherwise the risk of graft atrophy is enhanced.

12.8.6 Avoid Dissection to Expose Extraocular Muscles

In secondary implantation, it is advantageous to treat the socket as atraumatically as possible. Extensive dissection, in order to expose and visualize the extraocular muscle, should be avoided. Unnecessary manipulation enhances the risk of bleeding and late fat atrophy. However, it is important to anchor the sutures in the best possible position, which means deep enough in the socket in the region where the rectus muscles are suspected.

12.8.7 Fornices

A particular advantage of dermofat grafting is the fact that good and deep fornices can be created, because with wound closure the conjunctiva is minimally shortened. With spontaneous epithelialization, the conjunctival lining can be

expanded [14]. In our experience, the proportion of bare dermis is dependent on the condition of the socket and the amount of available conjunctiva available. The smaller the amount of raw dermis, the faster wound healing will occur.

12.8.8 Motility

Motility is usually of great concern to the patient. One has to distinguish between the motility noted in the socket alone and the motility of the artificial eye. Motility of the socket after primary dermofat grafting is usually excellent. This can be explained by the relatively peripheral insertion of the rectus muscles.

In contrast to spherical orbital implants dermofat grafts create a flatter surface for fitting an artificial eye [33]. Ocularists often prefer the primary dermofat graft to other implants [16].

The problems of transmission of the socket motility onto the artificial eye in integrated orbital implants have been pointed out by Guthoff [12]. With an adequately fitted prosthesis this transmission of motility in dermofat-grafted sockets with a flat surface is very good, resulting in excellent motility of the artificial eye. Quantification of the prosthetic motility in dermofat sockets using Kestenbaum spectacles showed motility values that were comparable to composite implants and slightly better than primary baseball implants [18]. Bosniak found better socket motility in dermofat-grafted patients compared with those with alloplastic spherical implants, and a comparable, slightly reduced motility for the artificial eye [6]. In our experience, however, fine motility of the artificial eye is excellent, whereas motility into extreme positions is modest.

12.8.9 Rehabilitation Following DFG Implantation

It takes 4–6 weeks for full vascular ingrowth and re-epithelialization of the graft surface to occur. Usually, the conformer is left in place until the first artificial eye can be fitted. This should happen under stable conditions. If necessary, a first provisional prosthesis can be fitted after about 3 weeks. A second artificial eye is then fitted 3–6 months after the first fitting. The prosthesis is custom-made by an experienced ocularist. An open-minded exchange of information regarding the patient's situation and concerns of the ophthalmic surgeon and the ocularist is extremely important for an optimal rehabilitative result.

12.9 Conclusion

The autologous dermis fat transplant can be used as a primary or secondary orbital implant. Specific advantages of dermofat grafts are the combination of volume replacement, restitution of orbital architecture, and augmentation of the conjunctival surface without the disadvantages of alloplastic implants. The method does not require preserved sclera, thus excluding, even theoretically, a possible transfer of pathogens such as viruses or prions in alcohol-preserved sclera. Mechanically caused complications, like migration, exposure, and extrusion, are unknown. As a primary graft it is particularly valuable both in children and young patients and in patients with difficult conditions, e.g., after trauma or chemical burn. It provides volume as well as helps to maintain the fornices in order to create an adequate socket.

For the management of anopththalmic sockets with challenging conditions, such as chronically exposed orbital implants, empty sockets after extrusion of an orbital implant and various forms of contracted socket, a secondary dermofat graft is often the only procedure available for reconstructing this type of socket with any chance for success.

Volume stability is good, and even better in primary implants. The aesthetic and functional results are usually reliable. However, a number of minor complications, like hair growth, granuloma formation, and fat growth can occur with a reasonable incidence, but are also easily treated. Major complications are relatively rare. The patient should be informed, however, particularly about graft failure and insufficient volume replacement. Moreover, dermofat grafts are cost effective compared with most alloplastic orbital implants.

Disadvantages are the need for a donor site with inevitable scar formation and possible secondary pathology, as well as a longer rehabilitative period postoperatively.

References

1. Aguilar GL, Shannon GM, et al. (1982) Experience with dermis-fat grafting: an analysis of early postoperative complications and methods of prevention. Ophthalmic Surg 13:204–209
2. Barraquer J (1901) Enucleatio ingerto de tejido adiposo en la capsula de Tenon. Arch Ophthalmol Hisp Am 1:82
3. Bartels M (1908) Verpflanzung von Fett in die Tenon'sche Kapsel zur Erzielung eines guten Stumpfes nach Enucleatio bulbi. Berl Dtsch Ophthalmol Ges 35:333–335
4. Beyer-Machule CK, Riedel KG (1993) Plastische Chirurgie der Lider: Wundversorgung, Stellungskorrektur und Rekonstruktion. Enke, Stuttgart
5. Bonavolonta G, Tranfa F, Salicone A, Strianese D (2000) Orbital dermis-fat graft using periumbilical tissue. Plast Reconstr Surg 105(1):23–26
6. Bosniak SL, Nesi F, et al. (1989) A comparison of motility: autogenous dermis-fat vs synthetic spherical implants. Ophthalmic Surg 20:889–891
7. Collin JRO (1989) A manual of systematic eyelid surgery. Churchill Livingstone, Edinburgh
8. Grossmann D (1927) Fettimplantation nach Enucleation und Exenteration. Klin Monatsbl Augenheilk 78:804
9. Guberina C, Hornblass A, et al. (1983) Autogenous dermis-fat orbital implantation. Arch Ophthalmol 101:1586–1590
10. Guberina C, Hornblass A, et al. (1987) Pitfalls of autogenous lipodermal implantation to the orbit. Ophthal Plast Reconstr Surg 3(2):65–70
11. Gundlach KK, Guthoff RF, Hingst VH, Schittkowski MP, Bier UC (2005) Expansion of the socket and orbit for congenital clinical anophthalmia. Plast Reconstr Surg 116(5):1214–1222
12. Guthoff R, Vick HP, et al. (1995) Zur Prophylaxe des Postenukleationssyndroms: das Hydroxylapatitsilikonimplantat. Ophthalmologe 92:198–205
13. Handler LF, Heher KL, Katowitz JA (2002) Management of the microphthalmic orbit. In: Katowitz JA (ed) Pediatric oculoplastic surgery. Springer, Berlin, pp 576–580
14. Hatt M (1992) Orbitaplastiken bei Prothesenträgern. Klin Monatsbl Augenkeilk 200:424–427
15. Heher K, Low J, Katowitz J (1998) Unilateral dermis-fat implantation in the pediatric orbit. Ophthal Plast Reconstr Surg 14(2):81–88
16. Hintschich C, Baldeschi L (2001) Rehabilitation of anophthalmic patients. Results of a survey. Ophthalmolge 98(1):74–80
17. Hintschich C, Beyer-Machule C (1996) Dermis-Fett-Transplantat als autologes Orbitaimplantat. Klin Monatsbl Augenheilk 208:135–141
18. Hintschich C, Beyer-Machule C (1996) Dermis-Fett-Transplantat als primäres und sekundäres Orbitaimplantat – Komplikationen und Ergebnisse. Ophthalmologe 93:617–622
19. Katowitz JA (1991) Orbital expansion with dermis-fat grafts in the pediatric age group. Presented at the Annual Meeting of the American Academy of Ophthalmology, Anaheim, California, 14 October 1991
20. Krastinova D, Kelly MB, Mihaylova M (2001) Surgical management of the anophthalmic orbit. I. Congenital. Plast Reconstr Surg 108(4):827–837
21. Lauber H (1910) Enukleation mit Fettimplantation. Z Augenheilk 23:426–431
22. Lexer E (1919) Fettgewebstransplantation in "Die freien Transplantationen". Neue Deutsche Chir 25:272
23. Lexer E (1925) 20 Jahre Transplantationsforschung in der Chirurgie. Arch Klin Chirurg 138:251–302
24. Lisman RD, Smith BC, et al. (1989) Current concepts in dermis-fat grafting. Int Ophthalmol Clin 29:252–264
25. Loewe O (1913) Über Hautimplantation anstelle der freien Faszienplastik. Münch Med Wochenschr 24:1320
26. Löwenstein A (1928) Über die operative Behandlung des "eingesunkenen Oberlids" nach Enukleation des Augapfels. Klin Monatsbl Augenheilk 80:233–237
27. Marx G (1910) Über Fettransplantation nach Eviszeration und Enucleatio bulbi. Arch Augenheilk 66:15–24
28. Morax S, Hurbli T (1992) Orbito-palpebral reconstruction in anophthalmos and severe congenital microphthalmos. Adv Ophthalmic Plast Reconstr Surg 9:67–80
29. Neubauer H (1989) Enukleation und Eviszeration des Augapfels, Höhlenplastik. In: Mackensen G, Neubauer H (eds) Augenärztliche Operationen. Springer, Berlin, pp 738–773
30. Neuber GA (1893) Fettransplantation. Verhandl Deutsche Ges Chir 22:66
31. Nunery WR, Hetzler KJ (1985) Dermal-fat graft as a primary enucleation technique. Ophthalmology 92:1256–1261

32. Patrinely JR, Anderson RL, Shore JW (1987) Macrocystic enlargement of orbital dermis-fat grafts. Ophthalmic Surg 18(7):498–502
33. Przybyla VA, La Piana FG, et al (1981) Fitting of the dermis-fat grafted socket. Ophthalmology 88:904–907
34. Rodallec A, Dufier JL, Ernest C, Haye C (1988) Congenital anophthalmos. Control of osteogenesis with an expanding intraorbital prosthesis. J Fr Ophtalmol 11(10):661–668
35. Rohrschneider W (1945) Ophthalmologische Operationslehre. Leipzig, pp 744
36. Rose G, Collin R (1992) Dermofat grafts to the extraconal orbital space. Br J Ophthalmol 76(7):408–411
37. Sattler CH (1922) Operationen zur Verbesserung der Kosmetik nach Enukleation. Graefes Arch Ophthalmol 108:229–236
38. Sattler CH (1922) Enucleatio und Exenteratio bulbi, Implantation zur Verbesserung der Kosmetik nach Enukleation und Exenteration, Resectio opticociliari. In: Graefe-Saemisch (ed) Handbuch der gesamten Augenheilkunde, Augenärztliche Operationslehre. Elschnig. Springer, Berlin, pp 1763–1855
39. Schebitz-Walter K, Hintschich C (2005) Results after primary and secondary dermofat grafting 24th Annual Meeting of ESOPRS, Crete
40. Schittkowski MP, Guthoff RF (2006) Injectable self inflating hydrogel pellet expanders for the treatment of orbital volume deficiency incongenital microphthalmos: preliminary results with a new therapeutic approach. Br J Ophthalmol 90(9):1173–1177
41. Shore JW, McCord CD Jr, Bergin DJ, Dittmar SJ, Maiorca JP, Burks WR (1985) Management of complications following dermis-fat grafting for anophthalmic socket reconstruction. Ophthalmology 92(10):1342–1350
42. Sihota R, Sujatha Y, et al. (1994) The fat pad in dermis fat grafts. Ophthalmology 101:231–243
43. Smith B, Petrelli R (1978) Dermis-fat-graft as a movable implant within the muscle cone. Am J Ophthalmol 85:62
44. Smith B, Bosniak SL, et al. (1983) Dermis-fat orbital implantation: 118 cases. Ophthalmic Surg 14:941–943
45. Smith P, Bosniak SL, et al. (1982) An autogeneous kinetic dermis-fat graft orbital implant. An updated technique. Ophthalmology 89:1067–1071
46. Sourdille (1916) Prothese oculaire chez les blessés de guerre. Arch d'Oculist Ref Klin Monatsbl Augenheilk 666
47. Von Blaskovics L, Kreiker A (1938) Eingriffe in der Augenhöhle. Enke, Stuttgart
48. Wicherkiewicz (1913) Sur l'implantation de la peau dans la capsule de Tenon après enucleation. Bull Soc Belge Ophthalmol 38

Chapter 13

Rehabilitation of the Exenterated Orbit

13

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Core Messages

- Orbital exenteration is a radical procedure consisting of removal of the orbital contents, including orbital fat, conjunctival sac, globe, and part or all of the eyelids.
- Since orbital exenteration is a psychologically and anatomically disfiguring procedure, some modifications such as eyelid-sparing techniques, retention of conjunctiva, and preservation of the periorbita have been introduced to aid in facial rehabilitation.
- Orbital exenteration is reserved for the treatment of potentially life-threatening malignancies or relentlessly progressive conditions unresponsive to other treatments.
- Cosmetic reconstruction is a challenge. Satisfactory reconstructive results for both the physician and the patient may need multistage operations that are often time-consuming and disfiguring.
- Since the detection of recurrent disease is one of the main goals of the reconstruction, healing by granulation of the exenterated orbit may be indicated to permit visualization of the cavity.
- A variety of techniques have been described for replacing the orbital contents and eyelids in order to permit the patient to wear a prosthesis. The eye socket has been augmented by a variety of techniques utilizing dermal fat grafts, cartilage grafts, bone grafts, artificial materials, and local or free flaps. Conventional eyelid reconstruction techniques with local facial skin flaps have also been utilized in efforts to retain a prosthesis.
- All of the above-mentioned techniques may be suitable in selected cases for rehabilitation of the exenterated orbit. However, complications and disadvantages have been demonstrated with every technique, and, therefore, the choice must ultimately be based on the experience of the individual surgeons.
- In this chapter a new procedure will be presented based on the use of a midline forehead flap using a modified technique. This procedure has been developed by the authors.
- When the surgical reconstruction of the exenterated orbit provides poor aesthetic results and especially when involvement of the complex midfacial structures occurs, the use of an oculofacial prosthesis may be indicated. In recent years, use of oculofacial prostheses has become more common. Implants and technology have also been significantly improved resulting in expanded use.

13.1 Introduction

13.1.1 Basics

Orbital exenteration, first described by Georg Bartisch in 1583 [2], and popularized in the modern era by Arlt, is a disfiguring operation that involves total removal of the orbital contents with partial or total excision of the eyelids. Cosmetic reconstruction is a major dilemma in exenterated patients, especially in the younger age group. Eyelid-sparing techniques, retention of conjunctiva, and preservation of the periorbita are methods that have been introduced as modifications of exenteration in an effort to aid facial rehabilitation. The exenteration procedure can be classified as follows:

- Subtotal exenteration: preservation of the eyelids (complete: preservation of all the layers; partial: including only the skin)
- Simple total exenteration: complete removal of the eyelids
- Radical exenteration: removal of the bony wall with varying degrees of extension to the nearby structures such as paranasal sinus, anterior cranial fossa, etc.)

13.1.2 Indications

Indications for exenteration include:

- Malignancies originating in the paranasal sinuses, eyelids, and adnexal tissues
- Primary malignant tumors of the orbit – infiltrating malignant lacrimal gland tumors, or different types of sarcomas
- Primary benign orbital neoplasms and inflammatory processes that behave as local malignant disease leading to uncontrolled pain and compromised visual function. This includes entities such as infiltrative plexiform neurofibromas, advanced meningiomas, idiopathic orbital inflammation (pseudotumor), fungal infection
- Palliative procedures in the presence of metastatic disease

Nonmalignant disease may occasionally be an indication for orbital exenteration, but the vast majority of exenterations are undertaken to treat malignant disease. Bartley [3] reported that 100 of their 102 exenterated cases resulted from malignant disease. This is similar to Levin and Devin's study (93 of 99 cases) [14] as well as that of Rahman et al. [20] (74 of 77 cases). Although the value of some of the above-mentioned indications is questioned, exenteration has still been used with increasing frequency in recent years. Therefore, even though exenteration for orbital sarcomas in children (especially for rhabdomyosarcomas) is now used much less frequently due to the use of new therapeutic protocols, the reduced frequency is balanced by an increasing number of cases of secondary malignancies infiltrating the orbit. In a recent study [15] based on 13 years' experience from a tertiary referral center, a significant increase in the number of exenterations being undertaken for orbital invasion from a basal cell carcinoma (BCC) was reported. Furthermore, 69% of these patients had treatment for neoplastic lesions before exenteration. This may indicate that other factors are likely to have influenced these statistics, including inappropriate surgery, inappropriate follow-up, and neglect of the lesion by the patient until too late a stage in the disease. Moreover, the improvement in the survival rate, because of the use of new therapeutic protocols, has resulted in a higher number of patients with malignancies living longer than in the past. This has resulted in an increased request for cytoreductive or palliative surgery by means of exenteration surgery.

13.2 Rehabilitation

The main objective of reconstruction of an exenterated orbit is to restore the orbital cavity and eyelids so that a cosmetically acceptable prosthesis can be accommodated.

When surgical ablation is limited to the orbital contents, reconstruction is focused on the support and retention of a removable prosthesis. However, when the resection includes partial or total excision of the eyelids and adjacent soft tissues, multistage operations are often necessary and frequently do not achieve acceptable results. The consequent deformity is often considered to be complicated because of the multifocal nature of reconstruction.

A variety of techniques can be used for replacing orbital contents with well-vascularized tissues. Different methods have been advocated, many of which involve several stages [15] and most take advantage of local or regional flaps [1, 18, 26]. Options include temporalis muscle transposition [21], midline forehead flaps [8], dermal grafts [16], dermis fat grafts [25], split skin graft [9], globe-sparing exenteration [5], eyelid-sparing techniques [24], and spontaneous granulation [19]. For extensive orbito-cutaneous defects, microsurgical flaps have been described as an alternative [7, 23, 27]. The facio-cervico-pectoral flap has been described and is basically used for covering cutaneous defects of the mid-third of the face [11, 13] or of the lower eyelid [6].

More natural eye socket and facial reconstruction necessitates a wide range of methods for the reconstructive procedures. Once performed, the cosmetic rehabilitation is long, with multiple postoperative visits, no matter which method is used to close the orbital defect.

In this chapter, the more popular surgical techniques of rehabilitation such as temporalis and frontalis muscle transfer will be discussed, as well as the use of oculofacial prostheses. A new procedure using the midline forehead flap, developed in recent years by the authors, will be also presented.

13.2.1 Temporalis Muscle Transposition

The exenterated orbit reconstructed with a one-stage technique has been accepted as the most satisfactory by both the patient and the physician. Among the regional flaps used, the temporalis muscle flap is the most popular and the easiest method of filling the orbital cavity after exenteration. However, in some cases, it does not provide sufficient tissue to cover the orbital rims completely. The technique is generally carried out through a skin incision made from the lateral external canthus horizontally for 2–3 cm; the dissection of this skin can be continuous with the skin of the upper and lower lids. If the exenteration is carried out first, the coronal incision provides a different approach (Fig. 13.1). Once the upper and lower skin flaps, including the skin of the upper and lower lids and the skin of the temporal region, are reflected, the entire orbital cavity is exposed together with a wide area in the temporal region. An incision is made in the deep fascia along the origin of the temporalis muscle. The deep fascia with its underlying temporalis muscle is reflected from the temporal fossa. The fascia is incised from the upper margin of the zygomatic process where it is adherent (Figs. 13.2, 13.3). The muscle is dissected down under the zygomatic process to its insertion into the coronoid process of the mandible. The muscle and fascia are freed until they are sufficiently mobile to reach the orbital cavity. Using a bone saw or Burr, a round opening is made in the lateral wall of the orbit. Then, the temporalis muscle can be transferred into the orbital cavity (Fig. 13.4). A conformer could be placed in the orbital cavity (Figs. 13.5, 13.6)

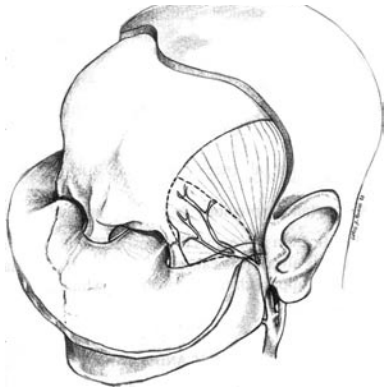

Fig. 13.1 Coronal incision exposes the bony orbit and permits mobilization of the temporalis flap, which can then be rotated through the lateral orbital wall to serve as a vascular base for soft tissue socket reconstruction

13.2.2 Frontalis Muscle Transfer

As an alternative to temporalis muscle transfer, a technique conceptually similar, but utilizing the frontalis muscle, was described by Bonavolonta in 1992 [4]. This technique is particularly useful in those patients with a subtotal exenterated orbit in whom the eyelids have been spared. The technique involves approaching the frontalis muscle via a midline forehead incision (Fig. 13.7). A

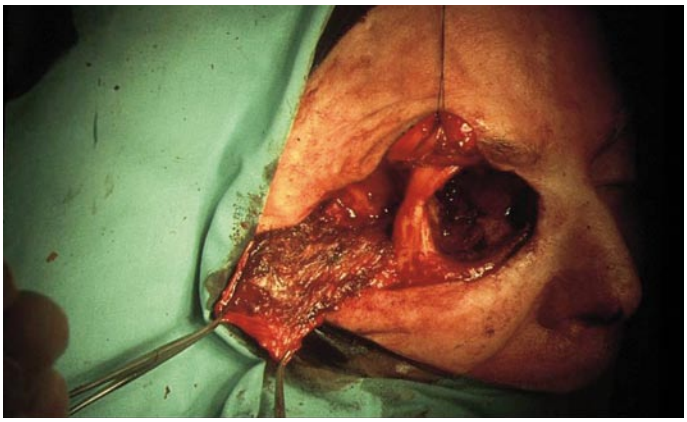

Fig. 13.2 Mobilization of the temporalis flap for post-exenteration socket reconstruction

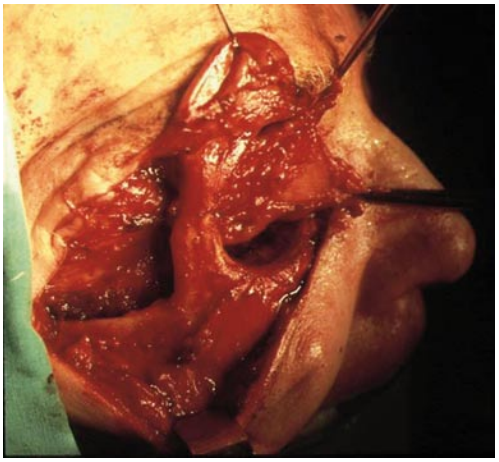

Fig. 13.3 Placement of the temporalis flap through the lateral wall of the orbit

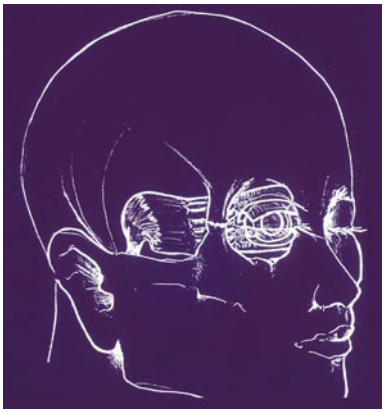

Fig. 13.4 Schematic diagram showing placement of the flap with the conformer in place behind the reconstructed lids

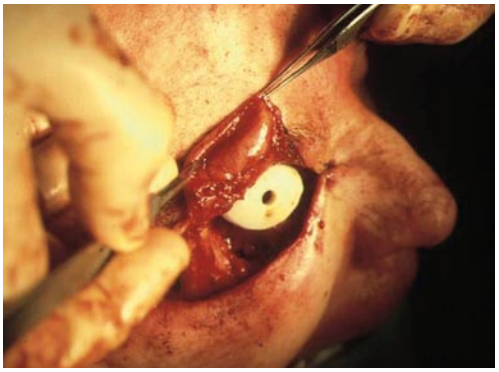

Fig. 13.5 Clinical example of the conformer placed over the temporalis flap prior to reconstruction of the eyelids

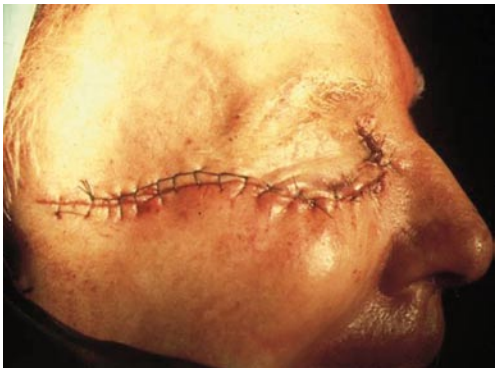

Fig. 13.6 Closure of the skin flaps over the conformer

rectangular muscular flap, which includes the galea capitis, is undermined, taking care to preserve the muscle's blood supply, which derives from the superficial temporal artery (Fig. 13.8). The flap is rotated anteriorly into the orbital opening and behind the eyelids; it remains attached to its insertion at the dermis under the eyebrow. Its posterior surface then faces anteriorly. Next, the flap is sutured to the periosteum of the inferior orbital margin. The skin is sutured using 3-0 prolene interrupted sutures. At the end of the operation both eyelids lie over the periosteum attached to the muscular flap (Fig. 13.9). A sterilized symblepharon plastic ring is inserted into this restored cavity to maintain the upper and lower fornices; a temporary tarsorrhaphy is advisable (Fig. 13.10).

After the expected postoperative contraction of the muscular flap and the underlying tissues is complete, the lids are opened and the fornices are examined; if significant shrinkage has occurred, they can be deepened using a free mucous membrane graft. A sterilized silicone conformer of an appropriate size is inserted at this stage. The prosthesis can be substituted for the conformer 2 weeks later (Figs. 13.11, 13.12).

13.2.3 Midline Forehead Flap

This technique involves a two-stage procedure in which the frontalis muscle and skin flap (myocutaneous) are transposed into the exenterated orbit. This method provides adequate orbital

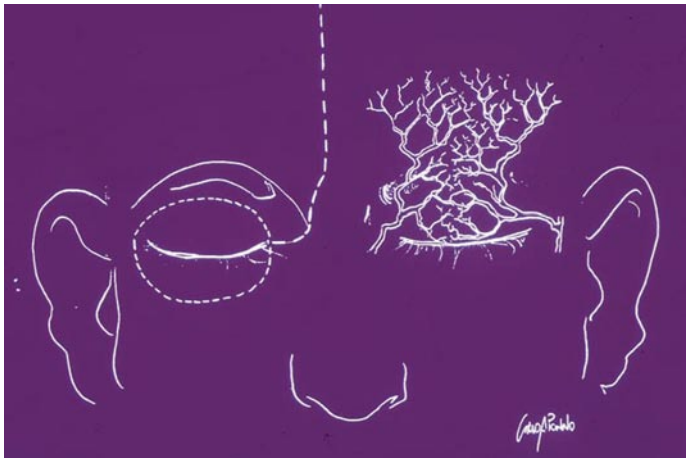

Fig. 13.7 Midline forehead incision to access the frontalis muscle and its vascular supply from the superficial temporal artery

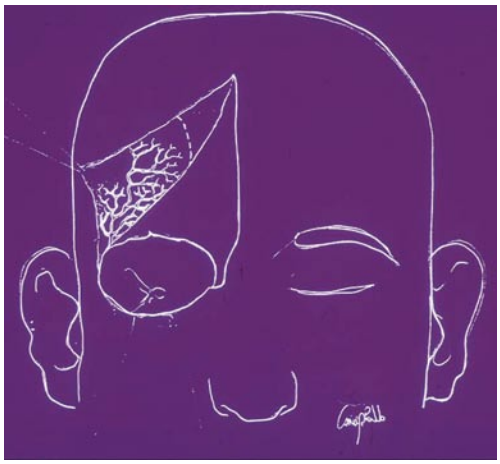

Fig. 13.8 Placement of the frontalis muscle flap into the orbit behind the preserved eyelids. The base of the flap remains connected to the dermis of the brow with the posterior surface of the periosteum now lying behind the eyelids to create a new lining to retain a prosthetic conformer

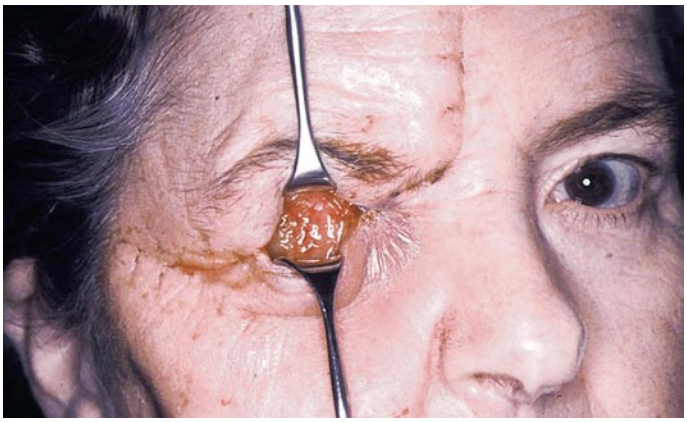

Fig. 13.9 Clinical demonstration of newly formed socket and cul de sacs created from the frontalis muscle flap with its periosteal lining now facing anteriorly

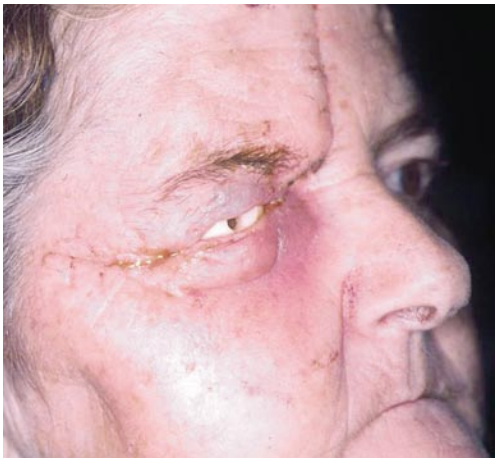

Fig. 13.10 Placement of the ring conformer into the reconstructed socket with periosteal lining prior to tarsorrhaphy

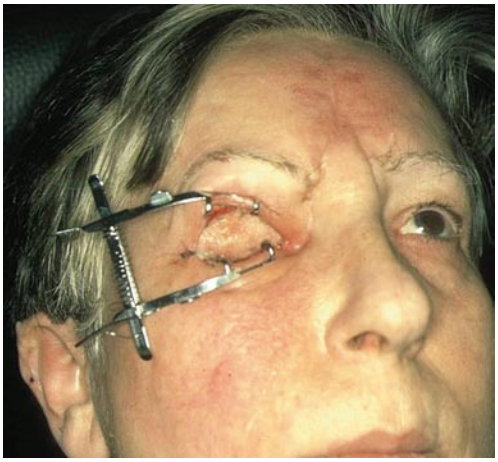

Fig. 13.11 Placement of an oral mucus membrane graft to repair excessive shrinkage of the muscle flap in order to deepen the fornices and permit eventual retention of a cosmetic prosthesis

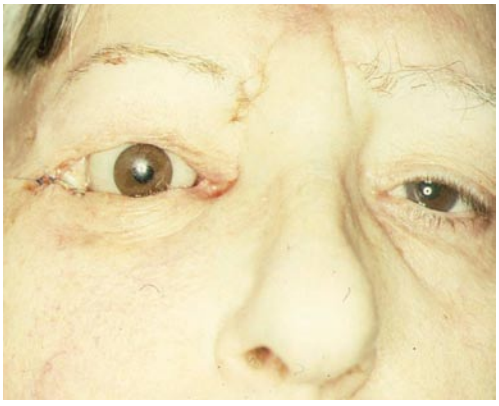

Fig. 13.12 Cosmetic prosthesis after post-exenteration socket reconstruction

space for retention of an ocular prosthesis. The first stage involves transposition of a myocutaneous midline forehead flap into the orbit. The myocutaneous pedicle is first outlined with a skin-marking pen, taking into consideration the extent of the orbital defect in a such a manner as to create a flap long and large enough to reach and cover the recipient site. The pedicle should be 3 mm wider than the defect to allow for subsequent tissue contracture. The base of the midline forehead pedicle will be the glabella and it may be dissected deep, right down to the periosteum, in order to create a thick myocutaneous flap with a good blood supply from both the frontal and supraorbital arteries (Figs. 13.13, 13.14). Once the flap is isolated, it can be gently rotated in the orbit and first secured to the lateral wall, just behind the orbital rim. The pedicle should be apposed to the posterior surface of the eyelid if present; or otherwise behind a frontal plane where the eyelids should be located. The whole deep portion of the orbit between the rim and the apex is mainly covered, more than filled, by the flap (Fig. 13.15). Then, a deep fornix is created in all directions using the anterior skin surface of the pedicle and the posterior part of the eyelid. If insufficient lid tissue is present because of a total exenteration, mobilization of any skin that has been covering the cavity can be used or can be obtained by utilizing skin from the midline forehead flap itself. The second stage is a simple procedure that consists of the cosmetic restoration of the glabellar portion of the flap, which, because of the previous transposition, has been elevated into a fold (Figs. 13.16–13.18).

