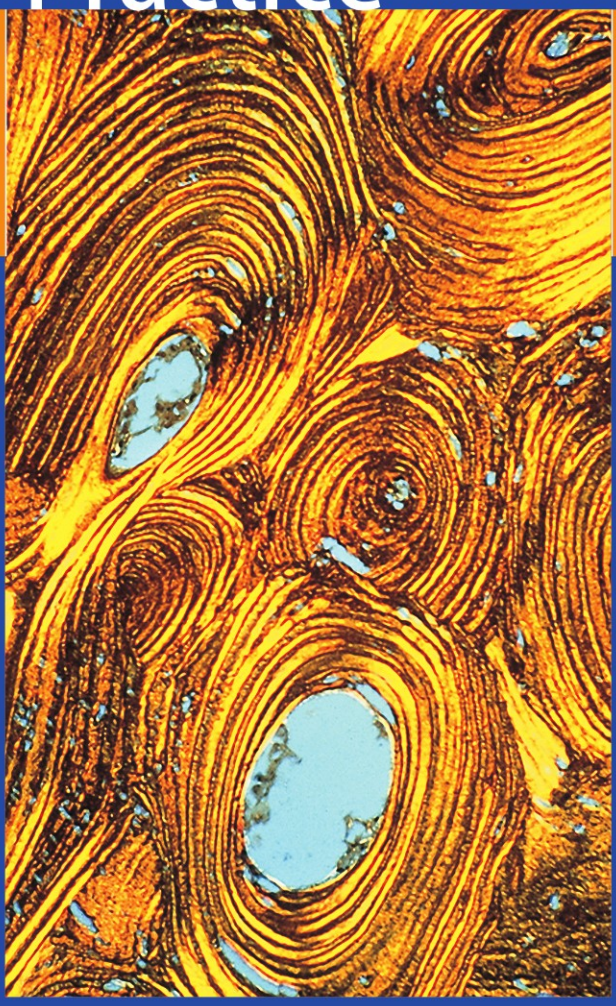
Reiner Bartl · Bertha Frisch
Emmo von Tresckow · Christoph Bartl

Bisphosphonates in Medical Practice

Actions
Side Effects
Indications
Strategies



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Bartl · Frisch · von Tresckow · Bartl

Bisphosphonates in Medical Practice

- Reiner Bartl
- Bertha Frisch
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- Christoph Bartl

Bisphosphonates in Medical Practice

Actions – Side Effects – Indications – Strategies

With 68 Figures

Springer

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Preface

On January 13, 2000, the World Health Organisation (WHO) in Geneva declared the first decade of the new millennium as "*The Bone and Joints Decade 2000–2010*".

Bone and joint diseases and their concomitant limitations and restrictions are the main causes of chronic pain and disability world-wide. It has been estimated that the number of people effected by these disorders will be doubled within the next 20 years or less in both industrialised and developing countries. *Osteoporosis* is already a global problem of epidemic proportions: according to a recent estimate about 28 million people in the USA alone are already effected by osteoporosis, together with many more millions in other countries, especially those with a high proportion of older and ageing people in the population such as China, Japan and the member states of the European Union. *A more recent survey (WHO Collaborating Center 2006) estimated that over 200 million people world–wide have osteoporosis and that the numbers are going to escalate in the immediate future.*

Parallel to the steady increase in longevity is an even steeper increase in the *costs of the health care* required and in the number of people needing it, due to the increase in chronic disorders in the elderly in addition to "primary" osteoporosis and fractures. Moreover it is now abundantly clear that the bones of the skeleton are adversely effected by most if not all of the chronic disorders that "flesh is heir to" (Shakespeare) especially as the body ages.

It is also clear that awareness and *recognition of this global problem* have been increasing steadily during the last decade of the previous century and the first 6 years of the current century. For example, a study on bone disorders published in 1998 was based on a Medline search which retrieved some 25,000 references for the years 1983–1996! In contrast, a Medline search on osteoporosis using only half a dozen key words revealed over 25,000 references for the period from January to December 2000 alone! Moreover these references included studies carried out in more than 40 different countries. And in the years 2000 to 2006 many more thousands of articles have been published on osteoporosis and its therapy, as well as other disorders of the skeleton. Since it is obviously impossible to include the vast majority of these, some prominent studies, the results of which are included in the text, have been added to the literature listed at the end of the text. It is also important to point out that nearly all of these are clinical studies of patients treated with bisphosphonates for osteoporosis and other disorders of bone thus amply demonstrating the very prominent place of these drugs in the treatment of

osteoporotic and osteolytic diseases of the skeleton in all age groups from babies to the elderly. Moreover, it is now abundantly clear that disorders of the bones are a consequence of many diseases in all branches of medicine and that these must be taken into account in the investigation and treatment of the patients.

The next decade will undoubtedly witness an ever *greater spread of knowledge* in all countries and at all levels of the population as the crucial importance of early education and appropriate life style habits are generally realised and put into practice! To quote one television advertisement "knowledge is power" and "you are what you know", and this is certainly true about the bones of one's skeleton! Knowing that preservation, maintenance and protection of the bones, as well as prevention of the skeletal complications of most of the common diseases occurring throughout life, are both feasible and attainable for everybody will motivate people to demand the opportunity and the means to do so. However, recent studies have indicated that there is still too little awareness of the risk of osteoporosis especially among the older age groups; and not all physicians provide patients with the information required to increase their awareness and encourage them to take the necessary steps to avoid it. In addition, unfortunately, another recent survey has pointed out that only one in four American adults meets the recommendations of the U.S. surgeon general for 30 minutes of physical activity a day!; this alone would reduce the risk of many chronic diseases as well as of osteoporosis. More optimistically, a survey on trends from 1988 through 2003 on the frequency of visits to physicians for osteoporosis, which had been stable till then, increased four-fold from 1994 (1.3 million visits) to the end of 2003 (6.3 million visits).

We now know that *protection, maintenance and prevention begin at birth*, continue throughout childhood and adolescence into adulthood and old age. To achieve this goal, more attention will be paid world-wide to 1) a healthy life style: nutrition, exercise and environmental factors to ensure that an optimal peak bone mass at adulthood is reached, 2) calcium and vitamin D supplements at times of increased physical need, 3) and protection in common diseases directly or indirectly effecting the bone. But, as pointed out in a study on national patterns of calcium use in the U.S.A. Calcium is being neglected as an essential component of osteoporosis management by doctors, as well as by patients. The common, frequently chronic diseases effecting the bones include respiratory, cardiac, gastro-intestinal, immunological, neurological and rheumatic disorders. Adequate measures must also be taken to counteract the possibly deleterious side effects of medications – a classic example is the therapy with glucocorticoids used to treat some of these disorders. All these considerations apply equally to neoplasias especially those with osteotropic metastatic potential such as cancers of the prostate and breast, particularly when surgical or chemical ablation of the gonads is involved; leading to the abrupt, immediate withdrawal of the estrogenic and androgenic factors which are crucial for maintenance and integrity of the skeleton.

Arguably the most comprehensive international and national efforts should be directed to the *prevention and treatment of age-related bone loss*, for the simple reason that this has the potential to effect any and every human being born on

this planet who lives long enough. Hormone replacement therapy for women is no longer advocated, due to its serious (possibly also carcinogenic) side effects. In special circumstances and only with appropriate precautions it is an option for hypogonadism in men. Other bone preserving medications are now readily available for postmenopausal women, and (somewhat later) for andropause in men. These should be given together with the measures outlined above, as well as bisphosphonates for prophylaxis and/or treatment of reduced bone mineral density (BMD). The expenses involved will be more than offset by the decrease in fractures and thereby in human suffering, as well as the corresponding reduction in surgical, hospitalisation and rehabilitation costs. Unfortunately, specific agents or factors for direct stimulation of bone formation (other than estrogen or its substitutes, anabolic steroids and parathyroid hormones) have not yet been developed and/or sufficiently tested– this is one of the aims of research in the new millennium.

Bisphosphonates, a group of pharmacological agents already employed worldwide for osteoporosis, also play a decisive role in the treatment and prevention of bone destruction due to primary and secondary disorders of bone such as bone tumors, osseous metastases, rheumatic disorders, and many others.

The following characteristics have contributed to the *success of bisphosphonates*:

- Modern bisphosphonates are 20,000 times more potent than those formerly used.
- Both oral and intravenous bisphosphonate preparations are well tolerated with few and relatively infrequent significant side effects (when correctly administered and appropriate precautionary measures are taken).
- Bisphosphonates have no hormone-like effects and can be taken by all patients and patients of all ages.
- *Long-term use (so far, follow-up of over 10 years) did not show any bone damage.*
- Clinical testing of bisphosphonates is extensive and exemplary.
- Their mechanisms of action are largely understood.
- They have a high therapeutic potential, which is underscored by their numerous applications, for example in oncology.
- The incidence of significant side effects is very low.

This is only the beginning of a long list of benefits of these therapeutic agents. The "*bisphosphonate success story" has now been established world wide*!

It is imperative to emphasise that every doctor has a personal responsibility to ascertain which bisphosphonates are authorised and for which indications in his/her particular country before starting treatment. This information is available from the ministry of health, from the pharmacists and from the representatives of the manufacturers. In addition, the patient's informed consent should always be obtained (this is essential for bisphosphonates not yet officially authorised for a particular indication), and documented preferably by signature on a standard consent form.

This book focuses almost exclusively and in detail on therapy with bisphosphonates. Nevertheless, it should be clearly stated that other medications and drugs are available, which in certain circumstances can be used for prevention and therapy of bone disorders. However, frequently the optimal choice will not only be a single agent, but a combination of measures symbolising a *flexible adaptive approach to the patient* as a whole. For example, how to treat osteopenia (a low bone density, also referred to as BMD) in an active postmenopausal woman in the late forties or early fifties with a family and a full time job? Considering the patient's circumstances an acceptable schedule would be: Raloxifen, (an estrogen receptor modifier also known as a SERM) plus a bisphosphonate once weekly or once monthly orally, or every few months by injection, because daily intake would interfere with work schedules and thus reduce compliance. The choice should be left to the patient as it has already been demonstrated that this increases long-term compliance. In addition, advice on life style: proper nutrition, calcium and vitamin D supplements and avoidance of bone robbers (such as too much coffee), a program for regular exercise and cessation of smoking which has negative effects on renal function and on calcium balance. Patients with cardiac problems would receive advice on controlled exercise programs, adequate nutrition and supplements, statins, anti-coagulants and bisphosphonates as indicated, particularly if the drugs prescribed for the basic condition are detrimental to the bones. *Put simply, effective treatment demands a "holistic" approach to the patient.*

In all probability, the bisphosphonates will constitute an indispensable component of the treatment of most of the diseases effecting the older age groups, even when, as the years go by, most people will have attained an ideal peak bone mass at adulthood and adopted a life-style attuned to preservation of physical fitness in the full meaning of the word. Recently published statistics have shown encouraging results – over 25 million adults in the USA are now exercising regularly, and just as many in the older age groups, though perhaps not as much as recommended by the Surgeon General.

Another important consideration receiving increasing attention today is that it is now clear that there are common causative factors for diseases such as atherosclerosis, peripheral vascular and coronary artery disease, and age-related disorders such as osteoporosis, dementia, Alzheimer's disease and type 2 diabetes. It has already been shown that medications effective in one may also benefit another – and among these drugs are the bisphosphonates. Consequently, their already numerous indications may be even further increased.

This book has been designed as an *up to date manual* to deal with the currently recognised indications for bisphosphonates, to outline situations and conditions for prevention of skeletal disorders, and to provide practical guidelines for treatment. It is intended for doctors who seek precise information on bisphosphonates in medical practice to enable them to treat patients with disorders of bone or better still to avoid their occurrence – as the age-old saying has it *"prevention is better than cure"! Significant advances have already been made in the first 6 years of the*

"Bone and Joint Decade" of the new century, it is our hope that this book will contribute to more progress in the same direction.

Clinical osteology is now an independent specialty which nevertheless encompasses all branches of medicine and effects each and every one of us:

Bone is Every Body's Business

Reiner Bartl, Munich
Bertha Frisch, Tel Aviv
Emmo von Tresckow, Starnberg
Christoph Bartl, Ulm

May 2007

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Abbreviations

BAG	Bone acidic glycoprotein
BDM	Bone density measurement
BIS	Bisphosphonate
BJ	Bence-Jones protein
BMD	Bone mineral density
BMP	Bone morphogenic protein
BP	Bisphosphonate
BMU	Basic multicellular unit
BRU	Bone remodeling unit
BSP	Bone sialoprotein
CAM	Cell adhesion molecule
CBC	Complete blood count
CEA	Carcinoembryonic antigen
CMF	Cyclophosphamide, methotrexate, 5-fluorouracil
CRPS	Complex regional pain syndrome
CT	Computerised tomography
CTX	Carboxy-terminal telopeptide
DISH	Disseminated idiopathic skeletal hyperostosis
DEXA	Dual-energy X-ray absorptiometry
ESR	Erythrocyte sedimentation rate
FGF	Fibroblast growth factor
GM-CSF	Granulocyte-macrophage colony stimulating factor
GnRH	Gonadotropin-releasing hormone
HER2	Human epidermal growth factor receptor 2
HPT	Hyperparathyroidism
HRT	Hormone replacement therapy
ICTP	C-terminal telopeptide of type I collagen
IGF	Insulin-like growth factor
IL	Interleukin
INF	Interferon
INF gamma	Interferon gamma
MDF	Myelopoiesis depressing factor
MGUS	Monoclonal gammopathy of undetermined significance
MM	Multiple myeloma

MMP	Metalloproteinase
MRI	Magnetic resonance imaging
MRT	Magnetic resonance tomography
NTX	N-terminal telopeptide
OAF	Osteoclast activation factor
ODF	Osteoclast differentiation factor
OI	Osteogenesis imperfecta
OIF	Osteoblast inhibitory factor
OPG	Osteoprotegerin
PCLI	Plasma cell labeling index
PDGF	Platelet-derived growth factor
PG	Prostaglandin
pHPT	Primary hyperparathyroidism
PINP	Amino-terminal propeptide of type I procollagen
PSA	Prostate-specific antigen
PTH	Parathyroid hormone
PTHrP	Parathyroid hormone-related protein
PYR	Pyridinoline
QCT	Quantitative computed tomography
QUS	Quantitative ultrasound
RANKL	Receptor activator of NF-kB ligand
SB2M	Serum beta-2-microglobulin
SBU	Structural bone unit
SCF	Stem cell factor
SD	Standard deviation
SLE	Systemic lupus erythematosus
SMP	Sympathetically maintained pain
SRE	Skeletal related events
STIR	Short tau inversion recovery sequence
TGF	Transforming growth factor
TNF	Tumor necrosis factor
TRANCE	TNF related activation-induced cytokine (ODF, OPG-L, RANKL)
TRAP	Tartrate-resistant acid phosphatase
VAD	Vincristine, doxorubicin, dexamethasone
VCAP	Vincristine, cyclophosphamide, doxorubicin, prednisone
VEGF	Vascular endothelial growth factor
VID	Vincristine, idarubicin, dexamethasone
WHO	World Health Organization

CHAPTER 1 The Skeleton

There are 208 to 214 individual bones in the human body (excluding the sesamoid bones in some tendons). The bones constitute about 15% of the total body weight and include the following:

- 29 cranial bones (including 6 in the auditory canal)
- 28 to 32 bones in the vertebral column
- 25 in the rib-cage
- 4 in the shoulder girdle
- 2 hip bones
- 60 to 62 in the upper and
- 60 in the lower extremity

Functions of the Skeleton

Considered as an organ, the skeleton has five specific functions:

- Support: The skeleton supports the entire weight of the body. The skeleton also gives the body its size and shape.
- Locomation: The skeleton together with muscles, tendons and joints, comprises the body's apparatus for movement and locomotion of individual parts and of the body as a whole.
- Protection: The skeleton protects the vulnerable internal organs from potentially harmful outside effects. For example, the ribs act as a suit of armour that shields the heart and lungs, and the cranial bones enclose (in a kind of "strongbox") the delicate tissues of the brain.
- Production of blood cells: *the bone/bone marrow system: the osseous tissues are far more closely involved in hematopoiesis than previously recognised.* The normal physiological production of blood cells takes place within the confines of the bones, especially those of the axial skeleton. These two systems, i.e. hematopoietic and skeletal – are closely inter-twined. They share the same precursor cells and a common nerve and blood supply – including a specialised sinusoidal system with a substantial blood flow.
- Storage (depot) and supply of minerals: *The skeleton harbours most of the minerals in the body: 99% of the calcium, 85% of the phosphate, and 50% of the magnesium are stored in the bones*. One to 1.5 kg of calcium is incorporated into the

bones as hydroxyapatite. Mineralised bone consists of approximately 50% inorganic materials (apatite mineral in gaps between and at the ends of collagen fibres, that is intra- and interfibrillar), 25% organic ground substance: the matrix (collagen and other organic molecules), and 25% water (bonded to collagen and mucopolysaccharides). Ninety percent of the bone matrix consists of collagen type I, and 10% of other non-collagenous proteins such as the glycoproteins osteocalcin, osteonectin, bone sialoprotein, osteopontin and various proteoglycans. Collagen is an essential constituent of all types of connective tissue and is crucial for the structure and function of the bones as demonstrated by the anomalies which characterise the congenital disorders of connective tissue and bone. Thus, the skeleton serves as a well-nigh inexhaustible depot for the body's homeostasis of calcium, whose deposition in and mobilisation from the bones is regulated by parathyroid hormone and active vitamin D metabolites. Put simply the skeleton is a sophisticated mechanical apparatus containing a biochemical storehouse.

Structure of the Skeleton

Bone fulfils two mechanical tasks: *weight-bearing and flexibility at the lowest possible weight. This is accomplished by the combination of an elastic matrix for flexibility, hardened by the deposition of calcium and phosphate which gives bone its rigidity, while the highly developed architecture contributes to both (Figs. 1.1 and 1.2).*
The layers, i.e. the "lamina" of the matrix are laid down according to the stress lines and are composed of a specialised mixture of building materials known in the construction industry as "the principle of the bi-phasic or two phase components" whereby bone consists of an inner elastic matrix in which the elongated collagen molecules are arranged in parallel layers (Fig. 1.2) between which plate-like crystals (in the nano size range) of calcium and phosphate are deposited and attached. *Animal experiments and clinical studies have demonstrated that every structural alteration within bone, especially enlargement of the crystals, causes a decrease in bone quality.* Water and large molecules such as mucopolysaccharides serve as paste or glue which binds the lamellae and crystals firmly together and forms the superficial "cement lines". Collagen ensures the elasticity, and the crystals are responsible for the strength and rigidity of bone. The simplicity of the bone's external appearance hides the complexity of the internal architecture, which becomes evident in X-ray films and in bone biopsies (Fig. 1.2).

The macroscopic skeleton consists of two major components:

- *Compact or cortical bone*
- *Cancellous, trabecular or spongy bone*

The skeleton weighs about 5 kg depending on sex, height, build and age. Cortical bone weighs about 4 kg and trabecular bone only 1 kg, but it has 10 times the

Fig. 1.1a,b Normal trabecular bone. **a** Cut surface of a bone biopsy showing trabecular network and intertrabecular spaces. Note the honeycomb-like arrangement of the interconnected horizontal and vertical trabeculae and the nodes connecting them. The density of these 'nodes' ensures mechanical strength. **b** Trabecula consisting of parallel layers of collagen fibrils. These lamellae ensure flexibility of bone

surface area of cortical bone. In summary, the structural organisation of bone is responsible for its stability and flexibility, as seen at the macroscopic, microscopic and molecular levels.

Modelling and Remodelling

Modelling

Modelling occurs only during growth of the skeleton, from intra-uterine development to adulthood. It is the process by which the "primary" woven bone is replaced by lamellar bone, or by which ossification of pre-existing cartilage takes place (enchondral bone formation). Modelling is responsible for the development and growth of the skeleton from birth to the end of puberty. As the long bones develop, their shafts grow in diameter as well as in length. All bones are shaped in various ways during this period of development. This implies that bone is removed

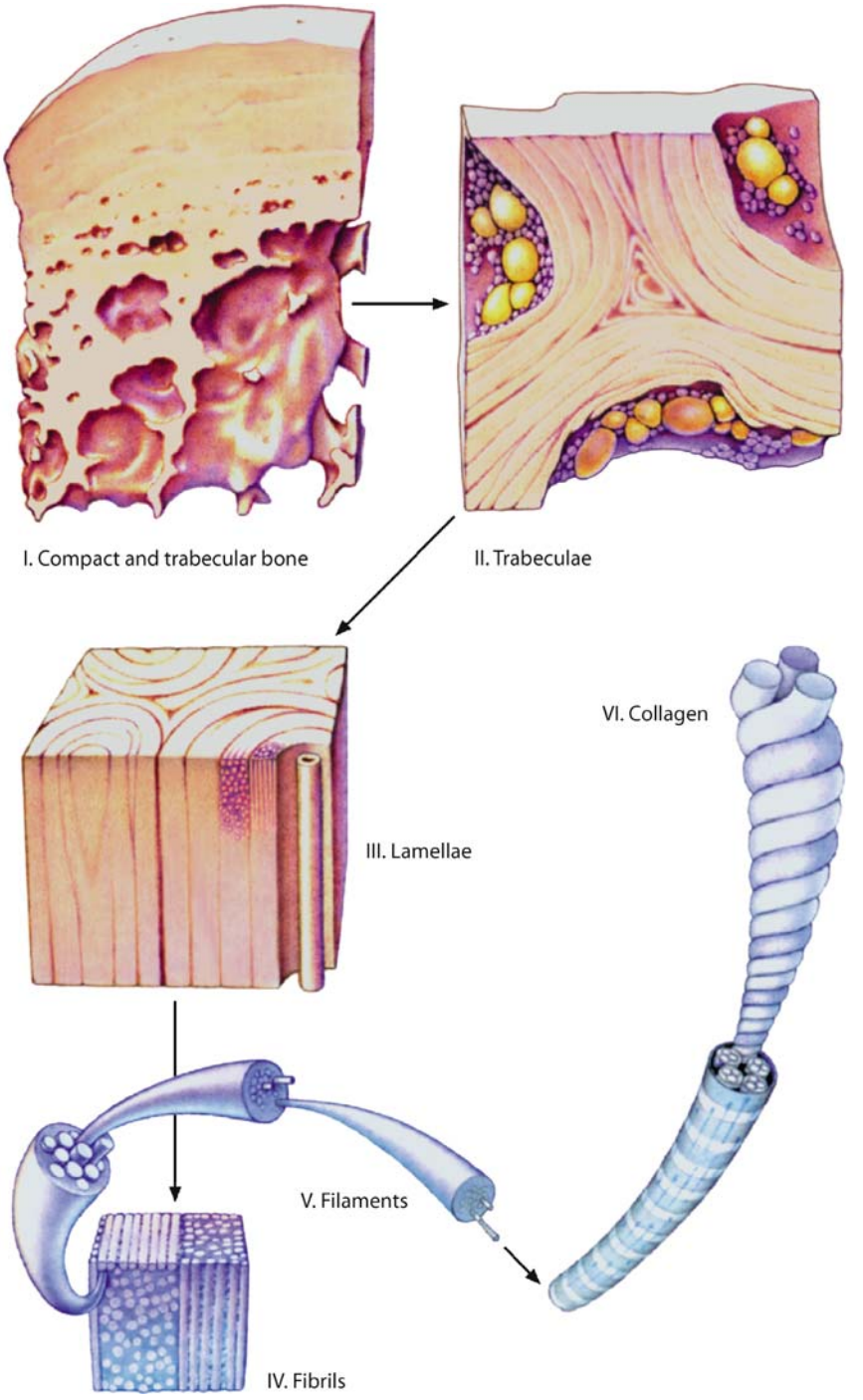

I. Compact and trabecular bone
II. Trabeculae
III. Lamellae
IV. Fibrils
V. Filaments
VI. Collagen

Fig. 1.2 Organizational levels of bone structure, which ensure both flexibility and rigidity of the skeleton: from macroscopic via microscopic to molecular levels

from some areas by osteoclastic resorption, while in other areas bone is enlarged by osteoblastic formation. Modelling terminates when the skeleton has reached its ultimate size at the end of puberty and when the "growth plates" have become ossified.

Remodelling

During normal aging, from cessation of growth onwards, both rigidity and flexibility of bone are decreased due to loss of minerals and alterations of the matrix, thus increasing its 'breakability'. To counteract these effects of aging, *bone is maintained by constant turnover – focal remodelling – which ensures replacement of the entire skeleton 3 to 4 times in a lifetime*. During remodelling about 400 mg calcium are extracted from bone each day, so that about 20% of the skeleton is replaced annually. The ability of bone to remodel itself serves not only adaptation and renewal but also repair of cracked, worn and broken bones: this includes fractures of "whole" bones as well as thousands of "micro cracks", especially in the trabecular bone, the integrity of which together with bone density determine the strength of bone and therefore the risk of fracture. *Consequently, remodelling is a life-long process of repair and maintenance required for the preservation of the skeleton's structural and functional integrity.*

Modelling and remodelling are distinguished from one another in several ways:

- Modelling involves independent activities of osteoclasts and osteoblasts, while remodelling involves "coupled" actions of these two types of bone cells.
- Modelling results in changes in the shape and size of bone, while remodelling maintains but usually does not change size and shape.
- Modelling is continuous during skeletal development then it is greatly reduced and ceases completely after skeletal maturity, while remodelling takes place throughout life.

Remodelling is episodic, and each episode has a definite beginning and end, it is carried out by the two major bone cells: the osteoclasts which resorb bone and the osteoblasts which form bone.

It has been shown that trauma to the bone marrow stimulates the formation of medullary as well as periosteal callus; the cells responsible for these processes are derived from the bone marrow as well as from the periosteum and endosteum. *Healing of a fracture can be divided into inflammatory, reparative and remodelling phases which lead to complete healing of the fracture.*

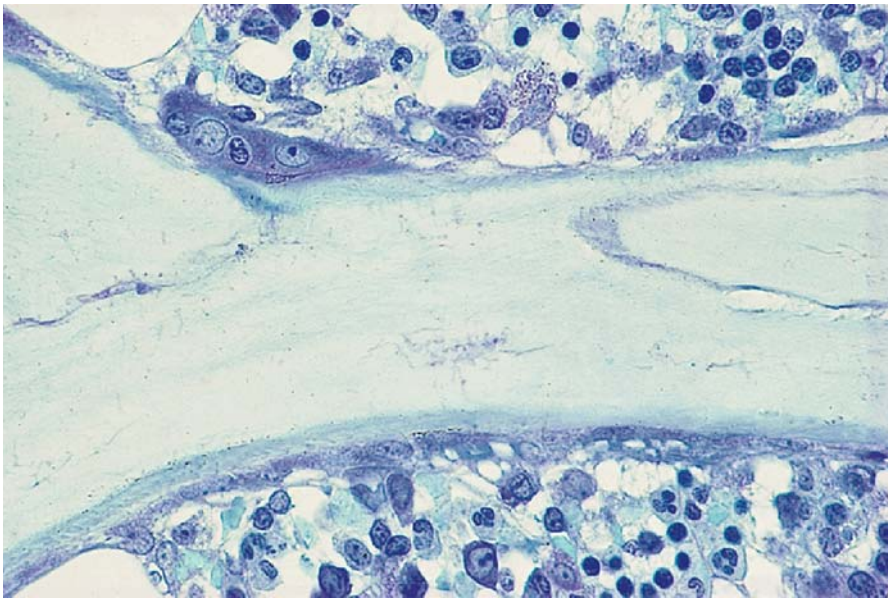


Fig. 1.3 Trabecula showing osteoclastic resorption (note osteoclast, left) on the upper surface and bone formation with layer of osteoblasts and osteoid seam (darker blue) on the lower surface. Example of normal, balanced remodelling of bone

Bone Cells

Remodelling, (as described above) is responsible for the constant maintenance and repair of the skeleton. It is carried out by two major bone cells: the osteoclasts which break down and resorb the "old" bone and the osteoblasts which produce and form the "new" bone. The osteoclast is a fast and efficient excavator when required physiologically, but can also be highly destructive in disease and pathological processes.

Osteoclasts (Bone Resorbing Cells)

Osteoclasts are multinucleated giant cells ranging from 20 to 100 μm in diameter (Fig. 1.4). It takes only a few days to resorb bone and then the osteoclasts lie within the resorption cavities (Howships lacunae) they have formed. Osteoclasts have 2 to 20 nuclei, though more than a hundred may be present depending on the pathologic condition and the cell's functional activity. The osteoclasts are derived from mononuclear phagocytes, produced by the hematopoietic system. Monocytes (the potential phagocytes) circulate in the blood and are attracted to sites of injury, infection or the surface of bone; here they fuse to form osteoclasts, which are mobile cells as are their precursors. There are complex relationships

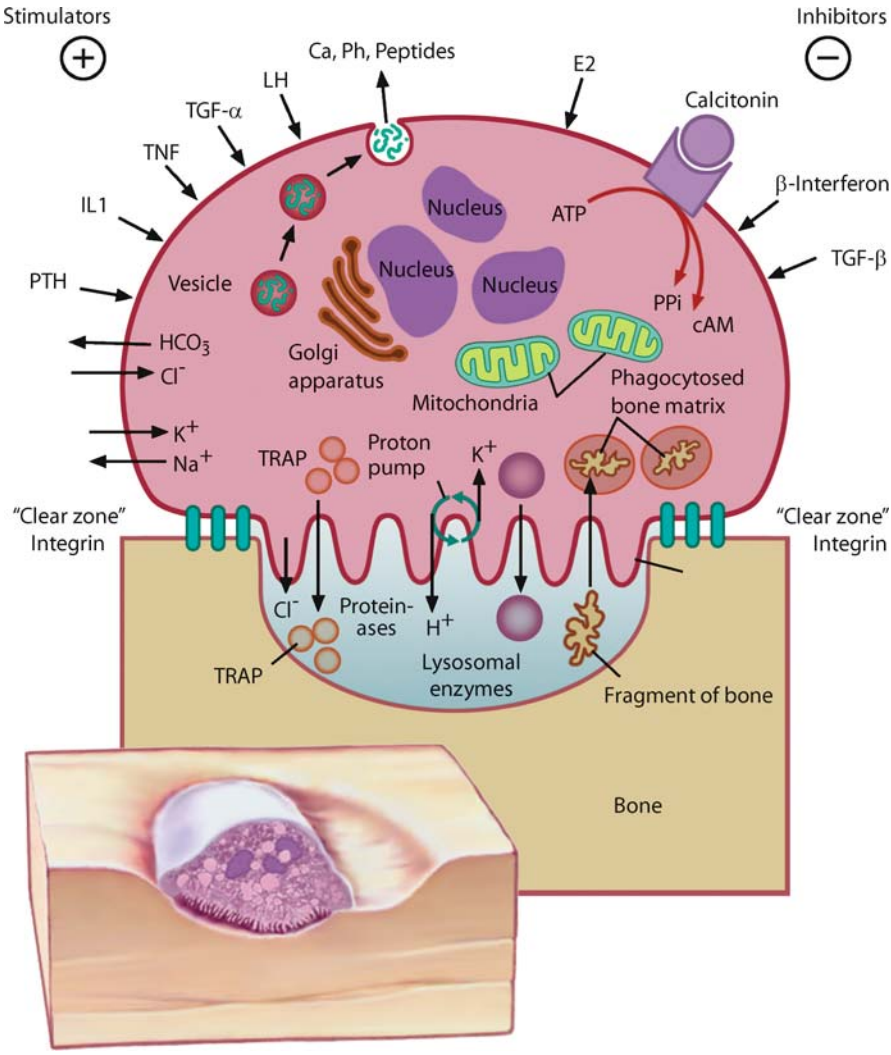


Fig. 1.4 Schematic drawing of structure and function of an osteoclast indicating stimulators and inhibitors of osteoclastic activity. The main targets of pharmacologic interventions are multiple signaling pathways, various enzymes produced, apoptosis, sealing zone, ruffled border and resorption pH

between osseous and hematopoietic cells, and close correlations between inflammatory reactions and bone remodelling, as well as between osteoclasts and lipoproteins, cholesterol and lipid metabolism.

Characteristic of active osteoclasts are their "ruffled borders" which lie directly on the surface of the bone. Howship's lacunae also known as resorption bays, pits,

cavities or niches are formed as the osteoclasts carve out the bone. The depth of these lacunae graphically illustrates the agressivity of the osteoclasts. Attachment of osteoclasts to bone is mediated by integrin-type receptors. Once attached, the osteoclasts secrete large quantities of proteolytic enzymes, e.g. matrix metalloproteinases and cathepsin which remove the organic matrix of the bone; they also secrete hydrogen ions for dissolution of the hydroxyapatite crystals. *Tartrate-resistant acid phosphatase (TRAP) is one of the classical enzymes used as a marker for osteoclasts*. Other lytic enzymes are found in the endoplasmic reticulum, in the Golgi apparatus, and in transport vesicles within the cytoplasm of the osteoclasts.

In summary the osteoclast has developed various cellular and intra-cellular mechanisms for rapid breakdown of resorbed material. Minerals, released as bone is resorbed, are dissolved; and collagen fibres are broken down into amino acids such as hydroxyproline. The presence of numerous cytoplasmic mitochondria within the osteoclasts provides an unequivocal indication of the high energy requirements of the process of bone resorption.

Osteoclasts and their precursors have receptors for estrogen, whose main effect is inhibition of recruitment of osteoclasts.

Important *cytokines* for osteoclast differentiation and function are:

- Stimulators: RANK ligand, CSFs, IL-1, IL-6, IL-11, IL-17 and TNF α and β
- Inhibitors: osteoprotegerin, IL-1 ra, IL-4, IL-10, IL-12, IL-18, IFN γ, TGF β

Osteoblasts (Bone Forming Cells)

Osteoblasts are the cells that produce new bone – and while bone resorption takes only days, bone formation takes weeks. Osteoblasts are derived from precursors in the bone marrow – the mesenchymal or stromal stem cells also known as the colony forming units-fibroblasts or "CFU-f". Osteoblasts are smaller and less mobile than osteoclasts and have only one nucleus. Recently bone marrow stromal cell cultures have shown that there is a common precursor cell for both osteogenic cells (osteoblasts, osteocytes and bone lining cells) and adipocytes. Important events for osteoblast induction include the activation of specific "master" genes for skeletal development, notably cbfa1. Many hormones and cytokines regulate osteoblast activity. These include IGFs, TGFs, FGFs, PDGF, BMPs and prostaglandins. In addition mechanical loading is required for osteoblasts to differentiate from their precursors. *Osteoblasts form an epithelial-like lining at the surface of bone and are connected by gap junctions, 100–400 cells may be joined in this way. They synthesise osteoid, the organic bone matrix and are responsible for its mineralisation*. Osteoblasts form single or multiple layers with their nuclei facing away from the bone. Their cytoplasm is strongly basophilic (appears dark blue in Giemsa staining) and contains large amounts of alkaline phosphatase, an indicator of protein synthesis. Osteoblasts secrete osteocalcin, osteonectin and bone morphogenic protein (BMP) in addition to osteoid (mainly collagen type I). They have

receptors for estrogen, $1.25(OH)_2$, vitamin D_3 and parathyroid hormone, but not for calcitonin. Fluoride, strontium, certain statins and PTH activate osteoid production, whereas leptin inhibits it (see below).

Osteocytes (Bone Supervisors)

Osteocytes are by far the most numerous of the bone cells. Osteocytes develop directly from osteoblasts about one in ten osteoblasts is enclosed within the newly formed osteoid, thus becoming an osteocyte. Osteocytes are located in lacunae (small cavities within both cortical and trabecular bone) and are connected to each other and to the surface lining cells by cytoplasmic extensions (processes) that run through narrow channels (canaliculi) within the bone and end in "gap junctions" similar to those of neurons. In this way the osteocytes have established an extensive and complex circulatory and communication system with each other within the bones and with the endosteal surface lining cells, and thus indirectly, with osteoclasts and osteoblasts. In this way the osteocytes form a kind of "surveillance system," always alert and able to react rapidly to both internal and external stimuli. Unlike osteoblasts and osteoclasts, which each have one primary, specific function, osteocytes appear to be multi-functional bone cells possibly even consisting of different sub-types (Bonewald 2003). *Most importantly, osteocytes appear to be the "directors" of many of the processes the other bone cells are engaged in: current theories suggest that remodelling – resorption and formation – is also controlled by signals mediated by osteocytes.*

Osteocytes are essential for survival of bone; if deficient osteocytes are not replaced, the involved bone cannot be maintained and a sequestrum is formed, rejected and removed.

The surface area of lacunae and canaliculi has been estimated at 1.200 mm^2, emphasizing the crucial role played by osteocytes in the transport of organic and inorganic substances within the bone. Osteocytes also act as sensor cells for changes in strain levels: such changes are then translated into second messengers. These in turn activate lining cells and osteoblasts on the surface of the bone. Possibly osteocytes also relay information concerning aging and weight-bearing to the surface lining cells, thereby triggering a flow of ions along the canaliculi which then produce an electric current or potential that stimulates bone formation. There is evidence that damage to the osteocytic/canalicular network itself induces activation signals to initiate bone repair. *It appears that both hormones and nerves utilise the osteocytic intra-osseous system for communication and implementation*.

Endosteal Lining Cells (Bone Protectors)

These are flat cells which cover 80–95% of the internal surface of the bones. They are continuous with and are derived from osteoblasts. *Endosteal lining cells form a protective layer, a boundary between the bone and bone marrow, i.e. the front-line*

between bone and the surrounding tissues. Together with the osteocytes they constitute a maintenance and surveillance system enclosing the bone and determining its microenvironment. The endosteal lining cells are also involved in the activation of osteoclasts. Certain surface molecules on the endosteal cells and on osteoclast precursors react with the RANK receptor and thereby initiate the remodelling cycle in which they also participate directly by removal of collagen fragments left by the osteoclasts; thereby clearing the resorption surface and initiating the subsequent bone formation.

Periosteal Lining Cells (Bone Protectors)

These cover and protect the outer surface of the bone and participate in remodelling of the cortical bone.

Origin of Osseous Tissue

Bone can be regarded as a specialised, "petrified" (ossified) branch of the bone marrow stroma. Bone cells and their precursors are derived from the bone marrow: osteoblasts and osteocytes from multipotent mesenchymal precursors of stromal components, and osteoclasts from precursors of the mononuclear macrophage hematopoietic cell line. *Thus bone and bone marrow share the same precursor cells. Put in a nut shell, bone cells together with stromal cells, fibroblasts, adipocytes, adventitial and endothelial cells, blood vessels and nerves form a complex network that regulates and maintains both bone marrow and bone.*

Steps (or Phases) of Bone Remodelling

There are normally 2 to 5 million bone remodelling units (BRU) charged with the daily maintenance of the skeleton. Each unit consists of relatively few osteoclasts but more numerous osteoblasts (Fig. 1.5). It is essential to realise that their activities are "coupled" i.e. following osteoclastic removal of the old bone; the osteoblasts lay down the new bone. Activation of the one inevitably leads to activation of the other so that the quantity of new bone formed equals the amount of old bone resorbed.

The degree of remodelling is reflected in the amount of calcium and of breakdown products of collagen released during the process of resorption; these enter the blood stream and are excreted in the urine.

Remodelling takes place in cycles of approximately 120 days. The following stages are recognised (Fig. 1.6):

- Quiescence endosteal lining cells present
- Activation – recruitment of osteoclasts

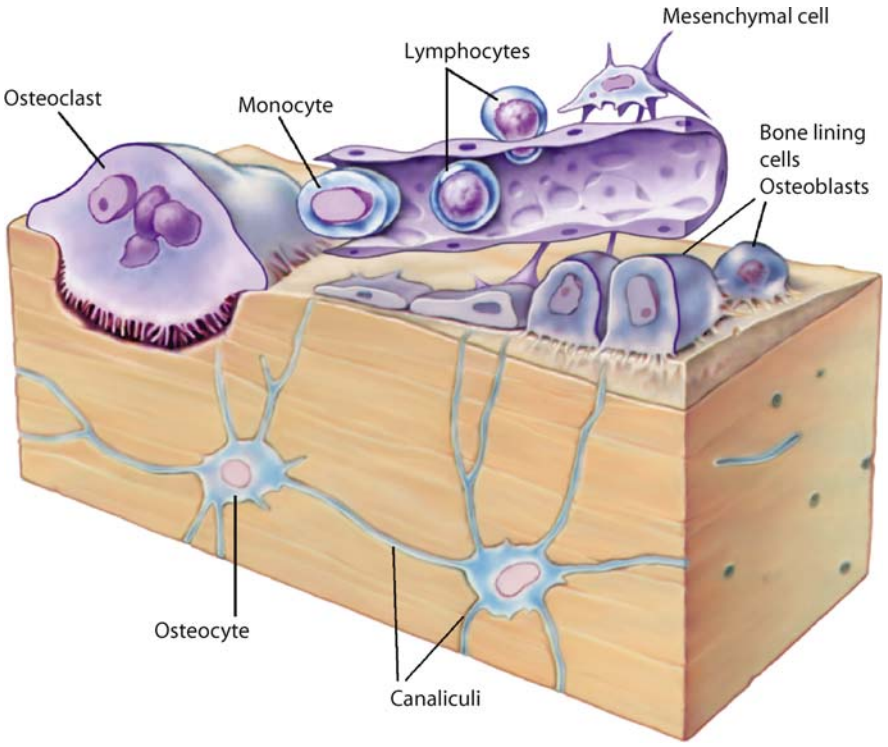


Fig. 1.5 Bone remodelling unit (BRU), consisting of bone resorbing cells (osteoclasts), bone matrix synthesizing cells (osteoblasts) and bone protecting cells (osteocytes and endosteal lining cells) as well as various progenitor cells

- Resorption: osteoclasts resorb bone – formation of resorption cavity
- Reversal: apoptosis or migration of osteoclasts, clearance of debris by lining cells
- Preparation of osteoblasts followed by deposition of cement lines
- Early formation of new bone – production of osteoid by osteoblasts
- Late formation – mineralisation of osteoid
- Quiescence – transformation of osteoblasts into endosteal lining cells and osteocytes

Resorption is completed within about two weeks, whereas formation and mineralisation of the newly formed osteoid may take months and depends on the presence of metabolites of active vitamin D. Mineral is deposited within and between the collagen fibres. This process is called mineralisation lag time and lasts about 10 days. During the next 6 months the remainder of the mineral is added so-called "secondary mineralisation". *A complete remodelling cycle forms one structural bone*

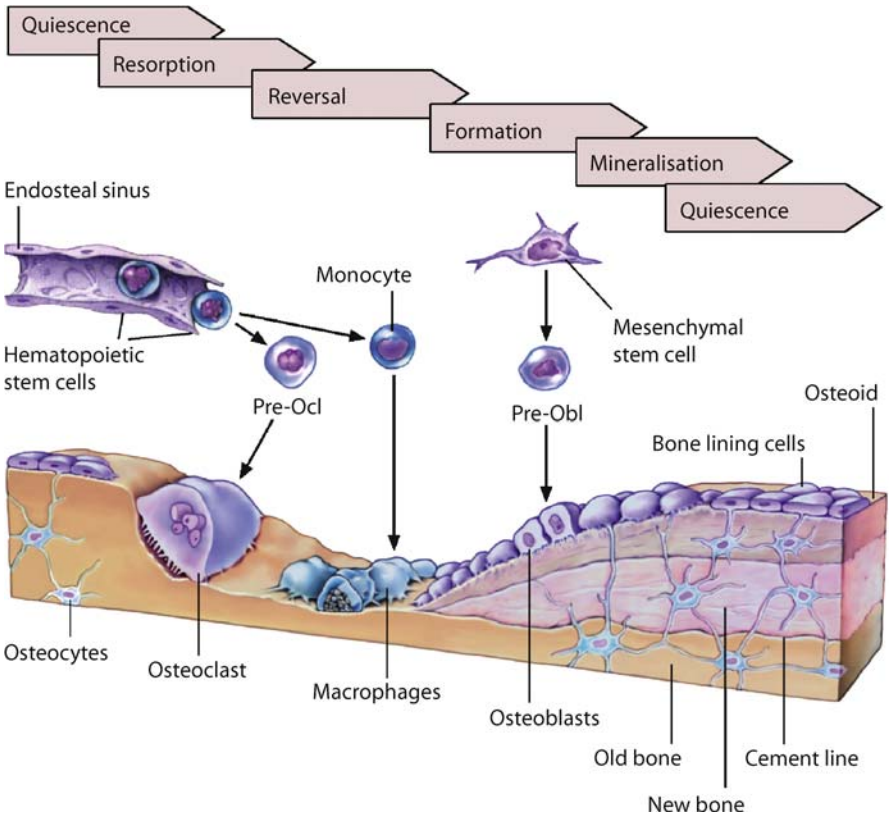


Fig. 1.6 Steps of bone remodelling in adult trabecular bone, *Ocl* = osteoclast

unit (SBU) and it has been estimated that there are about 35 million SBUs in the skeleton – this implies that at any time there are millions of bone cells constantly at work. Eight percent of the skeleton is remodelled and replaced annually, while the rate of bone turnover varies widely throughout the bones of the skeleton.

Regulation of Bone Remodelling

In addition to systemic hormones, local signals mediated by intercellular reactions, cytokines and electromagnetic potentials all play important roles in bone remodelling. The osteoclasts and osteoblasts are closely connected and exchange information about their respective activities. *This process is called coupling and it serves to achieve a perfect balance between the amount of resorption and formation: that is, maintenance of bone mass; and thereby indirectly also muscular activity and weight-bearing.* Current knowledge concerning the physiological mechanisms of

regulation of remodelling, includes the roles of growth factors and connective tissue hormones, but research is still ongoing.

Modulators of bone remodelling are listed in Table 1.1 and Fig. 1.7. The most important systemic hormones are: parathyroid hormone (PTH), calcitonin, thyroid hormone, insulin, growth hormone, cortisone and sex hormones (see below). Hormonal regulation acts mainly through calcium homeostasis and effects the kidneys and gastro-intestinal tract as well as the skeleton.

- Vitamins essential for collagen metabolism and mineralisation are: D, K, C, A, B_6 and B_{12}.
- Bone cells themselves secrete whole families of cytokines including IGF-I, IGF-II, β2-microglobulin, IL-1, IL-6, TGFβ, TNF, interferon, BMPs, FGFs and PDGF.
- Osteoclasts, osteoblasts and osteocytes also express the peripheral cannabinoid receptor type 2 (CB2) which has no psychotropic effect, but enhances osteoblast number and restrains osteoclastogenesis.

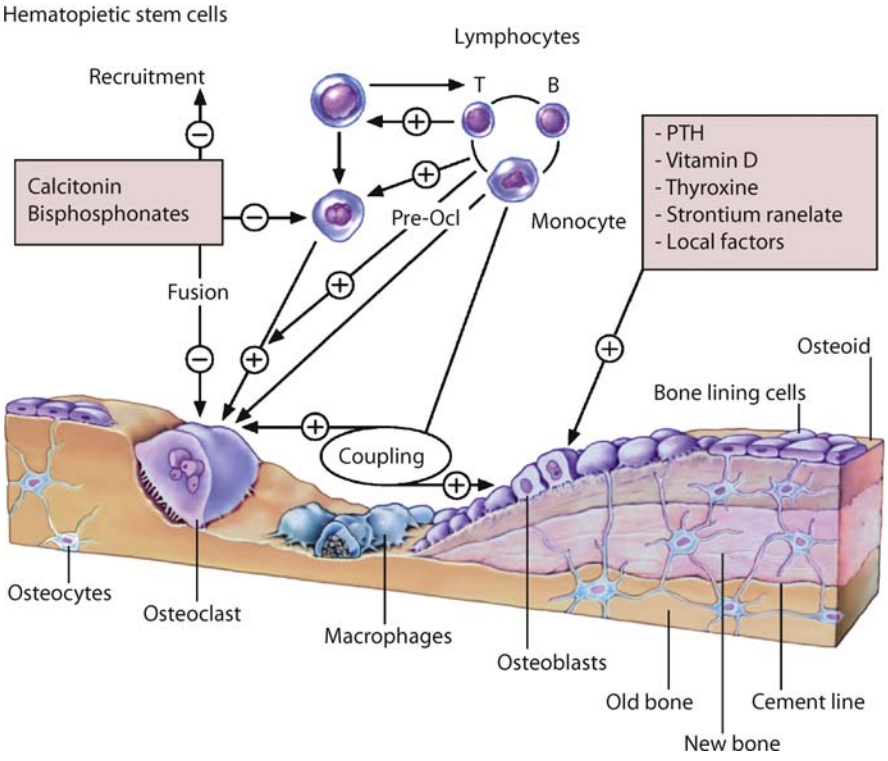


Fig 1.7 Regulation of bone remodelling involves hormones, cytokines, drugs, mechanical stimuli and cellular interactions ("coupling" of bone resorption and formation)

Table 1.1. Modulators of bone remodelling

Bone Resorption		
Increase		**Decrease**
Systemic		
PTH		Calcitonin
PTHrP		Estrogen
Calcitriol		Testosterone
Thyroxine		
Glucocorticoid		
Local		
IL-1	TNFα	TGBβ
IL-6	TNFβ	IFNγ
IL-11	TGFα	IL-4
IL-17	M-CSF	IL-10
FGFs	GM-CSF	IL-13
Prostaglandins	SCF	OPG
RANKL		IL-1ra

Bone Formation		
Increase		**Decrease**
Systemic		
Fluoride		Corticosteroid
PTH		
Prostaglandins		
Cytokines		
Local		
BMPs	FGFs	
TGFβ	PDGF	
IGFs	Prostaglandins	

- Prostaglandins are specialised fatty acids which act on bone cells locally. They increase proliferation and formation of osteoblasts; they also participate in osteolysis in inflammatory processes.
- The actions and correlations of all these factors are outlined in detail below. They can be divided into five groups of mechanisms which regulate the homeostasis of calcium and maintain the strength and rigidity of bone.
- It should be stressed that the complex mechanisms of bone physiology are still under investigation and new factors and insights are still being reported.

Systemic Hormones

The modulators of resorption are given in Table 1.1. Parathyroid hormone and Vitamin D together are considered the most important regulators of calcium homeostasis. They influence bone, the kidneys and the gastro-intestinal tract. Parathyroid hormone in particular participates in the regulation of resorption. Androgens on the other hand are required for the formation of bone. Osteoblasts, osteocytes, mononuclear cells and endothelial cells in the bone marrow all have receptors for androgen. The types and expression of these receptors are independent of sex. It is noteworthy that adipocytes (fat cells) have receptors for steroid hormones (produced by ovaries, testes and adrenals) which they metabolise by means of cytoplasmic enzymes – the aromatases. Significant levels of both estrogens and androgens are found in the serum of both sexes. *Male and female sex hormones play important – though not necessarily identical – roles in the metabolism of bone in men and women*. Thus, for example, androgens affect osteoblasts during the phase of mineralisation while estrogens exercise their influence at an earlier stage, i.e. during matrix formation. Moreover, the sex hormones influence different parts of the skeleton in different ways; for example androgens control periosteal bone formation which is responsible for the greater width of the long bones in men. *Osteoclasts, osteoblasts and osteocytes have receptors for estrogen and androgen but neither of the sex hormones predominates at any stage of the remodelling cycle.* However, androgens exercise a strong influence on bone resorption and formation by means of local enzymes, cytokines, adhesion molecules and growth factors. In contrast, recent evidence suggests that estrogen exerts an inhibitory effect on resorption and thereby prevents bone loss. This is accomplished by regulation of T cell function and of immune-bone cell interactions. *In summary, bone cells of both men and women have receptors for estrogens and androgens, and estrogen levels are also significant in males.*

Local Cytokines and Signals

As stressed above local cytokines as well as electromagnetic potentials and signals, distributed through the osseous intercellular network, are also required for

remodelling. Bone cells synthesise whole families of cytokines for example: IGF-I, IGF-11, β2-microglobulin, IL-1, IL-6, TGF-β, FGFs and PGDF. Prostaglandins play an important part in osteoporosis during immobilisation.

Vitamins and Minerals

Vitamins, minerals and other factors influence bone cells and their associated cell systems. Vitamins D, K, C, B_6 and A are required for the normal production of collagen and for the proper mineralisation of osteoid. The critical role of metabolites of vitamin D has recently been re-emphasised. Vitamin A is important for DNA synthesis and influences the width (thickness) of bone. A recent study of 2.576 patients showed that a low level of Vitamin B_{12} constitutes a risk factor for osteoporosis. It has now also been suggested that deficiency of zinc may contribute to involutional osteoporosis. Conversely, a diet low in sodium may be beneficial to skeletal health.

Mechanical Stress and Weight-Bearing

Physical activity increases bone mass and weight-bearing ability and is especially important for children and young individuals during the period of growth. Osteogenic potential decreases markedly after puberty and when longitudinal growth has ceased; so that mechanical weight- bearing has only a minimal effect on the adult skeleton. However pressure and traction are effective in strengthening the bones.

A new technique for strengthening adult bone is application of high frequency "vibrations" alternating with periods of rest. Clearly, the bone cells are able to convert extracellular signals into intracellular responses. Mechano-receptors have recently been identified; these consist of extra- and intracellular proteins, connected to trans-membrane canals, which are transformed into stimuli. Osteocytes possess processes (extensions) which are in direct contact with the extra-cellular matrix; therefore, it is quite possible that the flow of extra-cellular fluid in the canaliculi triggers changes in the cell membranes of the osteocytes and these changes are then conveyed into the cytoplasm by the mechano-receptors.

Genes and Regulation of Transcription

Various transcription factors which control osteoblastic differentiation and osteogenesis have now been identified. These include the runt-related transcription factor (Runx), Osterix (Osx), the sex determining region Y-box, and "master" regulators of osteogenesis. Moreover, newly discovered genes responsible for congenital disorders of the skeleton may possibly be utilised as therapeutic agents in

the future. For example LRP5 has recently been recognised as a key molecule in the differentiation of osteoblasts and in the regulation of bone.

Leptin and the Central Nervous System

The observation that obese people rarely develop osteoporosis lead to the supposition that there is a direct correlation between adipose tissue and bone mass. Initially, it was assumed that the additional weight was responsible for the relatively high bone mass, now it is thought that weight does contribute, but is not the major cause. Experimental studies have pointed out the role played by the hormone leptin. *Leptin is produced by the adipocytes – the fat cells – it acts on neurons in the brain and thereby influences energy balance, appetite and body weight as well as many other physiological processes.* Animal experiments have demonstrated that leptin also has an anti-osteogenic effect. The level of leptin in the blood corresponds to the quantity of body fat. However, there is no apparent relationship between lipid levels in the blood and bone mineral density. Apparently leptin controls the energy balance of the body (in addition to regulation of bone mass) by binding to certain specific protein receptors of neurons in the hypothalamus. These activate sympathetic nerve cells whose processes terminate in the bones where they stimulate the secretion of nor-adrenalin which in turn stimulates osteoblastic beta-adrenergic receptors which decrease osteoblastic activity.

To summarise: *leptin inhibits formation of bone by direct action on mature osteoblasts; it also has some influence on the differentiation and activity of osteoclasts and therefore in the balance of their respective activities.* Research on the metabolic activities of leptin is still in progress. However, results of the many studies so far carried out demonstrate that the skeleton, as every other organ in the body, is also supervised by the CNS and in this leptin plays an important part. There are numerous nerve fibres in bone and bone marrow; their function in the regulation of bone is under intense investigation and it appears that leptin is also involved. *Beta blockers appear to increase bone density, thereby underlining the significance of the nerve supply to the bones.*

Bone remodelling differs in cortical and cancellous bone:

- Cortical bone (80% of the skeleton) is very compact; 90% is calcified, and there is a low surface-to-volume ratio. Therefore remodelling of cortical bone is very slow.
- Cancellous bone with its high surface-to-volume ratio has a much faster rate of remodelling, so that 25% is replaced annually in contrast to only 2–5% of cortical bone.
- *The variable vulnerability of different skeletal areas to osteoporosis depends on*

the relationship between the amounts of cortical and trabecular bone in that particular bone or area.

The proportion of cancellous bone in different parts of the skeleton:

- Lumbar vertebrae 75%
- Ankle bones 70%
- Proximal femur 50–75%
- Distal radius 25%
- Middle of radius <5%

Regions of the skeleton with a high proportion of trabecular bone have a correspondingly high endosteal surface and are therefore more liable to undergo unbalanced remodelling and to loose bone. Consequently, it is in these areas that bone loss can first be measured.

The RANK / RANKL / Osteoprotegerin System

The RANK/RANKL/Osteoprotegerin cytokine system plays a key role in the regulation of and in "coupling" within the processes of remodelling. The discovery of this cytokine system was a milestone for understanding osteoclastogenesis and the regulation of bone resorption as well as the processes of local bone remodelling. Osteoprotegerin is an important member of the tumor-necrosis factor-receptor family which is produced by osteoblasts and which blocks the differentiation of osteoclasts from their precursor cells and thus inhibits resorption of bone. RANKL (receptor activator of NF-kb ligand also known as osteoprotegerin ligand, OPGL) and its receptors RANK and osteoprotegerin (OPG) are the key components of the regulation of remodelling units. RANKL, a member of the TNF-family is the main stimulus for osteoclast maturation and is essential for osteoclast survival. *The elucidation of the RANK/RANKL/Osteoprotegerin system constitutes a breakthrough for understanding the processes of local remodelling (Fig. 1.8).*

Thus, an increase in the expression of RANKL leads directly to increased resorption and loss of bone. RANKL is also produced by osteoblastic cells and by activated T-lymphocytes. Its specific receptor RANK is located on the surface membranes of osteoclasts, dendritic cells, smooth muscle cells and endothelial cells. The production of RANKL by T-lymphocytes and the consequent activation of dendritic cells represent a connection between the immune system and bone tissues. The close collaboration between bone and hematopoiesis is reflected in the fact that M-CSF is important for osteoclastic differentiation.

