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Nursing interventions of patients with endocrine disorder

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Contents

- Review of anatomy and physiology of endocrine system
- Assessment and examination of patients with endocrine disorder
- Common diagnostic techniques and nursing responsibilities

Contents …

- Common endocrine system disorders:
  - Disorders of pituitary gland (DI & SIADH)
  - Disorders of Thyroid gland (hypo/hyper thyroidism, endemic goiter, thyroiditis, and thyroid cancer)
  - Disorders of parathyroid gland (hypo/hyper parathyroidism)
  - Disorders of Adrenal gland (Cushing syndrome, Addison's disease, pheochromocytoma, & primary aldostronism)
  - Disorders of Islets of Langerhans (DM, short & long term omplications of DM)

Anatomy & physiology overview of the Endocrine System

- The **endocrine system involves the release of chemical substances** known as **hormones to regulate and integrate body** functions.
- Generally, these hormones are produced by the endocrine glands, but some are also produced by other tissues.
- The immune system & NS have unique relations with endocrine system.

Overview of the Endocrine System …

- Chemicals such as neurotransmitters (eg, epinephrine) released by the nervous system can also function as hormones when needed.
- The immune system responds to the introduction of foreign agents by means of chemical messengers (cytokines), which are hormone like proteins, while it is also subject to regulation by adrenal corticosteroid hormones

Overview of the Endocrine System …..

- A structure which makes hormones in the body is called **endocrine glands** (also called ductless glands)
- The **endocrine system** is a network of ductless glands that secrete chemicals called hormones to help your body function properly.
- **Hormones** are chemical signals that coordinate a range of bodily functions.

Overview of the Endocrine System ….

- Hormones are “messenger molecules”
  - Circulate in the blood
  - Act on distant target cells which respond to the hormones for which they have receptors
  - The effects are dependent on the programmed response of the target cells
  - Hormones are just molecular triggers

Classification and Action of Hormones

- Hormones are classified into four categories according to their structure:

1. Amines and amino acids (eg, epinephrine, norepinephrine, and thyroid hormones)
2. peptides, polypeptides, proteins, and glycoproteins (eg, thyrotropin releasing hormone, FSH, and GH)
3. Steroids (eg, corticosteroids); and
4. Fatty acid derivatives (eg, eicosanoid, retinoids)

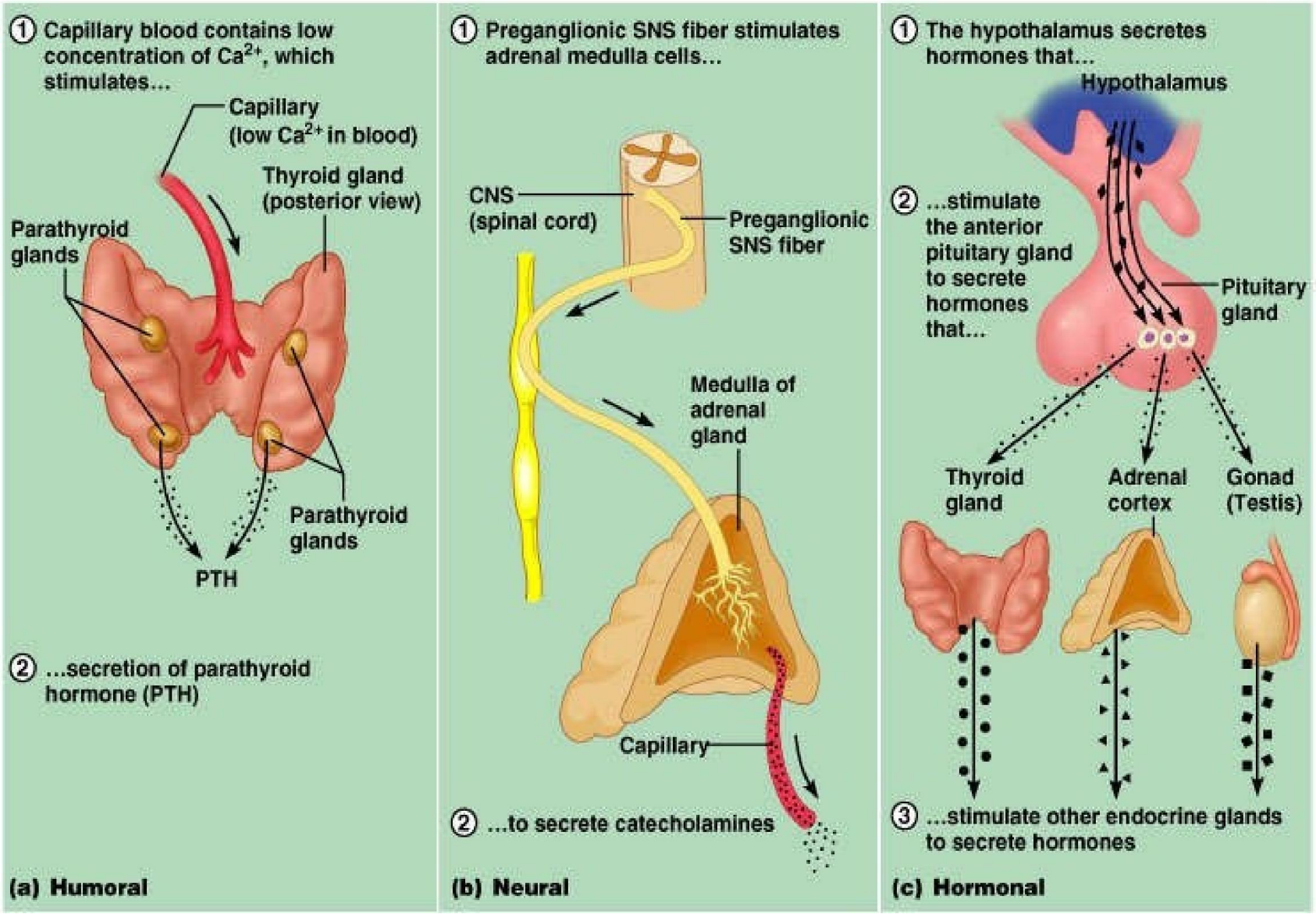
Mechanisms of hormone release

a) **Humoral**: in response to changing levels of ions or nutrients in the blood

b) **Neural**: stimulation by nerves

c) **Hormonal**: stimulation received from other hormones

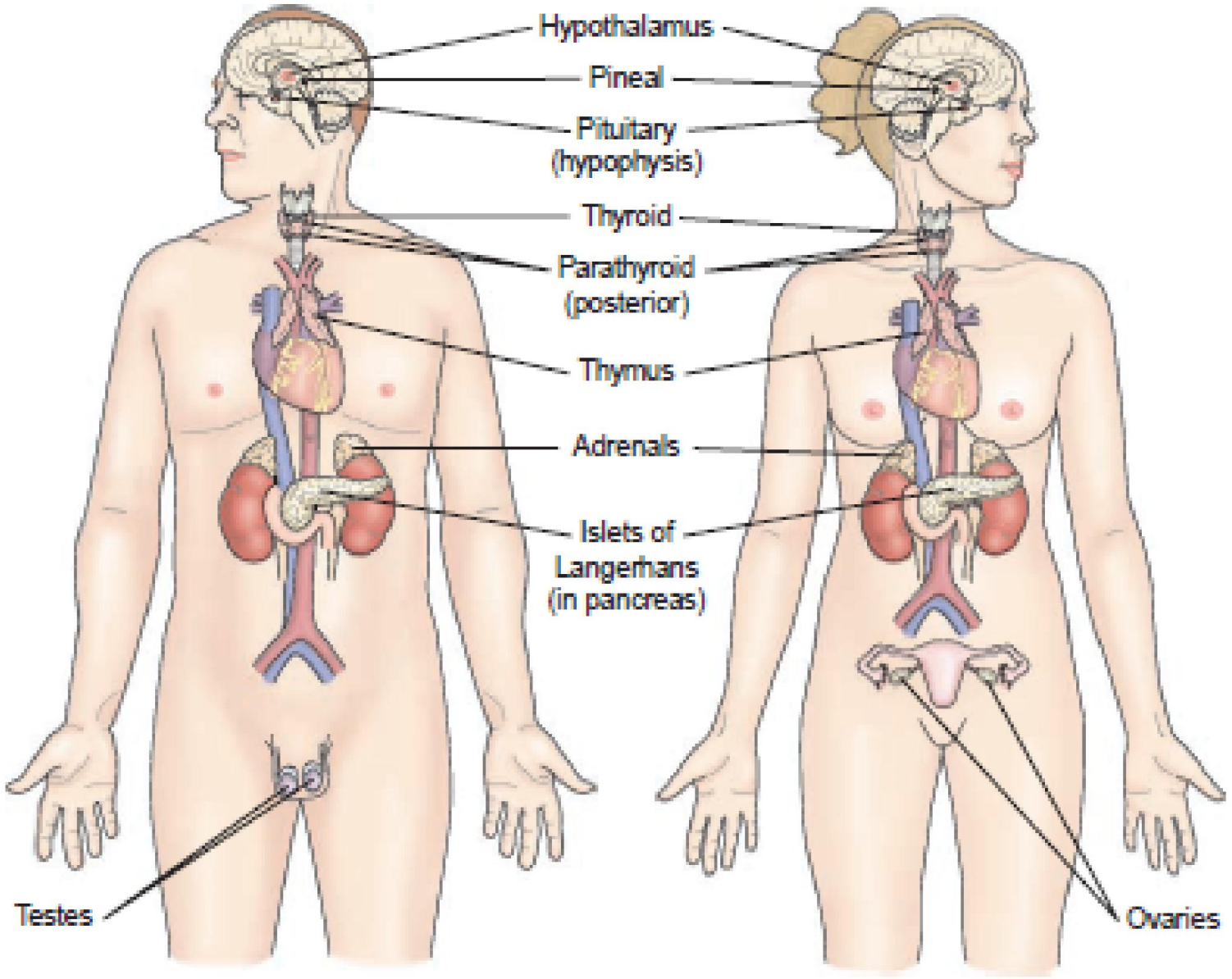
Mechanisms of hormone release….



Glands

- Glands are specialized tissues that excrete some substance.
  - Endocrine glands (also called ductless glands) secrete chemicals inside of the body, directly into the blood stream.
  - Glands are commonly made of cuboidal epithelium.

Endocrine Organs



Endocrine Organs

Purely endocrine organs

- Pituitary gland
- Pineal gland
- Thyroid gland
- Parathyroid glands
- Adrenal: 2 glands
  - Cortex
  - Medulla

Endocrine cells in other organs

- Pancreas
- Thymus
- Gonads
- Hypothalamus

Hypothalamus

- Is a portion of the brain that contains a number of small nuclei with a variety of functions.
- One of the most important functions of the hypothalamus is to link the nervous system to the endocrine system via the pituitary gland.

Functions of Hypothalamus

- Responsible for certain metabolic processes and other activities of the autonomic NS.
- It synthesizes and secretes certain neurohormones, often called releasing hormones or hypothalamic hormones, and these in turn stimulate or inhibit the secretion of pituitary hormones.
- The hypothalamus controls body temperature, hunger, fatigue, sleep, etc.

The Pituitary Gland (Hypophysis)

- considered as the "Master Gland" because it releases many hormones that regulate other glands.
- Acts as the control center for the endocrine system which controls all the hormones produced by other glands in the body.
- Located just under the brain, and has an anterior and posterior lobe.
- It communicated regularly with the hypothalamus

Hormones of the Pituitary Gland

Anterior

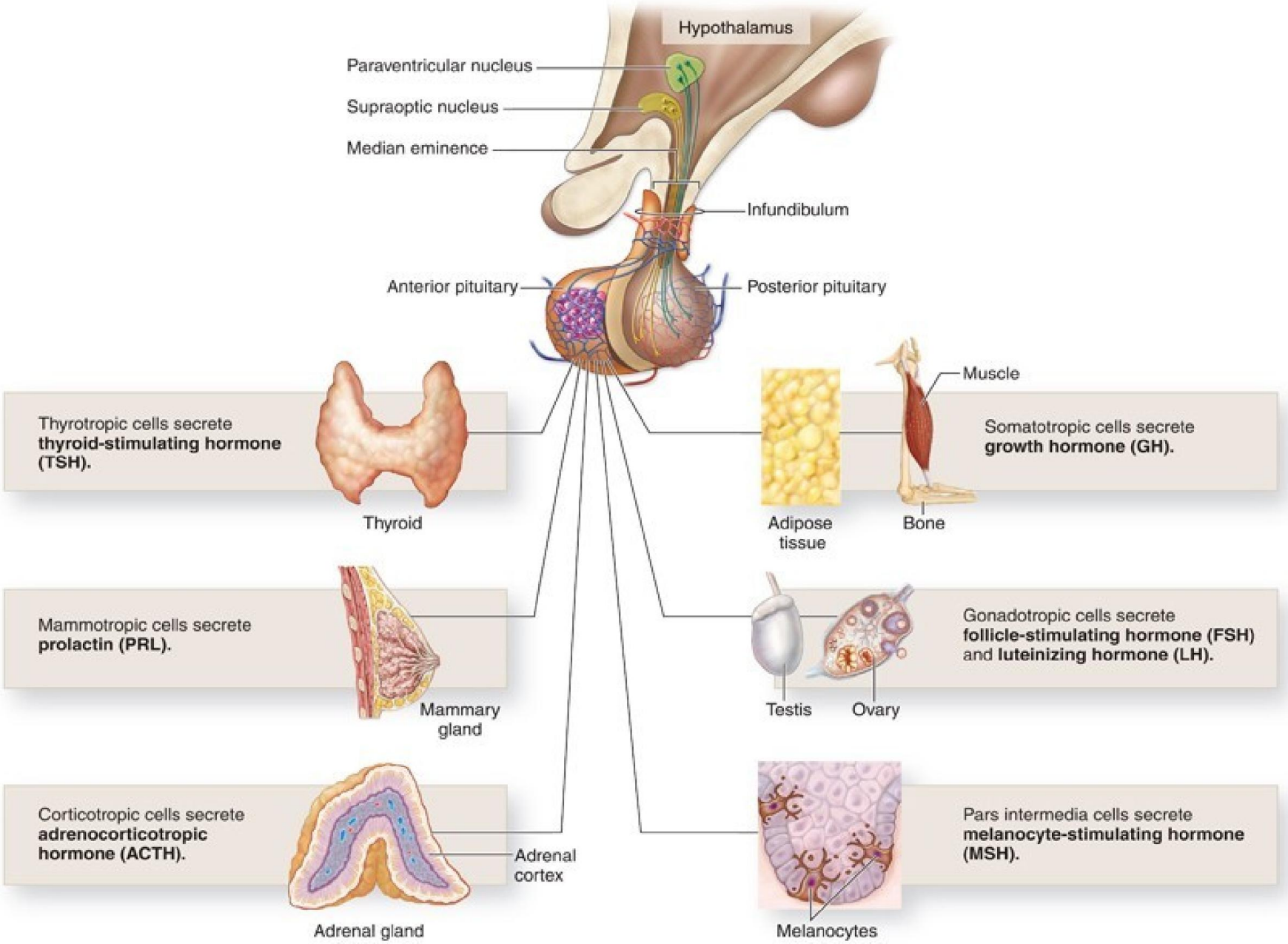
- Growth Hormone
- Prolactin
- Thyroid Stimulating Hormone
- Adrenocorticotropic Hormone
- Follicle Stimulating Hormone
- Luteinizing Hormone

Posterior

- Vasopressin (ADH)
- Oxytocin

Hormones of PT Gland…..

- Hypothalamic releasing and inhibiting hormones are carried directly to the anterior pituitary gland via Hypothalamic - hypophyseal portal vein
- Specific hypothalamic hormones bind to receptors on specific anterior pituitary cells, modulating the release of the hormone they produce.



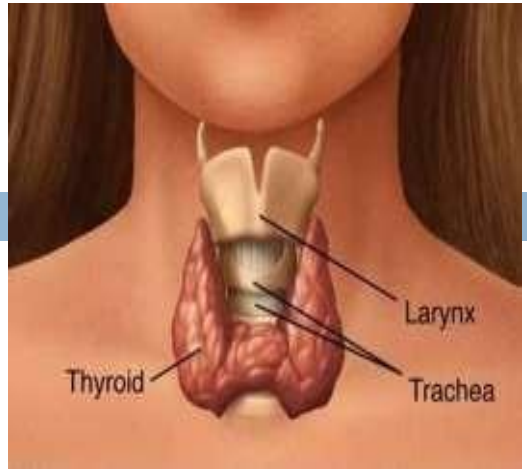
Functions of pituitary gland

- Growth
- Blood pressure
- Stimulation of uterine contractions during childbirth
- Breast milk production
- Sex organ functions in both males and females
- Thyroid gland function
- The conversion of food into energy (metabolism)
- Water and osmolarity regulation in the body
- Water balance via the control of reabsorption of water by the kidneys
- Temperature regulation

Functions of pituitary gland …

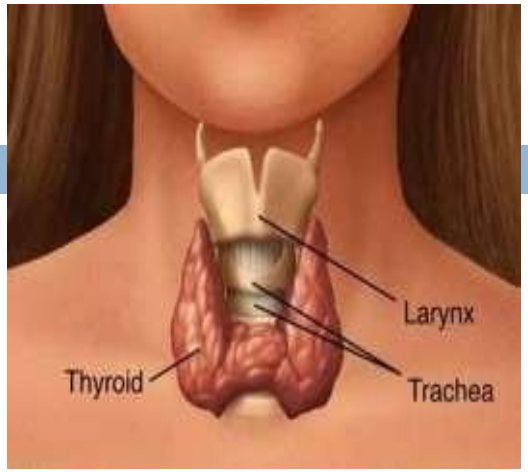
	Hormone	Major target organs	Major physiologic effects
Anterior Pituitary	Growth hormone	Liver, adipose tissue	Promotes growth (indirectly), control of protein, lipid and carbohydrate metabolism
	Thyroid stimulating hormone	Thyroid gland	Stimulates secretion of thyroid hormones
	Adrenocorticotrophic hormone	Adrenal gland cortex	Stimulates secretion of glucocorticoids
	Prolactin	Mammary gland	Milk production
	Luteinizing hormone	Ovary and testis	Control of reproductive function
	Follicle stimulating hormone	Ovary and testis	Control of reproductive function
Posterior pituitary	Antidiuretic hormone	Kidney	Conservation of body water
	Oxytocin	Ovary and testis	Stimulates milk ejection and uterine contractions

The Thyroid Gland



- Largest endocrine gland in humans.
- Butterfly Sharped and located in the neck, this gland releases three hormones:
  - **Thyroxine (T4)** and **Triodothyronine (T3)**: work together to control rate of glucose and oxygen metabolism, protein synthesis, and break down of stored energy

The Thyroid ….



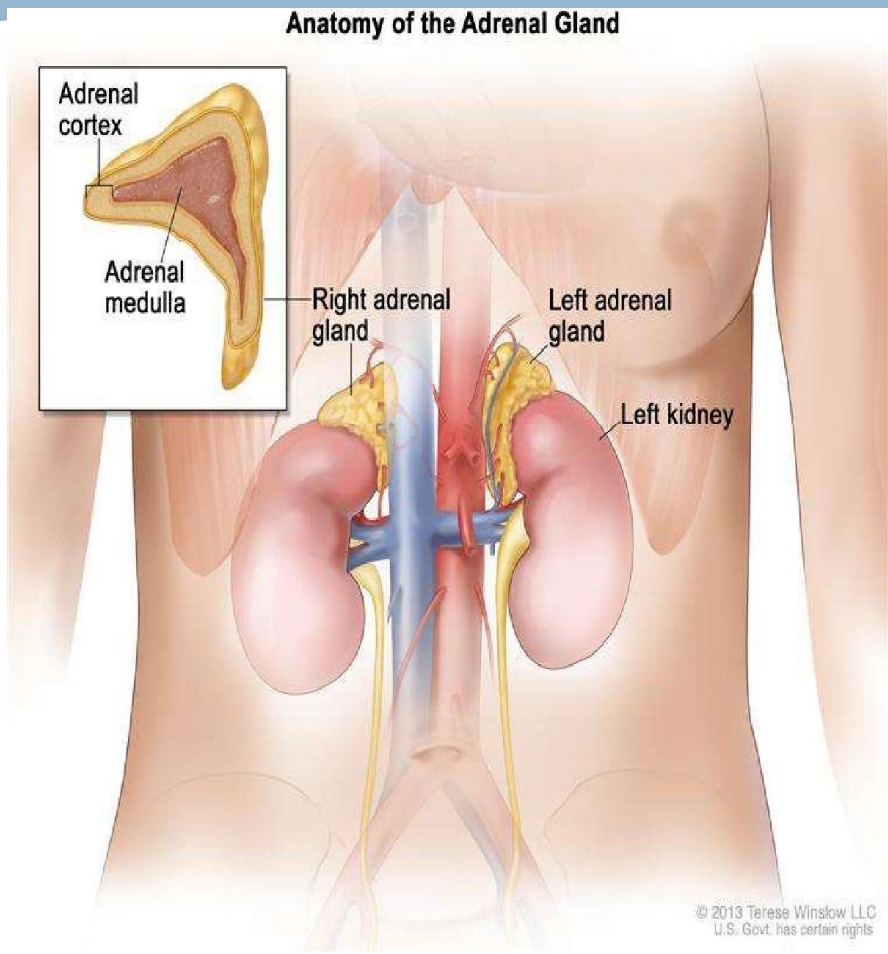
- **Calcitonin**: regulates amount of Calcium in blood by stimulating osteoblasts to add calcium to bone, therefore lowering the blood levels

The Parathyroid Glands

- Are tiny glands located on either side of the thyroid.
- They only produce one hormone (Parathyroid Hormone)
- Parathyroid Hormone has one job, which is to increase blood levels of calcium. It does this in 2 ways:
  - Stimulates osteoclast to release calcium from bone.
  - Reduce the amount of Ca eliminated by the kidneys.

Adrenal Glands

- Also called supra renal gland.
- Consists of outer cortex & inner medulla
- They are controlled by adrenocorticotropic hormones from the pituitary.



Hormones of the Adrenal Glands

Cortex

- Mineralocorticoids (esp. Aldosterone) which help regulate the levels of electrolytes in the blood stream (mostly K+ & Na+)
- Glucocorticoids (cortisone & cortisol) that ↑se the levels of glucose on the blood.
- Androgens, which are similar to male sex hormones but are in both genders.

Medulla

- Epinephrine, hormone of the sympathetic nervous system. Increase RR, cardiac output, metabolism, etc..
- Norepinephrine works with epinephrine, increased vascular tone & improves focus and concentration.

Gonads

- **Are** primary reproductive glands that produces reproductive cells (gametes).
- In males the gonads are called **testes** and gonads in females are called **ovaries**.
- The function of the gonads is to produce gametes for reproduction and secrete sex **hormones**

Gonads …

- **Ovaries**:
  - Produce estrogen & progesterone which stimulate female sex characteristics and the monthly cycle.
  - Respond to FSH & LH from anterior PT gland.

Gonads …

- **Testes:**
  - The **testicle** is the male generative gland.
  - Is to produce spermatozoa & to secrete male sex hormone.
  - The chief male sex hormone produced is the testosterone
  - Testosterone develops male sex organs & secondary sex X-cs.
  - They respond to LH from the anterior PT gland

Pancreas

- 2nd largest gland.
- Consists of exocrine & endocrine parts.
- Endocrine part consists of Islets of Langerhans.
- The hormones secreted are Insulin, Glucagon, Somatostatin & Pancreatic polypeptide
- The major disorders related to pancreas are : Diabetes mellitus, Hypoglycemia, Pancreatitis & Pancreatic cancer

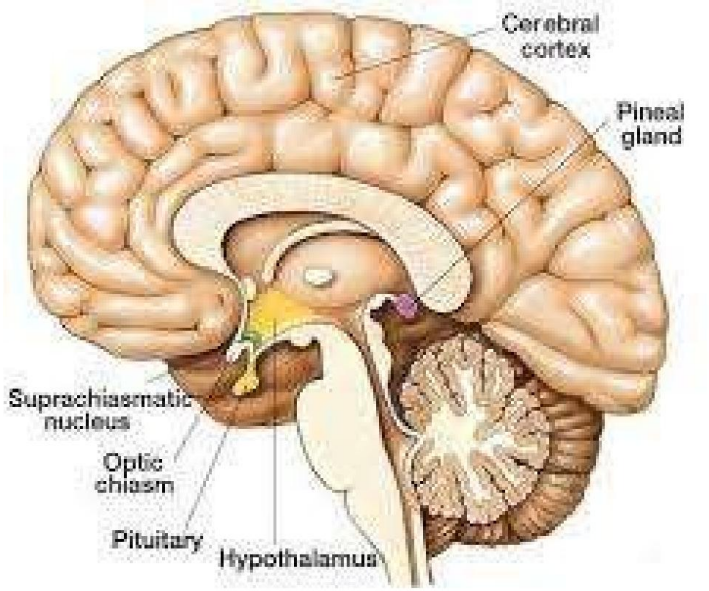
Pancreas ….

Islets of Langerhans:

- **Produce insulin which has 4 jobs**:
  - Facilitates transport on glucose into cell
  - Promotes fatty acid transport into cells
  - Promotes amino acid transport into cells
  - Stimulates protein synthesis
- **Make Glucagon**
  - Works as the opposite of insulin and increases blood glucose by releasing it from liver.

Pineal Gland

- Located in the third ventricle of the brain, this tiny gland makes Melatonin.
  - Melatonin drops body temperature and has some relationship to the sleep-wake cycle.
  - Release is stimulated by light levels detected by eyes.



Hormones Produces Elsewhere

- Prostaglandins are released by many tissues in the body, and activity depends on their origin. Generally, they act to constrict or relax blood vessels and cause muscle contracts as in labor.
- Neurohormones are released in the brain that travel to the body tissues. For example, the hypothalamus sends messengers to the pituitary gland.
- Leptin is produces by fat cells to suppress appetite.
- Ghrelin is mad in the stomach and stimulates appetite.

Control of Hormones

- Release and action of hormones typically follow a negative feedback loop
- Many hormones work as antagonistic pairs that regulate the same function.
- Hormones and glands are also controlled by NS which can control by direct monitoring and response, or indirectly by emotional or situational triggers.