13.2.4 Oculofacial Prostheses

Oculofacial prostheses present an attractive and viable alternative when aesthetic and functional demands are beyond the capacity of local reconstructive efforts. Several materials are used to build an orbital prosthesis such as silicone, rubber, vinyl plastic, and acrylics. The ideal materials should be compatible, translucent, flexible, durable, light, easy to clean, chemically and physically inert, and comfortable for the patient. No material in use today fulfills all of these criteria. For retention of the prosthesis, several methods have been proposed such as the use of adhesives, attachment to glasses frames, or straps, and, in the last 20 years, the use of osseointegration implants [12, 17, 22].

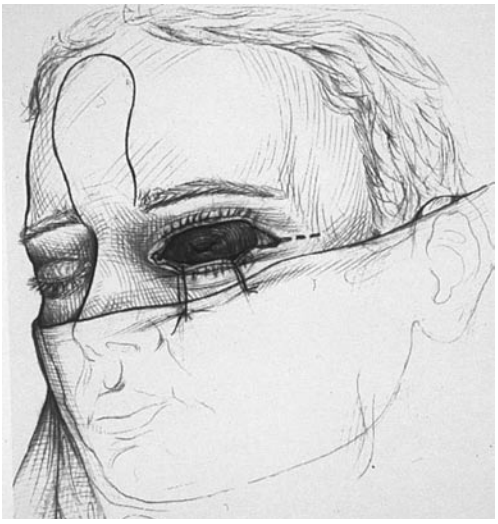

Fig. 13.13 Marking of mid-forehead myocutaneous flap for reconstruction of the exenterated socket

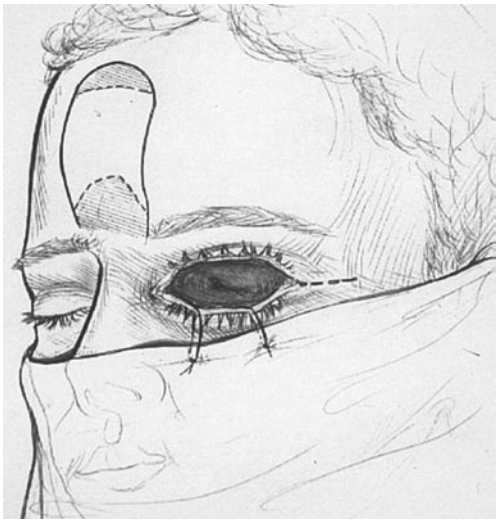

Fig. 13.14 Incision lines for the mid-forehead myocutaneous flap. The *dotted lines* represent areas where the overlying skin will be dissected from the pedicle of muscle

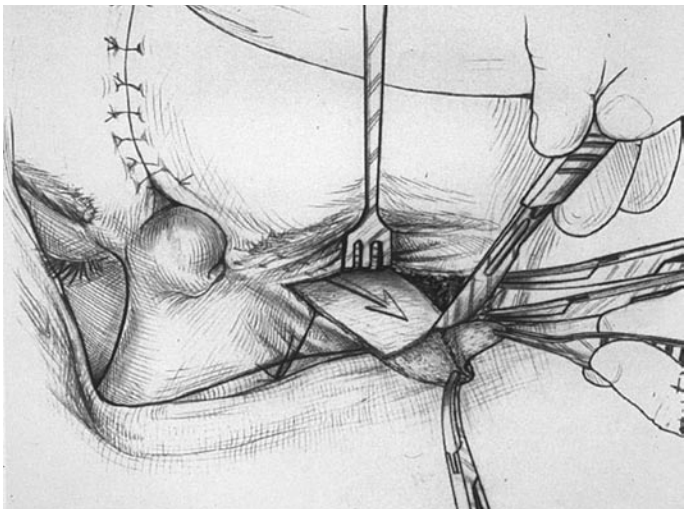

Fig. 13.15 Dissection of skin from the tip of the flap (*dotted line* in Fig. 13.14). This will permit better vascularization of the flap beneath the soft tissues at the lateral canthus. Note the fold of bunched up tissue at the base of the rotated flap

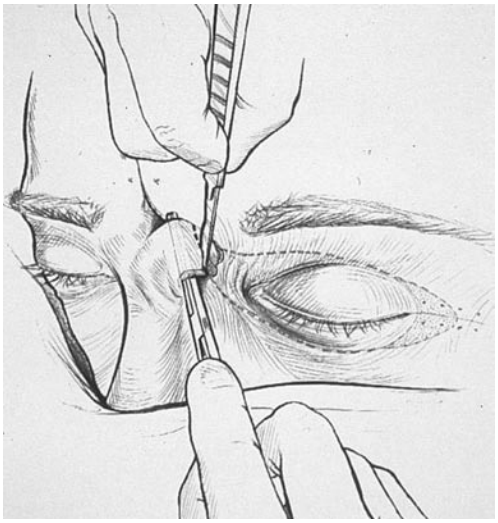

Fig. 13.16 Bunched up fold of skin at the base of the rotated midline flap can be carefully dissected from the underlying muscle with its blood supply intact. This will then permit mobilization of this skin as a flap for repairing the resulting midline defect

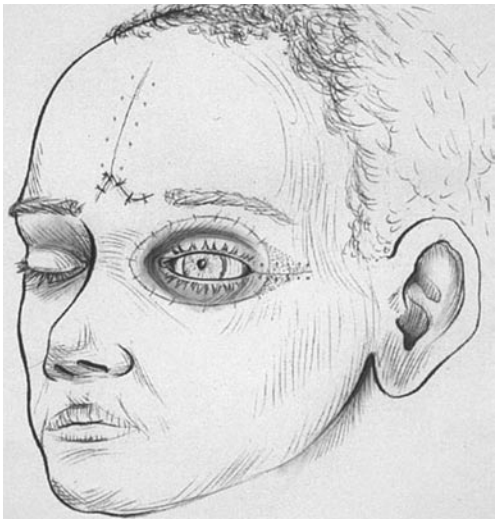

Fig. 13.17 Closure of the midline flap after rotating the dissected base of the flap back into a vertical position. This essentially creates a V plasty-type repair, which reduces the vertical length of the midline flap incision and mimics the glabellar frown line

Osseointegrated implants can be used successfully to support orbital prostheses and their importance has increased in recent years. Basically, the techniques used involve a two-staged procedure. In the first stage, three or four bone-anchored fixtures are placed into the bony orbital rim. Skin penetration and abutment placement are performed in the second-stage operation, performed 3–6 months later. More recently, some one-step surgical procedures, which have been undertaken in order to decrease rehabilitation time, have been described [12].

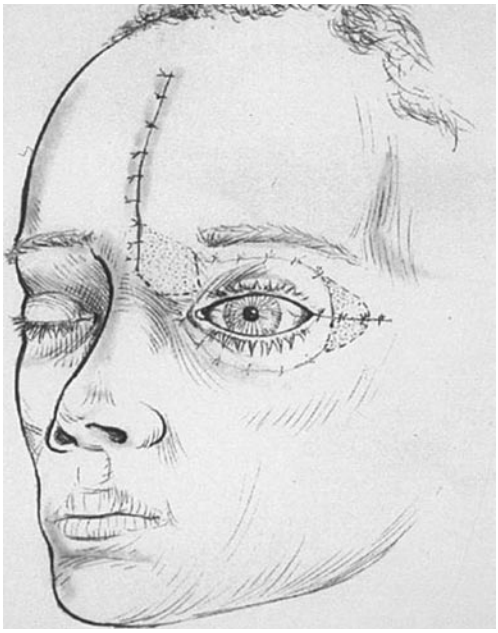

Fig. 13.18 Portions of vascularized muscle dissected from the skin as described in Figs. 13.16 and 13.17 with dermis over the muscle retained in the socket as lining for a conformer shell

13.3 Clinical Experience with the Described Technique

13.3.1 Temporalis Muscle Transposition

Since it was first described by Ovineer in 1898, use of the myofascial flap of the temporalis muscle has become a classical method of filling the orbital cavity after exenteration. It has been criticized for its limitations in volume, as in some cases it is not possible to completely fill the orbit. In addition, the atrophy following primary repair becomes increasingly obvious [10, 21, 28]. A modification of this technique involves additional implantation of costal bone or cartilage grafts to provide a stable volume over time. However, these methods are accompanied by a notable increase in the risk of infection and rejection, particularly in patients who later receive additional radiotherapy.

Despite the disadvantages described, transposition of the anterior part of the temporalis muscle flap has become the most popular technique, and many authors consider it the method of choice, owing to the simplicity of the dissection, its great reliability, low morbidity, and its proximity to the operative field. Some authors consider the depression created at the donor site an inconvenience, but more recently, this problem has been reduced by the use of improved implant materials [10, 28].

Summary for the Clinician

The use of the anterior half of the temporalis muscle with the multiple variants of the technique described in the literature is a suitable method of filling the orbital cavity for the following reasons:

- Great and long experience among many oculoplastic specialists.
- Most commonly used flap.
- Great reliability and low morbidity.
- Its proximity to the operative field.

However, some disadvantages exist:

- To transfer the muscle into the orbit, a hole in the lateral wall is necessary. This step is time-consuming with quite a long manipulation of the flap and the surrounding tissue.
- The muscle pedicle sometimes does not adequately cover the medial portion of the orbit, especially over time because of gradual contraction.
- Need for a second procedure to restore the eyelids. The temporalis muscle fills only the orbital cavity.
- Depression of the temporalis fossa worsens over time.

13.3.2 Frontalis Muscle Transfer

The authors have been using this technique for about 15 years. The procedure was applied mainly in cases in which an exenteration was done using an eyelid-sparing technique. Many patients underwent the frontalis muscle transfer procedure primarily, filling the orbit during the same opera-

tion in which the exenteration was carried out. Other patients had had a previous exenteration performed elsewhere for malignancy.

Summary for the Clinician

Advantages:
- Frontalis muscle transfer represents a suitable alternative technique to the temporalis muscle technique for rebuilding a socket capable of supporting a prosthesis

Disadvantages:
- Reduction of volume can occur because of the shrinkage of the flap
- Some patients do not like a scar in the frontal area even if it becomes more acceptable with time

13.3.3 Midline Forehead Flap

This technique is suitable after either subtotal or simple total exenteration. It can be used primarily, immediately after exenteration, or secondarily, even in contracted sockets with poor or absent blood supply. We have successfully used this procedure in patients with contracted sockets who have had extensive loss of tissue, few areas of granulation, and poor bloody supply. Usually, the cavity is covered by a thick layer of skin. All such patients who have undergone this technique have achieved a final orbital cavity with sufficient room to accommodate a prosthesis. Although this technique is a two-step procedure, the second stage is very quick and can be done under local anesthesia. The first stage of the procedure permits management of the deep orbit and the eyelids at the same time. The vascularized flap can "cover" the posterior part of the orbit and the skin layer that was previously lining the cavity can be utilized alone or with local flaps to form the eyelids. In this fashion, the deep orbit is "covered" by the flap (more than "filled") and this is an important advantage. Although the reduction in volume of the flap due to postsurgical shrinking can occur, it will not usually influence the postsurgical outcome because the reduction in volume involves the thickness of the flap more than the length, thus leading to a relatively stable result.

Summary for the Clinician

Advantages:
- The flap is already covered by the skin and therefore "ready" to accommodate the prosthesis without a second procedure
- No modification of the volume with time

Disadvantages:
- Scarring of the skin at the donor site can be cosmetically unacceptable

13.3.4 Oculofacial Prostheses

Successful osseointegration has been achieved in about 90% of the patients reported and because of this the use of these implants has increased in recent years. In cases of extensive resections, even when less bone substance remains, application of these techniques is still possible and usually recommended. Another advantage is that postoperative radiation is still possible.

Summary for the Clinician

Advantages:
- High rate of success with the recent techniques
- Favorable option for covering large defects
- Postoperative radiotherapy is more feasible than with the use of local flaps

Disadvantages:
- Deterioration of the materials
- Expensive procedure
- Unpleasant odors sometimes noticed from the covered areas

References

1. Atabay K, Atabay C, Yavuzer R, Demirkan F, Latifoglu O (1998) One-stage reconstruction of eye socket and eye lids in orbital exenteration patients. Plast Reconstr Surg 101:1463–1470
2. Bartisch G (1583) Ophthalmodoulcia. Dresden 3:208
3. Bartley GB, Garrity JA, Waller RR, et al. (1989) Orbital exenteration at the Mayo Clinic 1967–1986. Ophthalmology 96:468–474
4. Bonavolonta G (1992) Frontalis muscle transfer in the reconstruction of the exenterated orbit. Adv Ophthalmic Plast Reconstr Surg 9:239–242
5. Catalano PJ, Laidlaw D, Sen C (2001) Globe sparing orbital exenteration. Otolaryngol Head Neck Surg 125:379–384
6. Crow ML, Crow FJ (1976) Resurfacing large cheek defects with rotation flaps from the neck. Plast Reconstr Surg 58:196–200
7. Donahue PJ, Liston SL, Falconer DP, Manlove JC (1989) Reconstruction of orbital exenteration cavities. The use of the latissimus dorsi myocutaneous free flap. Arch Ophthalmol 107:1681–1683
8. Dortzbach R, Hawes M (1981) Midline forehead flap in reconstructive procedure of the eyelids and exenterated socket. Ophthalmic Surg 12:257–268
9. Harting F, Koorneef L, Peeters HJF, et al. (1985) Glued fixation of split-skin graft to the bony orbit following exenteration. Plast Reconstr Surg 76:633–635
10. Holmes AD, Marshall KA (1979) Use of the temporalis muscle flap in blanking out orbits. Plast Reconstr Surg 63:336–343
11. Kaplan I, Goldwyn RM (1978) The versatility of the laterally based cervicofacial flap for cheek repairs. Plast Reconstr Surg 61:390–393
12. Konstantinidis L, Scolozzi P, Hamedani M (2006) Rehabilitation of orbital cavity after total orbital exenteration using oculofacial prostheses anchored by osseointegrated dental implants posed as a one-step surgical procedure. Klin Monatsbl Augenheilkd 223(5):400–404
13. Kroll SS, Reece GP, Robb G, Black J (1994) Deep-plane cervicofacial rotation-advancement flap for reconstruction of large cheek defects. Plast Reconstr Surg 94:88–93
14. Levin PS, Dutton JJ (1991) A 20 year series of orbital exenteration. Am J Ophthalmol 112:496–501
15. Marques A, Brenda E, Magrin J, Kowalski LP, Andrews JM (1992) Critical analysis of methods of reconstruction of exenterated orbits. Br J Plast Surg 45:523–528
16. Mauriello JA Jr, Han KH, Wolfe R (1985) Use of autogenous split-thickness dermal graft for reconstruction of the lining of the exenterated orbit. Am J Ophthalmol 100:465–467
17. Nerad JA, Carter KD, LaVelle WE, Fyler A, Branemark PI (1991) The osseointegration technique for the rehabilitation of the exenterated orbit. Arch Ophthalmol 109(7):1032–1038
18. Ohtsuka H (1988) Eye socket and eyelid reconstruction using the combined island frontal flap and retroauricular island flap: a preliminary report. Ann Plast Surg 20:244
19. Putterman AM (1986) Orbital exenteration with spontaneous granulation. Arch Ophthalmology 104:139–140
20. Rahman I, Cook AE, Leatherbarrow B (2005) Orbital exenteration: a 13 year Manchester experience. Br J Ophthalmol 89(10):1335–1340
21. Reese AB, Jones IS (1961) Exenteration of the orbit and repair by transplantation of the temporalis fascia. Am J Ophthalmol 51:217–227
22. Sandner A, Bloching M (2004) [Experiences with a new plate-like implant system (Ti-Epiplating System) for rehabilitation of orbital and midfacial defects.] Klin Monatsbl Augenheilkd 221(11):978–984
23. Savage RC (1983) Orbital exenteration and reconstruction for massive basal cell and squamous cell carcinoma of cutaneous origin. Ann Plast Surg 10:458–466
24. Sheilds JA, Sheilds CL, Suvarnamani C, et al. Orbital exenteration with eyelid sparing: indications, technique and results. Ophthalmic Surg 122:292–297
25. Shore JW, Burks R, Leone CR Jr, et al. (1986) Dermis fat graft for orbital reconstruction after subtotal exenteration. Am J Ophthalmol 102:228–236
26. Uchinuma E, Sakurai H, Shioya N (1989) Anterofrontal superficial temporal artery island flap for full-thickness eyelid reconstruction. Ann Plast Surg 23:433

27. Urken ML, Turk J, Weimberg H, Vickery C, Biller HF (1991) The rectus abdominis free flap in head and neck reconstruction. Arch Otolaryngol Head Neck Surg 117:857–866

28. Van der Meulen JC (1998) Invited discussion (for Ata Goi et al.). One-stage reconstruction of eye socket and eye lids in orbital exenteration patients. Plast Reconstr Surg 101:1471–1472

Chapter 14

Salivary Gland Transplantation

14

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Core Messages

- Absolute dry eye can lead to bilateral blindness associated with severe, persistent dry eye pain.
- Mucous membrane transplantation alone does not provide sufficient substitute lubrication.
- Transplantation of minor labial salivary glands as well as all three major salivary glands (parotid, sublingual, and submandibular) has been used to substitute tears in absolute dry eyes.
- Similar to tears, saliva contains many nutrient and microbicidal factors. Salivary enzymes are not detrimental to healthy ocular surface epithelia. The osmolality of saliva is substantially lower than that of tears. The mixed seromucinous character of saliva of the submandibular gland (SMG) is most similar in composition to tears.
- Use of the four different donor tissues also involves principally different surgical approaches.
- Minor labial salivary glands are transplanted as a sheet of glands attached to a full-thickness graft of labial mucosa to the posterior lamella of the eyelid. Some early reports suggest beneficial effects. Thorough long-term follow-up of the procedure is lacking.
- The secretory duct of the parotid gland is transposed to the lower conjunctival sac without altering the gland itself. Due to the remaining innervation a gustatory reflex secretion results. No recent reports on the use of this procedure exist.
- The sublingual gland is used as a free graft to the upper conjunctival fornix without vascular supply. Due to graft necrosis this procedure frequently failed to improve ocular surface lubrication and is not currently used.
- The SMG is used as a free graft with microvascular anastomosis to the temporal vessels. Approximately 76% of the transplanted glands remain viable in the long term.
- Viable SMG transplants improve the volume of ocular surface lubrication, symptoms and some signs of dry eye.
- With time, excessive salivary tear flow results. This is frequently associated with a temporary microcystic corneal epithelial edema, which – if left unmanaged – can progress to corneal ulceration. Corneal transplantation following successful SMG transplantation remains unsuccessful due to recurrent immunologic or ocular surface problems.
- The salivary tear flow from SMG transplants can be controlled by systemic parasympathomimetics, periglandular injections of botulinum toxin or surgical reduction of the gland.
- The use of salivary glands to substitute tears remains limited to absolutely dry eyes with persistent discomfort, despite hourly application of artificial tear substitutes and the presence of a conjunctivalized ocular surface.

14.1 Introduction

14.1.1 Background and Surgical Principles

In absolute tear deficiency, severe ocular surface damage can progress despite copious use of artificial tear substitutes, resulting in persistent pain and permanent loss of vision [29]. In this situation, mucous membrane grafting alone will not provide sufficient lubrication to alleviate symptoms or to enable successful ocular surface reconstruction. Several studies have demonstrated that oral and nasal mucosa could successfully be used to reconstruct the fornices and provide mucin for lubrication. However, after neither oral nor nasal mucosal transplantation did lubrication increase to a level sufficient to sustain a healthy corneal graft [14, 17, 32].

The minor (labial) and the major salivary glands have been used as autologous sources of lubrication in severe dry eye [2, 5, 6, 7, 23, 30]. The surgical principles reported include (Fig. 14.1):

- Transplantation of labial mucosa with attached minor labial salivary glands to the posterior lamella of the eyelids
- Transposition of the excretory duct (Stensen's duct) of the parotid gland to the *lower* conjunctival sac

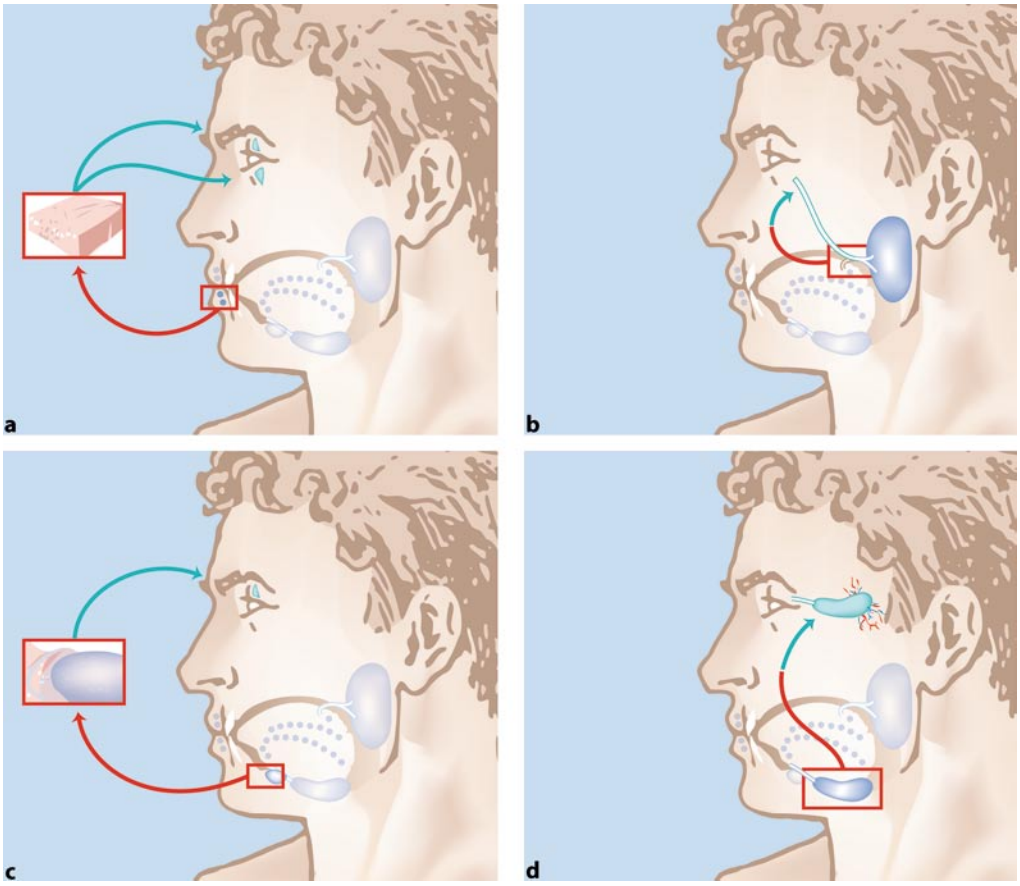

Fig. 14.1 Surgical principles of the four different approaches using salivary gland tissue for absolute dry eyes. **a** Full-thickness oral mucosa with attached minor salivary gland transplantation. **b** Parotid duct transposition. **c** Sublingual gland transplantation. **d** Submandibular gland transplantation

- Free transplantation of the sublingual gland to the upper conjunctival fornix *without* microvascular anastomosis
- Free transplantation of the SMG with implantation of the excretory duct into the upper lateral fornix and *with* microvascular anastomosis

These techniques vary significantly in the volume and quality of substitute lubrication they provide (Table 14.1).

14.1.2. Quantitative and Compositional Differences Between Saliva and Normal Tears

The total volume of saliva secreted per day is approximately 10^3 larger than the total tear volume, which is around 1–2 ml. The major salivary glands account for most of the stimulated secretion. Without gustatory stimulation approximately 50% of saliva is secreted by the minor salivary glands in the oral mucosal lining, 30% by the submandibular, 15% by the parotid, and 5% by the sublingual gland [25].

Although not identical to tears, saliva has an equally complex composition and contains many nutrient and microbicidal factors, such as albumin, lipids, immunoglobulins, and proteases. The secretion of the minor salivary glands is predominantly mucinous and contains high concentrations of antimicrobial peptides such as IgA and growth factors such as EGF [4, 16]. SMG saliva is seromucinous (predominantly serous), although it has a substantially higher viscosity than tears and the sublingual gland saliva is mucoserous (predominantly mucinous). The parotid gland produces a serous, and hence less tear-like, saliva (Table 14.1) [25].

Relevant differences between tears and saliva include some specific enzymes and the osmolality. In patients in whom a salivary gland or its secretory duct is transplanted or transposed, the quality of the ocular surface lubrication will be identical or similar to regular saliva [8]. Due to their specificity, the abundance of salivary enzymes such as amylase has no obvious detrimental effect on healthy human corneal epithelium [2, 9]. However, while tears are isotonic to serum, saliva is relatively hypo-osmolar. If the ocular surface is lubricated with large quantities of hypo-osmolar salivary tears this can result in a clinically significant, although temporary, corneal epithelial edema [8], which then requires surgical management to reduce the salivary tear volume.

Table 14.1. Comparison of surgical details with different approaches using salivary gland tissue for tear substitution

	Minor salivary glands – transplantation	Sublingual gland – transplantation	Submandibular gland – transplantation	Parotid gland – duct transposition
Quality of normal secretion	Mucinous	Mucoserous	Seromucinous	Serous
Volume of unstimulated saliva/day[a]	~500 ml	~50 ml	~300 ml	~150 ml
Vascularization after transplantation	None	None	Anastomosis	Natural
Secretory duct position after transplantation	Multiple	Unknown	Superotemporal fornix	Inferotemporal fornix

[a] Figures are estimates and refer to the total volume of secretion from both or all glands of each type into the oral cavity in the normal adult

Summary for the Clinician

- Mucous membrane grafting does not provide sufficient lubrication to alleviate severe dry eye symptoms or allow successful corneal transplantation.
- The minor and major salivary glands have all been used with different surgical principles to substitute tears.
- Saliva has an equally complex composition and contains many nutrient and microbicidal factors also present in tears.
- The seromucinous SMG saliva is most similar to tears, although it has a much lower osmolality.

14.2 Minor Labial Salivary Gland Transplantation

In 1998 Juan Murube was the first to describe the transplantation of minor labial salivary glands together with their covering mucosal sheath. In the lip, these glands form an almost compact submucosal layer of approximately 2 × 2 × 3 mm lobules, with each gland having a short excretory duct exiting onto the surface of the oral mucosa [25].

14.2.1 Surgical Technique

The complex graft of labial mucosa with attached minor salivary glands is usually taken from the lower lip, where access and density of lobules per surface area is highest [12, 23]. However, the upper lip or buccal mucosa can serve as alternative donor sites if more extensive graft material is required. Usually, an approximately 1.5 × 2.5 cm full thickness mucosal graft together with the attached salivary glands is harvested (Fig. 14.2). Care should be taken not to extend the incision closer than 1 cm to the mucocutaneous junction/0.5 cm to the midline of the lip, or to damage the underlying muscle. If left unsutured, the labial wound usually heals rapidly by secondary intention healing within 2–4 weeks.

The recipient bed is prepared by everting the upper or lower eyelid and separating the conjunctiva from the underlying Muller's muscle with an injection of saline or anesthetic. Next, an incision of approximately 2.5 cm is made along the posterior edge of the tarsal plate and the conjunctiva is dissected posteriorly for about 1.5 cm. The graft is placed in povidone, cleaned, and cut to fit the recipient bed, while carefully preserving any glandular structures, before it is sutured to the recipient bed with 7.0 or 8.0 long-acting absorbable su-

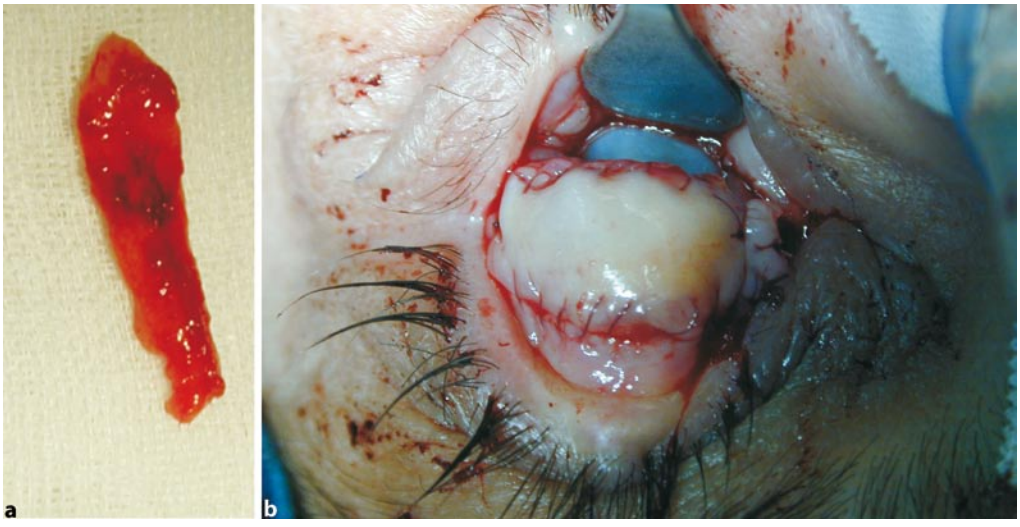

Fig. 14.2 **a** Minor labial salivary glands attached to full-thickness mucosa. **b** Graft used in lower fornix reconstruction in a patient with ankyloblepharon secondary to congenital lacrimal gland aplasia. The transplant is sutured to the conjunctiva with absorbable 6-0 sutures

tures. To avoid damage to the corneal epithelium a bandage contact lens should be applied until complete resorption of the sutures. A topical antibiotic ointment and a light pressure bandage are applied. Alternatively, the graft can be held in place with two submucosal horizontal running prolene sutures along its upper and lower end. For this the needle enters the eyelid through the skin on the temporal side and is passed in the tissues as an intramucosal and intraconjunctival suture until it exits the lid on the nasal side (Fig. 14.3). Since this avoids irritation of the ocular surface a bandage contact lens is not required postoperatively.

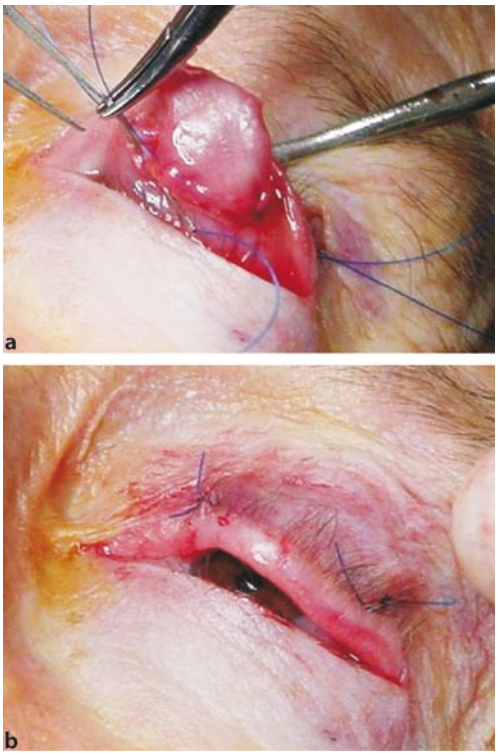

Fig. 14.3 **a** Two horizontal sutures running in the graft and subconjunctival tissue can alternatively be used to hold the graft in place. **b** The suture ends are externalized through the skin and tied together

14.2.2 Clinical Results

During the first postoperative month the upper lid is often fairly edematous and should not be everted to avoid damage to the graft. The initially chemotic and avascular graft is usually revascularized within 1 week, which is when patients begin to report some subjective improvement. After 2 weeks, secretion of saliva can often be seen clinically. This is initially fairly viscous, but will become more serous by the end of the first month.

With the original description of the surgical technique in 1998, Murube also reported the results of 6 patients with a mean follow-up of 11 months. In these patients, 1 graft became atrophic, but 5 grafts remained viable and led to increased lubrication and a reduction of symptoms in 4. Mean preoperative Schirmer test results improved from 5.7±3.8 mm to 11.7±9.5 mm [25]. Guerissi reported a patient with a 2-year history of dry eye secondary to Sjögren's syndrome and severe DE symptoms recalcitrant to any medical treatment who showed significant relief after minor salivary gland transplantation. A biopsy taken 3 months after surgery confirmed the presence of viable salivary gland acini and ducts with mucin content [13]. Soares reported about 37 transplantations in 21 patients with a graft survival rate of 97%. Most of these patients (12) suffered from Stevens-Johnson syndrome-induced severe dry eye and required additional surgery, such as amniotic membrane transplantation, symblepharolysis or other procedures to correct trichiasis. Signs and symptoms, including the need to use artificial tears, and vision improved in 92% of the cases. These results were found to be stable over a maximum follow-up of 4.5 years. Complications included infection ($n=1$) and ptosis ($n=3$) [31]. Potential donor site complications include temporary hypesthesia, delayed wound healing, and a reduced volume of the lip. More details on the amount of secretion resulting from this procedure and its impact on the ocular surface in the long term are still required.