The effect of RANKL is regulated by OPG. This is secreted in various organs: including bone, skin, liver, stomach, intestine, lungs, kidneys, placenta and acts as a soluble endogenous receptor antagonist. Numerous cytokines, hormones and

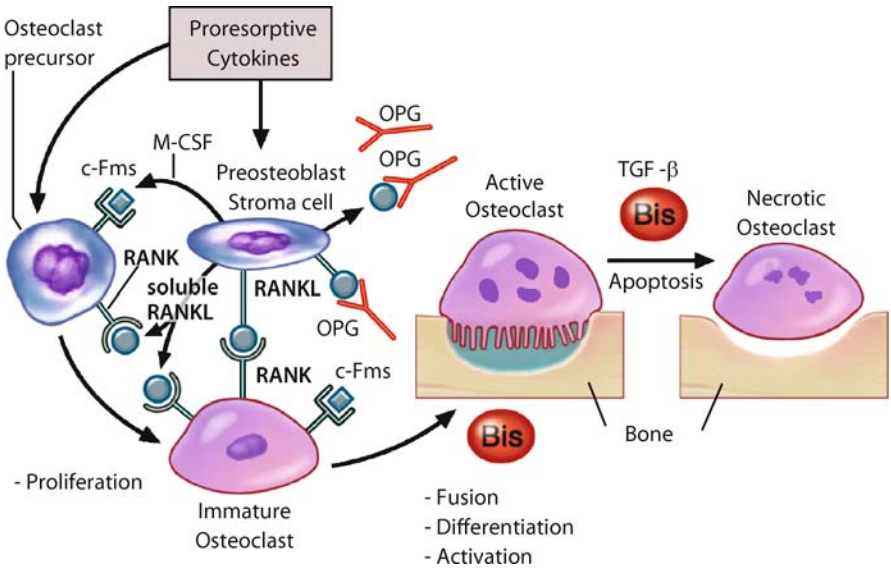


Fig. 1.8 The OPG/RANK/RANKL-System and its control of bone resorption

drugs may stimulate or inhibit the effects of RANKL or of OPG and thereby sway the results to the advantage or to the detriment of either of these two cytokines as follows:

- TGF-β – increased production of OPG
- PTH – increased RANKL/decreased OPG production
- Vitamin D3 – increased production of RANKL
- Glucocorticoids – increased RANKL/ decreased OPG production
- Estrogen – increased production of OPG

Other stimulators of OPG production are: vitamin K, leptin, genistein, raloxifen, statins, e.g. atorvastatin, bisphosphonates, and mechanical forces. However, new facets of these mechanisms are constantly being elucidated by ongoing research, such as the suppression of osteoclastogenesis by alpha-lipoic acid. Moreover it has become clear that the relationship between RANKL and osteoprotegerin contributes to preservation of the balance between resorption and formation in bone remodelling, i.e. "coupling" of these activities.

Animal experiments have also demonstrated the important part played by OPG in the regulation of bone resorption. Genetically manipulated mice, which over-express OPG, develop osteopetrosis; while OPG knock-out mice develop severe osteoporosis. These experiments indicate that OPG functions as a 'brake' for the effects triggered by RANKL.

Quite possibly in the not-so-distant future, OPG may well be introduced as a therapeutic agent in numerous disorders characterised by increased resorption, such as:

- Post-menopausal osteoporosis and osteoporosis of the elderly
- Disorders with locally increased resorption
- Paget's disease of bone
- Periodontitis
- Rheumatoid arthritis
- Transient osteoporosis (bone marrow edema syndrome)
- Osteoporosis in immunologic disorders
- Multiple myeloma
- Carcinomatosis of bone
- Hypercalcemic syndrome

Bone Pain

Clearly, the large number of disorders characterised by increased resorption demonstrates the correlation between, and the influence of the osseous regulatory systems on inflammatory, immunologic and oncologic disorders. Recognition of these insights should receive greater consideration in decisions on treatment strategies in the not-so-distant future.

It should be noted that in arthritis OPG inhibits the effects of the inflammation on the metabolism of bone, but does not influence the inflammation itself.

Age and Bone Mass

The peak bone mass is attained by the age of 25 to 30 years (Fig. 1.9). Some of the multiple pathogenic mechanisms that contribute to subsequent loss of bone (osteoporosis) are:

- Genetic factors
- Foetal and neonatal factors
- Factors during growth
- Nutritional and life style factors
- Menopause and reduction of estrogen in women
- Age and deficiency of testosterone in men
- Reduction of about 80% in adrenal steroids during aging
- Inadequate peak bone density
- Co-morbidities
- Other effects of aging

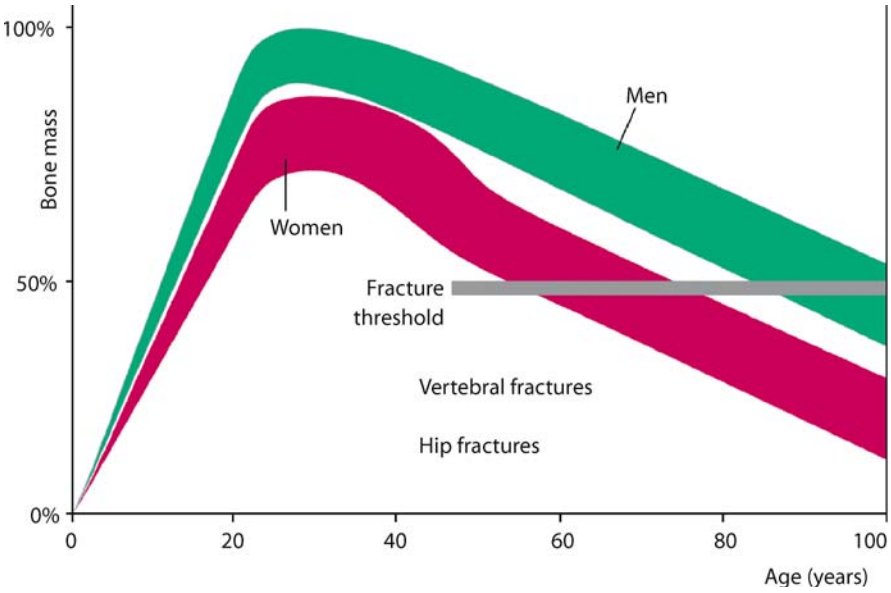


Fig. 1.9 Changes in bone mass with age. Peak bone mass is attained by the age of 30 years, then steadily declines in both men and women. In women there is a phase of rapid loss, which is associated with estrogen withdrawal (menopause). Low bone mass at 50 years of age can be due either to low peak bone mass or to accelerated bone loss in later life, or both

Genetically determined bone loss begins after 30 years of age at the rate of approximately 1% annually, independent of sex. Some of the genes that may influence bone mass and rates of bone loss include the genes responsible for:

- Vitamin D receptor
- Estrogen receptor
- Parathyroid hormone receptor
- IL-1 receptor antagonist
- TGF-β
- Sp1 site in alpha1 chain of type I collagen

Measurements of trabecular bone thickness taken between 20 and 80 years of age have shown that there is a decrease of about 50% during this time period indicating that this loss is genetically determined. In women hormone-associated bone loss begins in the premenopausal period, but increases rapidly to 4% per annum after the menopause. The net result is that women may lose up to 40% of their bone mass from the age of 40 to 70 years. The consequences of the age-related decrease

in bone mass have been illustrated in a study on the risks of fractures in women aged 55–99 (Siris et al. 2006, Results of the National Osteoporosis Risk Assessment (NORA)). Men lose only about 12% of their bone mass during the same period, because hygonadism in men begins about 10 years later than the menopause in women. *Production of adrenal steroids is reduced in both sexes during aging.*

The maximal peak bone mass, reached at the end of puberty with the ossification of the growth plates must be actively maintained during adulthood. For example when nutritional calcium and/or physical activity are inadequate, calcium is constantly extracted from the skeleton at the cost of bone density, rigidity and strength. It should be remembered that normally calcium is deposited in the skeleton during the day and slowly released into the blood at night. *It is also noteworthy that the whole skeleton, from head to feet, is subject to reduction in bone mass with age*. This may well be significant in the occurrence of osteonecrosis of the jaw bones, which has received so much attention lately.

A study carried out on bone biopsies of victims of fatal accidents demonstrated that this age and hormone related bone loss occurs fairly equally throughout the skeleton although slightly more in the spine and the proximal femur.

CHAPTER 2 Disorders of Bone

Manifestations of Abnormalities in Remodelling

As indicated in the previous chapter, bone is subject to constant stress, maintenance, adaptation and repair. Anomalies and alterations in activities of bone cells result in localised and/or systemic disorders of bone. Abnormalities in remodelling can manifest as:

- Skeletal deformities
- Restriction of movement
- Pathologic fractures
- Bone pain
- Hypercalcemic syndrome

Osteoclasts: The Leading Actors in Disorders of Bone

Hyperactive, abnormally activated osteoclasts are characterised by a high resorptive capacity and therefore a high destructive potential (Fig. 2.1a,b), so that numerous osteoblasts need months to repair an osteolytic lesion accomplished by a few osteoclasts in a week. The rate of radial erosion of an active osteoclast is about 12 μm/day; while the resorption cavity is carved out in about 8 days. In Paget's disease of bone for example, a single osteoclast can grow into a giant cell with more than 100 nuclei and correspondingly increased osteolytic activity. Why and how osteoclasts, e.g. in Paget's and in Gorham's disease are able to evade the established "coupling" mechanisms and independently, randomly resorb bone, is still a mystery. The average life span of a labelled nucleus in osteoclasts is 11 days. *Deregulation of osteoclasts is the main cause of nearly all osteopathies (about 90%),* such as osteoporosis (systemic) or osteolysis (local), accompanied by spontaneous fractures and hypercalcemia. *The deregulated and hyperactive osteoclasts are the key to over 90% of all progressively destructive disorders of bone.*

There are only two osteopathies in which increased osteolytic activity is not involved: *osteopetrosis* (osteosclerosis) due to osteoblastic bone formation with inadequate resorption, and *osteomalacia* due to inhibition of mineralisation by lack of vitamin D. However, even in osteomalacia, osteoclasts are indirectly involved through secondary hyperparathyroidism (HPT). In osteopetrosis, various

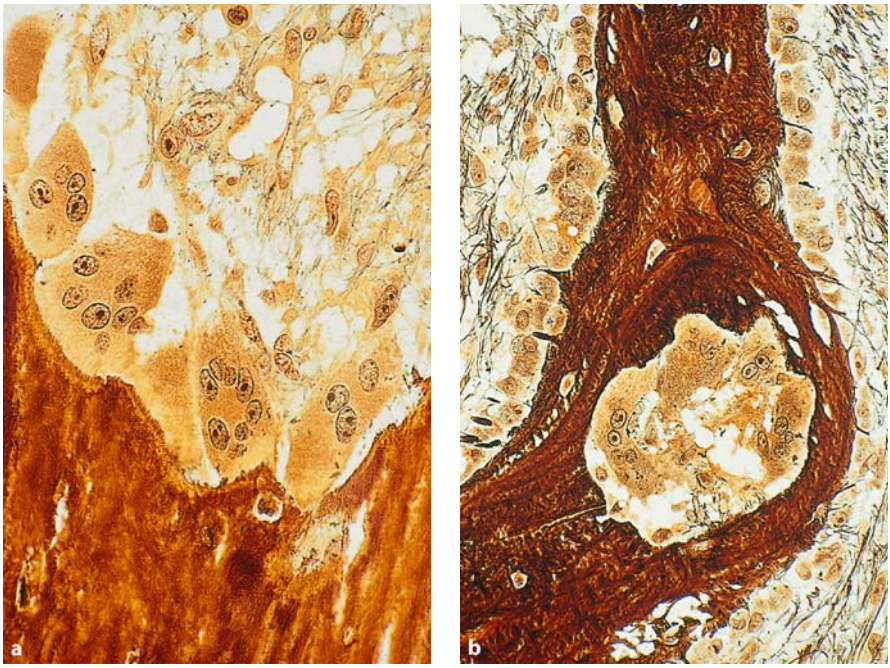


Fig. 2.1a,b Inordinate osteoclastic activity. **a** Numerous hyperactive osteoclasts and disorganized resorption of bone in Paget's disease of bone. **b** Classic appearance of dissecting osteoclastosis in HPT

genetic and other factors inhibit osteoclast development and function and lead to an increase in bone mass and finally to osteosclerosis/petrosis. But the dense bone produced is not proportionately strong and is therefore liable to fracture.

Deregulation of the following factors/activities is involved in osteopathies:

- Intracellular signalling
- Cellular receptors
- Cellular attachment
- Cytokine production
- Activities of various enzymes
- Various non-genomic factors, systemic hormones and others

Today, first and foremost, hormones and drugs that decrease osteoclastic activity are required for prevention and treatment of bone disorders. There are four possible approaches to correct the increased and unbalanced osteoclastic activity:

- *Inhibition* of recruitment of precursors – prevention of osteoclast formation:
- *Decrease* in survival of osteoclasts – induction of apoptosis

- *Inhibition* of osteoclastic activity – prevention of resorption/osteolysis
- *Interference* with the interaction between osteoclasts and the surface of bone – prevention of osteoclast attachment

Bisphosphonates, due to their high degree of efficacy and few side effects, have become the agents of choice for inhibition of osteoclastic activity. Calcitonin is now mainly used for fast relief of bone pain. Other substances are also utilised for their inhibitory effect on osteoclastic activity, but each has its own limitations. These agents include the following:

- Estrogen and analogues
- Selective estrogen receptor modulators (SERMs) (e.g. raloxifene and lasofoxifene)
- Testosterone
- Vitamin D and ipriflavone (a synthetic isoflavenoid)
- Anti-cytokines (IL-1, Il-6,TNFs)
- Osteoprotegerin
- Proton (H^+) pump inhibitors
- Calcium receptor modulators
- Nitric oxide modulators
- Statins
- Enzyme inhibitors (metalloproteinases, cathepsin K)
- Adhesion molecule inhibitors (RGD peptides)
- Intracellular signalling targets (c-src, TRAFs, NF kB)

These are dealt with in the appropriate chapters. However, it must be clearly stated that none of these has the "global applicability" of the bisphosphonates, which can be given to any patient, at any age, for any condition to inhibit bone resorption (possibility not to pregnant and lactating women, see appropriate chapter), although recent studies have not revealed adverse or teratogenic effects on the fetus.

Classification of Osteopathies According to Spread (Topography)

Two types of osteopathies are distinguished:

- *Generalised metabolic osteopathies* such as osteoporosis and osteomalacia. These affect the skeleton as a whole and typical for this group are osteoporosis, osteosclerosis and osteomalacia. Bone marrow metastases also belong to this group even though initially they manifest as focal lesions, solitary or multiple.
- *Localised focal osteopathies* such as Paget's disease of bone, fibrous dysplasia, and, initially, metastases. Bone scans are particularly useful in distinguishing monoostotic from polyostotic involvement. Due to the differences in structure of bone and bone marrow between axial skeleton and extremities, there are also differences in metastatic spread and in the osseous and medullary reac-

tions to the malignant cells. Osteopathies of the cranium, spinal column, flat bones, tubular bones as well as bones of the hands and feet are distinguished. Variable changes occur in the epi-, meta- and dia-physes of the tubular bones. There is one particularly decisive question in disorders of bone (as in oncology) namely: is the condition localised or systemic?

Classification According to Underlying Pathologic Anatomy of the Bones Involved

Five main osseous manifestations, singly or in combination, occur in all disorders of bone, (Fig. 2.2).

Abnormal bone remodelling: Balanced bone resorption and formation is abrogated, i.e. the two processes are *decoupled* – too much bone is resorbed or too little is

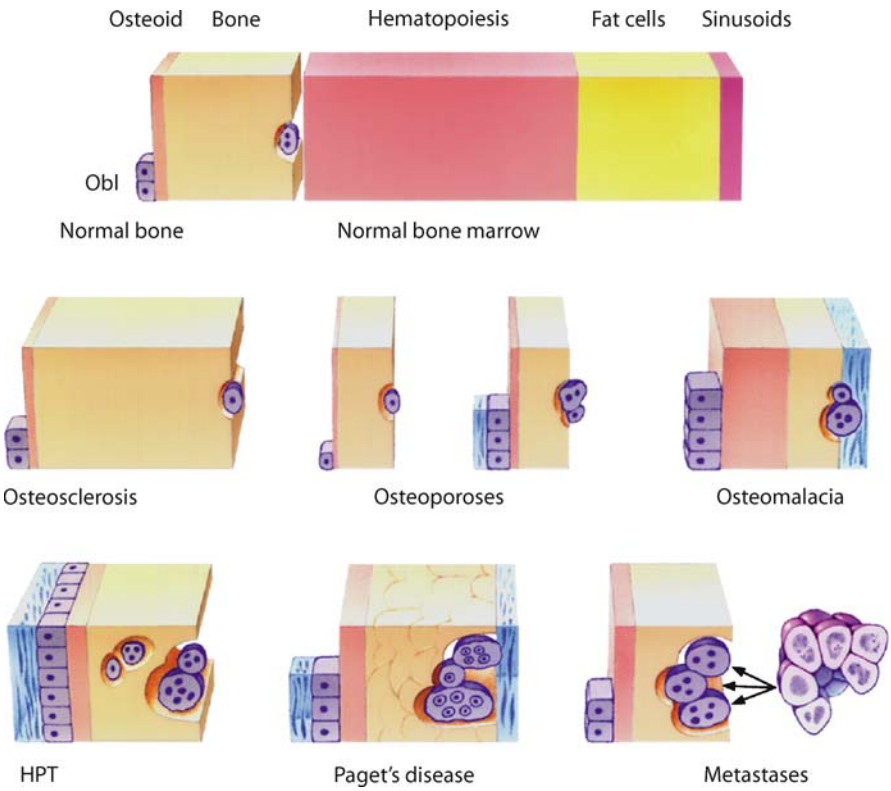


Fig. 2.2 Common osteopathies with examples of the anomalies of bone mass, mineralization and bone remodelling caused by them

produced, leading to alteration and weakening of the architecture of the involved bone and to a tendency to fracture. The inevitable consequence of a negative bone balance is a progressive loss of bone. Mixed pictures of both lytic and sclerotic areas, as well as local thickening may also occur.

Highly active remodelling is seen in hyperparathyroidism, in Paget's disease, in Gorham's disease, in fibrous dysplasia, in osteomyelitis and in some malignancies in the bones.

Functionally inadequate osteoclasts or insufficient numbers of osteoclasts results in osteosclerosis. When osteoclastic hypo-/aplasia is congenital, then the bone marrow spaces are not laid down –"modelled"– in the first year of life. The end result is total ossification of the skeleton - marble bone disease – with a tendency to fracture and insufficient hematopoiesis with life-threatening pancytopenias. Bone marrow transplantation with reconstitution of the normal moncyte-macrophage system is currently the only effective treatment

In summary: deviations from the normal level of bone turnover, and "decoupling" are the two main pathophysiologic abnormalities encountered in osteopathies.

- *Abnormalities of bone mass:* Osteopenia and osteoporosis are defined as conditions with a decreased bone mass and an increased fracture risk. The direct cause is a relative or absolute increase in osteoclastic activity in the absence of a corresponding osteoblastic reaction, leading to a negative bone balance, i.e. a reduction in the total amount of bone – trabecular bone volume and cortical thickness are both reduced. High and low turnover variants occur. Osteopenia may be widespread as in the generalised osteoporosis of aging; or confined to the axial skeleton, as in the osteopenia/ osteoporosis of young adults; or focal as in inflammatory or neoplastic processes. Osteosclerosis signifies expansion of bone volume at the expense of the bone marrow, resulting in poor bone quality (in spite of the greatly increased density) and thereby an increased risk of fractures.
- *Abnormalities of bone matrix: A healthy bone matrix is required to maintain the bone quality necessary for rigidity and strength.* Synthesis of defective collagen as in osteogenesis imperfecta or in Marfan syndrome, inadequate cross-linkage as in vitamin C deficiency, defects in other matrix proteins, all reduce bone quality and increase the risk of fractures.
- *Abnormal mineralisation:* Vitamin D is required for normal mineralisation of the newly produced osteoid. Deficiency or absence of vitamin D leads to increased osteoid production –hyperosteoidosis- which is inadequately mineralised, known as *osteomalacia* in adults and *rickets* in children. Increased formation of osteoid with normal calcification may occur in conditions associated with high bone turnover as in primary HPT.
- *Architectural abnormalities:* These are due to disturbances in modeling, remodelling, and in structure; they include macroscopic changes, microscopic changes, and anomalies occurring at the molecular level. Woven bone, mosaic structures, alterations of trabecular shape and size, discontinuities in the tra-

becular network, decrease in the number of trabecular connections known as the "nodes", micro-cracks and fractures all effect the architecture, strength and weight-bearing capacity of bone.

Pathophysiologic (Pathogenic) Classification

Developmental disturbances: these include congenital disorders such as osteogenesis imperfecta (OI), pycnodysostosis, osteosclerosis and others known as osteodysplasias.

The following *groups of osteopathies* are distinguished:

- Metabolic osteopathies
- Immunologic osteochondritis
- Infections in bone leading to osteopathies : osteomyelitis, granulomas
- Necroses in bone
- Primary bone tumors
- Metastatic bone disease

In many of these disorders of bone, as well as in oncologic and vascular diseases, the RANK/RANKL/OPG system plays a decisive role as mediator. RANKL is the key cytokine for stimulation of formation and activation of osteoclasts, and therefore for increased bone resorption, while OPG acts as an endogenous antagonist to these activities.Other situations are also conducive to unbalanced osteoclast activation, increased resorption and loss of bone. These include reduction in levels of estrogens and of androgens, administration of glucocorticoids, inflammatory diseases with T-cell activation such as rheumatoid arthritis, osteotropic tumors such as myeloma and osseous metastases. Under these circumstances, blockage of RANKL by means of a specific antibody appears to be a promising future option for therapy of bone disorders (in addition to the bisphosphonates).

Diagnostic Investigation

This includes clinical, biochemical and histological investigations as well as conventional X-rays, bone scans and other imaging techniques such as CT and MRI or MRT as indicated.

A careful and detailed clinical history and physical examination initiate the diagnostic investigation: crucial information is frequently gained by careful interrogation of the patient. The patient's symptoms, general state of health, risk factors and any additional illnesses/co-morbidities, as well as medications, are assessed, as these may also influence the state of the skeleton. *Special attention is paid to the oral cavity and the teeth in particular when i.v. therapy with the new more potent bisphosphonates is contemplated.*

Pain as a primary symptom must be thoroughly investigated with respect to its localisation, duration, intensity, characteristics and sensitivity. Meticulous palpation of the skeleto-muscular system in the effected areas can greatly aid this clarification. The physical examination should include inspection of the skin, eyes, teeth, spine, ribs, cranium and limbs. Observation of the patients' gait, coordination and other movements is required. Specific details are given in the appropriate chapters.

X-rays of the skeleton: Conventional X-rays are indispensable for diagnosis of skeletal disorders. X-rays of the spine are essential for investigation of unexplained back pain, suspected secondary osteoporosis and for the differential diagnosis. High quality X-ray pictures taken under professional guidance are one of the cornerstones of osteology.

Characteristic changes are observed in the following conditions:

- Degenerative, inflammatory changes in joints
- Established osteomalacia
- Advanced osteoporosis
- Bone lesions due to malignancy
- Hyperparathyroidism (HPT)
- Scleroses

Morphometry of X-ray films: X-rays of different skeletal regions are carefully aimed and taken according to the patient's symptoms and presumptive diagnosis. Quantitative morphometry of the X-ray pictures is applied especially in investigations of thoracic and lumber vertebrae and of the hips and the femur. The following calculations are used:

- Vertebral deformation score (Kleerekoper)
- Spine deformity index (Minne)
- Singh index
- Length of the femoral neck

Measurements of bone mineral density (BMD): Two methods are currently in use:

- Radiographic techniques (QCT, pQCT and DEXA)
- Ultrasound techniques (QUS)

The WHO advocates the use of DEXA for bone densitometry of the lumbar spine and/or hip, to establish the diagnosis of osteoporosis. The ankle, radius, tibia and phalanges can also be measured. However, measurement by DEXA of bone density at the hips and/or lumbar spine is considered by many as the gold standard of bone density measurements used to establish the diagnosis of osteoporosis. These techniques are described in detail in the chapter on osteoporotic syndromes (Chapter 4).

Bone scans: These are performed after administration of technetium 99, gallium, or a bisphosphonate labelled with technetium 99. The advantage of a bone scan lies in the rapid assessment of the whole skeleton. Focal *hot spots especially* in the spine indicate fractures, as well as degenerative, inflammatory or neoplastic lesions. Locally increased uptake may be seen within two days of a bone fracture. However, due to the poor structural detail in a hot spot targeted X-rays or other films are required for clarification.

Magnetic resonance tomography (MRT): This method does not involve radiation, it highlights the bone marrow and differentiates between yellow adipose tissue and red hematopoietic bone marrow. MRT is the method of choice for investigation of suspected malignant lesions or local edematous processes. *It is also the ideal method for distinguishing between osteoporotic and metastatic fractures of the spine.* When MRT is applied together with the latest methods of contrast enhancement and gradient-echo-sequencing, the quality of the pictures and therefore their diagnostic capacity is greatly increased so that MRT is now considered essential in the evaluation of soft tissue components and of the bone marrow.

Laboratory Investigations (Table 2.1)

These should be carefully chosen in the light of the clinical picture and results of the imaging techniques outlined above. However, it is worth mentioning that

Table 2.1. Biochemical parameters of important bone diseases

Disease	Cardinal Symptoms	Plasma			Urine		
		Ca	P	AP	PTH	Ca	Dpd
Osteoporosis	Fractures, habitus	N	N	N	N	N	N
Osteomalacia	Bone pain, deformations	(↓)	↓	(↑)	↑	↓	(↑)
Osteogenesis imperfecta	Fractures, blue sclerae	N	N	N	N	N	N
Paget´s disease of bone	Bone pain, deformities	N	N	↑	N	N	↑
pHPT	Bone pain, hypercalcemia	↑	↓	↑	↑	↑	↑
Renal bone disease	Bone pain, variable	(↓)	↑	(↑)	↑	(↓)	(↑)
Metastatic bone disease	Bone pain, anemia	↑–↓	(↓)	(↑)	N	(↑)	(↑)

AP alkaline phosphatase
PTH parathyroid hormone
Dpd deoxypyridinoline
P phosphate
Ca calcium
pHPT primary hyperparathyroidism

relatively few routine tests are diagnostically specific, exceptions are the acid and alkaline phosphatases, and of course the specific markers of bone resorption and formation (see below). Nevertheless, laboratory screening, including the following blood tests, has proved its value in clarification of osteopathies:

- Erythrocyte sedimentation rate (ESR)
- Complete blood count
- Calcium and phosphate (serum)
- Alkaline phosphatase (serum)
- Glucose (serum)
- Transaminases and gamma-GT (serum)
- Creatinine (serum)

In addition, when specifically indicated:

- T3, T4, TSH
- Estrogen and/or testosterone
- Vitamin D metabolites (1,25-hydroxy vitamin D and calcitriol)
- Parathyroid hormone (PTH)
- Electrophoresis and immunoelectrophoresis
- Tumor markers (PSA, CEA, CA 15-3 and others as clinically indicated)

Markers of bone remodelling: Methods are now available to identify products of bone remodelling in blood and urine:

Parameters of bone formation: Osseous alkaline phosphatase, osteocalcin, (e.g. N-MID osteocalcin), osteonectin and carboxyterminal propeptide of type I procollagen (PICP in serum, PINP).

Parameters of bone resorption: The *crosslinks* released when collagen is broken down enter the blood and are excreted in the urine. Markers of type I collagen, such as *deoxypyridinoline* and cross-link *telopeptides*, are commonly used as markers of bone resorption. Amino-terminal telopeptides (NTX) are distinguished from carboxy-terminal telopeptides (CTX, beta-crosslaps) telopeptides. *Tartrate-resistant acid phosphatase* (TRAP) is released by active osteoclasts, and because the level in the serum, in particular that of the TRAP isoform 5b reflects the rate of bone resorption it is used as an indicator of osteoclastic activity, and as a sensitive and specific marker for monitoring anti-resorptive treatment.

The RANKL/RANK/OPG-system: The serum levels of these substances in disorders of bone can now be determined by means of ELISA. These levels provide information required for diagnosis, staging, disease activity, i.e. degree of remodelling, estimation of risk factors, and of effects of therapy.

Bone biopsy: The unique attraction of a bone biopsy is that it allows direct visualisation of bone and its cells, as well as the bone marrow, i.e. all elements of hematopoiesis and of the stroma. Most biopsies are taken under local anesthesia from the posterior iliac crest using a manual needle or trephine. This procedure is relatively simple and is accomplished without complications in the vast majority of cases.

Modern techniques of fixation and embedding (especially embedding in methacrylate) and staining for conventional histology as well as immunohistology enable accurate assessment of bone structure, architecture, bone cells, remodelling, mineralisation and all components of the bone marrow; thereby providing a reliable tool for diagnosis as well as for monitoring the effects of therapy – the latest drugs require a detailed evaluation of the tissues comprising bone and bone marrow.

Histomorphometry is mainly carried out in clinical trials. It can be performed even on sections of relatively narrow biopsies. Today bone biopsies are widely used for investigation of unclear and malignant conditions of bone and bone marrow such as metastatic involvement as well as secondary osteoporoses. From a technical point of view, the Jamshidi and other similar needles are relatively easy to use, the biopsies are taken in the ambulatory day clinic without complications in the vast majority of patients. *Bone biopsies provide representative samples of bone and bone marrow for osteologic and hematologic evaluation.*

CHAPTER 3 Bisphosphonates

Historical Review

The bisphosphonates constitute a group of pharmacological agents first synthesised in the 1880s but developed over the past 30 years for diagnosis and treatment of disorders of bone and anomalies of calcium metabolism. The fundamental research carried out by H. Fleisch in the 1960s laid the ground work for the rapid development of the bisphosphonates in medicine.

The starting point was provided by the pyrophosphates which have a central P-O-P binding. Pyrophosphate was widely employed in industry due to its ability to dissolve calcium carbonate. Consequently pyrophosphates were used in washing powders and other soapy solutions to inhibit scale formation. Today they are also used worldwide in toothpaste to prevent and to reduce plaque formation. Due to its strong affinity for calcium phosphate and therefore for bone, pyrophosphate can be bound to 99mTc and utilised for scintigraphy of the skeleton (bone scans).

Moreover, in vivo studies demonstrated an inhibitory effect of pyrophosphates on calcification. Various forms of ectopic calcification could be effectively avoided by parenteral, but not by oral administration. However, there was no influence on osteoclastic resorption due to enzymatic splitting of pyrophosphate when taken orally (half-life of only 16 min).

The bisphosphonates were then discovered during the search for analogues of pyrophosphate. They have similar physical and chemical effects but are resistant to enzymatic splitting and to metabolic breakdown. *This is because, in contrast to the P-O-P binding of pyrophosphate, the P-C-P binding of the bisphosphonates is stable and above all cannot be broken down enzymatically so that their activity is retained. This switch of the binding from P-O-P to P-C-P represented a genuine breakthrough which enabled the development of the potent bisphosphonates which are now in use for therapy of disorders of bone all over the world.*

The first medical application of a bisphosphonate was published in the Lancet in 1969. A 16 month old baby, diagnosed as having progressive myositis ossificans, was successfully treated with oral etidronate to inhibit the extra-osseous calcification.

Subsequently H. Fleisch and coworkers demonstrated, by means of animal experiments, that bisphosphonates inhibit osteoclastic bone resorption and thereby achieve a positive calcium balance. The rapid advances in the diagnosis and therapy of the osteopathies is thus closely bound up with the history of the bisphosphonates – a story of genuine and lasting success in the treatment of disorders of bone.

During the past 30 years new, more potent bisphosphonates have been developed. These have now been extensively applied in medicine, particularly in the fields of osteology, orthopedics, surgery (as a consequence of accidents and other emergencies), as well as in hematology and particularly in oncology. *All osteopathies characterised by excess (absolute or relative) of osteoclastic activity are now treated with bisphosphonates, and it should be noted that this comprises about 90% of all disorders of bone*. Bisphosphonates are now the major drugs used in the treatment of postmenopausal osteoporosis and represent the first-line therapy in the majority of patients. The latest applications of bisphosphonates include their administration for prevention of osseous metastases (administered during adjuvant chemotherapy), for alleviation of bone pain, and for their modulation of the immune and stromal systems in the bone marrow and the bone. Their anti-proliferative activity is under close investigation and some results have already been published for example in multiple myeloma and in metastatic bone disease, and experimentally in sarcomas.

An additional novel application is inhibition of proliferation of the causative organisms in some parasitic infections.

Chemistry

Bisphosphonates are analogues of pyrophosphates which occur physiologically, and in which the oxygen atom of the central P-O-P structure has been replaced by carbon, resulting in a P-C-P group (Fig. 3.1), and this exchange has made them resistant to heat and enzymatic hydrolysis. These bisphosphonates exert strong effects on bone; they also have a high affinity for metal ions, forming soluble or insoluble complexes and aggregates, depending mainly on the pH of the solution.

Further substitutions have enabled synthesis of a series of biologically active bisphosphonates, each of which has its own characteristic potential activity and effect on bone (Table 3.1. and Fig. 3.2). Therefore every bisphosphonate has to be evaluated individually. This is of particular importance because of the rare occurrence of side effects such as renal damage and necrosis of the jaw bones (see below).

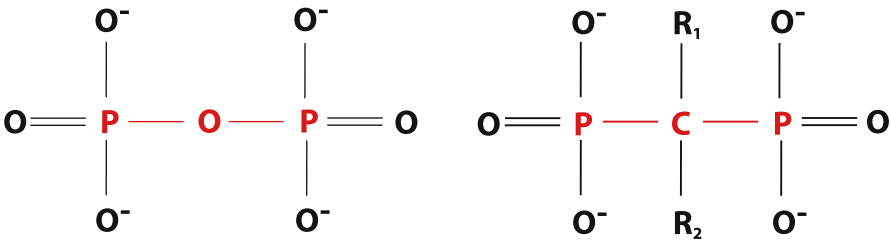
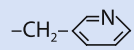
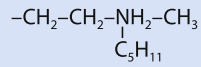
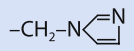


Fig. 3.1 Chemical structure of pyrophosphate and of bisphosphonates

Table 3.1. List of available bisphosphonates according to side chains and relative potency

Substance	Trade Name	R1	R2	Relative Potency
Etidronate	Didronel®	–OH	$-CH_3$	1×
Clodronate	Ostac®	–CL	–CL	10×
Pamidronate	Aredia®	–OH	$-CH_2-CH_2-NH_2$	100×
Alendronate	Fosamax®	–OH	$-CH_2-CH_2-CH_2-NH_2$	1000×
Risedronate	Actonel®	–OH		5000×
Ibandronate	Bondronat® Bon(v)iva®	–OH		10 000×
Zoledronate	Zometa® Aclasta®	–OH		20 000×

For practical purposes, the bisphosphonates are sub-divided into chemical groups according to the alphabetic order of the side chains (Table 3.1):

- Bisphosphonates without nitrogen substitution: etidronate, clodronate, tiludronate
- Aminobisphosphonates: pamidronate, alendronate, neridronate
- Aminobisphosphonates with substitution of the nitrogen atom: olpadronate, ibandronate
- Bisphosphonates with basic heterocycles containing nitrogen: risedronate – pyridine-ring, zoledronate – imidazol-ring

The bisphosphonates used to be given in grams, now only milligrams are given because of their greatly increased potency.

Pharmacodynamics

The bisphosphonates are poorly absorbed when taken orally, but this is compensated for by their greatly increased potency – even 1% of a given dose is effective! They are distributed in the body via the blood stream, stored in the bones, and excreted unchanged by the kidneys. Interactions with other pharmaceutical agents have not been observed. Four compartments of bisphosphonate distribution are distinguished; these determine their pharmacodynamics (Fig. 3.3):

- Gastro-intestinal tract
- Blood
- Bone
- Kidneys

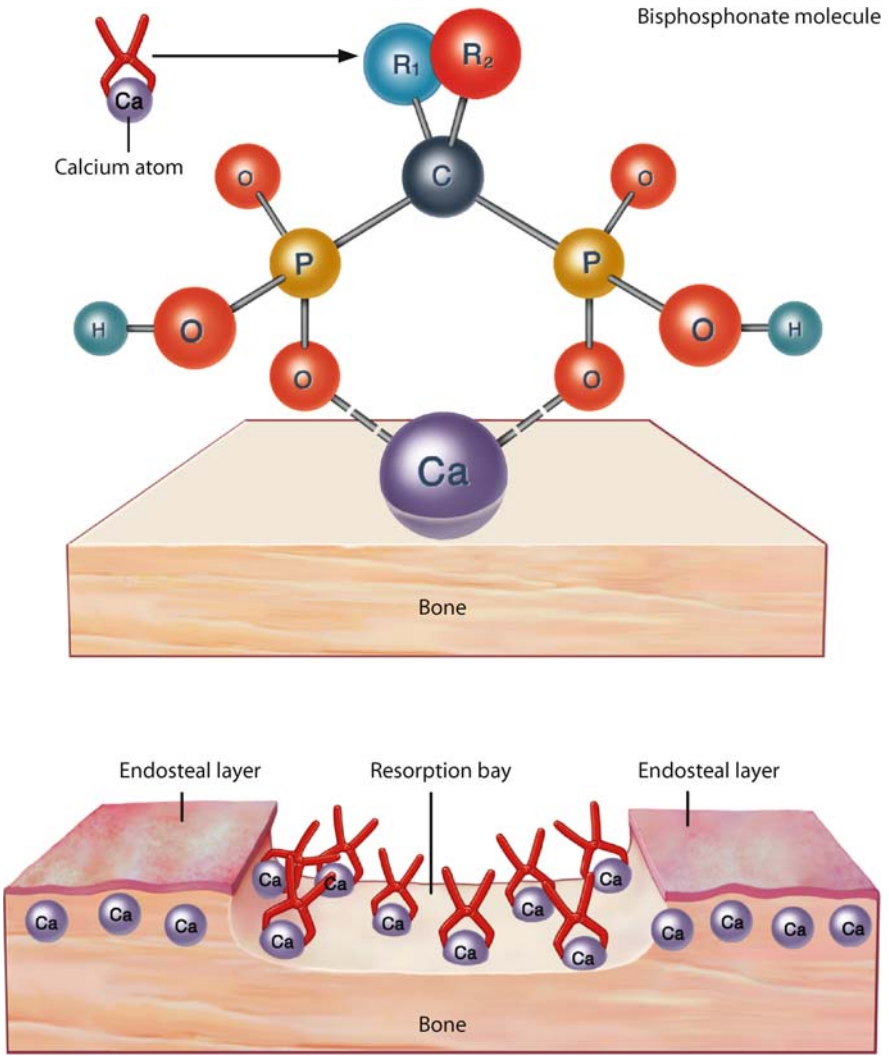


Fig.3.2 Molecular structure of bisphosphonates: they are stable analogues of pyrophosphate with a central P-C-P binding instead of the P-O-P. The various bisphosphonates are distinguished one from another by the ligands R1 and R2. The bisphosphonates depicted here as small tongs, are deposited on the surface of the bone in the resorption lacunae. Here they are taken up by osteoclasts or incorporated into bone by osteoblasts

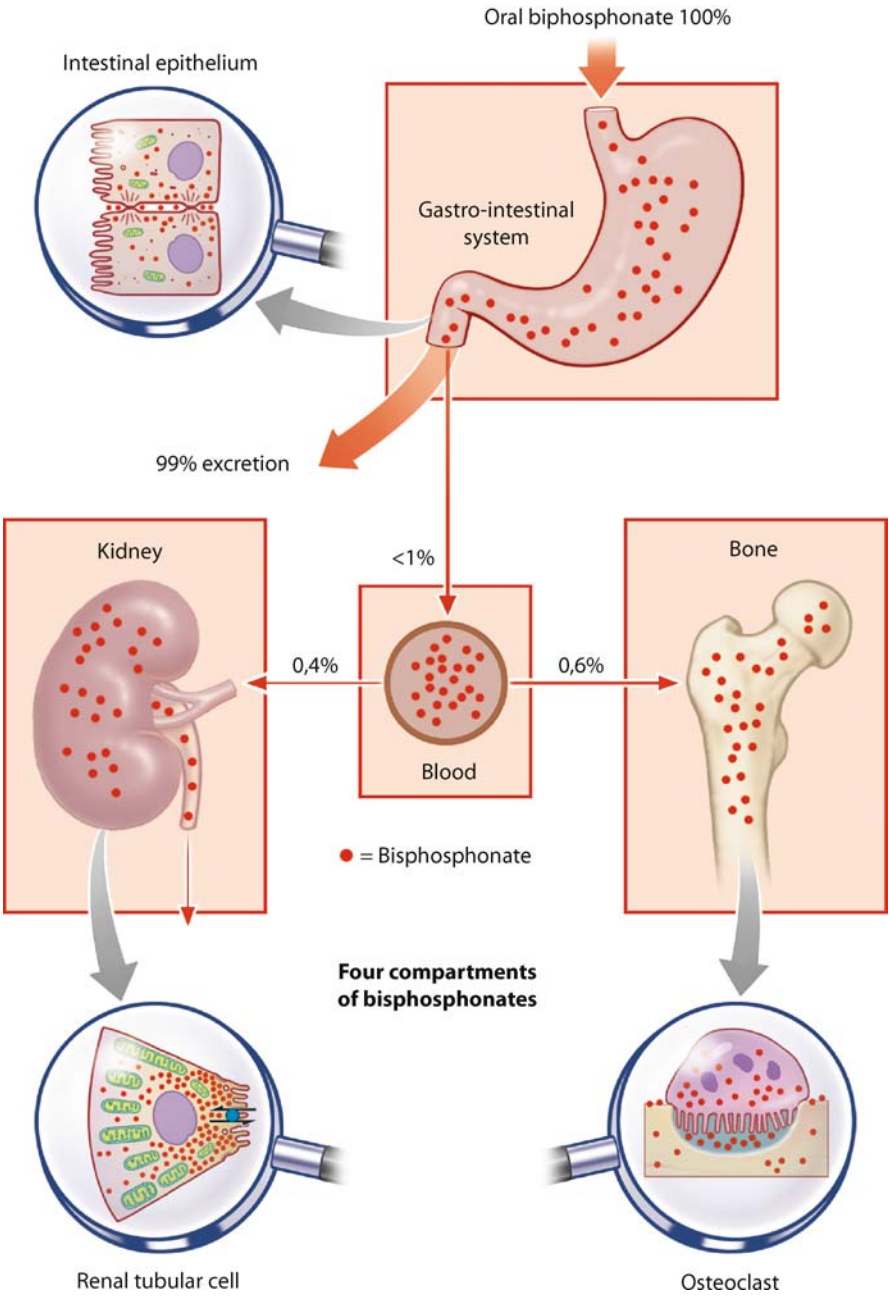


Fig.3.3 Diagrammatic representation of the four compartments of bisphosphonate absorption and excretion: Gastro-intestinal tract, blood, bone and kidney

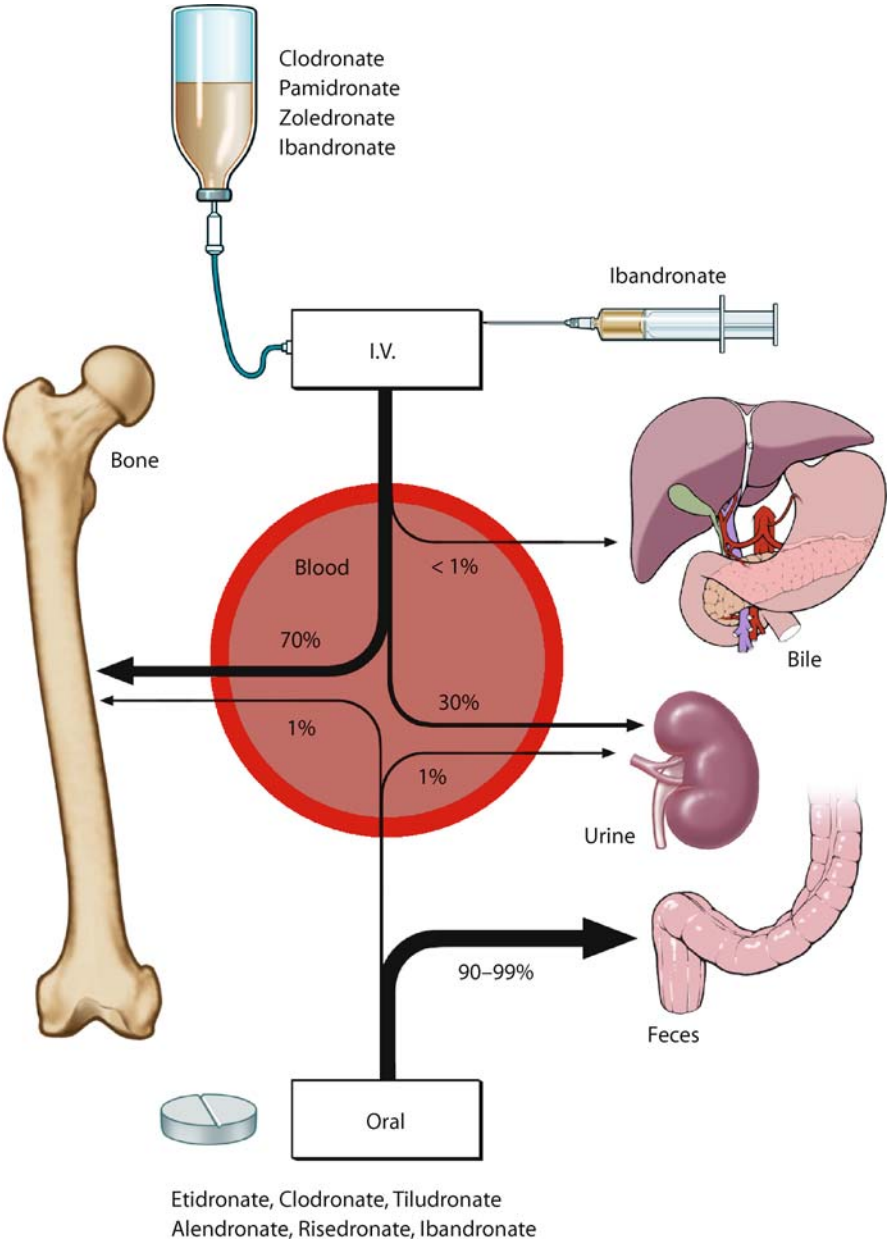


Fig. 3.4 Pharmacokinetics of bisphosphonates

Administration

Bisphosphonates may be taken orally as tablets, given intravenously as infusions, or more rarely as injections (Fig. 3.4). They are also effective when given intranasally or transdermally, and by intramuscular (multiple myeloma) and intra-articular (osteoarthritis of the knee) injections, but these forms of administration are no longer carried out.

Intestinal Absorption

The intestinal absorption of bisphosphonates is minimal. It varies from <1% to 10%, is dose-dependent, therefore increases with higher doses: alendronate 0.76%, risedronate 0.62% and ibandronate 0.63%. However, as mentioned above these doses are effective.

Two characteristics of bisphosphonates are responsible for their poor absorption: their low affinity for lipids, which hinders transport through membranes and into the cell, and their polarity, their negative charge, which prevents paracellular transport. Bisphosphonate absorption is further decreased when ingested together with food, especially food rich in calcium, such as milk and milk products because bisphosphonates form insoluble chelates with the calcium in these products. The presence of other substances in the gastro-intestinal tract such as fruit juices, iron, coffee etc. likewise decreases their absorption. Bisphosphonates are absorbed in the stomach and upper part of the intestine by passive diffusion within about an hour after ingestion. Studies are underway to increase their lipophilicity and facilitate their absorption.

Distribution Half-life

Bisphosphonates are bound to albumin in the blood. Insoluble complexes are formed by means of bi-valent cations: for example two bisphosphonate molecules are attached to magnesium, to calcium or to iron (Fig. 3.5). The variable polarity and lypophilia of the bisphosphonate side chains are responsible for considerable differences in their attachment to plasma proteins which in turn accounts for differences in their half–life values. There are also big differences in the strength of the albumin bonds (from 22% for zoledronate to 87% for ibandronate) and therefore in the time it takes for the bisphosphonates to be eliminated from the plasma (Fig. 3.6). The half-life of zoledronate in the plasma is only 1–2 hours, while that of ibandronate is 10–16 hours. The kinetics of the elimination of the bisphosphonates follows the 4 compartment model (see above). The plasma binding of the bisphosphonates determines their half-life and the kinetics of their elimination by the kidneys.

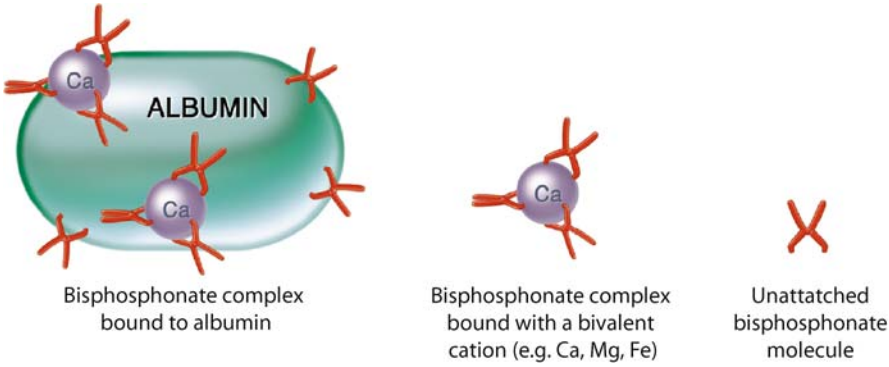


Fig. 3.5 Formation of complexes of bisphosphonates in the serum

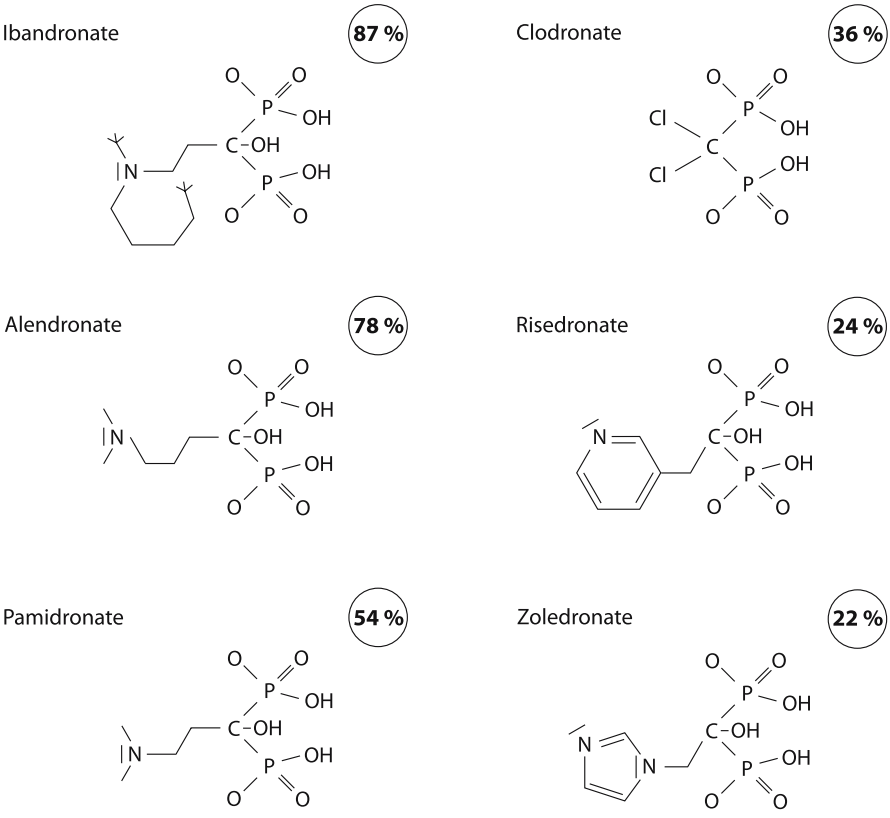


Fig. 3.6 Quantities of binding of various bisphosphonates to plasma proteins

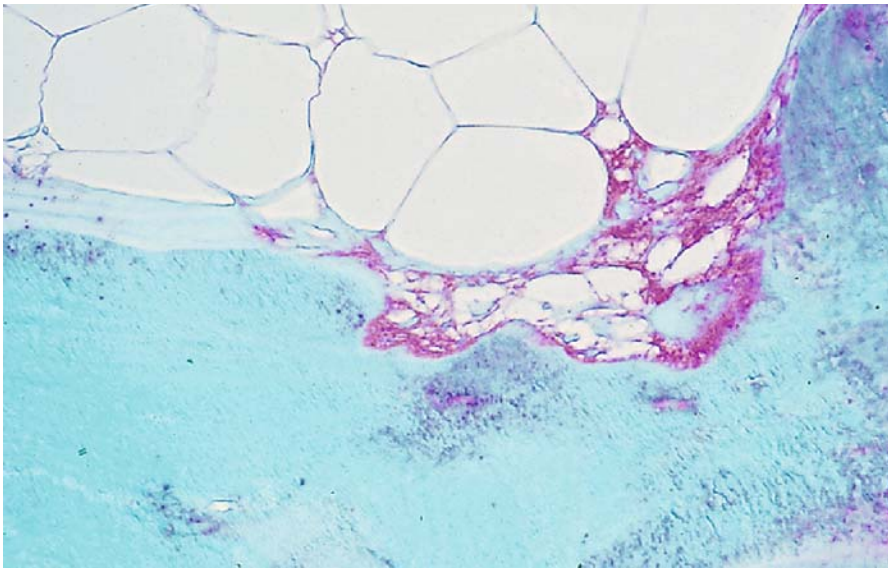


Fig. 3.7 Deposition of bisphosphonate (*red*) on bone in a resorption lacuna and in the cytoplasm of an osteoclast visualised by means of an antibody to ibandronate, in sections of a plastic embedded undecalcified iliac crest biopsy taken from a patient 2 days after 4 mg ibandronate i.v.

Bisphosphonates from the plasma are actively bound to the surface of the bones, especially in the resorption lacunae where they are attached to calcium (Fig. 3.7). *The amount of deposition depends on the extent of resorption surface of bone available.*

Affinity to Bone

By binding to hydroxyapatite, bisphosphonates accumulate at sites of bone resorption and are selectively internalised by actively resorbing osteoclasts. *The different bisphosphonates have different affinities for hydroxyapatite crystals*. The values (adsorption affinity constants, K_L l/mol × 10^6) that have been determined in vitro are:

- Clodronate 0.6
- Etidronate 1.2
- Risedronate 2.2
- Ibandronate 2.4

- Alendronate 2.9
- Zoledronate 3.5

These data extend earlier work on the potential important contribution of mineral binding to the potency and duration of action of different bisphosphonates. *These differences in binding affinities and effects on mineral surface properties are likely to be reflected in the clinical differences among these bisphosphonates: uptake and retention on the skeleton, diffusion of the drug within bone, release of absorbed drug from bone, potential recycling of the desorbed drug back onto bone surface, effects on mineral dynamics and effects on bone cellular function.* Higher affinity bisphosphonates such as alendronate and zoledronate have an avide uptake, a lower desorption, a higher re-attachment and a less diffusion in bone. Risedronate for example has lower kinetic binding affinity than alendronate for the mineral substrates hydroxyapatite and octa calcium phosphate. These differences in bone affinity may contribute to the shorter terminal bone half-life of risedronate and therefore to faster clinical on- and off-responses seen with risedronate compared with alendronate (Nancollas et al. 2006). And indeed, the results of the *FACT-Study* (direct comparison of the effects of two bisphosphonates on bone mass and parameters of bone remodelling) indicated a greater effect of alendronate than risedronate on the parameters measured (BMD and bone turnover markers).

Studies with hydroxyapatite crystals and later with fetal mouse bone explants showed that the presence of a OH substitution in R_1 increases their binding to bone mineral, and that this action was independent of the structure of the R_2 substitutions (van Beck et al. 1998). In contrast, bisphosphonates lacking an R_1 substitution or compounds with other substitutions such as Cl (clodronate) or H (etidronate) had significantly lower binding affinities. The following *ranking of binding affinities of bisphosphonates* for bone according to substitutions at R_1 can be given: OH and NH_2 > H > "no R_2" > Cl, provided that the phosphonate groups remained intact (vanBeck et al. 1998). *But in spite of the specific functions of the ligands R_1 and R_2, all studies strengthen the view that the whole molecule is necessary for the full range of their action on bone.*

Cellular Uptake

Few studies have addressed the question of how bisphosphonates actually enter the cell. Since no specific transport mechanisms have yet been elucidated, the assumption has been made that bisphosphonates are taken up from the surrounding fluid by non-specific pino- and endocytosis. Bisphosphonates have been demonstrated in the cytoplasm, in mitochondria and in other organelles within the cytoplasm of the osteoclasts. Relatively speaking, macrophages, a cell line to which osteoclasts belong, are also active in their up-take. *However, the concentration of bisphosphonates in extra-osseous cells is very low, which explains the lack of toxicity.*

Elimination

20–50% of the bisphosphonate in the plasma is deposited on the bone; about 1% is excreted with the gall, the rest is eliminated by the kidneys into the urine. There are considerable differences between the various bisphosphonates with respect to their elimination. *Long-term studies (more than 10 years) have now clearly demonstrated that the (relatively) minimal amount of bisphosphonate deposited on and in bone has absolutely no influence on bone "quality"; whether it has any biological or clinical significance when subsequently released and excreted and/or "recycled" is still unknown.*

Bisphosphonates exhibit a very strong affinity for hydroxyapatite crystals which are avid bisphosphonate grabbers, and this "binding" process is strictly pH-dependent, so that when, during active resorption, the interface between osteoclasts and bone becomes strongly acidic the previously bound bisphosphosnate is released from its binding to calcium. In contrast to the blood (half-life of 1 to 15 hours) the half-life on the surface of the bone varies from 150 to 200 hours; but once inside the bone, and after the resorption cavity has been filled by the osteoblasts (see below), the bisphosphonates remain attached even for years.

Skeletal retention varies with the different bisphosphonates and a major factor in retention is the rate of bone turnover and the amount of bone surface available. This retention in bone is similar to that of substances such as tetracyclines, fluoride and strontium.

The uptake on the osseous surface appears to be the major determinant of the antiresorptive effect simply because osteoclasts cannot attach to bone covered by a layer of bisphosphonate. *The bisphosphonates are also taken up by the joints and therefore may decrease bone resorption and cartilage degradation in disorders of the joints such as rheumatoid arthritis.*

The prolonged surface attachment of bisphosphonates explains their extended duration of action. The earliest pharmacologic effect is manifest 24 hours after administration and lasts for 2 to 3 weeks after a single dose. After longer periods of administration the effect lasts for 2 to 3 months. There is no evidence that bisphosphonates within the bones retain any pharmacologic activity or exert any harmful effects on the "quality" of the bone involved. Such bone can be resorbed normally even many years later and the bisphosphonates within the bone released.

Following resumption of bone remodelling at previously exposed sites, the incorporated bisphosphonate will be liberated once from the hydroxyapatite crystals, but the fate of this locally released compound is uncertain (Papapoulos 2006). While some will enter the circulation and will appear in the urine, it is not known whether and to what extent the released biphosphonate will be active for the suppression of bone resorption. In all studies with alendronate, risedronate and pamidronate, cessation of bisphosphonate treatment given for 2 to 7 years was not associated with a rebound increase in bone turnover and rapid bone loss, as it occurs after stopping hormone therapy. *These results support the hypothesis that some of the embedded bisphosphonate that is released later is active again at the bone surface* (Landman et al. 1995).