Hormone Regulation

- Negative feedback (most common)
  - Endocrine gland oversecretes hormone
  - Tissue becomes too active
  - Tissue negatively effects gland to decrease secretion
- Positive feedback
  - Hormone response produces more hormone
- Rhythmic pattern

Hormone Regulation

A. Hormones: chemical substances that act as messengers to specific cells and organs (target organs), stimulating and inhibiting various processes; two major categories

B. Negative feedback mechanisms: major means of regulating hormone levels

   1. Decreased concentration of a circulating hormone triggers production of a stimulating hormone from the pituitary gland; this hormone in turn stimuulates its target organ to produce hormones.
   2. Increased concentration of a hormone inhibits production of the stimulating hormone, resulting in decreased secretion of the target organ hormone

C. Some hormones are controlled by changing blood levels of specific substances (eg. calcium, glucose)

D. Certain hormones (e.g. Cortisol or female reproductive hormones) follow rhythmic patterns of secretion

E. Autonomic and CNS control (pituitary-hypothalamic axis): hypothalamus controls relase of the hormones of the anterior pituitary gland through releasing and inhibiting factors that stimulate or inhibit hormone secretion.

Structure and Function of Endocrine Glands

Pituitary Gland (Hypophysis)

A. Located in sella turcica at the base of the brain
B. "Master gland" of the body, composed of three lobes
    1. Anterior lobe (adenohphysis)
        a. Secretes tropic hormones (hormones that stimulate target glands to produce their hormone): adrenocorticotropic (ACTH), thyroid-stimulatiing (TSH), follicle stimulating (FSH), luteinizing hormone (LH)
        b. Also secretes hormones that have direct effect on tissues: somatotropic or growth hormone, prolactin
        c. Regulated by hypothalamic releasing and inhibiting factors and by negative feedback system

3. Posterior lobe (neurophysis): does not produce hormones; stores and relaxes antidiuretic hormone (ADH) and oxytocin, produced by the hypothalamus
4. Intermediate lobe: secretes melanocyte stimulating hormone (MSH)

Adrenal Glands

A. Two small glands, one above each kidney
B. Consists of two sections
   5. Adrenal cortex (outer protion): produces mineralocorticoids, glucocorticoids, sex hormones
   6. Adrenal medulla (inner portion): produces epinephrine, norepinephrine

Thyroid Gland

A. Located in anterior portion of the neck
B. Consists of two lobes connected by a narrow isthmus
C. Produces thyroxine (T4), triiodothyronine (T3), thyrocalcitonin

Parathyroid Gland

D. Four small glands located in pairs behind the thyroid gland
E. Produce parathormone (PTH)

Pancreas

F. Located behind the stomach
G. Has both endocrine and exocrine funtions (discussed in GI)
H. Islets of Langerhands (alpha and beta cells) involved in endocrine funtion
    1. Beta cells: produce insulin
    2. Alpha cells: produce glucagon

Gonads

A. Ovaries: located in pelvic cavity, produce estrogen and progesterone
B. Testes: located in scrotum, produce testosterone

Assessment

A. Presenting problem: symptoms may include:
   1. Change in appearance: hair, nails, skin (change in texture or pigmentation); change in size, shape, or symmetry of head, neck, face, eyes, or tongue
   2. Change in energy level
   3. Temperature intolerance
   4. Development of abnormal secondary sexual characteristics; change in sexual function
   5. Change in emotional state, thought pattern, or intellectual functioning
   6. Signs of increased activity of sympathetic nervous system (e.g. Nervousness, palpitations, tremors, sweating)
   7. Change in bowel habits, appetite or weight; excessive hunger or thirst
   8. Change in urinary pattern

B. Life-style: any increased stress

C. Past medical history: growth and development (any delayed or excessive growth); diabetes, thyroid disease, hypertension, obesity, infertility

D. Family history: endocrine diseases, growth problems, obesity, mental illness

Physical Examination

A. Check height, weight, body stature, and body proportions
B. Observe distribution of muscle mass, fat distribution, any muscle wasting
C. Inspect for hair growth and distribution
D. Check condition and pigmentation of skin; presence of striae
E. Inspect eyes for any bulging
F. Observe for enlargement in neck area and quality of voice
G. Observe development of secondary sex characteristics
H. Palpate thyroid gland (normally cannot be palpated): note size, shape, symmetry, any tenderness, presence of any lumps or nodules

Laboratory/ Diagnostic tests

- A variety of test may be performed to measure the amounts of hormones present in the serum or urine in assessing pituitary, adrenal, and parathyroid functions; these tests will be referred to when appropriate under specific disorders of the endocrine system.

Thyroid Function

A. Serum studies: nonfasting blood studies (no special preparation necessary)
   1. Serum T4 level: measures total serum level of thyroxine
   2. Serum T3 level: measures serum triiodothyronine level
   3. TSH: measurement differentiates primary from secondary hypothyroidism
B. Radioactive iodine uptake (RAIU)
   4. Administration of ^{123}I or ^{131}I orally; measurement by a counter of the amount of radioactive iodine taken up by the gland after 24 hours
   5. Performed to determine thyroid function; increased uptake indicates hyperactivity; minimal uptake may indicated hypothyroidism

3. Nursing Care:
    a. Take thorough history; thyroid medication must be discontinued 7-10 days prior to test; medications containing iodine, cough preparations, excess intake of iodine rich goods, and tests using iodine (eg.g IVP) can invalidate the test.
    b. Assure client that no radiation precautions are necessary

C. Throid Scan

4. Administration of radioactive isotope (orally or IV) and visualization by a scanner of the distribution of radioactivity in the gland
5. Performed to determine location, size, shape, and anatomic function of thyroid gland; identifies areas of increased or decreased uptake; valuable in evaluating thyroid nodules
6. Nursing care: same as RAIU

Pancreatic Funtion

A. Fasting blood sugar: measures serum glucose levels; client fasts from midnight before the test
B. Two hour postprandial blood sugar: measurement of blood glucose 2 hours after meal is ingested
   a. Fast from midnight before test
   b. Client eats a meal consisting of at least 75g carbohydrate or ingests 100g glucose
   c. Blood drawn 2 hours after the meal
C. Oral glucose tolerance test: most specific/sensitive test - DM
   4. Fast from midnight before test
   5. Fasting blood glucose & urine glucose specimens are taken
   6. Client ingests 100 g glucose; blood sugars are drawn at 30-60 minutes and then hourly 3-5 hours; urine specimens may also be collected
   7. Diet for 3days prior to test should include 200g carbohydrate and least 1500kcal/day
   8. During test, assess the client for reactions such as dizziness, sweating, and weakness

D. Glycosylated hemoglobin (hemoglobin A_{10} reflects the average blood sugar level for the revious 100-120 days. Glucose attaches to a minor hemoglobin (A_{10}).This attachment is irreversible)

1. Fasting is not necessary
2. Excellent method to evaluate long term control of blood sugar

Assessment

- **Health History**
- Some common signs and symptoms of endocrine imbalances include changes in energy level, tolerance to heat or cold, weight, fat and fluid distribution, secondary sexual characteristics, sexual dysfunction, memory, concentration, sleep patterns, and mood.

Assessment ….

- The health history should include information regarding

1. The severity of these changes
2. Length of time the patient has experienced these changes
3. The way in which these changes have affected the patient's ability to carry out activities of daily living, and
4. The effect of the changes on the patient's self-perception.

Physical Assessment

- The physical examination should include vital signs, a visual head-to-toe assessment, and tactile examination.
- Changes in physical characteristics such as appearance of facial hair in women, “moon face,” “buffalo hump,” exophthalmos, edema, thinning of the skin, obesity of the trunk, thinness of the extremities, increased size of the feet and hands, and edema may signify disorders of the thyroid, adrenal cortex, or pituitary gland.

Physical Assessment .....

- Exophthalmos and other eye symptoms may occur with hyperthyroidism and Graves' disease.
- Alteration in skin texture is associated with hypofunction and hyperfunction of the thyroid gland.
- Elevated blood pressure may occur with hyperfunction of the adrenal cortex or tumor of the adrenal medulla.
- Decreased BP may occur with hypofunction of adrenal cortex.
- Behavioral changes such as agitation, nervousness, or a lack of concern about personal appearance may also be present.

Diagnostic Evaluation

- A variety of diagnostic studies are used to evaluate the endocrine system.
- Blood tests: to determine hormone blood levels.
- Other blood tests are used to detect autoantibodies or to assess the effect of the hormone on other substances
- Radioimmunoassays are radioisotope-labeled antigen tests used to measure the levels of hormones or other substances.

Diagnostic Evaluation …

- Urine tests: to measure the amount of hormones or end products of hormones excreted by the kidneys.
- Imaging studies include radioactive scanning, MRI, CT, ultrasonography, etc
- DNA testing: lead the identification of specific genes
- Genetic screening: to determine presence of a gene mutation that may predispose an individual to a certain condition.

Disorders of pituitary gland

Disorders of pituitary gland

- Causes of disorder of pituitary gland are mainly of 2 reasons:
  - Hyperactivity
  - Hypoactivity

Disorders of pituitary gland …

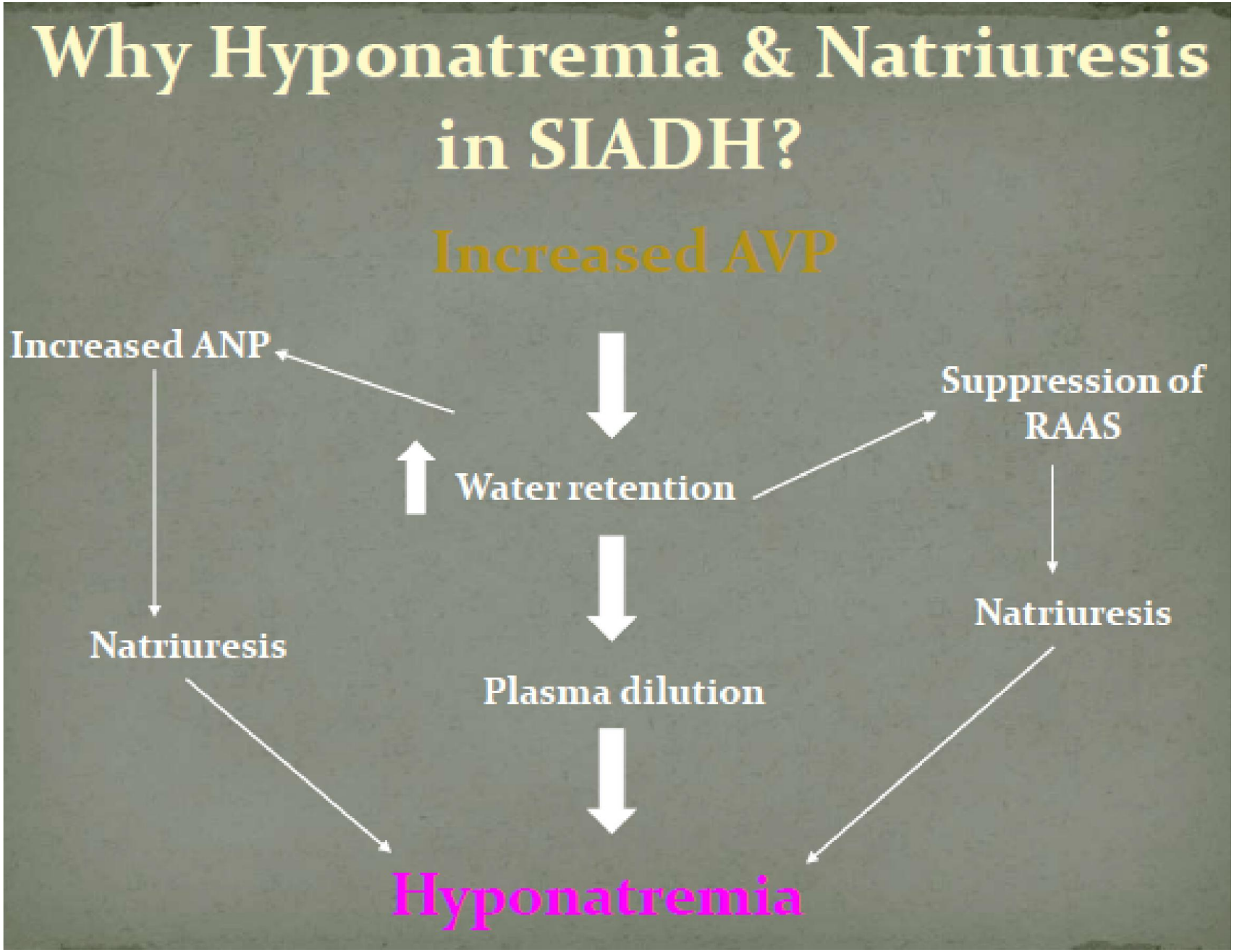
Parts involved	Hyperactivity	Hypoactivity
Anterior Pituitary	1. Gigantism 2. Acromegaly 3. Gigantism 4. Cushing's disease	1. Dwarfism 2. Acromicria 3. Simmond's disease
Posterior Pituitary	Syndrome of inappropriate hypersecretion of ADH (SIADH)	Diabetes insipidus

Syndrome of Inappropriate secretion of Antidiuretic hormone (SIADH)

- Disease characterized by loss of sodium through urine due to hypersecretion of ADH
- Is disorder of impaired water excretion caused by inability to suppress secretion or due to excessive secretion & action of ADH
- If water intake exceeds the reduced urine output (concentrated Urine), the ensuing water retention leads to the development of hyponatremia.
- Most common cause of Hypo osmolar euvolemic Hyponatremia

Pathophysiology of SIADH

- Inappropriate ADH secretion
- ADH-induced water retention → Hyponatremia
- Volume expansion activates secondary natriuretic mechanisms, resulting in sodium and water loss and the restoration of near-euvolemia.
- The net effect is that, with chronic SIADH, sodium loss is more prominent than water retention .
- However, since there is no impairment in volume regulatory hormones (aldosterone and natriuretic peptides), patients with SIADH are **euvolemic** unless there is a second problem leading to salt loss


Why Hyponatremia & Natriuresis in SIADH?
Increased AVP
Increased ANP
Suppression of RAAS
Water retention
Natriuresis
Natriuresis
Plasma dilution
Hyponatremia

Etiologies of SIADH

- Due to cerebral tumors, lung tumors and lung cancers because the tumor cells secrete ADH
- Normal secretion of ADH makes the plasma hypotonic
- Hypotonic solution inhibits the ADH secretion and restoration of plasma osmolarity takes place
- But in SIADH ,secretion of ADH from tumor is not inhibited by hypotonic plasma

Etiologies …

- CNS disturbances
  - Stroke, hemorrhage, infection, trauma, psychosis
- Malignancies
  - Small cell carcinoma of lung
  - Head and neck malignancies
  - Olfactory neuroblastoma
  - Extrapulmonary small cell carcinoma

Etiologies …

- Drugs
  - Chlorpropamide
  - Carbamazepine
  - Cyclophosphamide, vincristine, cisplatin, methotrexate
  - SSRIs – fluoxetine, sertraline
  - MAO inhibitors
  - NSAIDs, opiates
  - Sodium valproate
  - INF alpha, INF gamma

Etiologies …

- Trans-sphenoidal pituitary surgery
  - Inappropriate ADH release from injured posterior PT
  - Fall in plasma Na is most severe on 6th-7th post-op day
- Pulmonary disease: Pneumonia, asthma, pneumothorax
- Hormone deficiency: Hypopituitarism, hypothyroidism
- Iatrogenic
  - Desmopressin – for von Willebrand disease or hemophilia
  - Oxytocin
  - Vasopressin – for control of GI bleeding

Signs and Symptoms of SIADH

- Depending on the magnitude and rate of development, hyponatremia may or may not cause symptoms.
- Signs and symptoms of acute hyponatremia do not precisely correlate with the severity or the acuity of the hyponatremia.
- Some patients with profound hyponatremia may be relatively asymptomatic.

Signs and Symptoms …

- When serum sodium <125 mEq/L
  - Anorexia, nausea, malaise
- Further decrease
  - headache, muscle cramps, irritability, drowsiness, confusion, weakness, seizures, and coma
- Symptoms from CNS or pulmonary tumors
  - hemoptysis, chronic headaches

❑ In severe conditions patient die because of coma and convulsions

Diagnosis of SIADH

A. Laboratory tests

- Serum sodium: ..... <135 mmol/L
- Serum potassium: ..... unchanged
- Urinary Na excretion: ..... >20 mmol/L
- Urinary osmolality: ..... >100 mOsm/kg
- BUN: ..... <10 mg/dL
- Serum uric acid: ..... <4 mg/dL
- GFR: ..... increased

Diagnosis …

B. Imaging

- Chest X-ray: To find out an underlying pulmonary cause
- CT and MRI

Treatment Of SIADH

- Three components to the treatment of hyponatremia in SIADH:
  a) Treatment of the underlying disease, if possible
  b) Initial therapy to raise the serum sodium
  c) Prolonged therapy in patients with persistent SIADH

Treatment …

- A variety of causes of SIADH can be effectively treated, leading to resolution of the hyponatremia.
- These include:
  I. Hormone replacement in **adrenal insufficiency or hypothyroidism**
  II. Treatment of infections such as **meningitis, pneumonia, or tuberculosis**
  III. Cessation of offending drugs, such **as selective serotonin reuptake inhibitors or chlorpropamide**

Treatment …

- **Initial therapy to raise the serum sodium**

I. **Fluid restriction —** is a mainstay of therapy in most patients with SIADH, with a suggested goal intake of less than 800 mL/day .

- The associated negative water balance initially raises the serum sodium concentration toward normal and, with maintenance therapy in chronic SIADH, prevents a further reduction in serum sodium.

Treatment …

- **Initial therapy to raise the serum sodium …**

II. **Intravenous saline —** Severe, symptomatic, or resistant hyponatremia in patients with SIADH often requires the administration of sodium chloride.

  - If the serum sodium concentration is to be elevated, the electrolyte concentration of the fluid given must exceed the electrolyte concentration of the urine, not simply that of the plasma

Principles of Correction of Hyponatremia with IV saline

- Aggressive treatment of hyponatremia has a risk of inducing CMP which is a rare but serious complication
- Develops one to several days after aggressive treatment of hyponatremia- which is indicated in patients with severe symptoms such as **seizures, stupor, coma, and respiratory arrest, regardless of the** degree of hyponatremia.

Principles of Correction of Hyponatremia with IV saline

- The goal is to correct hyponatremia at a rate that does not cause neurologic complications.
- Raise serum Na+ levels by 0.5-1 mEq/h, and not more than **10-12 mEq / 24 hours, to bring the Na+ value to** a level of 125 -130 mEq/L.

Treatment ….

- **Loop Diuretic like Furosemide:**

- Increases excretion of free water and has been used along with hypertonic saline in severe cases to limit treatment induced volume expansion.
- The diuresis induced by furosemide has a urine solute concentration roughly equivalent to half-normal saline
- Oral Salt Tablets can also be administered to correct chronic hyponatremia

Treatment ….

- **The vasopressin receptor antagonists (V2 Receptor antagonists):**
- produce a selective water diuresis (aquaresis) without affecting sodium and potassium excretion .
- The ensuing loss of electrolyte- free water will tend to raise the serum sodium in patients with SIADH

Treatment ….

- The choice of therapy in patients with hyponatremia due to SIADH varies with the severity of hyponatremia and the presence or absence of symptoms.
- **severe symptomatic hyponatremia who present with** seizures or other severe neurologic abnormalities or with symptomatic hyponatremia in patients with intracerebral diseases, urgent intervention with hypertonic saline is preferred

Treatment ….

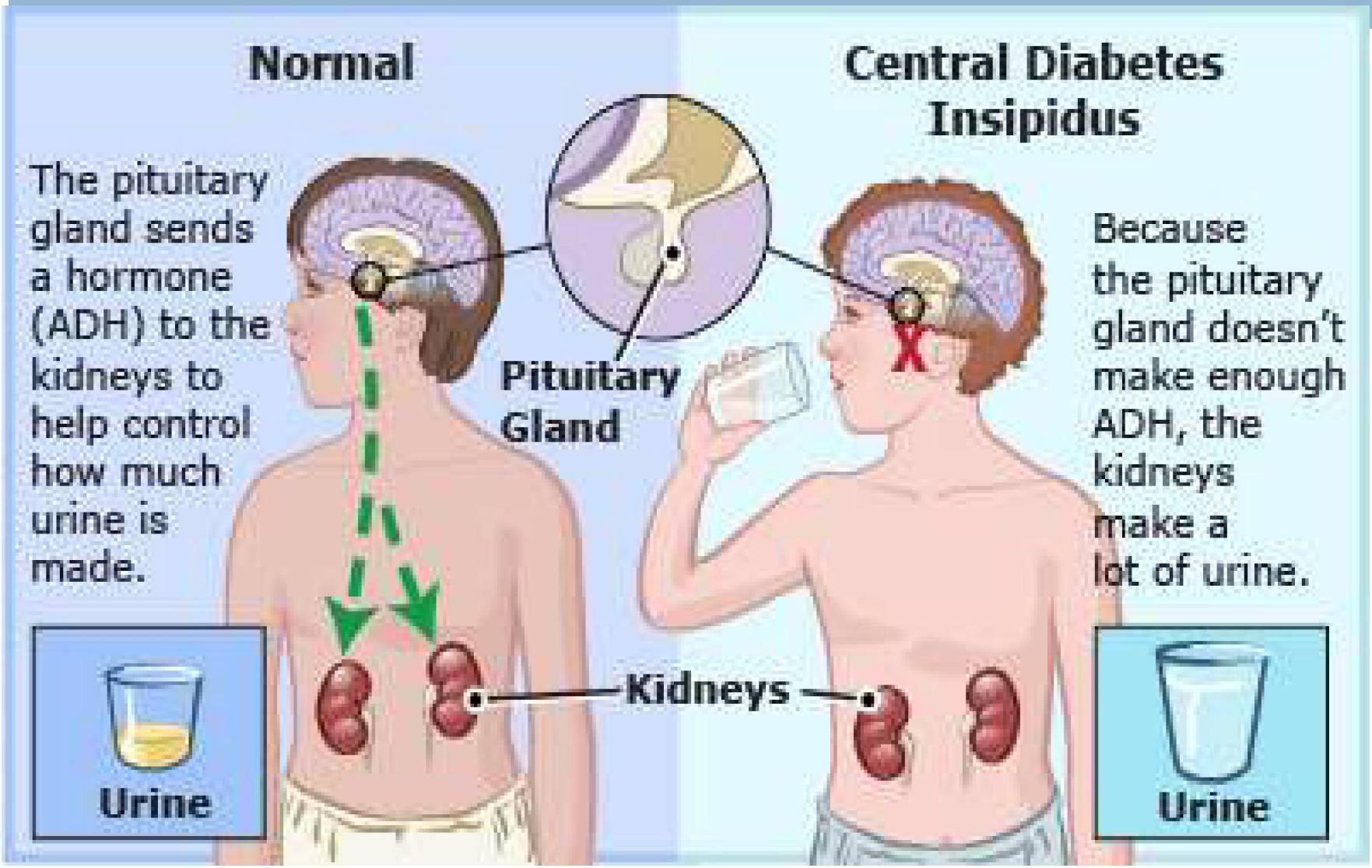
- Slow correction with fluid restriction, Added oral salts and if indicated hypertonic saline is preferred in case of chronic hyponatremia
- Resistant cases of Hyponatremia use of vaptans along with above measures can be considered

Diabetes Insipidus (DI)

Diabetes Insipidus (DI)

- DI is a disorder of the posterior lobe of the pituitary gland.
- Characterized by a deficiency of antidiuretic hormone (ADH), or vasopressin.
- Polydipsia and large volumes of dilute urine characterize the disorder.

Diabetes Insipidus ….



Types of DI

A. Central diabetes insipidus

- Is due to failure of the pituitary gland to secrete adequate ADH.

B. Nephrogenic diabetes insipidus

- Results when the renal tubules of the kidneys fail to respond to circulating ADH.

Causes of DI

1) **Central diabetes Insipidus :-**

- Head trauma or surgery
- Pituitary or hypothalamic tumor
- Intracerebral occlusion or infection
- Idiopathic (30% of cases)

Causes of DI …..