Summary for the Clinician

- Sheets of minor salivary glands attached to full-thickness labial mucosa can be transplanted as free grafts to the posterior lamella of the eyelids.
- A small number of early clinical case series reported beneficial effects on signs and symptoms of dry eye.

14.3 Parotid Duct Transposition

The concept of transposing the parotid duct from its original premolar position in the mouth to the lower conjunctival fornix was conceived by Filatov and Chevaljev in 1951 [5] and subsequently modified by others.

14.3.1 Surgical Technique

The initial technique described by Filatov used a cutaneous approach to the parotid duct, until Pierce et al. later described an entirely oral technique [27]. The direct approach uses a preauricular skin incision to visualize and mobilize the entire parotid duct. Following probing, the ostium is excised with a small cuff of buccal mucosa. From the lower anterior end of the incision a subcutaneous tunnel is created by blunt dissection to the inferotemporal conjunctival fornix [1].

The indirect or oral approach consists of the intraoral dissection of a 2 by approximately 7 cm long, anterior-posterior directed strip of full-thickness mucosa centered around and including the ostium of Wharton's or Stensen's duct. The duct itself is probed and freed over 2–3 cm from the muscle of the cheek (up to the anterior border of the masseter muscle). The mucosal strip is folded onto itself and sutured over a tube to achieve a total length of 7–8 cm of mobilized "ductal tube." This is then passed through a tunnel on the periosteum of the zygoma deep to all muscles, vessels, and nerves. Its end enters into and is sutured to the conjunctiva of the inferotemporal conjunctival sac [4, 27].

Early surgical complications include disinsertion/obstruction at the level of the fornix or fistulation of the duct at any position. Contraction or lack of length of the ductal tube frequently resulted in mechanical lower lid entropion or ectropion and this was more common with the transcutaneous approach [4].

14.3.2 Clinical Results

Parotid duct transposition provides copious wetting, but due to a maintained innervation of the parotid gland it is associated with a gustatory reflex epiphora. A number of case reports and descriptive studies exist, but there are no well-conducted prospective studies with detailed, (semi)quantitative follow-up data [2, 4, 27]. This can lead to traumatic keratitis since the patient frequently has to wipe the eye to remove excess secretion [2]. Until recently, the technique has been popular with veterinary ophthalmologists who have performed it in beagles, who frequently suffer from severe dry eye. From this we know that in addition to gustatory reflex tearing the postoperative course can be complicated by blepharitis, corneal calcifications, and an increased load of colony-forming bacterial units in the conjunctival sac, which, in addition, is altered from a predominantly gram-positive toward a more mixed bacterial flora, without inducing overt ocular surface pathology [11, 26].

Systemic anticholinergics and implantation of a lacrimal bypass tube were suggested to manage salivary epiphora, but these were associated with systemic side effects or were insufficient to drain the excessive volume of ocular surface lubrication. Also, parasympathetic denervation of the gland is impracticable since surgical access is difficult and collateral damage to the facial nerve during such maneuvers is likely. Therefore, the technique is currently rarely practiced in humans.

Summary for the Clinician

- Due to the remaining innervation this procedure results in gustatory reflex tearing, which is reportedly complicated by dermatitis and keratitis.
- The procedure should currently be classified as "historic".

14.4 Sublingual Gland Transposition

Murube was also the first to transplant autologous sublingual gland tissue to the conjunctival fornix in rabbits and humans. According to Sieg, salivary glands tolerate a maximum ischemia of up to one and a half hours at physiological temperatures [30] and without vascular anastomosis sublingual grafts should become completely necrotic within 6 h. From histological studies in rabbits Murube

found that the grafts first underwent partial atrophy before some acinar tissue was regenerated.

14.4.1 Surgical Technique

This involves transconjunctival preparation of a recipient in the temporal upper fornix. A block of sublingual gland together with overlying mucosa measuring approximately 25 × 10 × 6 mm is excised and then fixed with transpalpebral sutures to the recipient bed and the lacrimal gland. Finally, the conjunctiva and mucosa are sutured with interrupted absorbable sutures. The concept of surgery was based on the idea that the grafted tissue would become vascularized from the contact area in the recipient bed.

14.4.2 Clinical Results

When Murube performed such free sublingual gland transplants to the superolateral conjunctival fornix of 5 patients with severely aqueous-deficient dry eye, due to the absence of any primary vascularization the grafted tissue apparently became necrotic in 2 patients. Of the remaining 3, only 1 showed a minimal increase in Schirmer's test score from 0 to 2 mm [23]. Since the initial report, this approach seems to have been completely abandoned.

Summary for the Clinician

- Due to the absence of any vascular supply sublingual gland transplants become necrotic and offer little or no improvement in lubrication and symptoms of dry eye.

14.5 Submandibular Gland Transposition

Of all procedures involving the transplantation of major salivary glands for severe dry eye – due to some principle advantages – this is the only one currently practiced in humans. The concept involves a free autologous SMG transplanted to the temporal fossa. A microvascular anastomosis ensures blood supply to the graft and thus long-term survival of the acinar tissue of the gland. The secretion of the SMG is seromucinous and hence capable of replacing both the mucinous and the aqueous components of the normal tear film. The flow rate of saliva from a normal SMG exceeds normal tear production by far. However, intraoperative denervation of the graft reduces this and in addition avoids the gustatory reflex salivation seen after parotid duct transposition. In rats and rabbits the transplanted gland remained viable and successfully prevented corneal ulceration during a follow-up of 6 months [18, 19].

14.5.1 Surgical Technique

Prior to surgery it is of obvious importance to ensure that the potential donor tissue is viable and functional. Minor labial salivary gland biopsy is an accepted reference tissue for excluding a destructive inflammatory process directed against salivary gland tissue in general by means of histological examination. More direct, 99m-Technetium scintigraphy with or without parasympathomimetic stimulation is capable of quantifying the secretory capacity of a salivary gland [20].

Surgery is ideally performed under general anesthesia by a collaborative team of maxillofacial and oculoplastic surgeons. In trained hands, the procedure requires 5–6 h of surgical time. First, the SMG and its vascular pedicle are prepared, the secretory duct mobilized at the sublingual caruncle, and the parasympathetic fibers branching out from the lingual nerve severed [6, 7, 22, 23, 30]. Next, a recipient bed is prepared in the temporal fossa by fenestration of the temporalis muscle and preparation of the superficial temporal artery and vein. The original blood supply of the SMG is then ligated, the graft transferred to the recipient bed, and an arterial and venous microanastomosis with the temporal vessels created. The secretory duct is passed subcutaneously to the fornix where it is connected to the conjunctiva prior to skin closure.

14.5.2 Clinical Results

In humans, four independent groups of authors have published clinical results with this procedure

in severely aqueous-deficient dry eye. Murube reported that 5 out of 7 such grafts remained viable for up to 3 months. However, secretory activity was not clinically obvious in all cases. He therefore had to use amylase detection in the tear film rather than Schirmer's test to establish whether the graft was viable [23, 24]. Later, MacLeod and Robbins reported 12 successful procedures in 8 patients who all showed improvement by Schirmer testing and an increased fluid meniscus, but no detailed ophthalmic long-term follow-up was presented [21].

We have transplanted 42 grafts in 34 patients and completed a thorough ophthalmological follow-up for up to 7 years [6, 7, 29]. Based on the Schirmer test, improvement in clinical symptoms and Tc99m pertechnetate scintigraphy 32 of the 42 SMG grafts have remained viable as of the last follow-up [20]. Seven graft failures were observed due to complications associated with the vascular anastomosis, 2 due to obstruction of the secretory duct, and 1 due to newly induced autoantibodies to salivary gland tissue. In 2004, Yu et al. reported a group of 38 patients in whom SMG transplantation – although with undefined duration of follow-up – had been performed successfully in 87%. Five grafts had to be removed within 1 week of surgery due to early thrombosis of the venous drainage [33]. Yu et al. confirmed that from the fourth postoperative month onward patients with viable SMG grafts had a substantially improved volume of lubrication. Although their ophthalmic data analysis is limited, they stated that the patients could discontinue the use of artificial tear substitutes and that vision improved in 6 patients.

Along with Yu et al., we have also observed a specific pattern of postoperative salivary flow. This includes an early phase of hypersecretion of several days' duration, which appears to be due to "degeneration activity" caused by release of neurotransmitters from degenerating sympathetic and any sectioned post-ganglionic parasympathetic terminal axons. This is followed by a period of minimal secretion during which time the super-sensitivity of the acinar cells will develop. Over the subsequent months and years the amount of secretion then often increases until – contrary to short-term reports by others – excessive salivary epiphora results [7, 21, 28]. Although secretory flow did not depend on gustatory stimuli, it was obviously stimulated by physical activity, local hyperthermia or caffeine ingestion. Systemic application of carbachol resulted in a rapid increase in secretion from the graft, as documented by scintigraphy.

Histology specimens of the SMG taken prior to and more than 1 year after transplantation showed some parenchymal atrophy. However, cholinesterase-positive nerves were abundant and in a similar distribution to normal, with scattered positive ganglion cells. Adrenergic axons were also detected in the glands, but were less numerous than normal and irregularly distributed. The latter are thought to have originated from sectioned sympathetic nerves around reconnecting arteries and to have grown by sprouting down mainly formerly parasympathetic glandular nerves.

In a prospective, controlled clinical cohort study, we evaluated the long-term follow-up after autologous submandibular gland transplantation in the most demanding group of patients, i.e., with absolute dry eye due to cicatrizing conjunctivitis of Stevens-Johnson syndrome or ocular cicatricial pemphigoid. We recorded Schirmer's test score, fluorescein break-up time (F-BUT), degree of discomfort, use of pharmaceutical tear substitutes, visual acuity, conjunctival Rose Bengal staining, and hyperemia in 14 eyes with a successful SMG transplant and 11 dry eyes without salivary lubrication. Over a mean postoperative period of 3.3 years the transplantation group showed significant improvement in Schirmer's test score, F-BUT, use of pharmaceutical tear substitutes, discomfort, and Rose Bengal staining up to the last follow-up compared with the control group (Fig. 14.4) [29]. Mean visual acuity did not improve, which was felt to be due to severe preoperative corneal scars as well as microcystic epithelial edema that evolved postoperatively in patients with over-secreting transplants.

14.5.3 Late Complications

Excessive salivary epiphora was observed in 24–40% of eyes with a viable graft [3, 33]. This could be managed successfully, either by systemic application of a parasympatholytic,

such as oral benzhexol, or periglandular injections of botulinum toxin [15]. Since the effect of these modalities was limited to a maximum of 3 months, some of the grafts were surgically reduced [15]. We also frequently observed microcystic epithelial edema in eyes with excessive salivary epiphora, which was temporary and resolved when the salivary epiphora was controlled. Two eyes with microcystic edema developed a persistent epithelial defect, which healed in one eye after amniotic membrane transplantation, but went on to perforation in a second eye, later requiring repeated penetrating keratoplasty (Fig. 14.5). Later, four eyes with a

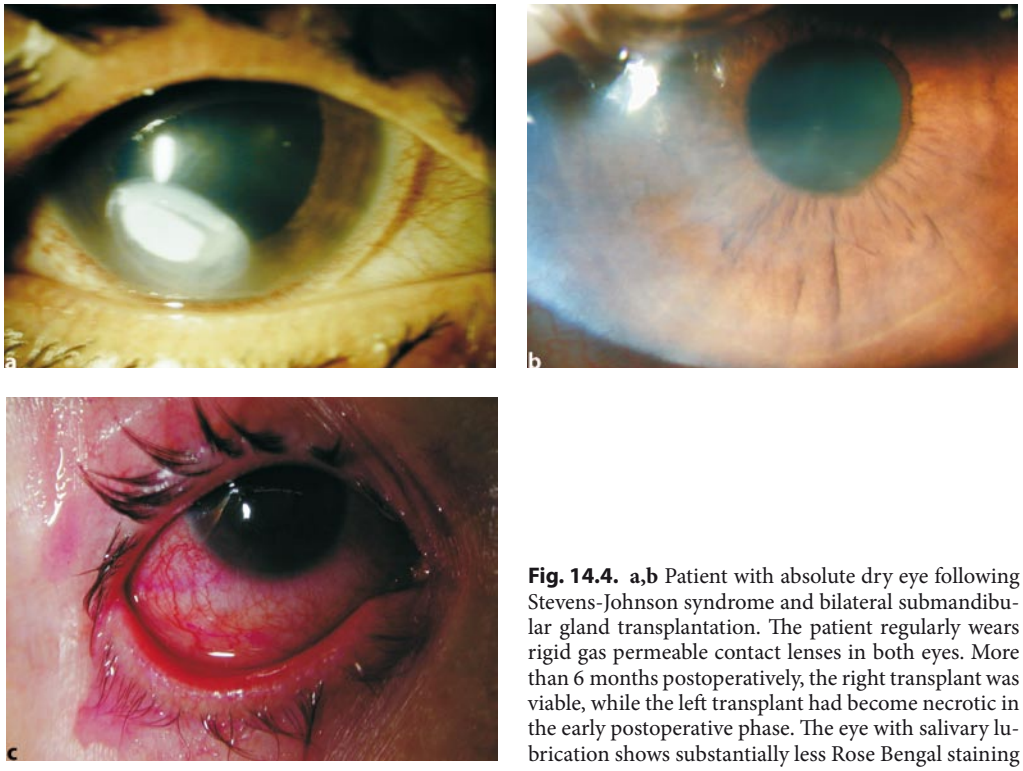

Fig. 14.4. **a,b** Patient with absolute dry eye following Stevens-Johnson syndrome and bilateral submandibular gland transplantation. The patient regularly wears rigid gas permeable contact lenses in both eyes. More than 6 months postoperatively, the right transplant was viable, while the left transplant had become necrotic in the early postoperative phase. The eye with salivary lubrication shows substantially less Rose Bengal staining

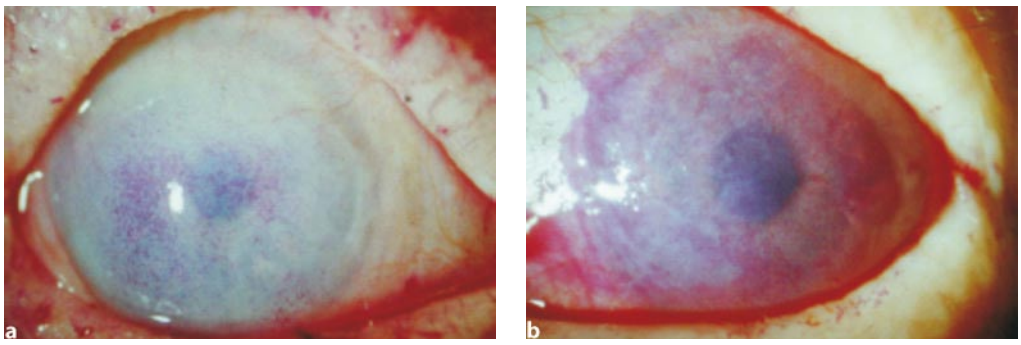

Fig. 14.5 **a** Right eye with acute calcific precipitates in a persistent epithelial defect 6 years following successful submandibular gland transplantation. **b** Defect healed after amniotic membrane transplantation. **c** Persistent conjunctival hyperemia due to permanently excessive salivary lubrication

Table 14.2. Results of techniques using different salivary glands as donor tissue to enhance ocular surface lubrication

	Labial salivary gland – transplantation	Sublingual gland – transplantation	Submandibular gland – transplantation	Parotid gland – duct transposition
Level of evidence [a]	IV to V	V	II to V	IV to V
Success (= actively secreting tissues)	Unknown	?20%?	~80%	100%
Volume [b]				
- Unstimulated	6 mm	0–2 mm	~10–30 mm	~10–20 mm
- Stimulated	Unknown	Unknown	Up to 150 mm	Unknown
Ocular complications	Ptosis, Infection, Ectropion (rare)	Persistent dry eye (very common)	Secretory duct occlusion (rare), Non-gustatory epiphora (common) → Microcystic corneal epithelial edema → Requires management	Entropion, Ectropion, Blepharitis, Gustatory epiphora (depending on surgical technique)

[a] Levels of evidence: I = high power RCT; II = low power RCT; III = nonrandomized clinical trial; IV = case series; V = expert opinion; case report

[b] Mean increase in Schirmer test over 5 min after topical anesthetic

viable SMG graft also underwent five penetrating corneal grafts. However, due to rejection, calcification or epiphora-associated edema and subsequent recurrent corneal ulceration, none of these was successful [3].

Summary for the Clinician

- Approximately 76% of free autologous SMGs survive transplantation due to microvascular anastomosis to the temporal vessels.
- The volume of ocular surface lubrication, symptoms, and some signs of dry eye improve after successful SMG transplantation.

Summary for the Clinician

- After 1 year postoperatively, salivary tear flow often becomes excessive. This salivary epiphora is frequently associated with a temporary microcystic corneal epithelial edema.
- If left unmanaged this can progress to corneal ulceration and prevent successful corneal transplantation.
- The salivary flow from transplanted SMGs can be controlled by systemic parasympathomimetics, periglandular injections of botulinum toxin or surgical reduction of the gland.
- The indication for SMG transplantation remains limited to cases of absolute dry eye with persistent discomfort despite hourly application of artificial tear substitutes and the presence of a conjunctivalized ocular surface.

14.6 Conclusion

Transplantation of autologous salivary glands to provide substitute lubrication in severe dry eye clearly remains limited to a very few selected cases. Of all the procedures described, a complex graft of minor salivary glands attached to labial or oral mucosa or a single SMG requiring microvascular anastomosis are currently used in humans. While it has been shown that SMG transplantation is capable of significantly improving the volume of ocular surface lubrication, the symptoms, and some signs of dry eye, this remains to be shown for minor labial salivary gland transplantation. However, for these few patients, the demand on time and financial resources is justified not only by significant relief of signs and symptoms, but also by substantial gains for society [10].

Although saliva contains many factors beneficial to ocular surface epithelia such as growth and microbicidal factors, its aqueous component – compared with normal tears – has a much lower osmolality. When successful SMG transplantation results in excessive flow of salivary tears, microcystic corneal epithelial edema frequently occurs. Managing salivary epiphora then becomes mandatory in order to prevent ocular surface complications such corneal ulceration and loss of vision in the long term. To date, several techniques have been described, which are either temporary and/or invasive and thus unsatisfactory. If, however, a simple, safe, and reliable measure to control secretory flow from transplanted submandibular glands existed, the indication for this procedure – although by nature demanding with regard to expertise and resources – would be much expanded. At present, we only recommend it for the small group of patients with absolute aqueous tear deficiency (Schirmer test ≤1 mm), persistent pain despite punctal occlusion, a trial of scleral or limbic rigid contact lenses, and at least half-hourly application of unpreserved tear substitutes, who also have a conjunctivalized ocular surface. The patients, and surgeons (especially if they are not ophthalmologists), must understand the ocular limitations and complications of the procedure as far as possible.

References

1. Ashley FL, Schwartz AN, Straatsma BR, et al. (1959) Transplantation of the parotid duct for xerophthalmia. Am Surg 25:815–818
2. Bennett JE (1969) The management of total xerophthalmia. Arch Ophthalmol 81:667–682
3. Borrelli M, Schröder C, Dart JKG, Collin JRO, Sieg P, Cree IA, Matheson MA, Tiffany JM, Proctor G, van Best J, Hyde N, Geerling G (2007) Long term follow up after submandibular gland transplantation in severe dry eyes secondary to cicatrising conjunctivitis. Ophthalmology (submitted)
4. Crawford B (1970) Parotid duct transplantation for ocular xerosis. Trans Aust Coll Ophthalmol 2:92–95
5. Filatov VP, Chevaljev VE (1951) Surgical treatment of parenchymatous ophthalmoxerosis. J Oftalmol (Odessa) 3:131–137
6. Geerling G, Sieg P, Bastian GO, et al. (1998) Transplantation of the autologous submandibular gland for most severe cases of keratoconjunctivitis sicca. Ophthalmology 105:32–35
7. Geerling G, Sieg P, Meyer C, et al. (1998) Transplantation der autologen Glandula submandibularis bei schwerster Keratoconjunctivitis sicca – 2-Jahres-Ergebnisse. Ophthalmologe 95:257–265
8. Geerling G, Honnicke K, Schroder C, et al. (1999) Quality of salivary tears following autologous submandibular gland transplantation for severe dry eye. Graefes Arch Clin Exp Ophthalmol 237:546–553
9. Geerling G, Daniels JT, Dart JK, et al. (2001) Toxicity of natural tear substitutes in a fully defined culture model of human corneal epithelial cells. Invest Ophthalmol Vis Sci 42:948–956
10. Geerling G, Liu CSC, Collin JRO, et al. (2002) Costs and gains of complex procedures to rehabilitate end stage ocular surface disease. Br J Ophthalmol 86:1220–1221
11. Gelatt KN (1991) Canine lacrimal and nasolacrimal diseases. In: Gelatt KN (ed) Veterinary ophthalmology, 2nd edn. Lea & Febiger, London, pp 276–289
12. Gaubenstock LM (1995) Dental caries and the secretory activity of human labial minor salivary glands. Arch Oral Biol 40:525–528
13. Guerissi JO, Belmonte J (2004) Surgical treatment of dry eye syndrome: conjunctival graft of the minor salivary gland. J Craniofac Surg 15:6–10

14. Heiligenhaus A, Shore JW, Rubin PA, Foster CS (1993) Long-term results of mucous membrane grafting in ocular cicatricial pemphigoid. Implications for patient selection and surgical considerations. Ophthalmology 100:1283–1288
15. Keegan DJ, Geerling G, Lee JP, Blake G, Collin JRO, Plant GT (2002) Botulinum toxin treatment for hyperlacrimation secondary to aberrant regenerated seventh nerve palsy or salivary gland transplantation. Br J Ophthalmol 86:43–46
16. Koski H, Konttinen YT, Hiertanen J, et al. (1997) Epidermal growth factor, transforming growth factor-alpha, and epidermal growth factor receptor in labial salivary glands in Sjögren's syndrome. J Rheumatol 24:1930–1935
17. Kuckelkorn R, Schrage N, Redbrake C, Kottek A, Reim M (1996) Autologous transplantation of nasal mucosa after severe chemical and thermal eye burns. Acta Ophthalmol Scand 74:442–448
18. Kumar PAV, MacLeod AM, O'Brien B, Hickey MJ, Knight KR (1990) Microvascular submandibular gland transfer for the management of xerophthalmia; an experimental study. Br J Plast Surg 43:431–436
19. Lasudry J (1992) Experimental approach to surgical treatment of lacrimal insufficiency by microvascular submandibular salivary gland autotransplantation. Bull Soc Belge Ophthalmol 245:45–51
20. Lauer I, Sieg P, Bahre M, et al. (1998) Salivary gland scintigraphy using technetium-99m-pertechnetate after autotransplantation of the submandibular salivary gland in the correction of dry eye. Eur J Nucl Med 25:128–131
21. MacLeod AM, Robbins SP (1992) Submandibular gland transfer in the correction of dry eye. Aust N Z J Ophthalmol 20:99–103
22. MacLeod A, Kumar AV, Hertess I, Newing R (1990) Microvascular submandibular gland transfer; an alternative approach for total xerophthalmia. Br J Plast Surg 43:437–439
23. Murube J (1986) Transplantation of salivary gland to the lacrimal basin. Scand J Rheumatol Suppl 61:264–267
24. Murube J, Marcos MG, Javate R (1994) Amylase in mare lacrimale in patients with submandibular salivary gland transplantation to the lacrimal basin. Adv Exp Med Biol 350:565–570
25. Murube J, Manyari A, ChenZhuo L, et al. (1998) Labial salivary gland transplantation in severe dry eye. Oper Tech Oculoplast Orbital Reconstr Surg 1:104–110
26. Peterson-Jones SM (1997) Quantification of conjunctival sac bacteria in normal dogs and those suffering from keratoconjunctivitis sicca. Vet Comp Ophthalmol 7:29–35
27. Pierce MK, Goldberg JL, Brooks CJ (1960) A direct approach for transposition of the parotid duct. Arch Ophthalmol 64:566–570
28. Schroeder C, Sieg P, Framme C, Honnicke K, Hakim SG, Geerling G (2002) [Transplantation of the submandibular gland in absolute dry eyes. Effect on the ocular surface]. Klin Monatsbl Augenheilkd 219:494–501
29. Schroeder C, Hakim SG, Collin JRO, et al. (2003) [Long-term follow-up after autologous submandibular gland transplantation in scarring keratoconjunctivitis with absolute dry eyes]. Ophthalmologe 100:1079–1084
30. Sieg P, Geerling G, Kosmehl H, Lauer I, Warnecke K, von Domarus H (2000) Microvascular submandibular gland transfer for severe cases of keratoconjunctivitis sicca. Plast Reconstr Surg 106:554–560
31. Soares EJ, Franca VP (2005) Transplantation of labial salivary glands for severe dry eye treatment. Arq Bras Oftalmol 68:481–489
32. Wenkel H, Rummelt V, Naumann GOH (1999) Long term results after autologous nasal mucosal transplantation in severe mucus deficiency syndromes. Br J Ophthalmol 84:279–284
33. Yu GY, Zhu ZH, Mao C, Cai ZG, Zou LH, Lu L, Zhang L, Peng X, Huang NL (2004) Microvascular autologous submandibular gland transfer in severe cases of keratoconjunctivitis sicca. Int J Oral Maxillofac Surg 33:235–239

Chapter 15

Recent Developments in the Diagnosis and Management of Congenital Lacrimal Stenosis

15

K.-H. Emmerich, H.-W. Meyer-Rüsenberg

Core Messages

- Epiphora is a common condition in newborn children.
- Persistence of Hasner's membrane is the most frequent cause of epiphora in newborns.
- Ninety-six percent of cases of epiphora resolve spontaneously in the first year of life.
- The ideal time for probing has to be chosen according to the clinical symptoms.
- Intubation of the lacrimal system is useful in older children and after repeated failed procedures.
- Acute dacryocystitis is a feared complication of congenital nasolacrimal duct obstruction (CNLDO) and requires immediate therapy.
- Dacryocystorhinostomy (DCR) in children is rarely necessary, but can be performed more easily after 2 years of age.

15.1 Anatomy and Embryology

The first parts of the lacrimal system develop as a cord of thickened epithelium that can be seen in the 10-mm embryo. This epithelial cord grows down into the mesenchyme without connection to the nasal mucosa or the eyelid borders.

In the 14–16 mm embryo this cord grows toward the eyelid and the nasal cavity and remains solid. Around 12 weeks after gestation in the 38- to 40-mm embryo, canalization begins. Punctal development occurs around 5 months' gestation, and the distal end of the nasolacrimal duct (Hasner's membrane) opens between the sixth month and delivery or in the first weeks after birth.

15.1.1 Anatomy of the Lacrimal System

Canalization of the lower and upper punctum begins about 2 mm from the lid margin, the upper punctum located a little more nasally. The canaliculi run first vertically and after 1 mm horizontally toward the common canaliculus just before opening into the lacrimal sac. The lacrimal sac is localized in the fossa lacrimalis. The lacrimal sac is connected to the nose via the nasolacrimal duct, and the ostium of the nasolacrimal duct is located at the junction of the anterior and the middle third of the inferior meatus.

15.1.2 Lacrimal System Variations

These are all anatomical changes that can occur during the very difficult process of development of the lacrimal system, e.g. aplasia, atresia, development, canalization, duplications (Fig. 15.1) [3, 9].

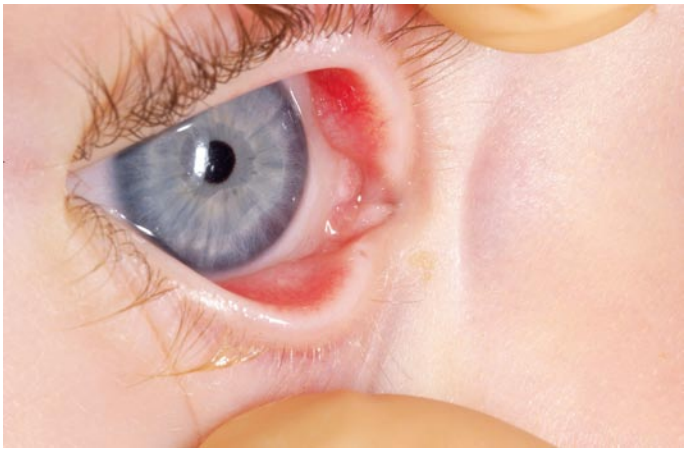

Fig. 15.1 Isolated aplasia of the upper punctum

Aplastic variations are commonly combined with other variations in facial development, for example, in Goldenhar syndrome. There are no general suggestions with regard to therapy in these cases, as each patient must be treated individually. For the most part, however, surgical procedures should be deferred until after the facial structures have matured.

Summary for the Clinician

- Development of the lacrimal system is a very complex process. A number of anatomical changes such as aplasia, atresia, and variations in canalization are possible.

15.1.3 Congenital Atresia

Failure of canalization can occur in any part of the lacrimal system. However, the most frequent location is the failure of the nasolacrimal duct to open [17].

15.1.4 Variations in Canalization

Variations in canalization, like fistulas or double puncta, occur quite frequently. For the most part, these represent anatomical variations like an accessory puntum, for example, and treatment is often unnecessary.

Surgical intervention should only be undertaken if irritating clinical symptoms are present. For example, in the case of a fistula, the track has to be dissected carefully under magnification to its connection with the lacrimal sac and then resected totally [22, 27].

15.2 Diagnosis and Examination

There are many reasons why the common symptom of epiphora is observed in newborns and during the first weeks of life. Increased secretion of tears can be observed with every form of conjunctival or corneal inflammation or even by mechanical irritation. Malpositioning of the lid margins, like congenital ectropion, entropion, and colobomas, can cause epiphora.

Therefore, all of these conditions have to be carefully evaluated and managed before probing or irrigation is undertaken in children.

Clinical examination starts with an inspection of the lid region. Compression of the lacrimal fossa with mucous discharge is a true sign of mucocele.

The form and position of the puncta has to be examined; many cases of facial clefts are combined with abnormalities of the lacrimal system.

Dacryocystography and secretion tests (Schirmer, Jones) may be informative, but are usually not required [13].

Ultrasonography (A- and B-mode) is simple to do and can give good information concerning the size of mucoceles.

Ear, nose, and throat (ENT) examination and nasal endoscopy are not mandatory in most cases of congenital lacrimal obstruction [24]. The view into the inferior meatus is often possible only after luxation of the inferior turbinate (e.g., with a Freer elevator). An ENT examination can be useful in special cases such as nasolacrimal duct cysts and for anomalies associated with facial clefts.

Summary for the Clinician

- Clinical examination including inspection of the lid region is necessary.

15.3 Congenital Nasolacrimal Duct Obstruction

15.3.1 Etiology

The most frequent symptoms of congenital nasolacrimal duct obstruction (CNLDO) are epiphora and secretion. This is observed as being unilateral more often than bilateral around the 3rd or 4th week after birth. Spontaneous resolution is very common during the first months of life, and 96% resolve in the first year without intervention. In the second year of life, however, only 60% of the children will demonstrate complete resolution without intervention [15, 16, 18, 29, 31].

The initial management of CNLDO includes the application of topical antibiotics combined with lacrimal sac massage [23].

If there is no resolution spontaneously or after topical therapy, the ideal timing of intervention has to be selected according to the clinical symptoms and with the consent of the informed parents. The ideal timing of intervention in our experience is between the 3rd and 6th month of life; probing and irrigation is more difficult in older children, and the success rate after the 13th month may continue to decrease rapidly [14].

Summary for the Clinician

- Congenital nasolacrimal duct obstruction resolves spontaneously in 96% of cases in the first year of life, but the ideal timing of intervention and probing has to be selected according to the clinical symptoms.

15.3.2 Differential Diagnosis of CNLDO

The time of onset of symptoms is the most important difference compared with other disorders associated with epiphora in early childhood.

In Germany, all newborns formerly had to be treated with silver nitrate ($AgNo_3$) 1% eye drops, according to Credé's prophylaxis. Frequently in these cases a transient bilateral conjunctival infection with a putrid watery secretion is noticed in the first days of life.

Chlamydial oculogenital infections can occur as a bilateral conjunctival infection with the onset of symptoms 6 to 10 days after delivery.