It should be born in mind that different bisphosphonates have different affinities for bone, which influence their activities at the time of initiation, duration, and termination of administration. Moreover, the total amount of bisphosphonate retained in the body varies widely and is related to many factors including type, mode of administration, duration of treatment and others.

Soft tissues and internal organs are only briefly exposed to bisphosphonates in the blood because of their rapid uptake by bone. Occasionally, bisphosphonates may be deposited in organs such as the liver and spleen but only in very small quantities – about 2% of the absorbed dose. The bisphosphonate complexes are then taken up by macrophages of the reticuloendothelial system and excreted. This extra-osseous deposition occurs only with high doses and rapid intravenous infusions.

Renal Clearance

Renal clearance of bisphosphonates is accomplished by glomerular filtration as well as active tubular excretion. Bisphosphonates are passively bourne by the blood stream to the kidneys, the quantity depends on the concentration gradient of the bisphosphonate in the blood. Bisphosphonates released from the surface of bone (T½ 150–200 h) also reach the kidneys by way of the blood stream and are actively eliminated by the proximal tubules.

The process of elimination varies for each of the bisphosphonates as it depends on the properties of their side chains which also determine the different half-lives of the bisphosphonates. *This elimination is supported by evidence for a tri-phasic excretory pattern*:

- T ½ alpha: rapid distribution of the infused bisphosphonates onto bone (and very little elsewhere), with concurrent renal elimination
- T ½ beta: elimination from the blood stream by way of the kidneys
- T ½ gamma: release from the osseous surface, renal elimination

Consequently, excretion of bisphosphonates given by intravenous infusion is multi-phasic – a fast bi-phasic elimination from the blood stream, followed by a lengthier phase with a final elimination half-life of several days. *Even after administration of a number of doses, accumulation in the plasma does not occur. The total body plasma clearance is 7.8 l/h for ibandronate, and 5.0 l/h for zoledronate.*

About half of the amount of bisphosphonate given at any time is excreted unchanged by the kidneys within 24 hours. This renal clearance is dose-dependent. Bisphosphonates have a negative charge so they are only minimally filtered by the glomerular membranes which also have a negative charge. In experiments with rodents, most of the absorbed bisphosphonate was eliminated by active excretion through the proximal tubules, and only about 15% by glomerular filtration.

In the event of very high doses of bisphosphonates (concentrations of more than 4000 ug/min/kg) glomerular excretion can rise to about 54%. The passage from the plasma into the cytoplasma of the tubular cells is passive and depends

on the concentration of the bisphosphonates and their binding to plasma proteins, especially albumin. The transport of the bisphosphonate across the tubular membrane into the lumen is active and therefore requires energy and is limited (Fig. 3.8). The *half-life-time of the bisphosphonates in renal tissue* is very variable from 24 days (ibandronate) up to 200 days (zoledronate). *It is clear that these dif-*

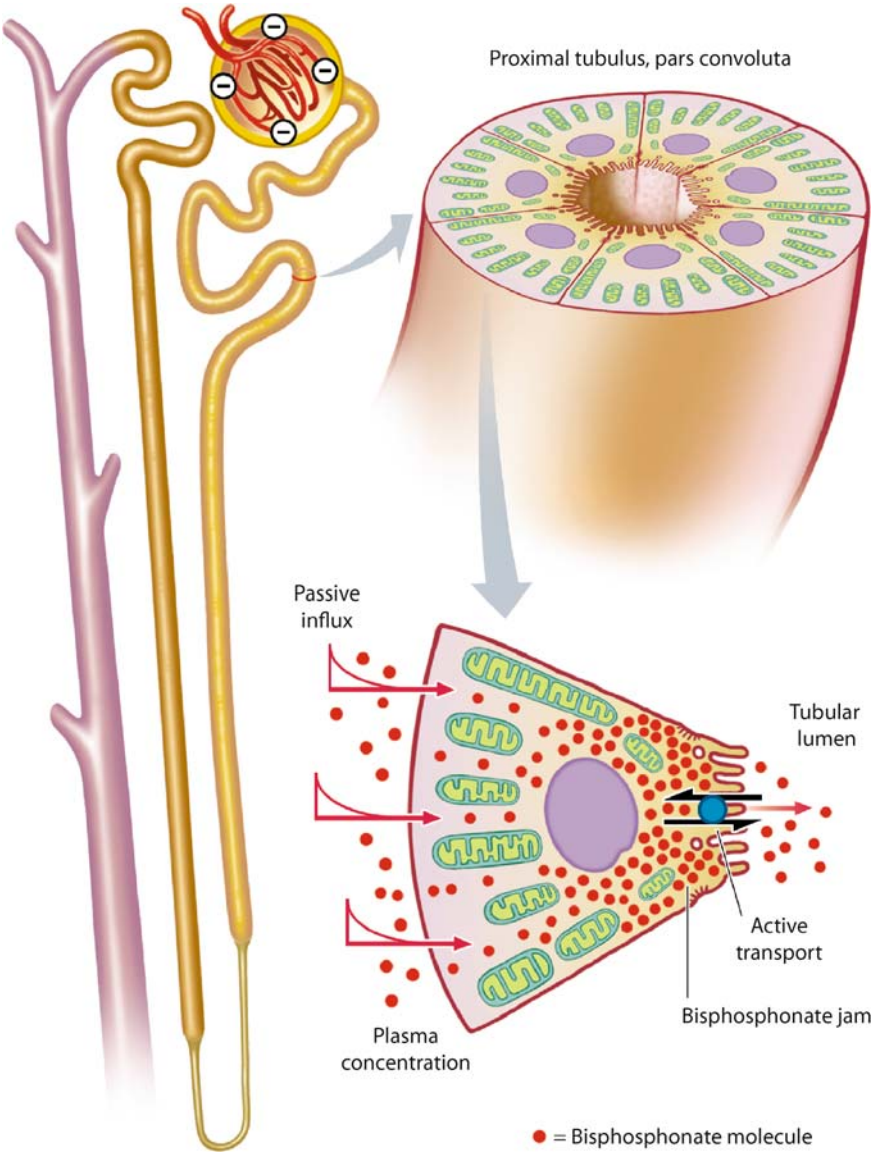


Fig. 3.8 Active elimination of bisphosphonate by renal tubular cells

ferences are responsible for differences in toxicity to the kidney, particularly if and when administration is repeated. These values should be taken into consideration when decisions are made concerning higher dosages and shorter time intervals.

The dose and half-life of the bisphosphonates given to patients with *renal insufficiency* and on hemodialysis must be carefully calculated individually for each patient. Patients whose renal function is limited to a creatinine clearance of 30 ml/min do not require a reduction in the amount of ibandronate administered. But with a lower creatinine clearance, the dose should be reduced from 6 mg to 2 mg. About a third of the dose given to patients on dialysis finds its way into the dialysate. Therefore, patients on dialysis should be given about a third to two thirds of the normal dose i.v. immediately on completion of the dialysis. Patients with renal insufficiency must be treated with special care. Recommendations of the manufacturer should always be followed. *In summary, when dealing with patients with impaired renal function the following precautionary measures apply:*

- Meticulous monitoring of renal function, including creatinine clearance.
- Increase time of the infusion to 1–2 hours.
- Increase the quantity of the infusion solution (cave overhydration).
- Reduce the dose to about 30% to 40% to attain the normal renal elimination rate.
- Check manufacturer's instructions for the particular bisphosphonate used.
- Administration of bicarbonate could be considered as required.

Actions of Bisphosphonates

Clinically bisphosphonates act almost exclusively on bone as outlined above. The mechanisms of action of the bisphosphonates include the following:

- *Inhibition of Crystallisation and Mineralisation*: The major physicochemical effects of the bisphosphonates on bone are decreased solubility of bone substance and changes in mineralisation because of their incorporation into hydroxyapatite crystals and into bone matrix. Due to their affinity for and adherence to solid-phase calcium phosphate, bisphosphonates inhibit the formation, aggregation and dissolution of crystals; but the aminobisphosphonates take up only 1/1,000 to 1/10,000 of the surface saturation capacity of the hydroxyapatite And this plays no part whatsoever in the clinical effects of the modern bisphosphonates. *Clinically significant inhibition of mineralisation with its attendant consequences of fractures and delayed healing simply does not occur. In addition, it is worth noting that the physico-chemical effects of the modern bisphosphonates are clinically insignificant.*
- *Inhibition of mineralisation* is however exploited clinically with the first generation etidronate for prevention and treatment of ectopic calcification. An additional future application of etidronate could be inhibition of calcification

of prosthetic heart valves. Etidronate decreases the experimental formation of kidney stones. It also inhibits plaque formation on teeth and therefore is incorporated in some tooth pastes. However, effective doses of etidronate inhibit normal mineralisation so that its use is strictly limited to the indications listed above.

- *Inhibition of bone resorption: Clinically the most important therapeutic action of bisphosphonates is inhibition of bone resorption, which commences within 1 to 2 days after administration, regardless of the route and frequency of administration, the total amount given determines the overall effect.* The reduction in bone resorption is accompanied by a positive calcium balance. The mechanisms of action of bisphosphonates in the inhibition of resorption are complicated and operate at both the cellular and molecular levels (Fig. 3.9). The target cells are osteoclasts and their precursors. At the biochemical level bisphosphonates interfere with the mevalonate pathway by inhibiting formation of the lipid chains of prenylated proteins and thus also with metabolism of steroids. Bisphosphonates inhibit the formation of lipid chains of prenylated proteins. While statins effect the synthesis of mevalonic acid by inhibition of HMG-CoA-reductase, the bisphosphonates interfere with the earlier phases of prenylation and of steroid synthesis (Fig. 3.9). The following steps in the process of mevalonic acid synthesis are clinically relevant and are targets of the bisphosphonates:
- *The first generation bisphosphonates* (Fig. 3.10) – together with adenosine monophosphate they form an ATP analogue (for example APPCCL2P) which cannot be hydrolised and thereby withholds the energy required for the synthesis of isopentenyl-pyrophosphate.
- *The second generation bisphosphonates* (Fig. 3.11) – these prevent the enzymatic switch of Dimethylallylpyrophosphate (DMAPP,C5-building block) to Geranyl-Pyrophosphate (GPP,C10-building block). The linear formulae demonstrate the steric likeness of ammonium bisphosphonate to the DMAPP-Carbocation stabilised within the enzyme.
- *The third generation bisphosphonates* (Fig. 3.12) – these additionally block the next step in the enzymatic reaction, i.e. conversion of Geranylpyrophosphate to Farnesylpyrophospate (FPP,C15) or to Geranylgeranylpyrophosphate (GGPP,C20). In this instance also, the linear formulae of the ammonium bisphosphonates demonstrate the steric likeness to the GPP-Carbocation which in turn enables competitive inhibition of the enzymic activity.

Small proteins, such as the GTPases, attach themselves to the cellular membrane with the help of the Farnesyl- and the Geranylgeranyl side chains and send specific signals into the cell which regulate numerous cellular functions (Fig. 3.13). However, since these proteins do not possess lipid side chains they are not able to transfer the signals to the cell membrane. Consequently the cells become inactive, they loose their membrane-specific properties, and eventually induce programmed cell death, i.e. apoptosis (Fig. 3.14 and 3.15). Initially, this blockage takes place in the osteoclasts, due to their uptake of bisphosphonates from the osseous

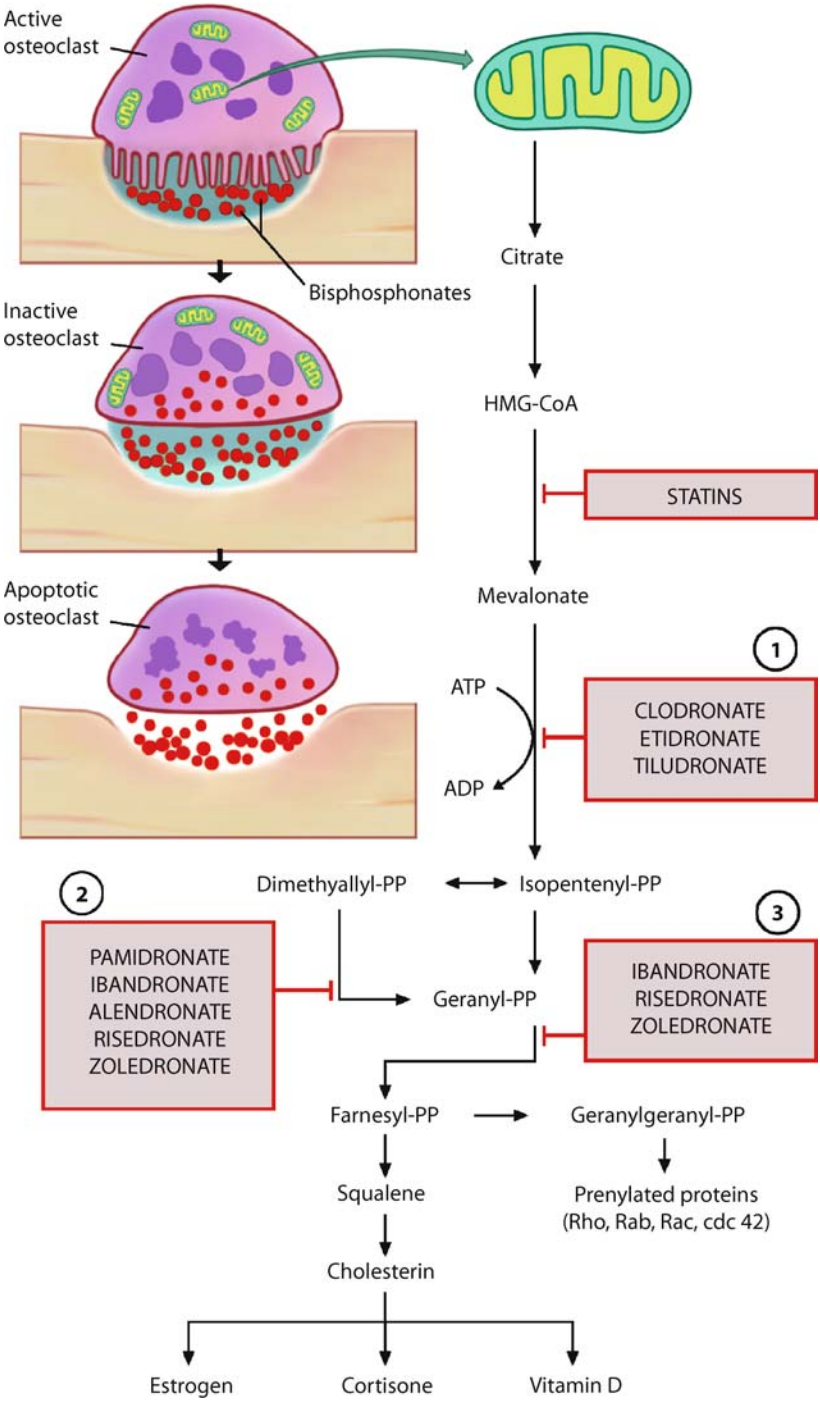

Active osteoclast
Bisphosphonates
Inactive osteoclast
Apoptotic osteoclast
Citrate
HMG-CoA
STATINS
Mevalonate
1
ATP
ADP
CLODRONATE
ETIDRONATE
TILUDRONATE
Dimethyallyl-PP
Isopentenyl-PP
2
PAMIDRONATE
IBANDRONATE
ALENDRONATE
RISEDRONATE
ZOLEDRONATE
Geranyl-PP
3
IBANDRONATE
RISEDRONATE
ZOLEDRONATE
Farnesyl-PP
Geranylgeranyl-PP
Squalene
Prenylated proteins
(Rho, Rab, Rac, cdc 42)
Cholesterin
Estrogen
Cortisone
Vitamin D

Fig. 3.9 Cellular and biochemical mechanisms of action of the nitrogen-containing bisphosphonates: Left: Layer of bisphosphonate (*red dots*) on bone beneath osteoclasts in resorption lacunae. The bisphosphonates are taken up by the osteoclasts which leads to their inactivation and retraction of the ruffled membrane. Higher doses lead to increased apoptosis of the osteoclasts. Right: Biosynthetic pathway for sterols and isoprenoids, which takes place in the cytoplasm of the osteoclasts. Steps of inhibition by statins and bisphosphonates. HMG Co-A = 3-hdroxy-3-methylglutaryl-Co-A, PP = pyrophosphate. 1, 2 and 3 shows the different generations of bisphosphonates each with its own specific targets. Effects of the 2nd and 3rd generation lead to an accumulation of isopentenyl-PP, which in turn stimulates the acute phase reaction. However, this may be reduced by simultaneous administration of clodronate

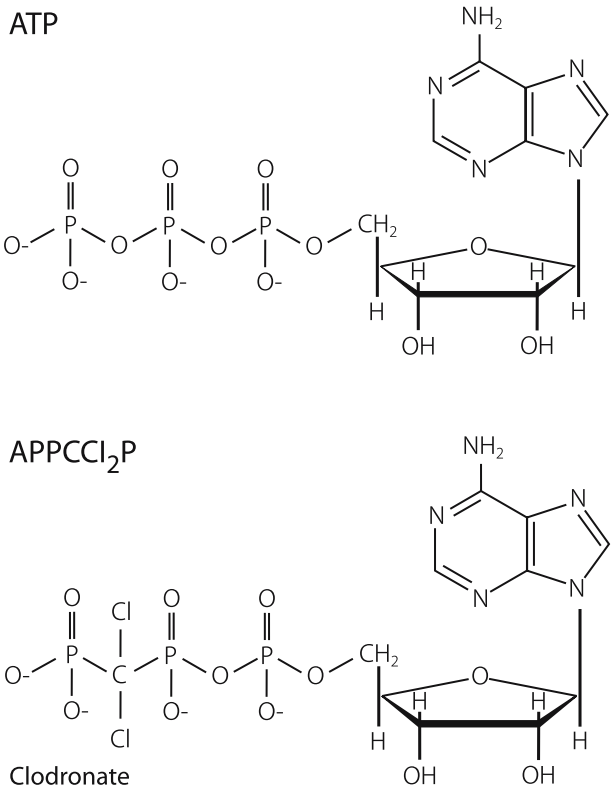


Fig. 3.10 First generation bisphosphonates: Formation of ATP-analogues

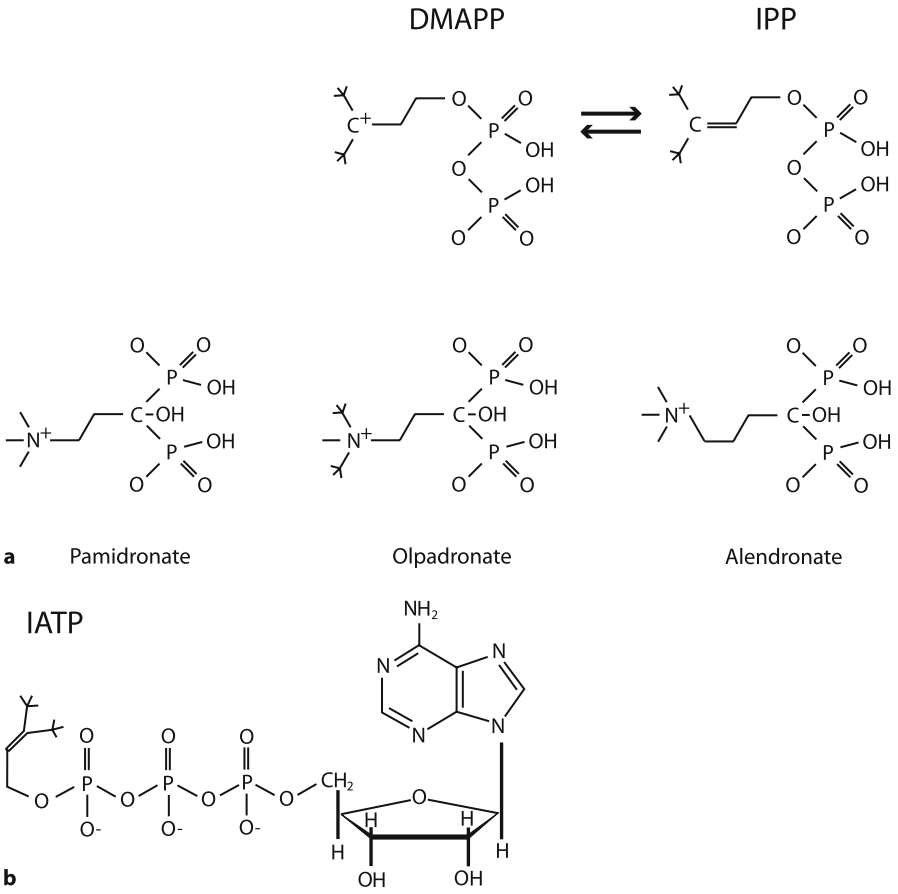


Fig. 3.11 **a** Second generation bisphosphonates: Competitive inhibition of dimethylallylpyrophosphate (DMAPP). **b** Reaction of IPP (isopentenyl-pyrophosphate) with AP (adenosin-phosphate) leads to IPPPA or IATP (isopentenyl-adenosintriphosphate). This substance triggers the release of caspases and thereby programmed cell death (i.e. apoptosis) of the osteoclasts or other macrophages

surface. Within osteoclasts, bisphosphonates cause many changes that affect their ability to resorb bone, such as loss of the ruffled border, disruption of the cytoskeleton and inability to migrate or bind to bone (Russell et al. 1999). Because of the inhibitory effect of nitrogen-containing bisphosphonates, there is an increase in the concentration of IPP, which in turn results in the formation of *isopentenyl ATP* by means of its reaction with AMP. *This combination triggers the excretion of caspases and thereby programmed cell death, i.e. apoptosis.* It should be stressed that the same process occurs in all cells in which bisphosphonates accumulate and it

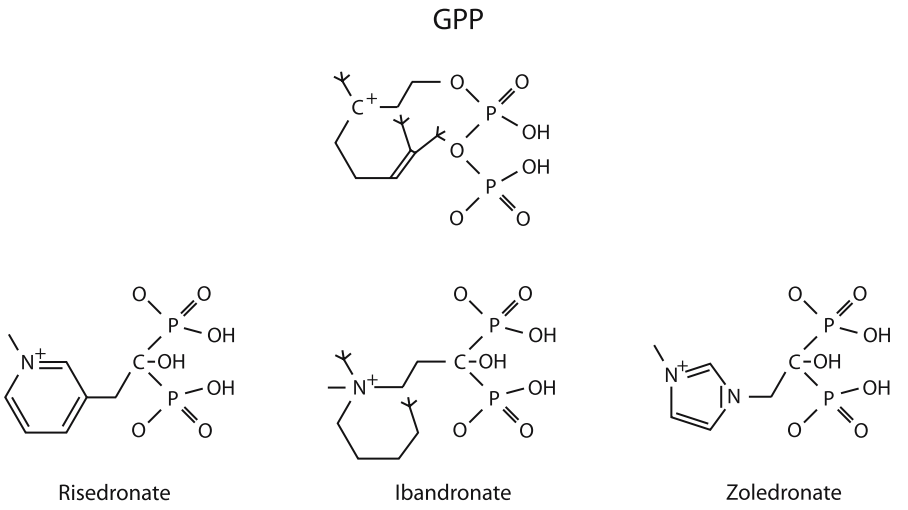


Fig. 3.12 Third generation bisphosphonates: additional competitive inhibition of geranyl-pyrophosphate (GPP)

is responsible for the (desired) effects as well as the (unwanted) side effects of the bisphosphonates. For example, excessive accumulation of bisphosphonates in the renal tubules results in apoptosis and in toxic damage to the renal tubules, leading to renal functional impairment.

Osteoclasts and their precursors are the target cells of the bisphosphonates. At the molecular level, effects such as the inhibition of protein-tyrosine phosphatases, as well as of cell growth and differentiation play important parts. Once inside the cell, bisphosphonates are able to inhibit production of acids, Proton-ATPase, lysosomal enzymes and prostaglandins. It should be stressed that given in sufficient dosages, bisphosphonates also act on tumor cells by inactivation of mevalonic acid metabolism and induction of apoptosis.

In summary, inhibition of osteoclastic resorption is accomplished by means of three different mechanisms corresponding to the 3 generations of bisphosphonates. At the molecular level, inhibition of tyrosine phosphatases (which participate in regulation of cell growth and differentiation) plays a significant role. Once inside the cell, bisphosphonates can inhibit the secretion of acids, proton ATPases, lysosomal enzymes and prostaglandins.

Direct Effects on Osteoclasts

- *Reduction of osteoclastic activity:* As soon as the bisphosphonates have entered the osteoclasts, their cellular activity decreases: synthesis of prenylated pro-

teins such as RAS, Rho, Rac and Rab stops, production of acids and enzymes is halted. Structural alterations of the cytoskeleton (actin, vinculin) can be seen on electron microscopy. Microtubules are depolymerised and the "ruffled membrane" is retracted. The levels of products of bone resorption in the serum are reduced, and the serum calcium concentration is lowered. The toxic damage to the osteoclasts can also be observed morphologically in 3 phases:

- *Inhibition of osteoclast adhesion:* The layer of bisphosphonates on the surface of bone prevents attachment of osteoclasts and thereby development of the appropriate acidic environment essential for resorption. Bisphosphonates are preferentially deposited on the osseous surface beneath the osteoclasts. In addition, as soon as the bisphosphonate has entered the osteoclast cytoplasm, it retracts its ruffled membrane.
- *Decrease in number of osteoclasts:* Bisphosphonates inhibit the proliferation of macrophages that are recruited and undergo fusion to become osteoclasts. This action is possibly mediated by TGFβ. Inhibition of osteoblastic recruitment of osteoclasts may also occur.
- *Induction of osteoclast apoptosis:* Bisphosphonates trigger apoptosis, that is premature cell death, by advancing the time of genetically programmed cell death (Fig. 3.13). This leads to a reduction in osteoclast numbers. The bisphosphonates vary considerably with respect to this action. For example, clodronate induces apoptosis after it has been metabolised and converted into the non-hydrolyzable ATP analogue AppCCl$_2$p. The nitrogen-containing bisphosphonates (N-BPs) induce formation of ApppI, an ATP-analogue, which evokes mitochondria-mediated apoptosis (Mönkkönen et al. 2006). The N-BPs exert their apoptotic effect by inhibiting the metabolism of mevalonic acid with subsequent modification of the prenylation of various intracellular proteins. *To*

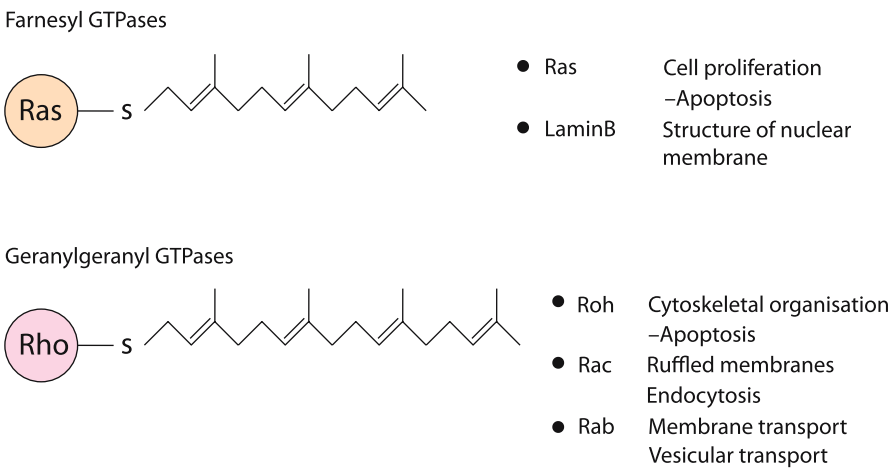


Fig. 3.13 The two most important membrane proteins inhibited by bisphosphonates and their functions

summarise: the bisphosphonates inhibit lipopolysaccharide and parathyroid hormone induced osteoclast differentiation, fusion, attachment, actin ring formation and activation, in simple terms, the whole process of resorption of bone.

Effects on Osteoblasts

It was recently shown that bisphosphonates stimulate osteoblasts to produce a factor (osteoclast resorption inhibitor, ORI), which inhibits osteoclast recruitment and activation (Fig. 3.14). *Bisphosphonates stimulate proliferation and osteogenic differentiation of bone marrow stromal cells and thus promote osteoblastic bone formation*; therefore the function of osteoblasts is influenced by bisphosphonates both directly and indirectly (Fig. 3.15). This was demonstrated in bone biopsies taken from patients with multiple myeloma under therapy with bisphosphonates. An increase in osteoblasts and osteoid seams was observed and confirmed by histomorphometry.

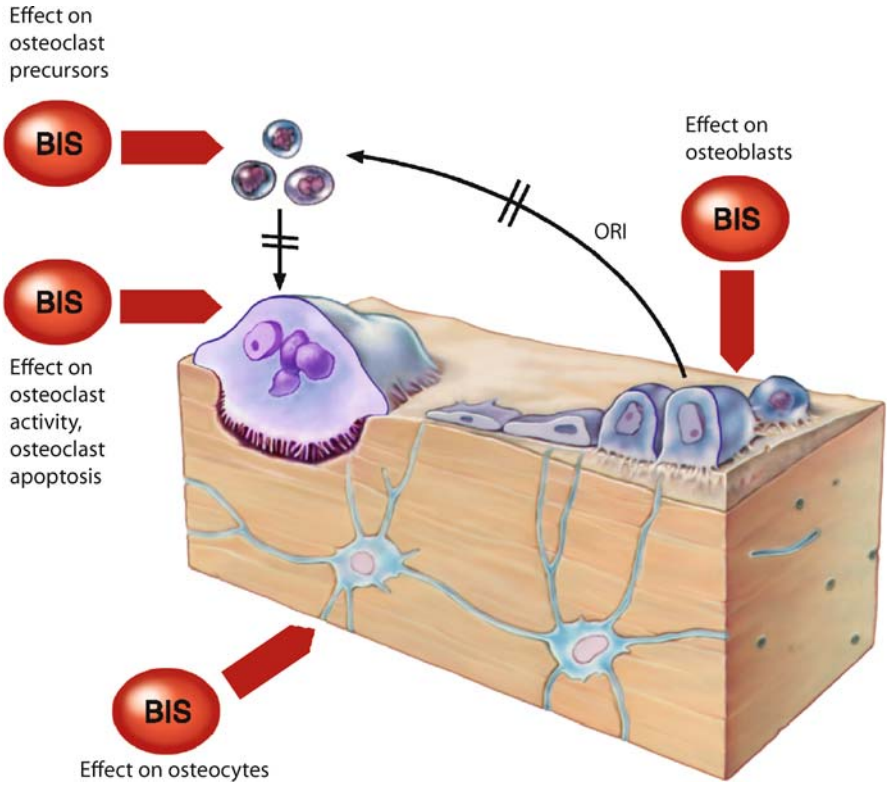


Fig. 3.14 The four most important cellular targets for bisphosphonates in the bone remodelling unit (BRU). *ORI* Osteoclast Resorption Inhibitor

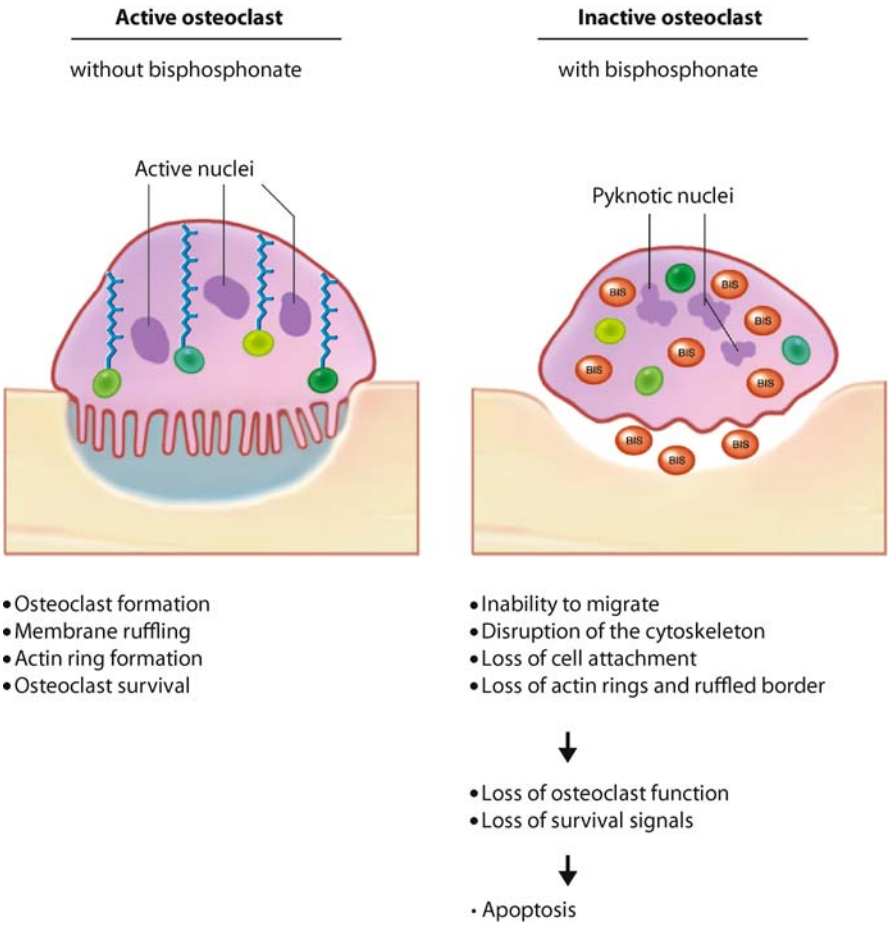


Fig. 3.15 Bisphosphonates inhibit the production of membrane proteins in the osteoclast causing its inactivation and apoptosis

Effects on Osteocytes

Few studies have dealt with the influence of bisphosphonates on osteocytes. It is well known that glucocorticoids have a negative effect on osteoblasts and osteocytes and that this may be mitigated by bisphosphonates, thereby increasing the pool of osteoblasts and osteocytes and exercising a positive influence on osteocyte function and on bone quality. The presence of bisphosphonates in osteocytes and in their canaliculi has been demonstrated by immunohistochemistry on sections of bone biopsies. Recent evidence suggests that the *inhibition of osteocyte apoptosis* by bisphosphonates is mediated through the opening of connection 43 hemichan-

nels and activation of extracellular signal-regulated kinases (Plotkin et al. 2005). More studies are urgently required to clarify the direct effects of bisphosphonates on the micro-architecture of bone, including the trabecular network, and on serologic estimates of osteocyte function.

Effects on Immune System

Some bisphosphonates (e.g. pamidronate) stimulate cytokine production by macrophages and other immunocompetent cells. There is also a significant decrease in the number of circulating lymphocytes, especially natural killer cells and T lymphocytes both CD4 and CD8 positive. This decrease is probably caused by an increase in acute-phase reactants such as C-reactive protein, IL-6 and TNFα. In contrast, ibandronate stimulates a moderate increase in lymphocytes within 10 hours, whereas clodronate has no apparent effect. *Afferent nerve fibres in bone may also be influenced by inhibition of release of neuropeptides and neuromodulators, which would explain the rapid analgesic effect of bisphosphonates on bone pain.*

Anti-angiogenic Effects

Both in vivo and in vitro studies have demonstrated the qualitative and quantitative anti-angiogenic actions of bisphosphonates, illustrated in bone biopsies of patients with multiple myeloma on therapy with bisphosphonates. The mechanism of endothelial cell inhibition presumably includes down-regulation of integrins and laminin receptors. Possibly negative actions on vascular endothelial growth factors (VEGFs) are also involved. This is indicated by the rapid decrease in the levels of these factors in the serum of patients shortly after administration of bisphosphonates. *Combinations with chemotherapeutic agents such as the taxanes increase the anti-angiogenic action of bisphosphonates.*

Effects on Tumor Cells

Interactions of tumor cells with the vascular system, the immune system and the bone marrow stroma are outlined in Fig. 3.16.

Bisphosphonates appear to slow down the rate of tumor growth by inhibiting intracellular signal transduction, which stimulates apoptosis, i.e. an antiproliferative effect. This apoptotic effect of pamidronate has been demonstrated in human myeloma cells. The inhibition of osteoclasts results in decreased IL-6 production and thereby release of growth factors from the bone matrix is also decreased. There are indications that bisphosphonates interfere with the establishment of osseous and probably also visceral metastases. Recent in vitro studies have highlighted the

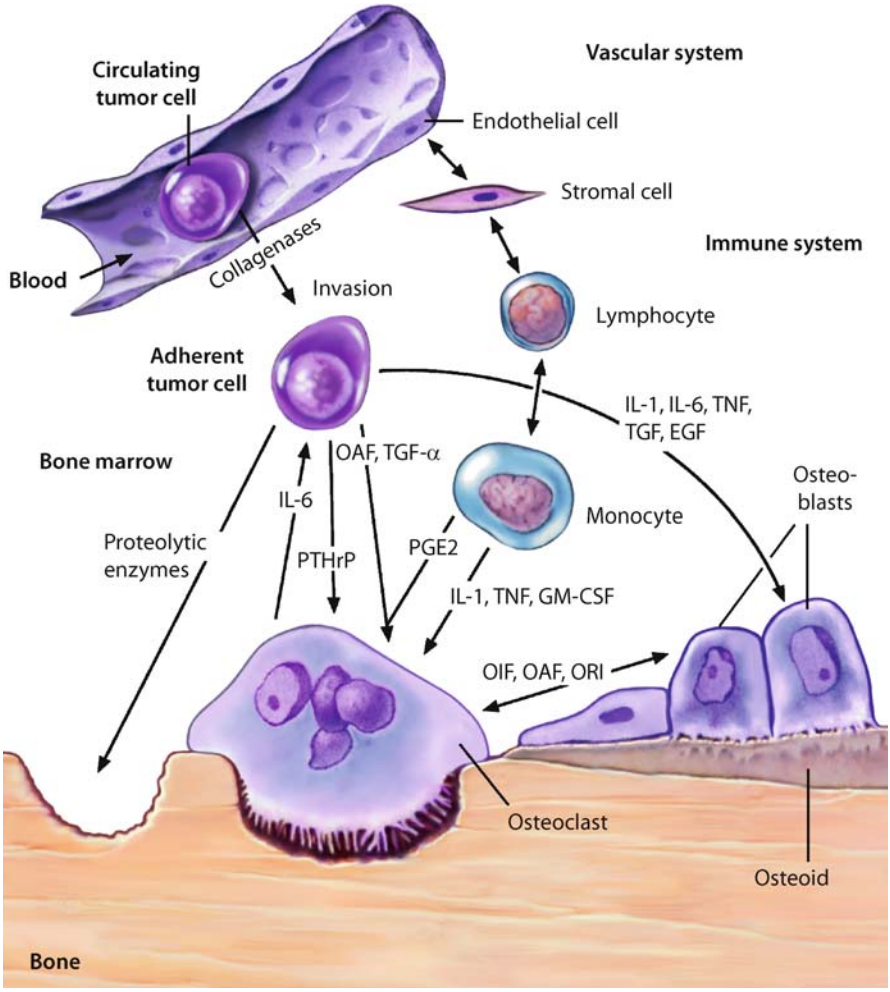


Fig. 3.16 Demonstration of interactions between tumor cells, blood vessels, bone, bone marrow, stroma and immune system

direct toxic effect of the modern bisphosphonates on tumor cells leading to their apoptosis. *Recently it was shown that nitrogen-containing bisphosphonates induce formation of a novel ATP analogue (ApppI), which evokes mitochondria-mediated apoptosis (Mönkkönen et al. 2006). This action may account for the direct antitumor effects of the nitrogen-containing bisphosphonates. They also prevent cancer adhesion to bone by their inhibitory effect on protein prenylation (Roelofs et al. 2006). In addition, as shown in these experiments, bisphosphonates together with standard chemotherapeutic agents induced a greater degree of toxicity and apoptosis of tumor cells than that achieved by chemotherapy alone.*

Effects on Protozoa

Bisphosphonates inhibit proliferation of trypanosoma cruzi, leishmania donovani, toxoplasma gondii and plasmodium falciparum. This has been demonstrated by studies in vitro and in animals, indicating the potential of bisphosphonates for treating parasitic protozoan infections responsible for major social hardships and economic losses in countries in which these parasites are endemic. One of the actions of bisphosphonates in these organisms is inhibition of sterol synthesis at the pre-squalene level, thereby inhibiting their proliferation.

Effects on Arterial Calcification

The bisphosphonates alendronate and ibandronate inhibit calcification of arteries and heart valves at doses comparable to those that inhibit bone resorption, as shown in experiments with rats. These results support the hypothesis that arterial calcification is linked to bone resorption. The mechanism of this linkage remains to be established; results of clinical trials have not yet been reported. New data have shown that the RANK/RANKL/OPG-system plays an important role in the linkage of osteoporosis and arteriosclerosis.

Effects on Fracture Healing

Animal experiments had previously shown that high doses of etidronate interfered with the healing and mineralisation of fractures. This does not apply to the modern aminobisphosphonates, which can be taken without risk by patients with fractures. In addition, animal experiments have shown that under therapy with these bisphosphonates

- the formation of callus as well as its calcium content were increased,
- the disruption of the healing process did not occur, and
- the final weight-bearing capacity of the healed bone was not reduced.

Effects on fractured bone in special conditions, e.g. osteogenesis imperfecta are dealt with in the appropriate chapters. *To summarise: bisphosphonates can safely be given to patients with osteoporosis who have sustained a fracture. In cases with severe osteoporosis and/or multiple fractures anabolic agents are preferable as first-line therapy followed by bisphosphonates, (see appropriate chapter).*

Effects on Resorption of Cartilage

Some of the modern bisphosphonates are able to suppress local resorption of cartilage. Moreover, it has been demonstrated that the inflammatory reactions ac-

companying artificially induced arthritis could be suppressed by bisphosphonates; thereby preserving the architecture of the joint involved. These encouraging experimental results have lead to clinical studies of bisphosphonates in patients with osteochondrosis and osteoarthritis; results of which are awaited.

Structure-Related Actions

Initial studies in the 1960s to explain the action of bisphosphonates on bone resorption focused on their physicochemical effects. However, it became apparent that these could not explain the antiresorptive action of bisphosphonates which was rather due to their cellular effects. It was demonstrated in the 1990s that bisphosphonates act mainly on osteoclasts and induce their apoptosis. This is achieved either by intracellular formation of a toxic ATP analogue (*first generation, bisphosphonates without a nitrogen functionality*) or by inhibiting the enzyme farnesylpyrophosphate synthase of the mevalonic acid metabolic pathway and subsequently the prenylation of small GTPase signalling proteins that leads to inactivation of the osteoclasts (*second and third generations, nitrogen-containing bisphosphonates*). Numerous bisphosphonates have been developed over the past 30 years. Their antiresorptive activity is 20,000 times greater than that of etidronate. They differ from each other with respect to the ligands bound to their carbon atoms.

Substitutions at R_2 determine the antiresorptive and antiproliferative activity – the *bioactive moiety;* while substitutions at R_1 determine the binding site for attachment to the bone: the *bone hook* (Fig. 3.17). The R_1 moiety confers additional

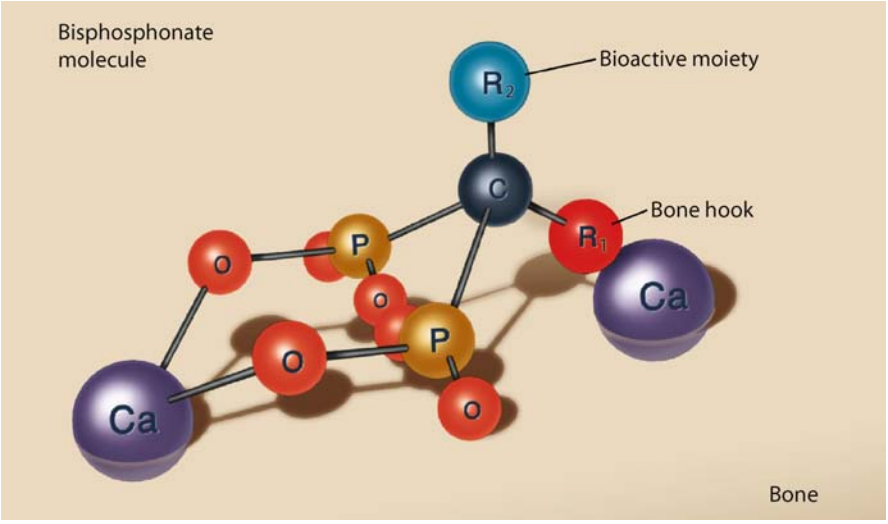


Fig. 3.17 Spatial structure of bisphosphonate binding to the surface of bone

binding activity, for example, replacing a hydrogen atom by a hydroxyl group at R_1 increases the affinity for hydroxyapatite by about two-fold. However, differences in bisphosphonate binding affinities suggest that the nature of the R_1 moiety may not be the sole determinant of binding ability. Derivatives with one amino group at the end of the side chain are particularly active. The introduction of nitrogen components such as primary and tertiary nitrogens or heterocyclic rings at the R2 position increased the antiresorptive potency of biphosphonates by up to three orders of magnitude compared to that of non-nitrogen containing bisphosphonates (e.g. etidronate or clodronate). However, it is not only the presence of the nitrogen atoms that is important but also their position in the molecule since potency can differ by >700-fold between isomers of the same bisphosphonate. According to the *molecular mechanism of action* two groups of bisphosphonates can be distinguished:

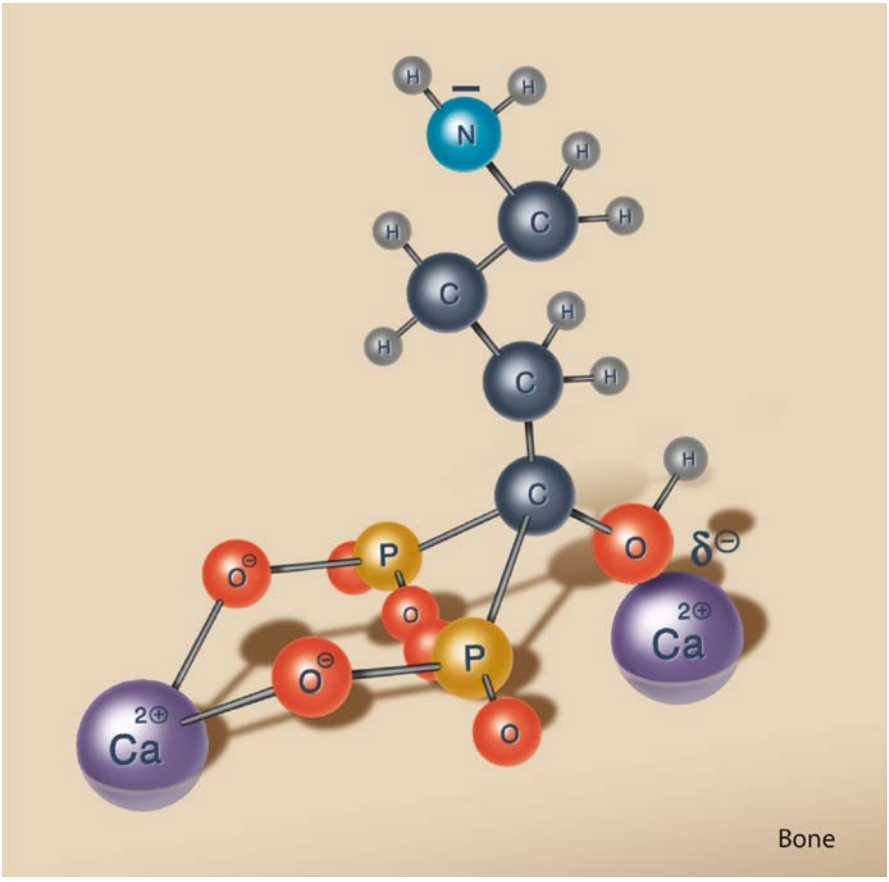


Fig. 3.18 Spatial structure of alendronate (second generation bisphosphonate) on the surface of bone

- *Bisphosphonates without nitrogen:* These are metabolised within the cell to form cytotoxic ATP analogues, which inhibit the mevalonate pathway in osteoclasts. This group comprises the first generation bisphosphonates: etidronate, clodronate and tiludronate.
- *Bisphosphonates with nitrogen* (Figs. 3.18 and 19): These inhibit mevalonate metabolism and prenylation of proteins. Ibandronate (Fig. 3.19) primarily inhibits the enzyme squalene synthase. The lack of prenylated proteins within the osteoclast leads to structural changes such as dissolution of the ruffled membrane, so that the osteoclast cannot function. All the data available indicate

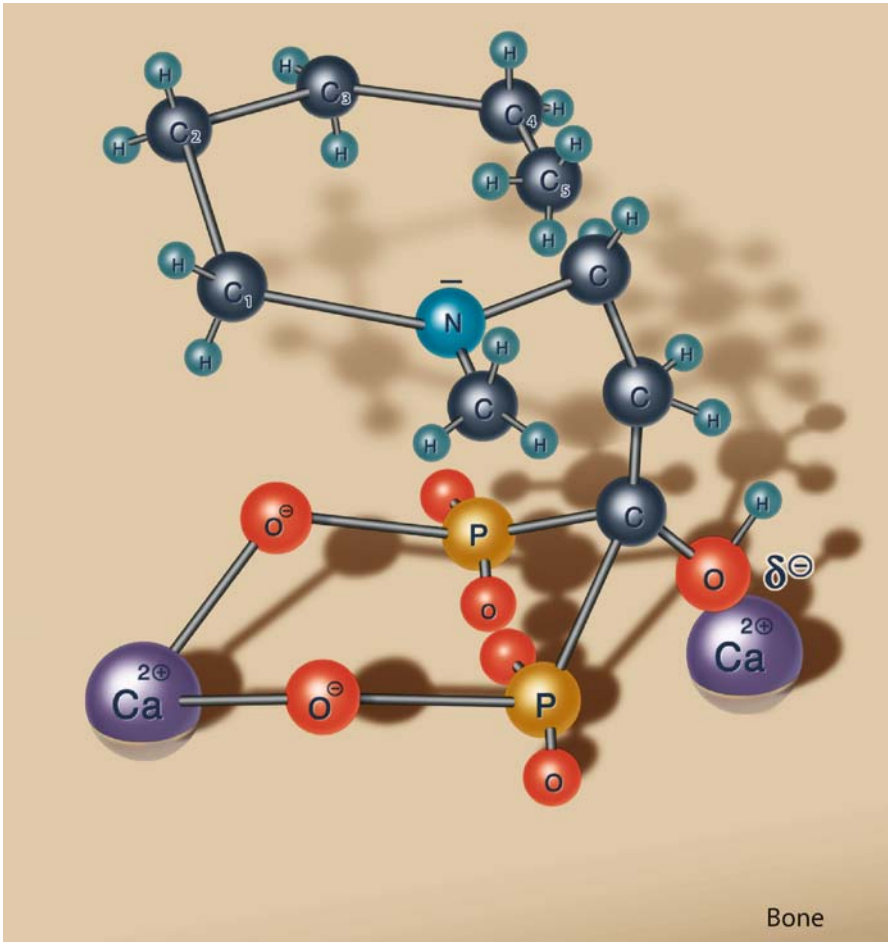


Fig. 3.19 Spatial structure of ibandronate (third generation bisphosphonate) on the surface of bone

that farnesyl diphosphate synthase is the major pharmacological target of the nitrogen-containing bisphosphonates in vivo, and that small changes to the structure of the R_2 side chain alter antiresorptive potency by affecting the ability to inhibit farnesyl diphosphate synthase (see also Fig. 3.9). The order of potency inhibiting farnesyl diphosphate synthase in vitro is closely matching the order of antiresorptive potency in vivo: zoledronate > ibandronate > risedronate > alendronate > pamidronate (Dunford et al. 2001). This group comprises both second and third generation bisphosphonates: risedronate, alendronate, pamidronate, olpadronate, ibandronate and zoledronate.

Both mechanisms, i.e. intra-cellular metabolic inhibition and structural alterations, induce apoptosis of osteoclasts and tumor cells (e.g. myeloma cells) as well as inhibiting proliferation of various microorganisms (e.g. trypanosoma cruzi).

Side Effects

The bisphosphonates are well tolerated. Their side effects are few and rarely significant (see below). Nevertheless, patients must be informed about possible complications and asked to report occurrence of any side effects and complaints during the course of treatment, particularly if the bisphosphonate prescribed has not yet been authorised for that particular indication. In such a situation, the patient's informed consent must be obtained in writing before the initiation of treatment. In addition, also before starting therapy, the patient must be examined, especially the oral cavity, and basic investigations must be carried out. These should include kidney and liver function, complete blood count, and levels of calcium, magnesium, phosphate and alkaline phosphatase in the serum.

Relatively minor and usually transient side effects which occur mostly after i.v. administration include: "flu-like" symptoms and bone pain 9%, fever 7%, fatigue 4%, occasionally arthralgia and myalgia 3%. Should significant side effects occur, these may warrant a change in the mode of administration or type of bisphosphonate. The most clinically important side effects are considered in detail below. Before treating children (for example suffering from osteogenesis imperfecta) written consent of the parents and of the responsible ethics committee must be obtained.

Hypocalcemia

This indicates acute toxicity due to formation of bisphosphonate-calcium complexes, which cause a drop in the serum calcium concentration. Usually it is transitory and does not cause symptoms. When bisphosphonates are administered intravenously, especially in high doses, it is important to monitor the speed of infusion. Clinically relevant hypocalcemia has been observed after rapid infusion of

high doses and with concomitant administration of aminoglycosides; both these substances may cause long-lasting hypocalcemia and they should not be given together. *Bisphosphonate-induced hypocalcemia has also been associated with vitamin D deficiency, especially in seriously ill and older patients.* Hypomagnesemia may also occur by similar mechanisms, i.e. due to the binding of bisphosphonate to magnesium cations.

Disturbance of Mineralisation

Etidronate given at high doses (>5 mg/kg body weight daily) for prolonged periods (>6 months) can cause osteomalacia. Mineralisation is usually normalised within 3 months after discontinuation of the bisphosphonate. However, osteomalacia can be avoided by administration of calcium and vitamin D concomitantly with the etidronate, so that even very long treatment for example with 400 mg etidronate daily for 2 weeks every 3 months does not induce any significant inhibition of mineralisation. *With the latest bisphosphonates (3rd generation) this side effect no longer occurs and is not seen in bone biopsy sections. In fact, a wider than normal osteoid seam denotes increased bone formation indicating that patients on bisphosphonates should always be given vitamin D and calcium.*

Gastro-intestinal Side Effects

Mild gastrointestinal side effects may occur when bisphosphonates are taken orally. These include diarrhea, nausea, bloating, gastric pain and other uncharacteristic abdominal complaints, which had previously been reported in 2–10% of patients. However, large placebo-controlled studies have not confirmed these reports. In one case of ulcerative esophagitis, the patient had received a nitrogen-containing bisphosphonate. *It should be emphasised that such serious side effects can occur only if:*

- the patient and doctor overlooked a reflux esophagitis or other similar pathologic conditions,
- the patient swallowed the tablets with too little water (minimum 200 ml recommended),
- the patient lay down within 30 minutes of taking the medication,
- the patient continued to take the tablets after symptoms of esophagitis had occurred.

This example highlights the importance of making all patients aware of exactly how these tablets should be taken. No cases of esophagitis have yet been reported with the latest tablets of 70 mg alendronate, taken once a week. The effects of the bisphosphonate on the bones have remained the same (that is, effects of daily or weekly inges-

tion). It is worth noting that monthly tablets have already become available and are equally effective.

Acute-Phase Reactions

The day after aminobisphosphonate infusion, 20–40% of all patients experience fever and lymphocytopenia as well as a rise in C-reactive protein, in IL-6 and in TNFα. These patients experience flu-like symptoms such as headache, bone and joint pains and fatigue. *The reactions begin 10 hours after the first infusion, last only 1 to 2 days and do not leave any long-term side effects. Symptomatic therapy can be given, but is rarely required.*

Elderly patients with cardiac insufficiency have reported occasional cardiac irregularities, but these paroxysmal disturbances in cardiac rhythm were never severe enough to require treatment. Generally speaking, an acute-phase reaction occurs only after the first infusion, rarely after the second and then is very mild. More such reactions have been observed after treatment of patients with CRPS (Sudeck's disease) and patients with asthma who are sensitive to aspirin: they occur less frequently in patients with osteoporosis and very rarely in patients with malignancies. It is prudent therefore to give lower doses to vulnerable patients when first starting treatment and to monitor the patients for several hours after completion of the infusions.

Renal Side Effects

In the past, rapid infusion (or injection) of large amounts of etidronate or clodronate led to acute renal failure, which is also a danger when hypercalcemia is accompanied by dehydration. Insoluble complexes formed in the blood most probably caused the impairment of renal function. Consequently, intravenous administration of bisphosphonates should be slow and considerably diluted. Highly potent bisphosphonates such as ibandronate are effective even at a dosage of 2 mg, which can easily be administered and which, so far, has not caused any significant renal complications. This was clearly shown in patients with breast cancer given infusions of 2–6 mg ibandronate. Minimal, short-term excretion of protein has also been observed in some patients. A low blood volume, for example in patients with multiple myeloma, must always be corrected before intravenous infusion of bisphosphonates. Moreover, it is particularly important to remember that patients with multiple myeloma are especially vulnerable to renal complications because of the possibility of the presence of light chains, paraproteins and deposition of amyloid in the kidneys, so extra care is required.

Renal insufficiency per se is not a contraindication for bisphosphonates. Administration of pamidronate is not limited by renal insufficiency. Ibandronate, on the other hand, should only be given to patients with creatinine values up to 5 mg/

dl. It is advisable to reduce the dose and prolong the infusion time in patients with renal insufficiency. In patients on hemodialysis, the dose should be reduced by 25%, and the different half-lives of the bisphosphonates must be taken into account (pamidronate 1 hour, ibandronate 10 to 16 hours).

No renal toxicity has been reported following oral ingestion of bisphosphonates, probably because of their minimal and slow absorption in the gastro-intestinal tract.

Bisphosphonates may cause a rise in plasma phosphate together with an increase in renal tubular reabsorption of phosphate, but this effect is not associated with any clinical problem.

Ocular Side Effects

Isolated cases have been reported of ocular side effects including visual disturbances in patients taking aminobisphosphonates, especially pamidronate. These effects included inflammatory reactions, such as *conjunctivitis*, *scleritis*, *episcleritis, uveitis* and even *retinitis*. *Any patient with a "red eye" or complaints of visual disturbances should immediately be sent for specialist examination.* These inflammations are generally unilateral and reversible after discontinuation of intravenous bisphosphonates, but may recur when the infusions are resumed. In one patient with unilateral uveitis, the condition slowly regressed under therapy with prednisone and atropine eye drops. In another patient with unilateral scleritis, the symptoms fully resolved under therapy with prednisone.