2) Nephrogenic diabetes insipidus

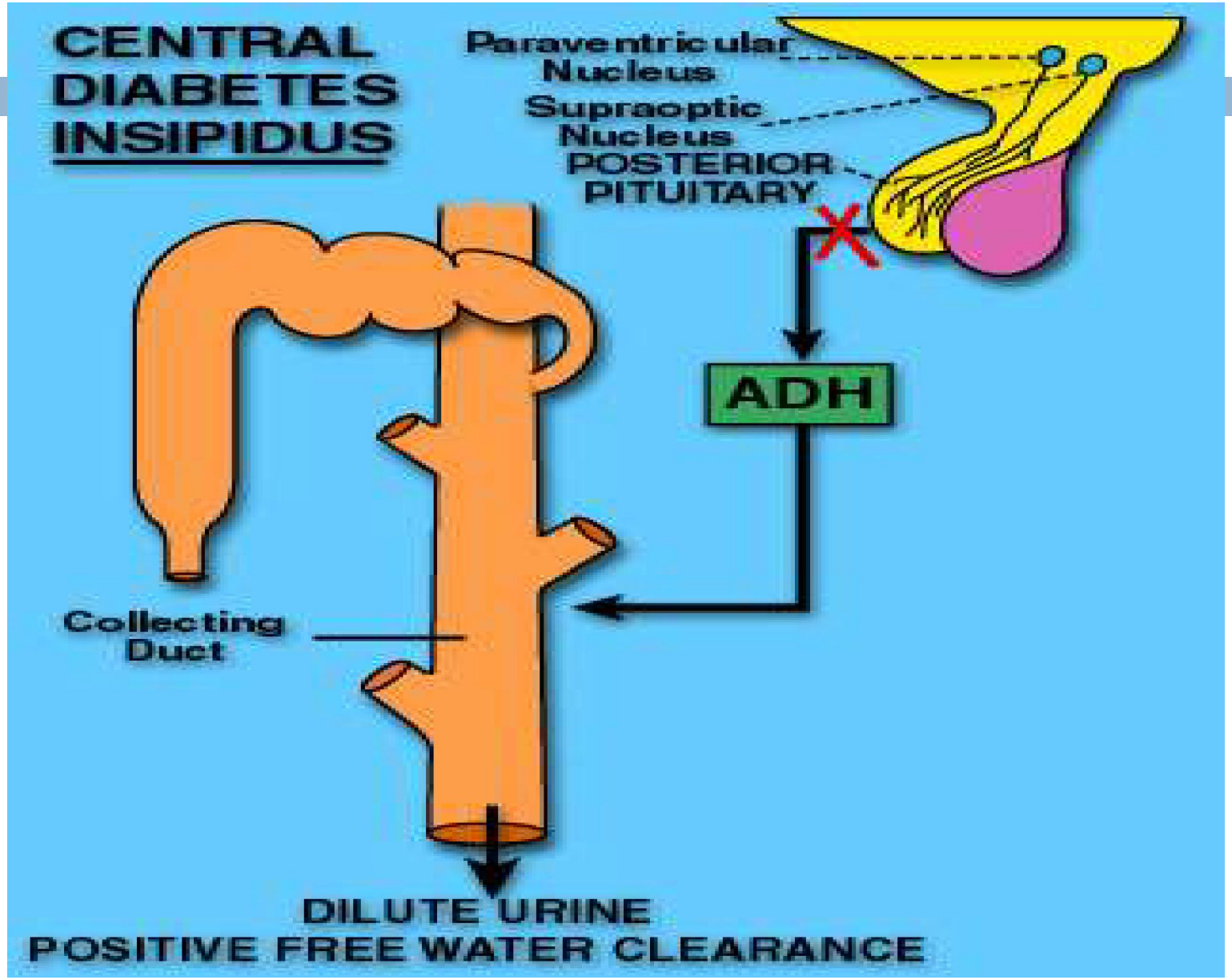
- Systemic diseases involving the kidney
- Multiple myeloma
- sickle cell anemia
- Polycystic kidney disease
- Pyelonephritis
- Medications such as lithium

Pathophysiology of DI

A. Central diabetes insipidus

- Loss of vasopressin-producing cells
- Causing deficiency in ADH synthesis or release
- Deficiency in ADH, resulting in an inability to conserve water
- leading to extreme polyuria and polydipsia

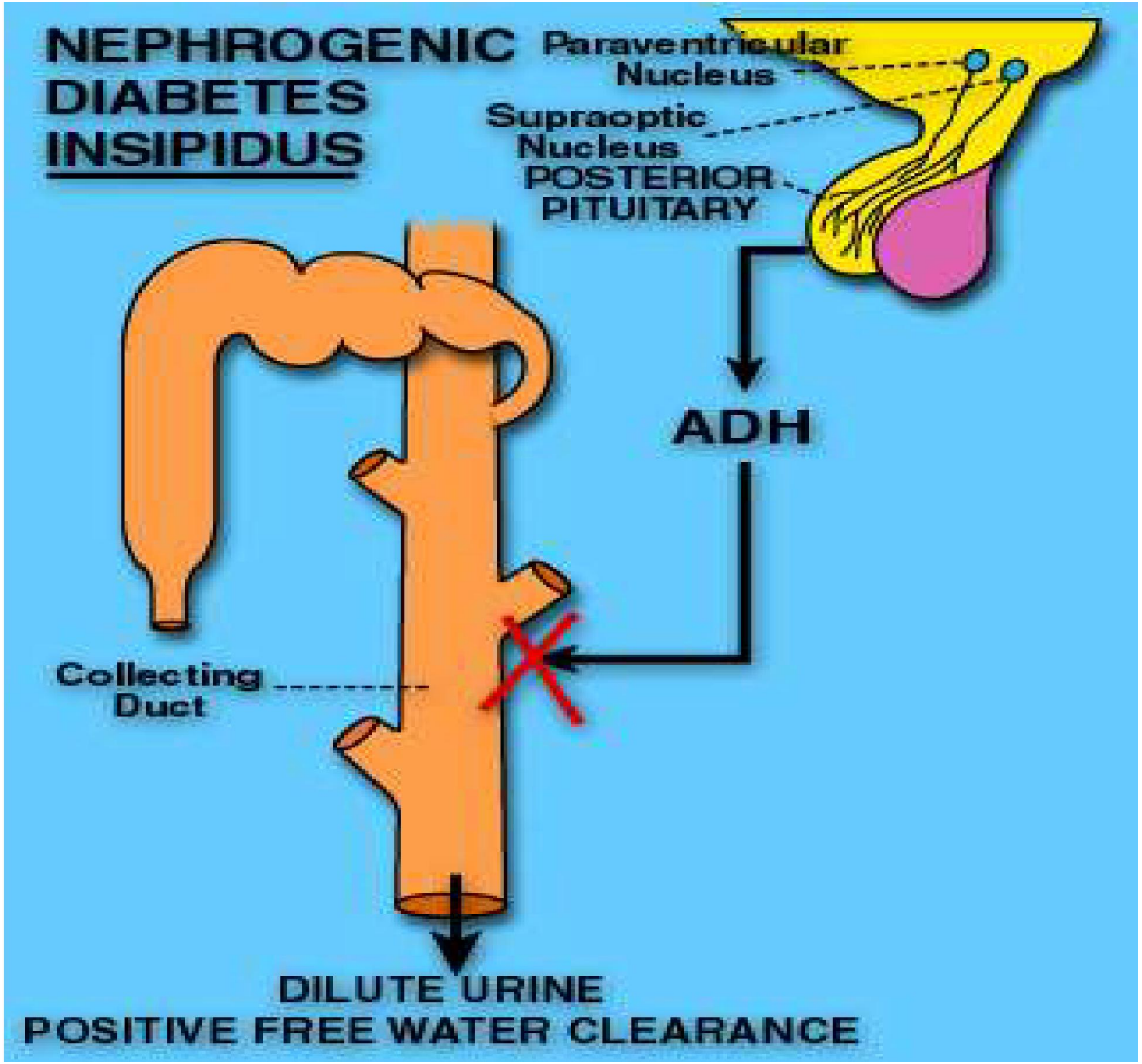
Pathophysiology of DI .....



Pathophysiology of DI …

B. Nephrogenic diabetes insipidus

- Depression of aldosterone release or inability of the nephrons to respond to ADH
- The resulting renal concentration defect leads to the loss of large volumes of dilute urine.
- This causes cellular and extracellular dehydration, hypernatremia, polyuria and polydipsia


NEPHROGENIC DIABETES INSIPIDUS
Paraventricular Nucleus
Supraoptic Nucleus
POSTERIOR PITUITARY
ADH
Collecting Duct
DILUTE URINE
POSITIVE FREE WATER CLEARANCE

Signs and symptoms

- Polyuria with urine output of 5 to 15 L daily
- Polydipsia, especially a desire for cold fluids
- Hyperthermia & lack of sweating
- Marked dehydration, as evidenced by dry mucous membranes, dry skin, and weight loss
- Anorexia and epigastric fullness
- Nocturia and related fatigue from interrupted sleep

Diagnostic test results

- High serum osmolality, usually above 300 mOsm/kg of water
- Low urine osmolarity, usually 50 to 200 mOsm/kg of water
- low urine-specific gravity of less than 1.005
- Increased creatinine and blood urea nitrogen (BUN) levels resulting from dehydration
- Positive response to water deprivation test: Urine output decreases and specific gravity increases

Goals of management

- The objectives of therapy are:

  a) to replace ADH (which is usually a long-term therapeutic program)

  b) to ensure adequate fluid replacement, and

  c) to identify and correct the underlying cause

Treatments of DI

- Replacement vasopressin therapy with intranasal or I.V. DDAVP (desmopressin acetate)
- Correction of dehydration and electrolyte imbalances
- A thiazide diuretic to deplete sodium and increase renal water reabsorption
- Restriction of salt and protein intake

Complications

- Hypernatremic dehydration & its Neurological sequelea
- Growth retardation
- Hydronephrosis (due to excessive Urine output)

Disorders of thyroid gland

By: Agazhe A.

What is thyroid gland?

- The thyroid gland is a butterfly-shaped endocrine gland that is normally located in the lower front of the neck.
- The thyroid's job is to make thyroid hormones, which are secreted into the blood and then carried to every tissue in the body.
- Thyroid hormone helps the body use energy, stay warm and keep the brain, heart, muscles, and other organs working as they should.

Hyperthyroidism

- Hyperthyroidism and thyrotoxicosis are used interchangeably, however each refers to slightly different conditions.
- Hyperthyroidism refers to over activity of the thyroid gland, with resultant excessive secretion of thyroid hormones and accelerated metabolism in the periphery.
- Thyrotoxicosis refers to the clinical effects of an unbound thyroid hormone, regardless of whether or not the thyroid is the primary source.

Hyperthyroidism …

- There are a number of pathologic causes of hyperthyroidism in children and adults.
- These include Graves disease, toxic adenoma, toxic multinodular, goiter, and thyroiditis.
- Graves disease accounts for approximately 95% of cases of hyperthyroidism.

Etiology

- Ectopic thyroid disease
- Grave's disease
- Multi-nodular disease
- Thyroid adenoma
- Subacute thyroiditis
- Ingestion of thyroid hormone
- Pituitary disease
- Ingestion of food containing thyroid hormone
- High dietary iodine intake or very low dietary intake.
- Genetic factor.

Pathophysiology

Hyperthyroidisms characterized by loss normal regulatory control of thyroid hormone secretion.

↓

The action of thyroid hormone on the body is stimulatory, hyper metabolism result

↓

Increase sympathetic nervous system activity

↓

Alteration secretion and metabolism of hypothalamic pituitary and gonadal hormone.

↓

Excessive amount of thyroid hormone stimulate the cardiac system and increase the adrenergic receptors.

↓

Tachycardia and increase cardiac –output, stroke volume and peripheral blood flow.

↓

Negative nitrogenous balance, lipid depletion and the resultant state of nutritional deficiency.

↓

Hyperthyroidism result

Clinical manifestation

- Symptoms & their severity depend on duration and extent of thyroid hormone excess, and the age of the individual.
- Individuals may experience:
  - Nervousness and irritability
  - Palpitations and tachycardia
  - Heat intolerance or increased sweating
  - Tremor
  - Weight loss or gain

Clinical manifestation …

- Increase in appetite
- Frequent bowel movements or diarrhea
- Lower leg swelling
- Sudden paralysis
- Shortness of breath with exertion
- Decreased menstrual flow
- Impaired fertility
- Sleep disturbances (including insomnia)

HYPERTHYROIDISM SYMPTOMS

BULGING EYES

GOITER

SWELLING

INCREASED PALPITATIONS

NORMAL THYROID

HAND TREMORS

HUNGER

ENLARGED THYROID

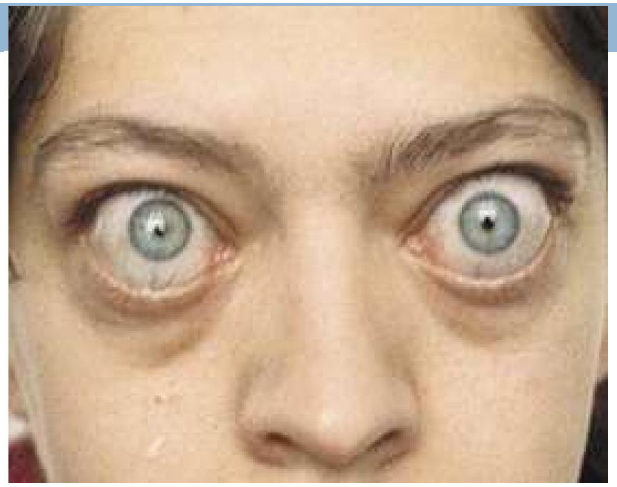
BREATHING PROBLEMS

MOOD SWINGS

WEIGHT LOSS

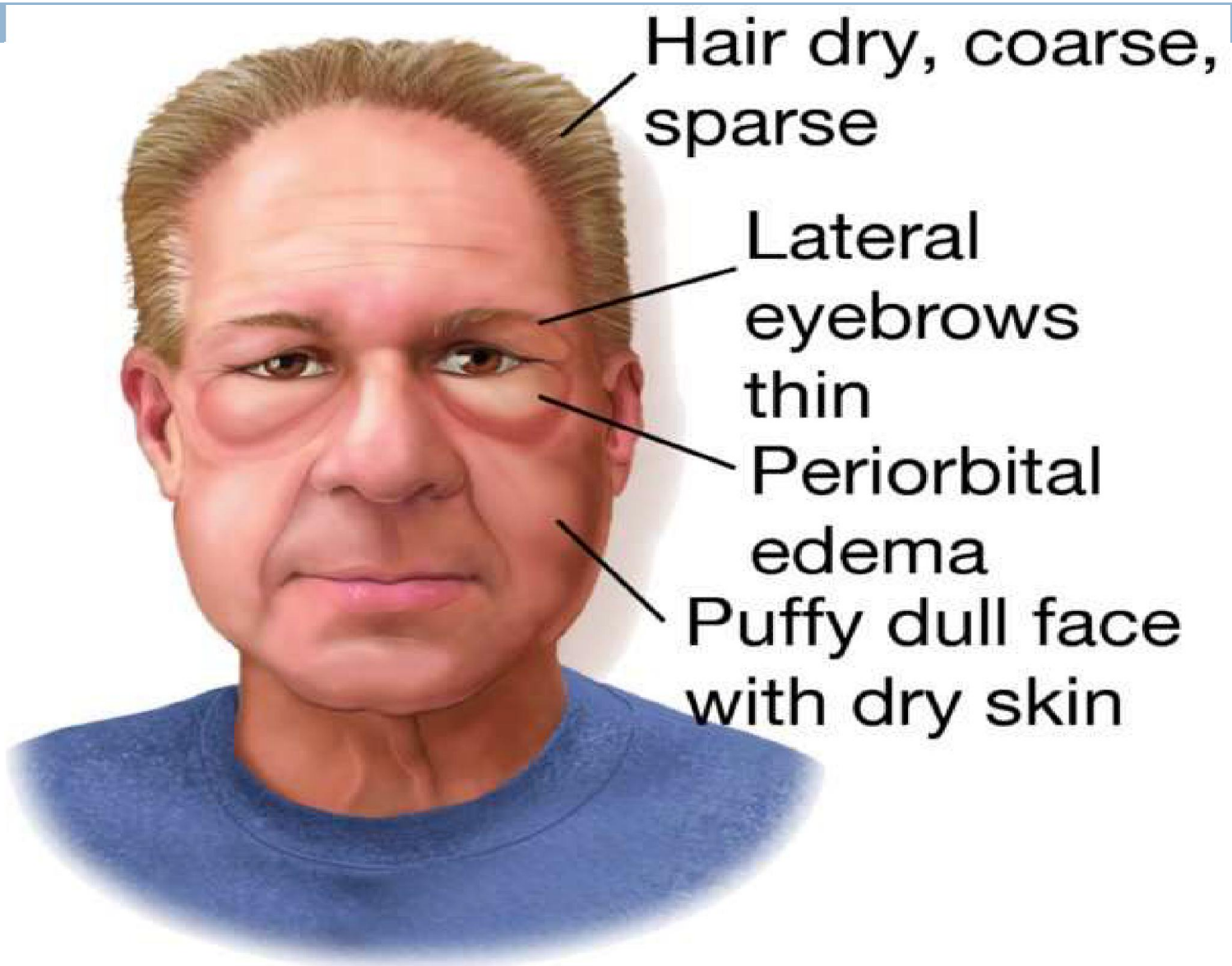
HAIR LOSS

Clinical manifestation …



- **Changes in vision**
  - Photophobia, or light sensitivity
  - Eye irritation with excess tears
  - Diplopia, or double vision
  - Exophthalmos, or forward protrusion of the eyeball
  - Fatigue and muscle weakness
  - Thyroid enlargement
  - Pretibial myxedema (fluid buildup in the tissues about the shin bone; may be seen with Grave's disease)

Clinical manifestation …



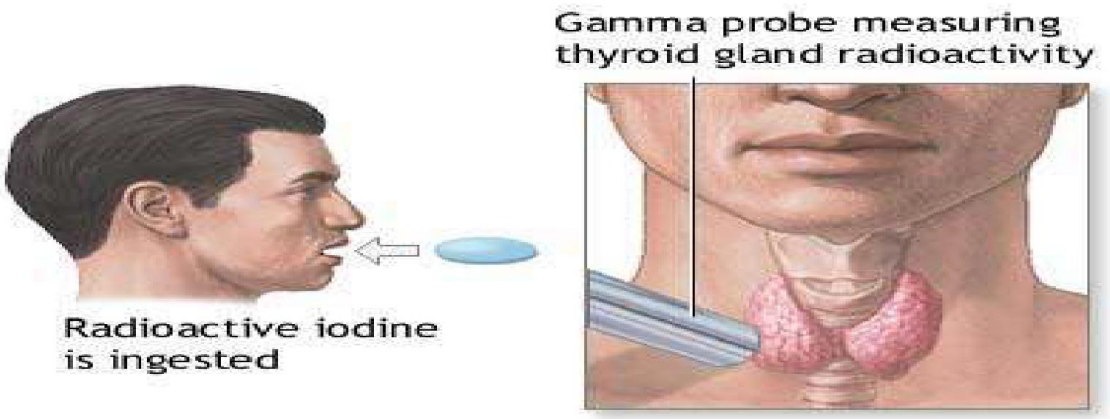
Investigation

- History and physical examination
- Ophthalmic examination
- ECG- atrial tachycardia
- Thyroid function test: T3 and T4
- Thyroid releasing hormone stimulation test
- Radioactive iodine uptake (RAIU)
- Thyroid scan

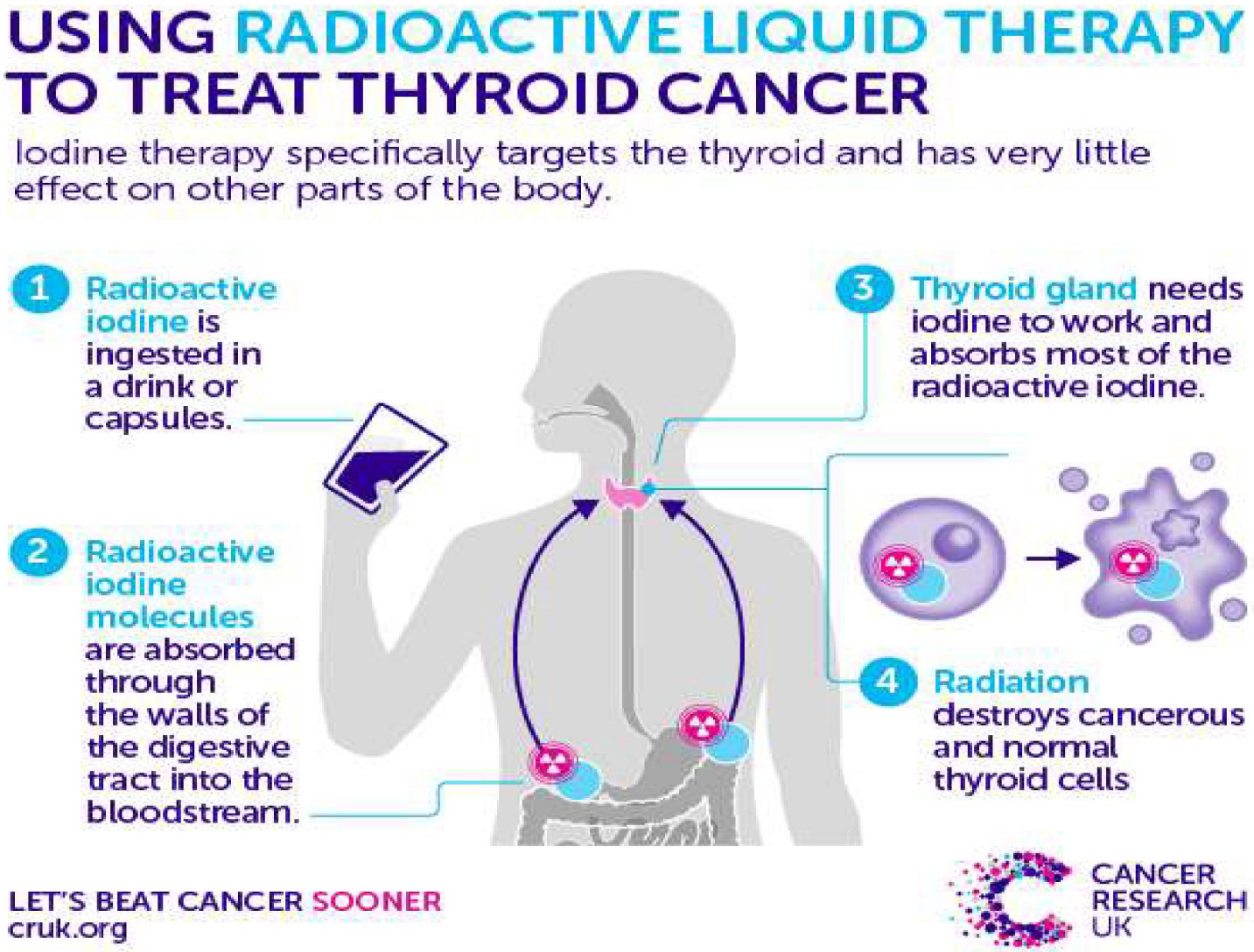
Treatment

1. Radioactive iodine

- Taken by mouth, radioactive iodine is absorbed by your thyroid gland, where it causes the gland to shrink and symptoms to subside, usually within three to six months.



Treatment …


USING RADIOACTIVE LIQUID THERAPY TO TREAT THYROID CANCER
Iodine therapy specifically targets the thyroid and has very little effect on other parts of the body.
1 Radioactive iodine is ingested in a drink or capsules.
2 Radioactive iodine molecules are absorbed through the walls of the digestive tract into the bloodstream.
3 Thyroid gland needs iodine to work and absorbs most of the radioactive iodine.
4 Radiation destroys cancerous and normal thyroid cells
LET'S BEAT CANCER SOONER
cruk.org
CANCER RESEARCH UK

Treatment ….

2. Anti-thyroid medications

- These medications gradually reduce symptoms of hyperthyroidism by preventing your thyroid gland from producing excess amounts of hormones.
- They include propylthiouracil and methimazole (Tapazole).
- Symptoms usually begin to improve in 6 to 12 weeks, but treatment with anti-thyroid medications typically continues at least a year and often longer.

Treatment ….

3. Beta blockers

- These drugs are commonly used to treat high blood pressure.
- They won't reduce your thyroid levels, but they can reduce a rapid heart rate and help prevent palpitations.
- Side effects may include fatigue, headache, upset stomach, constipation, diarrhea or dizziness.

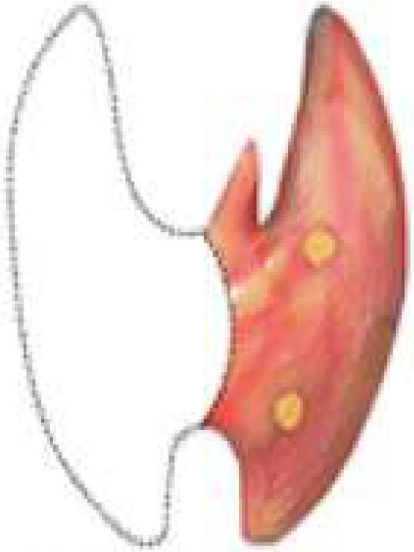
Treatment ….

4. Surgical management

- Several surgical options exist for treating thyroid disease and the choice of procedure depends on two main factors.
  a) The type and extent of thyroid disease present.
  b) The anatomy of the thyroid gland itself.
- The most commonly performed procedures include: lobectomy, lobectomy with isthmectomy, subtotal thyroidectomy, and total thyroidectomy.

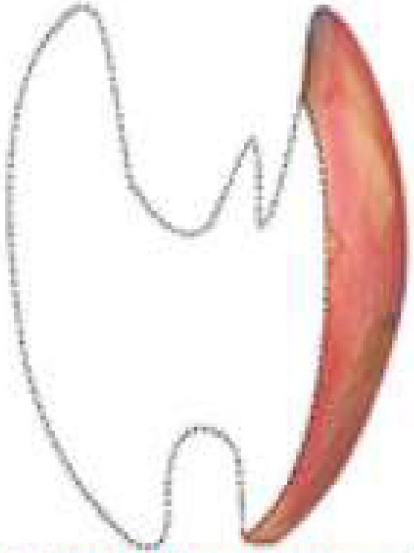
Methods/ Techniques of Thyroid Cancer Surgery

Thyroid lobectomy



Lobectomy is generally performed when tumor is restricted to one lobe of thyroid gland & has not yet started invading other organs or lymph nodes.

Subtotal thyroidectomy



Subtotal thyroidectomy is the procedure when most of the gland is removed, but a portion is left behind as well.

Total thyroidectomy

When the entire gland is removed, the procedure is known as total thyroidectomy.

{ MediFee.com }

Nursing management

1. Imbalanced nutrition less than body requirement related to anorexia and increase nmetabolic demand is inappropriate.

- Intervention:
  - High calorie diet (4000-5000 kcal/day)
  - High protein diet (1-2 g/kg of ideal body weight)
  - Frequent meals

Nursing management …

2. Activity intolerance related to exhaustion secondary to accelerated metabolic rate resulting in inability to perform activity without shortness of breath and significant increased in heart rate

- Intervention:
  - Assist with regular physical activity.
  - Assist in activities of daily living
  - Assist the patient to schedule rest periods.

Nursing management …

3. Risk for corneal ulceration related inability to close the eye lids secondary to exophthalmos.
4. Hyperthermia related to accelerated metabolic rate resulting in fever, diaphoresis and reported heat intolerance.
5. Impaired social interaction related to extreme agitation, hyperactivity, and mood swings resulting in inability to relate effectively with others

Hypothyroidism

- Abnormally low activity of the thyroid gland, resulting in retardation of growth and mental development in children and adults.

Epidemiology of Hypothyroidism

- Worldwide about one billion people are estimated to be iodine deficient; however, it is unknown how often this results in hypothyroidism.
- In large population-based studies in Western countries with sufficient dietary iodine, 0.3 – 0.4% of the population have overt hypothyroidism.
- A larger proportion, 4.3–8.5%, have subclinical hypothyroidism.
- Women are more likely to develop hypothyroidism than men.