Gonococcal infections are feared and can cause a very serious and frequently bilateral infection. Corneal complications leading to blindness are possible in the spontaneous course and were one of the most frequent reasons for loss of vision in past years.

Summary for the Clinician

- Differential diagnosis of CNLDO includes bacterial conjunctivitis and chlamydial oculogenital infections.

15.3.3 Treatment of CNLDO

Onset of treatment and the necessity of topical antibiotic application are dependent on the intensity of the clinical symptoms.

Lacrimal sac massage is useful in all cases. Treatment with topical antibiotics should be started in cases of bacterial infection with CNLDO. With persistent symptoms, probing and irrigation should be considered if spontaneous resolution does not occur by 1 year of age.

15.3.3.1 Procedures, Probing, and Irrigation

The ideal timing of intervention is controversial in the literature. The decision should be made according to the symptoms, the age of the child and in agreement with well-informed parents. In any case, probing and irrigation should always be the first step and usually performed by the 13th month of life [7, 19, 30].

In our experience, the ideal time for probing is between the 4th and the 6th month of life as an office procedure, without the need for general anesthesia. After sedation with a 2-mg diazepam suppository, anesthetic eye drops are applied. The baby is wrapped up and the head position is maintained by helping hands. After dilatation of the upper punctum with a conic probe, a blunt Bangerter probe or cannula with a length of 40 mm and a diameter of 0.8 mm to 1.0 mm is inserted. With irrigation by a 2 ml disposable syringe, the probe is advanced softly through the "soft stop" (Rosenmüller fold) to reach a "hard stop" (medial wall of the lacrimal sac).

After the hard stop, the probe, with continuous irrigation, is gently advanced vertically and directed into the nasolacrimal duct. At the end of the duct, the membrane, is perforated, and the nasal antrum is entered. A second syringing is obligatory.

In the postoperative period, treatment with topical antibiotics is combined with decongesting eye drops and nose drops, which are given for 1–3 weeks.

Before probing and irrigation, a topical antibiotic therapy is suggested to decrease the amount of bacteria in the lacrimal system.

Complications of the procedure include creation of a false passage and the subsequent persistence of symptoms. Mild bleeding from the nose or bloody tears are common, but harmless.

Summary for the Clinician

- Probing with a Bangerter probe is emphasized.

15.3.3.2 Intubation of the Lacrimal System

After the age of 13 months or after repeated failed probing procedures, the lacrimal system should be intubated with silicone tubes, which has to be done under general anesthesia [21].

After probing and irrigation in the nose, a modified Amboss probe, described by Juenemann, is pushed into the lacrimal system and through this probe a 4-0 prolene suture is brought into the nose. After removing this suture from the nose with a blunt hook, a silicone tube with a diameter of 0.64 mm is threaded over the suture and fixed by a clamp pulled out of the nose. After intubation of the first punctum, the second punctum, usually the lower one, is intubated in similar fashion. Afterward, the two ends of this intubation are fixed using a double knot tied three times.

Transnasal endoscopic control of this procedure is difficult in children and in most cases not necessary.

The use of transcanalicular microendoscopy depends on the diameter of the canaliculi, but this procedure is generally not necessary in most cases [8, 11].

Balloon catheter dilation is recommended by some for treatment of CNLDO. This method has a similar success rate to that of intubation procedures [1].

In cases in which intubation of the second punctum is not possible, monocanalicular intubation with a collar stent probe is useful, according to Fayet et al. [12].

Postoperative treatment after lacrimal intubations includes antibiotic eye drops, decongesting eye drops, and nose drops for 2–3 weeks.

Summary for the Clinician

- Intubation with a silicone tube is useful after the age of 13 months and/or after repeated failed probing procedures.

15.4 Acute Dacryocystitis

15.4.1 Clinical Symptoms

Acute dacryocystitis is a feared complication of unresolved CNLDO; the clinical picture depends on the causative bacterium. Acute dacryocystitis caused by *Staphylococcus aureus* produces more abscesses; that caused by *Streptococcus* is more phlegmonous.

The onset of acute dacryocystitis is characterized by a high fever and the onset of a reddish and painful swelling in the lacrimal sac area (Fig. 15.2).

Swelling of the lids is frequent, but the conjunctiva is often not inflamed. In many cases, purulent fluid can be pushed out of the puncta by pressure on the lacrimal sac region.

15.4.2 Therapy

15.4.2.1 Conservative Management

The microbiological examination of the purulent discharge is important for determining the species of the bacterium. Onset of therapy, however, should not be delayed pending results of cultures and sensitivity studies. Intravenous application of antibiotics, e.g., cephalosporin, should be begun immediately in young children. Topical treatment includes antibiotic eye drops and topical applications of ethacridin (1:1,000) solution. Children should be treated in conjunction with a pediatrician, depending on the severity of the disease (Fig. 15.3).

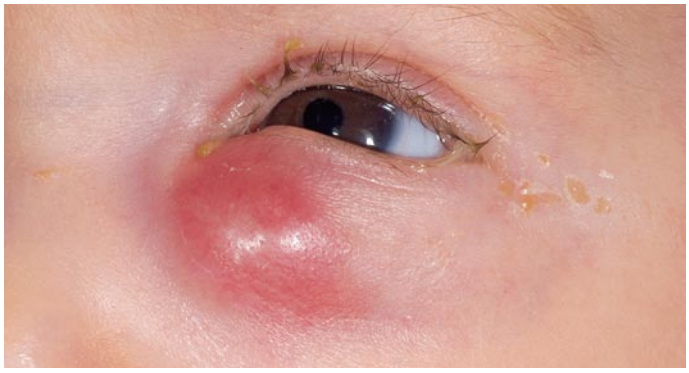

Fig. 15.2 Acute dacryocystitis in an 8-week-old girl

Fig. 15.3 Acute dacryocystitis after treatment

15.4.2.2 Incision

Sometimes an incision of the abscess is useful. In the case of inflamed mucoceles, it can be useful to inject antibiotic into the sac after incision. Sometimes, it is possible to draw out the purulent content of the mucocele with a Bangerter probe and a 2-ml syringe.

15.4.2.3 Intubation of the Lacrimal System

After treatment of acute symptoms, therapy is specifically aimed at the cause of obstruction. Probing and irrigation can be performed to open Hasner's membrane, which is the most common site of obstruction. In most cases, probing and irrigation is combined with silicone tube insertion. Even in cases of resolved acute dacryocystitis, tubes should be removed after 3 months.

Summary for the Clinician

- Acute dacryocystitis is a feared complication of CNLDO and requires immediate therapy.

15

15.5.1 Dacryocystorhinostomy in Children

In cases of unresolved CNLDO after probing and intubation, a dacryocystorhinostomy (DCR) may be necessary. This represents only a minority of cases in children [28]. Often, it is better to wait until the child is aged 4 years, although even the standard external approach is possible in younger children aged 12–18 months. The technique does not differ from the standard external approach utilized in adults [2, 4, 6, 10, 25, 26]. After packing the nose and injection of suprarenin (epinephrine; 1:1,000 solution) in the operation area, a 15- to 20-mm skin incision is performed to identify the medial canthal ligament. After dividing the orbicularis toward the anterior lacrimal crest, the periosteum is opened and the lacrimal sac is pushed laterally. An osteotomy is performed; unlike the adult DCR, ethmoid cells are not usually encountered in younger children.

After the osteotomy the nasal mucosa is incised vertically and horizontally to create mucosal flaps. A Juenemann probe is inserted into the canaliculi and the lacrimal sac is incised vertically and horizontally to create mucosal flaps. The canaliculi are intubated and the ends are tied with 3 double knots in the nose, and the nose is then packed. The intubation makes a perfect landmark for the inner ostium and helps to prevent postoperative mucosal swelling. Optionally, the posterior flaps can be sutured together with vicryl 6 x 0 or the mucosa can be removed. The anterior flaps are always sutured together with vicryl 6 x 0. The periosteum and orbicularis muscle are sutured with vicryl 6 x 0 and the skin with prolene 6 x 0. The skin sutures are removed after 6 days, the silicone intubation after 3–6 months.

Summary for the Clinician

- Dacryocystorhinostomy in children is rarely necessary, but can be performed, preferably after 2 years of age.

15.5.2 Endocanalicular Microendoscopic Procedures

In children under the age of 2 years, the small diameter of the lacrimal system, especially of the punctum, increases the risk of injury. Therefore, a purely diagnostic endoscopy should only be carried out in exceptional cases. Diseases of the lacrimal system in early childhood are mainly caused by malformations and in these cases the endoscopy will not provide any essential additional information. Only in cases of failure following irrigation and stenting endoscopy with subsequent endoscopic rechanneling should be performed in an effort to avoid a pediatric DCR [8].

Summary for the Clinician

- Endocanalicular microendoscopic procedures are usually unnecessary in most patients following intubation.

15.6 Removal of Silicone Tubing

Removal of the silicone tubes is suggested at 3 months postoperatively. In special cases, e.g., in canalicular laceration following trauma, a longer period may be useful.

The technique of silicone intubation described above includes three double knots in the nose with a loop of tubing resting in the medial lid angle. The children should receive sedation, e.g., with diazepam (2 mg suppository). Anesthetizing eye drops are placed into the conjunctival sac. In smaller children, the child is wrapped up and the head position is maintained by helping hands. The closed end of the intubation is fixed by a clamp and luxated out of the canaliculi. The silicone tube is incised using scissors and briskly pulled out of the upper punctum. After removal of the intubation, a topical therapy of antibiotic eye drops, decongesting eye drops, and decongesting nose drops is applied 3 weeks postoperatively.

15.7 Congenital Dacryocele

Congenital dacryocele is an uncommon neonatal swelling of the lacrimal sac, caused by a malformation of the lacrimal sac. A congenital dacryocele causes a firm bluish swelling present within 1–4 weeks of birth (Fig. 15.4) [5, 20].

Without inflammation and infection, dacryoceles produce a high rate of spontaneous resolution. In patients with onset of inflammation, a topical application of antibiotic eye drops, decongesting eye drops, and decongesting nose drops is necessary. Irrigation is useful to exclude a CNLDO. After successful irrigation, the diagnosis of a dacryocele is ensured and the content of the dacryocele can be pressed out by external pressure on the lacrimal fossa.

Summary for the Clinician

- Congenital dacryocele usually needs no surgical intervention.

15.8 Fistulas of the Lacrimal System

Fistulas of the lacrimal system are caused by congenital variations in canalization, most frequently located under the medial canthal ligament. Sur-

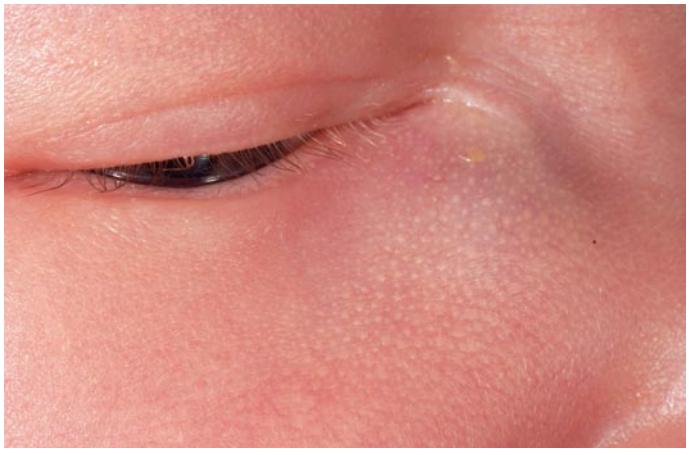

Fig. 15.4 Congenital dacryocele with bluish swelling but no inflammation

gical intervention is not obligatory and should only be indicated if irritating clinical symptoms are present. In those cases, the fistula should be dissected under the microscope up the lacrimal sac and then resected totally [27].

Summary for the Clinician

- Surgical intervention of fistulas is only necessary in patients with clinical symptoms like permanent epiphora.

References

1. Becker BB, Berry FD (1991) Balloon catheter dilatation in paediatric patients. Ophthal Surg 22(7):750–752
2. Busse H, Hollwich F (1977) Kurz- und Langzeitergebnisse Dacryocystorhinostomia externa nach Kaleff-Hollwich. Klin Monatsbl Augenheilkd 171:986–989
3. Busse H, Muller KM, Kroll P (1980) Radiological and histological findings of the lacrimal passages of newborns. Arch Ophthalmol 98:528–532
4. Cunningham MJ, Woog JJ (1998) Endonasal endoscopic dacryocystorhinostomy in children. Arch Otolaryngol Head Neck Surg 124:328–333
5. Divine RD, Anderson RL, Bumstead RM (1983) Bilateral congenital lacrimal sac mucoceles with nasal extension and drainage. Arch Ophthalmol 101:246–248
6. Dolman PJ (2003) Comparison of external dacryocystorhinostomy with nonlaser endonasal dacryocystorhinostomy. Ophthalmology 110:78–84
7. El-Mansour J, Calhoun JH, Nelson LB, Harley RD (1986) Results of late probing for congenital nasolacrimal duct obstruction. Ophthalmology 93:1052–1054
8. Emmerich KH, Meyer-Rüsenberg HW (2001) Endoskopische Tränenwegschirurgie. Ophthalmologe 98:607–612
9. Emmerich KH, Meyer-Rüsenberg HW (2002) Erkrankungen der ableitenden Tränenwege im Kindesalter. Z Prakt Augenheilkd 23:19–27
10. Emmerich KH, Busse H, Meyer-Rüsenberg HW, Hörstensmeyer CG (1997) External dacryocystorhinostomy: indications, method, complications and results. Orbit 16:25–29
11. Emmerich KH, Ungerechts R, Meyer-Rüsenberg HW (2000) Possibilities and limits of minimal invasive lacrimal surgery. Orbit 19:67–71
12. Fayet B, Assouline M, Bernard JA (1998) Monocanalicular nasolacrimal duct intubation. Ophthalmology 105:1795–1796
13. Hurwitz JJ, Welham RAN (1975) The role of dacryocystography in the management of congenital nasolacrimal duct obstruction. Can J Ophthalmol 10:346
14. Katowitz JA, Welsh MG (1987) Timing of initial probing and irrigation in congenital nasolacrimal duct obstruction. Ophthalmology 94:698–705
15. Kusher BJ (1982) Congenital nasolacrimal system obstruction. Arch Ophthalmol 10:597–600
16. Kushner BJ (1982) Congenital nasolacrimal system obstruction. Arch Ophthalmol 100:597–600
17. Lyons CJ, Rosser PM, Welham RAN (1993) The management of punctal agenesis. Ophthalmology 12:1851–1855
18. MacEwan CJ, Young JDH (1991) Epiphora during the first year of life. Eye 5:596–600
19. Mannor GE, Rose GE, Frimpong-Ansah K, Ezra E (1999) Factors affecting the success of nasolacrimal duct probing for congenital nasolacrimal duct obstruction. Am J Ophthalmol 127:616–617
20. Mansour AM, Cheng KP, Mumma JV, et al. (1991) Congenital dacryocele. A collaborative review. Ophthalmology 98:1744–1751
21. Pashby RC, Rathbun JE (1979) Silicone intubation of the lacrimal drainage system. Arch Ophthalmol 97:1318–1322
22. Pashby RC, Sullivan TJ, Clarke M, Brazel S, Morin JD (1992) Congenital lacrimal fistula associated with Down syndrome. Am J Ophthalmol 112:215–216
23. Paul TO (1985) Medical management of congenital nasolacrimal duct obstruction. J Pediatr Ophthalmol Strabismus 22:68–70
24. Ram B, Barras CW, White PS, et al. (2000) The technique of nasoendoscopy in the evaluation of congenital nasolacrimal duct obstruction in children. Rhinology 38:83–86
25. Toti A (1904) Nuovo metodo conservatore di cura radicale delle suppurazioni croniche del sacco lacrimale (dacriocistorinostomia). Clin Mod Firenze 10:385–387
26. Welham RA, Wulc AE (1987) Management of unsuccessful lacrimal surgery. Br J Ophthalmol 71:152–157

27. Welham RAN, Bergin DJ (1985) Congenital lacrimal fistulas. Arch Ophthalmol 103:545–548
28. Welham RAN, Hughes SM (1985) Lacrimal surgery in children. Am J Ophthalmol 99:27–34
29. Wong JF, Woog JJ, et al. (1999) A multidisciplinary approach to atypical lacrimal obstruction in childhood. Ophthal Plast Reconstr Surg 15:293–298
30. Young JDH, MacEwan CJ, Ogston SA (1996) Congenital nasolacrimal duct obstruction in the second year of life: a multicentre trial of management. Eye 10:485–491
31. Young JDH, MacEwan CJ (1997) Managing congenital lacrimal obstruction in general. Br Med J 315:293–296

Chapter 16

Cosmetic Rejuvenation of the Lower Face and Neck

16

Alan B. Brackup, Ari D. Abel

Core Messages

- Aging of the skin is multifactorial including genetics, age, UV light, and smoking.
- The aging process is also due to loss of support from subcutaneous tissues and ligamentous attachments.
- Repair of an aging face is not merely achieved by skin tightening, but also by subcutaneous augmentation.
- Facial restoration may benefit from the sculpting of abnormally placed fat in the face coupled with tissue resuspension.
- Alloplastic chin implants can be a useful adjunct to liposuction of the neck and tightening of the platysma muscle.
- Restoration of the lower face may involve tightening of the superficial musculoaponeurotic layer (SMAS) layer.
- More limited techniques are being advocated such as the S-lift.
- Tissue augmentation with fillers such as autogenous fat is a useful adjunct to facelifting techniques.

16.1. Introduction

16.1.1 Basics

The discipline of oculoplastic surgery has evolved dramatically over the past 10–15 years. An increased understanding of the mechanism of facial aging has necessitated an extension of surgery beyond the confines of the upper face, in order to achieve the most anatomic and harmonious facial restoration. Facial aging represents a continuum that defies segregation by arbitrary boundaries, flowing seamlessly without respect for artificial division and constructs. For many oculoplastic surgeons, the surgical alternatives for restoration of the lower face and neck are less familiar than those for upper and midfacial aging. Understanding the options available and the theories of facial aging underlying their selection are essential to obtaining optimal surgical results.

16.2 Pathophysiology of Lower Face and Neck Aging

16.2.1 Basics

Aging of the face results from a multiplicity of factors including intrinsic skin changes, gravitational effects, and soft tissue volume loss. Visually, damage to collagen and elastin fibers produces rhytides, dyschromias, and irregular skin texture. Gravity is responsible for a lifetime of downward pull upon facial tissues, and, coupled with a loss of ligamentous support and localized lipodystrophy, results in skin redundancy and loss of smooth facial contours. More recently, the concept of soft tissue volume loss as a critical component of the aging process has been advanced by Coleman and others [9, 11]. The loss of subcutaneous fullness results in panfacial deflation, the results of which were previously attributed solely to skin redundancy and descent. Recognition of this volume loss and its effects has resulted in a paradigm shift in our understanding and treatment of facial aging. Surgeons can no longer simply excise or reposition tissue in a superior vector and claim to have achieved a true restoration. Aging is a three-dimensional process and must be treated as such.

16.2.2 Skin

Skin aging results from multiple factors. Genetics, age, UV exposure, and smoking are among

the myriad influences that cause skin to age. Skin damage is evidenced by damage to collagen and elastic fibers, with resultant rhytides, dyschromias, and roughened skin texture.

16.2.3 Subcutaneous Soft Tissue Loss

The recent work of Coleman and others [9, 11] has demonstrated the importance of soft tissue deflation in facial aging. Critical patient assessment often demonstrates that the loss of facial volume is of far greater significance than gravitational effects. With a diminution of subcutaneous fullness comes a loss of radial support. The skin recontours around deeper structures, and also gives the appearance of descent. Within the lower face and neck, examples include the nasolabial fold, the chin, the pre-jowl sulcus, the jowl, and the mandibular rim. This concept of facial aging is demonstrated in Fig. 16.1. The central chin retains its fullness while losing lateral and inferior volume. Consequently, the chin becomes more pointed and the lower chin flattens, blending inferiorly into the submentum. Laterally along the mandible, loss of soft tissue allows the fat within the jowl to become unmasked. The jowl appears to have descended, when in fact the mandibular border has ascended as a result of soft tissue loss.

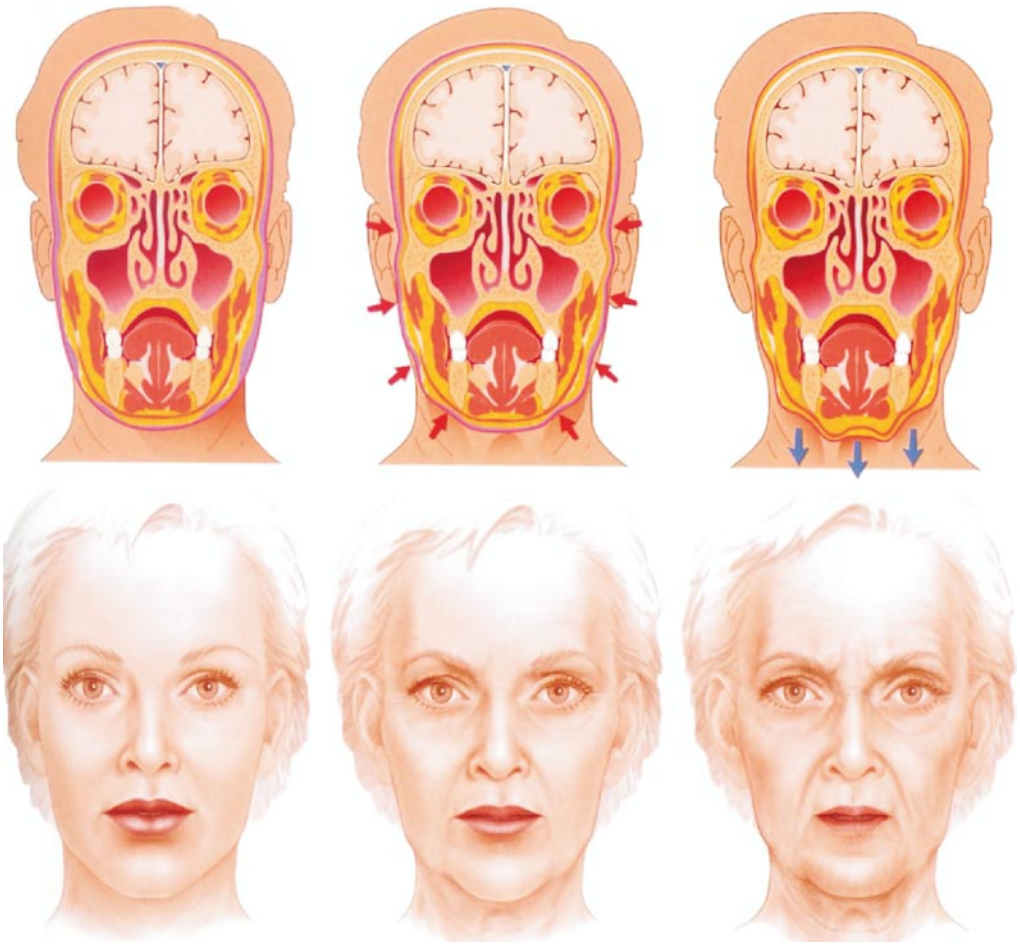

Fig. 16.1 Loss of facial fullness unmasks underlying facial contour irregularities [29]

The submandibular glands and digastric muscles are now exposed, and the unsupported skin drapes over the mandibular border, blunting the cervicomental angle.

While this concept of facial aging remains controversial, it is clear that for some patients, skin tightening and excision will achieve little restoration, whereas subcutaneous augmentation, most frequently using autologous fat as a structural graft, can result in dramatic improvement.

16.2.4 Loss of Ligamentous Support and Fat Deposition

Classical models of facial aging are in striking contrast to the more recent paradigm of soft tissue atrophy. In these models, it is a loss of ligamentous support coupled with gravity and localized fat deposition that results in the stigmata of facial aging [8].

Retaining ligaments are believed responsible for supporting the soft tissues of the face in its proper position (Fig. 16.2). The zygomatic ligaments are osteocutaneous and extend from the periosteum to the dermis in the malar region to fixate the malar fat pad. The masseteric cutaneous ligament extends from the anterior border of the masseter muscle to insert into the dermis, preventing migration of the medial cheek. Attenuation of these ligaments allows for facial soft tissue descent. The mandibular ligament is an osteocutaneous ligament extending from the bone to the skin in the parasymphyseal region of the mandible, and defines the anterior border of the jowl.

Within the neck, retaining ligaments extend from the caudal border of the mandibular symphysis inferiorly to the hyoid and superior surface of the thyroid cartilage. Attenuation of the ligaments allow the platysma to descend inferiorly into the neck, producing platysma banding and loss of a sharply defined cervicomental angle.

Advocates of this facial aging paradigm stress the need for both skin and superficial musculoaponeurotic layer (SMAS) repositioning to correct the stigmata of facial aging, rather than soft tissue augmentation as described above.

In concert with this model of facial aging is the concept that fat is deposited selectively in undesirable locations as we age. Regions of lipodystrophy include the jowls, within the subcutaneous plane in the neck, and in the subplatysmal

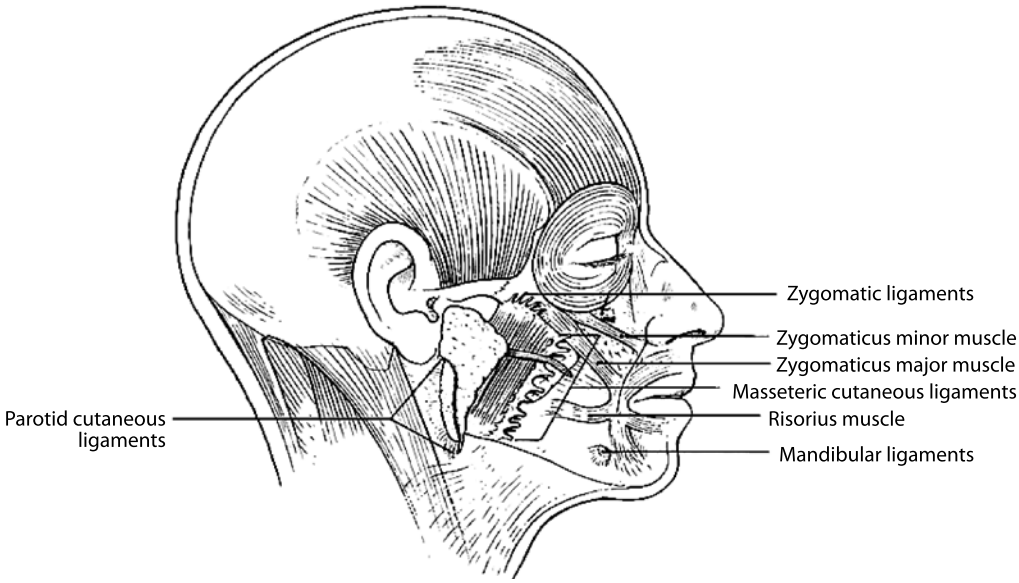

Fig. 16.2 Facial retaining ligaments, from [31]

space. Adequate facial restoration may require sculpting of this fat together with tissue resuspension.

16.3 Preoperative Analysis of the Lower Face and Neck

16.3.1 Photographic Analysis

Essential to procedure selection is the accurate assessment of facial aging changes. Older photographs of the patient can be extremely instructive in both analysis and patient education. The concept of volume deflation is intuitive to neither surgeons nor patients, and photographs can be illuminating to both. Especially useful is the juxtaposition of a digital photograph taken at the time of consultation and an older photograph to highlight areas of potential treatment.

16.3.2 Skin

The importance of skin evaluation cannot be over-emphasized. Skin assessment offers an insight into patient genetics and lifestyle. Elastotic skin will negatively impact upon the longevity of any excisional procedure. Advanced age, excessive UV exposure, and smoking are all associated with impaired skin elasticity. When elevated and repositioned, such skin will stretch more rapidly, often dramatically limiting the duration of improvement following a rhytidectomy. Additionally, prospective patients must recognize that while deeper folds and rhytides will be softened, rhytides and dyschromias will not be improved by rhytidectomy alone. If indicated, a simultaneous or secondary procedure directed at skin improvement can be considered [10].

16.3.3 Malar Region

Evaluation of the malar region reveals the extent of mid and lower facial aging descent and soft tissue atrophy. Both factors must be considered to determine treatment. If the malar region appears to be appropriately inflated, but signs such as a deepened nasolabial fold suggest tissue descent, resuspension alone is sufficient. If the cheek appears flat or sunken, soft tissue volume replenishment may be indicated, with or without surgical tissue resuspension. The possible use of both modalities, especially within this region, needs to be considered in the majority of patients. Direct treatment of the nasolabial folds is also possible, most typically with the injection of autologous fat [11].

16.3.4 Jowls

The presence of jowls creates a discontinuity in the jawline that is one of the most frequent areas of improvement desired by patients. Restoration of a smooth mandibular contour is an essential part of lower face restoration. When assessing the jowls, manual resuspension of the soft tissue to mimic a rhytidectomy is often beneficial. Persistence of the jowl suggests that another complementary procedure might be indicated in addition to tissue elevation. Frequently, liposuction of the jowl will enhance a rhytidectomy result. Additionally, autologous fat transfer to the pre-jowl sulcus, or posterior to the jowl along the mandibular rim, may soften the appearance of jowling and help re-establish a smooth mandibular contour.

16.3.5 Buccal Fat

Prominent buccal fat pads may be present throughout life, or become manifest with descent as part of the aging process. This fat, lying deep to the superficial musculoaponeurotic layer (SMAS), can be removed or repositioned to diminish undesirable fullness in the lower face, and heighten the prominence of the zygoma [40]. As this fat does not lie in the subcutaneous plane, it cannot be removed by liposuction, and requires either sub-SMAS or intraoral approaches. Recognition of buccal fat pad prominence is often critical in achieving patient goals for lower facial contouring.

16.3.6 Chin

Both anterior and lateral views of the patient are required for an assessment of chin projection and

fullness. Evaluation of old photographs assists in determining if chin projection has changed over time. Loss of soft tissue fullness as part of aging can produce an appearance of retrogenia that might not have been present in youth. Patients are frequently not aware of the importance of chin projection and fullness, and here computer imaging, if available, can be an aid to recognition. Imaging a more projected chin in a lateral view will often elicit a dramatic response, as the patient visualizes the simulated result of chin augmentation. Most commonly alloplastic implants are utilized, although autologous fat transfer is also successful and may appeal to those patients wary of implants.

Other aspects of chin aging include ptosis, also termed a "witches chin" deformity, and overprominence. These may be of sufficient concern to the patient to discuss potential corrective procedures [24].

16.3.7 Neck

The stigmata of aging identified in the neck include blunting of the submental fullness, blunting of the cervicomental angle, platysma bands, and prominent submandibular glands.

Submental fullness may be secondary to either subcutaneous or subplatysmal fat, which requires sculpting to correct. A poorly defined cervicomental angle may be genetic, or may have arisen over time as a result of submental fat deposition, anterior and inferior migration of the hyoid, and loss of platysma support (Fig. 16.3). Each possibility must be evaluated to determine how best to improve neck contour. Platysma bands arise from loss of support as well as redundancy and hypertrophy. Procedure selection will be based upon assessment of the etiology and severity for each individual. Submandibular glands may be resected and suspended, although potential post-

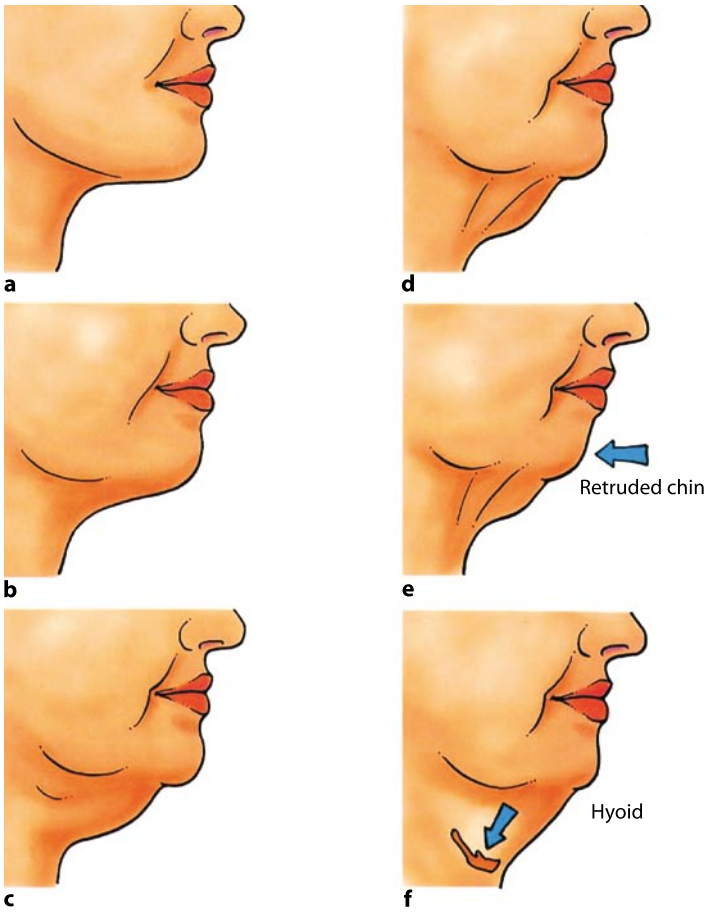

Fig. 16.3 **a–f** Aging of the neck, from [32]

operative complications restrict surgical correction to a limited number of surgeons well versed in the anatomy [7].