Central Nervous System (CNS)

Toxicity within the CNS is an extremely rare side effect, which may be expressed by the patient as "hearing voices in the head" and "as colored visual disturbances" (not connected to inflammatory manifestations in the eyes). *Visual, olfactory and auditory hallucinations* have also been reported after therapy with pamidronate.

Hematopoietic Side Effects

Effects on hematopoietic cells have rarely been observed, even after long-term bisphosphonate therapy. Occasionally, anemia or other cytopenias may be observed after zoledronate, but these are very rarely symptomatic.

Other Side Effects

Ototoxicity has been reported in a few isolated cases during pamidronate therapy, the cause is not known. Unilateral deafness was observed in one patient with osteogenesis imperfecta (OI) while on pamidronate therapy, but as this may also

occur in patients with OI who are not receiving any therapy there may not be a causal relationship.

Clodronate and etidronate have been known to trigger *asthmatic attacks* in patients with asthma who are sensitive to aspirin. Allergic *skin rashes* have also been reported, and rapid, highly concentrated infusions may cause *local phlebitis*. Infusions of bisphosphonates may cause a *transient loss or alteration of taste (metallic taste)*, observed in about 5% of the patients.

Osteomyelitis/Osteonecrosis of the Jaw Bones

These side effects were first reported in a single patient in 2003, and the literature reviewed in 2004 and 2005 (Fig. 3.20a,b). The following significant points were recognised: almost all cases reported had previously experienced a dental complication such as extraction of a tooth (or teeth), undergone a dental implant, had a buccal infection, or were receiving some other form of generally invasive dental treatment. *In one study, 56/63 of the patients were under long term therapy with bisphosphonates: pamidronate or zoledronate i.v.* The remaining 7 patients were taking oral bisphosphonates. All the patients were suffering from pain, non-healing extraction wounds, exposed bone with sequestration, and inflammatory reactions in the mouth. The lesions were refractory, i.e. did not respond to antibiotics. *All patients had malignancies: 44% multiple myeloma, 32% breast cancer, and 5% prostatic cancer (Ruggieri et al. 2004). So far, a satisfactory elucidation of the mechanism of the necrosis of the jaw bones has not been given*. The following possibilities have been put forward:

- Microfractures in heavily burdened jaw bones
- Anomalies of the vascular system in the jaws
- Infectious inflammatory processes during immuno-suppression
- Anti-angiogenic effects of bisphosphonates leading to local necrosis
- Inhibitory effect on local physiological bone remodelling
- Enhancement of inflammatory/necrotizing processes (caused by prior chemotherapy and corticosteroids) already present before administration of bisphosphonates

However, these explanations are only speculative. Histologic investigation of necrotic material obtained by bone biopsies taken from the jaw bones of 15 patients demonstrated vascular and inflammatory reactions as well as ostoclastic remodelling typical of a subacute to chronic abacterial osteomyelitis. Presence of bacteria was never documented. However, there were also clear signs of necrosis of bone, soft tissues and bone marrow, as well as the presence of newly formed bone containing osteocytes and showing cement lines. Practically all the cases reported so far, have implicated i.v. therapy with pamidronate or zoledronate. Only isolated instances have been reported of patients receiving a different bisphosphonate (i.e. ibandronate) because of a malignant condition or osteoporosis. *In the vast major-*

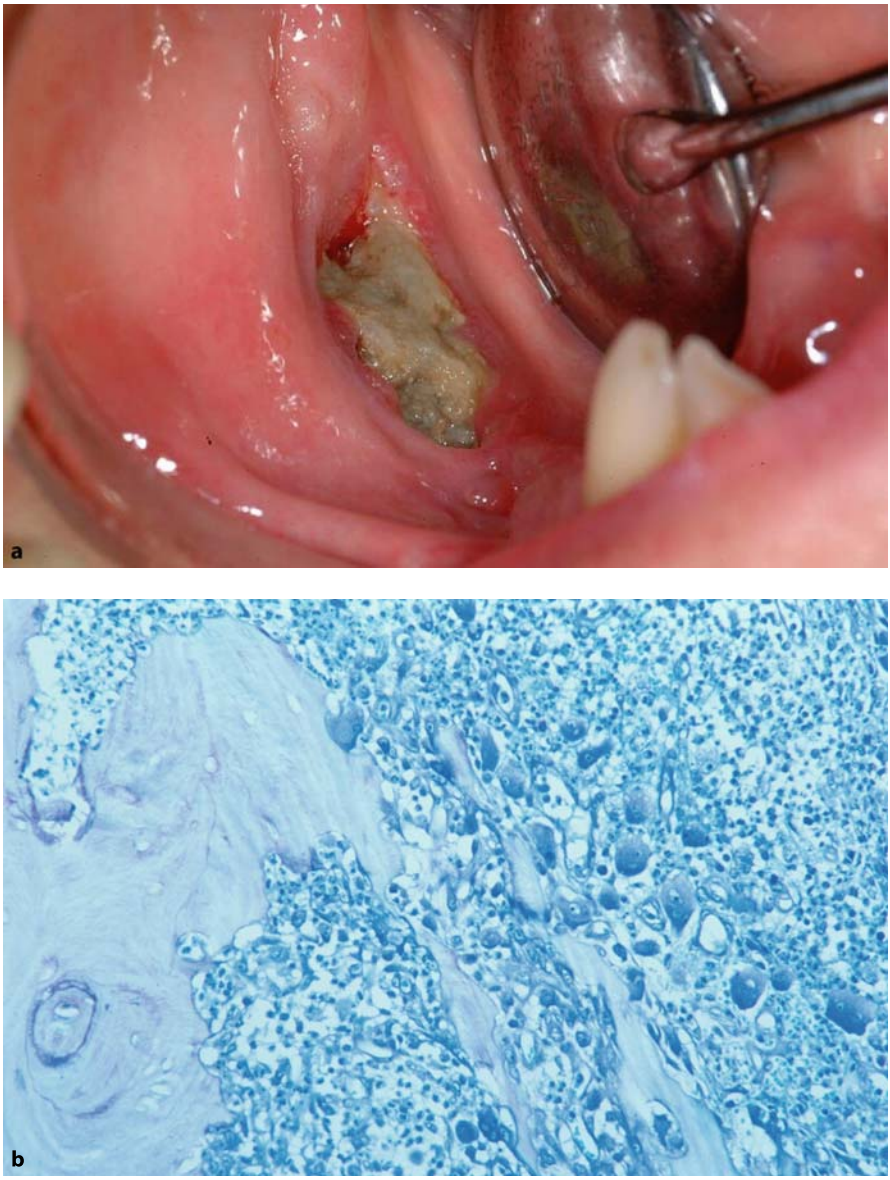


Fig. 3.20 **a** Osteonecrosis of the jaw in a patient with breast cancer, 1 year after therapy with zoledronate 4 mg monthly, **b** Histology from the necrotic jaw of the same patient showing chronic osteomyelitis with necrotic bone and osteoclastic bone resorption, and increase of large macrophages, plasma cells, lymphocytes and granulocytes in the surrounding bone marrow (Giemsa 100x, plastic embedded biopsy)

ity of the cases the occurrence of necrosis of the jaw bone was preceded by an invasive dental intervention, for example extraction of a tooth or teeth.

As outlined above, many speculative theories have been proposed, and intensive investigations are underway. But, more to the point, specific and detailed guidelines for the prevention, diagnosis and therapy have been published (2004), and one of the manufacturers (Novartis) has also sent round a circular outlining recommendations for the administration of zoledronate (Zometa®). It must be clearly stated that these cases emphasise the importance of a careful medical history and physical examination before starting treatment with bisphosphonates, especially with the new potent ones given i.v. long term and in patients with malignancies who possibly had already received, or were currently on chemotherapeutic protocols, possibly containing glucocorticoids. Only when the above precautions have been taken will it be possible to institute the preventive measures now recommended. *It is also worth while pointing out that international studies have clearly demonstrated that in more than 20 million patient years of oral therapy with bisphosphonates such problems have not been reported.*

Long Term Side Effects

Patients have now been treated with bisphosphonates for over 12 years without any recorded long term side effects. A single report has recently appeared expressing concern on the possibility of potential over-suppression of bone turnover during long term use (Odvina et al. 2004) so far this has not been confirmed. In a few patients *fracture healing* was delayed and both osteoclastic and osteoblastic activities were reduced. These observations stress the need for continued monitoring of patients on bisphosphonate therapy.

Non-traumatic Avascular Necrosis of the Femoral Head

This condition has been recognised for many years, even before the era of bisphosphonates. It occurs in children as well as in adults. A fairly frequent cause is steroid therapy, or other treatments which include steroids. Pardoxically, when compared to the situation outlined above, *patients with avascular necrosis of the femoral head treated with bisphosphonates showed reduction of pain, improvement of function, and retardation of progression, so that early surgical intervention could be avoided in many cases.*

Contraindications and Precautions

So far the only absolute contraindications are *pregnancy and lactation* because some bisphosphonates cross the placental barrier and may also be excreted in the milk. Animal studies have not demonstrated any mutagenic effects on the

fetus. Recent studies on maternal and fetal outcome after bisphosphonate treatment before conception found no evidence for adverse effects on mothers or babies.

The presence of fractures or orthopedic prostheses do not constitute contraindications to bisphosphonate therapy. On the contrary, callus formation is increased and fractures are repaired more rapidly under bisphosphonate therapy. *When rigidly defined indications are present, aminobisphosphonates can also be given to infants and children*. Disturbances of growth and mineralisation have not been reported. Bisphosphonates should be administered by the intravenous route to patients with difficulties in swallowing and inflammatory or other esophageal, gastric or intestinal disorders. Aminoglycosides should not be given together with bisphosphonates, nor should different bisphosphonates be given simultaneously. *Patients with multiple myeloma on therapy with thalidomide should not be given zoledronate.*

Practical Recommendations and Guidelines

Oral Administration of Bisphosphonates

Etidronate, clodronate, tiludronate, alendronate, risedronate, ibandronate:

The poor gastro-intestinal absorption of these modern bisphosphonates is offset by their high effectiveness. Before initiating oral bisphosphonate therapy, the following points should be considered:

- Exclusion of reflux esophagitis, difficulties in swallowing and elucidation of dental status in the patient's clinical history.
- Instructions provided by the manufacturer of the bisphosphonate to be noted and followed.
- Other medication(s) should not be taken together with bisphosphonates.
- The patient must not lie down for at least 30 minutes after taking the tablet, preferably should be active physically during this time.
- Bedridden patients should not be prescribed oral bisphosphonates.
- Possible side effects should be discussed with the patient to increase awareness and compliance.
- During trips abroad, mineral water poor in calcium and carbon dioxide can be used instead of tap water. Alternatively, the time abroad can be bridged by an intravenous infusion given beforehand.

Intravenous Administration of Bisphosphonates

Clodronate, pamidronate, ibandronate, zoledronate:

The infusions are usually administered on an ambulatory basis in the out-patients clinic. The following points should be noted:

- The doses and intervals between treatments depend on the type and severity of disease, on osteoclastic activity and urgency of achieving therapeutic success. The infusions are usually administered at intervals of 3 weeks to 3 months, in some cases 6 months or even annually.
- Calculation of the dose according to body weight is not required.
- Dehydration must be recognised and treated before bisphosphonate administration to avoid renal damage through precipitation of complexes in the renal tubules; basic biochemical values (e.g. creatinine) should also be obtained beforehand.
- The infusion should be slow, e.g. 250–500 ml physiological saline in about 1 hour (or longer as required), to avoid local and renal reactions as well symptomatic hypocalcemia. Recently an infusion time of 15 min has been approved also for ibandronate 6 mg.
- The instructions of the manufacturer must be followed when treating patients with partial renal insufficiency.
- The dose should be reduced by 25% for patients with complete renal failure, and be given immediately after completion of the haemodialysis.
- The half-life of the bisphosphonate must be taken into account when patients are on hemodialysis.
- Patients must be informed of the possibility of an acute-phase reaction on the day after the first infusion.
- The patient's mouth and jaws must be examined before i.v. therapy, and appropriate treatment given and completed beforehand. Surgical intervention in the mouth and jaws should be avoided during this period, i.e. while the patient is receiving bisphosphonates especially i.v.
- Bisphosphonates do not interact with other medications or drugs.
- Simultaneous administration of aminoglycosides may cause symptomatic hypocalcemia and should be avoided.
- Should drug resistance occur, the dose should subsequently be increased by about 50% if possible, alternatively switch to another more potent bisphosphonate.
- With the introduction of zoledronate in oncology three considerations are routinely applied: 1) Careful adherence to the manufacturer's instructions especially with respect to monitoring of renal function. 2) Attention to the possibility of a toxic reaction. 3) Reduction in dosage in patients with impaired renal function.

Effects of Cessation of Bisphosphonate Therapy

Within 2–4 months of stopping therapy with bisphosphonates, indices of bone turnover begin to increase and these should be monitored – a negative bone balance that is bone loss, becomes evident 1–2 years later. Therefore annual measurement of BMD is recommended so that appropriate preventive therapy can be re-instated. Data are not yet available on the incidence of fractures during this period.

Long Term Effects of Bisphosphonate Therapy

Investigations of the effects of bisphosphonates on bone for periods of up to 10 years have not revealed any deleterious or damaging effects on bone (Papapoulous 2005). The main 4 parameters which are responsible for bone strength (bone mineral density, bone architecture, bone remodelling and bone material) are all positively influenced by modern bisphosphonates in combination with calcium and vitamin D_3.

Combination of Bisphosphonates with Other Drugs

The combination of bisphosphonates with *other inhibitors of bone resorption* such as raloxifen has a positive additive effect on bone density and on fracture incidence. The addition of calcitonin to bisphosphonates appears to be useful in the treatment of bone pain because of the apparent stimulation of endogenous opiates in the brain. *Calcitonin* is a rapidly acting peptide hormone and therefore may control severe hypercalcemia faster than bisphosphonates, thus allowing time for their effect to take place.

Sequential administration of bisphosphonates after *stimulators of bone formation* such as *parathyroid hormone (PTH)* or with low doses of fluoride has proved to be effective and has so far induced the greatest increase in bone mass in clinical trials. It has recently been shown that statins given to reduce cholesterolemia also reduce fracture risk: they appeared to have additive effects on bone density in combination with a bisphosphonate.

As mentioned previously, it is mandatory to obtain the *patient's written consent* before administration of a bisphosphonate especially if it has not yet been officially authorised for that particular condition. The written consent of the parents must be obtained before children are treated. It is advisable to complete a special consent form which states the condition for which the bisphosphonate is recommended, the name of the bisphosphonate, the exact dose, and the duration of the oral administration and/or number of infusions.

CHAPTER 4 Osteoporotic Syndrome

The etiology and the pathophysiology of osteoporosis are multifactorial in the majority of the patients – from conditions in which osteoporosis appears to be a primary disorder to those in which it is clearly secondary to other diseases and/or their therapy. In addition there are genetic and environmental influences (and their interactions) which vary in different ethnic populations and various geographic locations, but which effect the skeleton throughout life – from birth to attainment of peak bone mass to maintenance of bone density and quality to prevention of fractures. *Osteoporosis can strike at all ages,* but men after 60 years of age, and women after the menopause are the most vulnerable due to the decrease in steroid hormones in both groups. This chapter, as well as Chap. 5, provides guidelines for specific therapy of the osteoporoses as well as addressing many of the factors that cause them.

Definition

The popular concept of osteoporosis is that of a bone disorder with "*too little bone*" and the increased risk of fractures that goes with it. Experts have defined osteoporosis as:

> *"A systemic skeletal disorder characterised by a decrease in bone mass and deterioration of the microarchitecture of the bones with a corresponding reduction in strength and an increase in fracture risk."*

A series of prospective studies has now confirmed the connection between bone mass (density) and fracture risk. According to the World Health Organization (WHO), osteoporosis in women is diagnosed simply on the basis of bone mineral density (BMD) for which the measurements obtained by DXA have gained worldwide acceptance, because this technique is simple, reliable and standardised and enables effective treatment before occurrence of fractures – prevention is always better than cure.

> *"Osteoporosis is present when the bone mass is more than 2.5 standard deviations (SD) below that of healthy premenopausal adult females, the T score". Dual-en-*

ergy X-ray absorptiometry (DEXA) is used to measure bone density in the lumbar spine and/or hip. With this technique a diagnosis of osteoporosis can even be made before fractures occur. This simple definition proposed by the WHO has gained widespread acceptance, and it has world-wide reproducibility".

Classification According to Extent of Spread

Two groups are distinguished by their pattern of spread:

- *Localised (focal, regional) osteoporosis*
- *Generalised (systemic, global) osteoporosis*

Unlike generalised osteoporosis, which is considered a metabolic disorder and is widespread, localised osteoporoses are relatively infrequent. In spite of its name, generalised osteoporosis is symmetric but rarely effects the entire skeleton.

Juvenile and postmenopausal osteoporoses preferentially effect the axial skeleton, while osteoporosis in the elderly effects the long bones in addition to the axial skeleton. *It should be stressed that no single bone is representative of the whole skeleton, therefore extrapolations should not be made.*

Classification According to Rate of Bone Turnover

Using the degree of bone remodelling as a criterion, two forms are recognised:

- *Low turnover osteoporosis*
- *High turnover osteoporosis*

These are distinguished by bone markers in serum and urine and, in certain cases, by bone biopsy. Osteoporotic patients with high levels of resorption are designated as "fast losers" or as patients with "very high turnover" osteoporosis; those with low levels of resorption are designated as patients with "low turn over" osteoporosis or as "slow losers"; indicating that the temporal dynamics of osteoporosis exhibit a broad spectrum from chronic which is measured in years, to progressive measured in months.

Classification According to Age and Sex

- *Idiopathic juvenile osteoporosis:* This is a rare, self-limiting condition which effects prepubertal children 8 to 14 years of age. It is characterised by vertebral compression fractures and severe back pain. The etiology is unknown.

- *Idiopathic osteoporosis of young adults:* This primarily effects men, 30 to 50 years of age, involves the axial skeleton and causes vertebral fractures. Biochemical investigations and bone biopsy findings demonstrate clearly elevated bone resorption. The etiology is unknown.
- *Postmenopausal (type I) osteoporosis:* This effects women between 51 and 70 years of age and is a consequence of cessation of ovarian function, though recent studies have shown that accelerated bone loss may begin well before the menopause (perimenopausal). About 30% of all women suffer from osteoporosis after the menopause.
- *Andropause in Men:* Whether or not men also experience a type of andropause or "change of life" accompanied by risk of osteoporosis is still regarded by many as an open question. *However, an andropause undoubtedly does occur because testosterone production is reduced with age, therefore appropriate preventive measures should be undertaken as required.*
- *Involutional Osteoporosis or Senile (type II) osteoporosis (osteoporosis of the elderly):* In women, postmenopausal osteoporosis merges imperceptibly into the "involutional" form, which represents the normal aging process and is associated with increased osteoclastic activity. *Involutional osteoporosis occurs after 70 years of age and is only twice as frequent in* women as in men. Cortical bone (especially in men) is also increasingly effected by resorption so that fractures of the femoral neck, radius and pelvis become more frequent. *Approximately 80% of all osteoporotic fractures occur in this age group, and it is important to point out that over 30% of osteoporotic fractures occur in men, in whom the risk factors are similar to those for women but possibly more numerous.*

Secondary Osteoporoses

Classification According to Etiology

Primary osteoporoses must be distinguished from the secondary osteoporoses caused by specific pathologic conditions. Primary or idiopathic osteoporosis refers mainly to postmenopausal and involutional forms of osteoporosis, although various causative factors, in addition to the aging process, have now been identified. *Secondary osteoporoses due to specific identifiable pathologic conditions, constitute only 5% of all osteoporoses, are more common in men and cause 20% of all osteoporotic fractures.*

The following groups are distinguished:

- *Endocrine:* Hypogonadism, hyperthyroidism, hyperparathyroidism, Cushing's syndrome, diabetes mellitus and others.
- *Hematologic/medullary (myelogenous):* Malignant and expansive diseases of the bone marrow directly influence bone remodelling and may cause severe osteo-

porosis. Such hematologic conditions include multiple myeloma, some of the malignant lymphomas, polycythemia vera, chronic myeloid leukemia, genetic hemolytic syndromes, storage diseases such as Gaucher's, and systemic mastocytosis. Early administration of bisphosphonates in systemic mastocytosis could limit bone involvement. Moreover, survivors of childhood acute lymphoblastic leukemia, in particular, require follow-up to monitor subsequent accretion of bone and to ascertain attainment of peak bone mass as their risk factors are increased.

- *Oncologic:* Diffuse metastatic involvement may mimic primary osteoporosis if localised osteolytic and osteosclerotic lesions are absent. Paraneoplastic osteoporosis can also occur when the malignant cells secrete substances mimicking parathyroid hormones (PTHrP) for example in bronchial carcinoma and melanoma.
- *Hepatic, gastrointestinal and nutritional:* Chronic hepatic or gastrointestinal diseases, e.g. malabsorption syndromes, Crohn's disease, pancreatic insufficiency, primary biliary cirrhosis, gastric or intestinal operations frequently cause osteoporosis as well as osteomalacia, osteoporomalacia or mixed osteopathy because of deficiencies of vitamin D and C. For example, bone loss is a frequent complication of primary biliary cirrhosis. Results of a recent randomised placebo controlled trial have demonstrated the beneficial effect of alendronate 70 mg once weekly orally on bone density. It is worth mentioning that the ability of the skin of elderly people to utilise sunshine for vitamin D production is greatly reduced and, in most cases their exposure to sunlight is also decreased, so that their requirement for vitamin D supplements is correspondingly increased. *In patients with the gastro-intestinal disorders mentioned above, bone loss may be further increased by glucocorticoid therapy, alcohol abuse, smoking, inadequate nutrition and decreased physical activity*.
- *Renal:* Chronic renal insufficiency leads to anomalies of vitamin D metabolism, and thereby causes mixed osteopathies with manifestations of osteoporosis, osteomalacia and secondary hyperparathyroidism (renal osteopathy or renal osteodystrophy). These diseases are dealt with separately (see below).
- *Rheumatologic and immunologic:* The combination of 1) inflammatory joint disease, 2) immobilisation and 3) glucocorticoid therapy inevitably induces rapid bone loss. Each of these three individually stimulates osteoclastic resorption, illustrating the many factors involved ranging from regulation of osteoclastic generation and activity, to stimulation of inflammatory cytokines. In such situations powerful bisphosphonates are the therapeutic agents of choice. In rheumatoid arthritis, bands of demineralisation occur near the effected joint ("arthritis collateral phenomenon"). Erosions and cysts are signs of damage to the bone surrounding the joint.
- *Cardiologic and pulmonary:* Patients on anticoagulant therapy (e.g., warfarin) because of cardiac conditions or after heart and valve operations are particularly susceptible to bone loss. This may be further aggravated by decreased mo-

bility due to chronic cardiac insufficiency, pain and other factors. Patients on long-term corticosteroid therapy because of bronchial asthma are equally at risk.

- *Drug toxicity: Many therapeutic agents are detrimental to bone on prolonged use, particularly the glucocorticoids and anticoagulants mentioned above.* Anti-epileptic drugs, by their effects on the liver, may induce a relative vitamin D deficiency which in turn effects bone remodelling resulting in varying degrees of osteoporosis/osteomalacia. Certain metals (aluminum, cadmium, arsenic) and other substances (ethylene, propylene, poly-vinylchloride) block incorporation of calcium hydroxyapatite into osteoid thus producing osteomalacia.
- *Genetic:* Studies of twins have demonstrated that the development of osteoporosis is genetically determined in about 50% of the cases and that numerous genes participate in its regulation. *The genetic programming of "peak bone mass" and of subsequent bone loss applies especially to cancellous bone – the major target of osteoclastic resorption!*
- *Osteogenesis imperfecta* (brittle bone disease) is the most important clinical example of a genetically determined osteoporosis. It may be incorrectly diagnosed as a non-congenital osteoporosis, therefore always check the eyes for blue sclerae in young patients.

Classification according to Sex

As the population ages in many countries, the incidence of osteoporosis and the concomitant risk of fractures have increased in men as well as in women. Some estimates have indicated that the rate of vertebral fractures in men today almost equals that of women; although differences remain in the relative prevalence of forearm and hip fractures.

Age related osteoporosis develops later in men than in women for a number of reasons which include:

- Men have bigger bones and therefore a greater peak bone mass.
- Age related decline in hormonal factors associated with bone loss–i.e. increased bone resorption and decreased formation occurs later in men. The factors responsible include: decrease in testosterone, in adrenal androgens, and in hormonal growth factors.
- There are differences in the type of bone loss between men and women.
- Cortical bone loss is less in men than in women. Cortical bone remodeling, i.e. endocortical resorption and sub-periosteal appositional bone formation continue longer in men.
- Trabecular bone loss in men leads to attenuated, thinner ossicles with preservation of the trabecular network. In contrast, osteoporosis in women is charac-

terised by discontinuities, reduced nodes and connectivity resulting in disruption of the trabecular micro-architecture.

Classification According to Severity

In daily clinical practice assessment of the severity of any condition is required in order to determine the urgency, the strategy, the therapy and its putative effects. *Prior to therapy of primary osteoporosis, (after exclusion of secondary causes) careful assessment of two factors is mandatory: bone density and evidence of previous or present fractures.* The following standards are used:

- *Normal bone:* When the bone density is less than 1 standard deviation (SD) of the average of the maximal density (T-score)
- *Osteopenia:* Bone density is more than 1 but less than 2.5 SD below the average of the maximal density (T-score)
- *Preclinical osteoporosis:* Bone density more than 2.5 SD below the average of the maximal density (T-score), but fractures have not yet occurred
- *Manifest severe osteoporosis:* When the first osteoporotic fractures have already occurred. Painful vertebral compressions must be distinguished from extravertebral fractures causing immobilisation

Diagnosis

The following recommendations are applicable to all patients. It should be noted that measurement of bone density, especially when possible risk factors are already present, is the first step in the evaluation of the patient's physical condition, after a detailed clinical history has been taken.

The following *key questions* must be addressed:

- Which area(s) of the skeleton should be measured? – depends on symptoms, motility and pain
- Is there a previous BMD measurement for comparison with the present result?
- Are there skeletal injuries, fractures, deformities, arthroses?
- Are the skeletal changes already present reversible?
- Has a primary condition responsible for the osteoporosis been definitively excluded?

The *investigations* include:

- Clinical history and physical examination
- Frontal and lateral X-rays of the lumbar, thoracic and possibly cervical spine

- DEXA of lumbar spine and/or hip
- Complete blood count and other laboratory investigations of serum and urine as indicated
- Magnetic resonance imaging (MRI) and/or bone biopsy in patients with suspected malignancies or osteoporosis of questionable etiology

Clinical History and Physical Examination

Backaches: Osteoporosis may be symptomless for long periods. Backaches start when compression and/or fractures of the vertebrae occur, for which many other causes may be responsible and must be ruled out. The causes include:

- Diseases of the spine: inflammatory, degenerative, myelogenous and neoplastic
- Extravertebral: visceral, neurologic, myelogenous, neoplastic and psychosomatic

Backaches are among the most important disturbances of health and well-being, as shown by the following data:

- More than a third of all people suffer from backache.
- The third most frequent diagnosis in general practice is backache.
- In some countries, backache (after sinusitis) is the second most frequent cause of loss of working days.

Symptoms: a careful *history and examination* provide diagnostic indications for localisation, duration, onset, nature, intensity and responsiveness to treatment. Limitations of sensory and motor functions must be carefully checked. The *physical examination* includes:

- Height and changes in height within recent years – height loss
- Body shape and posture, e.g. curvature of the spine causing "dowager's hump" or rounding of the back
- Pain on percussion of the vertebral spinous processes
- Flexibility of vertebral column
- Muscle tone and/or cramps
- Signs of secondary osteoporosis

Conventional X-rays

X-rays of the lumbar spine in 2 planes are required for initial diagnosis (Fig. 4.1) which illustrates the most important deformities of the vertebral column. Addi-

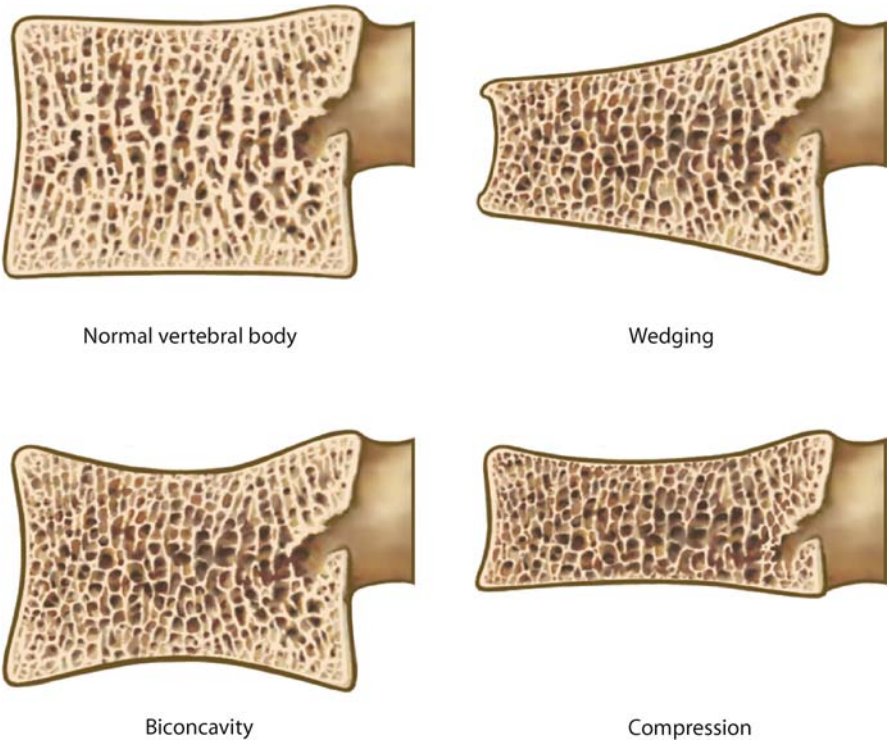


Fig. 4.1 Types of vertebral deformities in osteoporosis: wedge-shaped, biconcave and compressed

tional X-rays, e.g. of thoracic and cervical vertebrae, pelvis and extremities, especially the hands, are taken according to the clinical indications. X rays are indispensable for clarification of pain in the back of unknown etiology.

Bone Mineral Density Measurement (BMD)

This is an absolute requirement for the diagnosis of osteoporosis! A decrease of 10% in bone density doubles the risk of vertebral fractures and trebles the risk of hip fractures. Vast experience in the past has shown that: osteoporosis may be unmasked only on occurrence of a fracture! *This constitutes an indisputable reason for BMD measurement as a preventive investigation in any patient with risk factor/s.*

Results of bone density measurements provide the following information:

- Detection of osteopenia or osteoporosis possibly even before fractures occur
- Predict risk of osteoporosis and its complications

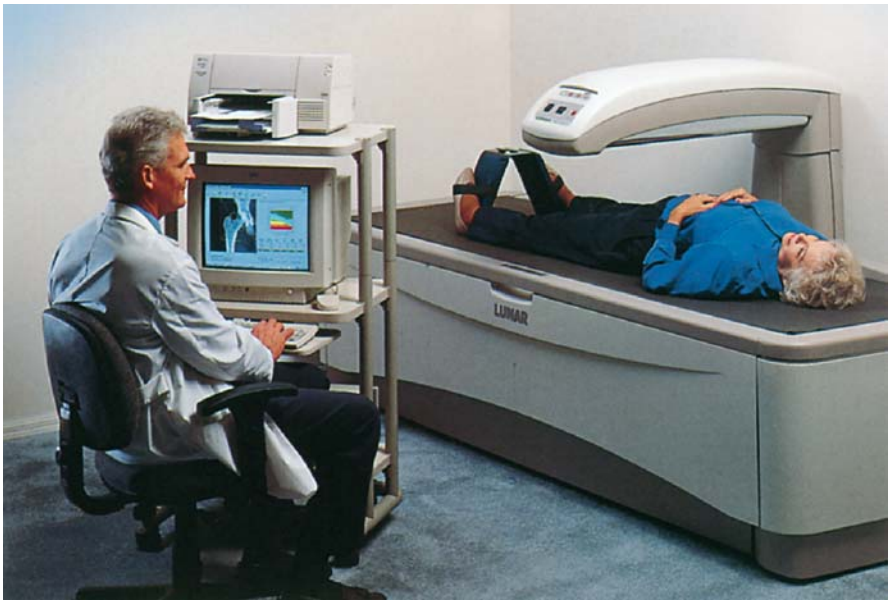


Fig. 4.2 Typical DXA unit for measuring bone mineral density (BMD) in the lumbar spine and the hips

- Estimate rate of progression of bone loss by serial measurements
- Document the efficacy (or failure) of therapy
- Encourage and increase patient compliance with therapy

Dual-energy X-ray absorptiometry (DXA, DEXA or QDR) is today the most popular as well as the most advanced technique for bone densitometry (Fig. 4.2), especially the lumbar spine (L1-L4) and proximal femur. World-wide it is still considered the "gold-standard" because of the unequivocal relationship between bone density and risk of fractures, and it is used in all large evidence-based and controlled trials.

Important advantages of the DXA technique are:

- It is noninvasive.
- It is no trouble or bother for the patient.
- It takes only a few minutes.
- It is cost-effective.
- The radiation exposure is minimal 1 to 3 mREM, which is 10- to 100-times lower than that of an average X-ray.
- The most sensitive and fracture-prone areas of the skeleton can be measured routinely.

- The measurements are accurate and therefore ideal for monitoring of therapy.
- It is the method recommended by the WHO and national organisations for diagnosis of osteoporosis.
- It enables lateral visualisation of the entire vertebral column.
- Results are immediately available.
- Results obtained in the early (1–2 years) postmenopausal period reliably predict long term (10 years) BMD and thereby enable preventive measures.
- Simultaneous measurement of lumbar vertebrae and hips reflects the axial skeleton.

Other techniques for BMD are:

- *Quantitative computerised tomography* (QCT) of the lumbar spine. This method is precise and permits separate measurements of cortical and of cancellous bone.
- *Peripheral quantitative computerised tomography* (pQCT) of the tibia and radius.
- *Quantitative ultrasound* (QUS) is used to measure BMD of the ankle and fingers. QUS is particularly effective for screening, especially in the elderly and when access to other techniques may be limited or unobtainable. For more accurate assessment, the results can be compared to panoramic radiography as used in dentistry. There may be differences between the two heels; in spite of which significant correlations may be observed especially in the elderly.

Monitoring of therapy: Follow-up measurements by the DXA-technique are important to record effects of treatment, to provide psychologic support for the patient, and to encourage compliance with therapy.

Blood and Urine Analysis

In primary osteoporosis, results of the usual blood and urine tests are generally within normal limits. Therefore their main value lies in investigation and exclusion of secondary osteoporoses and osteopathies.

Magnetic Resonance Imaging (MRI)

MRI is particularly useful for clarification of malignant disorders of the bone marrow and other soft tissues, e.g. extent of myeloma distribution in the vertebrae.

Bone Biopsy

Bone biopsy is indicated to answer the following questions:

- Type and degree of osseous remodelling: activities of osteoclasts and osteoblasts
- Thickness and porosity of cortical bone
- Micro-architecture of trabecular network: intact, discontinuous, thin trabeculae?
- Presence and extent of osteoid: is there osteomalacia?
- Presence of a different and/or additional osteopathy
- Presence of an abnormality of the bone marrow, or of fibrosis
- Presence of metastases in the bone marrow

The strength and weight-bearing capacity of the skeleton depends on bone density and on the micro-architecture of the trabecular network, especially thickness and frequency of the connecting nodes.

The main types and degrees of trabecular rarefaction in osteoporosis are shown in Fig. 4.3.

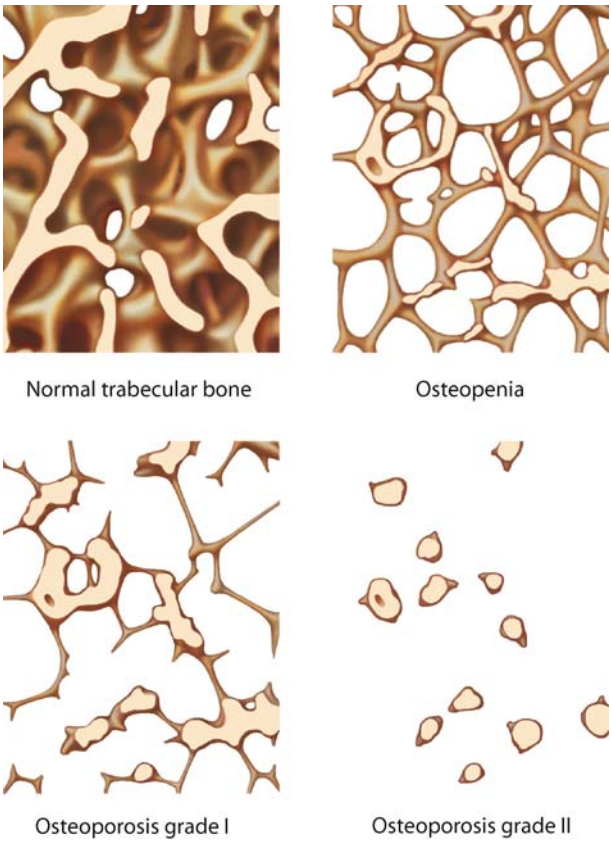


Fig. 4.3 Type and degree of rarefaction of the trabecular bone in patients with established osteopenia/osteoporosis

Therapeutic Strategies

Evidence Based Medicine and Osteoporosis

There are considerable differences in the *credibility and quality* of studies published so far on the drugs available at the present time and these differences give rise to problems in evaluation and comparison of the studies. However, today's criteria for evaluating the results of studies and other reports permit a more objective analysis of the data; and these criteria include meta-analyses of randomised controlled trials.
In 1999 Meunier published the results of a careful examination of 35 clinical studies of osteoporosis with respect to their credibility and reduction of fracture risk. The greatest relative risk reduction was achieved with alendronate which together with vitamin D and calcium also proved the most useful. *Today alendronate is widely used, especially in patients 65 to 95 years of age, both for prevention and therapy*. It should be emphasised that most of the studies on bisphosphonates are exemplary in the framework of "evidence-based-medicine". *More recent statistical analyses of the results of large-scale randomised studies have now also confirmed the efficacy of risedronate, zoledronate and ibandronate*. This has established the nitrogen-containing bisphosphonates as the most thoroughly investigated and the most effective for reducing fracture risk: a decrease of about 50% in vertebral and extravertebral fractures after one year of therapy has now been documented. In addition, on the basis of the results of other studies, raloxifen, strontium and the osteo-anabolic teriparatide and PTH are now counted among the "A classified drugs".

Development of New Drugs (Medications)

The disadvantage of the drugs described so far is that the activation or the de-activation of one cell-line simultaneously initiates changes in another, functionally opposed cell-line. For example, anti-resorptive substances decrease the resorption of bone, but at the same time also inhibit formation of new bone because of "coupling" the exact mechanism of which has not yet been elucidated. Conversely, when osteoblastic activity is increased by for example teriparatide, osteoclastic activity though unwanted, is also enhanced. New and especially short-acting drugs aimed at de-coupling the remodelling process at least for the period of therapy, are now under clinical observation, and if their efficacy is confirmed in clinical trials they will undoubtedly simplify the treatment of osteoporosis.

Examples of new anti-resorptive molecules are: osteoprotegerin, RANKL-antibodies, cathepsin K inhibitors, integrin, and prostaglandins, all have a considerably shorter biological half-life (T ½) than the bisphosphonates and they are

not deposited on or in bone. The RANKL-antibody AMG 162 (denosumab) is currently being tested in a phase III clinical trial involving 7,200 patients with post-menopausal osteoporosis. Cathepsin K, one of the substances produced by osteoclasts, is responsible for the breakdown of collagen type I and is currently also being tested in phase l and ll trials with respect to its potency in reduction/inhibition of bone resorption. The newer SERMs (lasofoxifen and BZA) have considerable influence on bone mass but only few and minimal side effects. Other new drugs called "ANGELS" (activators of non-genomic estrogen ligands) have a novel application in the modulation of bone tissue. Similar to the SERMs, the ANGELs have a positive effect on bone, but do not exert any actions on breast and uterine tissues. Other peptide sequences of PTH or PTH-like compounds with the capability of stimulating osteoblastic activity will undoubtedly soon be introduced as potent osteo-anabolic agents. Moreover, growth hormone (rhGH) has recently been re-discovered as a therapeutic agent for osteoporosis and is now under clinical investigation.

Concept of Osteoporosis Therapy

Successful treatment of osteoporosis includes the following aspects which are initiated according to the individual patient's requirements:

- Alleviation of pain
- Psychological support
- Physiotherapy and exercises
- Prevention of falls and use of protective clothing (also attention to balance, e.g. visual and auditory acuity, proper use of spectacles and hearing aids, presence or not and degree of cognitive impairment)
- Bone-conserving nutrition
- Daily supplements of vitamin D 1000 IU and 1000 mg calcium
- The SERMs (selective estrogen receptor modifiers) previously given only to women, have now also been authorised for men
- Testosterone for men, when serum levels are low and only if not contra-indicated
- Antiresorptive agents: bisphosphonates (possibly raloxifen, calcitonin, others)
- Osteoanabolic agents: teriparatide and PTH, (possibly strontium, others)
- Miscellaneous as well as new therapeutic agents in the future (AMG 126, statins, growth factors, tetracyclines, leptins)

Individual therapeutic strategies are selected to meet the needs of each patient. However, before the initiation of any therapeutic intervention, the patient must be carefully assessed for co-morbidities, and any medications already in use must be taken into consideration.

- Prevention of osteoporosis requires physical activity, a calcium-rich diet, prevention of falls and an appropriate bone-conscious lifestyle, particularly if risk factors are already present.
- All patients with osteopenia or osteoporosis should receive a daily supplement of 1000 IU vitamin D and 1000 mg calcium.
- Analgesics as required.
- Physical exercise – this must be properly planned to increase muscle strength as well as balance and thereby contribute to prevention of falls.
- SERMS and similar substances.
- Testosterone in men only after exclusion of contraindications.
- Nitrogen-containing bisphosphonates can be both preventive and curative and combined with a SERM (or testosterone in men) the bisphosphonates are particularly effective.

When osteoporosis is already present and/or fractures have already occurred, the use of *hip protectors* (special protective padded clothing or pads, similar to the pads used by children for protection when skating on roller-blades) should be advocated till bone density measurements indicate that a normal bone density has been restored. With proper education of both physicians and patients about the use and efficacy of hip protectors, they should become better known and more widely used. *They are especially recommended for patients who are at greater risk of falling, for example difficulties in balance in the older age groups, due to reduced visual acuity, slow muscular reactions, possibly also cognitive impairment*. More widespread use of hip protectors will lead to greater acceptability and eventually to fewer fractures. Awareness of the necessity of preventive measures among health professionals including surgeons has recently been investigated in a multinational survey. This included orthopedic surgeons in France, Germany, Italy, Spain, the U.K. and New Zealand. The results showed that in many areas in these countries, management of patients with osteoporosis/osteoporotic fractures was inadequate.

Treatment of Pain

Pain due to osteoporosis is usually acute and frequently due to a thoracic or lumbar vertebral fracture. The intensity of pain gradually decreases, but can transform into chronic pain after the fracture has healed. The first step is to alleviate the pain! Subsequently, the mainstays of therapy are psychological support, physiotherapy and physical exercise; attention to adequate nutrition and supplements; and analgesics as required. *Bisphosphonates are given to promote fracture healing especially in the vertebrae. Each patient should be thoroughly briefed on the personal contributions that he/she must make to ensure the success of the therapy*. In individual cases with very painful vertebral fractures, kyphoplasty should be considered (see subsequent chapter).

Basic Recommendations and Therapy

This applies to all patients with osteopenia/osteoporosis:

- A bone-conscious diet with avoidance of "bone-robbers" e.g. not too much coffee, 1–3 cups a day; and in life-style – no smoking! and moderate alcohol consumption only; and calcium and Vit D supplements (as above).
- Physical activity and muscle-strengthening exercises, especially for the spine, attention to balance and prevention of falls. This requires special attention when patients have sedentary occupations and/or habits. Maintenance of muscle strength also counter-acts weight loss related osteoporosis.

See also recommendations of the FDA, for example The Food and Drug Administration's osteoporosis guidance document "Past, present and future" (Colman et al. 2003).

Hormone Replacement Therapy (HRT)

A large prospective study, the *Women's Health Initiative* designed to provide answers to many questions regarding estrogen replacement therapy, included 25,000 generally healthy postmenopausal women. But the estrogen-progesterone arm of the study was discontinued when it became apparent that HRT lead to small increases in cardiac infarction, stroke, pulmonary emboli and breast cancer. *The disadvantages of HRT far outweighed the advantages*. In addition, the results clearly showed that this combination of hormones did not improve the quality of life of older women who suffered from climacteric complaints. Similar negative results were also documented for cognitive capabilities, depression and sexual function. *A study of 716,738 postmenopausal women in the U.K clearly demonstrated the greater increase in total cancer incidence with use of combined HRT either continuous or cyclic than with the use of other non-hormonal therapies*. Even before the menopause, incipient estrogen deficiency results in a steady loss of bone and without preventive measures 1–4% of the bone mass is lost annually after the menopause. Therefore in order to avoid this, and in the absence of preventive measures an aminobisphosphonate, a SERM or preferably both should be given depending on the state of the bones and the patient's general condition and life-style. A BMD is taken beforehand, so that the state of the skeleton can be monitored; this encourages compliance with therapy.

Replacement Therapy in Men with Testosterone Insufficiency

When substantial bone loss occurs in relatively young men, the possibility of secondary osteoporosis must be considered and carefully excluded (e.g., osteogenesis

imperfecta or an undiagnosed neoplastic condition). Replacement therapy with testosterone in hypogonadism, singly or together with a bisphosphonate, is the therapy of choice in primary osteoporosis in older patients as well as in younger ones after a secondary condition has been definitively excluded. *Today hypogonadism in men can easily be treated by plasters, gels or i.m. administration of testosterone. However, it is essential first to exclude prostatic cancer, for which, in most cases, the level of PSA is indicative and therefore a good starting point.*

Bisphosphonates

Oral bisphosphonates have been approved for the prevention and treatment of osteoporosis in both women and men. Studies successfully carried out on tens of thousands of patients have shown that bisphosphonates are safe, well tolerated, have minimal side effects, inhibit bone resorption, cause an increase in BMD and thereby reduce the risk of fractures. *Bisphosphonates have now been prescribed for well over 10 million patients in 80 different countries world-wide! This number is most probably an under-estimate. More precise up-to-date figures are currently awaited.*

In various countries, alendronate is now authorised for treatment of postmenopausal ostoporosis, for osteoporosis in men and as therapy of glucocorticoid-induced osteoporosis in postmenopausal women. Results of recent studies have shown that bisphosphonates can even be taken by osteoporotic patients with kyphosis. Results of some comparative studies have shown that bisphosphonates had the greatest effect on bone mass in postmenopausal women. Other large-scale studies are in progress and results are pending.

Alendronate

Therapy was successful in 95% of patients at the end of the first year. In addition, the Fracture Intervention Trial (FIT) demonstrated a reduction in bone pain and an increase in mobility in patients on alendronate therapy. Similar results were obtained in men as well as in patients with cortisone-induced osteoporosis. *It has now been established that alendronate not only reduces vertebral fractures but also all other types of osteoporotic fractures such as those of the forearm and hip.*

Moreover, the once weekly dosage of 70 mg alendronate has significantly increased acceptability and compliance. With the introduction of the once monthly tablet, the compliance is expected to increase even further. *The 70 mg weekly dose has also further decreased the already low rate of gastrointestinal side effects*. Pharmacokinetic studies have demonstrated that at dosages of 5–80 mg 0.1–1% of the alendronate is absorbed and 50% of this is deposited on the "exposed" surface of bone. Whether taken as 10 mg daily or 70 mg weekly, identical quantities of alendronate are absorbed and deposited; consequently the rates of increase in bone

density are also the same: vertebrae: 5–6% and hip 3–9% after one year. Tablets combining 70 mg alendronate with addition of 2,800 IU Vit D_3 are now available (Fosavance®). Moreover, a 70 mg solution of alendronate given orally to patients unable to swallow tablets significantly reduced biochemical markers of bone turnover. *Alendronate has now been used for over 10 years as therapy for osteoporosis in postmenopausal women. It is also recommended for osteoporosis in men.*

Risedronate

This bisphosphonate has now been tested on 15,000 patients in large international trials. After 3 years of 5 mg risedronate daily an increase in bone density of 5.4 to 7.7% was observed in the lumbar vertebrae (significantly higher than the control group). After one year the decrease in fracture risk for the whole vertebral column was significantly reduced by 65%.

These results are particularly important for patients at high risk and for those who have already sustained one fracture, in order to avoid additional fractures. Risedronate is authorised for treatment of postmenopausal, for glucocorticoid-induced osteoporosis and for osteoporosis in men. Risedronate is available as a once weekly tablet together with calcium.

Comparative studies, that are "head to head" trials of alendronate and risedronate: two such studies have examined the relative efficacies of these two bisphosphonates. In both studies alendronate 70 mg weekly for 12 months achieved a faster and greater increase in bone density of the spine and the hip than risedronate at 5 mg daily (n=549) or 35 mg weekly (n=1053), *FACT study* (Fosamax Actonel Comparison Trial). Moreover, markers of bone resorption showed significantly greater decreases in patients on alendronate than on risedronate therapy. *Put simply, these results demonstrate that alendronate was superior to risedronate in decrease of remodelling and in increase of bone density–both factors related to bone strength and reduction in fracture risk.*

The tolerability profiles of the two drugs were similar. Nevertheless the results of these studies did not indicate definitive differences in reduction of fracture risk. However, it should be noted that previous meta-analyses have confirmed the significant correlation between bone density and decrease in remodelling parameters under therapy on the one hand and decrease in fracture risk – especially extravertebral ones on the other.

In addition, on the basis of animal experiments, it has shown that there is a close correlation between increase in bone density in the vertebral column and bone strength.

Statisticians have now calculated that in order to arrive at a significant difference in fracture risk between two bisphosphonates, 30,000 to 50,000 patients would have to be recruited for the study. Considered from this point of view,

future head-to-head studies on differences between vertebral and extravertebral fractures will no longer be undertaken. Likewise, placebo-controlled studies of new drugs for treatment of osteoporosis will no longer be possible on ethical grounds.

Etidronate

This is the only bisphosphonate which can be given as cyclic intermittent therapy: 400 mg etidronate tablets daily for 14 days every 3 months, the tablets are swallowed with water no less than 2 hours before and 2 hours after meals to avoid difficulties in absorption. On completion of the etidronate cycle, calcium 500 mg is taken daily. *However, this bisphosphonate is no longer given for osteoporosis because of its long term effects on mineralisation and because it has been replaced by the newer, more potent bisphosphonates currently in use.*

Ibandronate

Ibandronate is a potent nitrogen-containing bisphosphonate that possesses a tertiary nitrogen group on its R_2 side chain and a hydroxyl group on its R_1 side chain, which together confer one of the highest antiresorptive potencies of all bisphosphonates. Due to this greater potency, this bisphosphonate can be given in lower dosages and at longer intervals than the other bisphosphonates authorised for osteoporosis. Ibandronate was the first *to become available as a once monthly tablet*, as well as having the option of i.v. administration. It can be taken orally once a month, for which it has already been authorised; and it is currently being tested both orally and intravenously for therapy of postmenopausal osteoporosis, as infusion or as bolus given i.v. every 3 months. In a previous placebo-controlled trial, the optimal daily dose was shown to be 2.5 mg, which resulted in increases in bone density of up to 10% after 2 years. In the *BONE Study* the efficacy of ibandronate was established with respect to reduction of fractures, increase in bone density and decrease in remodelling parameters. The outcome of the BONE-study, in which 2,946 postmenopausal patients (T score <-2; one or more vertebral fractures) were given 2.5 mg ibandronate daily, showed that after 3 years the relative risk of vertebral fractures were significantly reduced by 62% when compared to patients who received placebo. However, the effect of this therapy on hip fractures was not recorded at the time, probably because this was not one of the primary endpoints of the BONE-study. *Nevertheless, as shown by post-hoc analysis, the risk of non-vertebral fractures was also decreased by 69% in 375 patients with an increased risk, i.e. T score <-3.0.* In this study longer intervals between doses were also investigated (Chesnut et al. 2005). A patient-friendly regimen for ibandronate, i.e. a monthly oral or i.v. administration was then developed on the basis of the results of the BONE Study. The *MOPS Study* ("Monthly Oral Pilot Study") of 144 postmenopausal patients was the first to apply the once a month tablet of 100 or 150 mg

ibandronate. This dose was well tolerated and lead to reduction in the biochemical levels of bone resorption markers to normal premenopausal values. Thereafter, the *MOBILE Study* (Monthly Oral Ibandronate in Ladies) comprising 1,600 patients was initiated and this study, carried out over a two year period, demonstrated the efficacy of the once a month therapy of postmenopausal osteoporosis. *European authorisation for a monthly dose of 150 mg ibandronate (Bonviva®) has already been granted, and patient preference for the once monthly tablet has already been documented. The efficacy of ibandronate in reducing the risk of fractures has been conclusively established, in addition to its efficacy in a randomised controlled trial (Reginster et al. 2006). It should be also noted that ibandronate has the potential to be utilised for treatment of many diseases of bone from prevention of osteoporosis to therapy of osseous metastases.*

Intravenous Therapy of Osteoporosis

Ibandronate

The *DIVA Study* ("Dosing Intra Venous Administration"), a multicentric placebo-controlled study of 1,400 patients with postmenopausal osteoporosis, demonstrated the efficacy of ibandronate in this setting. Ibandronate i.v. 2 mg every 2 months or *3 mg every 3 months*, was fairly rapidly injected (20 to 30 seconds). Both were as effective as the 2.5mg oral dose which had already proved its value in reduction of fractures in the BONE Study (see above). European authorisation for the i.v. application has already been granted and this i.v. application constitutes an alternative to the monthly tablets.

Zoledronate

Clinical studies of zoledronate in osteoporosis are now in progress, including trials of half yearly and of annual injections for its prevention. In one of these studies postmenopausal women with low bone density were treated with zolendrate 4 mg per annum. A once-yearly infusion of 5 mg zoledronate during a 3-year period significantly reduced the risk of vertebral, hip and other fractures (Black et al. 2007). The effects on bone density and parameters of bone remodelling were similar to those of daily oral bisphosphonates. *Zoledronate is possibly both a manufacturer's and a patient's dream come true – in the form of a single annual infusion of 5 mg for prevention and treatment of osteoporosis*. Though final recommendations cannot yet be made, the following considerations are applicable: an effective therapy for manifest age-related osteoporosis falls within the range of 2 x 4 mg zoledronate per annum. Data are not yet available for glucocorticoid-induced osteoporosis, but the same range of dosage could apply. It is advisable to begin therapy with a bisphosphonate prophylactically together with the glucocorticoid therapy, after DXA bone density measurement for baseline values. High risk patients should re-

ceive higher doses: e.g. 4 x 4 mg zoledronate per annum: for example after testosterone deprivation therapy in patients with prostate cancer, and after chemotherapy induced cessation of ovarian function and/or aromatase inhibitors in patients with breast cancer. *A single annual i.v. infusion of 5 mg zoledronate (Aclasta®) has now been authorised to postmenopausal women*. (Black et al. 2007)

Clodronate and Pamidronate

These two bisphosphonates have already proved their value in hypercalcemia and in skeletal metastases. However they have not yet been authorised for therapy of osteoporosis, therefore they should only be given within the setting of an Osteoporosis Center and only after the patients have been fully informed and have given their written consent to the treatment.

Recommendations for intravenous therapy

This has now gained a high degree of compliance, especially with patients who are already taking a number of other drugs orally. *Additional advantages are 100% bioavailability and no gastrointestinal side effects;* moreover, the effects on bone density and fracture rate are comparable to those of oral therapy. The following dosages and time intervals are currently used:

► *Clodronate (Ostac®, Lodronat®, Bonefos®)*	600 mg infusion every 3 months
► *Pamidronate (Aredia®)*	30 mg infusion every 3 months
► *Ibandronate (Bonviva®)*	3 mg infusion or injection every 3 months
► *Zoledronate (Aclasta®)*	5 mg infusion annually

The administration of bisphosphonates at intervals of 3 months is based on the observation that a single intravenous dose inhibits resorption of bone for several weeks; zoledronate 5 mg i.v. every 12 months results in the same increase in bone density as a bisphosphonate taken orally daily or weekly. It should be stressed that i.v. administration is not yet authorised for therapy of osteoporosis, and should only be given in Osteoporosis Centers and after the patient's written consent has been obtained. *This type of i.v. therapy is most suitable for patients who experience difficulty with taking the drug per os. This includes immobilised patients, patients with various co-morbidities such as gastro-intestinal diseases, esophagitis, post-transplantation, and of course children.*

Duration of Therapy with Bisphosphonates and Long-Term Studies

The optimal *duration* of bisphosphonate therapy is 3 to 5 years, depending on the initial severity of osteoporosis and the subsequent increase in bone density. Three phases are recognised:

- *Repair* (up to 12 months)
- *Rebuilding* (6 to 36 months)
- *Maintenance* (24 to 60 months).

Bisphosphonate therapy is a matter of years – this must be explained to each patient and re-emphasised at the start of and during therapy. The highest rate of increase in bone density occurs during the first 12 months when the resorption lacunae are repaired and refilled with bone. During the rebuilding and maintenance phases, the increase is less because during these periods the trabecular structure and width are being restored. It is assumed that repair of the trabecular bone network, plus the increase in bone density during the first year of therapy, are together responsible for the rather remarkable decrease in fracture rate which occurs during this period. An increase of more than 3% in bone density under alendronate therapy showed about the same decrease in fracture risk as an increase of 3% in bone density. Similar correlations were observed in patients on risedronate therapy: an additional decrease in fracture risk was not observed with bone density increases above 3%. Annual increases in bone density of up to 10% are possible but do not necessarily imply a proportional decrease in fracture risk. Under risedronate therapy, markers of bone resorption show similar relationships. For example a decrease in urinary NTx of more than 40% did not lead to a further reduction in fracture risk.

There is relatively less increase in bone density during the phases of repair and maintenance because the increase in mineralisation is now in the foreground. On cessation of bisphosphonate therapy in post-menopausal women, there is a moderate decrease in bone density during the first year, more pronounced in the lumbar spine than in the hip, this does not occur in men. *On completion of 1 to 3 years of treatment, results of annual measurements of BMD will determine when bisphosphonate therapy should be resumed*. Some studies have already shown that the positive effect on mineral density of both cortical and trabecular bone is maintained for one year after cessation of bisphosphonate therapy. This should be checked by BMD measurement in each patient.