Risk factors of hypothyroidism

- Although anyone can develop hypothyroidism, you're at an increased risk if you:
  - Are a woman older than age 60
  - Have an autoimmune disease
  - Have a family history of thyroid disease
  - Have other autoimmune diseases, such as rheumatoid arthritis or lupus, a chronic inflammatory condition
  - Have been treated with radioactive iodine or antithyroid medications
  - Received radiation to your neck or upper chest
  - Have had thyroid surgery (partial thyroidectomy)
  - Have been pregnant or delivered a baby within the past 6 month

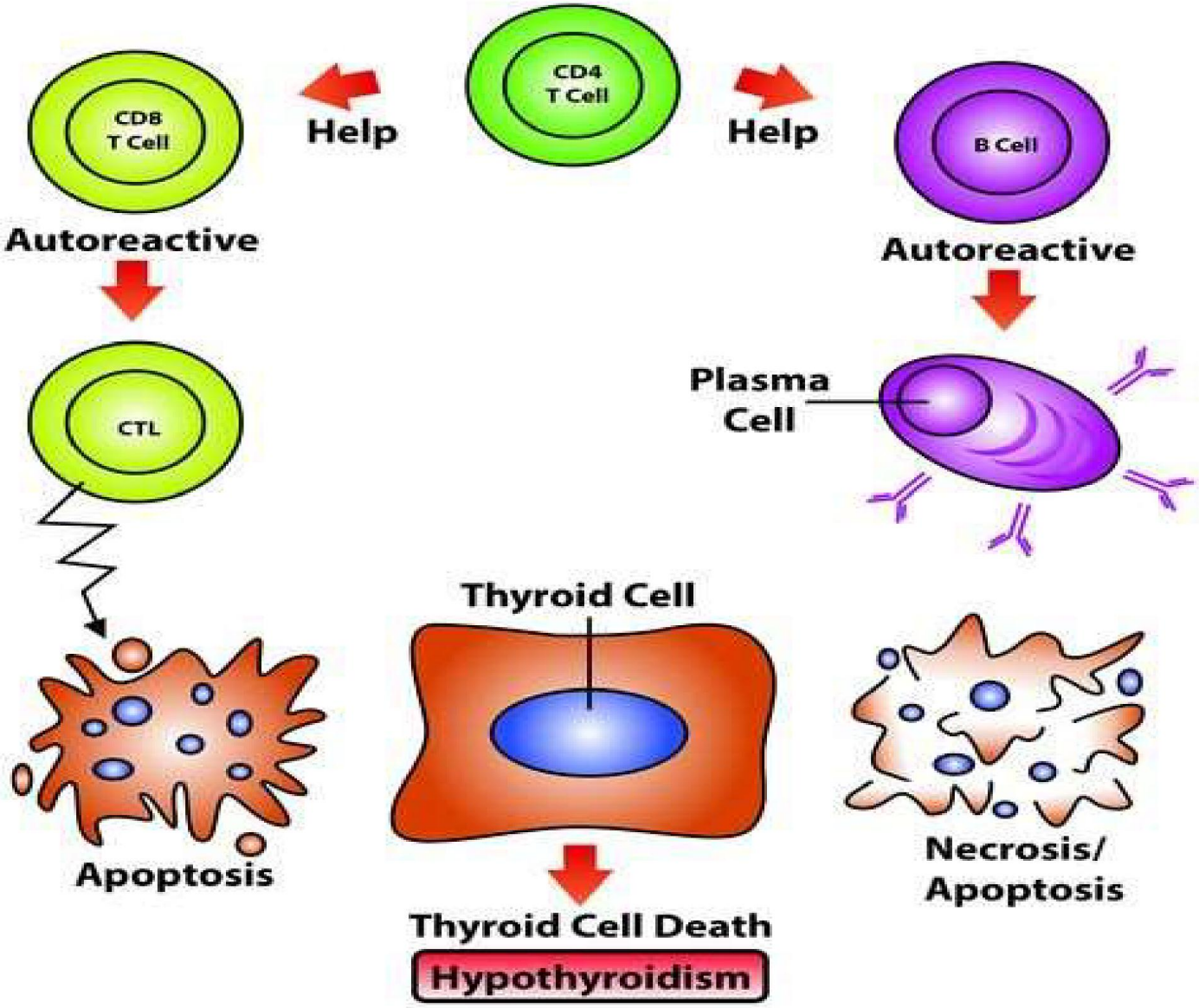
Causes of hypothyroidism

- **Medication:** A number of medications can cause Hypothyroidism. Lithium, which is used to treat certain psychiatric disorders, can also affect the thyroid gland.
- **Genetic dysfunction: The thyroid gland may be** dysfunctional at birth, or may fail at some phase in adult life.
- **Previous thyroid surgery: Removal of a large** portion or the entire thyroid gland may reduce or stop the process of thyroid hormone production.
- **Treatment for Hyperthyroidism: Treatment for** Hyperthyroidism may sometimes result in Hypothyroidism.

Causes of hypothyroidism …

- **Radiation therapy:** Exposure of the thyroid gland to radiation therapy for the treatment of cancers of the head and neck region may result in Hypothyroidism.
- **Damage to the Pituitary Gland:** The pituitary gland may be damaged due to disease or surgery which may result in decreased level of thyroid hormones.
- **Autoimmune Thyroid Disease:** This is the most common cause of Hypothyroidism. This happens when the body's immune system produces certain antibodies that attack its own thyroid gland leading to a reduced thyroid hormone production.

Hashimoto's Thyroiditis



Sign & symptoms of Hypothyroidism

- Fatigue
- Increased sensitivity to cold
- Constipation
- Dry skin
- Weight gain
- Puffy face
- Hoarseness
- Muscle weakness
- Elevated blood cholesterol level
- Muscle aches, tenderness and stiffness
- Pain, stiffness or swelling in your joints
- Heavier than normal or irregular menstrual periods
- Thinning hair
- Slowed heart rate
- Depression
- Impaired memory

Investigation

- History and physical examination
- Serum T3, T4
- Serum TSH
- Serum cholesterol
- TRH stimulation test

Treatment

- TH replacement e.g. levothyroxine
- Monitor TH level and adjusted dosages
- Nutritional therapy to promote weight loss

Iodine deficiency related /endemic goiter

Endemic goiter

Introduction

- The most common type of goiter, once encountered chiefly in geographic regions where the natural supply of iodine is deficient, is the so-called simple or colloid goiter.
- In addition to being caused by an iodine deficiency, simple goiter may be caused by an intake of large quantities of goitrogenic substances in patients with unusually susceptible glands.
- These substances include excessive amounts of iodine or lithium, which is used in treating bipolar disorders.

Endemic goiter

- Endemic goiter is a type of goiter that is associated with dietary iodine deficiency
- Iodine deficiency is a lack of the trace element iodine

Endemic goiter ….

- If the prevalence of goiter is more than 5% of the population (mostly children), it is considered an endemic goiter
  - <5% no endemic
  - 5-19.9% mild endemic
  - 20-29.9% moderate endemic
  - >30% severe endemic

Iodine requirements

- Iodide is essential for thyroid hormone synthesis.
- In order for the thyroid gland to synthesize adequate amounts of thyroxine (T4), approximately 52 mcg of iodide must be taken up daily by the thyroid gland.
- Severe iodine deficiency develops when iodide intake is chronically <20 mcg/day.
- Iodine can be obtained by consumption of foods that naturally contain it (fish, seafood, kelp, some drinking water, and vegetables grown in iodine sufficient soil) or to which it is added (table salt).

Iodine requirements

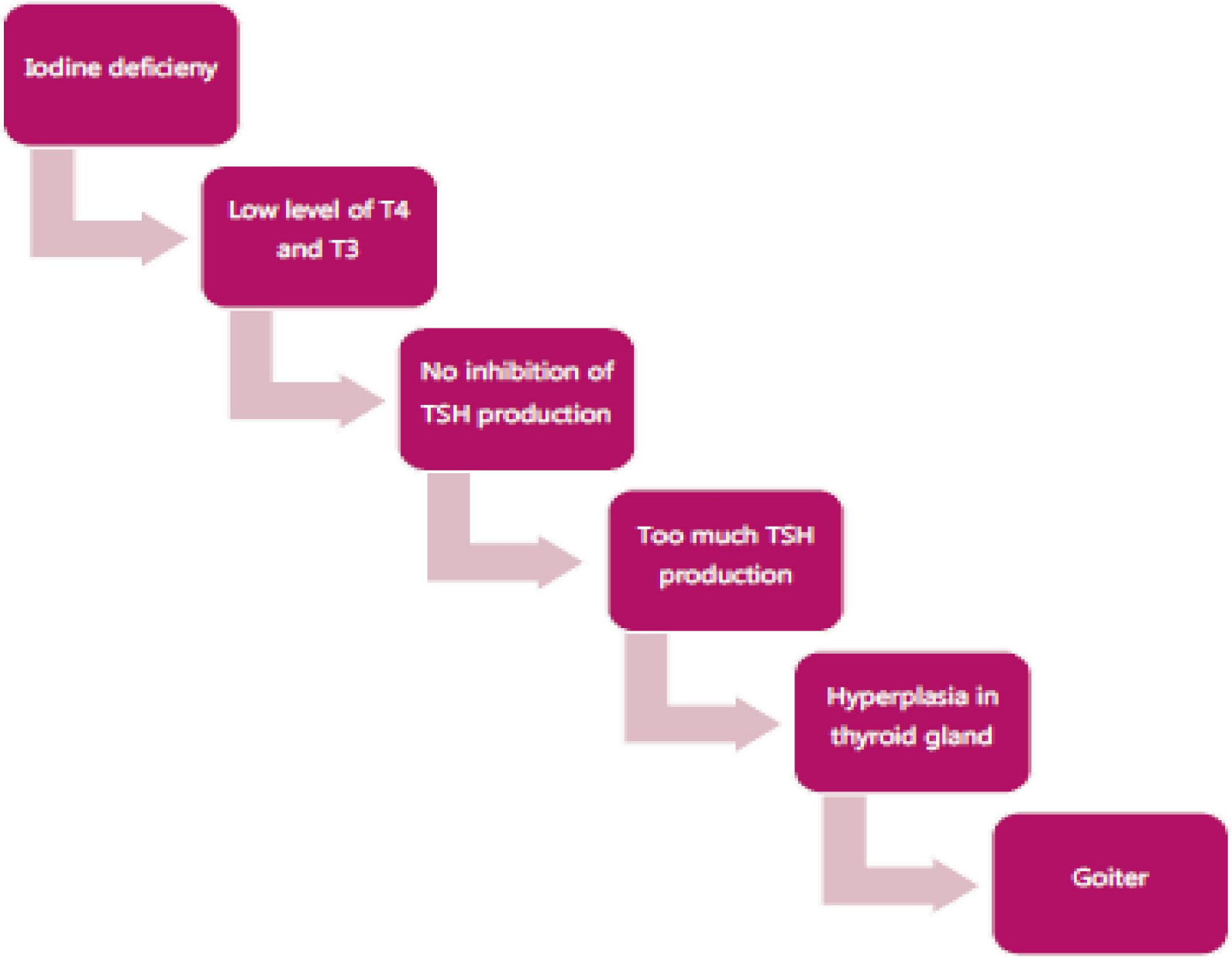
- Dietary iodine is absorbed as iodide and rapidly distributed in the extracellular fluid, which also contains iodide released from the thyroid and by extrathyroidal deiodination of the iodothyronines.
- Iodide leaves this pool by transport into the thyroid and excretion into the urine.
- WHO recommends 90 mcg of iodine daily for infants and children up to five years, 120 mcg for children 6 to 12 years, 150 mcg daily for children ≥12 years and adults, and 250 mcg daily during pregnancy and lactation.

Pathophysiology of Endemic goiter

- Goiter: A swelling of the neck resulting from enlargement of the thyroid gland
- Iodine I2 (Iodide ion in food, such as in salt, Iodide bonds with Na+) is necessary for the secretion of thyroid hormones (T4, T3).
- Iodine accounts for 65% of the molecular weight of T4 and 59% of the T3

Pathophysiology …

- The amount of TSH secreted by anterior pituitary is regulated by negative feedback loop.
- If the amount of T4 and T3 gets high, TSH secretion will be decreased
- But in iodine deficiency there is very little amount of thyroid hormones, thus no inhibition of TSH production, leaving the anterior pituitary to produce TSH freely
- Excess amount of TSH will cause thyroid gland cells to multiply and divide excessively resulting in goiter.


Iodine deficieny
Low lewel of T4 and T3
No inhibition of TSH production
Too much TSH production
Hyperplasia in thyroid gland
Goiter

Causes/Risk factors of endemic goiter

- Low dietary iodine
- Iron and selenium deficiency (iron, selenium are contained in proteins that are important for synthesis of thyroid hormones)
- Pregnancy
- Exposure to radiation
- Increased level of goitrogens, such as some drugs and antibiotics (substances that interfere with iodine uptake in the thyroid gland)
- Gender (higher occurrence in women)
- Oral contraceptives
- High consumption of conserved, pickled foods that contain thyrostatics

Signs & symptoms/ consequences

- **Fetus/Neonates**
  - Cretinism (commonly characterised by mental deficiency, deafness, squint, disorders of stance and gait, stunted growth and hypothyroidism)
  - Increased prenatal and infantile mortality
  - Increased risk of deaf-mutism
  - Retarded bone growth

Signs & symptoms/ consequences …

- **Children:**
  - Goiter
  - Physical development delays
  - Mental development delays
  - Impaired sense of hearing and problems with speech
  - Paralysis of limbs

Signs & symptoms/ consequences …

- **Pregnant and women of child bearing age:**
  - Congenital anomalies
  - Reduced fertility
  - Irregular menstrual cycle
  - Increased incidence of spontaneous abortions
  - Still birth

Signs & symptoms/ consequences …

- **Adults:**
  - Goiter
  - Reduced IQ (about 10-15 points)
  - Risk of compression of the upper airways
  - Increased risk of thyroid cancer
  - Hypothyroidism
  - Constipation
  - Dry, flaky skin
  - Generally inactive and sleepy
  - Cold intolerance

Diagnosis

- Patient lives in a country with high iodine deficiency risk (mountanies regions and 3rd world countries)
- Low level of median urine iodine
- High absorption of radioactive iodine (I 131) during scintigraphy
- Goiter
- Euthyroid or hypothyroid state
- T4 synthesis ↓; T3 synthesis ↑
- TSH ↑

Treatment of endemic goiter

- Drugs
- Surgery
  - If drug treatment is ineffective, the size of the goiter is not lowering
  - If the size of the goiter is really large
  - Nodule, malignancy

Treatment …

Euthyroid	Hypothyroid
-increase the intake of high **iodine food** (use of iodized salt) -**iodine supplements** (potassium iodide) -**iodized oil**	• **L-Thyroxin** 25-50mcg/ tab; daily dosage of 100-200mcg • **Triiodothyronine hydrochloride** starting dosage: 2-5mcg/tab. Increase the dosage up to 50mcg/tab, 50-100mcg/day • **Thyreotom**: 1 tab contains 40mcg T4, 10mcg T3. Start by 1/4 -1/8 of a tablet and increase to 1-1.5 tab/day.

Prevention of endemic goiter

- Discuss the prevention strategies of endemic goiter

Thyroiditis

Thyroiditis

- A heterogeneous group of inflammatory disorders involving the thyroid gland
- The etiologies range from autoimmune to infectious origins.
- The clinical course may be acute, subacute, or chronic.

Classification of Tyroiditis

1. **Acute thyroiditis**
   - Infectious
   - Non-infectious
2. **Subacute thyroiditis**
3. **Autoimmune thyroiditis**
   a. Chronic autoimmune thyroiditis:
      - Hashimoto's thyroiditis
      - Atrophic thyroiditis
      - Focal thyroiditis
      - Juvenile thyroiditis

   b. Silent thyroiditis

   c. Postpartum thyroiditis
4. **Riedel's thyroiditis**

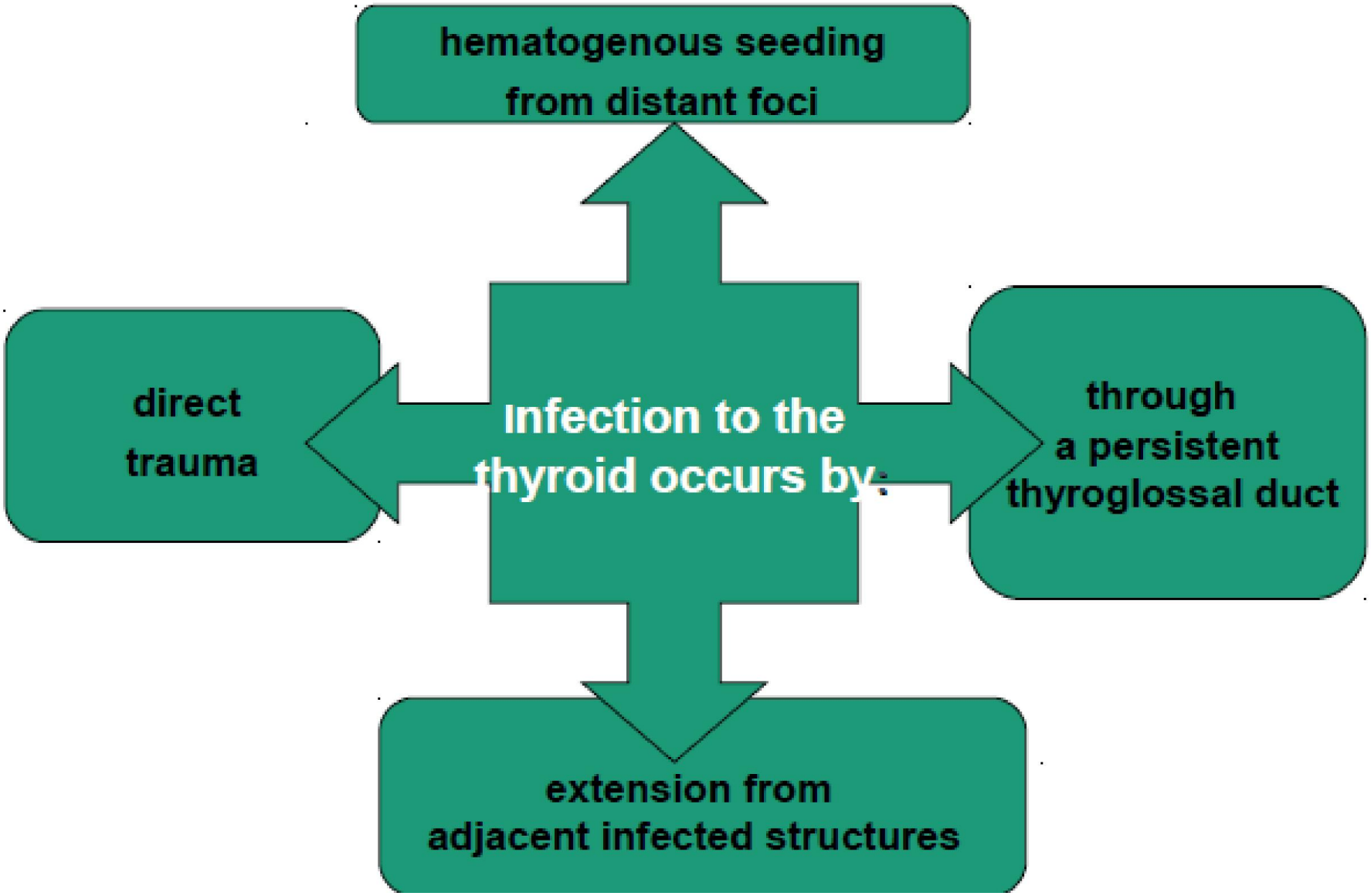
Acute infectious thyroiditis

- Rare, serious, bacterial inflammatory disease of the thyroid gland.
- **Etiologic agents:**
  - *Streptococcus pyogenes*
  - *Streptococcus pneumoniae*
  - *Escherichia coli*
  - *Pseudomonas aeruginosa*
  - *Salmonella typhi*
  - anaerobes of the oropharyngeal cavity.

Rare Forms of Infectious Thyroiditis

- The thyroid is rarely the seat of tuberculosis, syphilis, fungal infections (Aspergillus species), or parasites.
- Pneumocystis carinii infection of the thyroid has been reported in patients with AIDS.

How thyroid becomes infected



Clinical Picture of Acute Infectious Thyroiditis

- severe anterior neck pain of abrupt onset, pain may radiate to the ear, mandible, or occiput
- Dysphagia, dysphonia, fever, rigor, diaphoresis
- palpation shows a unilateral or less-frequently bilateral tender swelling of the thyroid which is associated with cervical lymphadenopathy

Clinical Picture of Acute Infectious Thyroiditis ….

- Erythematous, warm skin over the infected area
- Elevated WBC count and ESR
- Thyroid antibodies are absent
- Serum T4 and T3 levels are usually normal
- Ultrasonography shows an enlarged irregular mass of mixed echogenicity
- Purulent material at fine-needle aspiration is confirmatory of suppurative thyroiditis

Treatment of Infectious Thyroidtis

- **This type of thyroiditis requires:**
  - administration of appropriate antibiotics based on the findings of the culture, and
  - surgical drainage of any area of abscess.
- **Before the results of the ulture:**
  - a combined regimen of nafcilin and gentamicin or a third generation cephalosporin be appropriate

Non-infectious acute thyroiditis

- Clinical picture depends on causative agents

A. After Iodine therapy

- Tender swelling of the thyroid
- Itching of the skin over thyroid
- Subfebrile body temperature

B. After radiotherapy of thyroid & breast cancer

- Asymptomatic or oligosymptomatic course, leading into hypothyroidism

C. After Neck Trauma: bleeding to thyroid parenchyma

- severe anterior neck pain of abrupt onset
- swelling of the thyroid
- fluctuation

Non-infectious thyroiditis treatment

- In milder cases disappear spontaneously
- In some cases: Salicylates or NSAIDs (Polopiryni S 2-3 g/day, Paracetamol 1.5-2.0g/day)
- Exceptionally: Corticosteroids (Prednisone 20-30mg/day)

Subacute (granulomatous) thyroiditis

- A spontaneously remitting, painful, inflammatory disease of the thyroid, probably of viral origin.
- It is the most frequent cause of anterior neck pain.
- Most prevalent in the temperate zone.
- Afflicts more frequently women between the third and sixth decades of life.

Subacute thyroiditis etiology

- **Probably viral infections**
- There are some evidence:
  - Often preceded by an upper respiratory tract viral infection
  - Prodromal viral symptoms
  - Seasonal distribution (summer and fall)
  - Occurs in coincidence with outbreaks of viral diseases (mumps, measles, influenza)
  - Elevated titers of viral antibodies have been found in patients with subacute thyroiditis

Clinical picture of Subacute thyroiditis

- There is usually a viral prodrome with: myalgias, low-grade fever, sore-throat and dysphagia
- Anterior neck pain occurs abruptly, which is sometimes unilateral, and may radiate to the ear, mandible or occiput
- pain may shift to the contralateral lobe (creeping thyroiditis): moving the head, swallowing, or coughing aggravate the pain.
- Symptoms of thyrotoxicosis may occur

Clinical picture of Subacute thyroiditis …

On palpation:

- The thyroid is slightly to moderately enlarged
- Sometimes asymmetrical or even nodular
- Firm, tender, and painful

Laboratory Findings of Subacute Thyroiditis

- Elevated ESR (>55mm/h)
- Normal or slightly elevated leukocyte counts,
- Increased serum IL-6 and tg concentrations during the thyrotoxic phase,
- Thyroid antibodies are transiently detectable at low titers in a minority of patients

Phases of subacute thyroiditis

1) **Thyrotoxic:**
   - high T4 and/or T3 level
   - low TSH level
   - RAIU value <5%
2) **Hypothyroid:**
   - low T4
   - high TSH level
   - normal RAIU value
3) **Recovery:**
   - normal T4 & T3 level
   - normal TSH level
   - normal RAIU value

Treatment of Subacute thyroiditis

- **In milder cases:**
  - salicylates or NSAIDs provide some relief of pain and tendernees.
- **In more severe cases:**
  - Corticosteroids (prednisone 40-60mg/day) have a more dramatic and rapid effect;
  - Corticosteroid is slowly tapered over the next 6 to 8 weeks and then discontinued.

RX of Subacute thyroiditis …

- Symptoms of thyrotoxicosis should be managed with B-adrenergic blocking agents (Propranolol 20-40mg, 3 to 4 times daily)
- In patients with hypothyroidism L-T4 replacement is needed.

Subacute thyroiditis …

- The course of the disease may last 2 to 6 months without treatment.
- Recurrences of the subacute thyroiditis are reported in about one-fifth of the patients.
- Permanent hypothyroidism is rare (1-5%).
- The disease may evolve into chronic autoimmune thyroiditis.

Autoimmune thyroiditis

- the disease is most often diagnosed between the ages of 50 - 60 years,
- 5 to 7 times more frequently in women than in men;

Autoimmune thyroiditis etiology

- Organ-specific autoimmunity is the cause of the disease
- The thyroid is infiltrated by lymphocytes
- Thyroid antibodies are present in serum
- and there is a clinical or immunological overlap with other autoimmune diseases.
- Activated, autoreactive T-helper recruit in the thyroid: cytotoxic T cells (T cells may kill directly thyroid cells or also cause tissue injury by release of cytokines) and B cells (are transformed into plasmacytes which produce antithyroid antibodies)

Autoimmune thyroiditis etiology …

- **Antithyroid antibodies:**
  - thyroid peroxidase antibodies (TPOAb)
  - thyroglobulin antibodies (TgAb)
  - TSH-blocking antibodies
- **Environmental factors** (infectious agents, physical and emotional stress, and increased iodine intake), etc

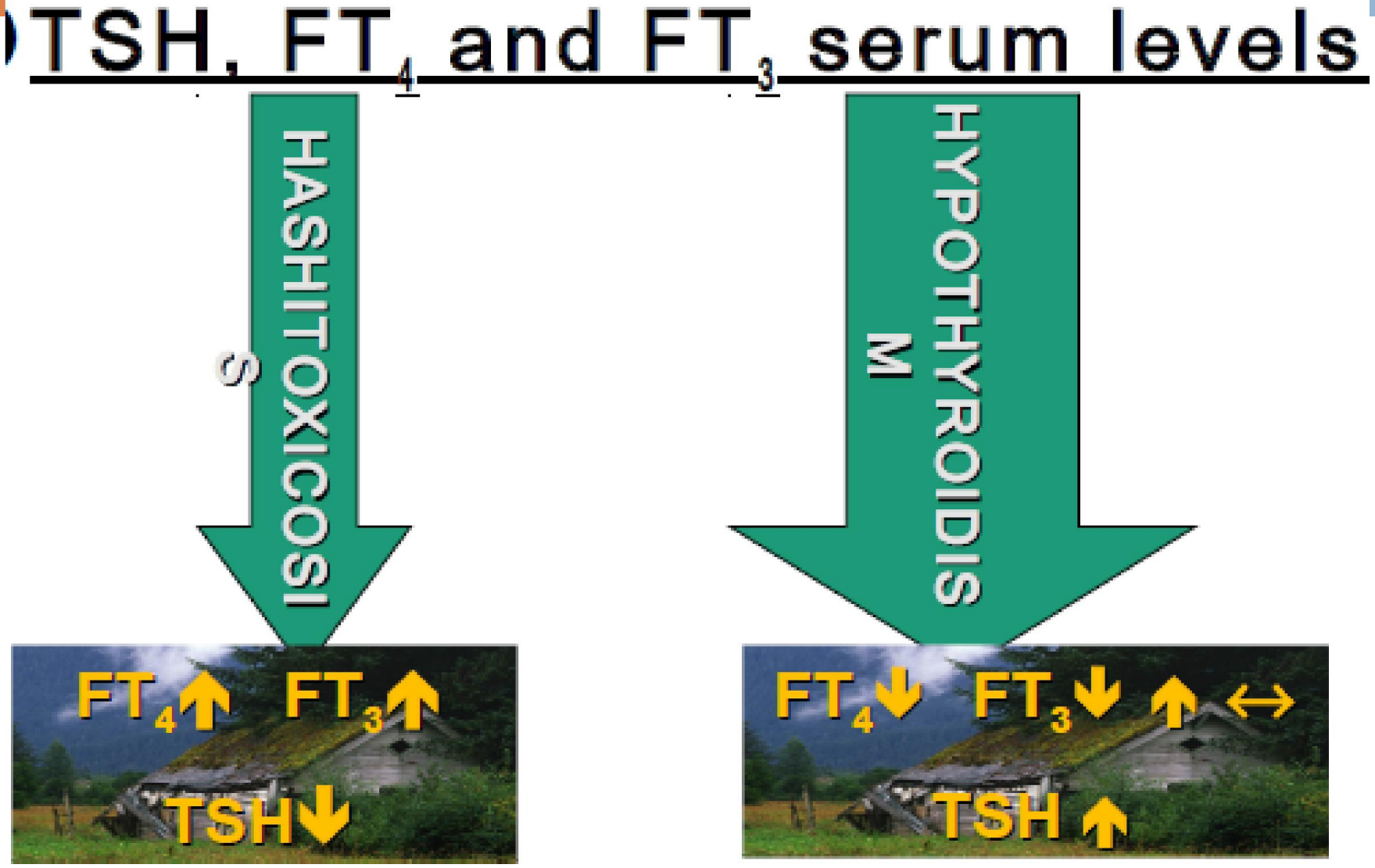
Autoimmune thyroiditis Clinical Feature

- Patients may present a goiter with or without hypothyroidism.
- A feeling of tightnees in the neck may occur, but compression of the trachea is uncommon.