16.4. Procedure Selection

16.4.1 Tumescent Infiltration

One of the great advances in aesthetic surgery has been the advent of tumescent infiltration and anesthesia. The tumescent technique for liposuction was first described by Klein in 1987 [31]. In this technique a large volume of solution using dilute lidocaine and epinephrine is injected into the subcutaneous space. The use of tumescent infiltration for rhytidectomy was termed the lipodissect technique by Newman and Kotoske [38]. Other authors [29, 33] have also reviewed its use in face-lift surgery and numerous advantages have been identified:

- Hydrodissection of the skin from the underlying SMAS and platysma for easier and safer skin flap elevation
- Shorter operative time
- Less intraoperative bleeding, often with a virtually bloodless field
- Diminished bruising and edema, with more rapid recovery
- Eliminates the need for general anesthesia by markedly decreasing operating time

The authors utilize this technique for the procedures described herein.

16.4.2 Limited Procedures

The cervicofacial rhytidectomy, or face-lift, procedure has traditionally been considered the most comprehensive approach to facial rejuvenation. There are, however, patients who may be fearful of more extensive surgery, or who may not require a procedure as broad in scope. For these patients a spectrum of more focused techniques is available to achieve the desired result.

16.4.2.1 Neck Liposuction

For many younger patients, excellent improvement in neck contour can be achieved without extensive surgery. The simplest case is that of an individual with submental fullness as a result of lipodystrophy. In this case, the patient frequently has had a full neck with poor contour since childhood. There is blunting of the cervicomental angle with little definition along the mandibular rim. Liposuction alone can often yield a dramatic result.

For this procedure, the authors use tumescent infiltration, and access the neck via 3-mm incisions in the submental crease and retrolobular creases bilaterally. Two- and three-millimeter Mercedes cannulas, and a 3-mm spatula cannula are used. Only the 2-mm Mercedes cannula is used for jowl liposuction, accessing the jowl through the retrolobular incisions. Care must be taken not to over-contour the neck or jowl to prevent contour irregularities. It is far better to leave too much fat than to remove too much (Fig. 16.4).

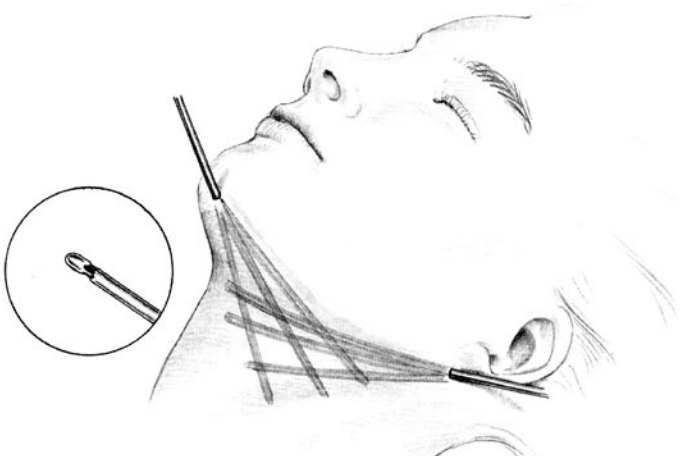

Fig. 16.4 Neck liposuction, from [42]

A 2-mm cannula can also be inserted into the central subplatysmal space to remove a small amount of fat. The blind suctioning must remain central to prevent possible perforation of the multiple large vessels that traverse this plane.

This limited approach can also be extended to older patients with the caveat that skin elasticity must be sufficiently good to allow for smooth skin retraction. Additionally, in older patients, cervical lipodystrophy may mask platysma banding, which becomes visible following liposuction. The platysma may then need to be addressed separately.

16.4.2.2 Chin Augmentation

Chin augmentation can be used alone, or in conjunction with other facial restorative procedures. Frequently, those patients with lifelong cervical lipodystrophy will often have accompanying poor chin projection, and a chin implant can be of great benefit (Fig. 16.5). It is also useful to improve the appearance of apparent microgenia that develops with age as an adjunct to more extensive surgical procedures.

Alloplastic chin implants are available through numerous manufacturers. Different styles are offered, with selection based upon the anatomic deformity to be corrected. The most common implant material is silastic, being both versatile and well tolerated.

If chin augmentation is to be performed following liposuction, the submental crease incision is enlarged to 2 cm and dissection continued to the periosteum. The dissection is continued cephalad and centrally in the preperiosteal plane. The periosteum is incised bilaterally, and a subperiosteal dissection performed along the mandibular rim to allow placement of the wings of the implant. The central implant remains in the preperiosteal plane, where it may be less likely to induce bone resorption [47]. Care is taken not to violate the mental or mandibular nerves. Implant sizers are utilized to confirm appropriate implant size, and the implant placed. The implant is sutured to the periosteum centrally before the incision is closed in layers.

Summary for the Clinician

- The aging face can be enhanced significantly by augmentation of subcutaneous tissue.
- Resection of skin with tightening of ligamentous attachments is a useful approach.
- Chin implants may be essential for enhancing the lower face.

16.4.2.3 Platysmaplasty

The presence of an obtuse cervicomental angle or platysma banding can be treated alone, or in conjunction with rhytidectomy procedures. In patients with modest facial aging changes for whom their primary concern is the neck, the platysma muscle can be approached from a central submental incision alone [17, 28, 41]. The procedure is frequently performed with neck liposuction, and benefits greatly from tumescent infiltration.

There is a wide spectrum of surgical alternatives to treatment of platysma bands. McKinney proposed a grading system of platysma bands to use for treatment selection [35]. Among the commonly accepted procedures are midline platysma plication, sagittal excision of redundant platysma, wedge resections at or below the hyoid, muscle flaps, and sling suspension.

When a face-lift procedure is performed, lateral SMAS tightening is often sufficient to correct modest platysma banding. Greater degrees of banding are often associated with muscle hypertrophy and shortening, producing a bowstring effect. In these cases, a submental approach is mandatory.

A central 3-mm incision is centered at, or slightly posterior to the submental crease. Under headlight illumination the skin and subcutaneous fat are elevated off the platysma muscle, extending laterally to the anterior borders of the sternocleidomastoid muscle. The platysma muscle is assessed for laxity, and redundant platysma excised. Wedge resections may be made laterally at the level of the thyroid cartilage to allow for more superior and posterior repositioning of the muscle. If subplatysmal fat is to be excised it is performed at this time, under direct visualization.

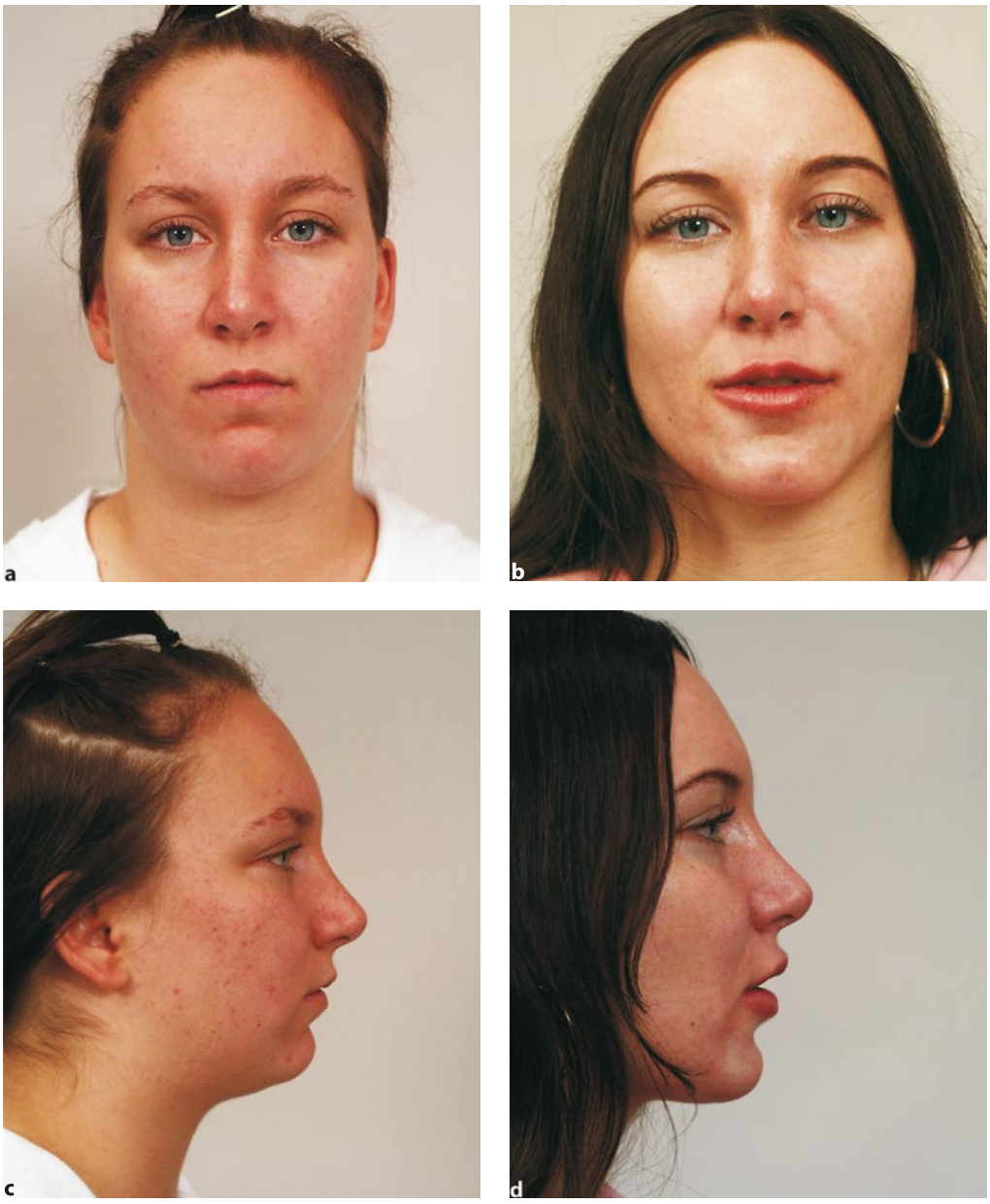

Fig. 16.5 **a** Preoperative frontal view of a patient before neck liposuction and chin augmentation. **b** Postoperative frontal view. **c** Preoperative lateral view. **d** Postoperative lateral view

The platysma is then reapproximated centrally using permanent sutures to prevent recurrence of bands (Fig. 16.6).

Other techniques, most notably Feldman's corset platysmaplasty [18], do not advocate platysma resection, but rather tighten the muscle in a layered fashion. In this approach, relaxing incisions are not performed, as proponents argue that by sufficient tightening the platysma is repositioned to achieve a more defined cervicomental angle, without the need for wedge resections.

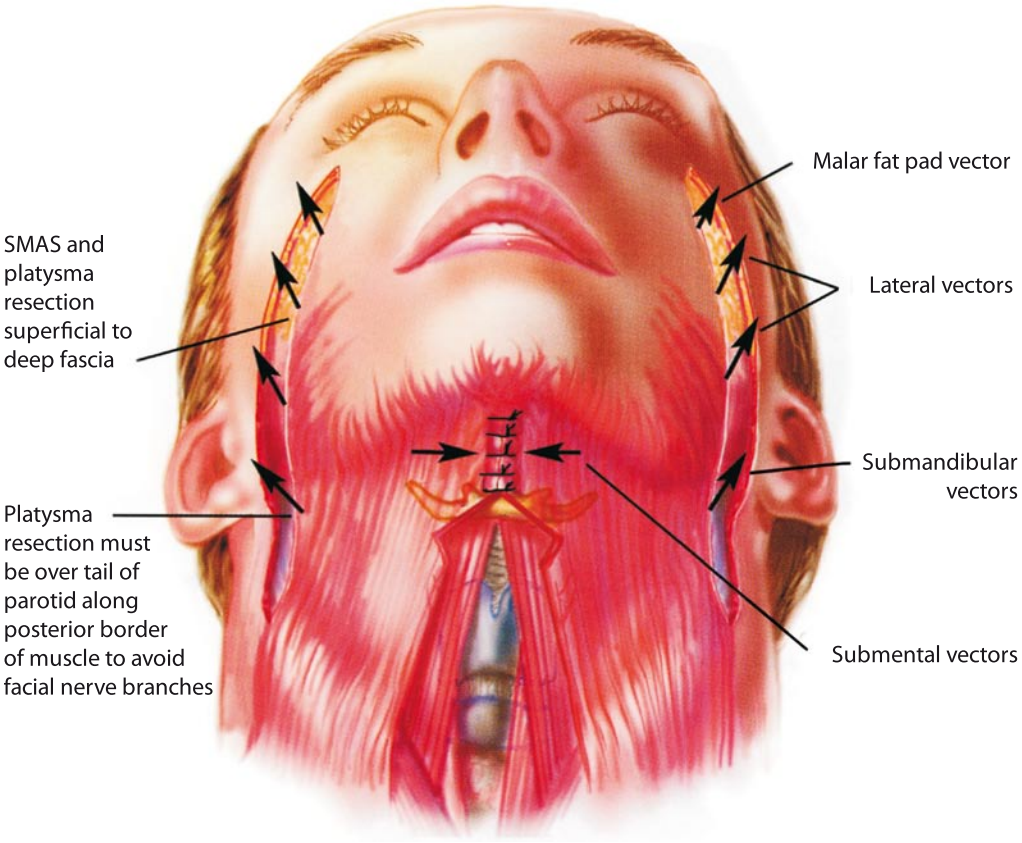

Fig. 16.6 Rhytidectomy with platysmaplasty, including midline plication and wedge resections [40]

Another adjunctive technique to assist in creating a deeper cervicomental angle is the use of platysma suspension sutures. The sutures may be utilized with or without platysma resection or midline plication. Originally described by Guerrerosantos et al. [22], numerous modifications have been reported [15, 19, 20]. These sutures are especially useful in more difficult necks, with greater platysma laxity and obtuse cervicomental angles (Fig. 16.7). The sutures typically affix the platysma border to the contralateral mastoid fascia. Two or more sutures are placed, with the tension adjusted to achieve the desired result. These sutures can be utilized either alone, together with liposuction, or as part of a face-lift procedure.

Botulinum toxin A (Botox) can also be used to temporarily improve muscle bands [30]. Botox is injected directly into the platysma muscle, often resulting in significant amelioration of bands, presumably by relaxing the muscle and allowing it to retract superiorly and posteriorly. Improvement is temporary, requiring reinjection at approximately 3-month intervals.

Achieving a well-contoured neck has been an accepted priority for years. Extensive operations [12–14, 45] including resection of subplatysmal fat down to the mylohyoid muscle, resection of the anterior belly of the digastric muscles, and submandibular gland resection have been termed the "radical neck rhytidectomy" by Baker [7]. In his paper, Baker makes a cogent argument for less radical cervical surgery, noting that commonly held criteria for a youthful neck [16] are no longer valid. To attempt to achieve the "ideal neck" for all patients is both "unrealistic and poor aesthetic judgment." Postoperative deformities resulting from more invasive neck surgery are well documented and difficult to correct.

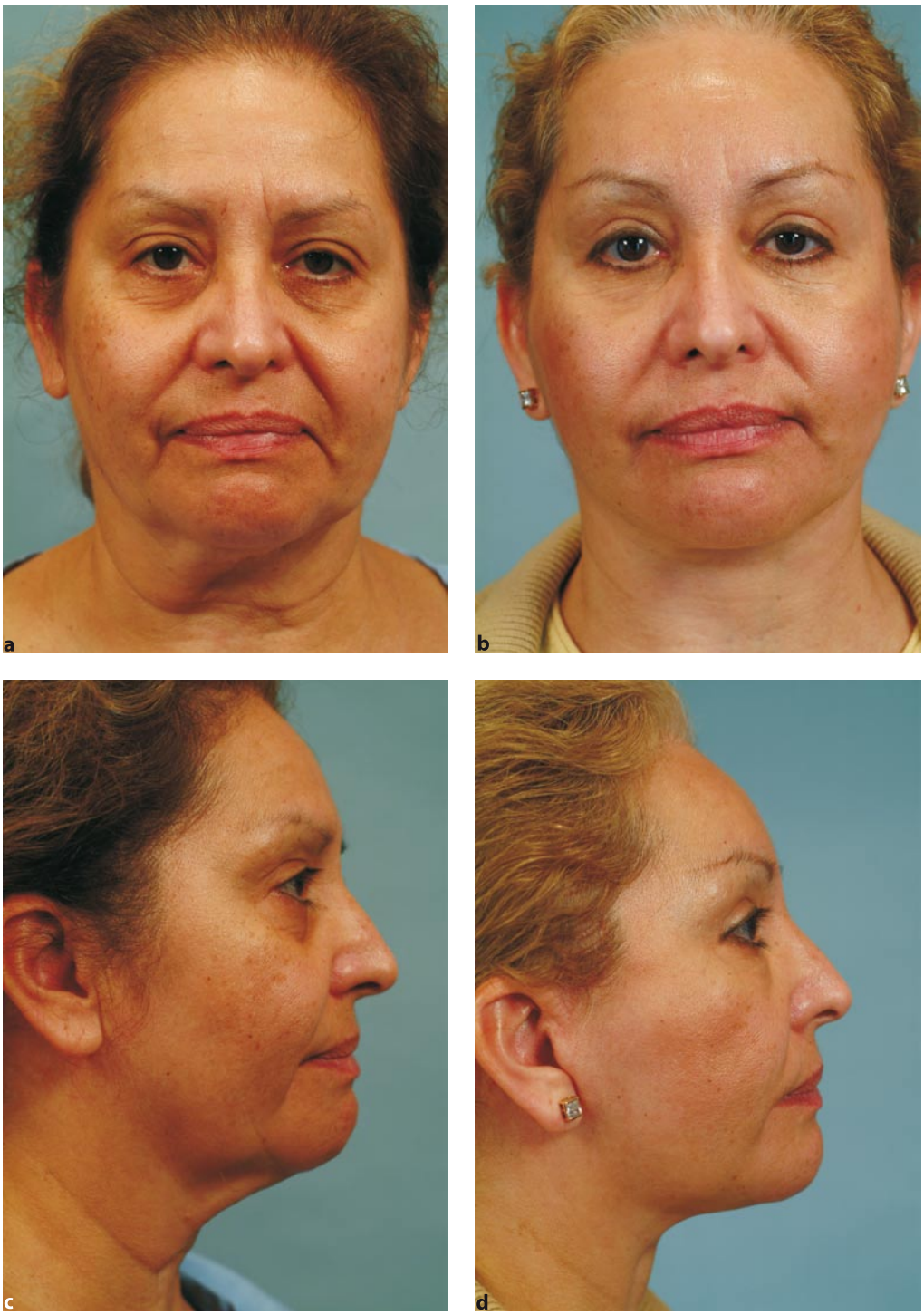

Fig. 16.7 **a** Preoperative frontal view of a patient prior to rhytidectomy with platysmaplasty and suspension sutures, autologous fat transfer, and endoscopic brow lift. **b** Postoperative frontal view. **c** Preoperative lateral view. **d** Postoperative lateral view

16.4.3 Face-lift Surgery

16.4.3.1 Basics

The definition of the SMAS in 1976 by Mitz and Peyronie [37] marked the beginning of the common era of face-lift operations. Prior to this, face-lift procedures involved elevation and tightening of the skin envelope alone. With greater understanding of facial anatomy, face-lift procedures became increasingly aggressive, with larger incisions and deeper planes of dissection. These procedures carried with them an increased risk of facial nerve paresis, prolonged postoperative edema, and ecchymosis [3, 24, 44]. While anatomically sound, these procedures may not offer any prolonged benefit to justify the increased risk and extended healing period [26, 27, 42, 48, 49].

The academic arguments are becoming increasingly moot. Societal shifts have made prolonged postoperative recovery unacceptable for most patients. These patients will be pleased with a more subtle result in exchange for a rapid recovery and return to normal activities. Additionally, as patients seek restoration at a younger age, more limited procedures are often more than adequate to enhance face and neck contours. The ideal procedure marries safety, efficacy, rapid recovery, and patient satisfaction.

16.4.3.2 Alternative SMAS Approaches

The main alternatives in face-lift surgery have traditionally been based upon SMAS modification. More recently, incision length has also been used to stratify procedures into either standard or "short-scar" face-lifts.

In a conventional SMAS lift, the SMAS is elevated over the parotid gland and redraped in a more cephalad vector than the skin flap [46]. In extended SMAS dissection, the sub-SMAS dissection is continued to the zygomaticus major muscle, allowing for greater SMAS advancement and repositioning [8]. In the deep-plane technique [23] a single flap of skin and SMAS is elevated, which is argued by Hamra to improve malar fat pad suspension and improvement of the nasolabial fold compared with alternative approaches. When the orbicularis oculi is included in the deep-plane flap it is termed a composite rhytidectomy [24].

More extensive SMAS dissection places the facial nerve at increased risk and prolongs postoperative recovery time. The pendulum has swung back, and both patients and surgeons have sought to optimize efficacy, safety, and recovery with less extensive SMAS dissections. To this end, Baker developed the lateral SMASectomy technique [4].

The SMAS is firmly adherent to the parotid gland, but mobile anterior to the gland. It is the more mobile SMAS that must be elevated and tightened to achieve the desired facial contour changes. The previously described procedures in which the SMAS is formally elevated anteriorly places the facial nerve at risk. Additionally, the thin SMAS flap often tears, making it useless for elevation. Baker proposed excision of a strip of SMAS overlying the anterior parotid gland from the malar eminence to the angle of the mandible, allowing the mobile anterior SMAS to be repositioned and adhered to the fixed SMAS overlying the parotid in a vector parallel to the nasolabial fold (Fig. 16.8). The senior author (ABB) has used this technique in over 1,000 patients, and can attest to its efficacy and safety.

In performing face-lift surgery we have found the tumescent infiltration technique extremely useful. Cervical contouring, including liposuction and/or platysmaplasty, is performed initially based upon preoperative assessment. After flap elevation the SMAS strip is excised as described by Baker, taking care to be superficial over the zygoma to prevent injury to the zygomatic nerve. The anterior SMAS is fixed to the posterior SMAS using absorbable sutures. This prevents the later complication of externalization of permanent sutures we have encountered. At this point in the procedure the cervicofacial flaps are rotated, trimmed, and fixed into position.

Ivy et al. in 1996 published results of 21 patients who underwent face-lift surgery, with different procedures performed on each side [27]. These included conventional SMAS lift, lateral SMASectomy, extended SMAS lift, and composite rhytidectomy. At both 6 and 12 months, differences between the facial sides were not identified. Those who championed more extensive approaches argued the study was flawed [25], although other studies mirror these results in comparing more and less extensive SMAS dissections [42, 48, 49].

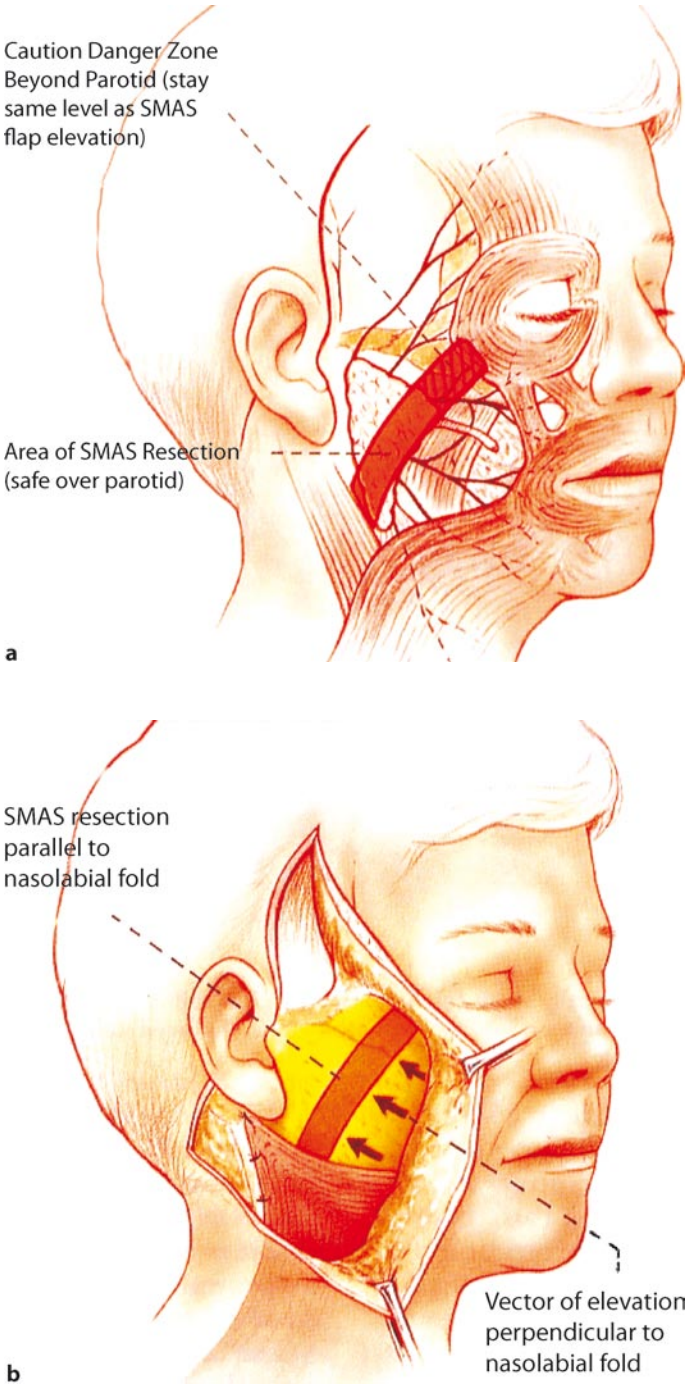

Fig. 16.8.a,b Lateral SMASectomy (superficial musculoaponeurotic layer) [10]

The most recent survey of face-lift surgeons revealed no consensus regarding the ideal procedure [36], emphasizing that each surgeon must develop a technique that best fulfills their own criteria for a successful procedure.

16.4.3.3 S-Lifts

One of the most interesting developments over the past 10 years has been the increased acceptance of shorter incisions, often accompanied by limited SMAS modification, for appropriate patients. Younger patients with more modest jowling and neck laxity do not require traditional retroauricular incisions to achieve excellent results. The retroauricular incision can result in visible or hypertrophic scarring, hairline distortion and skin necrosis, all limitations to hair styling. Additionally, more limited dissection decreases postoperative ecchymosis, edema, and healing time. As skin incision and dissection decrease, patient goals of rapid recovery are more readily attained.

The concept of limited surgery is not new. The first description of small-incision face-lift surgery dates back to 1919 [39]. In 1983, Ansari used the term "S-lift" to describe an S-shaped incision extending from the sideburn or temporal hair bearing scalp to just posterior to the earlobe [1, 2]. The incision was repopularized by Saylan in the late 1990s [43]. Saylan described a conservative skin flap of 5–7 cm, with U and O sutures used to plicate the SMAS and fixate it to the zygoma. The procedure carries a high rate of satisfaction with minimal complications and brief recovery.

16.4.3.4 S-Lift with SMASectomy

The next progression was to couple the S-lift incision with a SMASectomy. Baker reported a series of 749 patients in 2001 using this technique he termed the "short scar face-lift" [5, 6]. The senior author (ABB) has used this technique in over 500 patients, and like Baker, has found equal success with short and standard incisions in midface elevation, jowl repositioning, and submental skin tightening. As the SMASectomy technique has its greatest effect upon the midface and jowl, and it is the vertical component of the lift that tightens the submentum, this would be expected. The retroauricular flap is required, however, for patients with greater degrees of cervical skin laxity. We now perform the S-lift with SMASectomy in over 50% of our patients undergoing face-lift surgery (Fig. 16.9) [34].

Summary for the Clinician

- A variety of techniques can be employed to tighten the SMAS with an S face-lift and/or a SMASectomy.

16.4.3.5 Face-lift with Soft Tissue Augmentation

The face-lift techniques described above are all based upon traditional models of facial aging. Where does soft tissue deflation fit in? Surgeons as early as the mid-1990s were reporting on combined face-lift and autologous fat transfer techniques [21]. Over the past 10 years we have continued to utilize this combination modality in our quest to achieve optimal results (Fig. 16.10). Our enthusiasm for this composite technique is tempered by the recognition that it is accompanied by increased edema and ecchymosis, often prolonging recovery time significantly. The edema is often most evident at the lid–cheek junction, perhaps secondary to lymphatic compromise. The edema typically resolves over a period of weeks to months.

16.4.4 Autologous Fat Transfer

Advocates of the theory proposed by Coleman that facial aging is primarily the result of facial deflation believe that true restoration can only be achieved through volume augmentation. It is not, however, the ideal procedure for everyone. Patient expectations of rapid recovery with minimal edema and ecchymosis are not met by large volume fat transfer. These procedures often require up to a month or longer before patients

Fig. 16.9 **a** Preoperative frontal view prior to S-lift with SMASectomy. **b** Postoperative frontal view of the patient. **c** Preoperative lateral view. **d** Postoperative lateral view

are secure to return to a social setting. Additionally, results are often more subtle than excisional surgery, and many patients desire a greater degree of change. In our practice, younger patients are often well-served by focused autologous fat transfer, while patients with greater degrees of aging are best treated with a combination of facelift and volume restoration.

The technique for successful autologous fat grafting is beyond the scope of this chapter. The

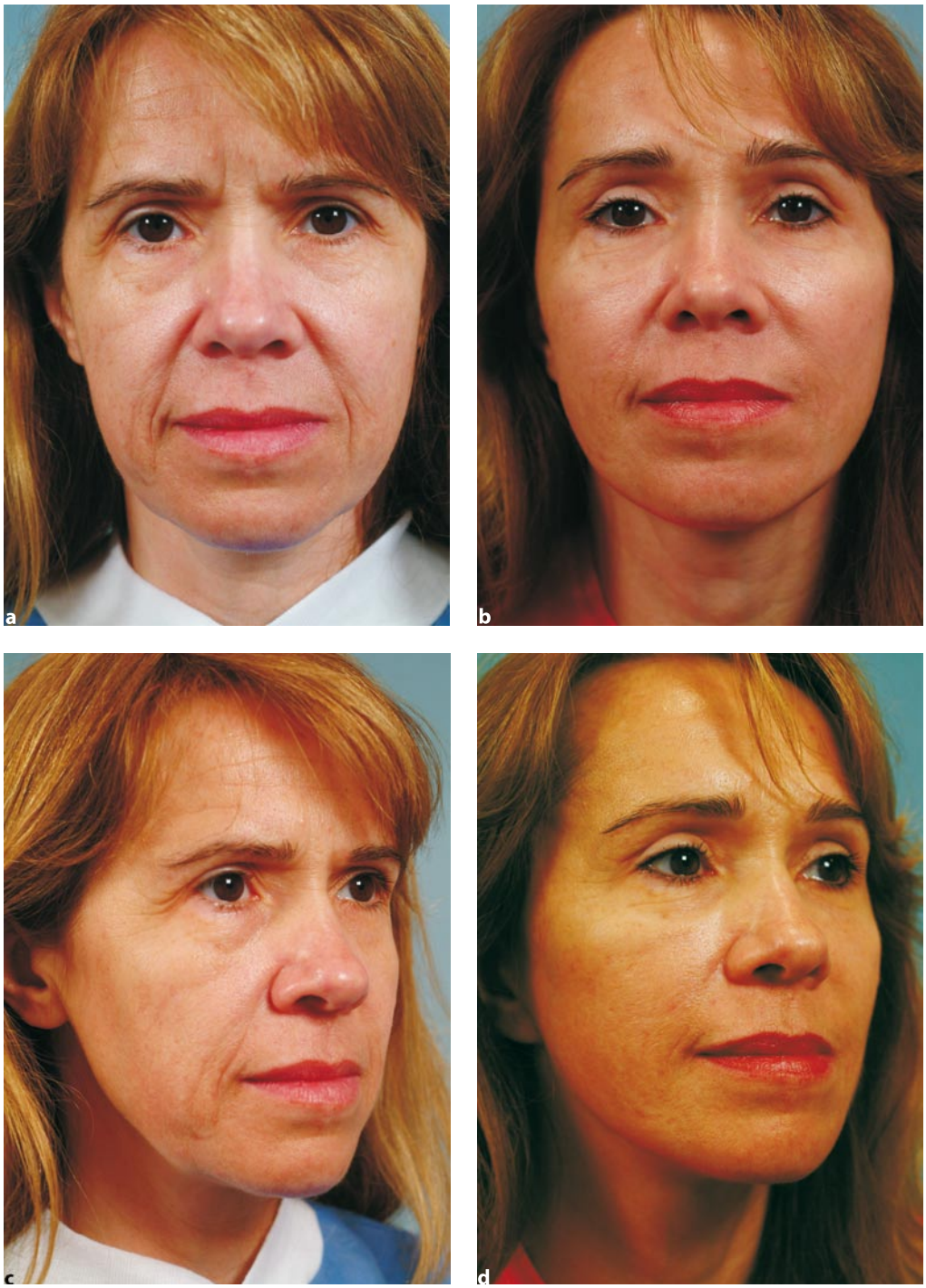

Fig. 16.10 **a** Preoperative frontal view of a patient prior to S-lift with SMASectomy, autologous fat transfer, endoscopic brow lift, and upper eyelid blepharoplasty. **b** Postoperative frontal view. **c** Preoperative partial profile. **d** Postoperative partial profile

reader is referred to Coleman's text [11] for details. Our use of these techniques supports Coleman's assertion that structural fat grafting can be permanent if performed properly. We believe there is no doubt that soft tissue deflation plays a prominent role in facial aging, and fat grafting can achieve results for patients that are otherwise unobtainable.