Long-term follow-up studies: Previous fears of a "frozen, poor-quality bisphosphonate bone" liable to micro-fractures "cracks" have not been confirmed. Results of long-term clinical studies of bisphosphonates to date have allayed these fears (Fig. 4.4). Clinical studies of alendronate conducted for more than 7–10 years have demonstrated that bone density consistently increased by approximately 0.7% per annum. Therefore over a 10-year period bone density increased by an

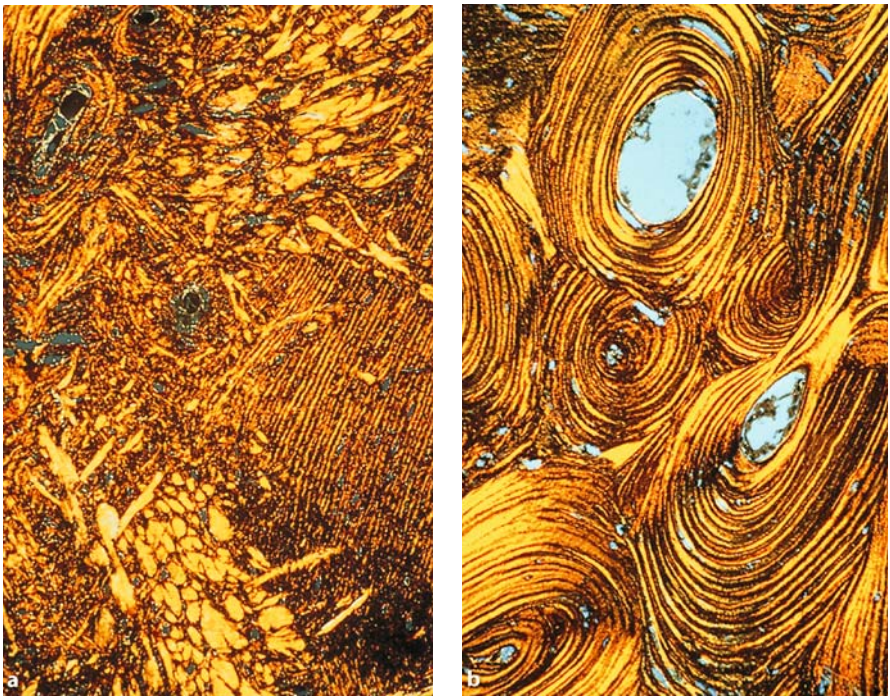


Fig. 4.4a,b Bone structure after 3 years of treatment for osteoporosis. **a** Disorganized woven bone after fluoride treatment, **b** Regular parallel lamellae of trabecular bone after bisphosphonate therapy. Biopsies taken from the iliac crest

average of 13%. This indicates that *apparently there is no time limit for therapy with bisphosphonates – the one important factor is the state of the patient's skeleton and this should be regularly monitored*.

To summarise results so far achieved:

- Over a period of approximately 1 to 3 years 70 mg of alendronate are incorporated into the bones. With such a minute amount of bisphosphonate, when the skeleton contains 2,000,000 mg of hydroxyapatite, physicochemical damage is excluded for all practical purposes. The same holds true for the other modern bisphosphonates. Moreover, disturbances of mineralisation do not occur with these bisphosphonates.
- After 7 years of therapy with alendronate, the bone mass still increased by about 1% a year, indicating that basic remodelling with a positive bone balance remains unchanged.
- Bone biopsy findings have shown that after 7 years of therapy with alendronate the trabecular architecture and lamellar structure remained unaltered (i.e. were preserved) and that microfractures were not found.

- The number of normal hydroxyapatite crystals increased, thereby rendering bone more resistant to compression.
- In contrast, fluoroapatite crystals, which are incorporated into the mineral phase of bone during fluoride poisoning, though denser than hydroxyapatite crystals, are brittle and shatter easily.

The following parameters can be used to estimate *success of therapy*:

- Decrease in collagen breakdown products and TRAP in urine and/or serum. These biochemical markers of bone resorption provide the earliest information on the effects of therapy
- Increase in biochemical markers of bone formation
- Increase in BMD (DEXA of lumbar spine and hip)
- Decrease in fracture rate (vertebral and extravertebral)
- Decrease in osteoporotic bone pain
- Increase in quality of life and mobility
- Decrease in duration of hospitalisation

After 3 to 6 weeks of therapy a decrease in markers of bone resorption should occur. If such markers have not been reduced by 30 to 40% after 2 to 3 months of oral therapy, the patient should be questioned as to whether and in what form the drug was ingested, and appropriate measures taken according to the circumstances. Subjective parameters such as pain, mobility and quality of life can only be accepted as secondary criteria.

Bone mineral density (BMD) should be measured annually during therapy with a bisphosphonate; although, as shown in large studies of bisphosphonates, the risk of fractures may be decreased even in the absence of a measurable increase in density. *Should there be no increase in BMD after a year of therapy, four possibilities should be considered:*

- Medication was not taken: Telopeptides (markers of bone resorption) should be checked.
- Medication was not taken according to instructions: Discussion with patient for information and clarification.
- Possible "non-responder" when therapy was indeed taken: change to intravenous administration of nitrogen-containing bisphosphonates.
- Possibly the case is not a primary but a secondary osteoporosis: for example an undiagnosed primary malignant disorder may be present: Investigations – including MRI and bone biopsy – must be carried out as quickly as possible.

Even when there is no direct correlation between increase in bone density and decrease in fracture risk under anti-resorptive therapy, the measurement of bone density (DXA) is still the most practical and quantifiable parameter for estimation of fracture risk both within the framework of diagnostic evaluation as well as monitoring of therapy. In addition it has world-wide acceptance which simplifies

comparison of results. Results of two large meta-analyses of vertebral fractures have conclusively demonstrated that the reduction of 24% to 54% in risk of fractures under bisphosphonate therapy is unequivocally due to the increase in bone density. This relationship is even more pronounced with respect to non-vertebral fractures. These meta-analyses also indicate that bisphosphonates increase bone density not only by inhibition of osteoclastic activity, but also by their influence on osteoblasts and osteocytes (inhibition of apoptosis). *The bisphosphonates improve the micro-architecture of bone, and thereby also decrease the risk of fractures. This graphically illustrates the close correlation between bone density, strength and micro-architecture.*

Moreover, studies of bone biopsies have shown that the increase in bone density is closely connected to the improved micro-architecture of trabecular bone. This was demonstrated by Recker et al. by means of micro-CT and histomorphometry. Their results provide a convincing argument for DXA measurement in the evaluation of effects of bisphosponate therapy on bone. These and other studies have demonstrated increases in trabecular thickness, as well as in numbers and connections, i.e. "the nodes" of the trabecular network while the porosity of cortical bone was also decreased. *These micro-CT studies have clearly demonstrated improvement and preservation of the trabecular micro-architecture under bisphosphonate therapy. It should be mentioned that though increases in bone density usually occur under therapy, lower values have also been registered by DXA*. This apparent paradox has been observed especially in hip measurements after 6 months of teriparatid therapy: decreases in DXA values occurred together with increases in bone surface areas. In contrast, measurements with QCT did register an increase in bone density. Under teriparatide therapy measurements may show a decrease in density, but bone volume and strength are increased – therefore this is only an apparent paradox. These results demonstrate that *DXA measurements underestimate the increase in density only in the presence of an increase in bone surface.*

In practice, the success of anti-resortive therapy depends on regular and consistent administration, i.e. patient compliance. However, as shown in one study (Recker et al. 2004), this is attained by only a small percentage of the patients. With introduction of the once weekly tablet, there was a 60% increase in compliance therefore a further improvement is to be expected with the monthly tablet. *The once monthly and possibly annual tablets (or i.v. administration) are expected to work wonders with compliance.* Few studies have actually been carried out on compliance with long time intervals. One such study did show that a demonstrable increase in bone density contributes to better patient compliance with the therapy.

Meta-Analyses of anti-resorptive substances

According to the principles of evidence-based-medicine, randomised studies and meta-analyses have the highest priority. However, classification and comparison

of drugs pose methodological problems which are easily overlooked and/or underestimated (see Chap. 3). Meta-analyses provide data for comparative studies. However, reliable comparison between two drugs is only possible in "head-to-head" studies as outlined previously.

Frequently significant findings are 1) only revealed in sub-groups, 2) obtained after retrospective evaluation, 3) require re-definition of the inclusion criteria, and 4) require utilisation of specialised statistics. Nonetheless, a team of experts (in methods of evidence-based medicine) has recently undertaken the task of comparing the efficacy of various anti-resorptive agents to decrease fracture risk in spite of all the difficulties involved. These studies were commissioned by The Osteoporosis Methodology Group (*OMG*) and the Osteoporosis Research Advisory Group (*ORAG*). The experts confirmed that the most reliable method is undoubtedly the "head-to-head" study. *This implies that estimation of the 9 most important anti-resorptive agents alone would require 36 such studies! In addition, extremely high numbers of patients would be needed to recognise significant differences between 2 drugs!* However, the ORAG analyses did show that there are differences between the drugs in degree and location of fracture reduction. *The results demonstrated that after one year of therapy alendronate achieved significant reduction in fractures of both hip and spine. Indeed alendronate was more effective in reducing extra-vertebral fractures than all the other drugs investigated.*

Practical Recommendations

Calcium and Vitamin D

- *Calcium* 1000 mg daily in food and/or in tablets
- *Vitamin* D_3 1000 IU daily with food for postmenopausal osteoporosis

CAVE: Osteoporosis in men: the level of testosterone in the serum must be determined and hypogonadism carefully investigated to exclude prostatic cancer before any testosterone therapy is given (in any of the many forms available today).

Bisphosphonates

These can be taken daily, weekly or monthly per os or can be given i.v. quarterly, semiannually or annually.

- *Alendronate* (Fosamax®): 10 mg daily or 70 mg weekly, or (Fosavance®): 70 mg and 2800 IE vitamin D weekly (see manufacturer's instructions for ingestion)
- *Risedronate* (Actonel®): 5 mg daily or 35 mg weekly (see manufacturer's instructions for ingestion)

- *Ibandronate* (Boniva®, Bonviva®): 150 mg monthly (see manufacturer's instructions for ingestion)

Alternatively, some bisphosphonates can be given by *infusion*, but when these are not yet officially authorised, appropriate precautions must be taken. It is important to remember that if and when oral ingestion is problematic, i.v. administration is always available: so there is no reason not to give a bisphosphonate whenever indicated. The once monthly orally or intermittent i.v. administration of ibandronate has already proved to be effective in the management of osteoporosis in some clinical trials and additional multinational clinical trials are ongoing (Reginster, 2005).

- *Ibandronate* (Bonviva®) 3 mg injection every three months
- *Zoledronate* (Aclasta®) 5 mg infusion annually
- *Pamidronate* (Aredia®) 30–60 mg every three months.

Other medications also effective in osteoporosis:

- *Raloxifen* (Evista®) is an A-classified SERM and is given 60 mg daily per os for postmenopausal osteoporosis. In addition to its effect on bone density it reduces the risk of breast cancer by 75%, and it also has a positive effect on lipid metabolism.
- *Teriparatide* (Forsteo®) is a fragment of parathormone (1–34) with osteoanabolic activity, i.e. it stimulates bone formation. It is administered by subcutaneous injection 20 ug daily, for a maximum period of 18 months. It has been authorised for severe postmenopausal osteoporosis, in some countries also for osteoporosis in men. Also the use of *full-length parathyroid hormone (1–84)* (Preotact®) has been authorised for postmenopausal osteoporosis in a daily dose of 100 µg for 2 years. The increase in bone volume improves bone structure and bone microarchitecture by trabecular thickening and by an increase in inter-trabecular nodes. *In addition, more lasting and effective results have been obtained by administration of an antiresorptive agent after the anabolic one, i.e. a year of parathyroid hormone followed by a year of bisphosphonate (Black et al. 2005).*
- *Strontiumranelate (Protelos®):* At a daily dose of 2 g this drug inhibits osseous resorption while simultaneously stimulating bone formation. Several studies have confirmed a significant reduction in vertebral fractures (*SOTI Study*) and in hip fractures (*TROPOS Study*).
- *Active Vitamin D metabolites* such as Alfacalcidol (0.5–1 µg) or Calcitriol (0.5 µg.) tablets should be taken daily; especially for secondary osteoporoses, e.g. after renal, hepatic and other organ transplantations together with a bisphosphonate.

- *Calcitonin:* 50–100 IU subcutaneously or intranasally. Today mainly used for quick relief of bone pain.
- *Denosumab* (formerly known as AMG 162) is a monoclonal antibody which binds RANKL and thereby inhibits its activity. The efficacy of denosumab in postmenopausal osteoporosis has been demonstrated in a 12 month clinical trial. Results were comparable to those achieved by alendronate.

CHAPTER 5 Glucocorticoid Induced Osteoporosis

Definition

Long-term steroid therapy leads to osteoporosis in about 50% of the treated patients. *It has been established beyond all doubt that osteoporosis and fractures are frequent and important consequences of glucocorticoid therapy (Pennisi et al. 2006, Service of Bone Diseases, WHO Collaborating Center).*

Diseases Treated with Glucocorticoids

The underlying disorder also frequently contributes to the osteoporosis; examples are Crohn's disease, rheumatic disorders, transplantations, bronchial asthma, multiple myeloma and malignant lymphomas. Glucocorticoids are also included in many chemotherapy protocols, see appropriate sections and chapters.

Rheumatic Disorders

Rheumatic disorders of bones and joints are characterised by inflammatory processes involving whole families of cytokines and receptors which provoke resorption of bone leading to erosions in and around the joints by osteoclastic stimulation and resorption – causing juxta-articular osteopenia and generalised osteoporosis. These processes can be prevented or greatly reduced by timely administration of bisphosphonates. *It is worth noting that bisphosphonates also enter into and are retained within the joints, for example in rheumatoid arthritis so that resorption of both bone and cartilage are decreased following administration of bisphosphonates.* Patients with some rheumatic disorders such as polymyalgia rheumatica and temporal arthritis require long term therapy, therefore attention must be paid to the preservation of skeletal integrity right from the initiation of treatment. This has been recommended in the Guidelines published by the American College of Rheumatology (Liu et al. 2006). Nevertheless, in other rheumatic disorders such as ankylosing spondylitis, a literature review carried out by the American college of Rheumatology for 2001 to the end of 2004, showed that a bisphosphonate had been used to some effect in only one random controlled study. This situation will undoubtedly be rectified in the near future.

The bones of children, young men and postmenopausal women are particularly vulnerable, therefore early preventive therapy is mandatory. *There is also a correlation with aseptic osteonecrosis in children and adolescents who had been treated for hemato-oncologic diseases with protocols including corticosteroids. This can be alleviated with bisphosphonates.*

Individual patients may be particularly sensitive to corticosteroids. For example, children with severe burn injury of more than 40% total body surface area suffer subsequent bone loss attributed in part to therapy with glucocorticoids. Early i.v. pamidronate may help to preserve bone mass, possibly by inhibition of the glucocorticoid-induced apoptosis of osteoblasts and osteocytes. *It has been estimated that glucocorticoid induced osteoporosis is the most frequent of all secondary types of osteoporosis, and that bisphosphonates protect patients from bone loss and reduce vertebral fracture risk (see below).*

Glucocorticoid-induced osteoporosis has the following characteristics. Trabecular bone is primarily involved, so fractures occur in the vertebral bodies, the ribs and hips that is, in the bones with hematopoietic marrow. There is a rapid loss of bone: *"high turnover osteoporosis" or "fast bone losers"*. Within the first 6–12 months of glucocorticoid therapy a 20% or more decrease in bone density may occur.

Pathophysiology

Glucocorticoids have multiple effects on bone:

- Inhibit osteoblast function
- Decrease proliferation of osteoblasts
- Increase apoptosis of osteoblasts
- Increase osteoclastic activity
- Decrease apoptosis of osteoclasts
- Decrease intestinal absorption of calcium
- Increase renal excretion of calcium
- Increase secretion of parathyroid hormone
- Decrease secretion of sex hormones
- Inhibit secretion of growth hormone
- Decrease secretion of calcitonin
- Decrease the number of bone remodelling units
- Induce development of aseptic necroses (cave jaw bones)
- Increase production of collagenase.
- Induce changes in lipid metabolism

Because the effects of glucocorticoid therapy on the musculoskeletal system are multifactorial, all the more reason to take them into account as much as possible and as soon as possible – prevention is always better than cure!

Certain interactions of glucocorticoids with other factors are also significant in the pathogenesis of corticosteroid osteoporosis:

- Increased sensitivity of osteoblasts to PTH and $1,25(OH)_2$ vitamin D
- Decreased local production of prostaglandin E
- Decreased local production of IGF-1
- Decreased binding of IGF to proteins
- Decreased biologic action of IGF-1
- Increased production of collagenase

Prevention

When treatment with glucocorticoids is expected to continue for 6 months or more and the daily dosage is more than 7.5 mg, significant bone loss can be anticipated. At higher doses a bone loss of 15% or more can occur annually. When long-term cortisone therapy is contemplated, the BMD should be measured beforehand to establish the baseline bone density, and a bisphosphonate prescribed concomitantly with initiation of glucocorticoid therapy to avoid a decrease in bone density. No patient should be allowed to enter the "possibility of a fracture zone" when the means to avoid it are at our disposal. On the other hand, short-term (several days) or local cortisone treatment given as cream, spray or injection usually poses no threat of osteoporosis. Possibly the length of time the local cortisone is given is significant, as it has recently been demonstrated (albeit in rabbits) that after 8 weeks of dexamethasone eye drops bone mineral density was reduced. In general, when prescribing cortisone, the following points should be considered:

- Check for the lowest effective dose
- Shortest possible duration of therapy to avoid atrophy of the adrenal cortex
- Use glucocorticoids with the shortest half-life
- Use local preparations when possible
- Emphasise physical activity and muscular exercise
- Regular monitoring in cases of long term application
- Preventive therapy in the presence of risk factors

Treatment Strategies

The same principles apply as for treatment of postmenopausal osteoporosis:

Application of preventive measures:

- Physical activity and muscular exercise
- Vitamin D and calcium

- Check for and treat steroid-induced diabetes mellitus
- Antiresorptive therapy with one of the nitrogen-containing bisphosphonates after a BMD has been carried out to obtain base-line values

Bisphosphonates

Alendronate and risedronate have now been approved for prevention and treatment of cortisone induced osteoporosis:

► *Alendronate (Fosamax®)*	10 mg daily or 70 mg weekly
► *Risedronate (Actonel®)*	5 mg daily or 35 mg weekly

When resorption has already increased or after transplantation, intravenous takes precedence over oral administration. It has already been shown that risedronate, given to patients with rheumatoid arthritis on glucocorticoid therapy, significantly reduced new osteoporotic fractures.

► *Ibandronate (Bonviva®)*	3 mg bolus infusion every 3 months for prevention and therapy

This method of treatment is highly acceptable to physicians and patients alike. BMD should be measured by DEXA of the lumbar spine and hips every 6 months during the first 2 years of therapy. Ringe (2006) treated patients with glucocorticoid-induced osteoporosis for 2 years with ibandronate 2 mg as bolus every three months. Bone density was increased by 11% in the lumbar spine. *Positive effects of once weekly oral alendronate in children on glucocorticoid therapy have also been reported.*

CHAPTER 6 Tumor and Chemotherapy Induced Osteoporosis

Definition

Many treatment protocols in oncology lead to manifest osteoporosis. Radiotherapy causes local atrophy of bone and bone marrow, while chemotherapy and hormone ablative therapy induce systemic rarefaction of both trabecular and cortical bone. Moreover, these iatrogenic effects may even be aggravated by a direct effect on bone of the tumor itself because in some cases the malignant cells have the capacity to resorb bone and cause osteolytic lesions. This may occur in primary neoplasms, such as giant cell tumor of bone, as well as in secondary processes such as metastases of mammary and some other carcinomas. *In addition, both chemo- and radiotherapy may damage the bone cells themselves.* These aspects of therapeutic interventions are now more widely understood and appreciated and therefore taken into consideration when treatment strategies are planned. This has actually been the case for years in multiple myeloma, and is now being applied to other cancers as well especially those with osteotropic metastases (see subsequent chapters).

Pathophysiology

Causes of osteoporosis during treatment of neoplasias are:

- Treatment-induced hypogonadism
- Glucocorticoids in chemotherapy protocols (these possibly also contribute to osteonecrosis especially of the jaw bones)
- Toxic effects of chemotherapy
- Radiotherapy; also of the CNS, in children because of brain tumors or acute leukemias
- Immobilisation
- Gastro-intestinal and nutritional disturbances
- Decreased physical activity
- Psychological influences

Types of Tumor Therapy with Direct Effects on Bone

Tumor Therapy with Induction of Secondary Hypogonadism

Any chemotherapy with this effect will eventually cause severe osteoporosis if no preventive measures are taken. Two groups of tumors are distinguished:

- Sex hormone-dependent neoplasias such as breast or prostate cancer. Here hypogonadism is part of the treatment strategy.
- Sex hormone-independent tumors such as Hodgkin's disease and other malignant lymphomas. In these cases hypogonadism is an unwanted side effect, especially significant in young people.

Hypogonadism in Breast Cancer

Premenopausal patients with breast cancer develop irreversible ovarian insufficiency, with the corresponding postmenopausal symptoms, early during the first month(s) of chemotherapy. *More than 200,000 women in the USA alone are diagnosed annually with breast cancer. Since approximately 55% of the USA population of 50 years and over has osteopenia/osteoporosis many of these women will unfortunately suffer from both these diseases.* Therefore measures should be taken to prevent bone loss and as a first step all women with breast cancer should have a bone density measurement at initial diagnosis. *The bone mineral density decreases by 8–10% in the lumbar spine and by 4–6% in the hips within 2 years of chemotherapy. However, if bisphosphonates are given at the same time as the chemotherapy, this bone loss can be avoided/compensated so that skeletal integrity is maintained.* Ablation of ovarian function is one of the aims of treatment, especially in patients with estrogen receptor-positive tumors. This is achieved by the chemotherapy itself or by administration of gonadotropin-releasing hormone (GnRH) analogues. Inhibitors of aromatase and estrogen antagonists are also given. Such anti-hormone therapy entails a considerable risk of osteoporosis as stated above. Tamoxifen, a synthetic anti-estrogen, has an antiresorptive effect on bone but cannot make up for the lack of stimulation of bone formation. Tamoxifen, however, is now being replaced by the aromatase inhibitors.

Aromatase Inhibitors

These inhibitors suppress the estrogen levels in the blood by inhibition of the enzyme aromatase, which is responsible for the conversion of androgenic precursors to estrogens. However the aromatase inhibitors do not have a positive, i.e. a protective effect on bone. Development of osteoporosis due to chemotherapy and/or therapy with aromatase inhibitors can be avoided by simultaneous administration

of anti-resorptive drugs. *Trials of combined therapy of an aromatase inhibitor plus an anti-resorptive agent are underway and the results so far are promising.* Consequently, all patients with breast cancer should have a bone density measurement (DXA of lumbar spine and hips) before commencing chemotherapy to establish a base-line; and preventive administration of bisphosphonates should be started:

- Clodronate: 1600 mg daily per os will increase the bone mass and most probably also decrease the risk of skeletal and visceral metastases.
- Alendronate (70 mg once weekly) or risedronate (35 mg once weekly) for prevention and treatment of osteoporosis; or the once monthly tablets if available.
- Alternatively, 3 mg of ibandronate i.v. at intervals of 1–3 months according to the severity and type of osteoporosis (i.e. high or low resorption as indicated by levels of markers).
- It should be emphasised that early administration of bisphosphonates is recommended for example with adjuvant chemotherapy prior to surgery, to counteract effects of chemotherapy, both direct and indirect, on bone; and possibly also as prophylaxis against osseous metastases.

Patients (no matter what age) with osteoporosis and a history of breast cancer should not receive hormone replacement therapy, but only an oral or intravenous aminobisphosphonate. Possible effects of raloxifen or other SERMs, (estrogen receptor modifiers) on bone as well as other tissues, have not yet been sufficiently elucidated in such patients; studies are in progress.

Hypogonadism in Prostate Cancer

Hypogonadism is one of the aims of therapy, particularly in metastatic cancer and in patients with a high postoperative (or post-therapeutic) PSA level. Hypogonadism can be achieved by orchidectomy, GnRH analogues and anti-androgens. Patients who have received such treatments are at great risk of developing osteoporosis and preventive measures should be instituted early, and as always beginning with a bone density measurement. *The appropriate diagnostic and therapeutic measures, i.e. bisphosphonates to be taken are the same as those indicated for patients with breast cancer (see above).*

Hypogonadism in Hodgkin's Disease and other Malignant Lymphomas

Hypogonadism resulting from chemotherapy is most frequent in this group of non-hormone-dependent neoplasias. Irreversible ovarian insufficiency and early menopause are induced in 30–60% of premenopausal women after radiotherapy and intensive chemotherapy therefore early preventive measures are required (as outlined above). Because of the low proliferative index of Leydig cells, men are less

likely to develop severe osteoporosis, though some degree of bone loss will become manifest later. Therefore BMD measurements should also be made in all patients with lymphomas so that if and when needed, bisphosphonate therapy can be given for prevention or treatment. *It should be noted that osteopenia/osteoporosis may be present at diagnosis even in children, therefore the same considerations apply, especially to ensure growth and development of peak bone mass.*

Anti-Tumor Therapy with Direct Effects on Bone

Many protocols used in oncology contain substances which, when given systemically, have adverse effects on bone and/or bone cells and thereby also cause osteoporosis. However, the degree of damage and the extent of bone loss depend on the frequency and/or duration of the cycles of chemotherapy. *Bone densitometry indicates when osteoporosis should be forestalled and/or treated.*

Protocols Including Corticosteroids

Patients (premenopausal women and men less than 60 years) with malignant lymphomas or with multiple myelomas are treated with chemotherapy protocols that include high doses of corticosteroids, which can damage bone cells by any or all of the various mechanisms previously outlined. However, since these patients do not have hypogonadism they do not suffer direct bone loss, although high cumulative doses of prednisone are given. One possible explanation may be the relatively short exposure time to the corticosteroids, due to their cyclic administration. In addition, by reducing the bone marrow infiltration in lymphomas and especially in myelomas, cytotoxic therapy also reduces their adverse effects on the adjacent trabecular and possibly cortical bone. *Nevertheless, bone density measurements indicate if/when bisphosphonates should be given.*

Treatment Protocols with Methotrexate and Doxorubicin

Many chemotherapeutic agents have not yet been investigated for their possible harmful effects on bone. Methotrexate is an exception. Increased bone resorption together with decreased formation resulting in high levels of renal excretion of calcium have been demonstrated in patients treated with methotrexate for rheumatoid arthritis. Methotrexate apparently also inhibits recruitment of osteoblast precursors. Children treated with methotrexate (e.g. in acute lymphoblastic leukemia) are especially liable to develop considerable resorption of bone although the resulting osteopenia/porosis is partially reversible when the methotrexate is stopped. *Children treated for hematological malignancies are particularly vulnera-*

ble and may even develop aseptic osteonecrosis, the early detection of which requires regular monitoring and prompt intervention including bisphosphonates.

Therapy with Ifosfamide

This alkylating agent combined with cisplatin is used mainly for treatment of solid tumors. Depending on the dosage, ifosfamide causes either reversible or permanent damage to the proximal renal tubules, resulting in metabolic acidosis, loss of phosphate and hypercalciuria which in turn result in the clinical picture of osteomalacia. The question as to whether or not ifosfamide has a direct toxic effect on bone cells awaits clarification.

Treatment Strategies

The problem of osteoporosis in patients with malignancies is underestimated. Frequently therapy is given when the patient has already sustained one or more fractures. This unfortunate situation is slowly being corrected but will only cease to occur when osteoprotection becomes an absolute "must" in all treatment protocols in oncology! Osteoprotection starts with a bone density measurement when the diagnosis of a malignancy is established, the appropriate steps are taken according to the results of the BMD, and the putative effects of the treatment which is planned are taken into consideration. *In cases with increased risk factors for fractures, immediate inhibition of bone resorption is indicated.*

Bisphosphonates

The choice of bisphosphonate, the dose, duration and interval of therapy are determined by the severity of bone loss and the patients´ risk factors. When carefully chosen and correctly administered, bisphosphonate therapy can eradicate the deficit and achieve a positive bone balance with an increase in bone density of up to 10% annually. *Just as important today is the anti-tumor effect of bisphosphonates, which has already been demonstrated in many different types of cancer – including multiple myeloma and cancers of the breast, prostate and lung (see appropriate chapters). A broad spectrum of bisphosphonates is available:*

Oral bisphosphonates:

► *Alendronate (Fosamax®)*	70 mg weekly
► *Risedronate (Actonel®)*	35 mg weekly

Bisphosphonates for intravenous administration:

► *Ibandronate (Bonviva®)*	3 mg injection every 3 months
► *Pamidronate (Aredia®)*	30 mg infusion every 3 months
► *Zoledronate (Aclasta®)*	5 mg infusion every 6 to 12 month
► *Clodronate (Ostac®)*	600 mg infusion every 1 to 3 months

Intravenous administration has some important advantages:

- Suitable for supportive treatment when i.v. chemotherapy is given at 1 to 6 week intervals
- Avoids gastrointestinal side effects
- Avoids problems of absorption due to complete bio-availability by i.v. administration
- Avoids problems of compliance in patients already burdened with other serious medical situations

CHAPTER 7 Transplantation Osteoporosis

Definition

Over the past decade transplantation of solid organs, such as the kidneys, liver, heart, lungs and pancreas has steadily increased. Even more impressive is the rise in the rate and duration of survival: the 1-year survival is now 98% for kidney transplants, 87% for liver transplants and 69% for heart transplants; and 5 years after liver transplantation 60–70% of patients are still alive. *Many of these patients already had some degree of osteopenia/osteoporosis before the transplantation, especially in cases of prolonged functional impairment of the organ involved, and this requires immediate initiation of bisphosphonate therapy, if not already started.* Moreover, loss of bone is a continuous process, i.e. it starts before and continues during and after the organ transplantation. To date, half of all patients with transplants still develop manifest osteoporosis often with fractures that considerably diminish their quality of life. This applies to patients with autologous as well as allogeneic bone marrow transplantation. The loss of bone is due to the basic disease as well as to the high doses of chemotherapeutic agents, corticosteroids and immunosuppressants administered before, during and after transplantation. *However, as with malignancy-related osteoporosis, bone loss within the framework of transplantation has numerous causes – and one main therapy: prevention!*

Pathogenesis

The pathogenesis is multifactorial and only partly elucidated. General and specific risk factors are involved. The general factors include menopause (in women), decreased testosterone in men and, in both, life-style factors such as alcohol, nicotine, inadequate nutrition, vitamin D and calcium insufficiency and most importantly physical inactivity. This last in turn has many (mostly undesirable and unfortunate) consequences for the patient. These include reduction in personal well-being and quality of life from psychological, social, and economical points of view.

The specific risk factors include: diuretics, anticoagulants and glucocorticoids. Moreover, as mentioned above, the diseased organ itself probably caused damage to the bones long before transplantation. Biochemical markers of bone remodel-

ling are generally high before transplantation. Immunosuppression with glucocorticoids, cyclosporin A and tacolimus (FK 506), is mostly responsible for the occurrence of fractures. *Bone loss is especially pronounced in the early post-transplantation period, except with azathioprine as immunosuppressant.*

To summarise, the pathogenic factors include:

- Pre-existing osteopenia or osteoporosis
- Immunosuppressive agents
- Anticoagulants
- Calcium and vitamin D deficiency
- Hypogonadism
- Lack of physical activity
- Poor nutrition
- Other life-style factors

Treatment Strategies

As soon as the possibility of a transplant is considered (generally long before the actual transplantation) a BMD should be carried out and measures taken to treat and/or prevent osteoporosis. This includes therapy with aminobisphosphonates, vitamin D and calcium; personalised physical exercises and an appropriate life style to minimise risk factors. Hypercalcemia should be prevented especially in patients with kidney transplants. Recommended screening and preventive measures for long term survivors of hematopoietic stem cell transplantation have now been published.

Bisphosphonates

Recommendations are identical to those listed in the previous section. Bisphosphonate therapy should be started in the pre-transplantation period. *Some studies have shown that after allogeneic stem cell transplantation, the bisphosphonate zoledronate not only increases bone density by osteoclastic inhibition but also by stimulating osteogenic progenitors in the stromal cell compartment.*

CHAPTER 8 Immobilisation Osteoporosis

Possible causes are spinal cord injuries, strokes, hospitalisation (prolonged), post-fracture and others.

Examples of Bone Loss

Insufficient physical activity is one of the most important overall risk factors for osteoporosis. This is especially true for young bed-ridden patients who can loose up to 30% of their bone density within a few months while years are required for its replacement – that is for restoration of density as it was before, i.e. "restitutio ad integrum" (see also Bartl and Frisch: Atlas of Bone Biopsy in Internal Medicine). For example, when an arm is enclosed in plaster for 3 weeks after a fracture, the immobilised bones may loose up to 6% of their bone mass during this short period. A study of patients confined to bed has shown that, on average, trabecular bone decreases by about 1% a week. When physical activity is resumed, bone density increases by 1% a month – considerably slower than its loss.

Examples of Causes of Immobilisation Bone Loss

- Damage to the vertebral bone marrow with deleterious effects on the bone
- Hemiplegia after cerebrovascular incidents
- Paraplegia of the lower half of the body
- Immobilisation after fracture of the lower extremities (rapid bone loss especially in children)
- Immobilisation after operations on the legs or feet with subsequent reduced mobility for prolonged periods
- Immobilisation due to muscular diseases or neurological disorders, e.g. multiple sclerosis

It has recently been demonstrated that there is a significantly increased prevalence of osteoporosis in both men and women with *multiple sclerosis*. Consequently bone density screening and appropriate measures including bisphosphonates need to be undertaken to avoid fractures in these patients. Shortly after the occurrence of a paraplegia, bone loss can be so rapid and extensive that relatively

minimal efforts can cause fractures (for example transfer from bed to wheelchair, or the effort of pulling up tight supportive socks). *After one year, 42% of paraplegic patients have osteoporosis of the femoral neck*. However, the muscular spasms some patients undergo may have a positive effect on bone density, but early initiation of physical training and activity is essential for all patients. *Prophylactic initiation of bisphosphonate therapy does avert and reduce bone loss but therapy must be continued to maintain bone in the long term.*

Patients who already have osteoporosis and are immobilised for several weeks because of a fracture, are likely to incur another one during the re-mobilisation period, unless preventive measures are taken as early as possible. The period of post-operative bed rest should be kept as short as possible and the bones protected by 1) effective medication, e.g. bisphosphonates to prevent further loss of bone mass, 2) especially by physiotherapy if at all possible, and 3) attention to proper nutrition and supplements.

Space Travel and Force of Gravity

Weightlessness in Space due to Lack of Gravitational Force

Astronauts undergo specialised and regular musculoskeletal training before and during the space flight to counteract the absence of the force of gravity in outer space. In spite of this they loose about 1% of their bone density every month. *In the conditions prevailing in outer- space, astronauts are subject to a 10-fold higher bone loss than earth-bound osteoporotic patients. This demonstrates unequivocally that the earth's gravitational force is nature's way of preserving the skeleton.* The mechanisms of bone loss in astronauts have been thoroughly investigated and are used today as models for immobilisation osteoporosis. Three main factors are recognised:

- Demineralisation of bone
- Inhibition of osteoblastic activity
- Activation of osteoclasts

Timely preventive measures, i.e. before and during the flight are mandatory.

Therapy of Immobilisation Osteoporosis

The emphasis is on physical activity as early and as varied as possible, adapted to each patient's condition and ability. The primary aim of medication is prevention, therefore bisphosphonate therapy should be started as early as possible and in accordance with the results of bone density measurements. This is especially important as the massive decrease in bone density which occurs immediately after the

onset of paralysis (immobilisation) should and can be prevented. The following are recommended: the first two only if the patient is able to sit up straight for at least 30 minutes after ingestion and there are cogent reasons for oral administration. Intravenous administration, as indicated below, is definitely preferable!

- Alendronate (Fosamax®) 70 mg weekly
- Risedronate (Actonel®) 35 mg weekly
- Ibandronate (Bonviva®) 3 mg injection monthly, later every three months
- Zoledronate (Aclasta®) 5 mg infusion annually

CHAPTER 9 Pregnancy Associated Osteoporosis

Pathogenesis

During pregnancy the higher levels of sex hormones increase calcium absorption and thereby balance the loss of calcium due to the pregnancy itself. The female body has compensatory mechanisms to supply the increased demand for calcium during pregnancy and lactation so that problems only arise if the calcium depots (in the bones) are not full to begin with. Therefore, *supplements of calcium and vitamins are recommended and should be taken from the beginning of pregnancy. However pregnancy per se is not a risk factor for osteoporosis.* But risk factors for osteoporosis are incurred if the pregnant woman is subjected to bed-rest and/or is treated with muscle relaxants and/or sedatives. In some cases even corticosteroids are given. In these situations a massive withdrawal of calcium from the bones is unavoidable, and should be compensated at the very least with adequate supplements of calcium and vitamin D. During pregnancy there is normally a slight decrease in bone density; but this loss is soon replaced after birth. However, it should be remembered that during lactation, about 500 mg calcium are excreted daily into the milk, which should be compensated for on a daily basis by increased ingestion of appropriate foods and supplements. In reality, very few women suffer from osteoporotic fractures during (and because of) the pregnancy itself.

Prevention and Therapy

If a fracture has occurred in a pregnant woman it is advisable not to breast-feed or at least to shorten the nursing period as much as possible. Though bisphosphonates are not yet authorised for premenopausal women, they should be considered when confronted by a manifest, severe premenopausal osteoporosis, together with the ancillary measures already outlined. In addition, the patient must be fully informed about the use of bisphosphonates including the indications and contra-indications. In these patients questions concerning residual bisphosphonates within the bones and subsequent pregnancy and lactation are still open.

CHAPTER 10 Osteogenesis Imperfecta (OI)

Definition

This is a congenital metabolic bone disorder, also known as *"brittle bone disease"*. It is the commonest of the congenital disorders involving bones and muscles and is caused by a defect in the synthesis of collagen type I, the principal component of bone matrix. Osteogenesis Imperfecta (OI) occurs in about 1 of 20,000 live births. In the USA there are about 15,000 patients with OI. *The clinical picture varies according to the severity of disease, which ranges from lethal to pronounced skeletal anomalies in childhood to an apparently typical picture of osteoporosis in later life*. Due to the variable clinical manifestations, OI is often missed altogether, or the diagnosis is delayed, or the condition is even misdiagnosed as something else.

Four types are distinguished:

- Type I Mild with blue sclerae
- Type II Perinatal, lethal
- Type III Progressive, deforming
- Type IV Mitigated, without blue sclerae

Inspection of the patient's eyes is an essential part of the physical examination.

Pathophysiology

OI is caused by various mutations of the genes for collagen type I which result in abnormalities of the helical structure of collagen and these, in turn, are responsible for the development of abnormal bone, the absence of lamellae and the increased sensitivity to dissolution by collagenases. *Other organs which contain collagen are also effected. These include:*

- Eyes: Thin blue sclerae liable to rupture (Fig. 10.1)
- Teeth: Appear somewhat transparent and discolored (brownish), liable to loosening

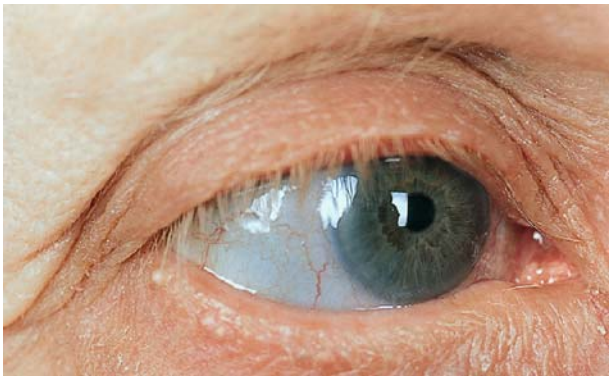


Fig. 10.1 Blue sclerae in patient with osteogenesis imperfecta

- Ears: Deafness (bi or uni-lateral) due to damage to the bones (stapes) of the middle ear
- Heart and vessels: Anomalies of cardiac valves and aorta
- Kidney: Stones and hypercalcemia
- Hyperplastic callous formation after injuries or surgery

Diagnosis

Any young patients with osteoporosis of unclear etiology and/or with multiple, mainly peripheral fractures are suspect for OI and should be investigated. The investigation should include:

- Family history
- Physical examination
- Test of hearing
- Examination of eyes and teeth
- Cardiac examination
- Results of imaging techniques: skeletal deformities, evidence of previous fractures and deformities

However, today the diagnosis is established much earlier, and even very young patients – infants – have been treated successfully.

Treatment Strategies

Previous treatments with fluoride or by means of bone marrow transplantation were not successful. Today the treatment of choice is the early administration of

bisphosphonates orally or i.v. in patients with severe OI. Moreover, bisphosphonates have been given to infants and young children to prevent consequences of OI. Therefore it is worth-while emphasizing that early and effective treatment is possible at any age – it could even spare the patient a life-time in a wheel-chair!

Bisphosphonates

The results of long-term clinical trials of aminobisphosphonates in children with OI and young adults with juvenile osteoporosis have now been published and their efficacy confirmed. The rationale for the therapy is simple: the collagen synthesised in OI is qualitatively inferior which stimulates the osteoclasts to resorb the bone produced and this resorption is inhibited by bisphosphonates. *Side effects of bisphosphonates, such as disturbances of growth and of mineralisation were not observed. Moreover, bone biopsies have demonstrated no deterioration of bone structure, even after years of therapy with bisphosphonates.* In one study, 50 OI patients were treated with ibandronate or pamidronate for a period of three years, and the following effects were demonstrated:

- Increase in bone density
- Improvement of bone quality
- Fewer clinical symptoms and complaints

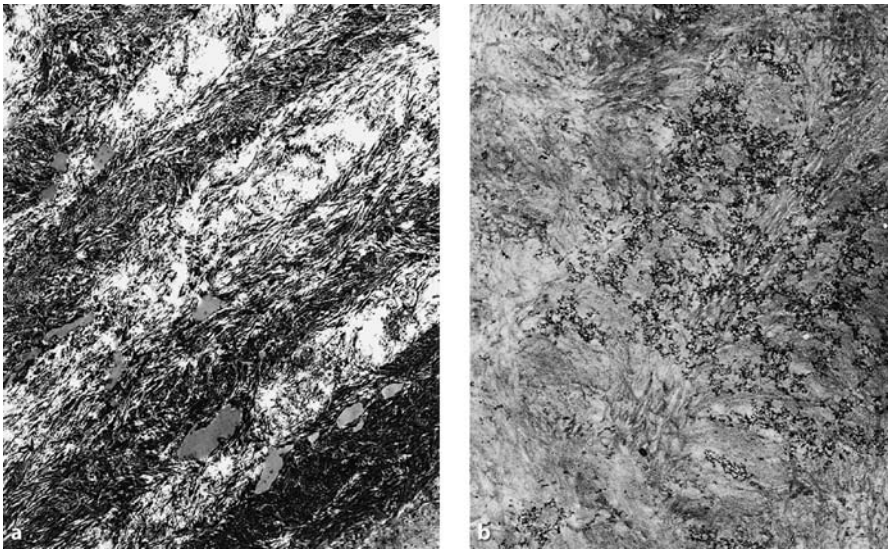


Fig. 10.2a,b Qualitative anomalies of bone structure in osteogenesis imperfecta (OI). **a** Lamellar bone in a healthy subject for comparison. **b** Almost complete loss of lamellae in patients with OI, indicating disruption of collagen metabolism

- Dramatic reduction in fracture rate
- In another study, four years of cyclic pamidronate therapy i.v. lead to a significant height gain in moderately to severely effected OI patients

This last effect cannot be due entirely to the increase in bone density. Improvement of bone quality probably also played a role: bone examined by electron microscopy showed a distinct lamellar structure in contrast to that of the previously disorganised tissue (Fig. 10.2). Moreover, in adults treated with risedronate, an increase in radial width was observed, which supports the hypothesis that bisphosphonate therapy induces structural changes not detectable by BMD measurements, and these changes substantially decrease the fracture risk in OI.
The following *protocols* are recommended:

► *Ibandronate (Bonviva®)*	3 mg infusion (15 min) every 3 months
► *Pamidronate (Aredia®)*	30–60 mg infusion (30–60 min) every 3 months
► *Zoledronate (Aclasta®)*	5 mg infusion (15 min) annually
► *Alendronate (Fosavance®)*	70 mg orally weekly

Results of long-term studies of children treated with aminobisphosphonates, both for OI and for juvenile osteoporosis, have now been published. Most importantly these studies have demonstrated that *alendronate therapy is safe, effective and has improved the quality of life of children with OI. In addition, oral alendronate was also convenient especially for children of school age.* Side effects such as clinically relevant disturbances of growth or of mineralisation were not observed. Bone biopsies demonstrated a normal bone structure even after years of therapy. These studies clearly showed that treatment of children is possible and effective but therapeutic decisions must be taken together with the parents and an experienced pediatrician and approved by the ethics committee of the hospital. Consent must be obtained and documented.

Osteopenia of Prematurity

Since it has now been demonstrated that bisphosphonates can be given to young children even infants with OI, the question arises could they also be used for the osteopenia of prematurity? The survival rate of premature infants has been steadily increasing so that other problems are also steadily emerging including that of *osteopenia which has been reported to be as high as 30% of infants born before 28 weeks of gestation*. This poses a challenge because prevention of continued bone loss is crucial in order to enable normal growth and attainment of peak bone

mass. *Can bisphosphonates do the job? Time will tell.* In addition other studies have shown that passive range of motion of the extremities of premature infants results in a significant increase in bone formation markers and bone density and are important in the prevention and treatment of osteopenia of prematurity.

CHAPTER 11 AIDS Osteopathy

Clinical Settings of Disorders of Bone in AIDS

It is important to emphasise that today in 2007 there are well over 40 million people world wide who are infected with the AIDS virus; and according to information given recently at an international televised meeting (Clinton Foundation) over 5 million more people are still infected annually. A high proportion of these are children. Many AIDS patients live in circumstances which do not enable them to receive the care and treatment outlined below; though greater international efforts in this direction are now being made.

Manifestations of AIDS Osteopathy

Many of the problems experienced by patients with AIDS (Acquired Immune Deficiency Syndrome) require hematologic, immunologic and osteologic investigations. These problems include: cytopenias, lymphomas, infections, fever of unknown origin (FUO), hemorrhages, bone pain, and pathologic fractures. It is essential to emphasise that osteopathy in AIDS is an important, highly complex complication which has so far received too little attention. Hematologic disorders and neoplasias have been extensively described and are well recognised, but not osteological problems. *Since the latest treatments for AIDS now achieve longer survival times, it is all the more important to pay attention to the quality of life for which mobility and therefore skeletal integrity are crucial, particularly for the millions of children involved, because many of the more than 40 million people with AIDS are young.*

Drugs used to treat AIDS may also be harmful to the bones; as is the decreased physical activity of many patients. In one study, evaluation of aspirates and bone marrow biopsies (n=120) frequently demonstrated dysplastic/aplastic changes in hematopoiesis, as well as inflammatory reactions in the stroma of the bone marrow. The bone itself also regularly exhibited changes designated as *"AIDS-Osteopathy"*. These changes are summarised as follows:

- Reduced bone density (osteopenia – osteoporosis)
- Increased osteoclastic activity (secondary HPT)
- Disturbances in mineralisation (osteomalacia)

Table 11.1 Etiology of AIDS osteopathy

Basic disorder	Malnutrition	Glucocorticoids
Hemopoietic cell defect?	Gastrointestinal infections	Antibiotics
T-cell activation	Immobilisation	Protease-Inhibitors
Bone marrow inflammation	Lipodystrophy	
	Testosterone deficiency	
	Vitamin D deficiency	
	Infections	
	Hyperparathyroidism	

Recent studies on the interaction of the AIDS infection and bone have postulated that the constant stimulation of T cells leads to activation of osteoclasts and thereby increased resorption via osteoprotegerin. In addition to the direct viral and drug-induced damage to bone cells, marrow cells and stroma, as well as the anomalies of vitamin D metabolism, many other secondary risk factors are also involved (Table 11.1). *Recent international studies of bone density by DXA measurements in AIDS patients have now confirmed the frequent occurrence of osteopenia/osteoporosis and pathological fractures, and in some cases even of osteonecrosis, as shown in a large study of patients from 1999 to 2002*. The causes of the osteopathies in AIDS are very complex (as noted above) and are also influenced by the various therapies the patients have received. These in turn effect the clinical, biochemical and radiological manifestations. Moreover, fractures in AIDS patients have a very strong influence on quality of life, by the additional suffering and incapacity, the added requirements for care and nursing, the effect on mortality, as well as contributing greatly to the cost of treating the patients.

Diagnosis

Consequently all AIDS patients should undergo an osteological evaluation at time of diagnosis, including the following if at all possible:

- X ray of the lumbar spine in two planes
- DXA of lumbar spine and hip (annual monitoring)
- Examination of peripheral blood for calcium, phosphate, alkaline phosphatase, crosslaps, PTH, Vitamin D, TSH and testosterone/estrogen
- Complete blood count (CBC)

Results of clinical trials published in 2005 have now been summarised and suggestions as to screening and treatment have been made.

When appropriate indications are present (cytopenias, atypical cells in blood films etc), and possibly (unclarified) osteopathies, a bone biopsy and aspirate should be obtained for clarification and diagnosis. It should be stressed that in AIDS the disorders of the bones of young people and adults begin in childhood – even in the neonatal and perinatal periods, therefore appropriate management of the pediatric patient is crucial.

Treatment Strategies

All AIDS patients would benefit from implementation of the guidelines given under "Basic Therapy of Osteoporosis" which include physical activity (physiotherapy if possible), bone-preserving life-style, adequate nutrition and supplements of calcium and Vitamin D. However should there already be osteoporosis at diagnosis (T<–2.5 SD) or if the density measurements decrease in spite of the basic therapy (as above), then addition of an oral aminobisphosphonate is indicated. If difficulties arise with the oral route, then an aminobisphosphonate can be given i.v. which also forestalls problems of compliance and uncertainty as to whether or not the medication has been taken. The schedule is the same as previously noted:

- Alendronate 70 mg orally weekly
- Risedronate 35 mg orally weekly
- Ibandronate 3 mg i.v. every 3 months
- Zoledronate 5 mg i.v. annually

When osteomalacia and secondary hyperparathyroidism dominate the clinical picture, the daily supplement of Vitamin D can be increased to 3000 IU; alternatively an active metabolite of Vitamin D can be substituted. Serum calcium must of course be monitored.

To summarise, every second AIDS patient develops some form of osteopathy during the course of the disease. This can be a combination of osteoporosis, osteomalacia and secondary hyperparathyroidism and frequently entails difficult clinical situations involving pathological fractures and bone pain. Studies are in progress to clarify to what extent the viral infection itself and/or the anti-viral therapy are/is responsible for the loss of bone mass. Secondary infections and lipodystrophy also add to the "osteoporomalacia". If the diagnostic investigations (as described above) are applied and the basic therapy implemented, then AIDS osteopathy can be diagnosed and prevented in its early stages and even successfully treated in the later ones. Studies have already been published on the efficacy of alendronate plus calcium and Vitamin D on bone mineral density – however, most of the patients were male with an average length of 8 years HIV infection. Results of additional studies are pending.

CHAPTER 12 Renal Osteopathy

Definition

Patients with chronic renal insufficiency and on long-term dialysis develop complicated bone disorders, also known as renal osteodystrophy or renal bone disease, often accompanied by severe bone pain, multiple fractures and extra-osseous calcifications, all of which considerably reduce the patient's quality of life. On a more optimistic note, it has recently been shown that therapy with statins inhibits or prevents decline in creatinine clearance and slows impairment of renal function. Moreover, statins also participate in the regulation of bone turnover.
Renal osteodystrophy consists of a mixture of three sub-groups: hyperparathyroidism, osteomalacia, and osteoporosis as seen in the three types of renal bone disease recognised:

- High turnover osteopathy with characteristics of primary hyperparathyroidism (Fig. 12.1a)
- Osteomalacia with manifestations of severe inhibition of mineralisation (Fig. 12.1b)
- Low turnover osteopathy with the picture of severe osteoporosis (adynamic bone disease)

Pathophysiology

Many factors influence both the type and extent of osteopathy:

- Nature of the renal disorder
- Associated diseases (e.g., diabetes mellitus, amyloidosis, collagen diseases and others)
- Severity of renal insufficiency
- Age of the patient (young patients are more severely affected)
- Vitamin D deficiency
- Nutritional state of the patient
- Levels of parathyroid hormone
- Deposition of toxic substances in bones (e.g., aluminum, fluoride, iron)
- Glucocorticoid therapy

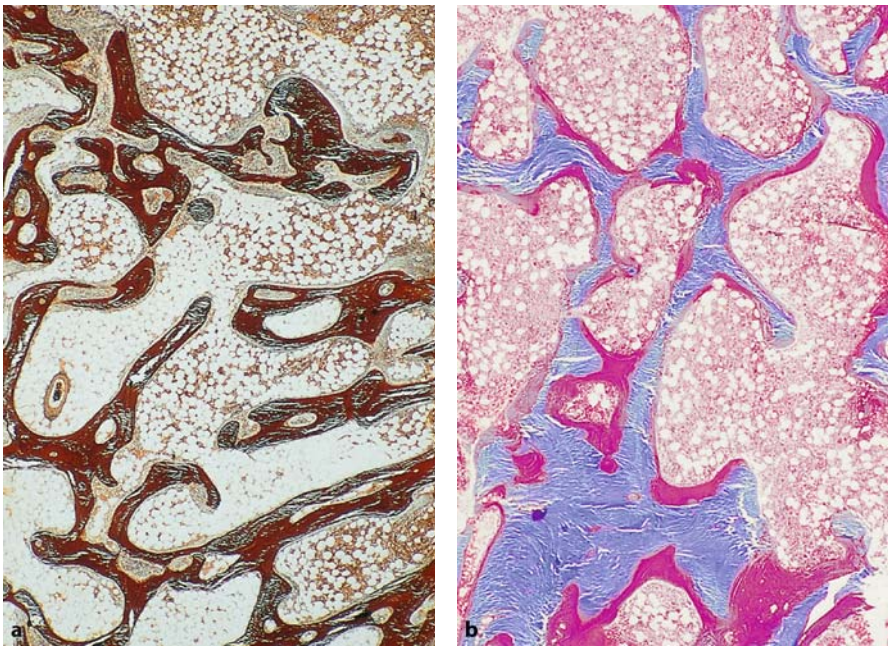


Fig. 12.1a,b Variants of renal osteodystrophy. **a** High turnover osteopathy with the typical picture of HPT. **b** Osteomalacic type with the picture of a severe disturbance of mineralization (*red* = unmineralized osteoid)

- Type and duration of dialysis: osteoporosis is the main component of renal bone disease in patients on dialysis

The most significant of the above in the mechanism of renal bone disease are:

- Anomalies of vitamin D metabolism
- Degree of secondary hyperparathyroidism
- Deposition of aluminum on bone (prevents mineralisation, is now infrequent)
- Immunosuppressive therapy inducing a negative bone balance

Diagnosis

Symptoms

The most important symptoms are *bone pain, skeletal deformities, muscle weakness and anomalies of growth in young patients.*

Biochemical investigation

The following parameters of bone metabolism should be measured: calcium and phosphate, alkaline phosphatase and osseous alkaline phosphatase, parathyroid hormone, metabolites of vitamin D 25 and 1.25, aluminum and the desferal test.

Radiological Investigation

All the characteristic signs of osteomalacia (Looser's zones) and of secondary hyperparathyroidism may be present (e.g. subcutaneous and arterial calcifications, subperiosteal erosions). The "rugger jersey" sign (three layers) in the cancellous bone of the vertebral bodies is found in 60–80% of the patients. However, in daily practice the diagnosis may not be straightforward because biochemical and radiological findings do not always match or accurately reflect the extent of damage to the bones.

Bone Biopsy

A bone biopsy is indicated for recognition of the type, probable extent, and manifestations of the osteodystrophy; and for co-ordination with results of imaging techniques. *Renal bone disease is classified according to three histological features best evaluated in a bone biopsy:*

- *Anomalies of bone remodelling* (osteitis fibrosa cystica or adynamic bone disease)
- *Disturbances of mineralisation* (osteomalacia, previously also associated with aluminum)
- *Reduction in bone mass* (osteopenia/osteoporosis, possibly partly glucocorticoid-induced)

Treatment Strategies

Advances in techniques of hemodialysis as well as administration of active vitamin D metabolites have greatly modified both the expression and treatment of renal osteodystrophy. Whereas previously the problems outlined above were the most significant, today they are overshadowed by severe and intractable osteoporosis. This varies from adynamic bone disease to high-turnover osteodystrophy, and until recently was further complicated by aluminum deposition on the surface of the bone (derived from the dialysate and phosphate binders).

Bisphosphonates

Today the situation has changed due to the increasing application of bisphosphonates. The aim of therapy is prevention by means of early intervention with bisphosphonates and active metabolites of vitamin D. Since patients on dialysis require protection of the gastrointestinal tract, intravenous bisphosphonate therapy is the method of choice. The following *protocol* is recommended:

► *Ibandronate (Bonviva®)*	3 mg injection every 3 months

Because of its long half-life in the serum of 10 to 16 hours, patients should receive the bisphosphonate on completion of dialysis. When resistance to bisphosphonates occurs in patients with high PTH levels and demonstrable enlargement of the parathyroid glands, parathyroidectomy is indicated.

Children with renal osteodystrophy require special evaluation and individual therapy for which European Guidelines have been published.

CHAPTER 13 Paget's Disease of Bone

Definition

Paget's disease, or Morbus Paget (named after Sir James Paget who first accurately described the disease in 1877) is also called *osteodystrophia deformans* or *osteitis deformans*. It is a localised non-inflammatory disease of bone caused by uncontrolled, increased bone resorption by pathological osteoclasts which in turn induces disorganised bone formation. This disease illustrates graphically what happens when there is complete local deregulation of osteoclasts together with abrogation of "coupling" in the osteological meaning of the term. Osteoblasts are stimulated to replace the resorbed bone, but the osteoid is randomly produced and not laid down as lamellae, so that the resulting bone is dense but mechanically inadequate. The focally greatly increased bone turnover is accompanied by hypervascularisation and increased blood flow. Deformities of the effected bones are the rule. Mono- and polyostotic forms of Paget's disease are recognised.