On physical examination:

- most Hashimoto's glands are diffusely enlarged, but one lobe may be larger than the other, and the pyramidal lobe may be palpable
- the goiter is generally moderate in size, though massive enlargements may occur
- the gland is nontender, firm or rubbery in consistency, with a bosselated surface
- the thyroid gland is reduced in size in atrophic thyroiditis.

Autoimmune thyroiditis diagnostic procedures



Autoimmune thyroiditis diagnostic procedures …

- Antithyroid antibodies are positive:
  - TPOAb: 95% patients
  - TgAb: 60-80% patients
- In few patients anti-thyroid antibodies are in low or undetectable titers (seronegative Hashimoto's thyroiditis)
- An ultrasound → diffusely reduced echogenicity
- Thyroid radionuclide scan and radioactive iodine uptake (RAIU) are not crucial to the diagnosis

Autoimmune thyroiditis treatment

- Corticosteroids are not recommended
- Substitution therapy with L-T4 at a dose that normalizes serum TSH levels
- the averaage daily replacement dose of L-T4 in adults is 1.6ug/kg body weight

  =75-100ug/day in women and 100-150ug/day in men.

Autoimmune thyroiditis …

Can be classified as:

a. Chronic autoimmune thyroiditis:

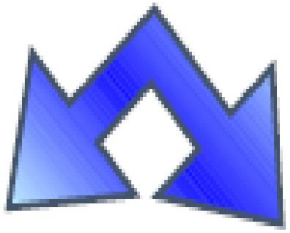
- Hashimoto's thyroiditis
- Atrophic thyroiditis
- Focal thyroiditis
- Juvenile thyroiditis

b. Silent thyroiditis

c. Postpartum thyroiditis

Autoimmune thyroiditis …

Chronic Autoimmune Thyroiditis Presents with 2 Clinical Entities:



a goitrous form *(Hashimoto thyroiditis)*

an atrophic form *(atrophic thyroiditis or primary myxedema)*

Hashimoto's Thyroiditis

- It is characterized by gradual thyroid failure because of autoimmune destruction of the thyroid gland.
- The name *Hashimoto thyroiditis is* derived from the 1912 report by Hashimoto describing patients with goiter
- The amost common cause of thyroiditis.
- This form of thyroid disease may also be referred to as *chronic lymphocytic thyroiditis*.

Hashimoto's Thyroiditis …

- Hashimoto thyroiditis is an autoimmune disease in which the immune system reacts against a variety of thyroid antigens.
- There is progressive depletion of thyroid epithelial cells (thyrocytes), which are gradually replaced by mononuclear cell infiltration and fibrosis.

Epidemiology

- It is primarily a disease of older women.
- Can occur in children " nonendemic goiter"
- The concordance rate in monozygotic twins is 30% to 60%.
- Several chromosomal abnormalities have been associated with thyroid autoimmunity.

Clinical Features

- Many of the symptoms associated with TH *deficiency*.
  - *Fatigue*
  - *Drowsiness*
  - *Difficulty with learning*
  - *Dry, brittle hair and nails*
  - Dry, itchy skin, Puffy face
  - Constipation
  - Weight gain
  - Heavy menstrual flow
  - Increased frequency of miscarriages

Silent (painless) thyroiditis

- Characterized by transient thyrotoxicosis with low RAIU, and a small, painless, nondender goiter.
- Thyrotoxicosis results from damage of follicular cells by the inflammatory process, with leakage of performed thyroid hormones in the bloodstream.
- The overall prevalence of silent thyroiditis as a cause of thyrotoxicosis ranges from 4 to 15%;
- greater prevalence in previously iodinedeficient areas, but recently exposed to sufficient iodine
- the female/male ratio is ~ 2:1

Silent thyroiditis clinical picture

- Silent thyroiditis presents with a relatively abrupt onset of symptoms of mild thyrotoxicosis:
  - Tachycardia
  - heat intolerance
  - Sweating
  - Nervousness
  - weight loss

Serum Tg and urinary iodine concentrations are increased

Silent thyroiditis clinical picture …

- **There are 3 phases:**
  - thyrotoxicosis
  - hypothyroidism
  - recovery
- Persistent hypothyroidism may also develop in about 5%.

Silent thyroiditis clinical picture …

- Differentiation from Graves' hyperthyroidism is important.
- **In silent thyroiditis:**
  - Abrupt onset
  - Thyrotoxicosis less severe
  - Duration of thyrotoxicosis < 3 months,

Silent thyroiditis clinical picture …

- thyroid bruit, ophthalmopathy and dermopathy absent
- T3/T4 ratio < 20/1
- RAIU low
- TSH-R antibodies usually negative
- thyrotoxicosis transient

Silent thyroiditis treatment

- Anti-thyroid drugs or radioiodine are inappropriate for treatment of silent thyroiditis.
- **In thyrotoxic phase:** β-adrenergic blocking agents
- **In hypothyroid phase:** L-T4 replacement therapy

Postpartum thyroiditis (PPT)

- During pregnancy all autoimmune reactions are inhibited by a number of physiologic factors, and following delivery there is a reversal of these alterations with rebound of autoimmune phenomena.
- The incidence of PPT ranges from 1% to 16% of women during the first year after delivery.

Postpartum thyroiditis …

Risk factors for the development of PPT include:

- positive TPOAb in the first trimester of pregnancy
- type 1 diabetes mellitus
- history of chronic autoimmune thyroiditis or Graves' disease, or a previous episode of PPT during a preceding pregnancy.

❑ The clinical course and treatment are the same as described above for silent thyroiditis

Riedel's thyroiditis

- Also called Sclerosing thyroiditis, invasive fibrous thyroiditis
- It is a rare, chronic inflammatory disorder of unknown etiology
- characterized by dense fibrosis involving the thyroid and adjacent tissues, and extracervical areas
- It occurs mainly in middle-age or elderly women.

Clinical pictures

- A patient will present with a long history of a painless, progressively increasing anterior neck mass.
- Pressure symptoms: dysphagia, cough, hoarseness, stridor, attacks of suffocation may appear.
- Most patients are euthyroid

On physical examination:

- a stony-hard or woody thyroid mass that varies in size from small to very large, may involve one or both lobes, and is fixed to surrounding structures.

Clinical pictures …

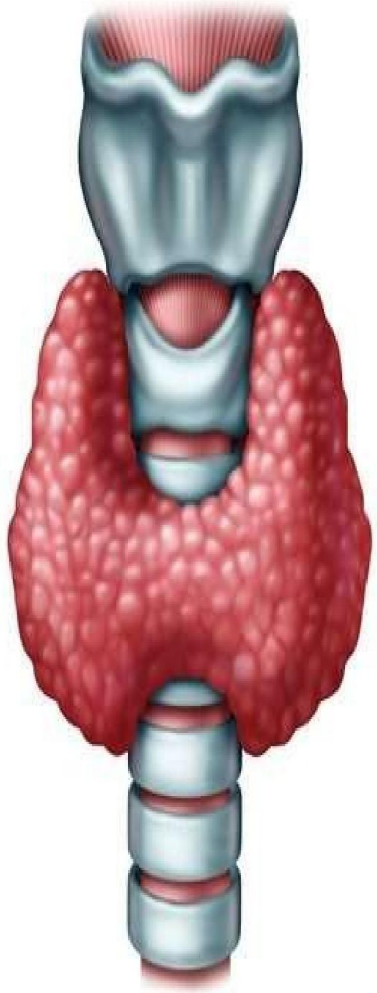
- Thyroid antibodies are present in up to 45% of patients.
- Serum calcium may be low due to parathyroid invasion.
- Differentiation from thyroid carcinoma or lymphoma of the thyroid requires open biopsy

Treatment

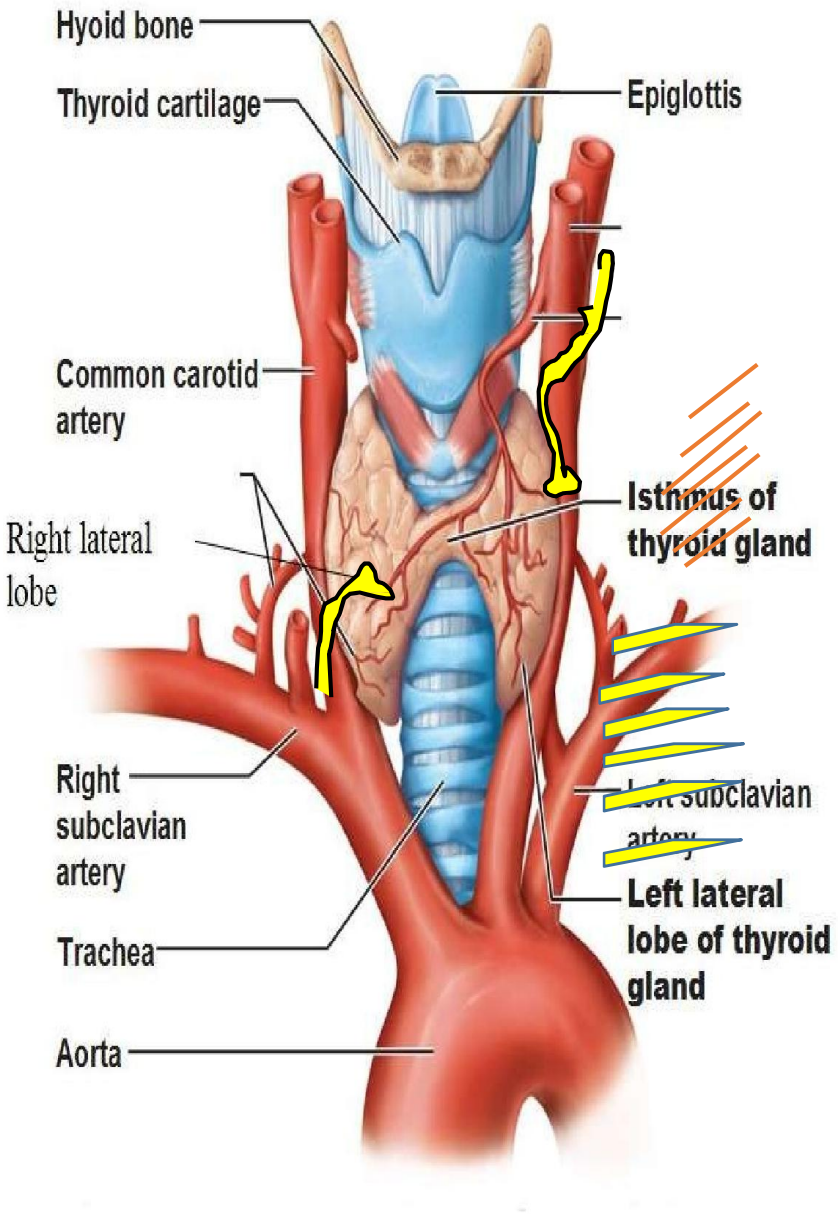
- Surgical treatment is necessary to relieve pressure on the trachea and to establish diagnosis.
- Corticosteroids are of little or no value.
- **Prognosis:**
  - The course of the lesion may be slowly progressive, may stabilize, or remit.
  - Extrathyroidal fibrotic lesions may complicate the prognosis.

Thyroid Cancer

Anatomy of the Thyroid Gland



- Two lateral lobes
- 50% have Pyramidal lobe
- Weighs 10-20 gm , size 5*5 cm
- Extension:- Mid Thyroid cartilage to 6th Tracheal ring
- Recurrent laryngeal nerves, sympathetic trunks, vagus and phrenic Nerve lies posteriorly



- Arterial supply :-
  - Superior thyroid artery
  - Inferior thyroid artery
- Venous drainage :-
  - Superior thyroid vein and middle thyroid vein
  - Inferior thyroid vein
- Lymphatics :-
  - First Echelon nodes Level 6
  - Second echelon nodes Level 3-4, supraclav LN, Level 7 LN
  - Lesser extent Level 2
  - Rarely Level 1

Thyroid Cancer Classification
(cell of origin)

1. Follicular epithelial cell
   - A. Differentiate Thyroid cancers
     - a. Papillary and mixed papillary variants
     - b. Follicular cancer
   - B. Poorly differentiated thyroid cancer
     - Insular carcinoma
   - C. Undifferentiated Thyroid cancer
2. Parafollicular cell
   - A. Medullary Carcinoma

Papillary variants
- **Classic**
- **Papillary microcarcinoma**
- **Encapsulated**
- **Follicular variant**
- **Aggressive variant**

Follicular
- **Classic**
- **Hurthle cell variant**

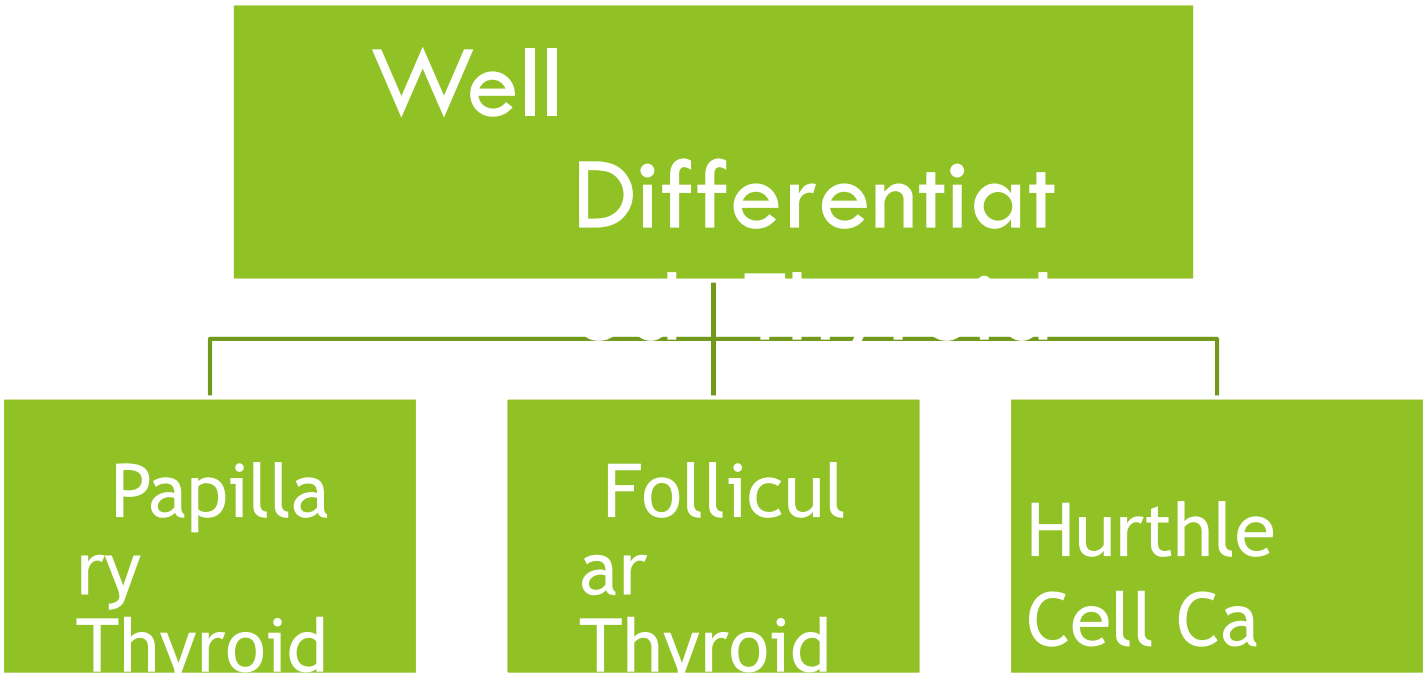
variant

Classification (ability to concentrate RAI)

A. Usually concentrate RAI
   - Classic papillary
   - Encapsulated papillary
   - Follicular variant and mixed follicular papillary
   - Follicular variant

B. Frequently do not concentrate RAI
   - Tall cell and columnar cell variant of papillary carcinoma
   - Hurthle cell
   - Poorly differentiated

C. Never concentrate RAI
   - Anaplastic
   - Medullary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Papillary Thyroid Carcinoma

- 80% of all thyroid malignancies.
- Predominant thyroid carcinoma in children.
- Individual exposed to external radiation.
- Women : Men = 2:1
- Mean age of presentation – 30-40 years
- Usually Euthyroid - a slow growing painless mass in neck.
- Dysphagia, dyspnoea, dysphonia - Locally advanced ca.
- Characterized by multi-focality in 80-85%
- Increase risk of lymph node mets – esp children & young adults – lateral aberrant thyroid.

PTC – Pathology

- Gross – Hard and Whitish
- Remain flat on sectioning in contrast to normal tissue/ benign lesions that tend to bulge.
- Histology – Exhibit Papillary projection

  - Mixed Papillary and Follicular pattern
- Diagnosis by – characteristic cellular features
  - Cells - cuboidal
  - Pale abundant cytoplasm
  - Crowded nuclei grooving
  - Intra-cytoplasmic inclusion – Orphan Annie nucleus
  - Multifocality is common, asso with increased risk of cervical node mets and these lesions may invade adjacent strctures such as trachea esophagus and RLN

Macroscopically

- Minimal / Occult / Micro-carcinoma
  - Tumours of 1cm or less with no local invasion through thyroid capsule/angio-invasion.
  - Not associated with lymph node mets.
  - Non palpable ,incidental finding, 2-36% thyroids at autopsy
  - Recurrence – 5% , Mortality – 0.5%

- Intra-thyroidal – confined to thyroid gland, no evidence of extrathyroid invasion

- Extra-thyroidal – invade through the thyroid capsule and/or into adjacent structures.

Prognostic Indicators

- Low risk patients
  - Young
  - Well differentiated tumour
  - No mets
  - Small primary lesion
- High risk patients
  - Older
  - Poorly differentiated tumour
  - Local invasion, Distant mets
  - Large primary lesion

Management

- High Risk/ B/l tumours – Total or near total thyroidectomy

Advantages :-

1. RAI - effectively detect and treat residual thyroid tissue or metastatic d/s
3. eliminates contralateral occult cancers as sites of recurrence (85% of tumors are multifocal)
4. reduces the risk of recurrence ; improves survival
5. 1% risk of progression to undifferentiated /anaplastic Ca
6. reduces need for re-operative surgery.

Follicular Carcinoma

- 10% of thyroid cancers
- F:M = 3:1
- Mean age of presentation – 50yrs
- More common in iodine deficient access.
- Usually present as a solitary thyroid nodule with a history of rapid increase in size and long standing goitre.
- Pain – uncommon
- Cervical lymph node mets – uncommon
- Distal mets may be present
- < 1% hyper-functioning with feature of thyrotoxicosis.

Pathology

- Solitary lesions, usually surrounded by a capsule.
- Histologically, follicles are present, but lumen may be devoid of colloid.
- Malignancy - defined by presence of capsular and vascular invasion.
- Minimally-invasive tumours –
  - grossly encapsulated
  - evidence of microscopic invasion through the tumour capsule/ into small- to medium-size vessels (venous calibre)/ immediately outside the capsule.
- Widely invasive tumours –
  - large-vessel invasion/ broad areas of tumour invasion through the capsule.
  - May be un-encapsulated.

Management

- Total thyroidectomy should be performed when thyroid cancer is diagnosed.
- Frankly invasive carcinoma- completion of total thyroidectomy primarily (so that ^{131}I can be used to detect and ablate metastatic disease.)
- Total thyroidectomy in patients with angioinvasion is also recommended.
- Prophylactic nodal dissection is unwarranted (nodal involvement is infrequent)
- In patient with nodal metastases, therapeutic neck dissection is recommended.
- Mortality - 15% at 10 years and 30% at 20 years.

Prognosis

- Poor long-term prognosis is predicted by:
  - Age >50 years at presentation
  - Tumour size >4 cm
  - Higher tumour grade
  - Marked vascular invasion
  - Extra-thyroidal invasion
  - Distant metastases at the time of diagnosis.

Hurthle Cell Carcinoma

- 3% of all thyroid malignancies.
- Subtype of follicular cancer.
- Characterized by capsular and vascular invasion.
- Can’t be diagnosed by FNAC.

Pathology

- Sheets of eosinophilic cells packed with mitochondria.
- Multifocal / B/l
- Don't take up RAI
- Mets to local nodes(25%) and distant sites.

Treatment

- Same fashion as FTC
- When Hürthle cells found –check for invasiveness and malignancy
- Treatment –Sx (same workup of a follicular neoplasm).

Risk factors of thyroid malignancies

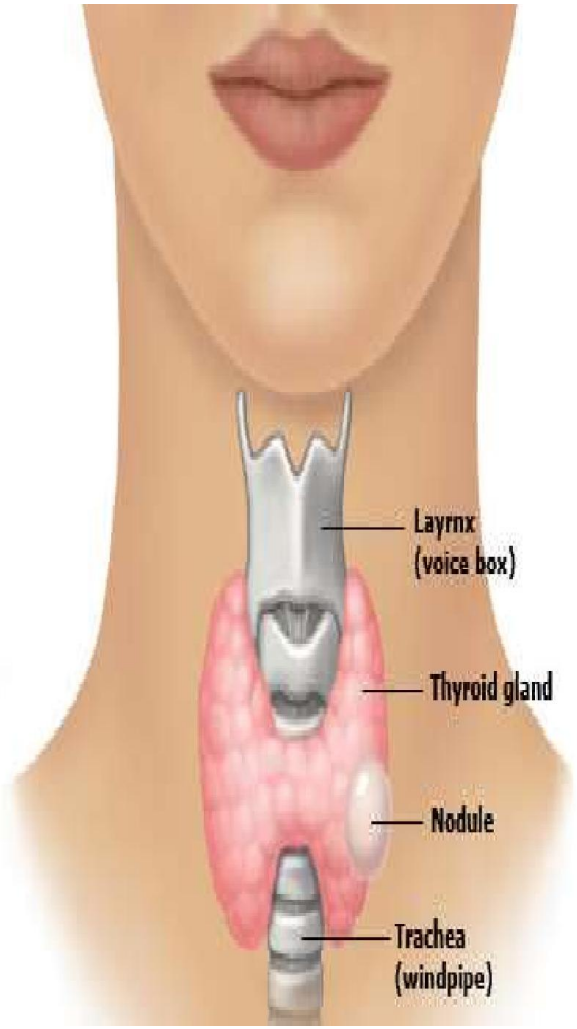
- Exposure to radiation in childhood #
  - Increased risk of well differentiated cancer (0.1Gy)
  - Latent period 3-5 yrs
  - Risk remain apparent even after 40 yrs
- Victims of nuclear disaster
- Family history (first degree relatives)
- History of thyroid cancer syndromes
- Medullary cancer thyroid syndromes
- Hashimoto thyroiditis (thyroid lymphoma)

Epidemiology

- Most common endocrine malignancy
- In Females 3 times more commonly affected than males.(5th most common cancer in females)
- Most common histology papillary thyroid cancer
- DTC (90%), Medullary (5-9%), Anapalstic (1-2%), lymphoma (1-3%), sarcoma (<1%).
- Mean age of presentation 40-45 yrs (females), 65-69 yrs (males)..

Presentation

- Thyroid nodule , incidental finding
- Increased suspicion of malignancy :-
  - Rapid growth
  - Firmness
  - Fixation
  - Vocal cord paralysis
  - Dysphagia
  - Cervical adenopathy
- Advance cases presents with :-
  - Airway compromise
  - Hoarseness of voice
  - Pain
  - Weight loss
  - Respiratory distress



Diagnosis

- Laboratory Studies :-
    - CBC
    - RFT/LFT
    - Serum TSH
    - Thyroglobulin, T3 and T4
    - Serum calcitonin (Medullary Thyroid cancer)
- Cervical (Neck) Ultrasound
- Ultrasound Guided FNA (for both palpable and incidental finding)
    - Limitation :- Inability to distinguish benign follicular adenomas from FC and Follicular PTC.
- CT scan and MRI
    - Generally not recommended because of the use of iodinated contrast, which hamper RAI therapy.

TNM

Tumour

TX	Primary cannot be assessed
T0	No evidence of primary
T1	Limited to thyroid, 1 cm or less
T2	Limited to thyroid, > 1 cm but < 4 cm
T3	Limited to thyroid, > 4 cm
T4	Extending beyond capsule, any size

Nodes

NX	Cannot be assessed
N0	No regional node metastases
N1	Regional node metastases

Metastases

MX	Cannot be assessed
M0	No metastases
M1	Metastases present

Stage	Under 45 years	Over 45 years
I	Any T, any N, M0	T1, N0, M0
II	Any T, any N, M1	T2, N0, M0 or T3, N0, M0
III		T4, N0, M0 or any T, N1, M0
IV		Any T, any N, M1

Note the effect of age on stage; only patients older than 45 years can have stage III or IV disease.

Management

- Surgery
  - Primary treatment
  - Total thyroidectomy is preferred
  - Complications:-
    - Recurrent laryngeal nerve injury
    - Hypoparathyroidism
    - Injury to Vagus nerve, spinal accessory nerve, superior laryngeal nerve

- **Lobectomy Indications:**
    - Patients Age 15-45 yrs
    - Tumour size <4 cm without prior RT
    - Lymph nodes or Distant metastases
    - Extra thyroidal extension
    - Aggressive histology

❖ Radio active iodine therapy

Goals

- Thyroid remnant ablation
- Adjuvant therapy for residual microscopic disease

- Patient Selection for RAI
  - Distant metastases
  - Gross extra Thyroidal extension
  - Tumour size 1-4 cm with
    - LN metastases
    - High risk features
    - Age >45 yrs
    - Intrathyroidal vascular invasion
    - Multifocal disease
    - Aggressive histological variants
  - Follicular and Hurthle cell variants are high risk tumors always requiring RAI
  - Not recommended when
    - Tg <1 ng/ml
    - Anti Tg antibodies and RAI imaging are negative

Role of Radiotherapy

- No Randomise trial to indicate benefit of RT
- European multicentre study on DTC trial was planned but terminated prematurely
- Converted to prospective cohort study but fails to show any benefit
- In general patients with unresectable Thyroid cancer are treated with primary EBRT
- Palliation in symptomatic metastatic tumours (20-30 Gy in 5 - 10 #).