Summary for the Clinician

- True restoration of facial deflation can be achieved with autogenous fat transfer, which can be useful as a focused augmentation in younger patients, but needs to be combined with face-lifting in older patients.

References

1. Ansari P (1983) Neue Methode der Gesichts- und Halsstraffung. Kosmet J 8:14–15
2. Ansari P (2003) Elimination of the retroauricular incision in face lifts. Aesthetic Surg J 23:14–19
3. Baker DC (1994) Deep dissection rhytidectomy: a plea for caution. Plast Reconstr Surg 93:1498
4. Baker DC (1997) Lateral SMASectomy. Plast Reconstr Surg 100:509–513
5. Baker DC (2001) Minimal incision rhytidectomy (short scar face lift) with lateral SMASectomy: evolution and application. Aesthetic Surg J 21:14–26
6. Baker DC (2001) Minimal incision rhytidectomy (short scar face lift) with lateral SMASectomy. Aesthetic Surg J 21:68–79
7. Baker DC (2006) Face lift with submandibular gland and digastric muscle resection: radical neck rhytidectomy. Aesthetic Surg J 26:85–92
8. Baker TJ, Gordon HL, Stuzin JM (1996) Surgical rejuvenation of the face. Mosby-Year Book, St. Louis
9. Berman M (1998) The aging face: a different perspective on pathology and treatment. Am J Cosmetic Surg 15:167–172
10. Brackup AB (2002) Combined cervicofacial rhytidectomy and laser skin resurfacing. Am Soc Plast Reconstr Surg 18:24–39
11. Coleman SR (2004) Structural fat grafting. Quality Medical, St. Louis
12. Connell BF (2002) Male face lift. Aesthetic Surg J 22:385–387
13. Connell BF, Hosn W (2000) Importance of the digastric muscle in cervical contouring: an update. Aesthetic Surg J 20:12–16
14. Connell BF, Shamoun JM (1997) The significance of digastric muscle contouring for the rejuvenation of the submental area of the face. Plast Reconstr Surg 99:1586–1590
15. Conrad K, Chapnik JS, Reifen E (1993) e-PTFE (Gore-tex) suspension cervical facial rhytidectomy. Arch Otolaryngol Head Neck Surg 119:694
16. Ellenbogen R, Karlin JV (1980) Visual criteria for success in restoring the youthful neck. Plast Reconstr Surg 66:826–837
17. Evans TW, Stepanyan M (2002) Isolated cervicoplasty. Am J Cosmet Surg 19:91–113
18. Feldman JJ (1990) Corset platysmaplasty. Clin Plast Surg 39:566–572
19. Giampapa VC (2000) Suture suspension technique offers predictable, long-lasting neck rejuvenation. Aesthetic Surg J 20:253–255
20. Giampapa VC, DiBernardo BE (1995) Neck recontouring with suture suspension and liposuction: an alternative for early rhytidectomy candidates. Aesthetic Plast Surg 19:217
21. Guerrerosantos J (1998) Simultaneous rhytidoplasty and lipoinjection: a comprehensive aesthetic surgical strategy. Plast Reconstr Surg 102:191–199
22. Guerrerosantos J, Ramirez M, Espaillat L (1972) Ritidoplastia cervicofacial. Rev Latinoam Cir Plast 14:31
23. Hamra ST (1990) The deep-plane rhytidectomy. Plast Reconstr Surg 86:53
24. Hamra ST (1993) Composite rhytidectomy. Quality Medical, St. Louis
25. Hamra ST(1996) Discussion: is there a difference? A prospective study comparing lateral and standard SMAS face lifts and extended SMAS and composite rhytidectomies. Plast Reconstr Surg 98:1114–1117
26. Hamra ST (2002) A study of the long-term effect of malar fat repositioning in face lift surgery: short-term success but long-term failure. Plast Reconstr Surg 110:940–951

27. Ivy EJ, Lorenc ZP, Aston SJ (1996) Is there a difference? A prospective study comparing lateral and standard SMAS face lifts with extended SMAS and composite rhytidectomies. Plast Reconstr Surg 98:1135–1143
28. Jasin ME (2003) Submentoplasty as an isolated rejuvenative procedure for the neck. Arch Facial Plast Surg 5:180–183
29. Jones BM, Grover R (2004) Complications in cervicofacial rhytidectomy by tumescent infiltration: a comparative trial evaluating 678 consecutive face lifts. Plast Reconstr Surg 113:308–402
30. Kane MAC (2003) Nonsurgical treatment of platysmal bands with injection of botulinum toxin A. Plast Reconstr Surg 112:115S–122S
31. Klein JA (1987) The tumescent technique for liposuction surgery. Am J Cosmet Surg 4:263
32. Larabee WF, Makielski KH (1993) Surgical anatomy of the face. Raven, New York
33. LaTrenta GS (1998) Tumescent cervicofacial rhytidectomy. Aesthetic Surg J 18:423–430
34. McCarty ML, Brackup AB (2005) Minimal incision facelift surgery. Ophthalmol Clin N Am 18:305–310
35. McKinney P (1996) The management of platysma bands. Plast Reconstr Surg 98:999–1006
36. Matarasso A, Elkwood A, Rankin M (2000) National plastic surgery survey: face lift techniques and complications. Plast Reconstr Surg 106:1185–1195
37. Mitz V, Peyronie M (1976) The superficial musculoaponeurotic system (SMAS) in the parotid and cheek area. Plast Reconstr Surg 58:80–88
38. Newman J, Kotoske TG (1996) Tumescent lipodissect neck and mandibular rim contouring with augmentation. Am J Cosmet Surg 4:19–32
39. Passot R (1919) La chirurgie esthétique des rides du visage. Presse Med 27:258–262
40. Pitman GH (1993) Liposuction and aesthetic surgery. Quality Medical, St. Louis
41. Ramirez OM (2003) Cervicoplasty: nonexcisional anterior approach. A 10-year follow-up. Plast Reconstr Surg 111:1342–1347
42. Rees TD, Aston SJ (1977) A clinical evaluation of the results of submusculoaponeurotic dissection and fixation in face lifts. Plast Reconstr Surg 60:851
43. Saylan Z (1999) The S-lift: less is more. Aesthetic Surg J 19:406–409
44. Seckel BR (1994) Facial danger zones. Quality Medical, St. Louis
45. Singer DP, Sullivan PK (2003) Submandibular gland. I. An anatomic evaluation and surgical approach to submandibular gland resection for facial rejuvenation. Plast Reconstr Surg 112:1155–1156
46. Tardy ME, Thomas JR (1995) Facial aesthetic surgery. Mosby-Year Book, St. Louis, Missouri
47. Terino EO, Flowers RS (2000) The art of alloplastic facial contouring. Mosby, St. Louis
48. Tipton JB (1974) Should the subcutaneous tissue be plicated in a face lift? Plast Reconstr Surg 54:1
49. Webster RC, Smith RC, Papsider MJ (1982) Comparison of SMAS plication with SMAS imbrication in face lifting. Laryngoscope 92:901

Chapter 17

Facial Sculpting with Injectable Filler Materials

17

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Core Messages

- Atrophy of subcutaneous soft tissue rather than gravity is the cause of skin falling into wrinkles and folds.
- Redistribution of fat or volume replacement can restore a more youthful appearance.
- Fillers can elevate the brow.
- The midface can be aided by lifts and cheek augmentation.
- Augmentation with filler enhances the appearance of lips.
- Implants are useful for enhancing the chin.
- Facial sculpting with injectable fillers range from temporary to permanent.
- Fillers can be combined with Botox to produce more effective and lasting results.

17.1 Introduction

Often considered first-line treatment for aging skin, soft tissue fillers are used alone or in combination with other rejuvenation procedures to correct wrinkles, improve facial contours, and restore volume naturally lost as fat diminishes from the face, particularly around the eyes and cheeks. Until recently, it was believed that sagging skin was due to gravity, but new evidence points to the atrophy of subcutaneous soft tissues – allowing unsupported skin to fall into wrinkles and folds – as the cause and suggests that a redistribution of fat or volume replacement may restore vitality [2, 5, 14, 16–18]. In the brow, the natural attrition of periorbital fat over time causes loss of lateral brow projection, in addition to lateral brow ptosis. While brow ptosis has primarily been treated surgically, fillers allow re-projection of the lateral brow with a renewed youthful appearance. Similarly, midface lift and cheek augmentation can re-sculpt the face into the normal heart-shaped contour that is lost during the aging process or as a result of facial lipoatrophy associated with human immunodeficiency virus (HIV) infection. In the lower face, lip augmentation with soft tissue agents has climbed in popularity across all ages and is one of the easiest ways to improve overall appearance and aesthetic beauty of the face during a short office visit with minimal recovery time. Chin augmentation has also become more popular; changing the shape of a chin can alter a profile dramatically. Unlike traditional surgical options, treatment sessions with injectable fillers are convenient and are associated with instant results, fewer complications, and no downtime.

Summary for the Clinician

- Unlike traditional surgical procedures, soft tissue augmentation addresses the increasing demand for less invasive treatments
- They may prove to be the ideal rejuvenation modality, producing a more natural and youthful countenance with little inconvenience or recovery time

17.2 Facial Sculpting with Injectable Fillers

There are a number of options for the experienced clinician when choosing fillers alone or in combination for facial sculpting and volume enhancement, subtly restoring the face to a more youthful aesthetic (Table 17.1).

17.3 Temporary Filling Agents

Temporary filling agents – ideal for first-time clients or those "testing" new looks or procedures – can last from 2 months up to a year, although most typically last around 6 months before re-absorption.

17.3.1 Hyaluronans

Some of the most popular products in use today, animal-based and non-animal-based hyaluronans were developed for soft tissue augmentation by cross-linking hyaluronic acid (HA) chains. Found naturally in the skin, HA is a glycosaminoglycan biopolymer that provides structure and holds moisture within the dermis. When injected into the dermis, HA gels join forces with the body's own HA to create support and add volume for a period of 4–12 months before undergoing degradation and clearance by the liver [19]. Treatment with hyaluronans is easy and quick and can be performed in as little as 30 min. The effects are immediate, there is little to no recovery time, and the clinical effects persist for up to a year, depending on the product and density of the hyaluronic acid used (Fig. 17.1).

Available hyaluronans include Hylaform (INAMED Aesthetics, Santa Barbara, CA, USA), Restylane, Restylane Fine Lines, Perlane, and Restylane SubQ (Q-Med, Uppsala, Sweden); Juvéderm 18, Juvéderm 24, and Juvéderm 30 (including the 24 HV and 30 HV forms; LEA Derm, Paris, France); and Captique (INAMED Aesthetics). Hyaluronans appear to provide durability and aesthetic improvement superior to that of bovine collagen [33] and rarely cause an allergic reaction. In our experience, Hylaform and Captique do not last as long as the Juvéderm and the Restylane group of products, which last from 4–6 months before re-absorption.

Most HA side effects are transient and mild and include pain and intermittent swelling, edema, and erythema at the injection site [27]. Localized hypersensitivity reactions are by far the most common adverse effects, some of which may be delayed by months following treatment [31]. However, hypersensitivity reactions may be related to protein content; studies show a decline in reactions when the amount of protein in the raw product decreased [3, 23]. Other reported complications include granulomatous reactions [22, 26, 37], angioedema-type hypersensitivity [30], and ischemic complications [25, 38]. The use of impure or contaminated material contributes to the development of infection or foreign body reaction [42], and granulomas often respond to injected corticosteroids, topical antihistamines, and digital pressure or manipulation [37]. Intracutaneous hyaluronidase has been shown to dissolve hyaluronans and relieve patient discomfort within 24–48 h of treatment for persistent granulomatous reaction and misplacement of hyaluronic acid [6], and may be useful in rare cases of occlusion [25].

17.3.2 Collagen

Collagen replacement therapy is an excellent option for temporary augmentation. Zyderm and Zyplast (INAMED Esthetics) are composed of purified collagen fibrils derived from processed bovine skin, in a suspension of phosphate-buffered physiologic saline with 0.3% lidocaine. Supplied in pre-filled syringes and stored at a temperature of 4°C, the dispersed collagen fibrils remain small and fluid. When implanted, the product rises in temperature, forming a more cohesive gel. Zyplast is the most viscous and less immunogenic of the three products and is of longer duration than Zyderm. Bovine collagen typically requires two treatment sessions before the desired effect is achieved, and its effects last from 3 to 6 months (Fig. 17.2). Good results with bovine collagen demand the injection of sufficient volume of product; an overly conservative approach, injecting too little, will produce unsatisfactory effects of short duration. In addition, using sufficient volume ensures simpler maintenance – and less correction – at follow-up.

Table 17.1. Sculpting procedures, injection techniques, and appropriate fillers

	Injection tips	Fillers
Lateral brow lift	Use soft white pencil to mark ellipse into which filler will be injected. Insert filler in subdermal space at temporal end of lateral brow cilia (replacing brow fat pad); place subsequent injection 7 mm medially to the first. Use push-ahead technique to elevate subdermal region with filler, rather than the needle tip. Mold filler for symmetry and anterior projection.	Restylane, Perlane, Juvederm 24 HV, Juvederm 30 HV
Midface lift	Outline area of zygoma requiring enhancement using soft white pencil. Check face for asymmetry. Inject filler into subdermal space.	Restylane, Perlane, Juvederm 24 HV, Juvederm 30 HV, Artefill Sculptra
Treatment of facial lipoatrophy	Same as above.	Radiesse, Silicone 1000, Restylane Sub Q, Sculptra, Bio-Alcamid, Artefill
Nasojugal fold lift	Place filler deep to orbicularis oculi muscle just along periosteum at the arcus marginalis to avoid cutaneous evidence of filler.	Restylane, Juvederm 24 HV
Lip augmentation	Start in mouth corners and work across the length of each lip, layering filler at even intervals across the lips inside the vermilion border. Massage lips to ensure even distribution and break up any irregularities. Inject precisely along the vermilion border and directly into the upper lip just above the corners of the mouth, enhancing lip border definition and creating a slight upturn to the corners of the mouth.	Restylane , Perlane, Juvederm 24 HV, Juvederm 30 HV CosmoPlast, CosmoDerm
Perioral augmentation	Treat complete perioral frame and vermilion lip. First elevate the lip corners and melomental folds, laying down a subdermal deposit of filler material, creating a subdermal strut of support to lift the lateral commissures.	Restylane, Perlane, Juvederm 24 HV, Juvederm 30 HV

Table 17.1. *(continued)* Sculpting procedures, injection techniques, and appropriate fillers

	Injection tips	Fillers
Perioral augmentation	Extend inferior portion of the strut laterally to fill in the prejowl sulcus. Layer fillers.	Radiessse and Sculptra and Artefill to subcutaneous level of melolabial folds, not into lips.
Chin augmentation	Inject filler subdermally into the region superior to the mentum, producing a fuller chin that projects forward to line up with the lower lip when the face is in the Frankfort horizontal.	Radiesse, Perlane, Juvederm 30 HV Artefill Sculptra

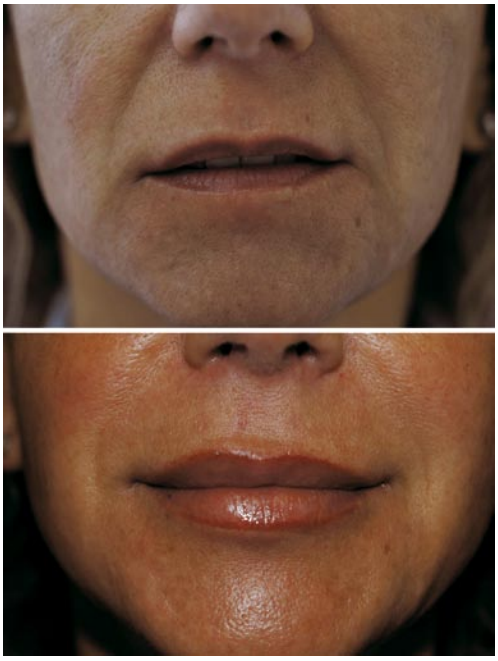

Fig. 17.1 Longevity of response in most areas may relate to volume of filler injected as well as density of the hyaluronan used

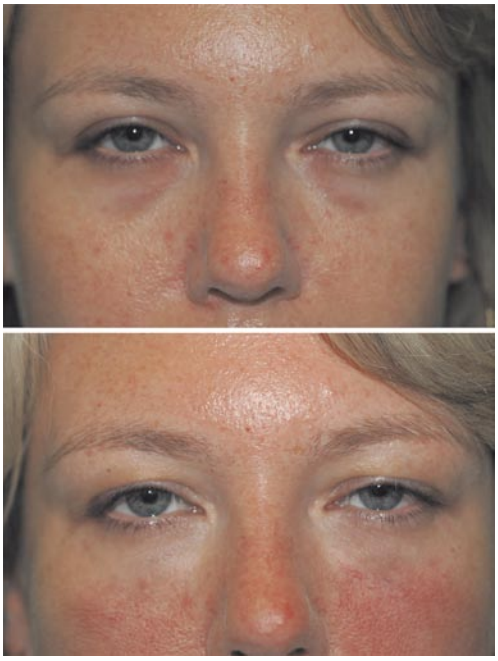

Fig. 17.2 Clinical effect of filling the nasojugal folds with Cosmoplast lasts 3–6 months (human bioengineered collagen; Allergan Pharmaceuticals, Santa Barbara, CA, USA)

CosmoDerm (for fine lines) and CosmoPlast (for deeper wrinkles and folds) (INAMED Aesthetics) are bioengineered human collagen replacement products approved for cosmetic use in Canada and the United States that contain human collagen purified from dermal tissue grown in the laboratory [27]. Because they are of human origin, CosmoDerm and CosmoPlast do not provoke allergic reactions, and skin tests are not required before injection.

The main disadvantages of injectable collagen include the temporary clinical effect and the need for repeated treatments. Since some patients will experience an allergic reaction to bovine collagen, double skin testing prior to treatment is required. Other adverse reactions are rare and

transient; redness at the injection site disappears within a few hours, and any bruising will resolve within a week or less.

A new collagen has recently come onto the Canadian market. Evolence™ is a porcine-based atelomeric collagen (ColBar, Herzliya, Israel) that has a natural glycated cross-linking. Because it is hypoallergenic, but has conservation of the natural amino acid sequencing in collagen, no skin test is needed. The product is distinguished from previous collagen injectables by the remarkable longevity of response. The product has been used as a dental membrane "Ossix" in 150,000 patients worldwide with no allergic reactions to date and also in Europe as an injectable filler – also without allergic reactions. When histologic evaluation is performed after injection, the injected collagen seems to incorporate native fibroblasts within its mass. No capsule is formed. It is indicated for the treatment of nasolabial folds, marionette lines, glabellar folds, lips and also for facial contouring. In clinical studies performed in the USA, the pivotal study compared Evolence and Restylane. Initiated in December 2005 at 6 sites, 149 patients were recruited and treated. No positive reactions were seen post-skin tests and no significant device-related adverse events have been observed so far. The data are not yet published as there is a 12-month follow-up to monitor safety and efficacy.

17.3.3 Autologous Fat

The oldest available filler, autologous fat allows for the correction of contour defects without risk of allergy, and some believe that fat grafting represents the ideal replacement of lost volume and contours [28]. However, the success of dermal fat procedures depends on the method of harvesting, the type of fat used, and the injector's level of experience, and disadvantages include donor site morbidity, calcification of the injected fat, and unpredictable reabsorption [12]. Available procedures include LipoStructure [14], the fat autograft muscle injection (FAMI) technique [2, 8], and "fat rebalancing" [17, 18]. Since the variable longevity of contour correction depends on technique, amount of fat injected, and location, improvements in harvesting, handling, and the injection process may have an impact on positive patient outcomes [28].

Despite improvements in technique over the years, autologous fat grafting still demonstrates unpredictable and sometimes temporary results with high reabsorption rates [11–13]. Moreover, harvesting and reinjecting fat are both significant procedures that are associated with downtime and the possibility of serious complications. Although largely technique-dependent, potential complications of autologous fat grafting include prolonged edema, bruising, under-correction, over-correction, clumping, irregularities, fat necrosis, migration, and infection, in addition to the other risks associated with surgical procedures [12].

17.3.4 Poly-L-lactic Acid Implants

Recently approved by the FDA for the treatment of HIV-related facial lipoatrophy, Sculptra (Dermik Laboratories, Berwyn, PA, USA) contains microparticles of poly-L-lactic acid, a biocompatible and biodegradable synthetic polymer from the alpha-hydroxy-acid family. Injected into the skin, Sculptra induces fibroblastic activity and leads to a progressive increase in volume (Fig. 17.3). Follow-up at 2 weeks to assess treatment is required; larger volume defects may require further treatment [32]. Improvements in dermal thickness have been reported to last up to 2 years (Sculptra Product Information, Dermik Laboratories, 2006).

Side effects associated with Sculptra are related to the injection procedure and include hematoma, bruising, edema, discomfort, inflammation, and erythema. The most common filler-related complications include delayed occurrence of subcutaneous papules that are palpable, asymptomatic, and nonvisible.

17.4 Permanent and Semi-permanent Injectable Agents

Semi-permanent and permanent fillers are not readily broken down or reabsorbed and are the ideal agents for clients searching for a long-lasting change.

Fig. 17.3a,b Sculptra (poly-L-lactic acid) is FDA-approved for the treatment of HIV-related facial lipoatrophy. Multiple treatments may be required to achieve sufficient fill from the resulting neocollagenesis. Age-related facial lipoatrophy is also responsive. Photos courtesy of Steve Mandy, MD

17.4.1 DermaLive/DermaDeep

DermaLive and DermaDeep (Euromedical Systems, Nottingham, UK) are semi-permanent soft tissue fillers composed of acrylic hydrogel in an hydroxyapatite vehicle that is reabsorbed after injection. The nonbiodegradable acrylic hydrogel particles remain and induce a tissue response, leading to long-lasting effects of at least 12 months [4, 7]. DermaLive consists of smaller acrylic hydrogel particles and is injected less deeply into the tissue to fill medium to deep skin depressions; DermaDeep is reserved for more pronounced tissue defects. Because of its longer duration of effect, DermaLive/DermaDeep is a good alternative to hyaluronans or collagen, although several injections are often required.

Injection-related side effects, such as pain on injection, itching, discoloration, tenderness, palpable lumpiness, redness, and edema, are transient and usually resolve within a week at most. Long-term side effects include nodules, swelling or redness at the point of injection appearing an average of 6 months after injection. More serious complications are due to improper injection techniques or contraindications to treatment [4]. Although rare, serious complications like granuloma, superficial necrosis, and urticaria can occur and have been detected more than 2 years after initial treatment [37]. A series of corticosteroid injections given at 1- to 3-weekly intervals at the first sign of a nodule or other complication is recommended.

17.4.2 Calcium Hydroxyapatite Beads

Soft tissue augmentation with calcium hydroxyapatite beads (Radiance, Radiance FN; BioForm, Franksville, WI, USA) delivered in a methylcellulose vehicle is an off-label indication that many believe holds great promise and has been shown to be effective and well tolerated when used in facial rejuvenation (Fig. 17.4) [41, 44] and in patients with facial lipoatrophy [15]. Once injected,

the gel is absorbed; what remains is a matrix of material that acquires characteristics of the cells that populate it, requiring precise placement of the filler in order for the permanent correction to occur. Although touted as a long-term filler, clinical experience has not been able to establish longevity of the implant as yet. Skin testing is not required prior to use.

There are few data on the potential complications or long-term safety of Radiance when used in cosmetic procedures. To date, there have been no reports of antibody formation or hypersensitivity. Erythema, edema, and ecchymosis are common, but transient. Injection-related pain can be treated with acetaminophen. Injections should be placed deeply rather than superficially to avoid visible material. Nodule formation in the lips is the most commonly reported complication; some nodules will require treatment with either intralesional steroids or incision and drainage [24, 41, 44]. Radiance should be used with great caution for lip augmentation and only in patients with previous experience using other fillers, as the constant motion of the mouth tends to cause migration of the implant. Unlike other fillers, Radiance does not require over-correction.

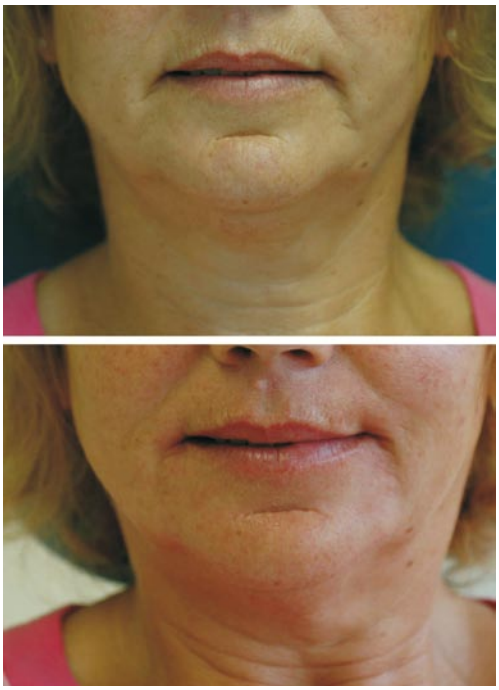

Fig. 17.4 Radiesse is composed of calcium hydroxyapatite beads suspended in a vehicle of carboxymethylcellulose. It has been successfully used for facial volume deflation as an off-label indication in the USA, but it is fully approved in Canada for this indication

17.4.3 Polyalkylimide

Approved for use in Canada in April 2006, Bio-Alcamid (Polymekon, Brindisi, Italy) is a long-lasting, semi-permanent filler consisting of an injectable gel polymer – 96% nonpyrogenic water and 4% synthetic reticulate polymer (polyalkylimide). When injected subcutaneously it is designed to replace depleted fat tissue, restoring the natural fullness and contours of the face. Once implanted, Bio-Alcamid becomes covered by a very thin collagen capsule (0.02 mm), which completely surrounds the gel, isolating it from the host tissues. Among its many uses, Bio-Alcamid effectively enhances the lips and corrects volume deficits in the cheek, chin, and jaw, and is currently used for the treatment of HIV-related facial lipodystrophy (Fig. 17.5) [43].

Reported side effects have been minimal; in our clinic, one client developed a secondary bacterial infection several months after treatment that subsequently responded to oral antibiotics. In the event of side effects or improper placement, Bio-Alcamid can be removed easily.

17.4.4 Polymethylmethacrylate Microspheres

Artecoll (Artefill; Artes Medical, San Diego, CA, USA) is a suspension of polymethylmethacrylate (PMMA) microspheres in 3.5% bovine collagen solution. After implantation, the collagen solution eventually dissipates, leaving behind the nonbiodegradable PMMA microspheres. Although the volume injected depends on the depth and size of the wrinkle, usually at least two injection sessions are required. Since the product is permanent, it is important to select

patients carefully and treat cautiously; partial correction, followed by re-injection after a few months, will produce a smoother, more natural appearance than over-correction. Applied by a skilled clinician, Artecoll is a powerful and effective filling agent that yields excellent results and does not require repeated touch-up treatments (Fig. 17.6). However, its permanence demands that great care be taken in choosing the appropriate patients who are comfortable with the risks associated with permanent facial augmentation. Skin testing is required prior to injection.

Beading, palpability, and visibility of the implant may occur with lip augmentation (or other areas of repetitive movement) and injections are not recommended for areas of thin skin (e.g., lower eyelid and neck). Reports of lumpiness in the lips has led to an FDA recommendation to avoid using Artecoll for perioral injections. Other reported complications include delayed granulomatous reactions [1], nodule formation, beading, and ridging causing disfigurement reversible only by surgical excision [37]. Even following the recommended conservative approach, with long intervals between injections [36], granulomas

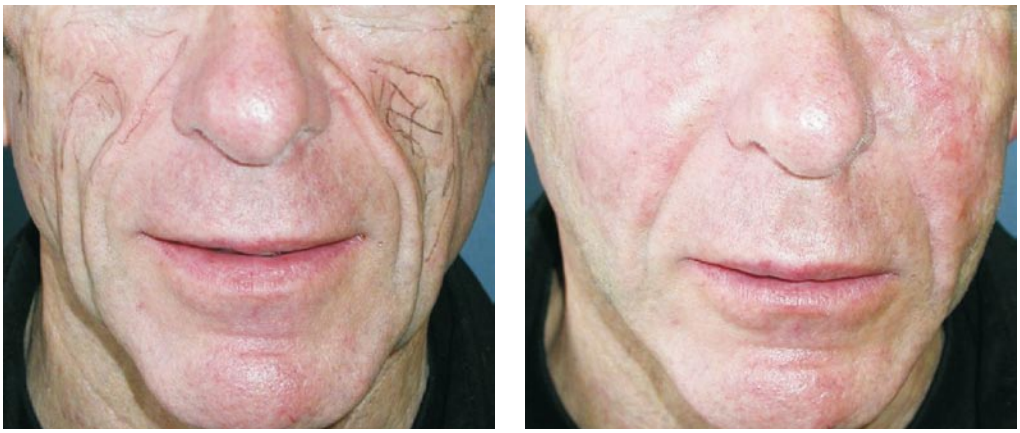

Fig. 17.5 Bio-Alcamid is a new polyalkylimide filler approved for the treatment of HIV-related facial lipoatrophy in Europe and Canada

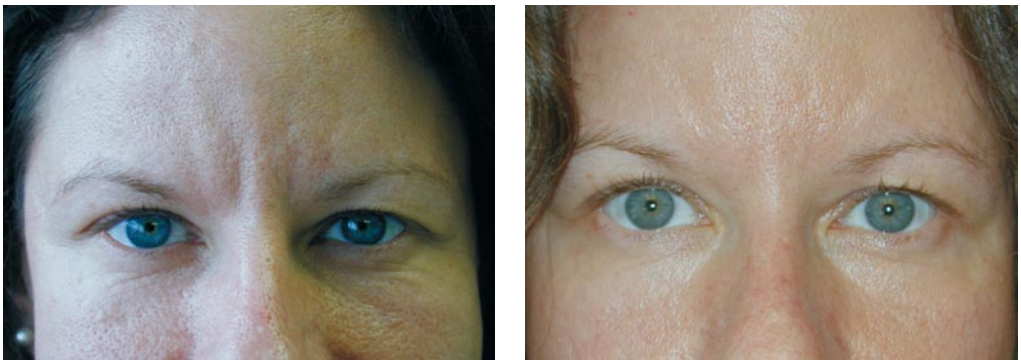

Fig. 17.6 Artecoll is the current trade name of the product that will soon be approved in the USA under the name Artefill. This product is composed of polymethylmethacrylate microspheres suspended in atelomeric bovine collagen. It is a permanent filling material

have appeared long after injection, though most respond to intralesional triamcinolone injections [29, 37].