About 1–3% of people over 40 years of age have Paget's disease of bone (more men than women 3:2), but initially only 5% are symptomatic or require therapy. The cause of Paget´s disease is presumed to be a viral infection of osteoclasts and/or an abnormality on chromosome 18, resulting in multinucleated, hyperactive and unregulated giant osteoclasts. *Why all osteoclasts are not involved is still a complete mystery!*

Clinical Findings

The following *symptoms* are indicative of Paget's disease:

- Pain and warmth of the effected area (pelvis, spine, extremities, skull).
- Bone pain that is stabbing and deep and often stronger at night. Pain could also be due to compression of nerves or associated arthrosis.
- Bending and deformities of the effected bones with risk of spontaneous fractures ("saber tibia", "hat that became too small" appearance).
- When the base of the skull is involved, hearing loss and damage to the cranial nerves can occur.

- Compression fractures may result if the vertebrae are involved.
- Secondary arthrosis can occur due to incorrect weight-bearing.
- When large areas of the skeleton are effected, the accompanying hypercirculation may cause cardiac insufficiency.
- Inner ear involvement can cause deafness. It has been assumed that Beethoven's deafness was caused by Paget's disease of bone.

The course of the disease can be divided into 3 stages which are identified locally:

- *Lytic stage*: The osteolytic process spreads at the rate of 1 cm annually.
- *Repair stage:* also called "mixed stage": After the period of rapid resorption osteoblasts fill the cavities with bone, thereby producing cement lines with the mosaic patterns characteristic of Paget's disease.
- *Sclerotic stage*: When the disease has progressed for several years, relatively large areas consist of dense bone, but this is not capable of weight-bearing or stress.

Transition from mono- to polyostotic forms of Paget's disease must be excluded by periodic x-ray examinations and bone scans.

Diagnosis

Bone scans

They highlight a focal increase in bone remodelling, and depict the extent of skeletal involvement (mono- or polyostotic). In addition, characteristic X-rays plus increased alkaline phosphatase levels in the serum confirm the diagnosis.

Conventional X rays and/or CT

These demonstrate typical changes (Fig. 13.1 and 13.2).
The following points are considered

- Alterations in contours of the bone
- Careful evaluation is required when the vertebrae are effected
- Thickening of the cortical bone
- Coarsened trabecular structure with alternating lytic and sclerotic regions
- Narrowing of the foramina of the spinal column
- Thickening of the skull
- Fibrosis and hypervascularisation of the bone marrow surrounding the foci of involved bone

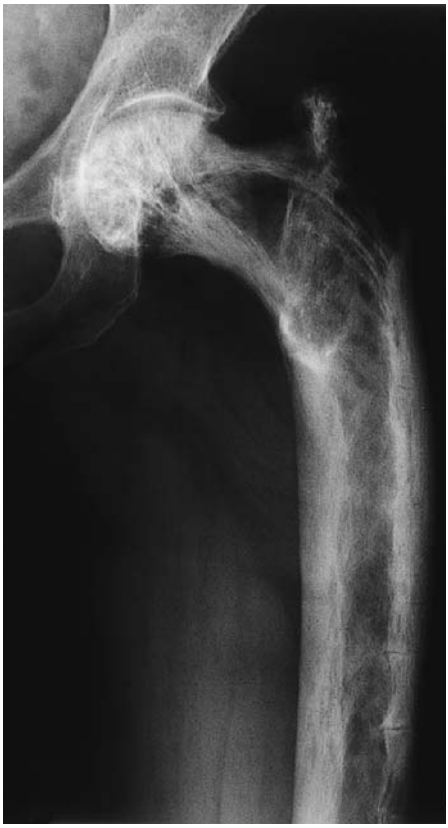


Fig. 13.1 Paget's disease of bone in the left femur. Note both deformation and thickening of the shaft, increase in width and 'trabecularization' of the compact bone and the irregular, stout cancellous bone with an especially large Ward's triangle. The trabeculae are particularly stout along lines of compression and tension. As a consequence of the completely disorganized osseous remodeling and replacement of lamellar by woven bone, numerous 'fatigue fractures' have occurred *(lower right)*. These were repaired within a year of bisphosphonate therapy. The patient became free of pain and the alkaline phosphatase in the serum returned to normal levels within six months

Bone Biopsy

Bone biopsy can be useful in the initial stages of Paget's disease for differential diagnosis and for ruling out metastasis or arthrosis. The most important features (Fig. 13.3 a,b) are:

- Cement lines forming mosaic structures, and woven bone
- Multinucleated osteoclasts containing nucleoli and showing signs of activity: localisation in resorption bays, presence of pronounced ruffled membranes
- Striking reactive osteoblastic bone formation
- Fibrosis and hypervascularisation of the surrounding bone marrow
- *Two histologically unmistakable features characterise M.Paget: the giant, multinucleated osteoclasts and the mosaic structure of the newly formed bone*

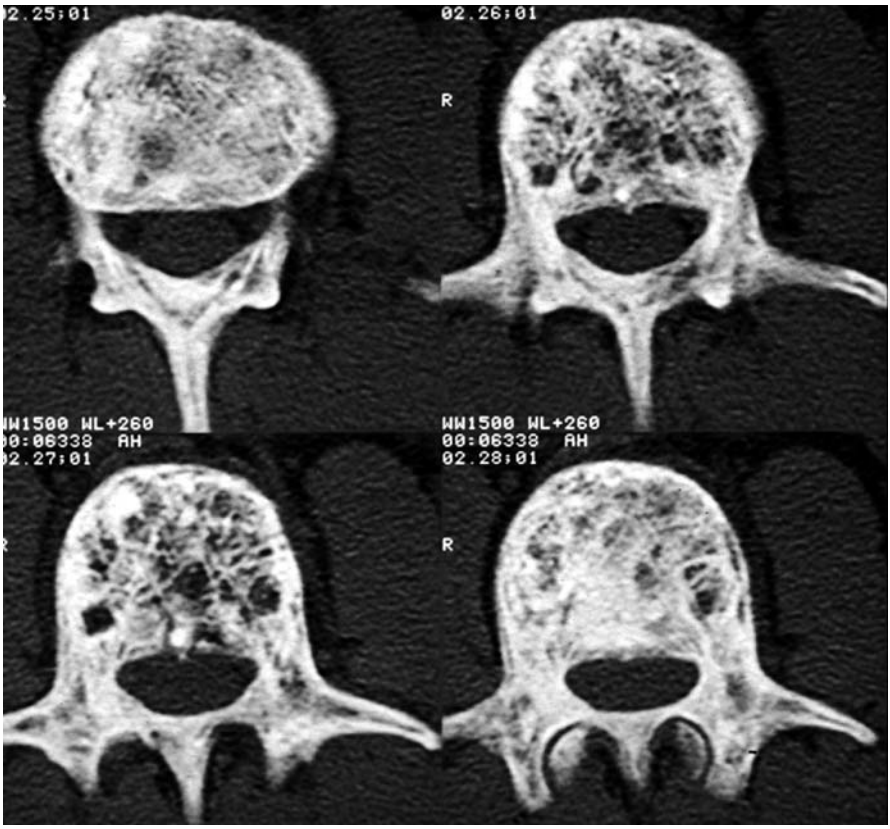


Fig.13.2 Morbus Paget in area of lumbar spine (CT). Note the altered structure of the trabecular bone. Significant narrowing of the vertebral canal is evident in lower right.

Biochemistry

Biochemical markers of disease activity are *alkaline phosphatase* in blood and pyridinoline crosslinks in urine. The level of osteocalcin in the serum is used for monitoring. Osteocalcin production by osteoblasts is dependent on vitamin K; the level reflects the degree of bone remodelling.

For differential diagnosis the following must be excluded:

- Skeletal metastasis
- Primary bone tumor
- Malignant lymphoma
- Severe arthrosis

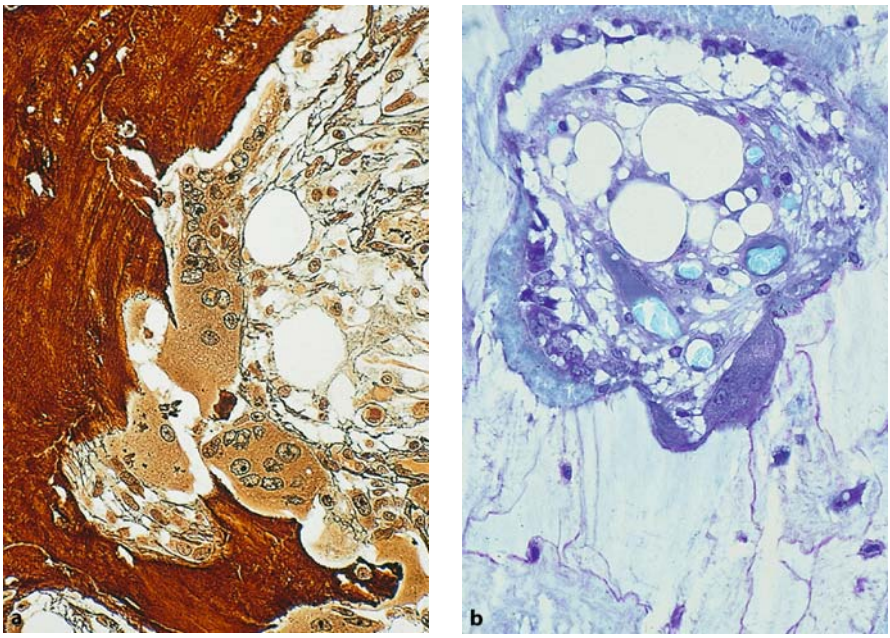


Fig. 13.3a,b Typical bone histology in Paget's disease. **a** Multiple nucleolated and active osteoclasts in deep resorption lacunae. Note the paratrabecular fibrosis. **b** Osteoblastic/osteosclerotic remodeling with mosaic structures in the adjacent bone

- pHPT and renal osteopathy

The danger of later transformation to sarcoma is minimal (<1%), particularly in the present era of bisphosphonate therapy. Tumor-associated Paget-like lesions seen on X-rays, CT or scans must be investigated by bone biopsy, but are rare.

Treatment Strategies

Treatment is indicated if there are local changes, pain, and risk of complications that may require neurosurgical or orthopedic intervention, and if there are high alkaline phosphatase levels (more than 5U/l). Skeletal deformities and fractures require orthopedic interventions. *Two separate indications for therapy are derived from the clinical course of the disease:*

- *Alleviation of symptoms*: severe headaches, backaches and radicular nerve pain
- *Prevention of complications:* fractures, deafness, paralyses, skeletal deformities, sarcomatous transformation

Bisphosphonates

Bisphosphonates are the treatment of choice, and many have been authorised for use in Paget's disease of bone (see below). The latest is zoledronate, and now that this is authorised, therapy of Paget's disease is simplicity itself. For patients with extensive and/or active disease (as indicated by high levels of alkaline phosphatase in serum), intravenous administration is the method of choice. Analgesics or non-steroidal anti-inflammatory agents are now rarely required.

The following *protocols for infusion* can be used:

► *Pamidronate (Aredia®)*	30 mg infusion to begin with, then 60 mg in 500 ml NaCl given slowly for 30–60 minutes monthly until the pain has been alleviated and the alkaline phosphatase level has returned to normal. Thereafter only regular clinical and biochemical monitoring is required.
► *Ibandronate (Bondronat ®)*	Given in 250 ml NaCl infusion for 15 minutes monthly, 2 mg for the first and 6 mg for subsequent infusions till normalisation as above.
► *Zoledronate (Aclasta®)*	5 mg infusion for 15 min. Usually one infusion is enough to normalise the bone markers. Thereafter monitoring as above.

Alternatively, *oral therapy* can be given, preferably one of the potent amino-bisphosphonates:

► *Tiludronate (Skelid®)*	400 mg daily for 3 months
► *Clodronate (Ostac®)*	800 mg daily for 3 months
► *Alendronate (Fosamax®)*	40 mg daily for 3 months (authorised in the USA)
► *Risedronate (Actonel®)*	30 mg daily for 2 to 3 months

Bisphosphonates halt progression and may even induce regression of Paget's disease. This is usually accomplished within 2 to 6 months depending on the intensity of therapy. Histologically, therapeutic success is indicated by decrease in osteoclast number, and by formation of lamellar bone. The effects of therapy can last for several years (Hosking 2006). Should symptoms such as bone pain and/or rise in markers of bone resorption recur, administration of a bisphosphonate should

be repeated. The following markers are generally involved: alkaline phosphatase, osteocalcin and beta-crosslaps. Therapy with a different bisphosphonate is given if resistance is suspected. Bone scans and X-rays are used to check for spread and/or malignant transformation and should be carried out annually (or semi-annually as required) as part of monitoring of the disease and the efficacy of therapy.

CHAPTER 14 Complex Regional Pain Syndrome (CRPS)

Definition

Also known as *algodystrophy*, *Sudeck´s disease* or *sympathetic reflex dystrophy*, this disorder is a highly unpleasant, unpredictable and painful complication of injuries and trauma especially fractures. The cause, development and effective treatment of CRPS are largely unknown. It has not been observed in children. Putative *causes* range from disorders of vegetative innervation to endocrine and psychosomatic disorders. Triggers include fractures, operations, infections and nerve injuries. The severity of the underlying injury bears no apparent relationship to the severity of the symptoms of Sudeck's disease, which can be triggered even by trivial trauma. *Most frequently effected are joints of the hand (90%), followed by ankle and knee joints*. Two types are recognised: *Type 1* develops after a trauma, while *Type 2* is triggered by a peripheral nerve injury.

Clinical Findings

These consist of a triad of sympathetic, motoric and sensory manifestations with five characteristic symptoms:

- Disproportionately strong pain
- Swelling and unusual warmth of the effected area
- Skin discoloration of the effected area
- Increased hair growth on the area involved
- Stiffness of the joints involved

Diagnosis

The results of the following investigations contribute to the *diagnosis*:

- Thermography (area of overheating)
- Bone scan (area of increased uptake)
- X-ray (patchy rarefaction of bone) (Fig. 14.1)
- MRI (edematous areas around the joints involved)

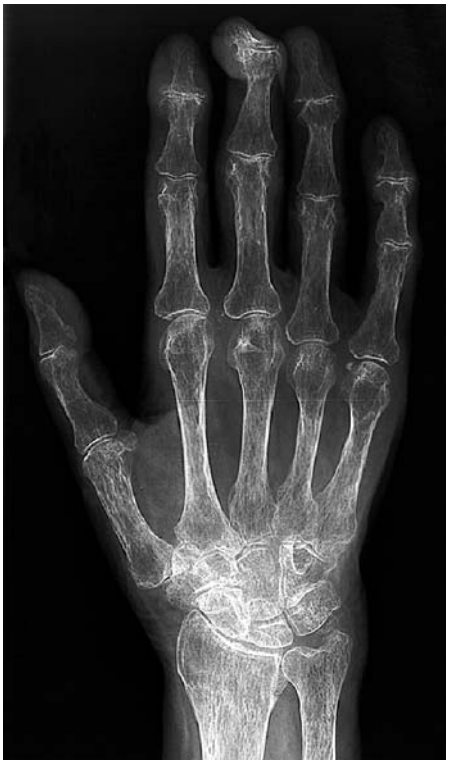


Fig. 14.1 Massive but spotty decalcification of the hand in CRPS (Sudeck's disease), stage III

- Alleviation of pain by sympathetic blockade – designated as "sympathetically maintained pain" (SMP) confirms the diagnosis

Course of Disease

This can be divided into three main stages (though questioned by some experts):

- Stage of *inflammation* (up to 3 months): Typical symptoms include localised pain, blue discoloration and overheating of the skin, dough-like edema and functional limitations of the joint. MRI shows presence of bone marrow edema.
- Stage of *dystrophy* (3 to 6 months): The dermatologic symptoms regress, leaving a trophic disorder of the skin. There is an increase in restriction of joint movement and spotty areas of demineralisation are seen on X-rays.
- Stage of *atrophy* (6 to 12 months): This end stage is characterised by generalised atrophy of skin, muscles and bone. Stiffness of the joint is further increased as massive rarefaction of bone occurs.

Treatment Strategies

A relationship of confidence and trust must be established between patient and doctor, to ease the fear, tension and anxiety which always accompany this chronic condition. First, it is essential to break the vicious circle of pain and dystrophy by rest and physiotherapy. Surgery is only indicated for stabilisation of a fracture or later for correction of a deformity. However, it should be noted that early surgical intervention carries the risk of aggravating the condition.

Immobilisation, analgesics, anti-inflammatory drugs and cold dressings to counteract overheating are useful measures in stage I. Blockade of the sympathetic nerve supply (stellate) and calcitonin therapy have also been successful at this stage. Physiotherapy and exercises are strongly recommended in stages II and III.

Bisphosphonates

Since 1988, 4 international trials performed with pamidronate showed alleviation of pain in most cases and cure in some. This constitutes genuine progress in the treatment of M. Sudeck. Clodronate and alendronate were equally effective. Similar results were also achieved in patients treated with one of the following aminobisphosphonates given for 4 to 6 months:

► *Ibandronate (Bondronat®)*	Infusion of 6 mg monthly, 4–6 times, the first infusion only 2 mg in 100 ml NaCl solution over 15 min
► *Pamidronate (Aredia®)*	Infusion of 60 mg monthly, 4–6 times, the first infusion only 30 mg in 500 ml NaCl solution over 30–60 min
► *Zoledronate (Aclasta®)*	5 mg infusion over 15 min given once only.

The initial low doses of 2 mg ibandronate or 30 mg pamidronate were used to avoid the possible acute-phase reactions (previously described), which could be much more pronounced in patients with Sudeck's disease than in other patients. Occasionally acute-phase reactions occurred after the second infusion, but were milder. Many patients – some already morphine-dependent – have been cured by this therapy. In others, the pain was alleviated to such a degree that analgesics were no longer required. Since the bisphosphonates have not yet been authorised for treatment of Sudeck's disease, the patient's informed consent must be obtained and documented.

CHAPTER 15 Transient Osteoporosis and the Bone Marrow Edema Syndrome (BMES)

This chapter deals with transient (or transitory) osteoporosis and the bone marrow edema syndrome (BMES) separately. However, it should be stressed at the outset that bone marrow edema and transitory osteoporosis occur sequentially and both are manifestations which may be due to any of a long list of possible causative factors (see below). Moreover, they are preceded by and associated with changes in vascularity (ischemia) which in turn can lead to osteonecrosis. Hence the urgency for early diagnosis and therapy.

The question as to whether BMES and transient osteoporosis should (or should not) be regarded as separate entities, has not yet been completely resolved (see references). Moreover, as mentioned above, both may occur in many different conditions, separately or in combination. Examples of such conditions are inflammatory and septic arthritis, synovial disorders, stress fractures, neoplasias, reflex sympathetic dystrophy, complex regional pain syndrome and others. There is also a link with vitamin C deficiency. These correlations are relevant both for the determination of the exact diagnosis and for the therapy of patients presenting with musculoskeletal pain, and they emphasise the need for early recognition both for treatment and as a preventive measure.

Transient Osteoporosis

Transient osteoporosis has been defined as a rapidly developing painful osteopenia/osteoporosis of benign nature and of various possible etiologies. Neural and circulatory mechanisms have been implicated as causative factors. This disease is more frequent in men, though women may also be effected, sometimes even bilaterally in the third trimester of pregnancy. Spontaneous remissions frequently occur. *Clinically two groups are recognised:*

- Regional transient osteoporosis of the hip
- Regional migratory osteoporosis with involvement of various joints

Diagnosis

The patients complain of severe pain and limitation of movement in the effected joints. In the later stages, X-ray films show local bone loss. *Initially, MRT is needed*

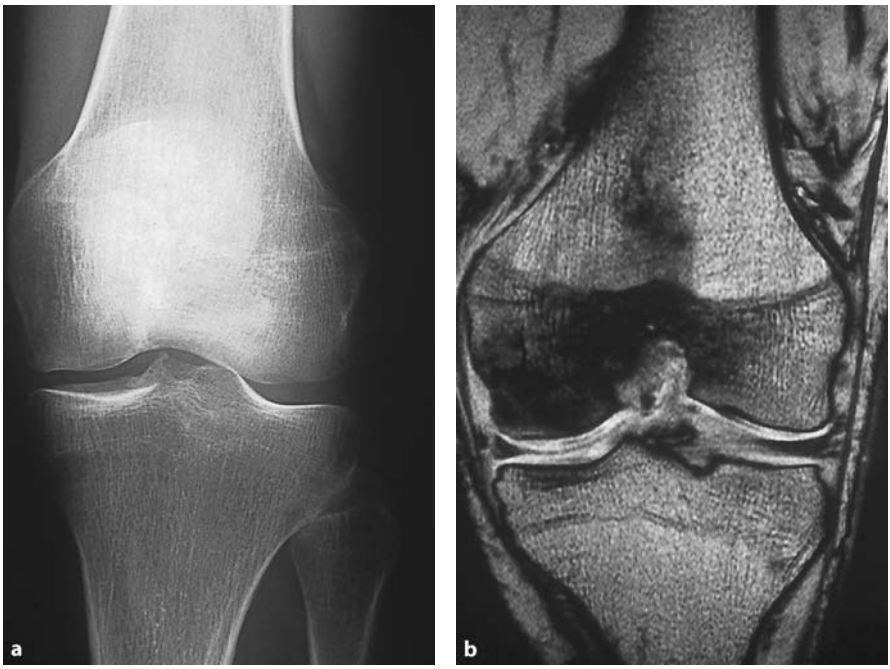


Fig. 15.1a,b Transient osteoporosis in the region of the distal femur. **a** No abnormalities visible on X-ray. **b** Widespread edema of bone marrow on MRI, T1-weighted

to demonstrate bone marrow edema near the effected joints (Fig. 15.1 a,b) and this is required in order to establish the diagnosis which should be made in the earliest possible stages as occasionally bone marrow atrophy and edema may precede osteonecrosis, which can later be demonstrated by MRI and CT. In some cases, areas of demineralisation around the hip joint may be seen in X-rays of that region. Occasionally healing of the transitory osteoporosis takes place in 4–6 months even without therapy. In cases with severe pain not relieved by medication, surgical intervention may be required to lessen the intra-osseous pressure. To establish the *diagnosis, various conditions such as localised immobilisation osteoporosis, osteonecrosis, osteochondrosis dissecans and Sudeck's disease must be ruled out by MRT (see above and also below).*

Treatment Strategies

An important therapeutic measure is to relieve the joint of any stress and weight-bearing. Frequently this is followed by spontaneous regression of the symptoms, which appears to indicate that overloading of the joint may have contributed to the cause.

Bisphosphonates

Bisphosphonates are recommended for rapid relief of pain and for reduction of the bone marrow edema. A bisphosphonate is given intravenously monthly for 4 to 6 months according to the following schedule:

► *Ibandronate (Bondronat®)*	6 mg infusion (15 min) monthly, the first infusion only 2 mg
► *Pamidronate (Aredia®)*	60 mg infusion monthly, the first infusion only 30 mg
► *Zoledronate (Aclasta®)*	5 mg (15 min) as a single infusion

After the final infusion (usually the 3rd or 4th infusion) an MRT should be made to monitor the effects of therapy and to check for residual edema or osteonecrosis as mentioned above.

Bone Marrow Edema Syndrome (BMES)

BMES is now recognised as a common cause of pain in the musculoskeletal system in general and in joints of the extremities in particular: hips, knees, feet, shoulders, elbows and hands as well as joints of the spinal column. Moreover, some patients may present with bilateral involvement, and a migratory transient BMES has already been characterised. In addition to the pain felt during movement and exercise, the patients also experience pain at rest, which is caused by the increased intraosseous pressure. BMES, possibly preceding aseptic, or avascular osteonecrosis also occurs in pediatric oncology patients, in sports men and women as well as in highly-trained athletes, for example tennis players with an upper limb syndrome, or in young soccer players at the pubic symphysis. Patients with osteoporosis and in particular patients with rheumatic disorders such as osteoarthritis of various joints are also prone to develop BMES in the effected joints. It stands to reason, therefore, that any patient with musculoskeletal pain should be carefully checked for BMES by MRI in addition to other clinically indicated investigations. Various *classifications of BMES* have been proposed; the following is practical and widely used:

- *Ischemic BME*
  Bone marrow edema syndrome (BMES)
  Osteonecrosis
  Osteochondrosis dissecans
  Complex regional pain syndrome (CRPS)
- *Mechanical BME*
  Injuries (bruises) to bone
  Stress fractures

- *Reactive BME*
  Osteoarthritis
  Rheumatoid arthritis
  Post-operative BME
  Neoplasias

Diagnosis

MRI, with or without various refinements, is indicated for the diagnosis of BMES (Fig. 15.2 a,b). Other clinical and laboratory examinations including X-rays of the effected joints and bones, are required to identify the specific pathology and this may vary in each patient, considering the many possible causes (see above).

During the past decade, *MRI* proved to be the imaging method of choice for evaluation of patients with painful bones and/or joints. The most important constituents of the joint, in particular the cartilage, the subchondral bone, the capsular-ligament system and the surrounding soft tissues can be evaluated with MRI. The correct interpretation of the MRI findings is of decisive importance for therapeutic decisions. Bone marrow edema, with its typical signal pattern in the MRI, is a common but nonspecific finding in painful local bone and joint lesions. Because only marrow structures are involved in the initial stages of BME, *X-ray, CT or even bone scan* are not useful for initial diagnosis. BME is also not visualised

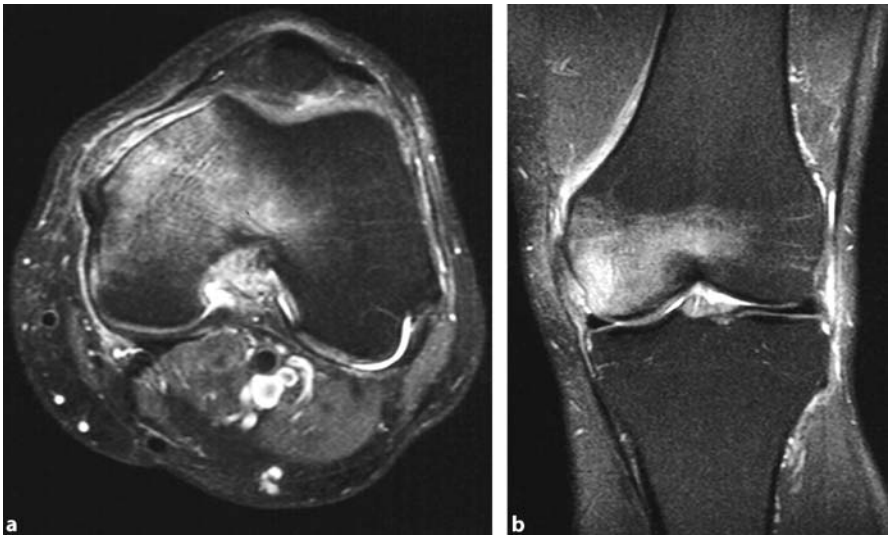


Fig. 15.2a,b Massive and widespread non-traumatic BME of the medial femur condylus, T2-weighted, fat saturated sequence images in a 54 year old male patient, with severe pain

on *arthroscopy*. BME is characterised by low signal intensity compared with unaffected cellular bone marrow on T1-weighted images. On T2-weighted images, especially when fat-suppression techniques are used, high signal intensities in the low-signal areas of the T1-weighted images are typical for BME.

A *bone marrow biopsy in* BME shows increased extracellular fluid together with inflammatory vascular reactions and decreased hematopoiesis. The *main histologic findings* are:

- Hypocellular marrow with edema in the marrow spaces
- Dilatation of sinusoidal lumina and disruption of their walls
- Spatial disorganisation of the hematopoietic cell lines
- Reactive plasmacytosis and fine fibrosis
- Increased osseous remodelling with hyperactive osteoclasts, osteoblasts and osteocytes.
- Increased osteoid volumes and seams (see Bartl and Frisch 1993, Biopsy of Bone in Internal Medicine)

The *characteristic symptom of BME is pain* during mechanical loading, but the severity of pain does not always correlate with the intensity and extent of BME seen in the MRI. Nevertheless, a final control by MRI is useful to document the efficacy of therapy

Treatment Strategies

Therapy ranges from operative, i.e. core decompression to conservative with drugs such as *iloprost*, a prostacyclin analogue (Aigner et al. 2001, Hofmann et al. 2004) and the *bisphosphonates*, in addition to measures such as *limited weight-bearing* and activity of the joint(s) involved, and physical therapy. Therapeutic management of BME also depends on the basic disease of the BME. Pain is mainly caused by the increased intraosseous pressure (normal pressure 20–30 mmHg). Therefore mechanical unloading by partial weight bearing or by *drilling the edematous lesion* may lead to pain relief. *Nonsteroidal anti-inflammatory drugs* (NSAID) and medications for pain are only of limited value.

Bisphosphonates

According to our experience however, *bisphosphonate* treatment proved to be the first choice for effective therapy. With respect to side effects, about 10% of the cases experienced an *"acute phase reaction"* with fever and flu-like symptoms one day after the first infusion. Symptomatic therapy can be given for this, but is rarely required. An acute phase reaction occurs only after the first infusion, rarely after the second and then is very mild. In the past 4 years we have treated 105 patients

with BMES of the knee, talus and/or femoral head (see Figs. 15.3 and 15.4). We used intravenous bisphosphonates of the third generation (see chapter 3), and a complete, rapid regression of the bone marrow edema was found in 78% of the cases, documented by MRI and clinical controls. Relapse within two years occurred in only 10 patients, but again there was a good response to bisphosphonate therapy.

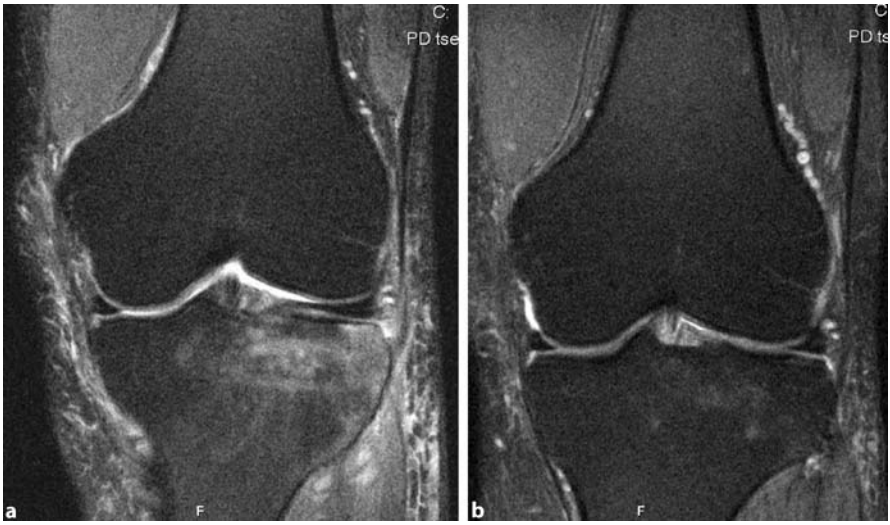


Fig. 15.3 **a** Non-traumatic BME of the proximal tibia in a 58 year old patient who had no signs of osteonecrosis, osteoarthritis or a stress fracture. **b** Almost complete regression of the BME after 3 infusions of 6 mg ibandronate. Three months later the patient is completely free of pain

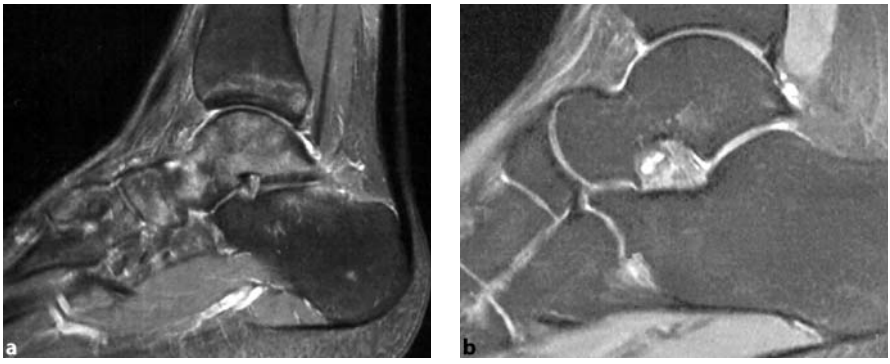


Fig. 15.4 **a** Traumatic BME of the talus, distal tibia and foot following an ankle supination trauma. The 19 year old patient had CRPS-like symptoms. **b** Complete reversal of the BME in all the previously affected bones after 3 infusions of 6 mg ibandronate. Three months later the patient is pain-free with full restoration of his sports activities

In all cases of BMES and independent of the basic disorders, we start with one of the following two bisphosphonate protocols:

Ibandronate (Bondronat®)	6 mg infusion (15 min duration) monthly, MRI control after the 3rd or 4th infusion, the number of infusions depending on the degree of pain relief
Zoledronate (Aclasta®)	A single 5 mg infusion (15 min duration), MRI control 3 months later

CHAPTER 16 Vanishing Bone Disease (Gorham-Stout Syndrome)

Definition

This syndrome is also known as "*massive osteolysis*", "*disappearing bone disease*" and "*phantom bone*".
Gorham's vanishing bone disease is the ultimate osteoporosis showing complete disassociation of the normal coupling mechanism. The cause is unknown, though over-activity of cytokines especially Il-6 has been implicated. Gorham's disease is occasionally fatal. This disorder was first described by Jackson in 1938 as "a boneless arm". In 1953, Gorham and Stout published 24 cases and emphasised the angiogenic component of the disease. Subsequent surveys of the literature revealed nearly 150 documented cases, more have been reported since then.

Etiology and Pathophysiology

The cause has not yet been elucidated. Hemangiomatosis and lymphangiomatosis have been implicated, possibly due to an endothelial defect, with production of abnormally high levels of cytokines which stimulate osteoclasts. Many investigators have described prominent osteoclasts particularly in the lytic front of the lesions. *However no reactive osteoblastic activity has ever been documented indicating that the physiological "coupling" between bone resorption and bone formation has been completely abrogated.* This clearly demonstrates a communication defect between osteoclasts and osteoblasts resulting in absence of stimulation of osteoblasts: i.e. no reaction to the osteoclastic activity. In one patient Interleukin 6 – a cytokine that stimulates osteoclasts and is produced by various cell types including endothelial cells, either directly or by way of VEGF, was implicated – initially high levels of IL-6 dropped after therapy with bisphosphonates and radiation.

Clinical Findings

A review of the recent literature based on findings in 46 patients revealed the following features (Fig. 16.1):

- It effects young adults without preference for male or female.

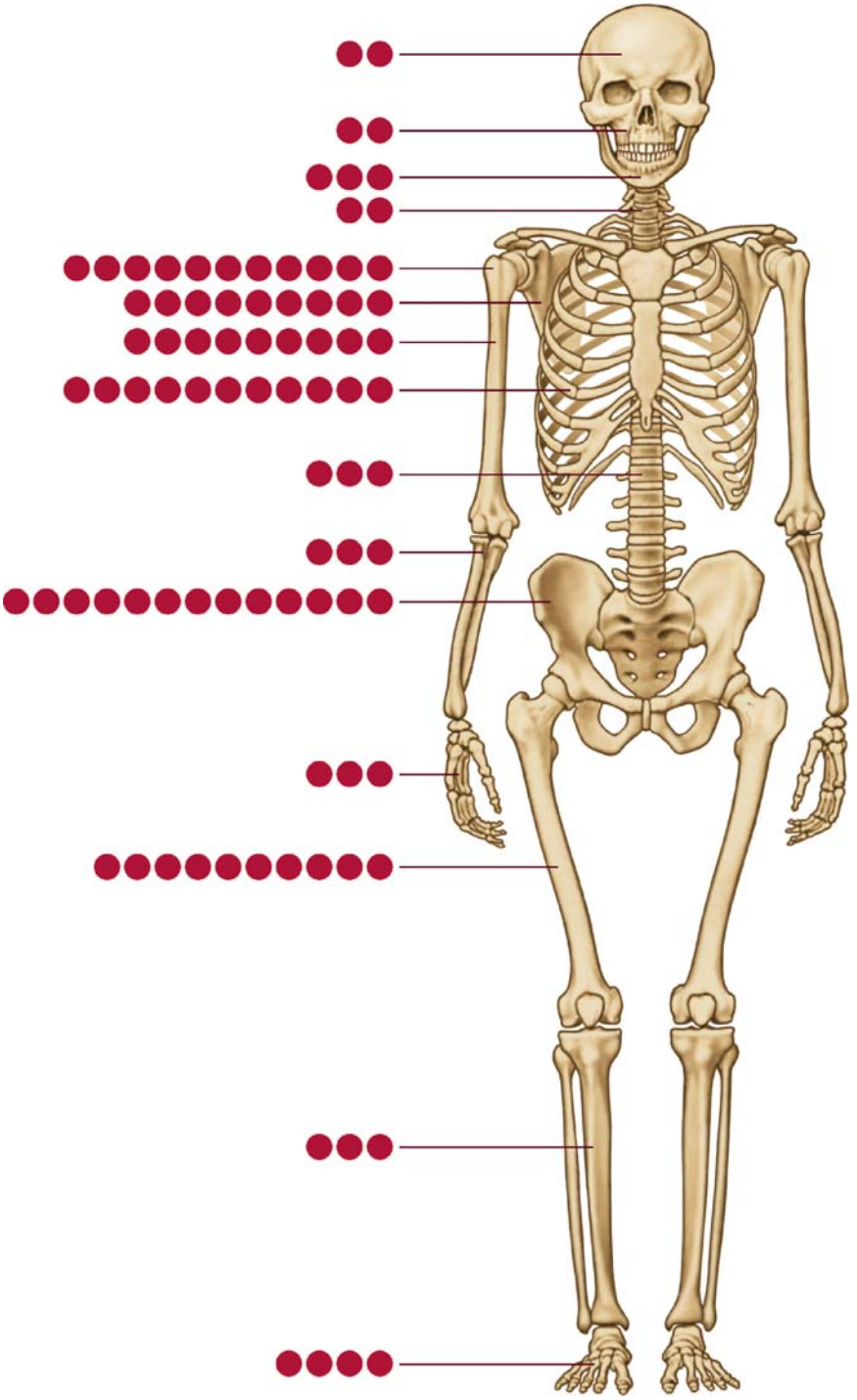


Fig. 16.1 Frequency and topography of skeletal involvement in vanishing bone disease (Gorham's syndrome). Every red dot represents one patient reported in the literature

- Genetic, endocrinologic and metabolic disturbances have not been found.
- It starts in a single bone and spreads to adjacent bones.
- In 38 of 46 cases the condition was already polyostotic at diagnosis.
- Pelvis, vertebrae, ribs, proximal bones of the extremities and cranial bones are frequently involved.
- Progression and spread of the disease are unpredictable.
- When the ribs are effected, pulmonary insufficiency is frequently a lethal consequence.
- Chylothorax is a common complication.

Diagnosis

The diagnosis of Gorham-Stout syndrome is established by X-rays which demonstrate the absence of bone in the effected areas. Occasionally vertebral compression fractures in severe osteoporosis must be considered in the differential diagnosis. When localised to the mandible it must be differentiated from osteonecrosis due to other causes (see also section on periodontitis). In early phases of the disorder, osteolytic lesions due to a malignancy must be ruled out. Bone biopsies taken from an involved area show increased osteoclastic resorption by morphologically normal osteoclasts. The absence of osteoblasts is particularly striking. This indicates complete abrogation of the "coupling" mechanism. The resorption lacunae are filled with fibroblasts, blood vessels and edematous connective tissue. Infiltration of the involved areas by plasma cells, lymphocytes and mast cells suggests an immunologic component.

Treatment Strategies

Before the introduction of bisphosphonates, progression of the Gorham-Stout syndrome was inexorable. All previous attempts to treat this condition have failed. But, as in all other states of skeletal destruction: immediate initiation of bisphosphonate therapy proved to be highly effective. Case reports have demonstrated rapid disappearance of local symptoms and pain after i.v. administration of bisphosphonates; and follow up over the subsequent 24 months revealed a stable condition with no evidence of progression.

Bisphosphonates

Focal osteolysis – the unbalanced hyperactive osteoclastic resorption – can be halted immediately by intravenous bisphosphonates, which stop progression of the disease.

The following are recommended:

► *Ibandronate (Bondronat®)*	6 mg infusion monthly for 4 to 6 months
► *Zoledronate (Aclasta®)*	5 mg single infusion

X-rays should be taken every 4 to 6 months for follow-up. Restitution of the vanished bone has not been observed, even under therapy with bisphosphonates. Trials with anabolic agents have not yet been reported.

CHAPTER 17 Fibrous Dysplasia

Definition

Fibrous dysplasia is a local developmental fibro-osseous aberration of the skeleton (Fig. 17.1). The etiology is not clear, but it does not appear to be hereditary. Increased production of IL-6 has been implicated as a causative factor. *The disease occurs mainly in the first two decades of life, and both sexes are effected.* When there are polyostotic fibrous dysplasia of bone, café au lait skin pigmentation and endocrine disorders, the condition is also known as *Albright's Syndrome*, or *McCune Albright Syndrome (MAS)* (Fig. 17.2). The underlying pathologic process is substitution of fibrous tissue for both bone marrow and bone with activation of osteoclasts. The aim of therapy is normalisation of the increased osteoclastic activity by administration of bisphosphonates.

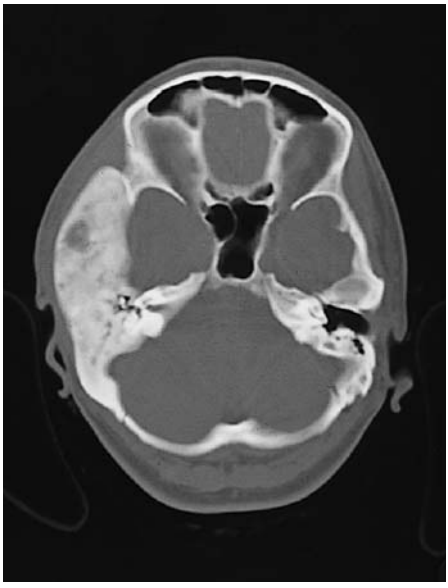


Fig. 17.1 Fibrous dysplasia. CT showing involvement of the cranial bone on the left. The diagnosis was confirmed by histology. A moderate reduction in size of the skeletal lesion and a significant decrease in bone pain were achieved by bisphosphonates, which were initially administered intravenously and later orally

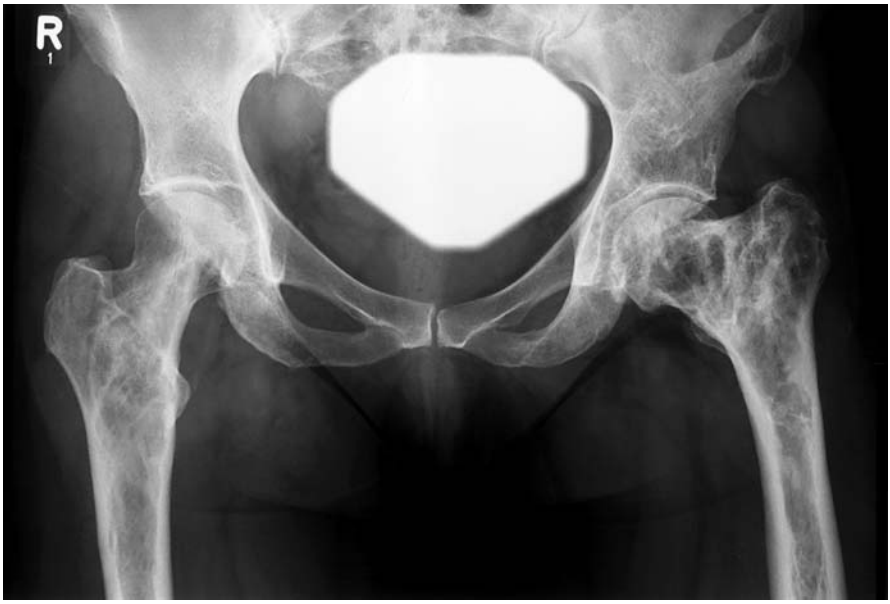


Fig. 17.2 McCune-Albright syndrome with involvement of both hips. Note the irregular and stout cancellous bone, similar to the radiological changes observed in Paget´s disease of bone. There was marked bone pain in the involved areas, and the alkaline phosphatase in the serum was increased

Clinical Findings

The main clinical symptoms and signs are:

- Bone pain
- Osteolysis
- Deformity of bone
- Spontaneous fractures

The pelvis, long bones and skull are particularly prone to this disorder (Figs. 17.1 and 17.2). Malignant transformation occurs in less than 1% of cases. Both mono- and polyostotic variants are recognised.

Treatment Strategies

Surgical correction was the only treatment available until recently.

Bisphosphonates

Early administration of bisphosphonates can curtail secondary osteoclastic bone destruction and thereby prevent deformity of bone. Successful treatment with bisphosphonates has already been reported, although the groups of patients were small. *The studies underscored the alleviation of pain, improvement in function, decrease of fracture risk and prevention of deformity*. In practice intravenous bisphosphonate therapy is recommended, but should be administered at an osteological clinic, after informed consent has been obtained and documented.

► *Ibandronate (Bondronat®)*	Monthly infusion of 6 mg
► *Pamidronate (Aredia®)*	Monthly infusion of 60 mg
► *Zoledronate (Aclasta®)*	5 mg infusion annually

X-rays, CT and/or bone scans can be used for monitoring.

CHAPTER 18 SAPHO Syndrome

Definition

SAPHO syndrome is a strange disease of skin and bone which also occurs in children. Generally SAPHO syndrome includes the following dermatologic and osteologic manifestations:

- *S*ynovitis
- *A*cne
- *P*ustulosis
- *H*yperostosis
- *O*steitis

Sternoclavicular hyperostosis, which occurs primarily in the 4th to 6th decades of life, is the most impressive; it has also been observed without dermatological changes (Fig. 18.1). *Characteristically this disorder involves the clavicle, sternum and the proximal sections of the adjoining upper ribs*. All the effected skeletal parts are swollen, sensitive to pressure and unduly warm. Occasionally the subclavian veins are obstructed and this results in edema. About 30% to 50% of the patients show a purulent plantar or palmar eczema which leads some experts to classify this syndrome as a particular type of psoriasis.

Diagnosis

Laboratory investigations demonstrate signs of an inflammatory reaction (high ESR, mild leucocytosis, and increase in alkaline phosphatase) while rheumatoid factor and histo-compatibility antigen HLA B27 are negative. *Paget's disease, osteitis and bone tumors must be excluded by imaging techniques. Chronic diffuse sclerosing osteomyelitis* should also be considered. It is a local inflammatory condition accompanied by intractable pain. Therapy with a bisphosphonate resulted in alleviation of symptoms and decrease in markers of bone turnover (Wright et al. 2005).

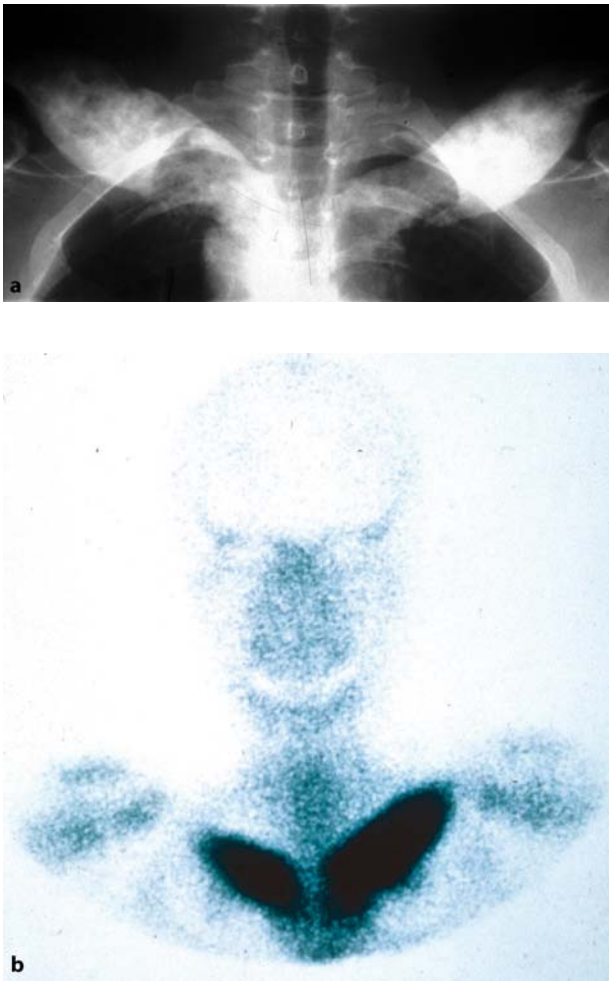


Fig. 18.1a,b SAPHO syndrome: **a** massive enlargement of both clavicles on X-ray, **b** same, as seen in bone scan

Therapy

Until recently therapy was confined to analgesics (NSAR and/or glucocorticoids). Although bacteria were isolated from some biopsies, attempts at therapy with antibiotics were unsuccessful. Other medications including colchicin, methotrexate, cyclosporine, calcitonin and vitamin D_3 were equally ineffective.

The almost unbearable bone pain is quickly alleviated by therapy with bisphosphonates especially i.v. which constitutes a breakthrough in the treatment of this disorder. With continued therapy, the symptoms decreased and progression of the disorder was halted. In 5 cases the following protocol was used successfully:

► *Ibandronate (Bondronat®)*	6 mg infusion (15 min) monthly

Children with SAPHO syndrome have been treated with cyclic pamidronate therapy. X-rays, CT, MRI, and/or bone scans can be used for monitoring. *Moreover, this bisphosphonate therapy has been highly successful even in patients with long-standing treatment – refractory sternoclavicular hyperostosis (Ringe et al. 2006).*

CHAPTER 19 Heterotopic Calcification and Ossification

Definition

Heterotopic or ectopic calcification is characterised by deposition or precipitation of calcium phosphate in tissues that normally do not undergo calcification. When woven bone is abnormally produced and calcified this is referred to as heterotopic ossification. The etiology is still unknown. *Various types are seen:*

- Metastatic calcification (seen in hypercalcemia and hyperphosphatemia)
- Dystrophic calcification (seen in scleroderma or SLE)
- Ectopic ossification (seen in burns or muscle injuries)
- Myositis (fibrodysplasia) ossificans progressiva
- Progressive osseous heteroplasia

Sites and Conditions of Occurrence

- *Heterotopic ossification* occurs mainly in muscles and primarily after trauma, for example, after hip surgery with or without implantation of a prosthesis. It can also occur after shoulder surgery, after brain injury or in paraplegia. *Historically, heterotopic ossification was the first of this group for which treatment with a bisphosphonate (etidronate) was successfully tried. Myositis fibrodysplasia ossificans is a congenital disorder*. Severe ossification has also been observed in joints and adjacent soft tissues in *disseminated idiopathic skeletal hyperostosis* (DISH)
- *Heterotopic calcification* may be found in vessel walls in arteriosclerosis as well as in primary hyperparathyroidism. It may also occur in the cardiac valves. In the urinary tract, it may result in stone formation. Calcification is also observed in calcinosis universalis, dermatomyositis, and scleroderma

Treatment Strategies

Unfortunately, no satisfactory treatment is available as yet. Surgical removal of large deposits, non-steroidal anti-inflammatory drugs, radiotherapy, dissolution

and local glucocorticoid injections have all been tried. In practice, radiation and indomethazine are most commonly used today for therapy of heterotopic calcification.

Bisphosphonates

Experimental trials have shown that bisphosphonates inhibit mineralisation and calcification of many soft tissues as well as heterotopic ossification. Unfortunately, they have not been successful in clinical situations, but so far only etidronate has been tested. Prevention of calcification of synthetic heart valves is a possible future application for etidronate. Bisphosphonates could also be considered for prevention of heterotopic ossification using the following protocols:

► *Ibandronate (Bondronat®)*	Monthly infusion of 2–6 mg
► *Pamidronate (Aredia®)*	Monthly infusion of 60 mg
► *Etidronate (Diphos®)*	2 g daily for a maximum period of 4 months

Higher doses of etidronate should not be given for extended periods because of the risk of osteomalacia. Currently, radiation therapy and indomethazine are the treatments used for heterotopic ossification.

CHAPTER 20 Periprosthetic Osteolysis and Aseptic Loosening of Prostheses in Total Joint Arthroplasty

Total joint arthroplasty of the hip and knee has become one of the most frequent and rewarding operations in orthopedic surgery. *World-wide more than one million such prostheses are implanted annually.* With the steady rise in life expectancy long term complications related to implant loosening and periprosthetic fractures are on the rise. Efforts to sustain and improve the clinical survival of total joint implants has thus generated great interest.

Pathogenesis

Stability of the prosthesis within the surrounding bone is the decisive factor for flawless functioning and longevity of the implants. Osteolysis is a multifactorial process stemming from host, prosthesis, and surgical factors. Billions of wear particles are generated at material interfaces and are dispersed along the effective joint space, into bone and the adjacent soft tissue, inducing an inflammatory reaction that leads to osteoclast activation and finally causing osteolysis. *Over time without proper treatment osteolysis may progress to aseptic loosening and failure of the implant.* Initially most patients may have no clinical symptoms despite radiographic evidence of osteolysis or bone loss. Usually patients only become symptomatic when implant loosening (Fig. 20.1), implant failure or periprosthetic fractures occurs.

The main factors involved in periprosthetic osteolysis and aseptic loosening following total joint arthroplasty are:

- *Wear-debris-induced osteolysis.* Integration of the implant into the surrounding bone can be hindered by an inflammatory reaction ("foreign body reaction") induced by macrophages absorbing small particles, mainly polyethylene and metallic wear debris, leading to activation of RANKL and OPG which then trigger osteoclastic activity. Another important factor is the inhibition of osteoblast function mediated by wear particles. Finally osteolysis and bone loss around the implant occurs.
- *Micromovement between surfaces:* Implants that do not achieve adequate initial fixation will exhibit micromotion in response to load. The greater the area of friction the more osteoclasts are activated causing osteolysis around the implant which leads to *fatigue failure at interfaces.* When the distance between bone

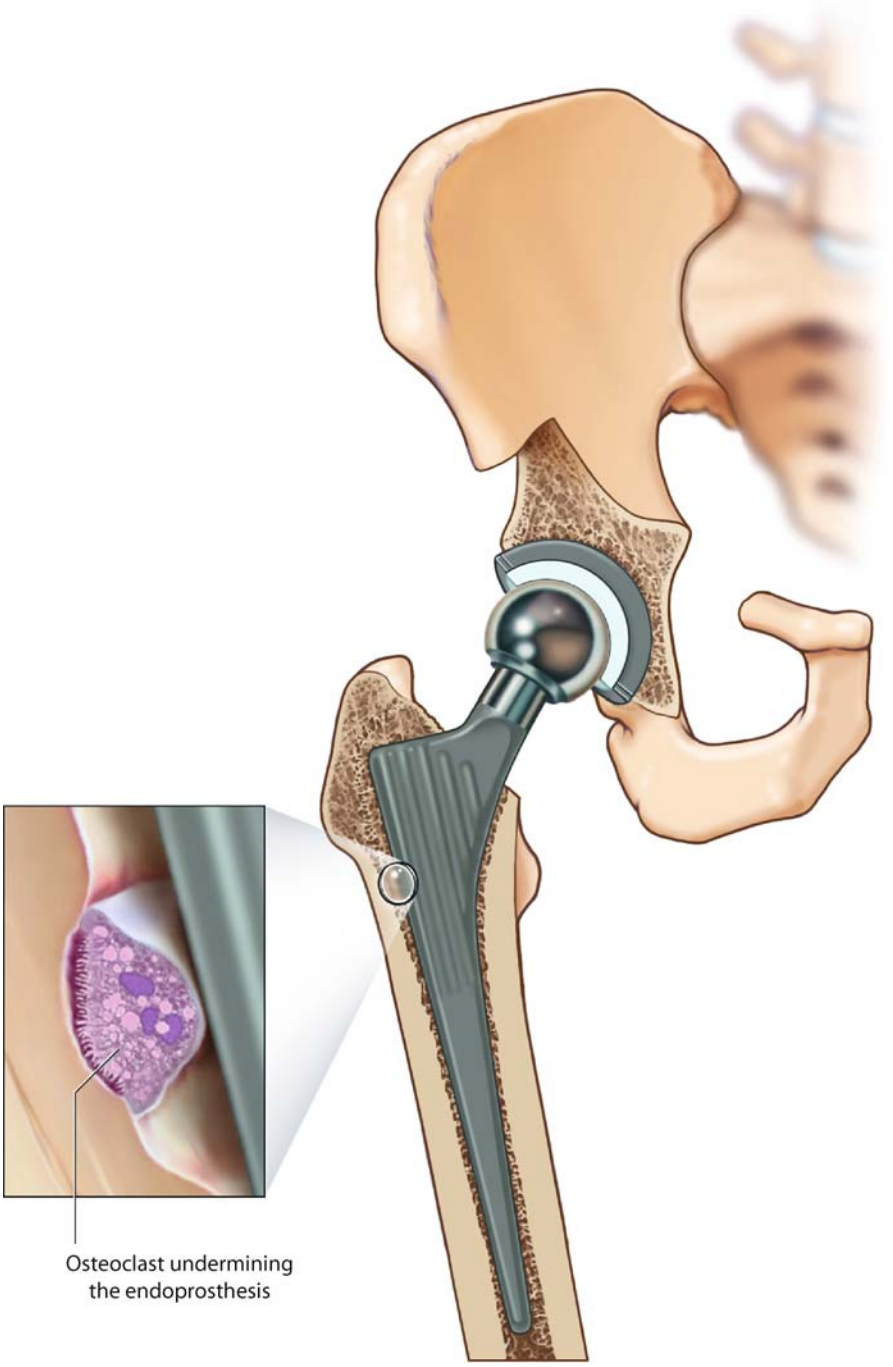

Osteoclast undermining
the endoprosthesis

Fig. 20.1 Periprosthetic osteolysis caused by activated osteoclasts at the bone-implant interface

and implant exceeds 150 µm connective tissue membranes are formed between implant and bone as well as between implant and cement. These membranes hinder the osteo-integration of the prosthesis. Many biochemical mediators are involved: cytokines, prostaglandins, metalloproteases and collagenases.

- *Inappropriate mechanical load and stress shielding:* Insertion of an implant leads to new biomechanical relationships between various regions of the surrounding bone and the implant. Bone regions around the implant receiving high loads of stress result in bone apposition and higher bone density, whereas bone regions receiving lower stress loading react with bone loss ("*stress shielding*" *according to Wolffs' law*). Appropriate load transmission is an essential factor in maintaining bone volume. Optimal load transfer is influenced by implant design and stiffness of the implant. Bone loss around the implant due to stress shielding can account for up to 50% of the former bone stock in underloaded regions, which has been demonstrated by DXA measurements (Fig. 20.2). *Finally periprosthetic fractures can occur.*
- *Postoperative immobilization:* The post-operative decrease in weight-bearing results in local immobilization osteoporosis. Overall the postoperative bone loss mainly occurs in the first 6 months and can reach up to 50% of the former bone stock.
- *Operative trauma:* Thermic and mechanical necrosis caused by the surgical procedure and cementing techniques alter bone quality.