	ATA Guidelines	University of Florida
Age <18 yrs	Metastases that are symptomatic or in critical location that are otherwise unresectable	Painful metastases or impending normal tissue damage
Age 19-45 yrs	Metastases that are symptomatic or in critical location that are otherwise unresectable	Gross unresectable tumours resistant to Iodine131 #
Age >45 yrs	Gross ETE, high likelihood microscopic residual or gross residual tumour not amenable to surgery	**Adjuvant treatment after surgery** : patient at high risk of locoregional recurrence ,T4 primary, nodal mets with ECE, gross residual disease **Salvage of recurrent disease:** Gross unresectable tumour with resistance to RAI.

resistance means recurrence after at least one >100 mci treatment under optimal condition.

RESEARCH Open Access

The effect of external beam radiotherapy volume on locoregional control in patients with locoregionally advanced or recurrent nonanaplastic thyroid cancer

Tae Hyun Kim*†, Ki-Wook Chung†, You Jin Lee†, Chan Sung Park, Eun Kyung Lee, Tae Sung Kim, Seok Ki Kim, Yoo Seok Jung, Jun Sun Ryu, Sang Soo Kim, Kwan Ho Cho, Kyung Hwan Shin*

Results: There were no significant differences in the clinical parameter distributions between the LF and EF groups. In the LF group, six (55%) patients developed locoregional recurrence and three (27%) developed distant metastasis. In the EF group, one (8%) patient developed locoregional recurrence and one (8%) developed a distant metastasis. There was a significant difference in locoregional control rate at 5 years in the LF and EF groups (40% vs. 89%, $p = 0.041$). There were no significant differences in incidences of acute and late toxicities between two groups ($p > 0.05$).

Conclusions: EBRT with EF provided significantly better locoregional control than that of LF; however, further larger scaled studies are warranted.

Chemotherapy

- Indicated in patients refractory to Radioiodine therapy and rapidly progressive disease.
- Drugs approved by FDA :- Doxorubicin, Sunitinib
- Newer drugs :-
    - Vandetanib
    - Pazopanib
    - Selumetanib (MEK inhibitor) shown to reverse the loss of RAI avidity.

Anaplastic Thyroid Cancer

- Rare but more aggressive
- Poor Prognosis (Median OS < 6 months)
- Female > Male
- All classified as Stage IV
    - IV A limited to thyroid
    - IV B with local invasion
    - IV C distant mets (Lungs and Bones m/c)

- Symptoms :- Rapidly progressing mass with LN met causing compression.
- Diagnosis :- USG guided FNA → Core biopsy
- Workup:- USG Neck, CT scan (neck thorax and brain), PET CT.
- Management:- surgery if resectable , unresectable NACT+ EBRT→ surgery.
- Adjuvant radiotherapy with or without chemo should be started as soon as possible.
- Chemo :- Doxorubicin + Platins (first line)
- Ongoing Trials:-
    - Pazopanib + paclitaxel
    - Imatinib
    - Fosbretabulin
    - Erlotinib
    - Geftinib

Medullary Thyroid carcinoma

- Genetic screening and testing indicated.
- Primary management → Surgery (total thyroidectomy).
- Central neck dissection should be done in all cases.
- No role of adjuvant RAI therapy
- Follow up by serum calcitonin level → marker for residual.

- EBRT
  - Children Age <18 yrs :- RT reserved for palliation.
  - Adults :-
    - Unresectable gross disease
    - High risk of microscopic disease (positive margin, T4, nodal mets, extracapsular extension.)
- No role of cytotoxic systemic therapy.

J Surg Oncol. 2010 August 1; 102(2): 175–178. doi:10.1002/jso.21557.

Adjuvant External Beam Radiation for Medullary Thyroid Carcinoma

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Results—After 12 years, EBRT did not significantly improve OS (log rank, $p<0.14$). In node-positive patients, univariate analysis demonstrated an OS benefit with EBRT (log rank, $p<0.05$). In a multivariate model of node-positive patients, only increasing age ($p<0.001$) and tumor size ($p<0.001$) significantly influenced OS.

Conclusions—The OS benefit attributed to EBRT in node-positive patients by univariate analysis could not be duplicated when controlling for known prognostic factors.

A role for radiotherapy in the management of advanced medullary thyroid carcinoma: the Mayo Clinic experience

Jason A. Call,[1] Jonathan S. Caudill,[1] Bryan McIver,[2] Robert L. Foote[1]

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Conclusions

Medullary thyroid carcinoma appears to be a radiosensitive tumor. EBRT may be most effective in the adjuvant setting for the prevention of locoregional recurrence, but it may also have a role in providing durable and sustained control of locoregionally advanced or metastatic disease (or both) in select patients.

Disorders of Parathyroid gland

Introduction

- Parathyroid glands is located in the posterior part of thyroid gland.
- Parathromones (parathyroid hormone), the protein hormone produced by the parathyroid glands.
- ↑sed secretion of parathromones results in ↑sed calcium absorption from the kidney, intestine, and bones.
- The serum level of ionized calcium regulates the output of parathromones.
- Increased serum calcium results in decreased parathromones secretion, creating a negative feedback system.

Functions of Parathyroid gland

- Parathyroid gland secrets parathromones which is responsible for metabolism of calcium and phosphors.
- **Ca+-** is very important for bone development and has great role in muscular relaxation and contraction specially on cardiac muscles by facilitating actins and myosin filaments.
- It is also act for blood coagulation mechanism
- Also facilitate for the transfer of energy by acting on ATP process
- About 99% Ca+ deposited in the skeletal system.

Function …

- **Phosphorous** – has a great effect on skeletal system development
- Deficiency of parathromones result in increased blood phosphate (Hyperphosphatemia) & decreased blood calcium (hypocalcaemia) levels.

Function …

- PTH is directly related to Ca+ but inversely related to phosphorus.
- When there is increased PTH secretion, there will causes increase Ca+; finally it causes potentially life treating.
- Decreased renal excretion of phosphate causes Hypophosphaturia, and low serum calcium levels result in hypocalciuria.

Types of parathyroid disorder

- There are two types of parathyroid problems depending on the etiological factors
  - Hyper Parathyroidism (hyper function)
  - Hypo Parathyroidism (hypo function)

Hyper parathyroidism

- Is caused by overproduction of parathormone by the parathyroid glands.
- Characterized by bone decalcification and the development of renal calculi (kidney stones) containing calcium.
- Hyper parathyroidism can be classified as either Primary or secondary disease type

Primary Hyper parathyroidism

- Primary hyper parathyroidism may be due to secreting tumors in or hyperplasia of the parathyroid glands (most cases are a single adenoma).

Secondary hyperparathyroidism

- Manifestations are similar to those of primary hyperparathyroidism
- occurs in patients who have chronic renal failure and so-called renal rickets as a result of phosphorus retention
- Other predisposing factors associated to secondary parathyroidism include:
  - Malabsorption
  - Chronic renal failure
  - Hyperphosphatemia

C/M of hyperparathyroidism

- Some patients are asymptomatic and show only an increased serum calcium
- Apathy, fatigue, muscle weakness, nausea, vomiting, constipation, HTN, and cardiac dysrhythmias may occur.
- All these signs and symptoms are attributable to the increased concentration of calcium in the blood.

C/M of hyperparathyroidism …

- Renal damage results from precipitation of calcium phosphate in renal pelvis & parenchyma, which causes renal calculi, obstruction, pyelonephritis, & renal failure.
- Incidence of PUD and pancreatitis is increased
- Patient may develop skeletal pain and tenderness, joints pain on weight bearing, pathologic fractures, deformities, and shortening of body stature

Diagnostic studies

Radiologic studies

- Bone cysts
- Demineralization of bone
- Long bone tumors

Blood tests

- Elevated serum calcium
- Low serum phosphate
- Parathromones
- Serum chloride& serum alkaline phosphates

Medical and surgical management

The objective of treatment

- To relieve symptoms and prevent complications due to excessive secretion of parathyroid hormone

The choice of therapy depends upon

- The urgency of the clinical situation
- The degree of hypercalcemia
- The underlying disorder
- The status of renal and hepatic function

Management …

Surgical management

- Surgical removal of parathyroid tumors

Medical management

To minimize the formation of calcium renal stones can be managed by:

- Forcing fluid intake to dilute the excess calcium
- Avoiding immobilization
- Administering certain drugs

Management …

- In severe hypercalcemic states, phosphate may be given to reduce the serum calcium in order to facilitate a positive response to surgery
- **Diuretics–** furosemide or Ethacrynic acid --To decrease renal tubular reabsorption of calcium.
- Administer Calcitonin
- **NB:** Avoid thiazide diuretics as they decrease renal excretion of calcium

Complication of hyper parathyroidism

Hypercalcemic crisis:

- can occur with extreme elevation of serum calcium levels.
- Which is acute sever from hyperthyroidism
- Seen Ca++ with levels greater than 15mg/dL
- Can result in life-threatening neurologic, cardiovascular and renal symptoms

Complication of hyper parathyroidism

Hypercalcemic crisis …

- Treatments include:
  - hydration, loop diuretics to promote excretion of calcium
  - Phosphate therapy to promote calcium deposition in bone and reducing GI absorption of calcium
  - Give calcitonin or mithramycin to decrease serum calcium levels quickly

Nursing management

- If surgery is performed close monitoring of the client's vital sign is required
- Prevent the major postoperative complications (Tetany, fluid and electrolyte imbalances)
- Limit ambulation to short walks because the client problem is fatigue and weakness

Nursing management …

- Provide a low calcium, or reduce milk and milk products to prevent increasing calcium levels.
- Encourage fluid intake
- Closely monitors the patient to detect symptoms of Tetany (an early postoperative complication)
- stool softeners and physical activity, along with increased fluid intake

Hypoparathyroidism

The most common cause are:

- Inadequate secretion of parathyroid hormone after interruption of the blood supply; or
- surgical removal of parathyroid gland tissue during thyroidectomy, parathyroidectomy.

Clinical manifestations

- Caused by the deficiency of PTH that results in
  - Elevated blood phosphate (Hyperphosphatemia)
  - Decreased blood calcium: Decreased contractility of the heart muscle
- In the absences of PTH, there is decrease intestinal absorption of dietary calcium & decreases reabsorption of calcium from bone and through the renal tubules .

C/M ....

- Decrease renal excretion of phosphate caused Hypophosphaturia
- Hypocalcaemia causes irritability of the neuromuscular system and contributes to the chief symptom of Hypoparathyroidism develops Tetany.
- Caused for Painful muscle cramps

C/M ….

- **Tetany is a general muscle hypertonia,** with tremor & spasmodic or uncoordinated contractions occurring with or without efforts to make voluntary movements.
- **Tetany has two phases**

A. Latent phase (numbness, tingling and cramps in the extremities and complains of stiffness in the hands and feet.)

C/M ….

B. Overt phase /severe tetany: the S/Sx include:

- ✓ Bronchospasm
- ✓ laryngeal spasm
- ✓ Carpopedal spasm
- ✓ Dysphagia
- ✓ Photophobia
- ✓ Cardiac dysarrthmias

Diagnostic findings

- **Positive chvostek's sign:** a spasm of the muscle in response to tapping the muscles or branch of the facial nerve cause spasm or twitching of mouth ,nose and eye
- **Trousseau's sign:** the patient develops carpopedal spasms when we apply BP cuff for 3minuts.
- Lower serum calcium & higher serum phosphate level
- x- ray of bones show increased density.

Medical management

- The main objectives of treatment are:
  - To prevent Tetany and seizures from hypocalcaemia
  - To prevent long term complications by keeping serum calcium levels within normal limits
- Acute Tetany is relived by Immediate IV administration of calcium gluconate (10-30 ml)

Maintenance therapy

- Oral calcium salts
- Vitamin D in large doses enhance calcium absorption
- Low phosphate diet
- Aluminum hydroxide: to lower serum phosphate level
- Sedative agents (e.g. pentobarbital) with closely monitoring for allergic reactions and changes in serum calcium levels

Maintenance therapy …

- Parenteral parathromones can be administered to treat acute Hypoparathyroidism with tetany
- An environment that is free of noise, drafts, bright lights or sudden movement
- Tracheotomy or mechanical ventilation, along with broncho dilating medications
- A diet high in calcium and low in phosphorus

Disorders of Adrenal gland

Addison's disease

- Is a clinical condition resulting from adrenocortical insufficiency due to primary acquired disease of adrenal gland.
- A chronic condition that results from the partial or complete destruction of the adrenal cortex
- Causes deficiencies of the adrenocortical secretions: glucocorticoids, sex hormones, and mineral corticoids
  - Cortisol, Aldosterone, Androgens and Estrogens
- An English physician, Thomas Addison, first described this disease almost 150 years ago.

Epidemiology

- Addison's disease is a rare endocrine or hormonal disorder that affects about 1 in 100,000 people.
- It occurs in all age groups (More common between ages 30 – 50) and afflicts men and women equally.

Causes of Addison's Disease:

- **Primary Adrenal insufficiency: Common causes**
  - Idiopathic Autoimmune Dysfunction (majority-80%)
  - Tuberculosis (of adrenal gland)-10%
  - Secondary deposit in adrenals
  - HIV infection, cancer
  - Bilateral adrenalectomy
- **Secondary Adrenal insufficiency:**
  - Steroid withdrawal
  - Hypophysectomy
  - Pituitary neoplasm
  - Sarcoidosis
  - Haemochromatosis

Pathogenesis

- Addison's disease occurs when more than 90% of adrenal gland tissue is destroyed (primary Addison's disease).
- The destruction can occur due to various causes listed before

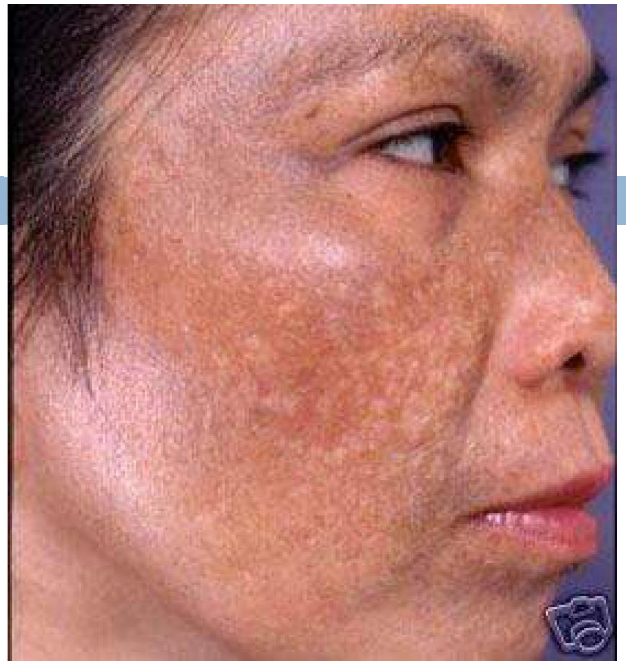
Clinical features:

- ***Due to glucocorticoid insufficiency:***
  - Weight loss, Malaise, Weakness
  - Anorexia
  - Nausea, Vomiting, diarrhoea or constipation
  - Postural hypotension
  - Shock
  - Hypoglycaemia
  - Hyponatraemia (dilutional)
  - Hypercalcaemia

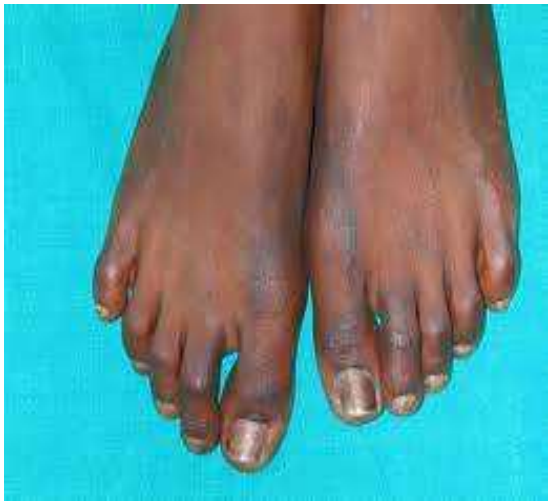
Clinical features ….

- ***Due to mineralocorticoid insufficiency-***
  - Hypotension
  - Shock
  - Hyponatraemia (depletional)
  - Hyperkalaemia

Clinical features ….



- ***Due to ACTH excess:***
  - **Pigmentation:**
    - Sun-exposed areas
    - Pressure areas, e.g. elbows, knees
    - Palmar creases
    - Knuckles
    - Mucous membranes
    - Conjunctivae
    - Recent scars



Clinical features ….

- ***Due to adrenal androgen insufficiency:***
  - Decreased body hair and loss of libido, especially in female

Clinical features ….

Symptoms:

Fatigue, lassitude, malaise, weakness, anorexia

Postural dizziness, syncope

Gastrointestinal Symptoms
- *Nausea*
- *Vomiting*
- *Abdominal Pain*
- *Diarrhea*
- *Constipation*

Myalgias, arthralgias, rarely flexion contractures

Decreased libido, amenorrhea

Signs:

Weight loss

Hyperpigmentation

Hypotension

Thinning of axillary and pubic hair

Vitiligo

Diagnostic criteria of Addison's disease

- **Triad of:**

  I. Weakness or emaciation (100% cases)

  II. Pigmentation (90% cases)

  III. Hypotension

Investigation

- **Random plasma cortisol level:**
  - Usually low but may be within normal range.Refute the diagnosis if the value is >460nmol/L
- **Short ACTH stimulation test/Tetracosactide or short synacthen test:**
  - 250microgram ACTH by i.m at any time of day -0 and 30min for plasma cortisol-in addison's disease plasma cortisol<460nmol/L
- **Long ACTH stimulation test:**
  - 1mg depot ACTH i.m daily for 3 daysplasma cortisol <700nmol/L at 8hrs after last injection

Investigation …

- **CBC:** For pernicious anaemia
- **Blood glucose:** Low or lower limit, specially during Addisonian crisis.
- **Electrolytes**
  - ✓Hyponatraemia: more important.
  - ✓Hyperkalaemia

Investigation …

- **Tests to find out causes:**
  - Chest X-ray (tuberculosis)
  - Plain X-ray of abdomen (adrenal calcification in TB)
  - Adrenal auto-antibody
  - Ultrasonography or CT scan of adrenals
  - HIV test
- **Other tests:**
  - Plasma calcium-high
  - Plasma renin activity-high
  - Plasma aldosterone-low

Treatment of Addison's disease

A. **Replacement of hormones:** to correct the insufficient levels of steroids that the adfenal glands can't produce.
   - Glucocorticoid (hydrocortisone-15 mg on waking and 5 mg at 6pm)
   - Mineralocorticoid (fludrocortisone 0.05 to 0.1mg daily)

B. **Supportive treatment and treatment of cause:**
   - e.g. if TB- antitubercular therapy

C. **General advice to the patient**
   - Good nutrition, regular meal, high carbohydrate and sufficient salt
   - When oral therapy is not possible, injection hydrocortisone should be taken

Complications of Addison's disease

- The complications of untreated Addison's disease include cardiovascular collapse, coma, and death.

Nursing Diagnosis examples

- Electrolyte Imbalance r/t vomiting and diarrhea AEB hyperkalemia and hyponatremia
- Imbalanced nutrition: less than body requirements r/t anorexia AEB 20% decrease in weight

Nursing interventions

- Monitor for fluid deficits and hypernatremia
- Monitor and treat hyperkalemia
  - Obtain serum potassium and ECG
  - Administer sodium polystyrene sulfonate, insulin, calcium, glucose, and sodium bicarbonate
- Monitor and treat hypoglycemia
- Maintain a safe environment

Nursing interventions …

- Monitor patient frequently for dysrhythmias
- Administer NaCl IV to increase sodium
- Administer an antiemetic as tolerated by the patient
- Provide high calorie snacks
- Daily weight measurment
- Nutritional supplements

Reading Assignment

1. Principle of glucocorticoid therapy
2. Addisonian Crisis

Cushing syndrome

Cushing syndrome

- An illness resulting from excess cortisol secretion, which has a high mortality if left untreated.

Cushing syndrome …

- Cushing's syndrome is caused by prolonged exposure of the bodies' tissue to high levels of the hormone **cortisol**
- Cushing syndrome is also called hypercortisolism
- Cortisol is a hormone secreted by the adrenal glands
- Helps maintain proper glucose metabolism, regulation of blood pressure, insulin released for blood sugar control, immune function and inflammatory response
- Most importantly cortisol helps the body respond to stress (called the "stress hormone")

Cushing syndrome

An array of symptoms as a result of abnormally high levels of cortisol or other glucocorticoids in the blood

•Cushing's Syndrome	•Cushing's Disease
• Excess cortisol due to any cause	• Excess cortisol due to pituitary micro-adenoma

Epidemiology of Cushing's disease

- Rare; annual incidence approximately 2/million.
- Commoner in ♀ (♀:♂, 3–15:1).
- Age—most commonly, 20–40 years.

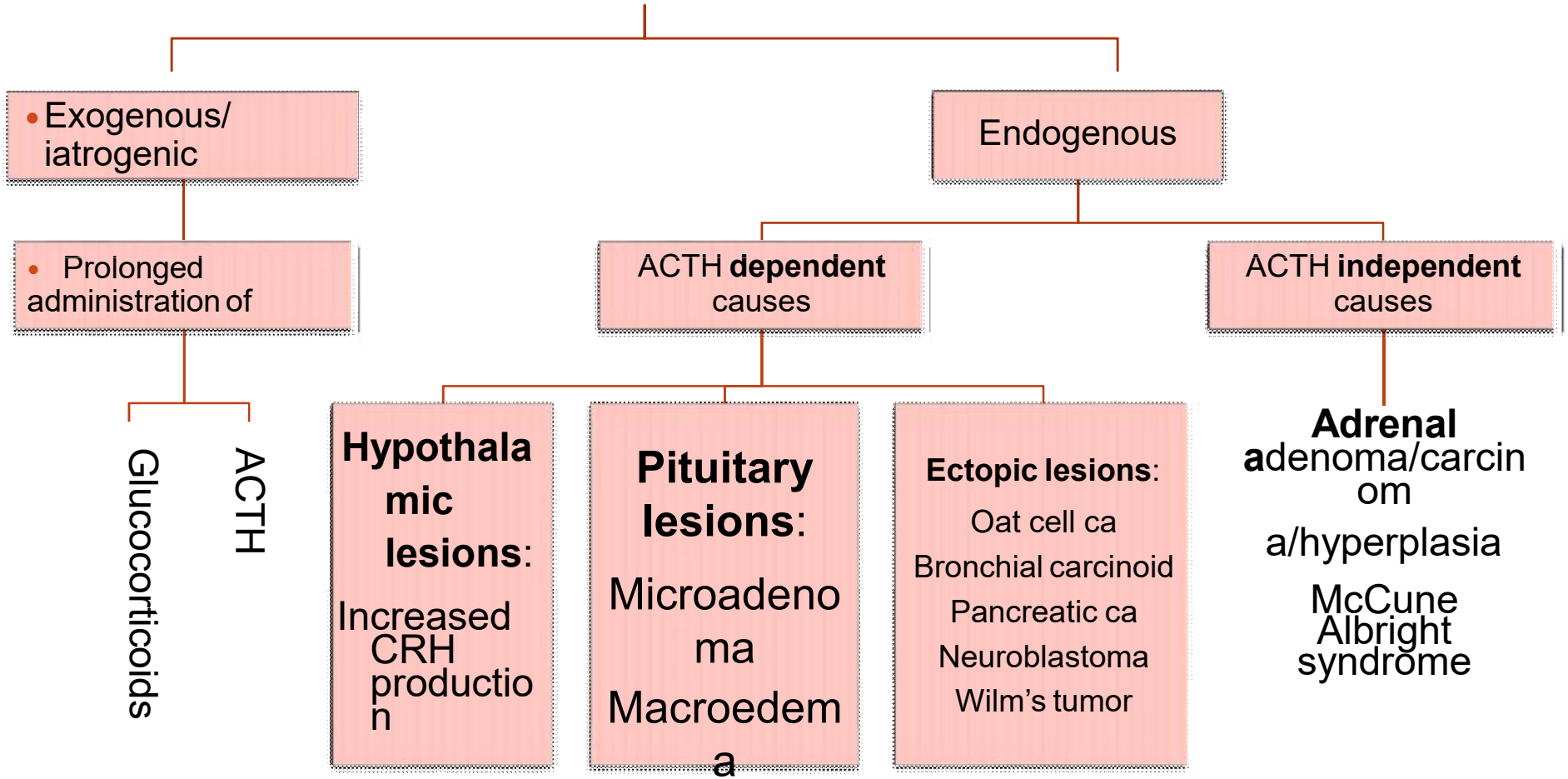
Causes of Cushing's syndrome

- Pseudo-Cushing's syndrome:
  - Alcoholism <1%.
  - Severe depression 1%.
- ACTH-dependent:
  - Pituitary adenoma 68% (Cushing's disease).
  - Ectopic ACTH syndrome 12%.
  - Ectopic CRH secretion <1%.

Causes of Cushing's syndrome …

- ACTH-independent:
  - Adrenal adenoma 10%.
  - Adrenal carcinoma 8%.
  - Nodular (macro- or micro-) hyperplasia 1%.
- Exogenous steroids, including skin creams, e.g. clobetasol.

Etiology


Exogenous/ iatrogenic
Endogenous
Prolonged administration of
ACTH dependent causes
ACTH independent causes
Glucocorticoids
ACTH
Hypothalamic lesions: Increased CRH production
Pituitary lesions: Microadenoma Macroedema
Ectopic lesions: Oat cell ca Bronchial carcinoid Pancreatic ca Neuroblastoma Wilm's tumor
Adrenal adenoma/carcinom a/hyperplasia McCune Albright syndrome

Clinical features

- progressive and may be present for several years prior to diagnosis.
- A particular difficulty may occur in a patient with cyclical Cushing's where the features and biochemical manifestations appear and disappear with a variable periodicity.
- Features may not always be florid, and clinical suspicion should be high.