A small number of visually devastating complications have occurred following periocular filler injections. These include central and branch retinal artery occlusion and posterior ciliary artery occlusion [35, 38–40]. These devastating complications are not well known in the non-ophthalmologic literature and deserve educational exposure.

17.5 Combination Therapy: Botulinum Toxin and Fillers

The combination of botulinum toxin type A (BTX-A; BOTOX, BOTOX Cosmetic; Allergan, Irvine, CA, USA) and soft tissue augmentation is a highly synergistic approach used routinely to achieve more effective, longer lasting results, especially in the mid- and lower face, by simultaneously treating static and dynamic aspects of rhytides (Fig. 17.7) [21]. Preceding the injection of filling agents by approximately 1 week, BTX-A may work on several levels, reducing the dynamic component of rhytide formation in newly remodeled skin and allowing more permanent eradication of wrinkles [9, 10, 20]. Studies have documented greater improvement in rhytides, clinical effects of longer duration, and higher patient satisfaction with combination therapy compared with single modality treatment [9, 10, 34].

Summary for the Clinician

- Fillers not only correct rhytides and folds, but can restore fullness naturally lost during the aging process and, in the hands of adept clinicians, can be used to sculpt and reshape almost all areas of the face.

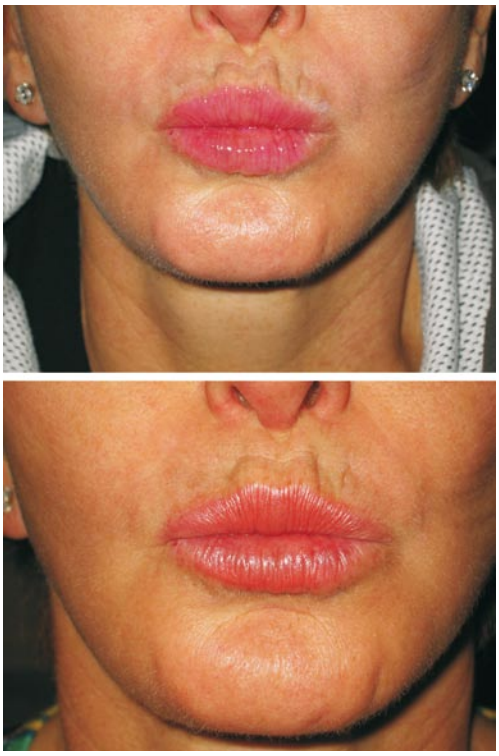

Fig. 17.7 Combined use of BTX-A and filler improves the aesthetic result and also allows the filler to last longer

References

1. Alcalay J, Alkalay R, Gat A, Yorav S (2003) Late-onset granulomatous reaction to Artecoll. Dermatol Surg 29:859–862
2. Amar RE (1999) [Adipocyte microinfiltration in the face or tissue restructuration with fat tissue graft]. Ann Chir Plast Esthet 44:593–608
3. Andre P (2004) Evaluation of the safety of a non-animal stabilized hyaluronic acid (NASHA – Q-Medical, Sweden) in European countries: A retrospective study from 1997 to 2001. J Eur Acad Dermatol Venereol 18:422–425
4. Bergeret-Galley C, Latouche X, Illouz Y-G (2001) The value of a new filler material in corrective and cosmetic surgery: DermaLive and DermaDeep. Aesthetic Plast Surg 25:249–255

5. Berman M (2000) Rejuvenation of the upper eyelid complex with autologous fat transplantation. Dermatol Surg 26:1113–1116
6. Brody HJ (2005) Use of hyaluronidase in the treatment of granulomatous hyaluronic acid reactions or unwanted hyaluronic acid misplacement. Dermatol Surg 31(8 Pt 1):893–897
7. Brown LH, Frank PJ (2003) What's new in fillers? J Drugs Dermatol 2:250–253
8. Butterwick KJ, Lack EA (2003) Facial volume restoration with the fat autograft muscle injection technique. Dermatol Surg 29:1019–1026
9. Carruthers J, Carruthers A (2003) A prospective, randomized, parallel group study analyzing the effect of BTX-A (Botox) and nonanimal sourced hyaluronic acid (NASHA, Restylane) in combination compared with NASHA (Restylane) alone in severe glabellar rhytides in adult female subjects: treatment of severe glabellar rhytides with a hyaluronic acid derivative compared with the derivative BTX-A. Dermatol Surg 29:802–809
10. Carruthers J, Carruthers A, Maberley D (2003) Deep resting glabellar rhytides respond to BTX-A and Hylan B. Dermatol Surg 29:539–544
11. Chajchir A, Benzaquen I (1989) Fat-grafting injections for soft tissue augmentation. Plast Reconstr Surg 84:921
12. Cheng JT, Perkins SW, Hamilton MM (2002) Collagen and injectable fillers. Otolaryngol Clin North Am 35:73–85
13. Coleman SR (1995) Long-term survival of fat transplants: controlled demonstrations. Aesthet Plast Surg 19:421
14. Coleman SR (1997) Facial recontouring with lipostructure. Clin Plast Surg 24:347–367
15. Comite SL, Liu JF, Balasubramanian S, Christian MA (2004) Treatment of HIV-associated facial lipoatrophy with Radiance FN (Radiesse). Dermatol Online J 10:2
16. Donofrio LM (2000) Fat distribution: a morphologic study of the aging face. Dermatol Surg 26:1107–1112
17. Donofrio LM (2000) Structural autologous lipoaugmentation: a pan-facial technique. Dermatol Surg 26:1129–1134
18. Donofrio LM (2002) Fat rebalancing: the new "facelift." Skin Ther Lett 7:7–9
19. Duranti F, Salti G, Bovani B, et al. (1998) Injectable hyaluronic acid gel for soft-tissue augmentation: a clinical and histological study. Dermatol Surg 24:1317–1325
20. Fagien S (2003) Botox for the treatment of dynamic and hyperkinetic facial lines and furrows: adjunctive use in facial aesthetic surgery. Plast Reconstr Surg 112:40S–52S
21. Fagien S, Brandt FS (2001) Primary and adjunctive use of botulinum toxin type A (Botox) in facial aesthetic surgery: beyond the glabella. Clin Plast Surg 28:127–148
22. Fernandez-Acenero MJ, Zamora E, Borbujo J (2003) Granulomatous foreign body reaction against hyaluronic acid: report of a case after lip augmentation. Dermatol Surg 29:1225–1226
23. Friedman PM, Mafong EA, Kauvar AN, Geronemus RG (2002) Safety data of injectable nonanimal stabilized hyaluronic acid gel for soft tissue augmentation. Dermatol Surg 28:491–494
24. Gladstone HB, Morganroth GS (2003) Evaluating calcium hydroxylapatite for facial augmentation. Presented at the Annual American Society for Dermatologic Surgery Meeting. New Orleans
25. Hirsch R, Cohen J, Carruthers JDA (2007) Successful management of an unusual presentation of impending necrosis following a hylauronic acid injection embolus and a proposed algorithm for management. Dermatol Surg 33(3):357–360
26 Honig JF, Brink U, Korabiowska M (2003) Severe granulomatous allergic tissue reaction after hyaluronic acid injection in the treatment of facial lines and its surgical correction. J Craniofac Surg 14:197–200
27. Jordan DR (2003) Soft-tissue fillers for wrinkles, folds and volume augmentation. Can J Ophthamol 38:285–288
28. Kanchwala SK, Bucky LP (2003) Facial fat grafting: the search for predictable results. Facial Plast Surg 19:137–144
29. Lemperle G, Gauthier-Hazan N, Lemperle M (1998) PMMA-microspheres (Artecoll) for long-lasting correction of wrinkles: refinements and statistical results. Aesthetic Plast Surg 22:356–365
30. Leonhardt JM, Lawrence N, Narins RS (2005) Angioedema acute hypersensitivity reaction to injectable hyaluronic acid. Dermatol Surg 31:577–579

31. Lowe NJ, Maxwell CA, Lowe P, Duick MG, Shah K (2001) Hyaluronic acid skin fillers: adverse reactions and skin testing. J Am Acad Dermatol 45:930–933
32. Moyle GJ, Lysakova L, Brown S, et al. (2004) A randomized open-label study of immediate versus delayed polylactic acid injections for the cosmetic management of facial lipoatrophy in persons with HIV infection. HIV Med 5:82–87
33. Narins RS, Brandt F, Leyden J, Lorenc ZP, Rubin M, Smith S (2003) A randomized, double-blind, multicenter comparison of the efficacy and tolerability of Restylane versus Zyplast for the correction of nasolabial folds. Dermatol Surg 29:588–595
34. Patel MP, Talmor M, Nolan WB (2004) Botox and collagen for glabellar furrows: advantages of combination therapy. Ann Plast Surg 52:442–447
35. Peter S, Mennel S (2006) Clinicopathological report: retinal branch artery occlusion following injection of hyaluronic acid (Restylane). Clin Exp Ophthalmol 34:363–364
36. Pollack S (1999) Some new injectable dermal filler materials: Hylaform, Restylane, and Artecoll. J Cutan Med Surg 3 [Suppl 4]:S27–S35
37. Saylan Z (2003) Facial fillers and their complications. Aesthetic Surg J 23:221–224
38. Schanz W, Schippert W, Ulmer A, et al. (2002) Arterial embolization caused by injection of hyaluronic acid (Restylane). Br J Dermatol 146:928–929
39. Shin H, Lemke BN, Stevens TS, Lim MJ (1988) Posterior ciliary-artery occlusion after subcutaneous silicone-oil injection. Ann Ophthalmol 20(9):342–344
40. Silval MT, Curill AI (2004) Blindness and total ophthalmoplegia after aesthetic polymethylmethacrylate injection: case report. Arq Neuropsiiquitr 62(3-B):873–874
41. Sklar JA, White SM (2004) Radiance FN: a new soft tissue filler. Dermatol Surg 30:764–768
42. Toy BR, Frank PJ (2003) Outbreak of Mycobacterium abscessus infection after soft tissue augmentation. Dermatol Surg 29:971–973
43. Treacy PJ, Goldberg DJ (2006) Use of a biopolymer polyalkylimide filler for facial lipodystrophy in HIV-positive patients undergoing treatment with antiretroviral drugs. Dermatol Surg 32:804–808
44. Tzikas TL (2004) Evaluation of the Radiance FN soft tissue filler for facial soft tissue augmentation. Arch Facial Plast Surg 6:234–239

Chapter 18

Overview of Skin Resurfacing Modalities

18

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Core Messages

- Skin rejuvenation is increasing in popularity among patients.
- By improving the appearance of the skin, all surgical results can be enhanced.
- Proper patient assessment is critical in selecting the correct treatment modality.
- Instituting a good pre- and post-procedure skin care regimen minimizes complications, enhances results, and helps maintain the results of any procedure.
- Early recognition and treatment of complications are critical.

18.1 Introduction

The skin takes center stage in the fight against aging. While the number of cosmetic surgery procedures continues to increase, the vast majority of this increase consists of minimally invasive procedures. Furthermore, patients are beginning to understand the importance of addressing the skin as part of their total facial rejuvenation plan. Surgical procedures only tighten or lift the skin, thus failing to address any photodamage or other flaws that may be present. To optimize surgical outcomes or to improve upon nonsurgical options, the skin must be addressed as an important component of the treatment plan.

Since patients are living longer, healthier lives, they are looking for ways to reflect on the surface the youthfulness they feel on the inside. Additionally, an increasing proportion of the cosmetic surgery patient population is male. Either they are interested in looking their best or they may be starting a new job and need that "extra boost" to feel competitive. It is beneficial to the patient psychologically, in that looking better often allows one to feel better and more confident in their career and social interactions.

However, this places a burden on the physician to ensure that patients' goals are realistic and that they understand that improvements in appearance do not necessarily result in improvements in their marriages, careers, or other goals that depend on factors other than appearance alone. Nevertheless, we live in a world in which looks do matter and appearance affects how one is perceived, which can affect all spheres of one's life: personal, social, and professional.

While there have been many technologic advances in the laser field, skin resurfacing remains an art requiring assessment of each patient's skin type, color, and depth of pathology. Each patient requires the formulation of an individualized treatment regimen that includes a combination of topical agents, lasers, peels, light sources, radiofrequency devices, and dermabrasion.

18.2 Indications

As the largest organ of the body and as a barrier to environmental insult, the skin undergoes many changes in response to daily insults. Various environmental (e.g., photodamage), systemic (e.g., hormonal), and inflammatory (e.g., acne) factors lead to changes in the skin that cause the patient to seek resurfacing. The indications for skin resurfacing include static rhytides, acne, and chicken-pox scars, photodamage, melasma/hyperpigmentation, and xanthelasma.

18.3 Pathophysiology of Aging

Wrinkling, freckling, and precancerous changes are the cutaneous correlates of epidermal atrophy, keratinocyte atypia, and most importantly, dermal atrophy, which results from decreased collagen formation and varying degrees of solar elastosis. These changes are typically associated with aging skin [7]. However, most of these changes are a manifestation of "extrinsic" aging [11]. Extrinsic aging causes changes in the skin due to the cumulative effects of senescence and environmental damage (ultraviolet rays, pollution, and tobacco smoke). Intrinsic aging, on the other hand, is simply the senescence changes that occur in the skin in the absence of environmental insult.

Although this chapter addresses skin resurfacing, the principles of skin conditioning and skin classification are applicable to all resurfacing procedures (peels, laser skin resurfacing, and dermabrasion). For a detailed explanation of skin anatomy, intrinsic and extrinsic aging, and the mechanisms of actions of products commonly used in preoperative and postoperative skin conditioning regimens, we refer the reader to the senior author's (SO) article *Lifetime Skin Care* [30].

18.4 Patient Assessment

The most important aspect for patient satisfaction with resurfacing procedures is proper patient assessment. Most of the dissatisfaction expressed by patients stems from the wrong modality being used to address their particular concern. Another source of dissatisfaction for patients was the failure of the physician to prescribe a topical regimen for patients to follow at home to help maintain the results of their in-office procedures. Therefore, part of the patient assessment is the correct patient classification.

While there are several methods of skin classification scales, such as the Fitzpatrick Phototype Classification and Glogau's Wrinkle Scale, they both fall short in helping to select which treatment modality is best for the patients. To address this shortcoming, the Obagi classification (Table. 18.1) was formulated to aid in the physical examination and in selecting the appropriate treatment modality or combination of modalities, based on the individual skin type and extent and depth of pathology being addressed [27].

The Obagi system takes into account skin color, thickness, oiliness, laxity, and fragility, and helps to guide the appropriate treatment modality, depth, and pre- and postoperative care, including anticipation and prophylaxis of pigmentary abnormalities. For example, patients with thicker skin do well with laser resurfacing or dermabrasion, but may require stronger peels than patients with thinner skin. On the other hand, patients with thinner skin do not tolerate the more aggressive resurfacing procedures, but do well by undergoing repeated papillary dermis level procedures to help tighten their skin.

Summary for the Clinician

- Assessment of the patient's skin color, thickness, oiliness, fragility, and laxity is necessary to select the correct resurfacing procedure.

18.5 History and Physical

Patients seek to enhance their appearance for numerous reasons, some of which may not be immediately apparent to the physician. It is important to perform an adequate history and physical examination of patients to help ascertain the patient's goals and expectations. Patients need to be educated about what each treatment can offer with regard to results, what the pre- and postoperative skin conditioning regimen is, the necessary time and monetary investment, and the duration of postoperative discomfort, erythema, and "downtime." While a lot of the current procedures tout the claim of "no downtime" or "no pain," oftentimes, the reality is quite different. It is best to prepare your patient for the realistic duration of recovery time. It is also important to assess the patient's pain threshold and have provisions in place to administer topical anesthetics, oral analgesia, and if needed, intravenous anesthesia.

Table 18.1 Obagi skin classification: modified from [27]. *PIH* post-inflammatory hyperpigmentation

Skin variable	Pre- and postoperative conditioning	Suitable procedures and potential complications	Postoperative management
Color	Darker complexion Caucasian patients Lighter complexion black, Indian, or Asian patients Require: *Aggressive* conditioning before and after a procedure to minimize PIH* Lighter Caucasian or darker black, Indian, Asian patients Melanocytes are more stable	Darker skin: Hypopigmentation: Superficial procedure: rare Medium-depth procedures: possible Deep procedures: more likely Hyperpigmentation: Common	Darker skin: Aggressive conditioning to minimize PIH
Oiliness	Interferes with effectiveness of preconditioning	Topical treatment needed to control and reduce surface oiliness prior to surgery	Interferes with postoperative conditioning effectiveness. Topical treatment should be used to reduce surface oiliness
Thickness	Thin skin needs more stimulation of collagen synthesis Thick skin needs correction of skin function and stimulation of collagen synthesis	Thin skin: lighter procedures such as blue peel or erbium:YAG resurfacing Medium-thick skin: good for peels, dermabrasion, CO_2 laser Thick skin: best for chemical peels and dermabrasion	Correction and stimulation as needed
Laxity	Long-term stimulation to prevent further laxity	Skin laxity: Medium depth peel or several blue peels are ideal Muscle laxity: Face-lift alone or in combination with a Blue Peel to correct any associated skin laxity	Correction and stimulation as needed
Fragility	Aggressive stimulation to strengthen the skin	Correlates with post-surgical scarring. In fragile skin, procedure depth should be limited to the papillary dermis	More cycles of correction and stimulation as tolerated

Additionally, whether due to media hype or an overly eager patient, many patients believe that skin resurfacing will "cure" all their problems. It is very important that the physician present the procedure in a manner that does not foster unrealistic expectations. We have all seen patients seeking treatment of barely perceptible defects. These patients are likely to be unhappy with their postoperative results, even when the physician considers the outcome to be a success. And on the off chance that these patients develop a complication postoperatively, they will be the most difficult patients to manage.

The history and physical examination should include a thorough medical and social history. The medical history should cover medications, recent surgery, nicotine use, radiation treatment to the face and neck, and the presence of inflammatory skin diseases. One must inquire about the patient's predilection for developing post-inflammatory hyperpigmentation, hypertrophic or keloid scars, or poor wound healing. Furthermore, certain dermatologic conditions such as vitiligo, psoriasis, lichen planus, and verrucae vulgaris and plana can spread to traumatized skin (Koebner phenomenon). Therefore, a skin examination should be performed to exclude the presence of these disorders. Patients undergoing resurfacing with laser or dermabrasion pose exposure risks to the staff and physician. In these circumstances, screening for hepatitis B and C, as well as human immunodeficiency virus (HIV), is recommended.

When inquiring about medications, it is important to ask about isotretinoin (Accutane™, Roche Laboratories, Nutley, NJ, USA) use and when it was last taken. Since there have a been a couple of isolated case reports of hypertrophic scarring related to Accutane use in the perioperative period, it is recommended that Accutane be discontinued at least 6 months before laser resurfacing and dermabrasion and should not be restarted until 3 months postoperatively [2, 36, 41]. However, from a large case series of patients undergoing "medium-depth" chemical peeling while using Accutane in the perioperative period, there did not appear to be an increased risk compared with control patients [32]. To minimize the postoperative flare of inflammatory conditions such as acne or rosacea, it may be necessary to use systemic anti-inflammatory antibiotics such as tetracycline, minocycline, and doxycycline as a safer alternative to isotretinoin.

Resurfaced skin requires intact and functioning pilosebaceous units to re-epithelialize correctly. Otherwise, impaired wound healing may occur postoperatively. Therefore, it is important to inquire about radiation or phototherapy, which destroys or reduces the number of pilosebaceous units in the skin.

It is critical to assess the depth of lesions being treated so that the appropriate treatment modality is chosen. Epidermal lesions such as lentigines, actinic keratosis, and epidermal melasma respond well to minimally invasive procedures such as light peels, microdermabrasion, and a good topical skin care regimen. Dermal defects such as scars, rhytides, and dermal melasma, require a modality that reaches the dermis in order to yield a clinical response.

Pre- and postoperative photographs are an absolute must. Patients never scrutinize their face more thoroughly than they do postoperatively. They may be bothered by things that they notice for the first time during the postoperative period and may not realize that the defect was present prior to surgery. In such instances, photographs serve as an important form of documentation. Therefore, it is recommended that all patients have preoperative photographs taken with no make-up on and in a standardized manner (same lighting, settings, and views).

Summary for the Clinician

- Patient's medical history should include past surgery, tobacco use, medications, psychiatric history, and HIV, hepatitis B, and C when indicated
- Preoperative photographs are imperative

18.6 Principles of Resurfacing

Resurfacing remodels the epidermis, dermis, or both such that postoperatively, it has an appearance closer to that of younger skin. This is accomplished by controlled skin injury that is either clinically apparent (traditional resurfac-

ing) or microscopically present (non-ablative resurfacing). To prevent scarring and hypopigmentation, it is critical that the depth of ablation does not extend below the mid-reticular dermis, yet it must be deep enough to address the clinical problem.

After skin injury, granulation tissue forms at day 30 and new collagen is formed at day 100, which is vital to obtaining enduring treatment efficacy [33]. With lasers, the longer the wavelength of energy emitted, the deeper the depth of action. Wavelengths of 1,200–1,800 nm reach the upper to mid-dermis and this level appears to be the minimum required to effect collagen remodeling [8]. The same principle applies to peels and dermabrasion. The depth of wounding must approach the papillary dermis to give "tightening," while the upper reticular dermis level wound results in "leveling."

However, injury to the mid to lower reticular dermis is fraught with risk. A wound at this level has a high likelihood of scarring, permanent hypopigmentation, and textural changes. Therefore, it is more prudent to perform a series of less aggressive resurfacing procedures than risk these complications.

Any resurfacing procedure that results in a visible wound to the skin will require appropriate pre- and post-resurfacing skin conditioning, appropriate monitoring during the healing process, and anti-herpes simplex virus (HSV) prophylaxis when treating the perioral area [29].

18.6.1 Pre-resurfacing Skin Care

The goals of a pre-conditioning regimen are repair of environmental damage and enhanced wound healing during the postoperative period by boosting cellular function. Tretinoin (0.05–0.1%) cream promotes collagen synthesis, enhances hydroquinone penetration, restores normal epidermal thickness and maturation, and improves solar elastosis [39]. Furthermore, studies show faster wound healing from skin resurfacing in patients pre-treated with tretinoin [16] as well as in an animal model [21]. Patients are instructed to apply 0.5–1 g of tretinoin to the entire face nightly.

Hydroquinone (4%) cream evens out dyspigmentation and reduces the risk of post-inflammatory hyperpigmentation in patients prone to this. This effect is mediated by inhibition of tyrosinase, which is a key enzyme in the melanin synthesis pathway. Since the half-life of hydroquinone is 12 h, it requires twice daily application. Patients are instructed to apply 1 g twice daily to the entire face and a bit extra to the areas of pigmentation problems.

A topical alpha-hydroxy acid (6–8%) can be applied in the mornings to help minimize acne flares and to further enhance the penetration of the hydroquinone or tretinoin. Alpha-hydroxy can deactivate tretinoin; therefore, it is not applied in the evenings. It is more critical to use an alpha-hydroxy acid cream in patients with thicker skin as they tend to have oilier skin, which prevents the penetration of tretinoin or hydroquinone. There are different commercially available alpha-hydroxy acids, but lactic acid and glycolic acid are the most commonly found.

Sunblocks are essential for the prevention of further sun damage and dyschromias. Both ultraviolet A (UVA) and ultraviolet B (UVB) rays are harmful. UVA levels are constant all year round and have the ability to penetrate through windows, windshields, and shallow water. UVA is now implicated in the formation of skin cancer and in overall aging of the skin. UVB levels peak in summertime and are responsible for the burns that occur with extended sun exposure. Typically, the best tolerated agents are those that contain zinc oxide or titanium dioxide rather than a chemical sunscreen. The sunblock takes the place of a daily moisturizer and is applied on the skin after the application of the other creams but before the application of any make-up.

Proper skin conditioning should be started at least 6 weeks (longer for darker skinned individuals) prior to resurfacing and resumed immediately after skin has re-epithelialized. Typically, the patient will use this regimen up until the night before his or her procedure.

All patients receive HSV prophylaxis to prevent reactivation and potential scarring, regardless of their personal history of previous viral infection. The newer antiviral agents such as valacyclovir have better absorption than acyclovir. For this reason, the former is the drug of choice. The usual dose is 500 mg of valacyclovir twice a day starting the day before surgery and continues until the skin has fully healed (7 days for peels,

15 days for laser or dermabrasion). If a patient has a significant history of HSV, a dose of valacyclovir (1 g) twice a day is used. This dose can be increased to 1 g three times a day if needed to control an outbreak.

Since the medical literature does not justify the use of antimicrobial or antifungal prophylaxis, it is not advocated. However, if an occlusive dressing is to be kept in place for over 48 h, prophylaxis may be warranted.

Summary for the Clinician

- Preoperative skin conditioning reduces postoperative complications and enhances the results of skin resurfacing procedures
- Every patient benefits from preconditioning of the skin

18.6.2 Post-resurfacing Skin Care

Laser resurfacing and dermabrasion patients are treated with either an open method of wound care [1] or an occlusive bandage. There are a number of occlusive bandages that can be used [26]. Usually, the selection is made based on patient acceptance of the bandage, cost of the materials, and ease of application. While use of preprocedural tretinoin and occlusive dressings can shorten healing time, some surgeons opt for an open technique using petrolatum-based agents. While an open technique reduces the risk of infection, the discomfort, especially in the first 1–2 days is greater for patients. The authors recommend a compromise, in which an occlusive dressing is used for 2 days, after which an open technique is used. Upon removal of the bandage, patients should wash their face gently to remove the adherent crust every 4 h while awake and perform Domeboro Astringent Solution (Bayer, Morristown, NJ, USA) compresses for 5–10 min. Patients then apply Aquaphor Healing Ointment (Beirsdorf, Wilton, CT, USA) to the skin after each compress or wash.

If an occlusive dressing is used for more than 48 h, it is recommended that prophylactic first generation cephalosporin and fluconazole (200 mg qd for 4 days) be given, starting the day of procedure [29]. Inflammation and erythema usually subside over 6 weeks; however, this can take up to 6 months. It is critical to resume the postoperative skin care regimen once re-epithelialization is completed.

Summary for the Clinician

- Postoperative skin care should be resumed once re-epithelialization is complete

18.6.2.1 Chemical Peels

While peels have been used in a variety of forms for centuries, excitement about peels began to wane with the advent of lasers for resurfacing the skin. Physicians abandoned what was perceived as the inability to control depth of penetration of trichloroacetic acid (TCA) peels for the comfort of being able to set the laser parameters for reproducible treatment results. However, as patient satisfaction with laser resurfacing began to wane and complications from lasers became more widespread [12, 19], many physicians and patients shared a renewed interest in chemical peeling. Advances in peeling techniques have helped rekindle this interest.

18.6.2.1.1 Mechanisms of Actions

There are many factors affect peel depth: acid concentration, the number of coats applied, skin thickness, percentage body surface area, skin preconditioning, and in some cases, the duration of contact of the acid on the skin. Thus, it is unfeasible to classify acids as those that cause a light peel and those that cause a deep peel. Instead, chemical wounding agents will be described with regard to their most common use as either keratolytic agents or protein denaturants. The keratolytics are mainly used for superficial, exfoliative procedures whereas the protein denaturants can be used for superficial or deeper peels. The cor-

rect choice of acid is determined by the depth of wounding desired, in addition to the degree of physician control desired.

Keratolytics

Keratinocytes are the cells that make up the epidermis of the skin. They are held together by adhesion molecules that can be disrupted by alpha-hydroxy acids (glycolic, lactic, citric, malic, tartaric) and salicylic acid. The two main acids used for exfoliative procedures are glycolic and salicylic acid. The main indications for these peels are agents for roughness, acne, mild dyspigmentation, and fine wrinkles. These exfoliative acids have the benefit of no "downtime" for the patient, no anesthesia requirement, and are easy to apply. Furthermore, many of these peels can be performed by aestheticians or nurses. However, proper training is crucial to minimize inadvertently peeling the skin deeper than the epidermis.

These peels are usually performed as a series of three or four peels spaced several weeks apart in order for clinical results to become apparent. The results of these peels can be enhanced considerably with the use of an appropriate pre- and post-peel skin-care regimen.

One in vitro study showed that the topical application of glycolic acid increases collagen production by fibroblasts [24]. However, it is unclear what clinical relevance this may have. Thus, it is imperative to carefully select the patient who would benefit most from these procedures, e.g., acne patients, those with freckling, those with superficial sun damage.

Protein Denaturants

Trichloroacetic Acid Peels

Trichloroacetic acid (TCA) is the workhorse of chemical peels having been in use for over a century. It acts by causing protein coagulation and denaturation of the cellular components of the skin. The benefit of using TCA is that it can be used to achieve a variety of peel depths ranging from exfoliation to deep peels, depending on the concentration or volume used. To minimize operator error and patient complications, it is important to limit the number of different TCA solutions carried in the office. Furthermore, there are four different ways in which TCA can be manufactured. However, the only accurate one is the standard pharmaceutical method of calculating concentration based on weight to volume (W:V) [3].

Initially, it may seem confusing to see the literature or speakers at meetings refer to TCA peels as light or deep according to the TCA concentration that is used. TCA concentration is only one component that determines peel depth. TCA (40%) can be used to perform a light peel or a deep peel simply by varying the volume used (1 ml vs. 6 ml). Thus, higher volumes or higher TCA concentrations will drive the peel even deeper. The body surface area being treated and the patient's skin thickness are other variables.

Just as lasers offer the physician a certain level of control and safety, TCA peels have evolved in this direction as well. There have been a number of modified TCA peel combinations that were developed in an attempt to obtain more consistent results, while giving the physician more control over the peel. The most common variations are the Monheit Jessner TCA peel, the Coleman Glycolic Acid TCA peel, and the Obagi Blue Peel.

These peels are designed to allow fairly consistent peeling into the papillary dermis and into the superficial reticular dermis if performed correctly. Thus, their main indications are for epidermal and upper dermal pathology such as photodamage, actinic keratoses, lentigines, ephelides, fine rhytides, and superficial, nonfibrotic (stretchable) scars. Deeper cutaneous abnormalities such as expression lines, furrows, or scars are somewhat amenable to correction with these peels. However, the risk of subsequent textural change or scarring increases with deeper peels.

The Monheit Jessner TCA peel utilizes Jessner's solution, prior to the application of TCA. Jessner's solution is a combination of keratolytic agents consisting of 14% each of resorcinol, salicylic acid, and lactic acid mixed in ethanol. This is then followed by the application of a small quantity of 35% TCA. By applying the keratolytic agent prior to the TCA application, faster and deeper penetration of the subsequent TCA can

be achieved [23]. The Coleman glycolic acid TCA peel uses 70% glycolic acid (keratolytic) prior to the application of 35% TCA [6].

In contrast to these two techniques, which attempt to increase the speed and depth of penetration of TCA into the skin, the Obagi Blue Peel attempts to slow this process down [31]. By doing so, the physician gains more depth control during the peeling process. The Obagi Blue TCA Peel combines a non-ionic blue dye, glycerin, and a saponin with a specified volume of 30% TCA to yield either a 15% or 20% TCA blue peel solution. Since TCA is colorless, the blue dye helps to ensure even application of the peeling solution. This minimizes the risk of inadvertent reapplication of the solution into a previously treated area. The skin is hydrophobic while the TCA is hydrophillic. In order to achieve even penetration of the TCA into the skin, glycerin is added, but requires a detergent to prevent the TCA and glycerin from separating out in the solution. Therefore, a saponin is added as well. Saponins have detergent-like properties that help to create a homogenous TCA/oil/water emulsion that penetrates the skin in a slower and more even fashion.

Phenol Peels

For the most part, phenol peels fall into the category of deep peels. In a fashion similar to TCA, phenol exerts its actions by protein denaturation and coagulation; however, it quickly penetrates the skin to the level of the reticular dermis [4]. Phenol requires hepatic metabolism followed by renal excretion. To minimize the risk of intraoperative systemic toxicity patients should be cleared from a cardiac, renal, and hepatic standpoint preoperatively. Since systemic absorption of phenol can directly cause cardiac arrhythmias, it is imperative to have patients on a cardiac monitor.

It appears that percutaneous absorption of phenol is more related to the body surface area treated than the concentration used [4]. For this reason, the face is usually divided into cosmetic units and the peel is performed on one unit at a time. A 15-min break is taken prior to the treatment of the next cosmetic unit. Weaker solutions of phenol (25–50%) can be used to achieve a lighter peel. However, the results are not better than TCA peels, while still carrying the risk of systemic toxicity. Laser resurfacing with CO_2 and erbium:YAG has largely replaced phenol in the treatment of deeper rhytides.