Diagnosis

Slight loosening of the implant remains symptomless for long periods. Significant loosening causes considerable pain on weight-bearing and on sudden movements, eventually resulting in a feeling of complete instability. Pain on rotation of the leg in a patient with a hip implant indicates loosening of the shaft and pain on axial compression may indicate loosening of the cup. Radiolucent lines more than 2 mm wide indicate loosening (Fig. 20.3), but localised and limited osteolysis, and incomplete radiolucent lines per se do not constitute evidence of loosening of the implant. Migration of the prosthesis over time is diagnostic: migration of >5 mm indicates loosening. Implant migration indicates local bone loss which is a great problem in revision surgery. Besides standard radiographs (Fig. 20.4) also bone scans are useful to detect regions of high bone turnover around implants, and computed tomography to quantify the amount of bone loss.

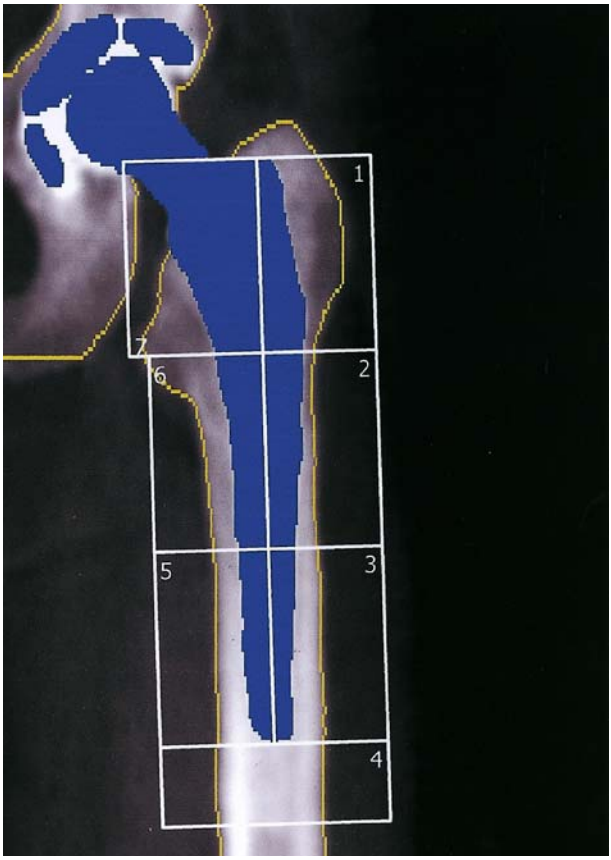


Fig. 20.2 DXA measurement of bone mineral density in periprosthetic region: division into 7 zones according to Gruen (Lunar Prodigy)

Treatment Strategies

Causative therapy consists of replacing the prosthesis. Indications for this are pain, functional limitations and migration of the implant. Accompanying osteoporosis and loss of bone stock around the implant can turn this operation into a more dangerous and more difficult one than the index operation. However recent advances in technology and in materials for cementing may improve long-term results in the future. Intensive research is underway to improve the survival of the implants including local application of bisphosphonates and implant coating with osteoinductive factors. Implantation of cementless implants is recommended for younger patients with bone of good quality, as less bone is removed, which ensures a more favorable situation if a revision procedure has to be made later.

Various *modifications to improve osteointegration of implants* are under investigation:

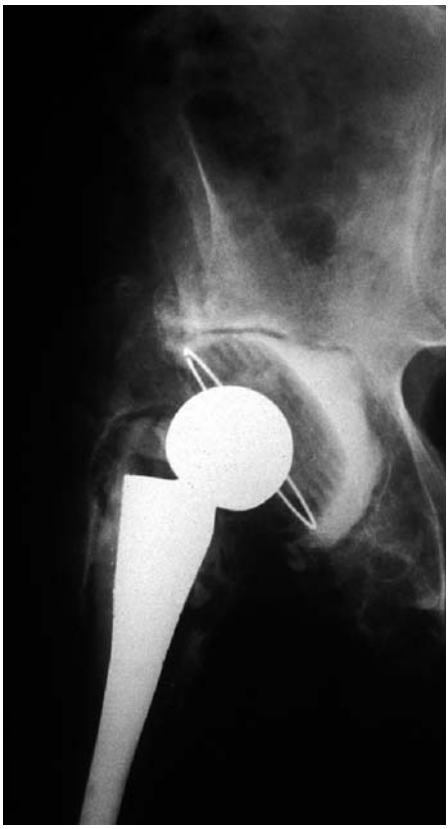


Fig. 20.3 Peri-implant bone resorption ("linear osteolysis") at the interface of the acetabular component, "radiolucent lines"

- Optimization of prosthetic design with optimal load transfer to the bone
- Better cementing techniques
- Local application of growth factors (Hydroxylapatite, TGF-β, BMP2) as well as PTH to improve osteo-integration of the implant

Bisphosphonates

Early administration of nitrogen-containing bisphosphonates inhibits peri-implant osteoclastic resorption. This has been demonstrated in numerous animal experiments which showed a decrease in bone loss around the implant. Current clinical studies are hampered by short follow ups. *A recently published meta-analysis of 6 randomised controlled studies showed that bisphosphonates given in the immediate post-operative period prevented periprosthetic bone loss and resulted in a higher*

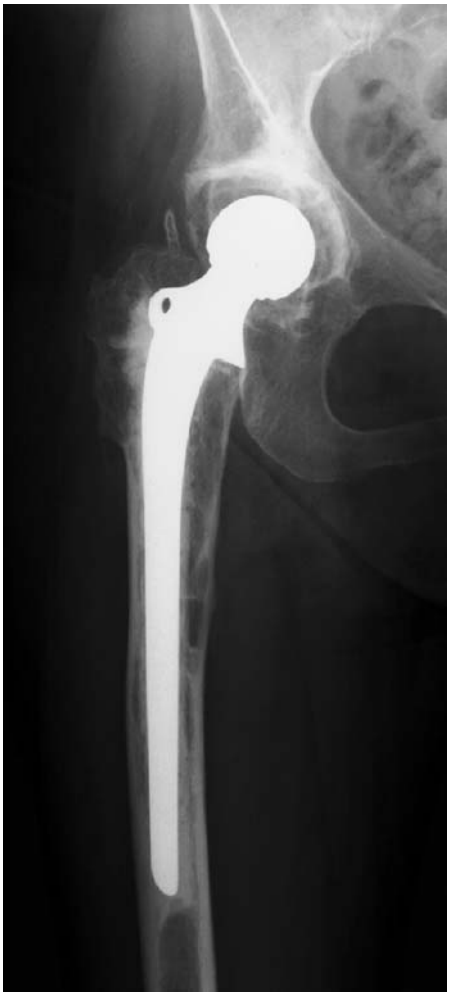


Fig. 20.4 Peri-implant bone resorption at the interface of the femoral ("geographic osteolysis") and acetabular component ("linear osteolysis")

periprosthetic bone mineral density at the end of the study period compared to controls.

In cases where total joint arthroplasty is planned, *therapy with bisphosphonates can be given in the following situations*:

- *Underlying systemic or local osteoporosis*: a higher bone density in the perioperative period may reduce the postoperative bone loss and extent of periprosthetic osteolysis.
- *Underlying chronic inflammatory joint disorder*: Inhibition of osteoclasts and suppression of osteoclast activating mediators, as well as an increase in bone

density can help to reduce postoperative bone loss and to increase the time of implant survival.

The following *treatment protocols* are recommended. Dosages and time intervals depend on the type and severity of the underlying condition:

► *Alendronate (Fosamax®)*	70 mg orally once weekly
► *Risedronate (Actonel®)*	35 mg orally once weekly
► *Pamidronate (Aredia®)*	30–60 mg intravenously every 3 months
► *Ibandronate (Bonviva®)*	3 mg intravenously every 3 months
► *Ibandronate (Bonviva®)*	150 mg orally monthly
► *Zoledronate (Aclasta®)*	5 mg intravenously annually

The following parameters are used to monitor therapy:

- Clinical examination
- Control radiographs
- DXA (bone densitometry)
- Markers of bone remodelling

To establish the efficacy of bisphosphonates in preventing bone loss after total joint arthroplasty more randomised clinical trials with large numbers of patients, long term follow up and clinically relevant endpoints (functional outcomes, revision rates) have to be conducted. However the current results for prevention of periprosthetic bone loss with bisphosphonates are very promising.

CHAPTER 21 Alveolar Bone Loss due to Periodontitis

Definition

Periodontitis (parodontitis, paradontosis) is an inflammation of the tissues (the gums) surrounding the teeth, which leads to resorption of the alveolar bone and can progress to abscess formation with loosening and shedding of teeth. *Inflammation of the gums with loosening of the teeth is a clear indication for an immediate DXA, dental investigation and appropriate treatment.*

Pathogenesis

Periodontal inflammation is due to bacteria in the plaques on the teeth causing inflammatory reactions and resorption of the alveolar bone of the jaws. Matrix metalloproteinases participate in the destruction of the periodontal tissues by splitting extra-cellular molecules. Mediators of inflammatory reactions such as prostaglandin (PGE_2), interleukin 1 (IL-1) and TNF are also involved in the resorption of the alveolar bone (Fig. 21.1). Other participants in the process are collagenases, macrophages and osteoclasts. The diagnosis usually is not in doubt. Rarely, however a specific cause may be found as for example Gorham's disease presenting as an osteolytic lesion confined to the mandible. The patient was successfully treated with the bisphosphonate zoledronate.

Clinical Findings

Examination of the inside of the mouth reveals inflammations, possibly even purulent, of the gums leading to resorption of the alveolar bone surrounding the teeth, which are loosened and may fall out on pressure.

Treatment Strategies

Elimination of the dental plaque harboring the bacteria is an essential pre-requisite for successful treatment. This is accomplished by mechanical removal, cleansing and topical application of antibiotics such as tetracycline or metronidazole.

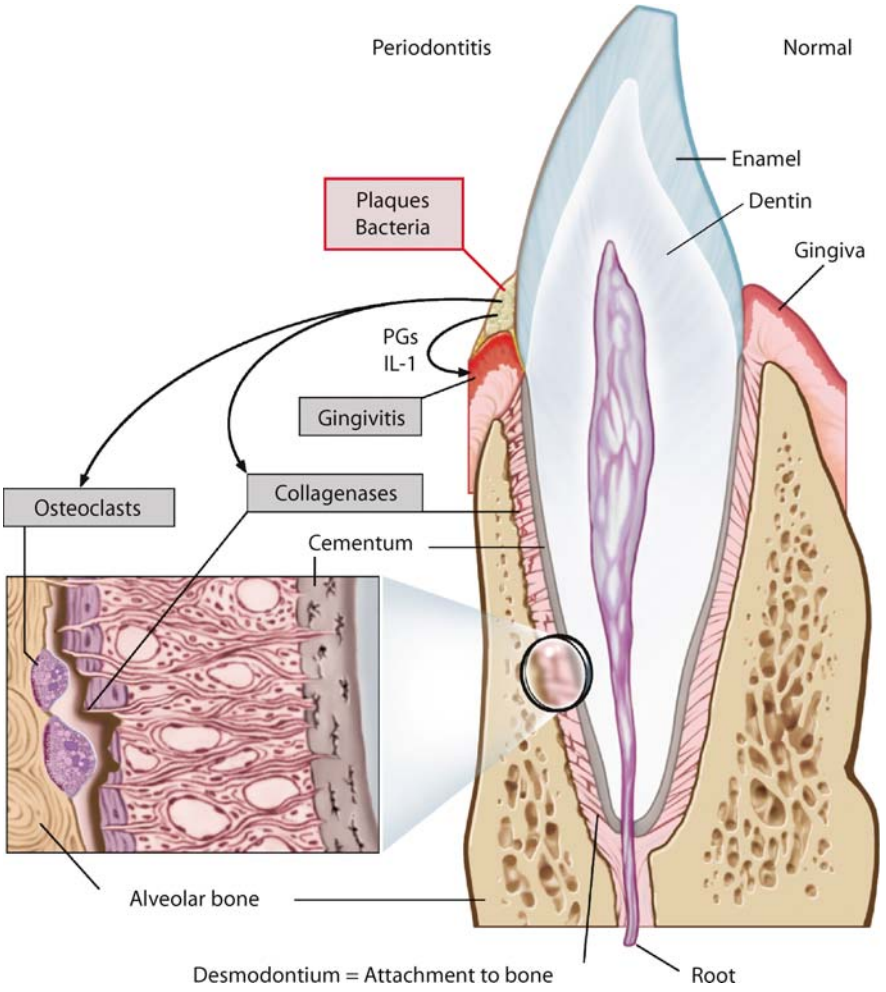


Fig. 21.1 Pathogenesis of alveolar bone loss induced by periodontitis

Nonsteroidal anti-inflammatory drugs decrease the level of prostaglandin in the area of the inflamed gums, and thereby reduce the loss of alveolar bone.

Bisphosphonates

Bisphosphonates minimise resorption and loss of alveolar bone in the inflamed areas. They inhibit both osteoclastic activity and collagenases (metalloproteinases). This has been demonstrated in many studies using oral alendronate preparations.

► *Alendronate (Fosamax®)*	10 mg daily or 70 mg once weekly orally

Local application of bisphosphonates in toothpaste has also been tested. Topical application of etidronate decreases plaque formation and thereby also bacterial infections. Many clinical studies have examined a possible connection between systemic ostoporosis and buccal bone loss leading to loosening and loss of teeth. Presumptive mechanisms include the following: all the bones of the skeleton are effected in generalised osteoporosis, including those of the jaws, therefore a systemic low bone mass in the skeleton includes the jaw bones so that there is a propensity for the teeth to fall out. Systemic factors which influence systemic bone loss also modify the local tissue reactions to a periodontal infections.

Necrosis of the Jaw Bones and Non-traumatic Avascular Necrosis of the Femoral Head

Systemic medications/drugs which influence the bones as a whole also effect the alveolar bones of the jaws. *Necrosis of the jaw bones* and a possible association with bisphosphonates is extensively discussed in Chap. 3 under the heading "Side Effects". It is worth noting that in many patients this condition is associated with preceding cancer chemotherapy.

Recent clinical and experimental studies have shown that (paradoxically) treatment of the patients with bisphosphonates results in improvement of the condition and decrease in the development of femoral head deformity. Details are given in Chap. 3 under the same heading as above.

CHAPTER 22 Hypercalcemia

Definition

The total calcium in the serum consists of 3 fractions:

- Free or ionised calcium (about 50% of the total calcium)
- Protein-bound calcium (mainly bound to albumin, about 45% of the total calcium)
- Anion complex-bound calcium (about 5% of the total calcium)

To measure calcium levels, either the level of total calcium in the serum or that of ionised calcium in anticoagulated blood is used. Ionised calcium is the better indicator of the two as it is the biologically active form and is under the direct control of PTH. The disadvantage of total calcium measurements is that they are influenced by the amount of protein in the serum. *Abnormal values must be clarified – and a malignancy should always be excluded.*

Hypercalcemia is defined as a total plasma concentration of over 10.4 mg/dl (2.6 mmol/L). Generally hypercalcemia is caused by a combination of factors:

- *Increased binding due to dysproteinemia*: Since ionised calcium levels remain normal this form of hypercalcemia has no physiological significance.
- *Hypercalcemia induced by parathyroid hormone*: This is nearly always due to primary hyperparathyroidism (pHPT). In 90% of the cases the underlying cause is an adenoma of the parathyroid glands, in 7% hyperplasia and in only 3% a parathyroid carcinoma.
- *Tumor-associated hypercalcemia*: this may occur as part of a paraneoplastic syndrome or because of tumor-induced osteolytic bone disease, in which case it may present as a life-threatening emergency requiring immediate treatment.

Frequency

Hypercalcemia is found in about 1% of all hospitalised patients, caused by malignancy in 46% of all cases, and by pHPT in 35%. In the remaining 19% other conditions are responsible. These include sarcoidosis, immobilisation and medications such as thiazides or active metabolites of vitamin D.

The following 4 factors are frequent causes of hypercalcemia and must always be checked:

- *Incorrect values* (technical reasons? Repeat the laboratory test)
- *Osseous metastases*
- *Multiple myeloma*
- *Primary hyperparathyroidism*

Less frequent causes which should be considered in the differential diagnosis are

- Sarcoidosis
- Hyperthyroidism
- Malignant diseases with production of PTH (PTHrP)
- Vitamin D and A intoxication
- Tertiary hyperparathyroidism
- Addison's disease
- Milk-alkali syndrome
- Lithium poisoning
- Hypereosinophilic syndrome
- Tuberculosis
- Familial hypocalciuric hypercalcemia (FHH)
- Miscellaneous, for example immobilisation, parenteral nutrition and renal failure

Hypercalcemia may occur in infants, premature infants are also vulnerable. For example when receiving parenteral nutrition a 17 day old infant developed hypercalcemia which was successfully treated with i.v. pamidronate.

Differential Diagnosis

Once the diagnosis of hypercalcemia has been confirmed, the cause must be established based on clinical findings and laboratory values such as levels of intact parathyroid hormone and calcium excretion in a 24 h urine sample.

Three main considerations are:

- In *pHPT* the iPTH is usually > 60 ng/L. A lower value indicates that the hypercalcemia is not triggered by the parathyroid glands.
- In *tumor-induced hypercalcemia* the iPTH level in plasma is low (< 40 ng/L) while phosphate is high.
- In *typical familial hypocalciuric hypercalcemia* calcium excretion in the urine is usually < 100 mg/24 hours.

Symptoms

Patients with mild hypercalcemia have no symptoms. The term hypercalcemic syndrome refers to a constellation of symptoms independent of the etiology including renal, gastro-intestinal and neuro-psychiatric changes. This syndrome has a wide clinical spectrum from asymptomatic to lethal. It is characterised by severe dehydration which is caused by the following sequence of events: hypercalcemia – hypercalciuria – polyuria – polydypsia – polyuria. Nausea and vomiting further increase the fluid and electrolyte loss. The result is hypopotassemia together with disturbances of cardiac rhythm. Moreover, fatigue, depression and a general deceleration of cognitive function indicate additional neuropsychiatric involvement. *In severe cases the condition may progress to a hypercalcemic crisis with somnolence and coma.*

Treatment Strategies

The management of hypercalcemia is determined by the level of calcium in the serum, the clinical symptoms, and the underlying disorder; but regardless of the cause, *treatment always starts with adequate hydration.* When calcium is < 2.88 mmol/L, investigation and correction of the underlying cause suffice. When the PTH level is elevated, the parathyroid glands must be investigated, and operated if necessary and feasible. *In cases of inoperable hyperparathyroidism, therapy with bisphosphonates is the second line treatment of choice, and this may be successful.*

If the level of iPTH is normal or low, a malignancy must be ruled out. In severe symptomatic hypercalcemia (>3.75 mmol/L) immediate measures must be taken to ensure a rapid decrease in calcium levels. These include rehydration (physiological saline) and forced diuresis (furosemide). Hemodialysis may be required in the event of renal failure. In patients with sarcoidosis, with certain neoplasms, and with vitamin D intoxication corticosteroids are also indicated to decrease the calcium levels.

Bisphosphonates

The main aim is inhibition of osteoclastic resorption of bone, and this is most easily, effectively and reliably accomplished by intravenous administration of bisphosphonates after rehydration.

The following *protocols* are used:

► *Clodronate (Ostac®)*	Infusion of 300 mg daily over 7 to 10 days. The total number of infusions depends on the calcium level. Duration of infusion: 2 hours.

► *Ibandronate (Bondronat®)*	Infusion of 2–6 mg, depending on the calcium level. Duration of infusion: 15–30 minutes.
► *Pamidronate (Aredia®)*	Infusion of 30–90 mg, depending on the calcium level. Duration of infusion: 1 to 2 hours.
► *Zoledronate (Zometa®)*	Infusion of 4–8 mg, depending on the calcium level. Duration of infusion: 15–30 minutes, together with a 2-hour infusion of saline.

Generally speaking, a single infusion of one of the aminobisphosphonates restores the calcium level to normal (Fig. 22.1). The treatment is repeated if the calcium levels rise again. The time required to stabilise the calcium level depends on the underlying condition and is usually about 2 weeks. Following infusion of zoledronate the calcium level is usually normalised and stabilised by day 10.

Hypercalcemia of Malignancy

Definition

All patients with cancer are subject to hypercalcemia in the advanced stages of a malignancy, in particular patients with breast cancer or with multiple myeloma, less frequently with neoplasms of the lung or prostate. *Hypercalcemic episodes occur in 30% of patients with metastatic tumors and in 50% of patients with multiple myeloma.*

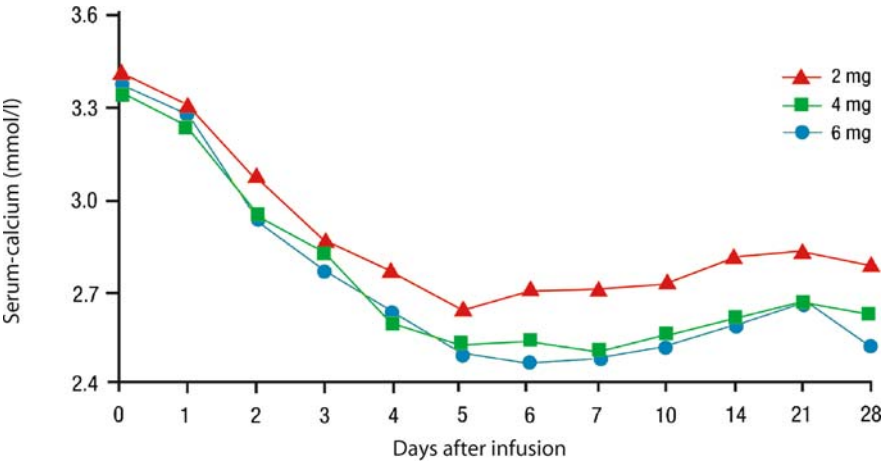


Fig. 22.1 Effect of different doses of ibandronate on hypercalcemia

Pathophysiology

Hypercalcemia of malignancy is characterised by elevation of serum calcium with suppression of normal parathyroid secretion. The increase in serum calcium is due to aggressive local osteolyses, increased renal excretion and increased tubular re-absorption of calcium. *Two types are recognised*:

- *Osteolytic hypercalcemia*: Tumor cells in the bone marrow secrete osteoclast-stimulating factors (IL-6, TGF), which stimulate massive osteoclastic resorption with release of calcium from the bone.
- *Humoral hypercalcemia*: Many tumors produce parathyroid hormone-like substances (PTHrP) which bind to PTH receptors in bone and kidney and trigger the normal physiological effects of PTH (para-neoplastic syndromes). In addition, granulomas, e.g. in tuberculosis, sarcoidosis and sarcomas and tumor-induced production of active vitamin D metabolites (e.g. in lymphomas) can lead to hypercalcemia.

Therapy

- In mild cases, chemotherapy alone can lead to a reduction in the serum calcium concentration.
- Rehydration: physiological saline (at least 3 liters in the first 24 hours) to replenish intra- and extracellular fluids and electrolytes. Treatment with diuretics (e.g. furosemide) must be considered in patients with cardiac and/or renal insufficiency.
- Corticosteroids: 20–60 mg daily in patients with multiple myeloma, lymphoma or breast cancer can help to reduce the hypercalcemia.
- Calcitonin: Since calcitonin and bisphosphonates have independent actions on bone and on the kidneys, additive effects can be expected if they are given together.
- Moreover, calcitonin and bisphosphonates do not act simultaneously, so their effects are also cumulative.
- Indeed, a rapid decrease in calcium levels is achieved with this combination. However, the danger of inducing hypocalcemia must be reckoned with and avoided.
- Therapy with bisphosphonates does not influence the levels of osteoprotegerin and RANKL when given to patients with hypercalcemia of malignancy.

Bisphosphonates

Bisphosphonates have greatly simplified the treatment of hypercalcemia. A single 2-hour infusion of one of the following is generally effective, especially those with high potency, e.g. ibandronate and zoledronate:

► *Clodronate (Ostac®)*	1500 mg
► *Pamidronate (Aredia®)*	90–120 mg
► *Ibandronate (Bondronat®)*	6 mg
► *Zoledronate (Zometa®)*	4 mg

After rehydration, the bisphosphonate is infused slowly (1 to 4 hours) in plenty of fluid (e.g., 500 ml of physiological saline), in order to avoid renal damage. The therapeutic activity comes into effect after a delay of 2 to 4 days (longer with pamidronate), and normal levels of calcium are obtained within 4 to 7 days and maintained for a period of several weeks, depending on the aggressivity of the tumor and which of the bisphosphonates was used (zoledronate 88%, ibandronate 78%, pamidronate 70%). Generally, the period of normalisation ranges from 2 to 4 weeks, with a success rate of 70–95%. If a satisfactory result is obtained with zoledronate then the second infusion should be given 7 days later. Treatment is repeated if and when elevation of serum calcium recurs. Four mg zoledronate via 15-minute infusion is the dose recommended for initial treatment of hypercalcemia of malignancy (HCM) and 8 mg for relapsed or refractory hypercalcemia. The median durations of complete responses were 32 (4 mg) and 43 (8 mg) days respectively.

Patients with renal failure should receive 30–50% lower doses, and longer infusion times are recommended (e.g. pamidronate 0.5 mg/min). Disturbances of renal function and/or local side effects at the site of infusion have not been reported for ibandronate. Moreover, as the hypercalcemia is normalised, an improvement in renal function is also achieved. *Bisphosphonate therapy is less effective and of shorter duration when there is a high level of PTHrP*. The extraskeletal effects of PTHrP are not influenced by bisphosphonate therapy. *In life-threatening situations, when the level of calcium must be lowered rapidly, the combination of a bisphosphonate with calcitonin is recommended, because this reduces the serum calcium level within a matter of hours by increasing the renal excretion of calcium. The calcitonin acts rapidly and bridges the gap till the bisphosphonate begins to exert its effect.*

CHAPTER 23 Bone Pain

Frequency

Not all pains described by the patients as "bone pain" are actually due to disorders of, or originate in the bones. Often the pain is due to faulty weight-bearing and transfer of muscle tension to bones and joints. *Bone pain must always be taken seriously, it may herald a malignancy.*

Genuine bone pain can be classified according to extent:

- Generalised bone pain: Usually due to a metabolic disorder or extensive metastases. This type of pain is often dull, aching and difficult to localise accurately.
- Localised bone pain: frequently, but not always, shows a typical X-ray picture.

Bone pain is the most frequent symptom in patients with osseous metastases. More than 50% of these patients experience bone pain before or at the time of diagnosis of skeletal metastases. The pain is constantly present and may increase in intensity. Multiple myeloma and osteomyelosclerosis are also often accompanied by severe bone pain.

Differential Diagnosis

This includes numerous conditions which must be excluded before therapy is instituted. The main causes are listed below.

Oncologic and hematologic conditions:

- Skeletal metastases
- Multiple myeloma
- Leukemias
- Osteomyelosclerosis
- Malignant lymphomas
- Storage disorders

- Systemic mastocytosis
- Granulomatous disorders
- Eosinophilic granuloma
- Osteomyelitis

Osteologic and orthopedic conditions:

- Fractures
- Arthroses
- Tendonopathies
- Osteoporoses with fractures
- Transient osteoporosis (bone marrow edema syndrome)
- Muscle cramps
- Osteomalacia
- Paget's disease of bone
- Complex regional pain syndrome (Sudeck's disease)
- Heterotopic calcification
- Aseptic loosening of prosthesis

Pathogenesis

Bone pain has a complex etiology, incompletely understood. Mechanical factors include:

- Increased pressure in the bone marrow
- Bending or distortion of bone
- Stretching of the periosteum and/or endosteum
- Destruction of bone

Inflammatory, humoral and neural factors also play a role. Prostaglandins, histamine, serotonin, bradykinin and other cytokines can all act as triggers or as modulators. Bone pain is mediated primarily by stimulation of nociceptors (pain receptors) in the periosteal and endosteal sheaths of the bones. It can also be caused by irritation and lesions of the afferent nerve fibers within the bone marrow. These fibers regulate blood flow through bone, bone marrow and sinusoids. Sensory nerve fibers are also present, as demonstrated for example by the pain induced when bone marrow is aspirated. Results of recent studies have implicated the RANKL/OPG system as a major factor in triggering bone pain. Moreover, tumor cells themselves secrete cytokines which stimulate T lymphocytes and osteoclasts which leads to further release of inflammatory mediators as bone is resorbed. Generalised bone pain is also caused by the increased pressure resulting from bone marrow infiltration (metastatic, leukemic) or by edema of the bone marrow. *Paraneoplastic bone pain is mediated indirectly by the tumor by way of the hormone-like substances it secretes.*

Diagnosis

Any *description of pain* should include the following aspects: onset, duration, intensity, type, localisation, radiation, temporal pattern. For example:

- Type: dull, stabbing, aching or variable?
- Intensity: remains constant or varies?
- Localisation: focal, delimited or generalised?
- Radiation: point of origin – where to?
- Time pattern: onset sudden or slow, transient or recurrent "comes and goes".

Bone pain is often dull or sharp and stabbing. Focal, penetrating pains are due to periosteal involvement. In practice, bone pain is often diffuse, referred and difficult to localise precisely. *Bone pain in patients with tumors* includes several clinical types, which may require different treatments:

- Dull, deep, constant ache
- Movement-associated pain (inflammatory?)
- Radiating neurogenic pain

The treatment of bone pain in patients with malignancies should be an integral part of the overall management.

Bone pain in cancer patients may have various causes:

- Due to the tumor itself (85%)
- Due to therapy (17%)
- Associated with the tumor (9%)
- Independent of the above (9%)

About 70–80% of the patients may suffer from more than one type of bone pain. Pain can be evaluated clinically using one or more of the *pain scores* available:

- Verbal rating scale (VRS)
- Visual analogue scale (VAS)
- Numeric rating scale (NRS)

Though there is a close correlation between these scales, changes are better documented by VAS. Careful observation of the patient also provides a good opportunity to evaluate the situation. The presence or absence of sleep disturbance is another important factor. Complete biochemical and hematological investigations should be performed to detect metabolic, inflammatory and malignant conditions and/or complications. Imaging techniques should be used to demonstrate osseous and other lesions; and directed bone biopsies should be taken in equivocal cases.

Treatment Strategies

The first aim is elimination of the cause of the bone pain by specific therapy of the condition diagnosed if possible, for example:

- Vitamin D for osteomalacia
- Antibiotics for osteomyelitis
- Radiotherapy for focal neoplastic lesions

Treatment of tumor-induced bone pain also includes:

- Physical therapy (exercises, physiotherapy)
- Central and peripheral analgesics
- Additional medications (antidepressants, tranquilisers, muscle relaxants)
- Invasive therapy (peridural or intrathecal opioids)
- Antineoplastic therapy (chemo and radio therapy)
- Antiresorptive therapy (bisphosphonates, calcitonin)

Administration of analgesics according to the "analgesic ladder" of the WHO:

Step 1 Non-opioids with adjuvants
Step 2 "Weak" opioids in combination with acetaminophen and adjuvants
Step 3 "Strong" opioids with adjuvants

More than 95% of patients can be treated satisfactorily with this stepwise approach to cancer pain management. Less than 5% require invasive pain therapy and before this is carried out, bisphosphonates or calcitonin should be given. Calcitonin inhibits local prostaglandin production as well as stimulating release of endogenous opiates in the brain, although this has not yet been confirmed by placebo-controlled studies.

Bisphosphonates

The alleviation of pain by bisphosphonates has been demonstrated in several placebo-controlled clinical trials (Fig. 23.1). The effect is often felt within a day and may last for weeks or months, depending on the dose administered. However, not all physicians, even experts in the field, are aware of the alleviation of bone pain by bisphosphonates. Markers of bone resorption correlate closely with the analgesic effect.

Success of bisphosphonate therapy is indicated by:

- Reduction of pain intensity

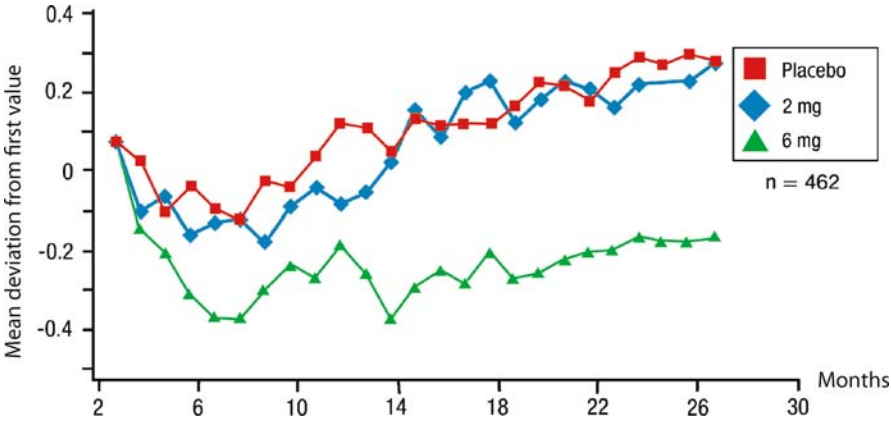


Fig. 23.1 Decrease of pain under therapy with ibandronate in patients with breast cancer

- Reduction in use of analgesics
- Reduction in need for radiotherapy
- Reduction in surgical interventions

The following *protocols* are recommended for tumor-induced bone pain:

► *Clodronate (Ostac®)*	600 mg infusion every 3–4 weeks
► *Clodronate (Ostac®)*	1600 mg orally daily
► *Pamidronate (Aredia®)*	60–120 mg infusion every 3–4 weeks
► *Zoledronate (Zometa®)*	4 mg i.v. infusion every 3–4 weeks
► *Ibandronate (Bondronat®)*	2–6 mg infusion every 3 to 4 weeks
► *Ibandronate (Bondronat®)*	50 mg orally daily

Until recently, bisphosphonates were given when bone pain was presumably caused by osteolytic lesions. Pain induced by *osteoblastic metastases*, or osteomyelosclerosis or systemic mastocytosis also responds rapidly and for long periods to bisphosphonate therapy. *In practice, all large studies of metastatic carcinoma and multiple myeloma have confirmed the analgesic effects of bisphosphonates on pain due to osteolytic as well as osteoblastic and mixed metastases.*

This indicates that relief of bone pain by bisphosphonates is not due exclusively to inhibition of osteoclasts, but that the bisphosphonates also act on other cells such as T lymphocytes and stromal cells and thereby exert an effect on the RANKL/OPG system.

CHAPTER 24 Multiple Myeloma

Definition

Multiple myeloma (MM) is a malignant hematologic disorder caused by a monoclonal proliferation of plasma cells and their precursors: B lymphocyte neoplasia with terminal differentiation. The plasma cells produce a monoclonal protein either a complete immunoglobulin (G, A, D or E) or fragments thereof (e.g. light chains, Bence-Jones protein).

Frequency

Multiple myeloma constitutes about 1% of all malignancies and about 10% of all hematologic neoplasms. Its incidence is about 3 cases per 100,000 people annually. The peak frequency lies between 55 to 75 years with a median age of 65 years, though in recent years the number of younger people has shown a tendency to increase.

Pathogenesis

The initial malignant transformation takes place in immature B lymphocytes, which originate in the bone marrow or in the lymphatic system and enter the circulation before settling down in the skeleton, occasionally in other organs. *Multiple myeloma is a typical disease of the bone/bone marrow system*. Once established, the myeloma cells activate monocytes, T lymphocytes and stromal cells by a battery of cytokines which also influence the growth and manifestations of the myeloma itself. These cytokines and other factors mediate complex interactions between the multiple myeloma, the bone marrow stroma, and the bone cells; finally these interactions result in osteoclastic destruction of bone.

Interleukin 6 (IL-6) plays a key role in these processes. It is produced by bone marrow stromal and endothelial cells, osteoblasts and osteoclasts. IL-6 stimulates the growth and inhibits apoptosis of myeloma cells. *Overall, the mechanisms responsible for the growth and development of multiple myeloma involve the activities and interactions of the tumor cells with stromal and bone cells.*

When soluble IL-6 receptors (sIL-6R) as well as IL-1 are also present, inhibition of bone formation and stimulation of bone resorption are particularly pronounced. The latest studies have shown that myeloma cells increase IL-6 production by osteoblasts either through indirect cell contact or by means of soluble factors. VCAM-1 and α4β1 integrin receptors also modulate complex interactions between myeloma and stromal cells. All these interactions are presumed to be responsible for the osteoclastic bone lesions. Soluble VCAM-1 ligands produced by stromal cells also stimulate myeloma cells to produce substances which trigger osteoclastic bone resorption. Additional important factors responsible for destruction of bone in MM are Il-1, RANK ligand, PTHrP, MIP 1a and of these the "macrophage inflammatory proteins MIP-1a and 1b" are particularly significant. Interleukin 8 produced by monocytes is also involved.

Angiogenesis plays an additional important role in the pathogenesis of MM. Myeloma cells themselves produce *vascular endothelial growth factor* (VEGF), receptors for which are located on the surface of bone marrow stromal cells. Moreover, it has been demonstrated that VEGF increases IL-6 production by stromal cells in MM.

Adhesion molecules (*integrins*) *are also important for proliferation of myeloma cells*. These molecules are demonstrable on the surface of osteoclasts, myeloma cells and endothelial cells. Tumor cells with high levels of integrins are particularly invasive. It is of interest that lack or inhibition of integrins on the osteoclasts leads to their inactivation and thereby possibly to osteopetrosis in special circumstances. On the other hand, inter-cellular contact between osteoclasts and myeloma cells generates resistance to the anti-tumor effects of some chemotherapeutic agents, e.g. doxorubicin, while osteoclastic resorption and the life-span of the myeloma cells are both increased. TRANCE, a new member of the TNF family, released by the interaction of myeloma and stromal cells, also activates osteoclastic resorption as well as stimulating the myeloma cells. Numerous experimental studies have now demonstrated the crucial role of the "micro-environment" and the RANKL/osteoprotegerin system not only for the growth of the myeloma itself but also for development of its resistance to radio- and chemotherapy.

In summary, three main pathogenic mechanisms are now held responsible for the osteolytic and osteoporotic effects of MM:

- The surface expression of RANK ligand on myeloma cells stimulates osteoclasts.
- Myeloma cells protect themselves against osteoprotegrin by means of phagocytosis and intra-cellular lysis.
- Myeloma cells produce DKK-1 which inhibits stromal cell differentiation into osteoblasts and thereby prevents new bone formation.

Clinical Findings

Kahler's classical triad of bone pain, cachexia and proteinuria are all symptoms of an advanced stage of MM which today is observed far less frequently at diagnosis

because now the disease is far more frequently exposed at an early or incipient stage. This is mainly due to the regular health checks many people undergo, because at this early stage the myeloma is mainly asymptomatic. The subsequent course is insidious and variable. *The first objective manifestations are weakness, fatigue, decreased capability, lack of appetite and weight loss – all nonspecific indications of a malignant condition.*

Frequently an elevated ESR, a pathologic M-peak on protein electrophoresis, or a cytopenia discovered incidentally by a routine check-up during a symptomless stage, provides the impetus for further investigations. As the condition develops, it evokes symptoms by the inter-actions of tumor products leading to organ damage.

The first relatively specific signs are bone pain, spontaneous fractures and increased liability to infections. The significant physiologic mechanisms and the complications of MM are summarised in Fig. 24.1.

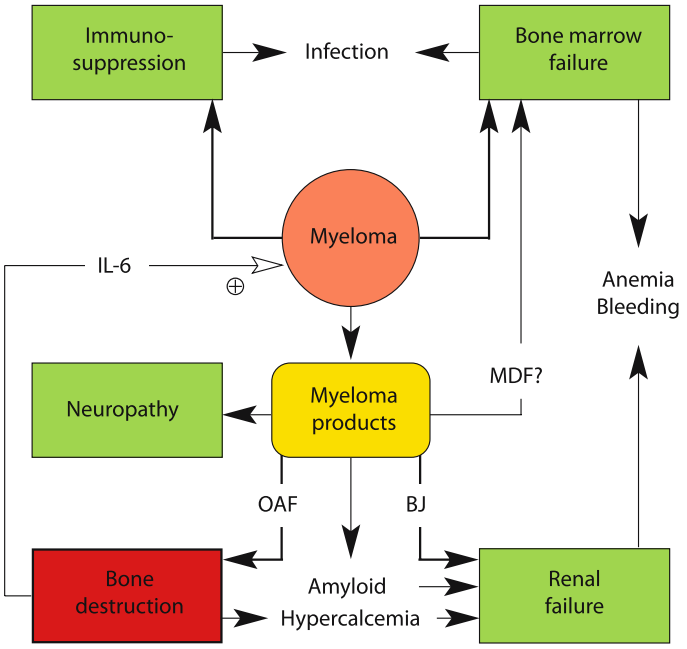


Fig. 24.1 Pathophysiology of multiple myeloma (MM). *OAF* = osteoclast activating factor, *BJ* = Bence-Jones protein, *MDF* = myelopoiesis depressing factor, *IL-6* = interleukin-6 secreted by osteoclasts

Diagnosis of Skeletal Manifestations

Multiple myeloma is not only a malignant disease of the bone marrow, it is also a generalised disorder of bone characterised by skeletal destruction. The skeleton must therefore be carefully examined together with investigation of hematopoiesis and of the myeloma itself. These investigations should ideally be completed before organ complications have developed so that early preventive and supportive measures can be undertaken.

Bone specific findings and symptoms at the time of diagnosis:

► Bone pain	55%
► Osteolyses	45%
► Osteoporosis	40%
► Spontaneous fractures	18%
► Hypercalcemia	16%

A systematic X-ray examination of the axial skeleton is essential for initial diagnosis and for monitoring. Bones most frequently effected are those of skull, thoracic and lumbar vertebrae, followed by other bones which enclose hematopoietic bone marrow. The structure of the osseous lesions is determined by the basic growth pattern of the MM within the bone marrow: osteolyses with the nodular type and osteoporosis with the interstitial type. Osteosclerosis has been found in less than 3% of myeloma patients.

MRI is becoming increasingly important for early detection and prognostic evaluation of multiple myeloma, particularly in the axial skeleton; so that *today early diagnosis and accurate staging of myeloma depend on MRI of the vertebral column*. Even in the presence of completely normal X-ray findings, MRI will reveal small focal or nodular infiltrations of plasma cells in the vertebral bodies, thereby complementing the findings in bone biopsies taken from the iliac crest. MRI is equally indispensable in the investigation of a suspected solitary plasmacytoma. *Bone scans are not suitable for diagnosis of MM* since there is no activation of osteoblasts, in contrast to the situation in many metastasizing tumors.

Bone density measurements should be made by DEXA or QCT at diagnosis to provide a base-line so that potential bone loss for example during glucocorticoid therapy can be monitored and the success of therapy with bisphosphonates can be assessed.

Parameters of bone metabolism (calcium, phosphate, alkaline phosphatase, creatinine, and markers of bone resorption such as deoxypyridinoline and telopeptides) should be checked in addition to performing a complete blood count and routine biochemical investigations, including indicators of hepatic and kidney function.

A bone and bone marrow biopsy and aspiration enable estimation of the type of plasma cells, the labeling index, quantity of infiltration, of residual hematopoiesis,

of stromal elements, of structure and micro-architecture of bone and of bone remodeling; all of which are important for a detailed diagnosis and for estimation of prognostic factors. Moreover, evaluation of blood vessels and connections between myeloma cells and bone marrow stroma have acquired increasing significance in light of the latest therapeutic possibilities, for example thalidomide. In addition detailed information on the tumor cells, reactions of the bone marrow and stromal cells and bone and its cells is obtained from a bone marrow biopsy. Furthermore, quantitation of the number and activity of osteoclasts also provides criteria for early preventive therapy with bisphosphonates.

The following histologic data are clinically relevant:

- Type of plasma cells (morphologic classification and grading)
- Quantity of plasma cells (morphologic staging)
- Growth pattern (diffuse – nodular)
- Hematopoiesis (quantity and maturation/dysplasia)
- Angiogenesis (normal vessels, neo-angiogenesis, amyloidosis)
- Stromal components (fibrosis)
- Resorption of bone (osteolysis, osteoporosis)
- Mineralisation defect (increased osteoid, osteomalacia)
- Number and activity of bone cells (osteoclasts and resorption bays, osteoblastic seams)
- Deposition of iron

When the histologic *growth pattern of the myeloma* is correlated with osteoclastic bone remodeling, two groups can be distinguished:

- *Paratrabecular* and/or nodular growth patterns with high-grade osteoclastic resorption
- *Interstitial* loose infiltration without apparent increased osteoclastic resorption (Fig. 24.2a,b)

The first is associated with a distinctly less favorable prognosis, and therapy with bisphosphonates is clearly indicated. Change to an interstitial type under bisphosphonate therapy carries a more favorable prognosis with it.

Myeloma Variants

Variant forms of multiple myeloma (MM) are occasionally encountered. These can readily be distinguished if the methods described above are applied. The variants include:

- Smoldering and indolent MM
- Plasma cell leukemia
- Nonsecretory MM

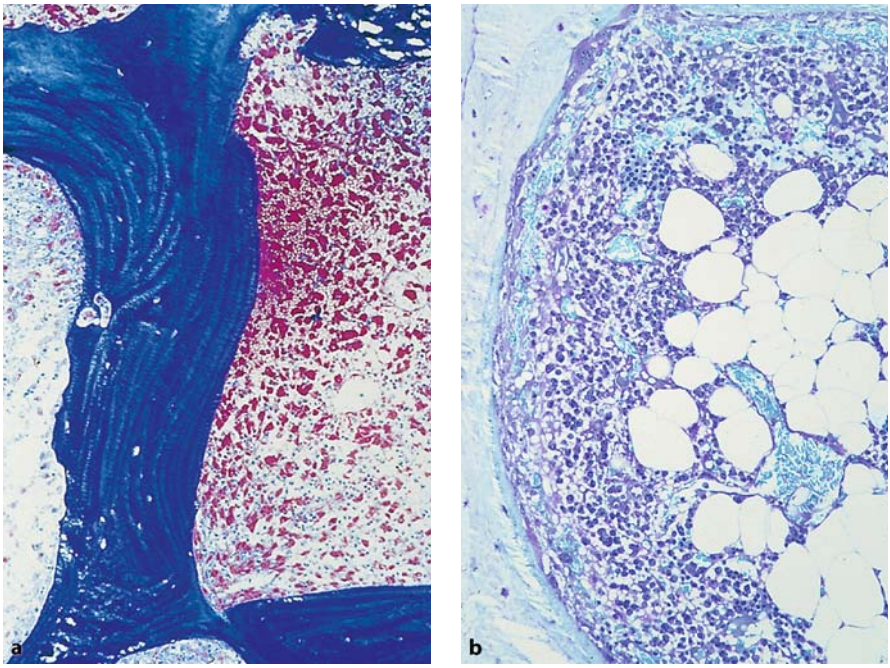


Fig. 24.2a,b Paratrabecular spread of myeloma cells, which is a sign of rapid progression of tumor growth and unfavorable prognosis. **a** Plasma cells radiating outwards from a point on the surface of the bone. **b** Wide endosteal seam of myeloma cells with osteoclastic bone resorption and with central marrow atrophy, i.e. replacement by fat cells

- Osteosclerotic MM
- Light chain amyloidosis
- POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, M protein, skin manifestations)
- Light chain deposition disease
- MGUS (monoclonal gammopathy of undetermined significance)
- Waldenström's macroglobulinemia

Treatment Strategies

Cures have only been achieved in rare cases of solitary plasmacytoma, or in younger patients treated by bone marrow transplantation. *Therefore, in the vast majority of patients the aim of therapy is to attain the longest survival with the best possible quality of life. To achieve this goal, skeletal destruction must be prevented* and this constitutes the most cogent argument for prompt administration of bisphosphonates as soon as the diagnosis is made.

The median *survival time* of a newly diagnosed patient with multiple myeloma is 30 months from the time of therapy. Nevertheless, the course of disease is very variable. For example, patients with rapidly progressive MM who do not respond to therapy may survive for only a few months. On the other hand there are patients with asymptomatic MM who have a smoldering course lasting for many years without any chemotherapy, or who survive for up to 20 years with only short periods of therapy. *Therefore it is now necessary to provide detailed information for a variety of therapeutic options which include the following questions:*

- When to treat?
- Bone marrow or stem cell transplantation?
- Which therapy protocol?
- Duration of primary chemotherapy?
- Quality of remission?
- Duration of remission?
- Early recognition of impending relapse – MRD (Minimal Residual Disease)
- Definition and methods for recognition of MRD
- Which second-line chemotherapy on relapse?
- Administration of thalidomide?
- Which supportive measures?
- How to investigate and to treat complications?
- Vertebroplasty and kyphoplasty in cases with advanced spinal disease

The possibility of high-dose chemotherapy followed by bone marrow or stem cell transplantation should be considered early on. Patients, especially those under 60 years of age, who fall into this category should not be treated with alkylating agents such as melphalan, as these substantially decrease the stem cell reserve. Therefore the VAD, VID or VCAP regimens should be chosen for first-line chemotherapy.

The timing of chemotherapy is particularly important because about 95% of patients in stage I and even about 40% in stage II are practically asymptomatic and show little progression of disease, but of course must be monitored regularly. In this large group of patients, postponing treatment until signs of progression occur does not have a negative effect on course of disease and survival. However with onset of progression in previously asymptomatic patients therapy should immediately be instituted prophylactically to forestall complications, such as osteolyses, bone pain and fractures.

Bisphosphonates

Though chemotherapy reduces the tumor mass considerably, it does little to repair osteolytic bone lesions or to prevent further loss of bone. First-generation bisphosphonates also showed little effect. On the other hand modern bisphosphonates such as clodronate or pamidronate given intravenously in placebo-con-

trolled trials were effective in the treatment of *skeletal related events* (SREs). The broad range of indications for therapy with bisphosphonates in myeloma should be taken into account when planning the management of each patient. The effect of ibandronate on osteoclastic bone remodeling and on myeloma cells is impressively demonstrated in Fig. 24.3a,b. Results of previous clinical experience as well as of clinical trials have highlighted the following *indications for bisphosphonate therapy in multiple myeloma:*

- Hypercalcemia
- Bone pain
- Osteoporosis
- Osteolyses
- After radiotherapy for osteolyses

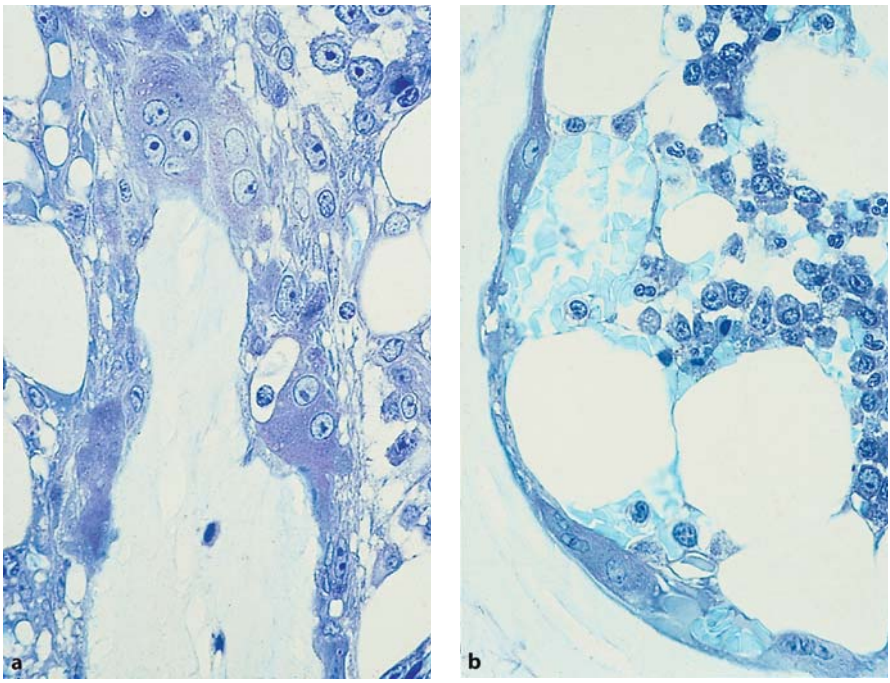


Fig. 24.3a,b Effect of bisphosphonates on destruction of bone and on proliferation of myeloma cells. **a** Massive osteoclastic bone resorption with polymorphic, nucleolated myeloma cells in the vicinity. **b** The same patient after i.v. ibandronate. Demonstration of unequivocal decrease in bone resorption with flat, inactive osteoclasts, absence of resorption lacunae, and mainly unremarkable plasma cells in the surrounding tissues

The *protocols used for therapy of skeletal related events (SRE) are given below:*

► *Pamidronate (Aredia®)*	60–120 mg infusion every 3 to 4 weeks
► *Clodronate (Ostac®, Bonefos®)*	600–900 mg infusion every 3 to 4 weeks
► *Ibandronate (Bondronat®)*	6 mg infusion (15 min) every 3 to 4 weeks or 50 mg orally daily
► *Zoledronate (Zometa®)*	4 mg infusion (15 min) every 3 to 4 weeks

These are practical guidelines only, and must be regarded as such. A comparative study has been carried out with pamidronate and zoledronate: a five-minute infusion of 4 mg zoledronate was as effective as 90 mg pamidronate in prevention of SRE. *In case of dehydration and/or hypercalcemia, infusion of a bisphosphonate should be carried out after rehydration and slowly to avoid renal damage, which is almost the rule in myeloma. Therefore it is best always to choose bisphosphonates with the longest half–life in the serum to minimise the possible renal damage.*

The significance of bisphosphonate therapy in multiple myeloma lies in *prevention* of skeletal complications. Institution of bisphosphonate therapy at the time of diagnosis will lead to significant abrogation or at least to a clearly delayed appearance of skeletal complications, such as osteolysis, osteoporosis, fractures, hypercalcemia and bone pain.

Furthermore, it has been demonstrated conclusively that the *aminobisphosphonates exert an antiproliferative effect on tumor cells: that is they inhibit growth of myeloma cells both directly and indirectly as described below.* Therapy with zoledronate or ibandronate triggered a number of activities which were even enhanced when dexamethasone or chemotherapy with paclitaxel was added:

- Increased apoptosis of myeloma cells
- Reduction of osteoclastic and stromal cell production of IL-6
- Anti-angiogenic effect on blood vessels and stromal cells (changes similar to those seen after therapy with thalidomide)
- Cytotoxic effect on myeloma cells through activation of T lymphocytes
- Interference with cellular interaction
- Inhibition of matrix metalloproteinase-1 secretion (stimulated by IL-1)

After 1 year of bisphosphonate therapy only (no other medication given) the following antiproliferative actions were demonstrated:

- Reduction of M protein by up to 20%
- Reduction of myeloma cell mass by up to 20%
- Switch to a prognostically more favorable growth pattern
- Reduction in rate of proliferation of myeloma cells (Ki67 and PCLI)

- Prolongation of survival, which should be confirmed by prospective studies

Taking into consideration the preventive and antiproliferative activities of the bisphosphonates, the conclusion must be drawn that *all patients with multiple myeloma should be given bisphosphonates once the diagnosis has been established.* However, the patient's mouth and jaws must be examined monthly and surgical intervention in the mouth and jaws should be avoided during therapy with a potent bisposphonate. New guidlines recommend to treat with bisposphonates not longer than 2 years.

It remains an open question as to whether bisphosphonate administration in patients with monoclonal gammopathy of undetermined significance (*MGUS*) can delay or prevent transition to overt MM.

The *anti-proliferative effect of bisphosphonates* on neoplastic cells has been confirmed in various other conditions. To give one example: remission of acute panmyelosis with fibrosis was achieved in a patient treated exclusively with zoledronate – 4 months after initial therapy the leukemic infiltration had disappeared.

CHAPTER 25 Bone Metastases

Introduction

Metastasis is a fundamental problem in clinical oncology. Once established in the skeleton or elsewhere, the malignancy is systemic and can no longer be cured by surgery alone. This is the reason that tumors are regarded as systemic from the moment osseous or other metastases are detected. Some even consider all malignant tumors as systemic from the moment they are established and certainly as soon as they have attained a clinically detectable size.

Skeletal metastases can remain dormant and symptomless for many years. But when they begin to spread, metastases cause a drastic reduction of the patient's quality of life due to complications such as pain, immobility, fractures, spinal cord compression, hypercalcemia and hematopoietic insufficiency. The situation is made even worse by the fear, depression and hopelessness which inevitably accompany the physical condition. Prevention of metastatic spread is as yet unattainable simply because it has already occurred in many patients before the tumor itself is diagnosed. Studies have shown that over 10% of patients with breast cancer have metastases which have been dormant for over 10 years. Cases of recurrence of metastatic spread after more than 20 or more years have also been reported. What intrinsic and/or extrinsic factors enable malignant cells to survive in a state of "hibernation" or dormancy, and what events/circumstances trigger their subsequent awakening and renewed growth are as yet completely unknown.