Clinical features …

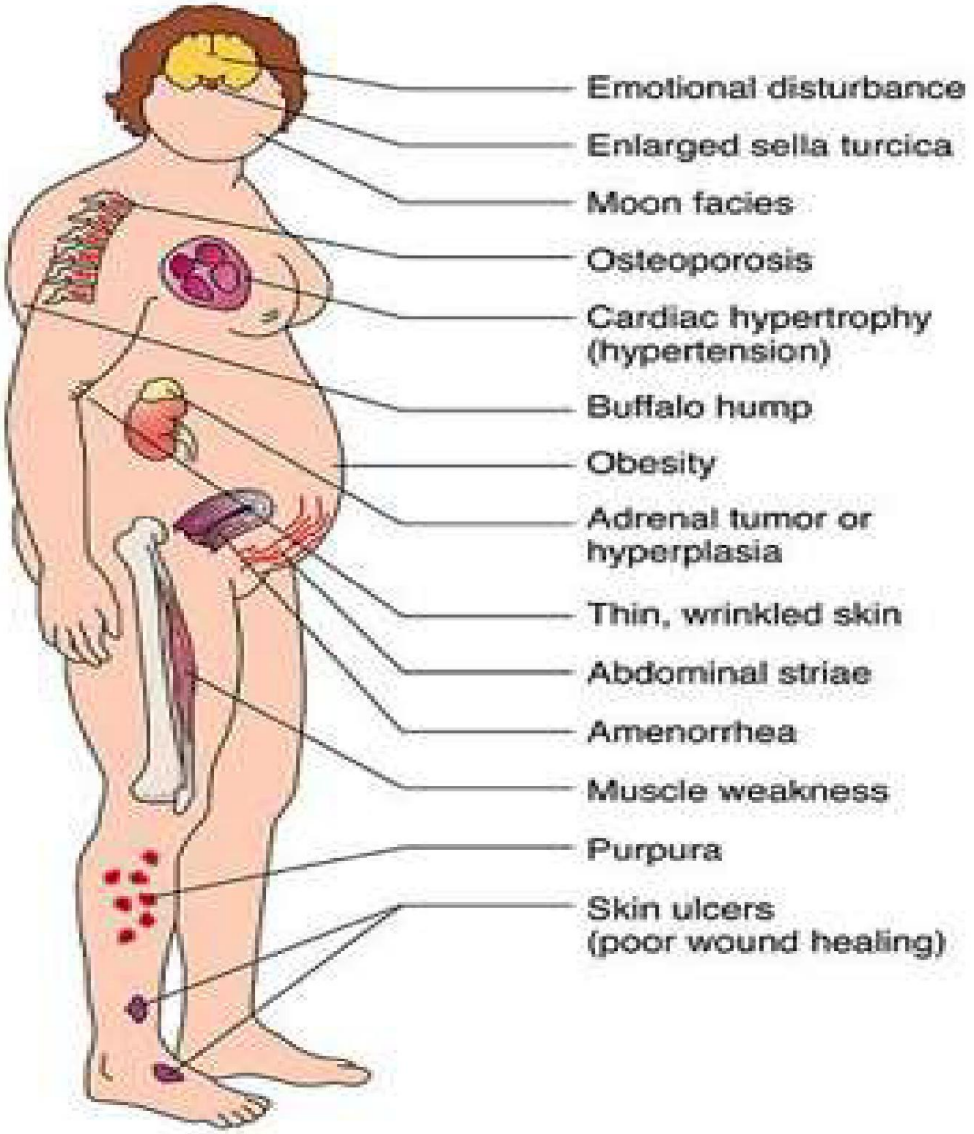
- Facial appearance—round plethoric complexion, acne and hirsutism, thinning of scalp hair.
- Weight gain—truncal obesity, buffalo hump, supraclavicular fat pads.
- Skin—thin and fragile due to loss of SC tissue, purple striae on abdomen, breasts, thighs, axillae, easy bruising, tinea versicolor, occasionally pigmentation due to ACTH.
- Proximal muscle weakness.

Clinical features …

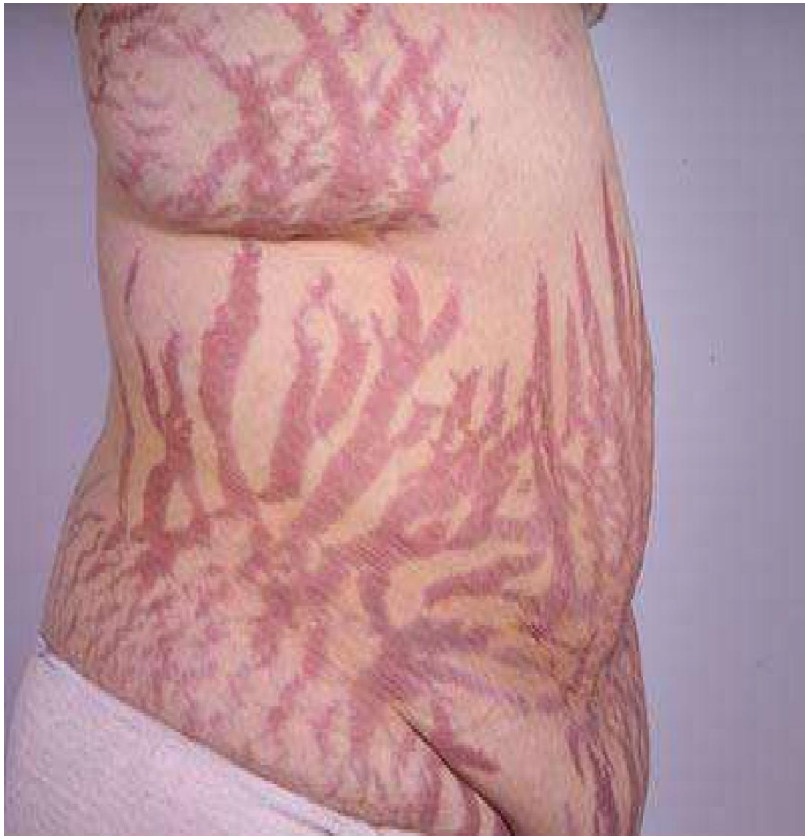
- Mood disturbance—labile, depression, insomnia, psychosis.
- Menstrual disturbance.
- Low libido and impotence.
- There is a high incidence of venous thromboembolism (careful during surgery).
- Overall mortality greater than of general population (by a factor of 6).
- Growth arrest in children.

Clinical features …

- Most patients don't have all these S/sx



Clinical features …



Clinical Features ….

Body fat
- Central (truncal) obesity
- Moon facies, Supraclavicular fat pads, and Buffalo hump

Skin
Thinning of the skin, with facial plethora, easy bruising, and violaceous striae

CVS
- Hypertension, Congestive heart failure,
- Hyperlipidemia, Diabetes

Reproductive
Gonadal dysfunction and menstrual irregularities

Muscle
Proximal muscle weakness, and atrophy

Wasting of the extremities

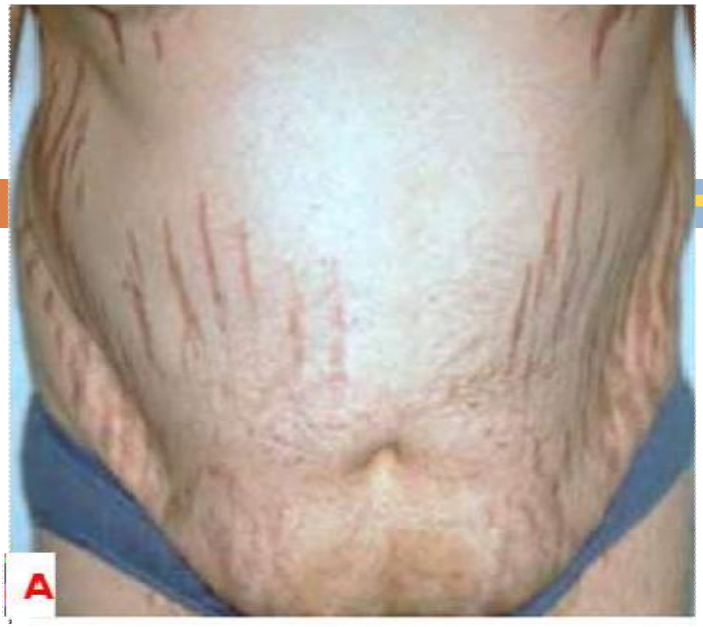
Bone
Osteoporosis and fractures

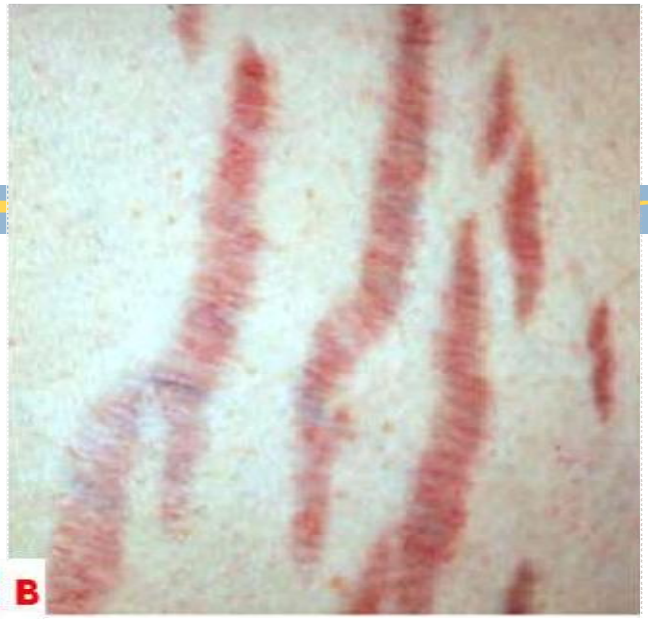
Immunity
Increased rate of infections

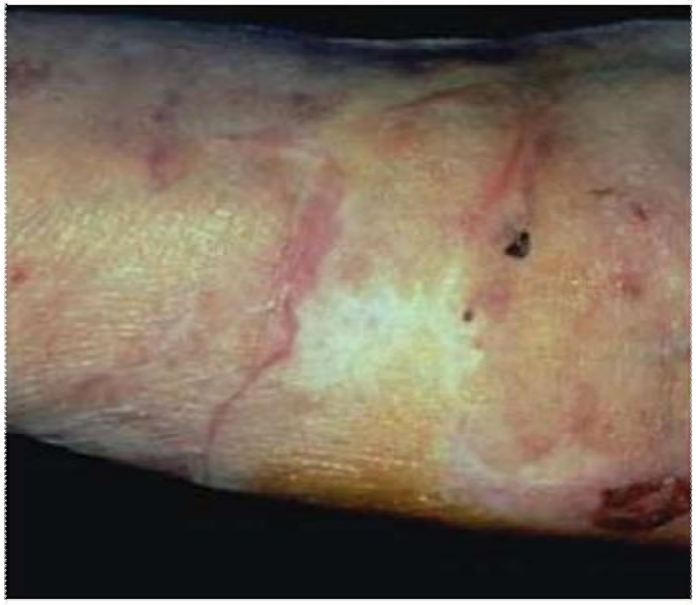
Poor wound healing

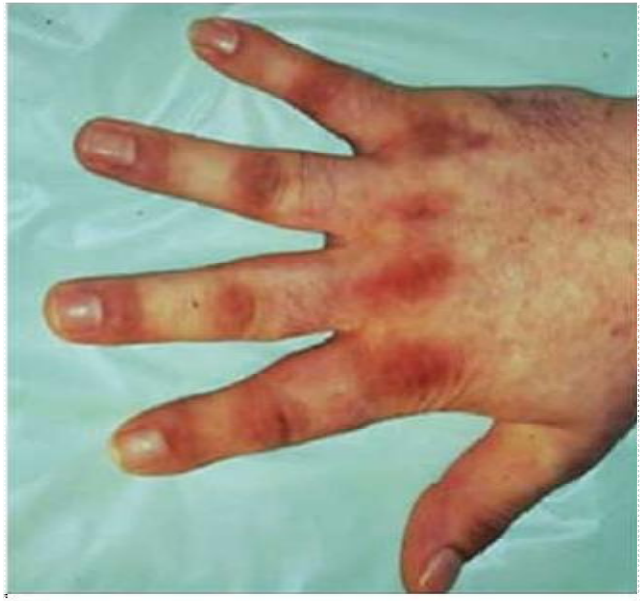
Psychologic disturbances (e.g., depression, emotional lability, irritability, sleep disturbances)

Ectopic ACTH production
Rapidly progressive hypokalemia, metabolic alkalosis, hyperpigmentation, hypertension, edema, and weakness









A. Note central obesity and broad, purple stretch marks (*B.* close-up)

C.Note thin and brittle skin in an elderly patient with Cushing's

D.Hyperpigmentation of the knuckles in a patient with ectopic ACTH excess.

Evaluation

- Most important step in suspected CS
  - is to establish the correct diagnosis
- Exclude exogenous glucocorticoid use
- Screening tests to confirm hypercortisolism

  Overnight/single dose dexamethasone suppression test (DST)

  24 hr urinary free cortisol

  - Late night salivary cortisol level

Cont'd...

A <u>single-dose DST</u>

- A dose of 25-30 ug/kg (maximum of 2 mg) given at 11 PM
- Plasma cortisol level measured at 8 AM the next morning
- Value <50 nmol/L→ Adequate suppression
  - Rules out Cushing syndrome

↓

2nd line screening test: **<u>Low dose DST</u>**

- Eight doses of dexamethasone (5ug/kg per dose every six hours for 2 days, 1.25 mg/m2/day four dose for two days
- Measure serum cortisol at 8 AM
- Suppression (<50 nmol/L) of cortisol rules out Cushing syndrome

Cont'd...

- If Dx of Cushing syndrome has been established then,
  - The next step is to find out the cause

↓

Serum ACTH level

- If low or undetectable– ACTH independent cause [Adrenal cause likely]
- If high– Cushing's disease or Ectopic ACTH syndrome
  - Two differentiate between these two: High dose DST is to be done

Cont'd...

High dose DST

- 2 mg 6 hrly for 2 days
- Cortisol level measured at 8 AM on Day 0 and Day 2
- Partial suppression of cortisol (>50%) confirms Pituitary cause (Cushing disease)
- Failure to suppress suggest Ectopic ACTH syndrome

CRH test

- 100 µg bovine CRH IV is given
- Serum ACTH and cortisol measured for 2 hours
- Incresed ACTH and cortisol– Pituitary Cushing
- No response– Ectopic ACTH syndrome

Common causes: Summary of findings

Disorder	UFC	HDDST	ACTH	CRH test
Adrenal lesion	High	Not suppressed	Low	-ve
Pituitary Microadenoma Macroadenoma	 High High	 Suppressed Not suppressed	 High High	 +ve +ve
Ectopic	High	Not suppressed	High	-ve
Exogenous	Low	Not suppressed	Low	-ve

Other Investigations

- Adrenal cause
  - USG abdomen
  - CT/MRI abdomen

Looking for Adrenal adenoma or carcinoma

- Cushing disease
  - CT/MRI head
    - ↓ No mass seen
  - Bilateral inferior petrosal blood sampling for ACTH level

Looking for Pituitary micro/ macroadenoma

- Ectopic ACTH syndrome
  - CXR
  - CT chest, abdomen

Looking for Oat cell ca, Bronchial carcinoid, Ca panc or Wilms tumour

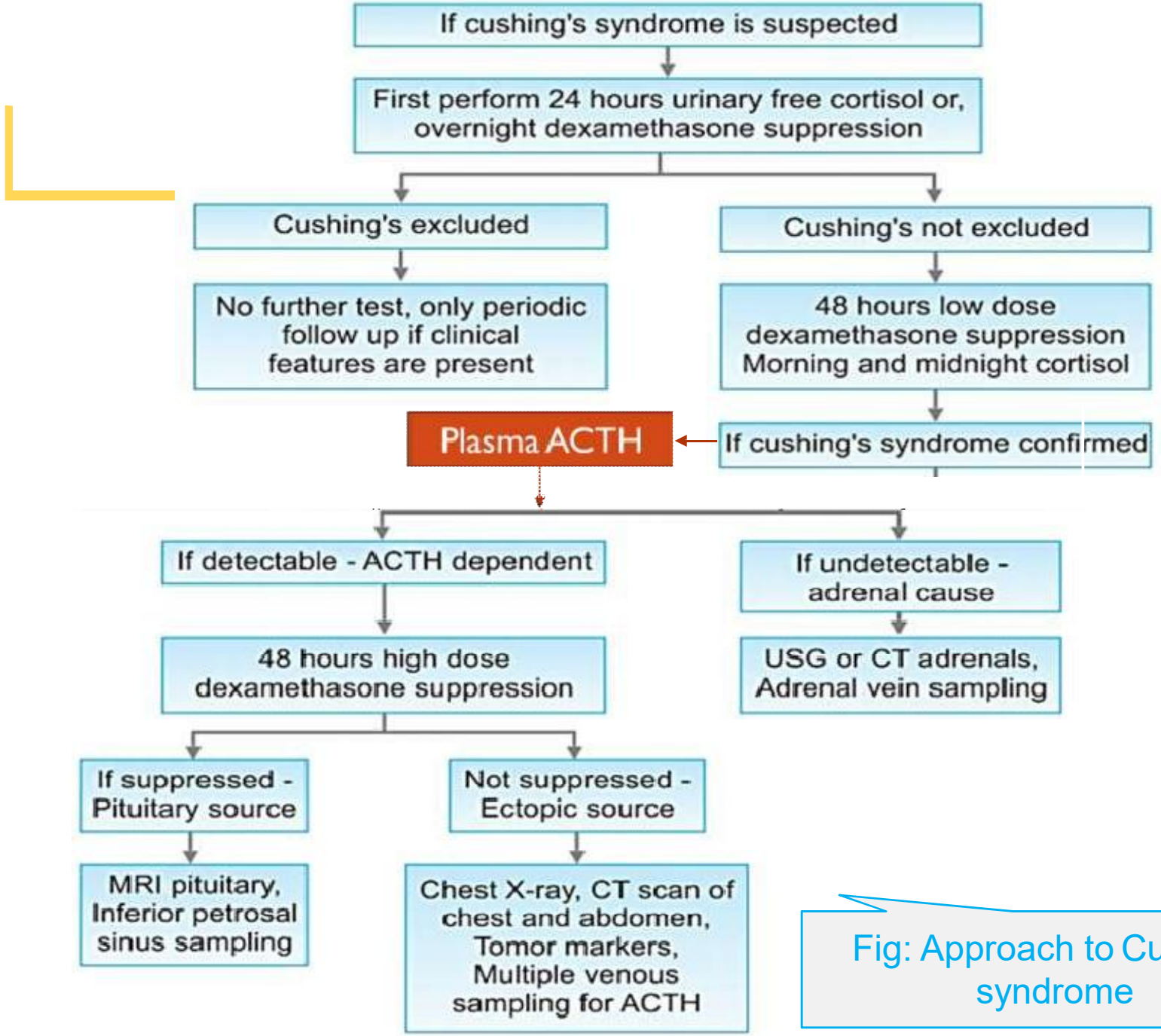


Fig: Approach to Cushing syndrome

Differential Diagnosis

1. Simple obesity

2. Generalized glucocorticoid resistance

3. Pseudo-Cushing syndrome
   - Chronic alcoholism
   - Severe depression

Features	Cushing Syndrome	Obesity
Height	Short	Usually tall
UFC	Elevated	Elevated
Salivary cortisol	High	Normal
Low doses DST	High	Suppressed

Generalized glucocorticoid resistance
Elevated levels of cortisol and ACTH
But no clinical evidence of Cushing syndrome
Patients may exhibit hypertension, hypokalemia, and precocious pseudopuberty

Treatment

Cause	Treatment
• IATROGENIC	• Discontinue or reduce the dose of steroids if possible
PITUITARY	• First-line trans-sphenoidal surgery (90% cure rate) ± pituitary irradiation • Consider bilateral adrenalectomy and medical therapy for recurrent Cushing's disease
ADRENAL	• Unilateral adrenalectomy
ECTOPIC	• Resection of ectopic source if appropriate • Otherwise, bilateral adrenalectomy and medical therapy

Trans-sphenoidal pituitary microsurgery

- Tx of choice in pituitary Cushing disease in children
- The overall success rate with follow-up of less than 10 yr is 60-80%
- Low postoperative serum or urinary cortisol concentrations predict–
  - long-term remission in the majority of cases.
- Relapses are treated with reoperation or pituitary
- irradiation

Adrenalectomy

- Irresponsive to treatment or if ACTH is secreted by an ectopic metastatic tumor
- May lead to **Nelson Syndrome,** when there is Increased ACTH secretion by an unresected pituitary adenoma
  - Evidenced mainly by marked hyperpigmentation
- Requires adequate preoperative and postoperative replacement therapy
- Postoperative complications may include
  - Sepsis, pancreatitis, thrombosis, poor wound healing, and sudden collapse

Medical therapy

- Inhibitors of adrenal steroidogenesis
  [Metyrapone, ketoconazole, aminoglutethimide, etomidate]
  - Used preoperatively to normalize circulating cortisol levels

- Centrally acting serotonin antagonist
  - [Cyproheptadine]
  - Blocks ACTH release

Pheochromocytoma

Pheochromocytoma

- Pheochromocytomas and paragangliomas are catecholamine-producing tumors derived from the sympathetic or parasympathetic nervous system.
- It is a tumour arising from chromaffin cells, from the adrenal medulla but can also arise from extraadrenal chromaffin tissues (*Organ of Zuckerkandl*).
- It is catecholamine secreting tumours

Epidemiology of Pheochromocytoma

- Pheochromocytoma is estimated to occur in 2–8 of 1 million persons per year, and ~0.1% of hypertensive patients harbor a pheochromocytoma.
- The mean age at diagnosis is ~40 years, although the tumors can occur from early childhood until late in life.
- The classic "rule of tens" for pheochromocytomas states that ~10% are bilateral, 10% are extraadrenal, and 10% are malignant.

The 10 percent tumor

- 10% are bilateral
- 10% are malignant
- 10% occur in pediatric patients
- 10% are extra-adrenal
- 10% are familial
- 10% multiple
- 10% not associated with hypertension
- 10% calcified

Etiology

- The etiology of sporadic pheochromocytomas and paragangliomas is unknown.
- However, about 25% of patients have an inherited condition.

Pathogenesis

- Pheochromocytomas and paragangliomas are wellvascularized tumors that arise from cells derived from the sympathetic (e.g., adrenal medulla) or parasympathetic (e.g., carotid body, glomus vagale) paraganglia.
- The name *pheochromocytoma reflects the black-colored* staining caused by chromaffin oxidation of catecholamines

Clinical Features

- Headaches
- Sweating attacks
- Palpitations and tachycardia
- Hypertension, sustained or paroxysmal
- Anxiety and panic attacks
- Pallor
- Nausea
- Abdominal pain
- Weakness
- Weight loss
- Paradoxical response to antihypertensive drugs
- Polyuria and polydipsia
- Constipation
- Orthostatic hypotension
- Dilated cardiomyopathy
- Erythrocytosis
- Elevated blood sugar
- Hypercalcemia

Clinical features …

- ✓ **Classic triad:** Headache, palpitations, and diaphoresis
- ✓ Commonest presentation is severe *headache*.
- ✓ Most common clinical sign is hypertension.
- ✓ Symptoms of sympathetic over activity such as Anxiety
- ✓ Symptoms can be incited by a range of stimuli including exercise, micturition, and defecation

Diagnosis

- The diagnosis is based on documentation of catecholamine excess by biochemical testing and localization of the tumor by imaging.
- Both are of equal importance, although measurement of catecholamines is traditionally the first step.

Biochemical Testing

- Pheochromocytomas and paragangliomas synthesize & store catecholamines, which include norepinephrine, epinephrine, and dopamine.
- ***Elevated plasma and urinary levels of catecholamines and the methylated metabolites, metanephrines, are the cornerstone for the diagnosis.***

Biochemical Testing ….

- Catecholamines and metanephrines can be measured by using different methods
- In a clinical context suspicious for pheochromocytoma, when values are increased three times the upper limit of normal, a pheochromocytoma is highly likely regardless of the assay used.

Biochemical & Imaging Methods for Pheochromocytoma Dx

Diagnostic Method	Sensitivity	Specificity
24-h urinary tests		
Vanillylmandelic acid	++	++++
Catecholamines	+++	+++
Fractionated metanephrines	++++	++
Total metanephrines	+++	++++
Plasma tests		
Catecholamines	+++	++
Free metanephrines	++++	+++
CT	++++	+++
MRI	++++	+++
MIBG scintigraphy	+++	++++
Somatostatin receptor scintigraphy*	++	++

Treatment of Pheochromocytoma

- Complete tumor removal is the ultimate therapeutic goal
- α-Adrenergic blockers (phenoxybenzamine)
- liberal salt intake and hydration are necessary to avoid orthostasis
- Adequate alpha blockade generally requires 7 days, with a typical final dose of 20–30 mg phenoxybenzamine three times per day.

Rx of Pheochromocytoma …

- Oral prazosin or intravenous phentolamine can be used to manage paroxysms
- BP should be consistently below 160/90 mmHg
- Beta blockers (e.g., 10 mg propranolol 3 – 4 times per day) can be added after starting alpha blockers
- Other antihypertensives; calcium channel blockers or ACEIs

Primary Aldosteronism (PAL)

Primary Aldosteronism (PAL)

- The principal action of aldosterone is to conserve body sodium.
- Under the influence of this hormone, the kidneys excrete less sodium and more potassium and hydrogen.
- Is excessive production of aldosterone, which occurs in some patients with functioning tumors of adrenal gland
- Nonsuppressible (primary) hypersecretion of aldosterone is an uncommon but underdiagnosed cause of hypertension. (5 - 13% of hypertensive patients)

Pathophysiology of PAL

- RAAS is a key regulator of BP and ECF Volume
- **Release of renin** from JG cells is the **rate-limiting step**
- Under normal physiologic conditions, renin release is stimulated by several conditions including low renal perfusion pressure, increased renal sympathetic nervous activity, and low sodium concentration sensed by the macula densa
- Renin then cleaves angiotensinogen to angiotensin I, which in turn is cleaved by angiotensin-converting enzyme to angiotensin II.