Although any resurfacing modality that reaches the reticular dermis is at risk for causing permanent hypopigmentation, it has been reported that this may be more frequent with phenol peels than with lasers [6]. This makes careful patient selection very important. It may be best to reserve phenol peels for treating deep rhytides in older, fair-skinned individuals because of the risk of permanent postoperative hypopigmentation.

In an attempt to minimize the complication of permanent hypopigmentation, various physicians have modified the formulation of phenol and croton oil to make the phenol peel penetrate less than the typical Baker-Gordon formulation [15, 38]. Furthermore, variations with regard to how the peel is performed have allowed patients of diverse skin types to be treated, with good results [37].

18.6.2.1.2 Lasers

While non-ablative therapies have become a popular trend among patients and physicians alike, the pendulum may be swinging back toward more time-tested techniques. Ablative laser resurfacing remains the gold standard with which these non-ablative systems are compared. Two laser systems have been developed for skin resurfacing: carbon dioxide (CO_2) and erbium:YAG (Er:YAG).

The term *laser* is an acronym for *l*ight *a*mplification by the *s*timulated *e*mission of *r*adiation. What makes lasers different from traditional light sources is that lasers emit predominantly a single wavelength of light, which is preferentially absorbed by a specific chromophore in the skin (Table. 18.2). On the other hand, light-based systems such as intense-pulsed light (IPL) emit a variety of wavelengths from 400 to 1,200 nm, but are controlled using various cut-off filters.

The lexicon of important technological terms includes thermal relaxation time, pulse duration

Table 18.2 Most commonly used lasers and light systems. Both the wavelength and clinical indications are given. With permission from [28]

System	Wavelength (nm)	Pulse duration	Indications
IPL (pulsed light)	400–1,200	5–100 ms	Non-ablative rejuvenation Hair removal Lentigines Vascular lesions
LED	410	N/A	Non-ablative rejuvenation
Copper bromide	511 and 578	10–900 ms	Non-ablative rejuvenation Vascular lesions Pigmented lesions
KTP	532		Pigmented lesions Vascular lesions
Diode	532	0–100 ms	Vascular lesions
Q-switched Nd:YAG (frequency doubled)	532	<20 ns	Non-ablative rejuvenation Pigmented lesions Tattoos: red, orange, yellow
Pulsed dye	585	0.45 ms	Non-ablative rejuvenation Vascular lesions
	595	0.45–40 ms	Non-ablative rejuvenation Vascular lesions
	585–595	0.5–40 ms	Non-ablative rejuvenation Vascular lesions
Q-switched Ruby	694	20–50 ns	Pigmented lesions Tattoos: blue, black, green
Q-switched Alexandrite	755	50–100 ns	Pigmented lesions Tattoos: blue, black, green
Alexandrite	755	5–50 ms	Non-ablative rejuvenation Hair removal
Diode	800–810	5–400 ms	Hair removal
Q-switched Nd:YAG	1,064	<20 ns	Non-ablative rejuvenation Pigmented lesions Tattoos: blue, black
Nd:YAG	1,064	0.4–300 ms	Non-ablative rejuvenation Hair removal Vascular lesions
	1,320	400 ms	Non-ablative rejuvenation
Diode	1,450	250 ms	Non-ablative rejuvenation
Erbium:glass	1,540	3.3 ms	Non-ablative rejuvenation
Radiofrequency	N/A	N/A	Non-ablative rejuvenation
Erbium: YAG	2,940		Skin resurfacing

Table 18.2 *(continued)* Most commonly used lasers and light systems. Both the wavelength and clinical indications are given. With permission from [28]

System	Wavelength (nm)	Pulse duration	Indications
CO_2	10,600		Skin resurfacing
Blended erbium: YAG and CO_2	2,940 10,600		Skin resurfacing

(pulse width), and selective photothermolysis. The laser emits a specific wavelength of light that is absorbed by a chromophore or target in the skin. The chromophore may be water, melanin, or hemoglobin. Different wavelengths are specific for different chromophores. Once the wavelength of light is absorbed by a chromophore, it heats that object. The thermal relaxation time is the time it takes for the heated object to cool to half its elevated temperature. Thermal relaxation time is closely related to the square of the size of the object. Thus, smaller objects cool faster than larger ones. Pulse duration is the unit of time during which a certain amount of laser energy is emitted. If the pulse duration is shorter than the thermal relaxation time of an object, selective photothermolysis occurs. This means that the chromophore heats up preferentially without heating the surrounding tissue. However, if the pulse duration exceeds the thermal relaxation time of the chromophore, the adjacent tissue heats up, resulting in thermal damage. Therefore, to target a particular chromophore effectively without damaging the surrounding skin, one must select a laser with the appropriate wavelength and pulse duration.

As the laser wavelengths increase, the depth to which they penetrate tissue increases as well. The two exceptions are the skin resurfacing lasers, carbon dioxide (CO_2) and erbium:YAG (Er:YAG). Both the Er:YAG and CO_2 lasers, 2,940 nm and 10,600 nm respectively, have tremendous affinity for water. This high affinity for the water in the skin results in literal vaporization of the tissue that serves to limit the depth of penetration of the laser beam. Therefore, although these two lasers have longer wavelengths, their depth of penetration is less than would be expected.

Laser resurfacing wounds consist of four zones of injury:

- Zone of ablated tissue
- Zone of charred or carbonized tissue (more so with CO_2)
- Zone of heat-denatured collagen
- Zone of collagen shrinkage

The thickness of the various zones of injury can be as small as a few micrometers to as large as over 150 μm depending on the laser system, settings used, and number of passes. Wound healing occurs from the lateral edges of non-injured skin in toward the center and from deep to superficial with regard to the remaining adnexal structures (mainly pilosebaceous glands).

18.6.2.1.3 Carbon Dioxide Lasers

Considered the gold standard in efficacy with which other modalities are compared, CO_2 lasers require a longer time before re-epithelialization and resolution of erythema (4.5 months for CO_2 laser vs. 4–6 weeks for TCA peel) [9]. Even compared with other lasers such as Er:YAG and the plethora of non-ablative laser, optical, radiofrequency, and combination devices, the CO_2 laser is the benchmark in clinical efficacy. CO_2 lasers have shown tremendous improvement in photodamaged and scarred skin.

Carbon dioxide lasers vaporize the epidermis and certain amounts of the dermis, removing superficial imperfections, as well as producing dermal heating, which shrinks collagen, thus tightening the skin. Laser energy is absorbed by water in the skin. This requires an ablation depth of 20–50 μm per pass [5]. There are pulsed and scanning CO_2 lasers, both of which emit 10,600 nm [5]. The pulsed laser vaporizes a 20–30-μm thickness and the scanning laser a 30–50-μm depth after a single pass [5].

18.6.2.1.4 CO_2 Laser Endpoints

Removal of the epidermis will reveal pink skin due to removal of the pigmented layer of the skin and the exposure of the subpapillary dermal vascular plexus. Penetration through the papillary dermis will cause heat damage and constriction of the subpapillary complex of blood vessels. The skin at this point takes on a gray color. Further resurfacing will then enter the reticular dermis and the skin begins to take on a "chamois" color. This is the endpoint for facial skin resurfacing with the exception of eyelid resurfacing, which should stop prior to reaching this depth.

18.6.2.1.5 Erbium:YAG lasers

As with all things in life, outcome alone is not adequate; patients must be accepting of the risks of discomfort and infection with the wound created in ablative modalities as well as the time investment in postoperative care and the longer recovery time. Patients were unhappy with the prolonged erythema, permanent hypopigmentation, and the risk of scarring with the traditional CO_2 laser. For this reason, Er:YAG lasers were investigated and found to give improvement in photodamaged [5] and scarred skin, albeit not to the extent seen with CO_2 lasers. Er:YAG lasers have a 16-fold higher affinity for water compared with CO_2 lasers, thus penetrating only 20–40 μm per pass. This results in more vaporization of tissue, but much less heating of adjacent skin [14]. Since it produces little to no dermal thermal damage, it does not tighten skin as much as CO_2 lasers. However, when used correctly, the Er:YAG laser can give impressive results [17].

To address this issue and to attempt to further approach the results of CO_2 lasers, modified Er:YAG systems have been developed. One of the newer Er:YAG lasers allows the use of longer pulse widths (up to 500 μs) to produce a larger zone of thermal necrosis, which comes closer to mimicking that seen with CO_2 lasers. This results in deeper tissue penetration and improved coagulation of dermal vessels.

Yet another Er:YAG laser system is a "blend" of both CO_2 and Er:YAG. It can deliver a pulse of energy made up of both Er:YAG and CO_2. The percentage of how much of each laser pulse is made up of CO_2 can be adjusted from 0 to 100%. This system also offers more coagulation and tissue tightening than traditional Er:YAG systems.

18.6.2.1.6 Erbium:YAG Laser Endpoints

The endpoints for erbium:YAG laser resurfacing are similar to those for CO_2 laser resurfacing. In addition, with erbium:YAG laser resurfacing, the depth of tissue ablation can be calculated by using the equation described earlier and by multiplying this number by the number of passes made. It is slightly more difficult clinically to visualize the microanatomy due to the bleeding that occurs when the reticular dermis is reached. When the reticular dermis is entered, the tops of sebaceous lobules (seen as small dots) will begin to be visualized. Penetration deeper into the reticular dermis will result in fewer bleeding points, but with brisker bleeding due to the larger size of the dermal vessels. Large, confluent sebaceous lobules also begin to be visualized.

18.6.3 Fractional Photothermolysis

While the gold standard in skin resurfacing is still ablative therapy of scars and rhytides, the attraction for patients remains the ability to resume their normal activities without interruption. The newest technology on the market is fractional photothermolysis (FP), a cross between non-ablative and ablative laser technology [20]. These laser systems use an ablative laser pulse that only hits a fraction of the skin at each pulse. This allows many "skip" areas in between the microthermal zones (MTZs) to quickly re-epithelialize the wounded skin. Thus, rather than 8–10 days of healing after a resurfacing procedure, the patient heals within 1–3 days. Since only 20–25% of the skin is resurfaced at each treatment, 4–5 treatments are performed to try to achieve full face resurfacing.

The practical advantage of fractional thermolysis technology is that the size, depth, and density of the MTZ energy delivered can be tailored to the exact 3-D burn parameters desired [18] to achieve better efficacy than the non-ablative devices and fewer side effects than with the ablative

laser. Similar to non-ablative devices, the stratum corneum remains intact with FP and is thus a natural bandage. MTZs allow delivery of high local irradiance to achieve efficacy while maintaining low overall irradiance to prevent side effects [18].

Wound healing following FP has been documented by serial histologic evaluation [18]. Micro-re-epithelialization in the MTZ areas appears to occur within 1 day by adjacent keratinocyte migration. This process occurs with almost no disruption in epithelial barrier function or inflammation, i.e., no crusting or weeping. Edema resolves by 1–2 days and erythema by 5–7 days. There is minimal to moderate pain during the procedure, which may be reduced with the use of topical anesthetics or nerve blocks. Patients may use make-up immediately to mask the erythema since the stratum corneum is intact.

There does seem to be improvement in epidermal pathology such as lentigines and dermal remodeling is detectable by 3 months, which may tighten the skin. The device can be used on darker skinned individuals, does not require anesthesia, and is safe for periorbital skin. Fractional photothermolysis is being evaluated for treating acne, scars, melasma, wrinkles, and other photodamage, on all areas of the body [10].

18.6.4 Dermabrasion

Dermabrasion is a surgical abrasion or planing of the skin with either a wire brush or diamond fraise attached to a hand engine capable of producing 1,000 to 60,000 rpm. The fraises are available in a multitude of sizes, shapes, and grades of coarseness. Dermabrasion is capable of "leveling" the skin, thus addressing problems such as traumatic or surgical scars (especially if performed 6–8 weeks postoperatively [40]), rhinophyma, superficial and saucer-shaped scars, rhytides, and superficial malignancies (Bowen's disease, superficial basal cell carcinoma).

While regional or localized dermabrasion may be performed with local anesthesia, more extensive resurfacing usually requires oral, intramuscular, or intravenous sedation in conjunction with nerve blocks, cryoanesthesia, or tumescent anesthesia. Furthermore, using tumescent anesthesia or cryoanesthesia offers a more solid surface upon which planing can be performed. This helps to decrease gouging or grabbing of the skin. Although a rigid surface will allow for more even abrasion and preservation of anatomic markings, the risk of tissue necrosis and scarring increases with use of refrigerants that lower skin temperature below -30°C [13].

The choice of the hand piece is determined by the depth of wounding desired, coupled with the level of expertise. The wire brush is capable of removing greater amounts of tissue with less generation of heat. This allows the physician to reach the mid-reticular dermis with less risk of scarring. However, the speed of the wire brush and the rapid depth achieved carries a higher risk of injury and requires more physician skill to master. Because wire brushes cannot be perfectly balanced, they should not be operated at speeds faster than 18,000 rpm. Moreover, because of their greater tendency to "grab the tissue and run," they are far safer when used with cryoanesthesia to freeze the skin to a solid state. Diamond fraises have the advantage of being used without cryogenic spray and since they cut tissue more slowly they offer a larger safety margin. In addition, pear-shaped fraises can be used along curved anatomic structures, such as the nose or oral commissure.

18.6.4.1 Dermabrasion Endpoints

Cutaneous anatomic landmarks serve as indicators of depth of injury. The removal of the epidermis will be indicated by the loss of skin pigmentation. Progression into the papillary dermis is noted by punctate bleeding (evident upon thawing) due to disruption of the capillary loops in this area. With the use of a wire brush (or a fraise on nonfrozen skin) the endpoint of dermabrasion is usually the appearance of small, parallel strands of collagen signifying the passage through the papillary dermis. Further abrasion will enter the reticular dermis and will increase the risk of scarring. The abrasion should stop when broad, coarse, frayed collagen bundles are seen. Special care should be taken to prevent ensnaring the lip by exerting adequate traction on the tissue and ensuring the direction of rotation is toward the orifice.

When abrading on frozen skin and using a diamond fraise, additional anatomical land-

marks are visible. When most of the papillary dermis has been removed, the lace-like network of subpapillary blood vessels is seen. With deeper abrasion, the vessels disappear and the tops of the sebaceous lobules are seen as small gray dots separated from one another. With deeper abrasion the sebaceous lobule dots are large and appear to touch one another, indicating the depth of the mid-reticular dermis. This is the usual stopping point. With deeper abrasion the dots disappear indicating the deep reticular dermis, a definite danger signal.

Summary for the Clinician

- Skin resurfacing, whether through lasers, peels, or dermabrasion, requires a learning curve for the surgeon
- Patient results are related to the depth of resurfacing rather than the modality used

18.6.4.2 Complications of Skin Resurfacing

Adhering to good surgical practices and gaining experience both reduce the risk of complications from skin resurfacing. Most postoperative complications are related to the depth of wounding rather than the modality used. In fact, complications such as hypertrophic scarring, prolonged erythema (over 3 months), and pigmentary changes are seen with peels [35], dermabrasion [9, 41], and laser [25].

Close postoperative monitoring of patients is critical during the wound healing period. This allows for rapid detection and treatment of infection. Infections usually are due to one of three main culprits: *Staphylococcus aureus*, *Candida*, and Herpes simplex virus. Appropriate treatment with antibiotics, anti-virals, and anti-yeast agents should be instituted based on the infecting organism. Anti-viral regimens should be continued up to postoperative day 15 (until re-epithelialization is complete) due to instances of herpes outbreaks after stopping anti-viral medications even as far out as day 10 or 11. Any delayed infection that occurs up to 1 month after skin resurfacing should raise the suspicion of atypical mycobacterial infection [34].

Milia, or epidermal microcysts, are a common occurrence 3–4 weeks after laser and dermabrasion and are relatively easy to treat with manual expression. Postoperative tretinoin use may also decrease the formation of milia.

A distressing occurrence for patients and physicians is that of permanent hypopigmentation. This occurs in areas where the depth of the wound enters the reticular dermis. While there are lasers that may temporarily help blend in these hypopigmented areas, unfortunately, there is no permanent treatment for this. Therefore, when operating on patients of Fitzpatrick skin type III or greater, patients should be warned of this possibility since it will be a more noticeable problem than in lighter skinned individuals. This must be differentiated from pseudo-hypopigmentation in which the newly resurfaced skin has a color identical to non-sun-exposed skin.

Post-inflammatory hyperpigmentation is usually transitory, lasting several months. Resolution can be expedited by resuming skin conditioning with hydroquinone (2–4%) twice daily and tretinoin (0.05–0.1%) in the evening once re-epithelialization is complete. Avoidance of sun exposure during the first month postoperatively is also beneficial.

Inflammatory conditions such as acne and rosacea can be exacerbated postoperatively. These conditions are best treated with systemic antibiotics (tetracycline, minocycline, doxycycline) and appropriate topical therapies. Postoperative use of isotretinoin should be avoided due to the potential for scarring during the healing period.

Persistent erythema (>3 weeks postoperatively) can be treated for up to 2 weeks with an ultrapotent topical steroid (betamethasone, clobetasol, halobetasol, diflorasone) applied to the red areas only, twice daily. Residual erythema that does not respond may be amenable to treatment with a flash lamp pulsed dye laser. Laser resurfacing, on the other hand, is accompanied by erythema lasting up to 6 months. This may be decreased by the use of a low viscosity silicone gel.

Scarring is the least common yet most difficult complication to manage. Scars can be atrophic, hypertrophic, or keloid-like. These are more common after infection, trauma, or depth

of wounding reaching the reticular dermis. Successful management is based upon early detection. At the earliest signs of scarring, ultrapotent topical steroids should be initiated twice a day for 3–4 weeks. To minimize atrophy and telangiectasia, the steroids should be applied only to the affected area. If topical steroids fail, intralesional steroids and manual massage should begin. Most commonly triamcinolone acetonide (1–40 mg/ml) is injected at 2- to 4-week intervals only into the mid-scar region (enough to raise a small wheal). Thicker scars will require higher concentrations (start with 5–10 mg/ml and increase by 5 mg/ml with each successive injection) while thinner scars require lower concentrations (2–3 mg/ml).

Oftentimes, an area that may go on to develop into a scar begins as an area of delayed wound healing, an area of itchiness, or an area of bright red induration. Progression to scar formation may be avoided by flash lamp pulsed dye laser treatments. These lasers also play an important role in instances of impaired wound healing. At the earliest concerns of scarring or impaired healing, laser treatments can be performed weekly or twice weekly for 1–2 months until the skin has healed fully.

With increased use of topical anesthesia for pain relief, one must bear in mind the pharmacology of these agents. A new complication, unrelated to the actual resurfacing modality, is that of lidocaine toxicity from topical anesthesia. It has been associated with fractional photothermolysis [22] and laser hair removal.

Summary for the Clinician

- Early recognition of complications is essential
- Complications include allergic reactions, infection, and scar formation
- Scarring is related more to the depth of wounding than the modality used

18.7 Conclusion

Skin resurfacing is an art and can yield results that are gratifying for physicians and patients alike (Fig. 18.1). However, optimizing these results depends on proper procedure (or procedures) selection, proper patient evaluation, and

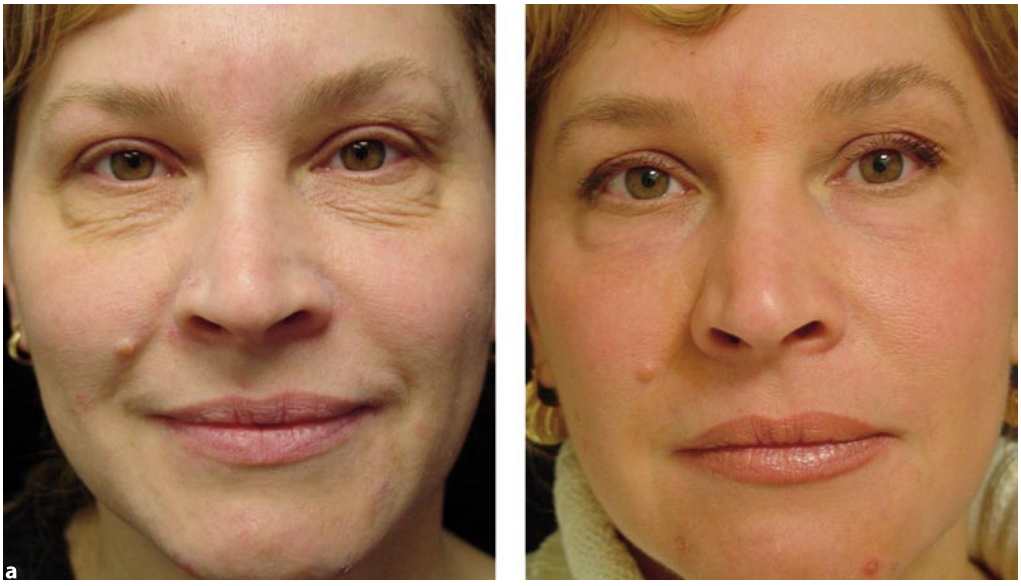

Fig. 18.1 **a** Before and after photograph of a patient with one full face peel and a total of three periorbital peels. **b** *(see next page)*

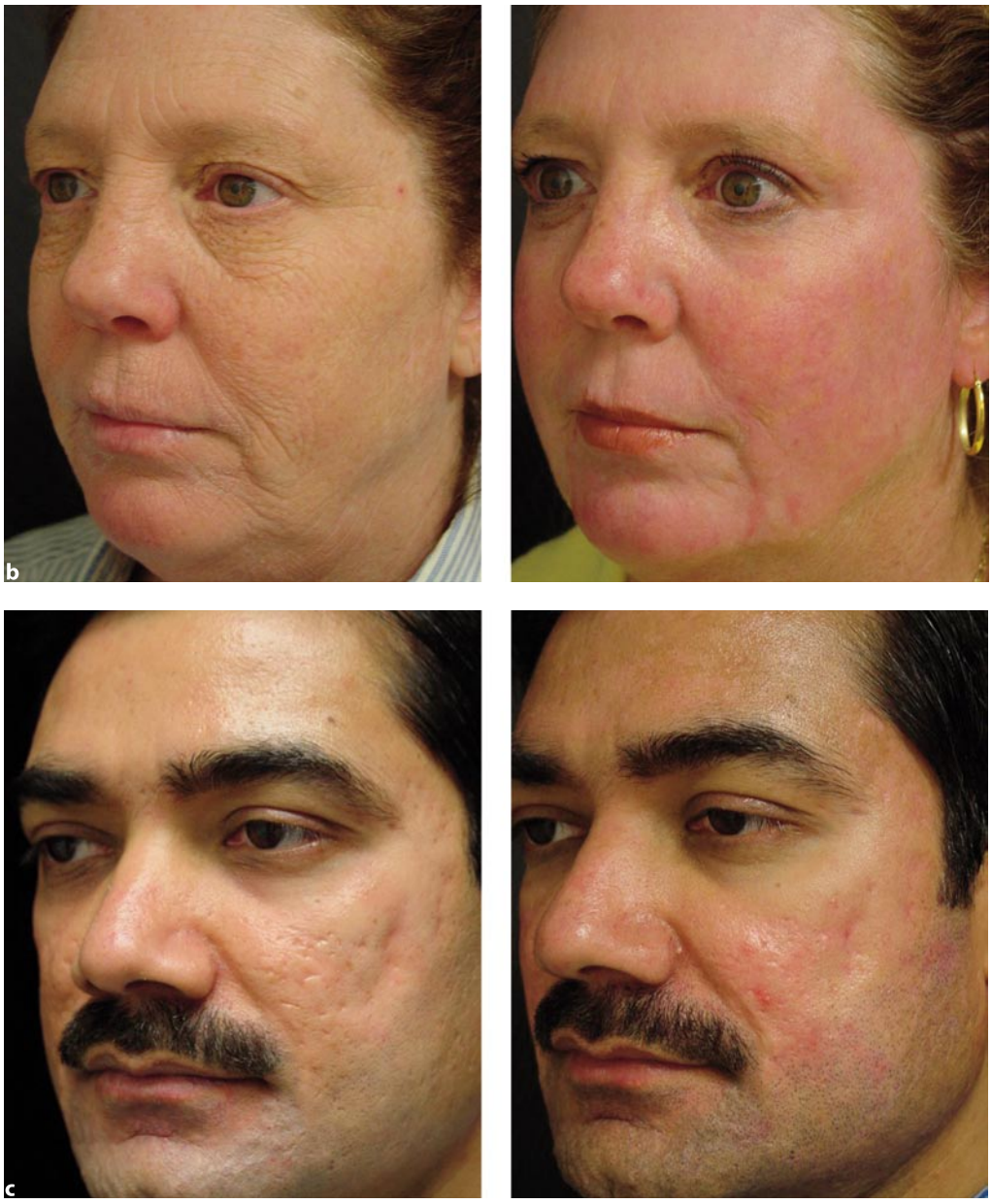

Fig. 18.1 *(continued)* **b** Before and after photographs of a patient with full face laser resurfacing with a blended erbium:YAG and CO_2 laser. **c** Before and after photograph of a patient with full face laser resurfacing and simultaneous dermabrasion of the cheeks

the institution of appropriate skin care regimens. The advent of newer technologies should serve to augment a physician's procedure repertoire rather than replace older modalities. Chemical peels, laser resurfacing, and dermabrasion have proven their long-term safety, and are important tools in skin rejuvenation.

References

1. Atiyeh BS, Costagliola M, Al-Amm CA, Belhaouari L (2004) Moist exposed therapy: an effective and valid alternative to occlusive dressings for postlaser resurfacing wound care. Dermatol Surg 30(1):18–25; discussion 25
2. Bernestein LJ, Geronemus RG (1997) Keloid formation with the 585-nm pulsed dye laser during isotretinoin treatment. Arch Dermatol 133(1):11–12
3. Bridenstine JB, Dolezal JF. Standardizing chemical peel solution formulations to avoid mishaps. Great fluctuations in actual concentrations of trichloroacetic acid. J Dermatol Surg Oncol 20(12):813–816
4. Brody HJ (1997) Deep peeling. In: Brody HJ (ed) Chemical peeling and resurfacing, 2nd edn. Mosby, St. Louis, pp 137–160
5. Caniglia RJ (2004) Erbium:YAG laser skin resurfacing. Facial Plast Surg Clin North Am 12(3):373–377
6. Coleman WP, Futrell JM (1994) The glycolic acid and trichloroacetic acid peel. J Dermatol Surg Oncol 20:76–80
7. El-Domyati M, Attia S, Saleh F, Brown D, Birk DE, Gasparro F, Ahmad H, Uitto J. El-Domyati M, Attia S, Saleh F, Brown D, Birk DE, Gasparro F, Ahmad H, Uitto J (2002) Intrinsic aging vs. photoaging: a comparative histopathological, immunohistochemical, and ultrastructural study of skin. Exp Dermatol 11(5):398–405
8. Fournier N, Mordon S (2005) Nonablative remodeling with a 1,540 nm erbium:glass laser. Dermatol Surg 31:1227–1236
9. Fulton JE Jr (1991) Prevention and management of postdermabrasion complications. J Derm Surg Oncol 17(5):431–437
10. Geronemus RG (2006) Fractional photothermolysis: current and future applications. Lasers Surg Med 38(3):169–176
11. Gilchrest BA, Yaar M (1998) Aging versus photoaging: postulated mechanisms and effectors. J Invest Dermatol Sym Proc 3:47–51
12. Grossman AR, Majidian AM, Grossman PH (1998) Thermal injuries as a result of CO2 laser resurfacing. Plast Reconstr Surg 102(4):1247–1252
13. Hanke CW, Roenigk HH Jr, Pinksi JB (1985) Complications of dermabrasion resulting from excessively cold skin refrigeration. J Dermatol Surg Oncol 11(9):896–900
14. Herd R, Dover JS, Arndt KA (1999) Skin resurfacing: laser. In: Freedberg IM, Eisen AZ, Wolff K, Austen KF, Goldsmith LA, Katz SI, Fitzpatrick TB (eds) Dermatology in general medicine, 5th edn. McGraw Hill, New York, pp 2950–2958
15. Hetter G (2001) Examination of the phenol-croton oil peel. IV. Face peel results with different concentrations of phenol and croton oil. Plast Reconstr Surg 105:1061–1083
16. Hevia O, Nemeth AJ, Taylor JR (1991) Tretinoin accelerates healing after trichloroacetic acid chemical peel. Arch Dermatol 127(5):678–682
17. Jasin ME (2002) Achieving superior resurfacing results with the erbium:YAG laser. Arch Facial Plast Surg 4(4):262–266
18. Laubach HJ, Tannous Z, Anderson RR, Manstein D (2006) Skin responses to fractional photothermolysis. Lasers Surg Med 38(2):142–149
19. Laws RA, Finley EM, McCollough ML, Grabski WJ (1998) Alabaster skin after carbon dioxide laser resurfacing with histologic correlation. Dermatol Surg 24(6):633–636
20. Manstein D, Herron GS, Sink RK, Tanner H, Anderson RR (2004) Fractional photothermolysis: a new concept for cutaneous remodeling using microscopic patterns of thermal injury. Lasers Surg Med 34(5):426–438
21. McDonald WS, Beasley D, Jones C. McDonald WS, Beasley D, Jones C (1999) Retinoic acid and CO2 laser resurfacing. Plast Reconstr Surg 104(7):2229–2235; discussion 2236–2238
22. Marra DE, Yip D, Fincher EF, Moy RL (2006) Systemic toxicity from topically applied lidocaine in conjunction with fractional photothermolysis. Arch Dermatol 142(8):1024–1026
23. Monheit, GD (1995) The Jessner's-trichloroacetic acid peel. An enhanced medium-depth chemical peel. Dermatol Clin 13(2):277–283
24. Moy LS, Howe K, Moy RL (1996) Glycolic acid modulation of collagen production in human skin fibroblast cultures in vitro. Dermatol Surg 22(5):439–441
25. Nanni CA, Alster TS (1998) Complications of cutaneous laser surgery. Dermatol Surg 24(2):209–219
26. Newman JP, Fitzgerald P, Koch RJ (2000) Review of closed dressings after laser resurfacing. Dermatol Surg 26(6):562–571
27. Obagi ZE (2000) Skin classification. In: Obagi ZE (ed) Obagi skin health restoration and rejuvenation. Springer, New York, pp 65–85

28. Obagi S (2004) Correction of surface skin deformities: botox, fillers, lasers and non-laser light sources. Atlas Oral Maxillofac Surg Clin North Am 12(2):271–297
29. Obagi S (2004) Pre- and post-laser skin care. Oral Maxillofac Surg Clin N Am 16:181–187
30. Obagi S, Bridenstine JB (2000) Lifetime skin care. Oral Maxillofac Surg Clin N Am 12(4):531–540
31. Obagi Z, Obagi S, Alaiti S, Stevens M (1999) TCA-based blue peel: a standardized procedure with depth control. Dermatol Surg 25:773–780
32. Obagi S, Obagi ZE, Bridenstine JB (2002) Isotretinoin use during chemical skin resurfacing: a review of complications. Am J Cosmet Surg 19(1):9–13
33. Papadavid E, Katsambas (2003) Lasers for facial rejuvenation: a review. International Journal of Dermatology 42:480–487
34. Rao J, Golden TA, Fitzpatrick RE (2002) Atypical mycobacterial infection following blepharoplasty and full-face skin resurfacing with CO2 laser. Dermatol Surg 28(8):768–771; discussion 771
35. Resnik SS, Resnik BI (1995) Complications of chemical peeling. Dermatol Clin 13(2):309–312
36. Rubenstein R, Roenigk HH, Stegman SJ, Hanke CW (1986) Atypical keloids after dermabrasion of patients taking isotretinoin. J Am Acad Dermatol 15(2 Pt 1):280–285
37. Rullan PP, Lemon J, Rullan J (2004) The 2-day light phenol chemabrasion for deep wrinkles and acne scars: a presentation of face and neck peels. Am J Cosmet Surg 21(4):15–26
38. Stone P (1998) Modified phenol peels – role of the application technique. Clin Plast Surg 25:21–44
39. Weinstein GD, Nigra TP, Pochi PE, et al. (1991) Topical tretinoin for treatment of photodamaged skin. A multicenter study. Arch Dermatol 127(5):659–665
40. Yarborough JM Jr. Yarborough JM Jr (1988) Ablation of facial scars by programmed dermabrasion. J Dermatol Surg Oncol 14(3):292–294
41. Zachariae H (1988) Delayed wound healing and keloid formation following argon laser or dermabrasion during isotretinoin therapy. Br J Derm 118(5):703–706

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