Frequency

The lungs, liver and bone marrow act as filters for disseminated circulating malignant cells and are the most frequent sites for hematogenic spread. And of these, the bone/bone marrow environment offers ideal conditions for establishment of metastases. However, the frequency of metastatic involvement of the skeleton at autopsy varies from 25% to 85% probably due to differences in the method and thoroughness of search (Table 25.1). Skeletal metastases are found at autopsy in 70–85% of patients with tumors of the breast, prostate and lung, but fewer than half of these

had been recognised clinically during the patients' lifetime. The overall impression from previous studies is that up to 90% of all patients who die of malignant tumors had skeletal metastases. Certain tumors exhibit *osteotropism*, that is, a par-

Table 25.1 Incidence of bone metastases in autopsy studies

Primary Tumor Site	Incidence (%)	Range (%)
Breast	73	47–85
Prostate	68	33–85
Bronchus	45	33–60
Thyroid	42	28–60
Kidney	35	33–40
Gastrointestinal tract	8	5–13

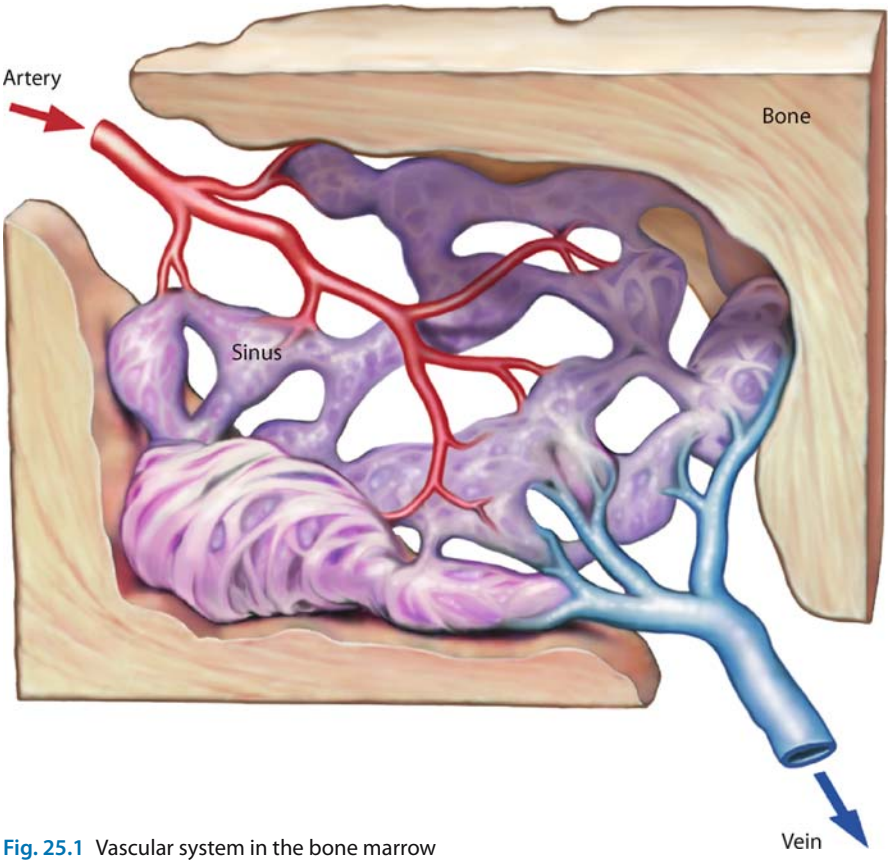


Fig. 25.1 Vascular system in the bone marrow

ticular affinity to metastasise to the bones. These include tumors of the breast, prostate, lung, kidney and thyroid, and they are responsible for over 80% of all metastases in bone.

Regional Distribution within the Skeleton

Metastases "home" to bones which house red hematopoietic marrow. Several factors are responsible for this proclivity: the extensive vascular system (Fig. 25.1), the thin vascular walls, often without a basal membrane, and the slow blood flow through the sinusoids. These are ideal conditions for intra-vascular tumor cells to migrate into the surrounding tissues and to implant, i.e. establish themselves (*seed and soil hypothesis*).

The retrograde venous plexus of the spine (*Batson's plexus*) also contributes to metastatic spread in the vertebrae and pelvis. First described in 1827 by G. Breschet, this valveless extensive plexus anastomoses with epidural, thoracic and abdominal veins (Fig. 25.2). Malignant metastatic cells are frequently found in the endosteal sinuses in iliac crest biopsies from patients with mammary or with prostatic carcinomas and from here they invade the surrounding stroma. It is also thought that the vertebral venous plexuses and the sinusoids in the bone marrow present tumor cells with ideal conditions for prolonged "hibernation/dormancy" until the opportunity for growth arises even many years later as mentioned above.

Development of Skeletal Metastases

Tumor cells circulate in the blood stream in the early stages of development of the primary tumor. The following steps are distinguished in development of skeletal metastases: (Fig. 25.3):

- Circulating tumor cells occupy niches in the sinusoids and invade the stroma. Alternatively they die or remain dormant and unrecognised in small colonies only to become active after years or earlier in aggressive cases.
- Activated tumor cells use proteinases to penetrate the thin vessel walls and the adjoining connective tissue. They must protect themselves from immune attacks and, if they survive, they attach themselves to the interstitium of the adjacent tissues.
- The cells of the endosteal sinusoids lie on the bone, are easily penetrated by the tumor cells which gives them access to the osseous surface to which they attach themselves; and so skeletal micrometastases are initiated Fig. 25.4a.
- Once established, the tumor cells secrete cytokines which stimulate neo-angiogenesis and stroma, at which point a micrometastasic nodule is established (Fig. 25.4b) and can be detected by MRI even when only 3 mm in size.

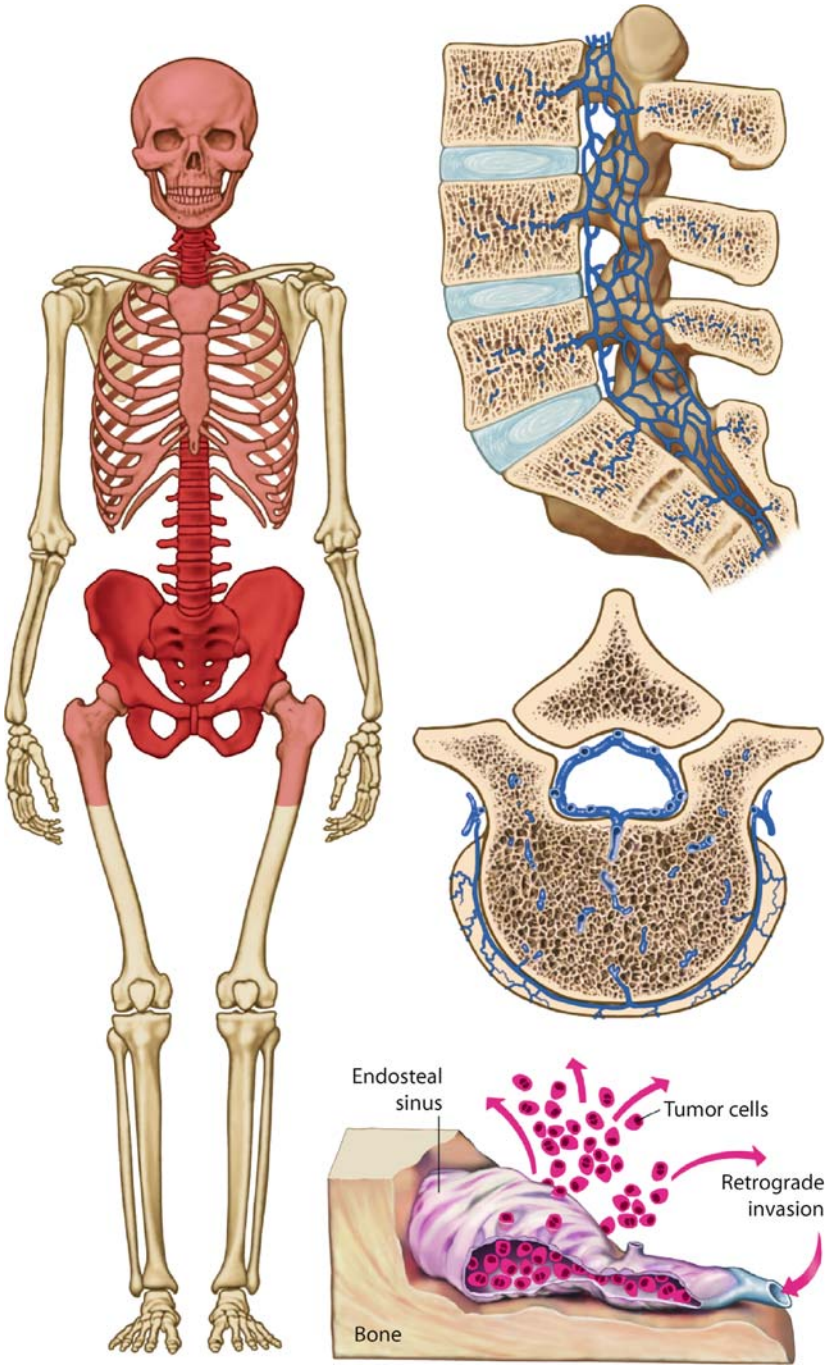

Endosteal sinus
Tumor cells
Retrograde invasion
Bone

Fig. 25.2 Retrograde spread of tumor cells via the venous complex (Batson's) in the vertebral column. This is a common route for metastases to the axial skeleton. The tumor cells invade the bone marrow by way of the endosteal sinuses, which are the terminal vessels of the venous system in the bone marrow

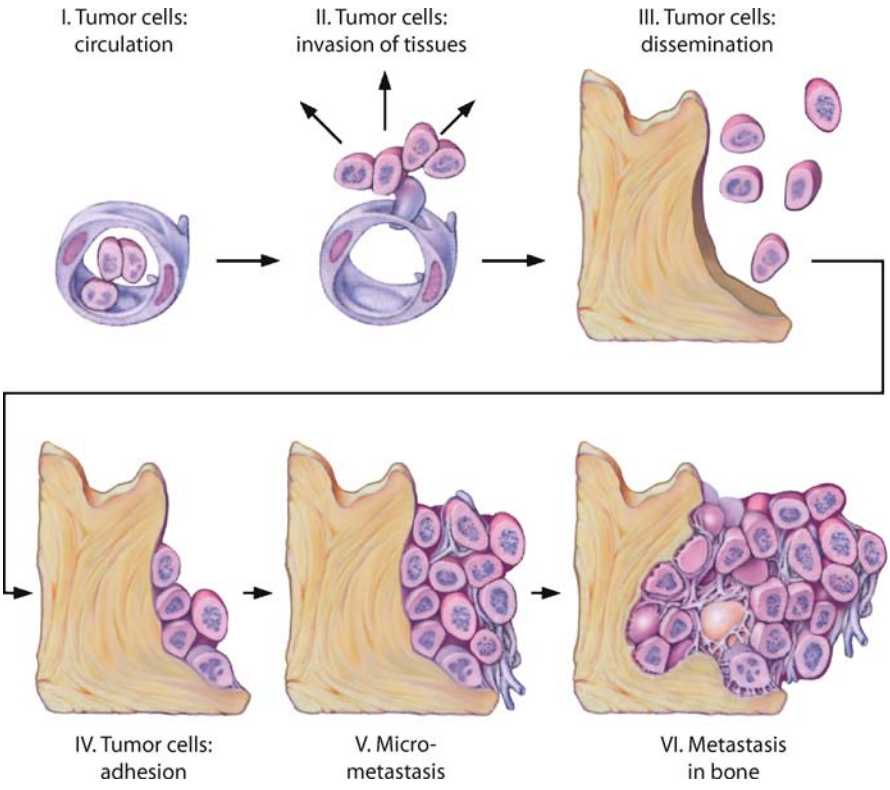


Fig. 25.3 Six stages in establishment of bone metastases

- The micrometastases then expand in the bone marrow and secrete cytokines that produce typical osteolytic/osteosclerotic lesions now demonstrable by bone scan and X-ray.

Osseous Reactions

As outlined above, an osseous reaction with markedly increased remodelling particularly resorption occurs in 93% of patients with skeletal metastases, and bone

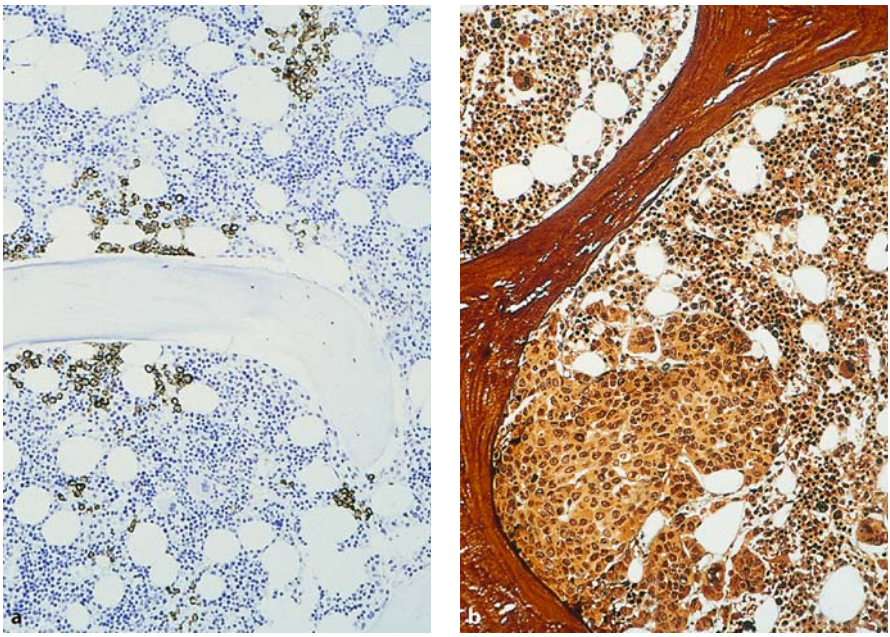


Fig. 25.4a,b Initial stages in the process of establishment of metastases in the bone marrow. **a** Dissemination of tumor cells in the marrow and incipient adhesion to the surface of the bone. **b** Development of a micrometastasis with induction of stroma

turnover markers are used for diagnosis, prognosis and as predictors of skeletal complications in many solid tumors. The type of osseous reactions to the metastases depends on the primary tumor. Usually osteoclastic resorption is accompanied by osteoblastic formation. Metastases of breast cancer exhibit this reaction, while the metastases of prostatic carcinomas evoke an almost exclusively osteoblastic reaction. *Five different histologic patterns can be distinguished in bone biopsies, their frequency depends on the primary tumor (Table 25.2).*

Table 25.2 Bone reactions in various primary tumors (% of the cases with metastatic bone disease)

	Breast	Prostate	Bronchus
Normal	5	0	28
Porosis/Osteolysis	20	7	18
Mixed form	41	38	27
Trabecular sclerosis	22	0	26
Woven bone	12	55	0

Two mechanisms are involved in the development of neoplastic osteolytic lesions:

- The most frequent is osteoclastic resorption stimulated by cytokines produced by the neighboring tumor cells. When the tumor cells are diffusely scattered in the bone marrow, the result may be a generalised osteoporosis.
- Occasionally, but only when the metastases are particularly aggressive, there is a direct expansive destruction of bone by lytic enzymes secreted by the tumor cells themselves.

Bisphosphonates

Targets for their Actions

The main steps in the establishment of bone metastases are all vulnerable to the effects of bisphosphonates:

- Adhesion
- Invasion
- Induction of stroma
- Growth: multiplication of metastatic cells
- Skeletal destruction

All these steps are inhibited by bisphosphonates which can therefore obstruct the establishment of metastases at many points in the process (Fig. 25.5):

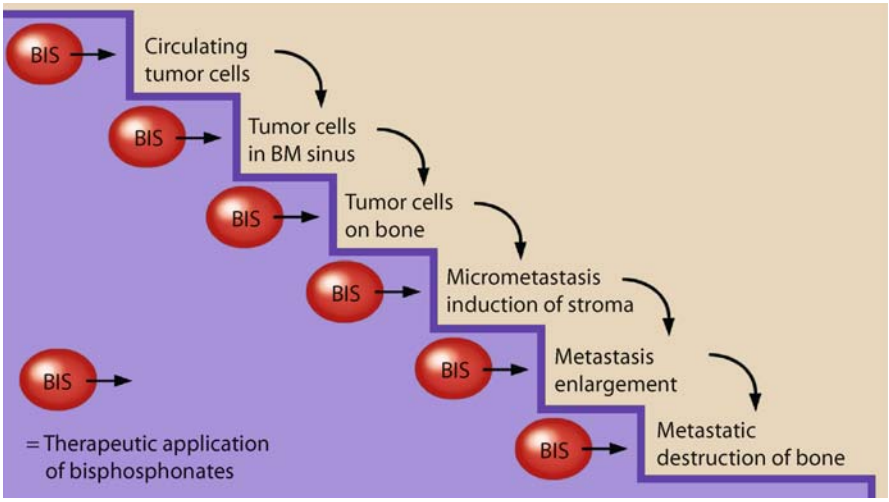


Fig. 25.5 Cascade of react*ions* in the development of skeletal metastases and the inhibitory effect of bisphosphonates (*BIS*), *BM* = bone marrow

- *Blockage of adhesion molecules*: Incubation of mammary and prostatic tumor cells with bisphosphonates in the incubation medium prevents their adhesion to mineralised and non-mineralised matrices as well as their passage through vessel walls and extracellular matrix. Even low doses of ibandronate and zoledronate produced these effects, which can be further increased by addition of taxoids. The inhibition of tumor cell adhesion was probably brought about by modulation of adhesion molecules such as cadherin, laminin and integrins. This may be one of the mechanisms by which bisphosphonates inhibit tumor cell invasion of the extra-cellular matrix.
- *Inhibition of proteinases*: Bisphosphonates inhibit the secretion and activation of numerous matrix metalloproteinases such as MMP2 and MMP9, thereby also inhibiting tumor cell mobility and vascular permeability. This inhibition can be abolished by adding zinc 50 μM to the medium.
- *Inhibition of growth factors*: There are many growth factors in bone (TGFβ, BMPs, FGFs, PDGFs, and IGFs) which are released during osteoclastic resorption and stimulate the proliferation of tumor cells. Moreover, tumor cells themselves produce PTHrP, which in turn stimulates osteoclasts, thus closing the vicious circle, in particular the interactions between PTHrP and TGFβ.
- *Inhibition of prostaglandins*: Bisphosphonates also inhibit secretion of prostaglandins and cytokines by osteoblasts, bone marrow stromal cells, monocytes and macrophages.
- *Inhibition of neo-angiogenesis*: Induction of blood vessels is essential for development and survival of metastases. In vitro, ibandronate and zoledronate inhibit proliferation of human endothelial cells obtained from umbilical cord veins (anti-angiogenesis). Therefore, inhibition of blood vessels in and around metastases in vivo is likely, and this is similar to the action of thalidomide, which is now used in patients with refractory myeloma and with myelodysplastic syndromes.

In summary, metastatic cancer cells possess the capacity to modulate the bone and bone marrow microenvironment by inter-actions with the marrow and the bone cells. Bisphosphonates can effectively and specifically disrupt this cycle and thereby inhibit bone metastases.

Anti-proliferative Effect

Bisphosphonates are able to induce apoptosis of both tumor cells and osteoclasts by activating caspase-3 and caspase-3 like proteases. Moreover, the aminobisphosphonates also stimulate Bcl 2, as well as preventing activation of RAS whereby intra-cellular signalling is interrupted and apoptosis is triggered. Clearly there is a highly complicated interplay between bisphosphonates, osteoclasts, various elements of the bone marrow and the tumor cells themselves. *Bisphosphonates also induce a significant decrease in telomerase expression in tumor cells, which in turn inhibits their multiplication.*

Moreover, there appears to be a relationship between skeletal retention, rate of resorption, degree of bone turnover and timing of therapy with bisphosphonates in patients with breast cancer. This is important with respect to metastases in bone, as well as, needless to say, in many other conditions.

In summary, there is no longer any doubt about the inhibitory effect of bisphosphonates on skeletal metastases. Whether or not bisphosphonates are able to inhibit primary tumors and visceral metastases currently being tested in large-scale clinical trials.

Figure 25.6 summarises the actions of the bisphosphonates on the various cascades of metastatic development. According to the data presently available there

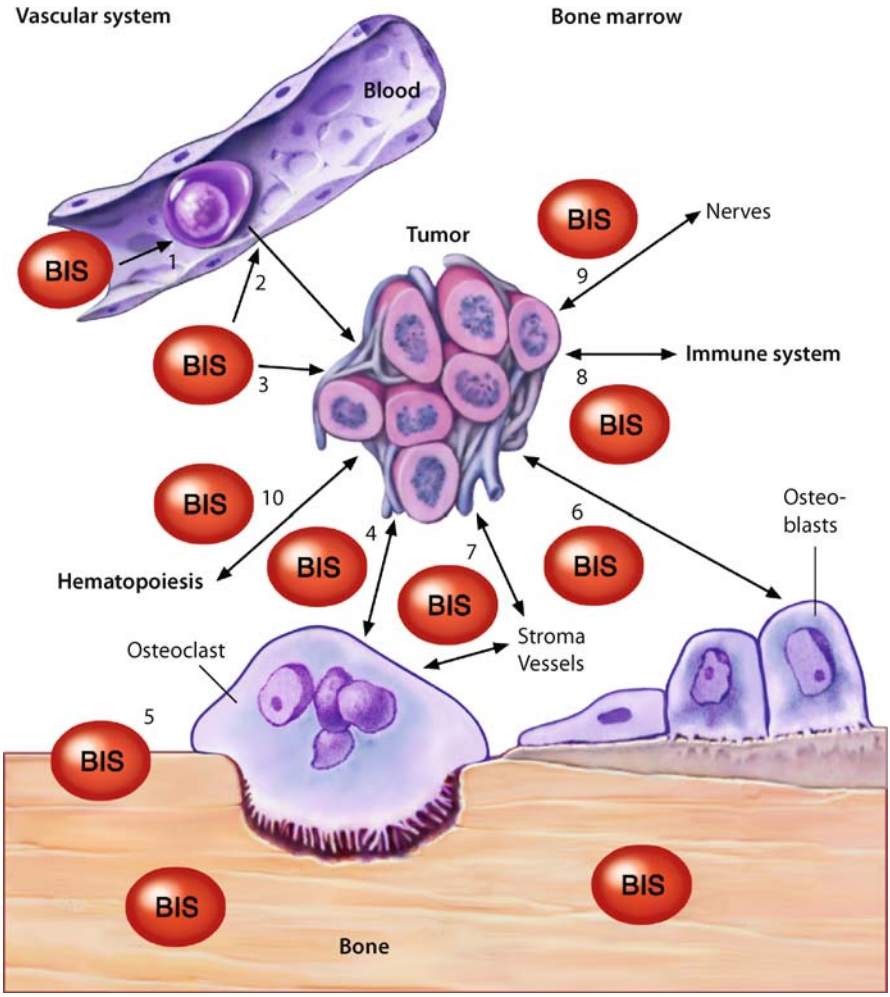


Fig. 25.6 Ten actions of bisphosphonates *(BIS)* on metastases in bone

are no fundamental differences in the qualitative effects of various bisphosphonates on tumor-induced osteopathy. But there are quantitative differences; and currently the most potent bisphosphonates used in oncology are ibandronate and zoledronate, as already demonstrated in clinical trials (Rosen 2002). Moreover, the renal safety of ibandronate both i.v. and oral has already been demonstrated.

CHAPTER 26 Skeletal Metastases of Breast Cancer

Frequency

Mammary carcinoma is the most frequent malignant tumor in women. It effects one out of ten women, is fatal in 30% of cases, and over 75% of patients will have osseous metastases with progression of the disease. *The average survival after the appearance of osseous metastases is approximately 2 to 3 years.* The prognosis is much worse (only a few months) when visceral metastases have occurred.

Circulating Tumor Cells

Cytologic examination of blood and bone marrow has shown that almost every woman with breast cancer has circulating tumor cells even before surgery. Consequently the apparently localised cancer at diagnosis must be considered a systemic disorder with potential for metastatic development at any time. Moreover, immunohistological studies of sections of iliac crest biopsies have confirmed an even higher frequency of bone marrow involvement by tumor cells and tumor cell emboli. This strongly confirms the assumption that every aggressive breast cancer (histologic grades G3 and G4), if not all cancers of the breast, have already spread by the time the diagnosis is established.

Complications

Destruction of bone and replacement of hematopoietic tissue by the tumor or by the cytotoxic effects of chemotherapy or both, lead to the following complications:

- Bone pain 60–80%
- Osteoporosis 40–50%
- Pathologic fractures 10–30%
- Hypercalcemia 10–30%
- Bone marrow failure 20%
- Spinal cord compression 10%

Treatment Strategies

Before beginning therapy for breast cancer, certain goals are set:

- Prevention of development of metastasis by tumor cells already dispersed in the body. Treatment of micrometastases and prevention of skeletal destruction once bone marrow involvement has been detected, for example, by MRI, bone scan or bone biopsy. The efficacy of bisphosphonates in this setting has already been established.
- Prevention and treatment of osteoporosis: It should be noted that bone loss may be due to the patient's age, to the disease itself, and to therapy, any or all of which can cause osteoporosis resulting in pathologic fractures. Recent studies have indicated that this bone loss can be prevented by bisphosphonates, and skeletal integrity maintained.
- Treatment of pre-existing skeletal complications or those associated with radiotherapy or other procedures (palliative treatment). Administration of bisphosphonates after radiotherapy can accelerate the re-calcification of osteolytic lesions after radiation.
- Prophylaxis with bisphosphonates is becoming even more significant, also in view of the minimal side effects of these drugs.

The following *treatment options* are available:

- Chemotherapy (various protocols)
- Radiotherapy (local osteolyses)
- Surgical intervention
- Hormone therapy (tamoxifen now largely replaced by inhibitors of aromatase)
- Bone marrow transplantation (usually in clinical trials)
- Antibodies against HER2 (in HER2 positive tumors)
- Bisphosphonates (adjuvant and palliative)

Bisphosphonates for Prevention of Metastasis

Bisphosphonates form an integral part of the management of breast cancer. Clinical studies of patients treated with clodronate over a 3-year period have shown a 50% reduction in skeletal metastases. The survival time of patients on long-term therapy with clodronate or ibandronate was significantly increased. However, these studies did not produce uniform results with respect to visceral metastases and survival. It is clear that patients who had circulating tumor cells or high levels of bone sialoprotein (BSP) benefit most from this type of adjuvant therapy. BSPs are produced by osteoclasts and tumor cells and play an important part in cell-matrix interactions in bone, e.g. adhesion of osteoclasts to collagen type I. The following bisphosphonate protocols were used in the studies described above:

► *Clodronate (Ostac®, Bonefos®)*	1600 mg orally daily
► *Ibandronate (Bondronat®)*	2–6 mg infusion (15 min) monthly

Studies have not yet demonstrated whether daily oral or intermittent parenteral therapy is more effective. Similarly, optimal doses and the possible advantages of a combination of bisphosphonates (e.g., clodronate orally and an aminobisphosphonate intravenously) still require clarification.

Micrometastases: groups of tumor cells with their own stroma. Today, these can be detected by means of MRI, bone biopsies and presence of tumor markers. Tumor cells in bone biopsies should be checked for estrogen and progesterone receptors HER 2 (human epidermal growth factor receptor 2) in addition to routine immuno-histochemistry. *There are now 2 specific options available for therapy of micrometastases:*

- Antibodies against HER 2 (Herceptin®, Trastuzumab). Over-expression of HER 2 in tumor cells in the bone biopsy has a 3-fold significance: as a prognostic factor, as an indicator of the reaction to anthracycline, taxane and tamoxifen, and as an indication for therapy with trastuzumab.
- Bisphosphonates. In this setting both their anti-proliferative and osteoprotective effects are utilised. Osteoclastic resorption is inhibited and micro-metastatic spread is prevented, Moreover, results of large clinical trials designed to elucidate the short and long term effects of bisphosphonate therapy in patients with mammary cancer, with and without demonstrable metastases, are now beginning to appear in the literature. *The reduction in incidence of skeletal metastases and improvement of survival have now been documented.*

The following *bisphosphonates* are currently recommended for use in oncological centers:

- Clodronate (Ostac®) 1600 mg orally daily
- Pamidronate (Aredia®) 90 mg i.v. monthly
- Ibandronate (Bondronat®) 6 mg i.v. monthly
- Zoledronate (Zometa®) 4 mg monthly/3monthly

In the meantime *other inhibitors of osseous resorption and of tumor cell growth* are also being investigated:

- osteoprotegerin
- RANK-fc
- Antagonists of endothelin-A-receptor
- Antibodies to PTHrP
- Vitamin D analogs

Bisphosphonates for Prevention of Skeletal Complications

Micrometastases – as well as larger established metastases – are demonstrable by MRI, tumor markers in blood and by bone biopsy. At this point, these metastases have not evoked any osseous reactions demonstrable by bone scan or X-ray, and administration of bisphosphonates can prevent their establishment and development on and in the bones.

Two additional therapeutic options are available:

- *Herceptin®* (trastuzumab), a specific antibody against HER2: Overexpression of HER 2 is demonstrable even in micrometastases in the bone marrow. This is significant for three reasons: for prognosis, for predicting response to tetracycline, taxane, tamoxifen and aromatase inhibitors, and as an indication for Herceptin® therapy.
- *Bisphosphonates*: *in this context bisphosphonates are utilised for their antiproliferative and osteoprotective effects* (Fig. 9.10). As outlined previously, inhibition of osteoclasts prevents the release of growth factors from bone, directly as well as through the action of cytokines. In addition, tumor cell adhesion to bone is prevented by inhibition of metalloproteinases secreted by tumor cells themselves. Bisphosphonates have not yet been authorised specifically for prevention of skeletal metastases, and therefore informed consent must be obtained. The following *protocols* are recommended for use in oncology:

► *Clodronate (Ostac®, Bonefos®)*	1600 mg orally daily
► *Pamidronate (Aredia®)*	90 mg infusion monthly
► *Ibandronate (Bondronat®)*	2–6 mg infusion monthly

Bisphosphonates for Treatment of Skeletal Complications

Bisphosphonates have strong antiresorptive effects and also some degree of osteoreparative (recalcification) effect. *They can prevent unwanted bone loss following radiotherapy*. Administration of bisphosphonates leads to increased formation of callus which accelerates healing of bone defects. 1000 IU vitamin D daily (after exclusion of hypercalcemia!) promotes mineralisation of the newly formed bone. However, since complete restoration of normal bone structure in large osteolytic lesions can take years, it is all the more important to prevent them. *Previous studies have shown that bisphosphonates can prevent skeletal related events (SREs): new osteolytic lesions, pathologic fractures, hypercalcemia, spinal cord compression, bone pain and thereby reduce the need for surgery and radiotherapy. Clinical studies on*

the renal safety and on the efficacy of bisphosphonates in patients treated for over 10 years have now been published.

A modest increase in survival of premenopausal patients was also observed. Administration of a bisphosphonate such as clodronate together with irradiation of an osteolytic lesion is thought to have an additive effect. The presence of visceral metastases, though probably predictive of a shorter survival, is no justification for not giving bisphosphonates. *In addition, numerous articles from many countries have now confirmed the efficacy of bisphosphonates for skeletal protection in patients with breast cancer.*

Treatment of skeletal complications is best achieved by *monthly intravenous or daily oral administration of bisphosphonate*s:

► *Pamidronate (Aredia®)*	90 mg infusion monthly
► *Ibandronate (Bondronat®)*	6 mg infusion (15 min) monthly
► *Ibandronate (Bondronat®)*	50 mg orally daily
► *Zoledronate (Zometa®)*	4 mg infusion (15 min) monthly

These protocols automatically include both treatment and prevention of osteoporosis; note that both oral and i.v. administration are now available. *The optimal duration of bisphosphonate therapy in this clinical setting has not yet been established.* A diet rich in calcium and a vitamin D supplement should also be prescribed after exclusion of hypercalcemia.

CHAPTER 27 Other Carcinomas with Osteotropic Metastases

Prostatic Carcinoma

10–20% of the patients with prostatic cancer have bone metastases at time of diagnosis. Whereas osteolytic lesions predominate in multiple myeloma and breast cancer, *metastases of prostatic cancer are characterised by their osteoblastic reactions (Fig. 27.1a,b) evoked by a number of mediators:*

- Transforming growth factor β2 (TGFβ2)
- Fibroblast growth factors (FGFs)

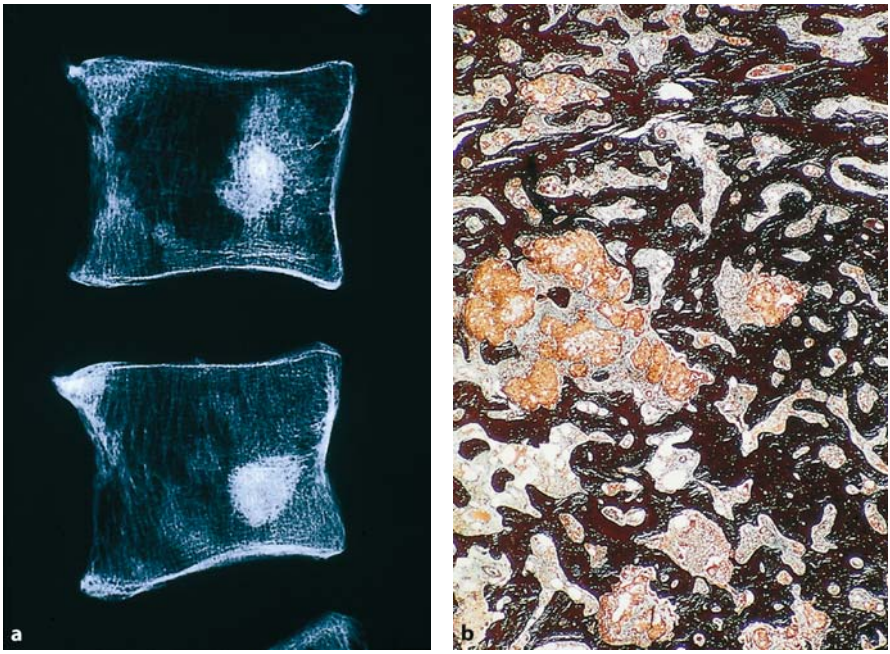


Fig. 27.1a,b Osteosclerotic metastases in a patient with prostatic carcinoma. **a** Within a vertebral body in the lumbar spine. **b** Small metastatic foci are walled in by an osteosclerotic reaction in a patient with prostatic carcinoma (section of iliac crest bone biopsy)

- Plasminogen activator sequence
- Bone morphogenic proteins (BMPs)
- Parathyroid hormone-related peptide (PTHrP)
- Prostate-specific antigen (PSA)
- Endothelin-1

In spite of the preponderance of bone formation, *bisphosphonates are also indicated both as a preventive and a palliative measure* due to the significant role played by the osteoclasts because of the "coupling" of processes involved in bone remodelling even in these metastases. Moreover, after therapy with bisphosphonates, a rapid and prolonged alleviation of pain, together with a reduction in requirements of analgesics, has been reported by patients with prostatic skeletal metastases. The improvement in the pain score also coincides with a decrease in resorption products in blood and urine. *The considerable risk of osteoporosis due to therapeutic hypogonadism constitutes another justification for the early initiation of bisphosphonate therapy.* Encouraging results have already been obtained with high doses of parenteral clodronate, alendronate, pamidronate and ibandronate. Bisphosphonate treatment of painful osseous metastases due to hormone refractory prostate cancer resulted in a significant decrease of pain and a corresponding significant reduction in the daily consumption of analgetics in 75% of patients (Table 27.1). Each parameter correlated with an increase in the Karnofsky index, mainly due to better mobility. Therefore, bisphosphonates have

Table 27.1 Bisphosphonate treatment of symptomatic hormone-refractory prostate cancer

Author (Year of the Study)	Number of Patients	Bisphosphonate used	Response %
Clarke (1992)	42	Pamidronate	44
Lipton (1994)	58	Pamidronate	60
Purohit (1994)	34	Pamidronate	60
Cresswell (1995)	27	Clodronate	37
Vorreuther (1992)	41	Clodronate	71
Heidenreich (2001)	85	Clodronate	75
Heidenreich (2002)	25	Ibandronate	88
Rodrigues (2003)	52	Clodronate	89
Fulfaro (2003)	20	Zoledronate	77
Saad (2004)	643	Zoledronate	Sign. less SRE

SRE= skeletal related events

a definite role in the palliative management of symptomatic hormone refractory prostate cancer. *It has already been established that therapy with bisphosphonates decreases the risk of skeletal complications in men with androgen independent prostate cancer and bone metastases*. Moreover, preliminary trials of chemotherapy (taxane) together with a bisphosphonate (zoledronate) have shown good results.

Consensus Guidelines have recently been published for introduction of bisphosphonates into the management of metastasizing cancers. Studies on the benefits of zoledronate in prevention of skeletal complications have already been published. In addition, studies aimed at prevention of skeletal metastases are currently under way with ibandronate.

Bronchial Carcinoma, Lung Cancer

Bone marrow biopsies demonstrated that at least 15% of patients with adenocarcinoma of the lungs already have bone marrow metastases at the time of diagnosis. Autopsy studies have shown an incidence of 35%. These metastases evoke variable osseous reactions. Relatively few studies on the effects of bisphosphonates have been carried out, possibly because of the short survival times – a matter of months – of patients with bronchial cancer once metastases are established. However, the *studies that have been published have shown a positive effect of bisphosphonates on reduction of SREs as well as delay in time to occurrence of the first SREs*. Moreover, in these patients, a prolongation of even a few months to occurrence of the first SRE is significant, and bisphosphonates reduce skeletal morbidity regardless of SRE history. The rapid analgesic effect of bisphosphonates (within 2 days) was also observed in these patients. Recent studies have emphasised the need for early identification of patients at risk, and the beneficial role of the latest bisphosphonates in the management of patients with advanced metastatic bone disease. *It is also of interest that bisphosphonates induced apoptosis in cells derived from adenocarcinomas of the lungs in experimental and in "in vitro" investigations. This has promising implications for future therapy*.

Renal Cell Carcinoma

Since the cells of these tumors have retrograde access to the vertebral venous plexus, bone marrow metastases are relatively frequent (25% of cases). Tumor-induced hypercalcemia was observed in 3–17% of the patients with renal cell carcinoma. However, large clinical studies have not yet been carried out, though a positive effect of bisphosphonates would be expected here also. In the event of bone pain, hypercalcemia or osteolysis, intravenous administration of aminobisphosphonates is indicated. *Experimental data have demonstrated that bisphosphonates*

also prevent metastasis of renal carcinoma. However adequate clinical studies are difficult to perform because of the low number of patients with renal carcinoma.

When complications of skeletal metastases occur in patients with carcinomas and sarcomas (bone pain, hypercalcemia, osteolyses, etc.), the following regimens are recommended:

► *Clodronate (Ostac®, Bonefos®)*	1600–3200 mg orally daily
► *Pamidronate (Aredia®)*	90–120 mg infusion monthly
► *Ibandronate (Bondronat®)*	6 mg infusion (15 min) monthly
► *Ibandronate (Bondronat®)*	50 mg orally daily
► *Zoledronate (Zometa®)*	4 mg infusion (15 min) monthly

The biological effect of Bondronat® 50 mg orally daily has been shown to correspond to that of Bondronat® 6 mg given i.v. monthly.

Finally a word of caution – the possibility of bisphosphonate-induced *necrosis of the jaws* must not be forgotten when giving potent bisphosphonates especially i.v.. The patient must be fully informed, consultation with the dentist is strongly recommended, and a consent form must be signed before therapy is started, particularly if used for indications not yet completely authorised. Therefore it is advisable to check whether administration of bisphosphonates for prevention of metastases in patients with the tumors mentioned above has already been authorised, as, for example zoledronate for treatment of patients with bone metastases in the USA. *The efficacy of bisphosphonates for prevention of skeletal metastases is now being investigated in many clinical trials and results are awaited.*

Other Malignancies with Implications for Skeletal Involvement

Neuroblastoma

The bones are the second most common site of metastases in neuroblastoma. As in breast cancer and in multiple myeloma the tumor cells themselves activate osteoclasts to resorb bone and thereby cause lytic lesions. Inhibition of osteoclast activation by bisphosphonates has already been demonstrated in preclinical trials and results of clinical studies are awaited.

Ewing's Sarcoma

Experimental studies have shown that zoledronate induced apoptosis and inhibited proliferation in human Ewing sarcoma cells. Clinical studies are awaited.

Giant Cell Tumor of Bone

This is an aggressive primary neoplasm of bone. Osteolytic lesions are produced by osteoclast-like giant cells stimulated by the neoplastic stromal cells which constitute the main neoplastic component of this malignancy. *Bisphosphonates inhibit the osteoclastic activity and also induce apoptosis of osteoclasts.*

Endometrial Carcinoma

Example of a cancer which usually does not metastasise to bone. Skeletal metastases are occasionally seen in patients who had been treated for primary tumors which usually do not metastasise to bone. For example, a patient who had been treated for endometrial cancer three years previously was given chemotherapy and i.v. bisphosphonates when an osteolytic lesion identified as metastatic was found. Three years later there was no evidence whatsoever of recurrence.

Cancers and Metastases in the Elderly

WHO Guidelines: Bisphosphonates for Quality of Life

Terminally ill patients – especially elderly patients – with skeletal metastases constitute a particular indication for treatment with i.v. bisphosphonates. The aim is to attain an immediate improvement in their quality of life by reduction of pain and by maintenance of autonomy and self-sufficiency.

CHAPTER 28 Bisphosphonates from A–Z

List of Indications

Indications for which bisphosphonates are already authorised

Osteology

- Prevention and treatment of postmenopausal osteoporosis
- Prevention and treatment of glucocorticoid-induced osteoporosis
- Prevention and treatment of osteoporosis in men
- Treatment of Paget's disease of bone
- Prevention of heterotopic ossification

Hematology and Oncology

- Hypercalcemia of malignancy
- Bone metastases
- Osteolyses in multiple myeloma

Clinical Trials have been Successfully Completed, but Bisphosphonates are not yet Officially Authorised for the Following Indications

Osteology, Orthopedic Medicine and Rheumatology

- Prevention and treatment of premenopausal osteoporosis
- Juvenile osteoporosis
- Transplantation osteoporosis
- Secondary osteoporoses
- Osteogenesis imperfecta
- Transient osteoporosis
- Bone marrow edema syndrome
- Rheumatoid arthritis
- Bone pain

- Renal osteopathy/osteodystrophy
- Complex regional pain syndrome (Morbus Sudeck)
- Vanishing bone disease (Morbus Gorham)
- Fibrous dysplasia
- SAPHO syndrome
- Aseptic loosening of prosthesis
- Periodontitis
- Hyperostosis (e.g., DISH)
- Early cases of osteonecroses
- Hypercalcemia not associated with malignancy (e.g., inoperable pHPT, sarcoidosis)

Hematology and Oncology

- Treatment of osteoblastic bone metastases (e.g. prostatic carcinoma)
- Prevention of osteolyses in patients with established bone metastases (e.g. from breast cancer)
- Adjuvant therapy for prevention of bone metastases (e.g. from breast cancer)
- Prevention of skeletal destruction in multiple myeloma
- Antiproliferative therapy in multiple myeloma
- Systemic mastocytosis
- Bone pain in osteomyelosclerosis
- Primary bone tumors and sarcomas with bone metastases

List of Indications in Medical Practice from A–Z

Cardiology	Patients on warfarin, long-term therapy
	Patients on heparin, long-term therapy
	Chronic heart failure
	Heart transplantation
Dentistry	Periodontitis (cave: necrosis of jaw bones)
Endocrinology	Hyperthyroidism
	Hyperparathyroidism
	Diabetes mellitus
	Cushing's syndrome
	Addison's disease
	Acromegaly
	Hypogonadism
	Klinefelter's syndrome

Gastroenterology	Primary biliary cirrhosis
	Chronic hepatitis
	Hepatic cirrhosis
	Gastrointestinal operations
	Crohn's disease
	Chronic pancreatitis
	Malabsorption syndromes
	Liver transplantation
Geriatrics	Immobilisation
	Involutional osteoporosis
Gynecology	Estrogen deficiency
	Postmenopausal osteoporosis
	Metastatic breast cancer
	Postpartum, after lactation
	Hysterectomy
	Bilateral ovariectomy
Hematology	Multiple myeloma
	Malignant lymphoma
	Osteomyelosclerosis
	Hemolytic anemias
	Aplastic anemia
	Systemic mastocytosis
	Eosinophilic granuloma
	Histiocytoses
	Bone pain
	Myelogenous osteopathies
	Bone marrow transplantation
Infectiology	Tuberculosis
	Leprosy
	AIDS
	Malaria
	Chagas' disease
	Leishmaniasis
	Toxoplasmosis
Metabolism	Hemochromatosis

	Oxalosis
	Hypercalcemia
	Storage diseases
Nephrology	Renal osteopathies/osteodystrophies
	Chronic hemodialysis
	Renal transplantation
	Metastatic renal cell carcinoma
	Hereditary hyperphosphatasia
Neurology	Antiepileptic drug use
	Peripheral paresis
	Systemic myopathies, e.g. multiple sclerosis
	Diabetic neuropathy
Oncology	Bone metastases
	Prevention of metastasis
	Bone pain
	Hypercalcemia of malignancy
	Chemotherapy-induced osteopathy
	Bone marrow transplantation
Osteology/	Osteoporosis syndrome
Orthopedics	Paget's disease of bone
	Gorham's disease
	Fibrous dysplasia
	Aseptic loosening of prosthesis
	Complex regional pain syndrome
	Early stage of osteonecrosis
	DISH (disseminated idiopathic skeletal hyperostosis)
	Transient osteoporosis (bone marrow edema syndrome)
	Fatigue fractures
	Giant cell tumor of bone
	Immobilisation
	Osteoarthritis
	Osteochondritis
	Ankylosing spondylitis
	Heterotopic calcification

	Fibrodysplasia ossificans progressiva
Pediatric Medicine	Idiopathic juvenile osteoporosis
	Osteoporosis of children
	Immobilisation osteoporosis
	Osteogenesis imperfecta
	Storage diseases
	Inherited collagen disorders
	Hypercalcemia of children
Physical medicine	Osteoporosis
	Immobilisation
	Arthrosis
Psychiatry	Anorexia nervosa
	Depression
	Antidepressant drug use
Pulmonology	Bronchial asthma (requiring cortisone)
	Cystic fibrosis
	Chronic obstructive pulmonary disorders
	Sarcoidosis
	Tuberculosis
	Metastatic lung cancer
	Lung transplantation
Rheumatology	Primary chronic polyarthritis
	Ankylosing spondylitis
	Systemic lupus erythematosus
	Connective tissue diseases
	Immobilisation
	Long-term glucocorticoid therapy
	SAPHO syndrome
Space medicine	Weightlessness-induced osteoporosis
Sports medicine	Long-distance running and walking
	Fatigue fractures
Radiation therapy	Post-irradiation osteolysis
Surgical traumatology	Immobilisation – whole body and regional
	Total endoprosthesis

Toxicology	Nicotine
	Alcohol
	Heavy metals
	Aluminum
	Lithium
	Hydrocarbon poisoning
	Barbiturates
Urology	Metastatic prostatic carcinoma
	Metastatic renal carcinoma

List of Subgroups of Bisphosphonates

Bisphosphonates without Nitrogen

Etidronate
Clodronate
Tiludronate

Aminobisphosphonates

Pamidronate
Alendronate
Neridronate

Bisphosphonates with Nitrogen Substitution

Olpadronate
Ibandronate

Bisphosphonates with Basic Heterocycles

Risedronate
Zoledronate

List According to Different Modes of Action

Incorporation as ATP-analogues (in ATP containing Compounds): "First-generation" Bisphosphonates

Etidronate

Clodronate

Tiludronate

Inhibition of the Mevalonate Pathway and Inhibition of Protein Prenylation: "Second-generation" Bisphosphonates: Inhibition of Dimethylallyl-PP

Alendronate

Pamidronate

"Third generation" Bisphosphonates: Inhibition of Dimethylally-PP and Geranyl-PP

Risedronate

Zoledronate

Ibandronate

List of Commercial Bisphosphonate Preparations from A to Z

Trade name	Bisphosphonate	Application	Company
Aclasta®	Zoledronate	I.V.	Novartis
Actonel®	Risedronate	Oral	Procter & Gamble, Sanofi-Aventis
Actonel® 35 mg plus calcium	Risedronate/ calcium	Oral	Procter & Gamble Sanofi-Aventis
Aredia®	Pamidronate	Oral	Novartis
Bondronat®	Ibandronate	Oral and I.V.	Roche
Bonefos®	Clodronate	Oral and I.V.	Medac/Schering
Bon(v)iva®	Ibandronate	Oral and I.V.	Roche/GlaxoSmithKline
Didronel®	Etidronate	Oral	Procter & Gamble

Trade name	Bisphosphonate	Application	Company
Didronel-Kit®	Etidronate/calcium	Oral	Procter & Gamble, Aventis
Diphos®	Etidronate	Oral	Procter & Gamble
Etidronat Jenapharm®	Etidronate	Oral	Jenapharm
Fosamax®	Alendronate	Oral	MSD
Fosavance®	Alendronate/Vit.D	Oral	MSD
Lodronat®	Clodronate	Oral and I.V.	Roche (Austria)
Ostac®	Clodronate	Oral and I.V.	Roche
Skelid®	Tiludronate	Oral	Sanofi
Zometa®	Zoledronate	I.V.	Novartis

List of Authorised Bisphosphonates from A to Z

Bisphosphonate	Trade names
Alendronate	Fosamax®, Fosavance®
Clodronate	Ostac®, Bonefos®
Etidronate	Didronel®, Didronel-Kit®
Ibandronate	Bondronat®, Bon(v)iva®
Pamidronate	Aredia®
Risedronate	Actonel®, Actonel® plus calcium
Tiludronate	Skelid®
Zoledronate	Zometa®, Aclasta®

CHAPTER 29 Summary and Perspectives

Bisphosphonates have been known for over 100 years, but previously were used mainly for industrial purposes. After the introduction of etidronate for a disorder of bone, these substances underwent rapid development for therapeutic applications so that today, the treatment and prevention of skeletal disorders has been revolutionised and simplified. The development of bisphosphonates with P-C-P, which made them resistant to enzymatic hydrolysis, proved to be the most significant breakthrough in the treatment of both primary and secondary disorders of bone.

Bisphosphonates have largely replaced other pharmaceutical agents such as fluoride and calcitonin previously given in these conditions. More than 90% of all osteopathies can now be successfully treated and improved if not cured with bisphosphonates, the few exceptions include osteomalacia and osteopetrosis but even here bisphosphonates have proved their value because the bone though dense, is of poor quality and liable to fracture.

The extensive application of the bisphosphonates in medical practice is due to the following factors:

- The P-C-P substitution
- Development of highly potent bisphosphonates
- Improvements in methods of administration
- Study of long-term effects
- Investigation of mechanisms of action
- Study of side effects and guide lines for their avoidance

There are few pharmaceutical agents which have been subjected to the same comprehensive, thorough and expensive clinical studies as the bisphosphonates.

They are now *authorised for use in the following conditions*:

- Postmenopausal osteoporosis
- Osteoporosis in men
- Glucocorticoid-induced osteoporosis
- Paget's disease of bone
- Hypercalcemia of malignancy
- Tumor-induced osteolyses

- Heterotopic ossification
- Skeletal metastases of certain cancers

Additional authorisations in oncology and osteology are due to follow shortly. Nevertheless in spite of the successes already achieved, many *practical questions* remain and should be addressed as quickly as possible in the interest of the patients. These include:

- What are the optimal dosages of the latest generation of bisphosphonates?
- What is the correct dose for each individual disorder (and patient)?
- When is continuous and when is intermittent therapy most appropriate?
- Would patients prefer once weekly or once monthly tablets, or intermittent injections/infusions?
- Would an annual injection really be effective for prevention and therapy of osteoporosis?
- When exactly is intravenous administration preferable to oral administration?
- Might different bisphosphonates act synergistically, e.g. clodronate and ibandronate?
- Do different bisphosphonates have different spectrums of action?
- Is the retention of bisphosphonates in bone significant?
- Could bisphosphonates be more widely used for transport of therapeutic agents to bone?
- Can side effects be reduced or eliminated entirely?
- Can the immune response to bisphosphonates be utilised to the patient's advantage?
- Apart from the treatment of bone disease, could other actions of bisphosphonates be utilised for other conditions in medicine?
- Is it possible to utilise more effectively the anti-angiogenic and antiproliferative effects of bisphosphonates in various malignancies?
- Why is the effect of bisphosphonates in CRPS and in bone marrow edema so fast and impressive?
- Can occurrence of necrosis of the jaw bones be definitively elucidated and prevented?
- Could bisphosphonates alleviate inflammatory processes in joints?
- How do bisphosphonates exert their action on bone pain?

Much more basic research is required to clarify all the aspects of bisphosphonate therapy. In addition, randomised studies of all the different disease groups would have to be carried out to answer all the clinically relevant questions. In the interest of the patients, such studies should be carried out concurrently at various medical centers, not chronologically over long periods of time. Financial support should not be too difficult to obtain.

The considerable medical success of the bisphosphonates has brought about a radical change in health care of the skeleton. Until recently only a few specialists

dealt with disorders of bone. Today, in the year 2007, both patients and doctors are aware of the far-reaching significance of healthy bones. Clinical osteology has now become a fascinating interdisciplinary specialty which has gained world-wide recognition and respect only since the introduction of therapy with bisphosphonates.

For example, the successful treatment and prevention of osteoporosis is now an important task for, and responsibility of, practically every branch of medicine. In oncology, the list of indications grows steadily longer, and in the not-too-distant future, it is safe to predict that bisphosphonates will be used in earlier stages of bone disorders to prevent skeletal destruction and avoid skeletal metastasis.

During the last few years the significance of the osteoprotegerin/RANKL/RANK System has been elucidated, not only in disorders of bone but also in skeletal-related and vascular conditions which include such common diseases as diabetes, atherosclosis, rheumatoid arthritis and metastases (Table 29.1). This confirms that the RANKL/osteoprotegerin system is a cytokine system with far reaching effects – from osteoporosis to arteriosclerosis to rheumatic disorders and to neoplasias. In all these conditions there are therapeutic windows for the inclusion of bisphosphonates – some are already being explored and applied.

Bisphosphonates also have the capability to inhibit the growth of various protozoans which is being utilised in new ways to combat infections with these organisms (Fig. 29.1).

The *knowledge of the human genome and the genetics* of osteoporosis and other disorders of bone will play an increasingly significant role in treatment in the not-too-distant future, as the responsible genes, the gene to gene interactions and their

Table 29.1 OPG/RANKL/RANK in the pathogenesis of bone, immune and vacular diseases

Metabolic Bone Diseases	Immune-mediated Bone Diseases	Malignant Diseases	Inherited Skeletal Diseases	Cardio-vascular Diseases
Postmeno-pausal osteo-porosis	Rheumatic arthritis	Multiple myeloma	Familial expansile osteolysis	Atherosclerosis
Glucocorti-coid-induced osteoporosis	Periodontal infection	Bone metastases	Familial Paget disease of bone	Peripheral vas-cular disease
Hyperparathy-roidism		Hypercalcemia of malignany	Idiopathic hyperphos-phatasia	Coronary artery disease
Sporadic Paget disease of bone				

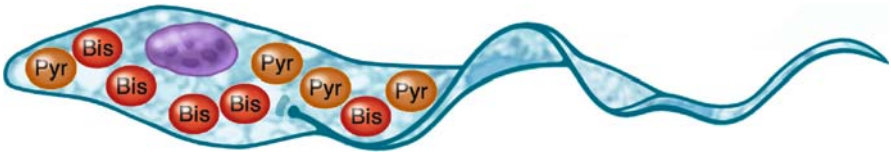


Fig. 29.1 Sketch of intra-cellular accumulation of bisphosphonates in parasite trypanosoma cruzi

products are clarified. One example is osteopetrosis. This disorder is characterised by bones that are dense, but qualitatively inadequate and lacking normal amounts of bone marrow due to encroachment of the bone on the inter-trabecular spaces. Osteoclasts that appear morphologically normal are unable to resorb bone. The consequences, as expressed in the severest form of the disease – infantile malignant osteopetrosis – include stunted growth, short limbs, neurologic complications and hematopoietic failure with pancytopenias; left untreated it is obviously fatal. Recent studies have shown that the protein CIC7 is required for the channel between osteoclast and bone enabling the passage of acidic enzymes from the osteoclast to the resorption surface on the bone. Mice with disruptions in the gene encoding CIC7 had all the hallmarks of osteopetrosis. Moreover a similar genetic alteration was identified in a patient with infantile malignant osteopetrosis. Based on these genetic and molecular discoveries of the cause and pathophysiology of the disease, specific therapy will not be far behind. This example clearly illustrates the type of impact that the information acquired by the human genome project will have on our understanding of the causes of disease processes as well as how to treat them. Another example of this is the latest treatment of chronic myeloid leukemia (CML) with imatinib which neutralises the effects of the tyrosine kinase activated by the abnormal gene produced by the translocation which is the hallmark of the disease – the Philadelphia chromosome. Studies of bisphosphonates administrated together with the tyrosine kinase inhibitor have already been reported, and they showed that zoledronate acted synergistically as an anti-leukemic agent together with the anti-Ph+ leukemic cell activity of imatinib also known as Glivec® or STI. This application of zoledronate has already been authorised by the FDA.

The anti-proliferative activity of zoledronate together with other drugs against various leukemic cell lines has also been reported.

Other combinations are being explored such as alternating an anti-TNF alpha agent with bisphosphonates in rheumatoid arthritis. Moreover, as new factors are discovered in the regulation of osseous remodeling, they offer molecular targets for therapy in the future, as for example CB2 in the regulation of osteoclastic activity.

Finally, the bisphosphonates already appear to have pleiotropic effects, in the same way that these are now recognised for the statins which have recently been shown to be beneficial also for the kidneys. The bisphosphonates, in addition to

their effects on various steps in the mechanisms of bone turnover, and their antiproliferative actions, are already known to participate in many other physiological processes such as inflammatory and immune responses, neovascularisation, arterial pressure and others. It is quite feasible that in the not too distant future the bisphosphonates will also be the starting point for development of novel therapeutic approaches in various clinical disciplines.

In conclusion, maintenance of bone and the health of the skeleton concern every physician. Moreover, all members of society at large must learn to take personal responsibility for the health and maintenance of their bones. In the same way that we learn from childhood onwards to clean and check our teeth regularly, we must all learn to become "*bone conscious*". The modern bisphosphonates have provided us with a kind of credit card which we can use successfully when indicated. As was stated in the preface, a healthy skeleton and the mobility that goes with it will be more and more significant for daily living in the future: *Remember the 3 B's:*

"Bone is Every Body's Business"

CHAPTER 30 Literature Survey

Introduction

As mentioned in the Preface there is now an enormous body of literature on bone, the skeleton and its disorders ranging from genetic mutations and anomalies, environmental, nutritional and life-style factors to the effects of acute and chronic acquired conditions and to the influence of the wear and tear which accompany aging. Equally impressive numbers of articles dealing with treatment of bone disorders from infancy and childhood to old-age have also been published.

It is clearly impossible to include more than a fraction of all these studies relating to treatment – which in turn range from in vitro experiments to animal studies to case reports to results of treatment in small numbers of patients to national and international trials.

Consequently we have included a list of books which should provide most of the original references on the subjects covered in the text; and we have supplemented this list with a selection of references published during the late nineties as well as from the literature search on the bisphosphonates from January 2000 to January 2007, as many of these are not included in the list of books provided.

Since computer searches from the Medline and other bases are now readily available world-wide, more detailed information is also within everybody's reach on any particular aspect of bone, its disorders, their prevention and treatment.

Moreover, numerous articles on various aspects of disorders of bone and of therapy with the latest bisphosphonates have been published in 2007. Results of some of these are included in the text and the articles themselves are cited in the literature survey of the dealing with that particular topic.

Books

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3. Bartl R (2004): Osteoporose, 2. Auflage, Thieme, Stuttgart
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Osteoporotic Syndrome, Glucocorticoid Induced Osteoporosis, Tumor and Chemotherapy Induced Osteoporosis, Transplantation Osteoporosis, Immobilisation Osteoporosis, Pregnancy Associated Osteoporosis, Osteogenesis Imperfecta, AIDS Osteopathy, Renal Osteopathy

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