Pathophysiology of PAL …

- Angiotensin II functions as both a potent vasoconstrictor and triggers the release of aldosterone from the zona glomerulosa.
- Additional regulators of aldosterone release include potassium and ACTH.
- Primary aldosteronism
  - Aldosterone secretion is independent of RAAS
  - Plasma renin levels → suppressed
- Secondary hyperaldosteronism
  - Elevated renin → elevation of aldosterone

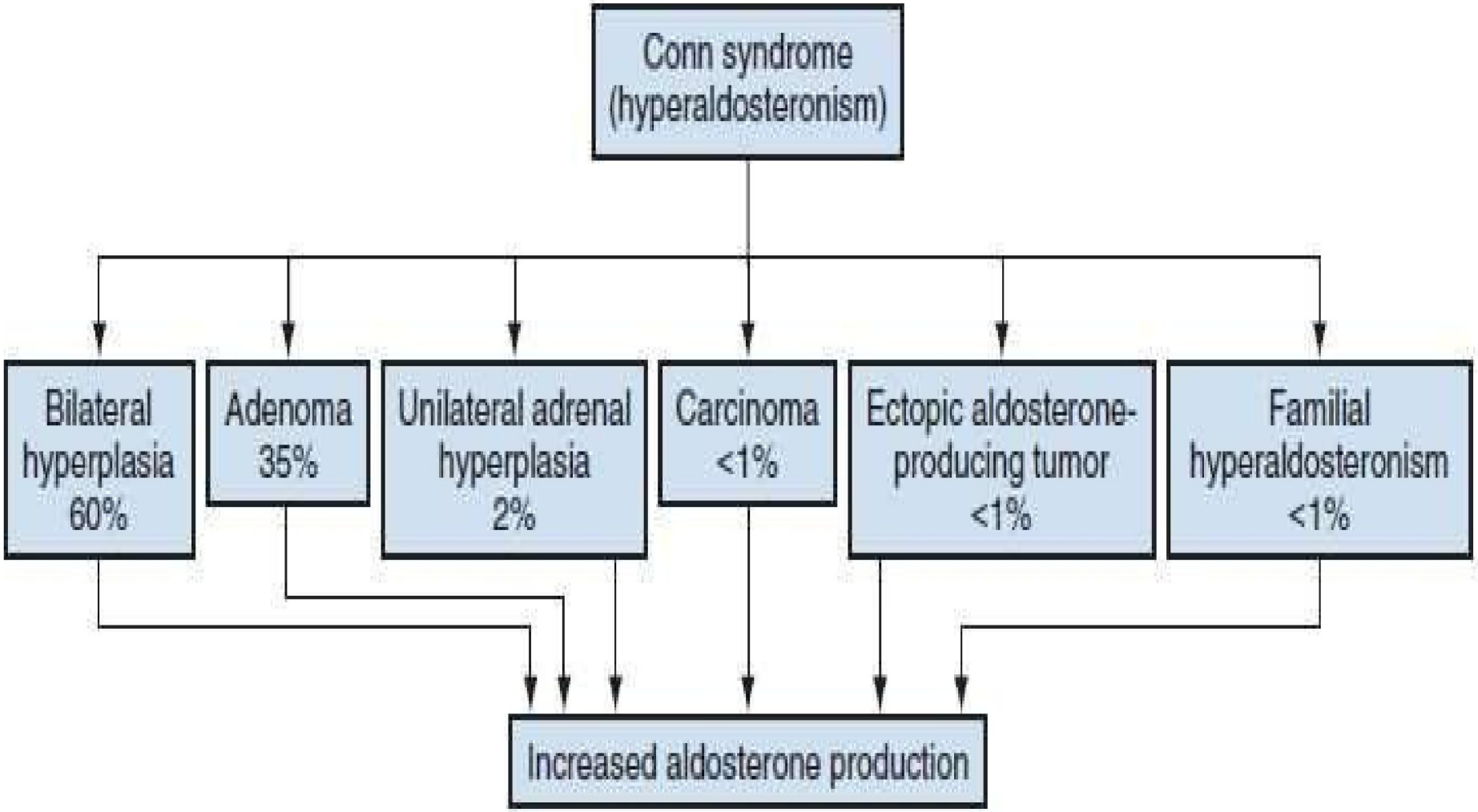
Pathophysiology of PAL …

- Following release from the adrenal cortex, aldosterone increases sodium reabsorption and potassium secretion in the distal nephron
- Hypernatremia does not occur as sodium reabsorption is accompanied by water uptake, thereby maintaining isotonicity.
- The resultant volume expansion is limited by **Mineralocorticoid escape.**

Pathophysiology of PAL …

- Mineralocorticoid escape is mediated by pressure-natriuresis, atrial natriuretic peptide secretion, and changes in electrolyte transporters in the distal nephron, which result in limiting volume expansion to approximately 1.5 kg or less
- Increased plasma aldosterone and decreased plasma renin activity is common to all subtypes with primary aldosteronism

Subtypes


Conn syndrome (hyperaldosteronism)
Bilateral hyperplasia 60%
Adenoma 35%
Unilateral adrenal hyperplasia 2%
Carcinoma <1%
Ectopic aldosterone-producing tumor <1%
Familial hyperaldosteronism <1%
Increased aldosterone production

Subtypes …

Subtypes of Primary Aldosteronism	
Surgically correctable	**Not correctable by surgery**
• Aldosterone-producing adenoma	• B/l adrenal hyperplasia
• Primary u/l adrenal hyperplasia	• Familial hyperaldosteronism type I
• Ovarian aldosterone-secreting tumour	• Familial hyperaldosteronism type II
• Aldosterone-producing carcinoma	

Clinical Manifestations of PAL

- ***The classic presenting signs of primary aldosteronism are hypertension and hypokalemia.***
- Patients with aldosteronism exhibit a profound decline in the serum levels of potassium (hypokalemia) and hydrogen ions (alkalosis), as demonstrated by an increase in pH and serum bicarbonate concentration.
- Serum sodium level is normal or elevated, depending on the amount of water reabsorbed with the sodium.
- Hypertension is the most prominent and almost universal sign of aldosteronism and is present in up to 10% of individuals with hypertension

C/M of PAL …

- Hypokalemia is responsible for:
  - ✓ the variable muscle weakness, cramping, and fatigue in patients with aldosteronism
  - ✓ as well as an inability on the part of the kidneys to acidify or concentrate the urine.
- Accordingly, the urine volume is excessive, leading to polyuria.
- Serum, by contrast, becomes abnormally concentrated, contributing to excessive thirst (polydipsia) and arterial hypertension.

C/M of PAL …

- A secondary increase in blood volume and possible direct effects of aldosterone on nerve receptors, such as the carotid sinus, are other factors that result in hypertension.
- Hypokalemic alkalosis may decrease the ionized serum calcium level and predispose the patient to tetany and paresthesias.
- Trousseau's and Chvostek's signs may be used to assess neuromuscular irritability before overt paresthesia and
- Glucose intolerance may occur, because hypokalemia interferes with insulin secretion from the pancreas.

C/M of PAL …

- As compared to patients with essential hypertension:
  - 4 times more likely to be diagnosed with a stroke
  - 6.5 times more likely to be diagnosed with a myocardial infarction
  - 12 times more likely to be diagnosed with atrial fibrillation
  - Increased proteinuria

Assessment and Diagnostic Findings

- In addition to a high or normal serum sodium level and a low serum potassium level, diagnostic studies indicate high serum aldosterone and low serum renin levels.
- The measurement of the aldosterone excretion rate after salt loading is a useful diagnostic test for primary aldosteronism.
- The renin–aldosterone stimulation test and bilateral adrenal venous sampling are useful in differentiating the cause of primary aldosteronism.
- Antihypertensive medication may be discontinued up to 2 weeks before testing

Diagnosis ….

- Involves screening, confirmatory testing, & subtype differentiation
- **Indications for Primary Aldosterone Screening (SHARE-USE)**
  - **S**evere hypertension (≥160/≥110 mmHg)
  - **H**ypertension with hypokalemia
  - **A**drenal Incidentaloma with hypertension
  - **R**esistant HTN (three or more oral agents with poor control)
  - **E**arly-onset hypertension (<20) or stroke (<50 years)
  - **U**nexplained hypokalemia (spontaneous or diuretic induced)
  - Whenever considering **S**econdary causes of hypertension (i.e., pheochromocytoma or renovascular disease)
  - **E**vidence of target organ damage disproportionate to degree of hypertension

Diagnosis ….

1. **Screening test:** prior to screening
   - Hypokalemia should be corrected
   - All contraindicated medications to be discontinued
- Can continue majority of antihypertensive agents
- Potassium-sparing diuretics and Mineralocorticoid (MC) receptor blockers greatly alter the RAA axis and should be stopped at least 6 weeks prior to aldosterone renin ratio (ARR) testing.
- Patients requiring MC Receptor blockers for control of severe hypertension should be transitioned to agents such as α1-receptor blockers or long-acting CCBs

Effect Of Antihypertensives On Screening For PAL

Beta blockers — consider discontinuing for several weeks prior to testing

$$\frac{\text{Aldosterone} \leftrightarrow}{\text{Renin} \downarrow} = \text{ARR} \uparrow \text{ (possible false positive)}$$

ACE inhibitors — no need to discontinue prior to testing (see text)

$$\frac{\text{Aldosterone} \downarrow\downarrow}{\text{Renin} \uparrow} = \text{ARR} \downarrow \text{ (small chance of false negative)}$$

Calcium channel blockers — no need to discontinue prior to testing

$$\frac{\text{Aldosterone} \leftrightarrow}{\text{Renin} \rightleftharpoons} = \text{ARR} \rightleftharpoons$$

Diagnosis ….

- Screening for primary aldosteronism begins by obtaining a morning (between 8 and 10 AM) plasma aldosterone concentration (PAC) and plasma renin activity (PRA)
- PAC and ARR are used to screen for autonomous aldosterone secretion
- ARR is dependent on PRA
- It is recommended that the lowest PRA value be set at 0.2 ng/mL/hr to avoid falsely elevated ratios

Diagnosis ….

- PAC and ARR that define a positive screen and suggest the diagnosis of PAL are not standardised.
- The National Institutes of Health (NIH) Consensus Statement (2002) on the management of the clinically inapparent adrenal mass suggests cut-offs of
  - > 30 for ARR
  - > 20 ng/dL for PAC
- All positive tests must be confirmed with further testing

Diagnosis …

2. Confirmatory testing

- Of the patients with positive screening tests, only 50% to 70% will be diagnosed
  with PAL on confirmatory testing
- Patient preparation is required
  - Correction of hypokalemia
  - Discontinuation of Mineralocorticoid receptor antagonists
- Of the confirmatory tests available
  - 3 evaluate suppression of aldosterone ff sodium loading
  - 1 evaluates suppression of ARR following administration of an ACE inhibitor.
- BP should be monitored closely in all patients

Diagnosis …

3. Subtype differentiation

- It is essential in selecting appropriate therapy, because surgical therapy is only successful for select subtypes
- In patients who are not surgical candidates, subtype differentiation is of little consequence
- Given the rarity of FH type I, genetic screening should not be performed in all patients
- However, patients with a family history of primary aldosteronism, early age of onset (<20 years), or patients with a family history of CVA at a young age should be considered for genetic testing
- An adrenal CT scan should be obtained in all patients with primary aldosteronism who are potential surgical candidates

Treatment of PAL

- Goal of treatment in primary aldosteronism is to control and prevent the morbidity associated with Mineralocorticoid excess.
- Treatment strategies aim to
  - Remove the source of Mineralocorticoid excess or
  - Block the effect of aldosterone on target organs
- Treatment strategies are primarily dependent on subtype classification and surgical candidacy
  - U/I adrenalectomy
  - Medical therapy

Treatment of PAL …

- Treatment of PAL usually involves surgical removal of the adrenal tumor through adrenalectomy.
- Hypokalemia resolves for all patients after surgery, but, hypertension may persist.
- Spironolactone (Aldactone) may be prescribed to control hypertension.
- Adrenalectomy is performed through an incision in the flank or the abdomen.
- In general, the postoperative care resembles that for other abdominal surgery.

Treatment of PAL …

- However, the patient is susceptible to fluctuations in adrenocortical hormones and requires administration of corticosteroids, fluids, and other agents to maintain blood pressure and prevent acute complications.
- If the adrenalectomy is bilateral, replacement of corticosteroids will be lifelong
- If one adrenal gland is removed, replacement therapy may be temporarily necessary
- A normal serum glucose level is maintained with insulin, appropriate IV fluids, and dietary modifications.

Treatment of PAL …

Surgery

- Aldosterone-producing adenomas:
  - Usually small sized
  - Offer laparoscopic adrenalectomy
- Adrenal cortical carcinoma
  - Open procedure recommended
- Improvement in blood pressure
  - 33 - 73% of patients do not require antihypertensives postoperatively

Treatment of PAL …

- Predictors of persistent hypertension following adrenalectomy for PAL:
  - Age > 50
  - Use of two or more antihypertensive agents preoperatively
  - Having a 1st degree relative with hypertension
  - Prolonged duration of hypertension prior to adrenalectomy
  - Renal insufficiency

Treatment of PAL …

Medical treatment

- In patients with nonsurgically correctable subtypes and those who are not surgical candidates
- **Aldosterone receptor antagonists** (Spironolactone and Eplerenone) are successful in lowering BP and are the antihypertensive agents of choice
- **Spironolactone**
  - Initiated at doses of 25 to 50 mg/day
  - Can be titrated up to 400 mg/day, depending on BP, serum potassium levels, and side effects.

Treatment of PAL …

- **Eplerenone**
  - More favorable side-effect profile
  - Increased selectivity for aldosterone receptor
  - Initiated with 25 mg twice per day
  - Titrated up to 100 mg per day
- Other antihypertensive agents will often be needed.
- Lifestyle modifications: weight loss, low- sodium diet, and regular exercise
- **FH type I** can be treated with oral Glucocorticoids.
  - Glucocorticoid → reduce ACTH release → decreased aldosterone production

  - When BP is not controlled with Glucocorticoids alone
  - Development of Iatrogenic Cushing's

  } Add aldosterone receptor antagonist

Nursing Management of PAL

- Nursing Mgt in the postoperative period includes:
  - Frequent assessment of vital signs to detect early S/Sx of adrenal insufficiency & crisis or hemorrhage.
  - Explaining all Rx and procedures, providing comfort measures, and
  - Providing rest periods can reduce the patient's stress and anxiety level.

Disorders of islets of langerhans

Diabetes mellitus

- Diabetes mellitus (DM) is a chronic condition that is characterised by raised blood glucose levels (Hyperglycemia).

Regulation of Plasma Glucose Level

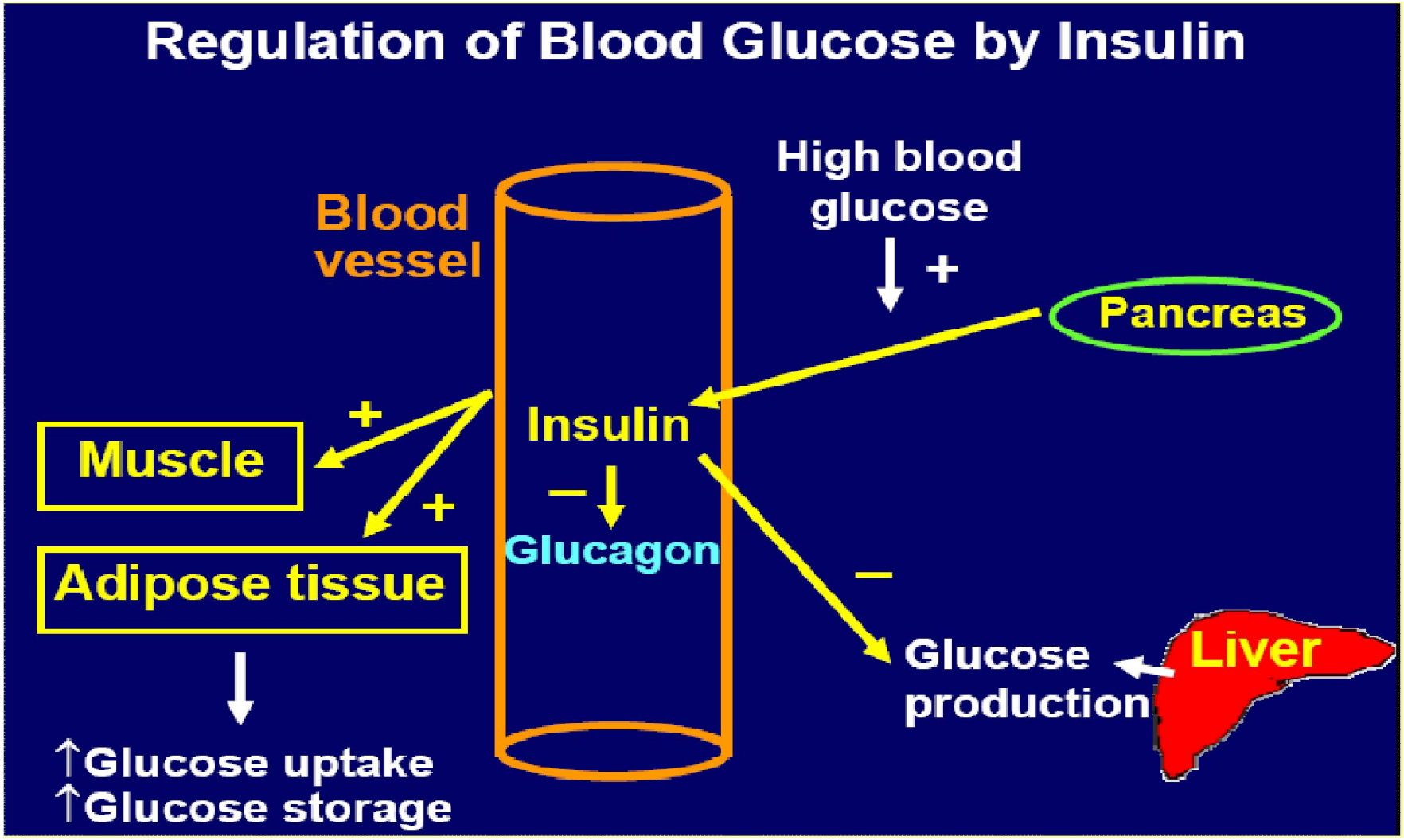
- Plasma glucose is tightly regulated by hormones:

Insulin: ↓ Plasma glucose

- **Glucagon**
  Epinephrine
  Cortisol
  Growth hormone

} **↑ Plasma glucose**

How Insuline Decrease Plasma Glucose Level?



Classification of DM

1. **Type 1 DM**: is due to insulin deficiency and is formerly known as:
   - Insulin Dependent DM (IDDM)
   - Juvenile onset DM
2. **Type 2 DM**: is a combined insulin resistance and relative deficiency in insulin secretion.
   - Noninsulin Dependent DM (NIDDM)
   - Adult onset DM

Classification of DM …

3. **Gestational Diabetes Mellitus (GDM):** developing during some cases of pregnancy but usually disappears after pregnancy.
4. **Other types:** secondary DM

Etiology of Type 1 Diabetes

- Autoimmune disease
- Selective destruction of β cells by T cells
- Several circulating antibodies against β cells
- Cause of autoimmune attack: unknown
- Both genetic & environmental factors are important

Etiology of Type 1 Diabetes

Environmental Factors

Viruses

e.g.
- Coxsackie
- Mumps
- Rubella

Nutrients

↓

e.g. Cow milk

Babies → Cow milk → Antibodies against cow insulin

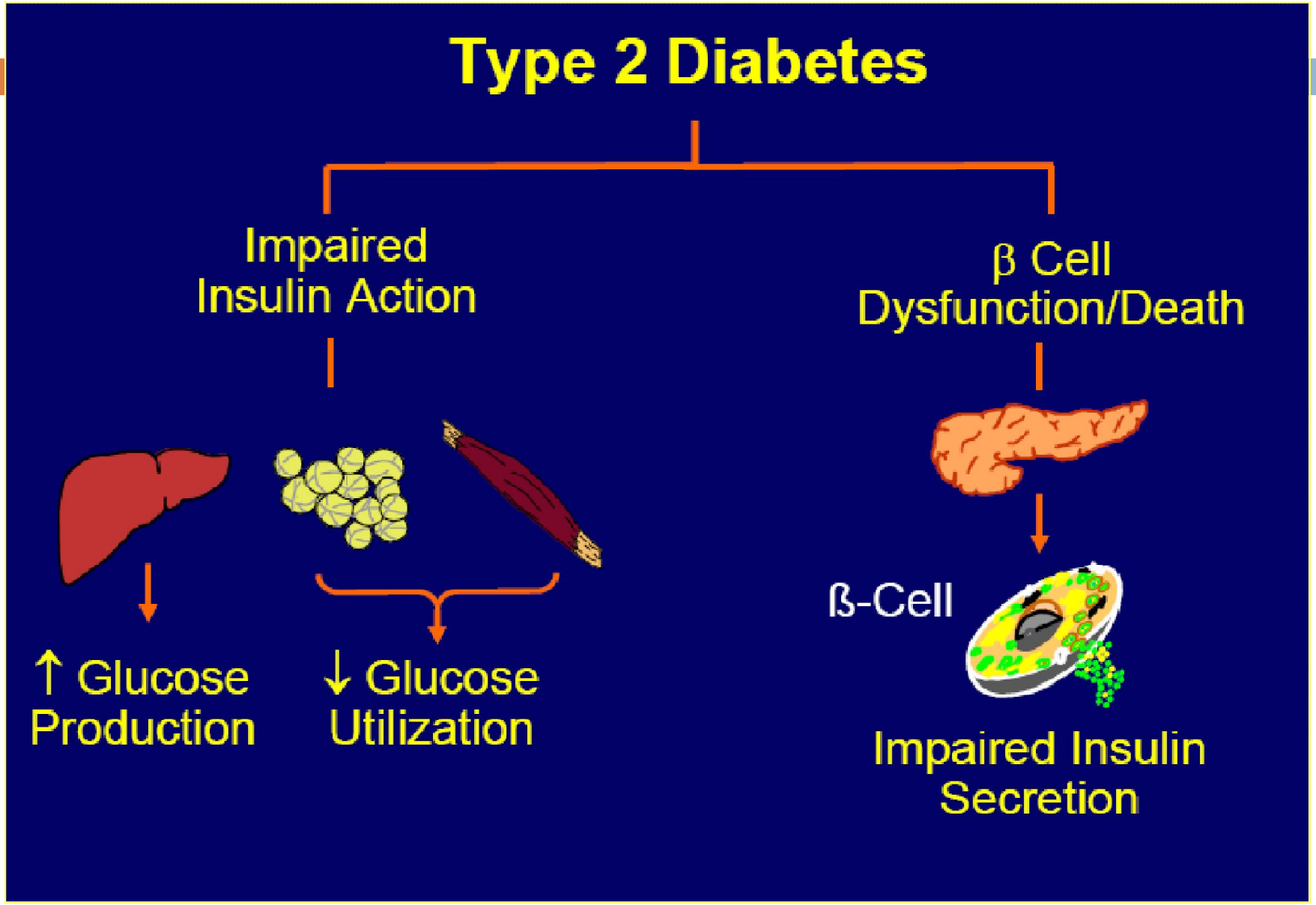
↓

Closely resembles human insulin

↓

May attack β cells

Etiology of Type 2 Diabetes



Etiology of Type 2 Diabetes

- Response to insulin is decreased
  - ↓glucose uptake (muscle, fat)
  - ↑glucose production (liver)
- The mechanism of insulin resistance is unclear
- Both genetic & environmental factors are involved
- Post insulin receptor defects

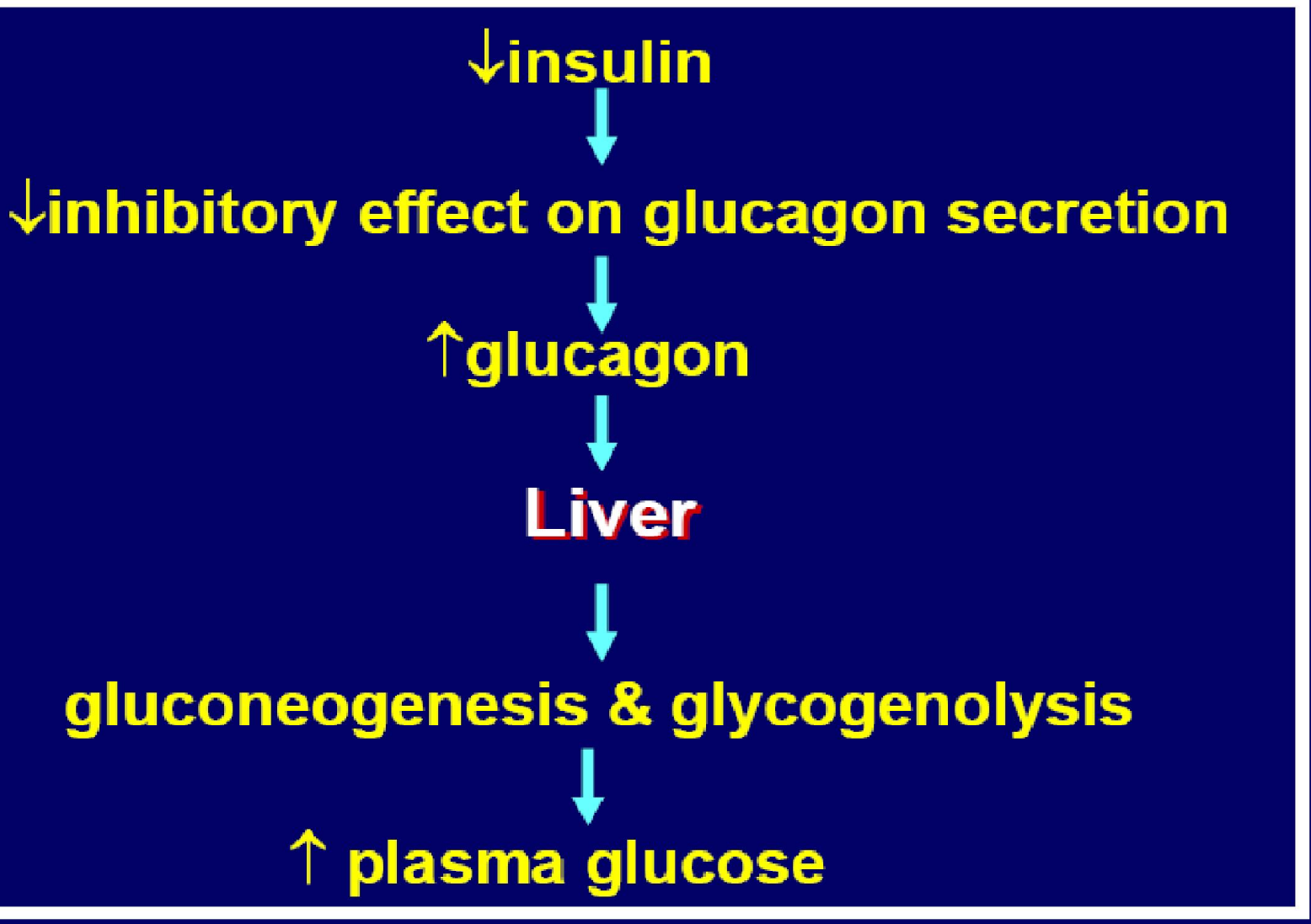
Mechanism of Hyperglycemia in Diabetes

Absolute (type 1 diabetes) or relative (type 2 diabetes) insulin deficiency:

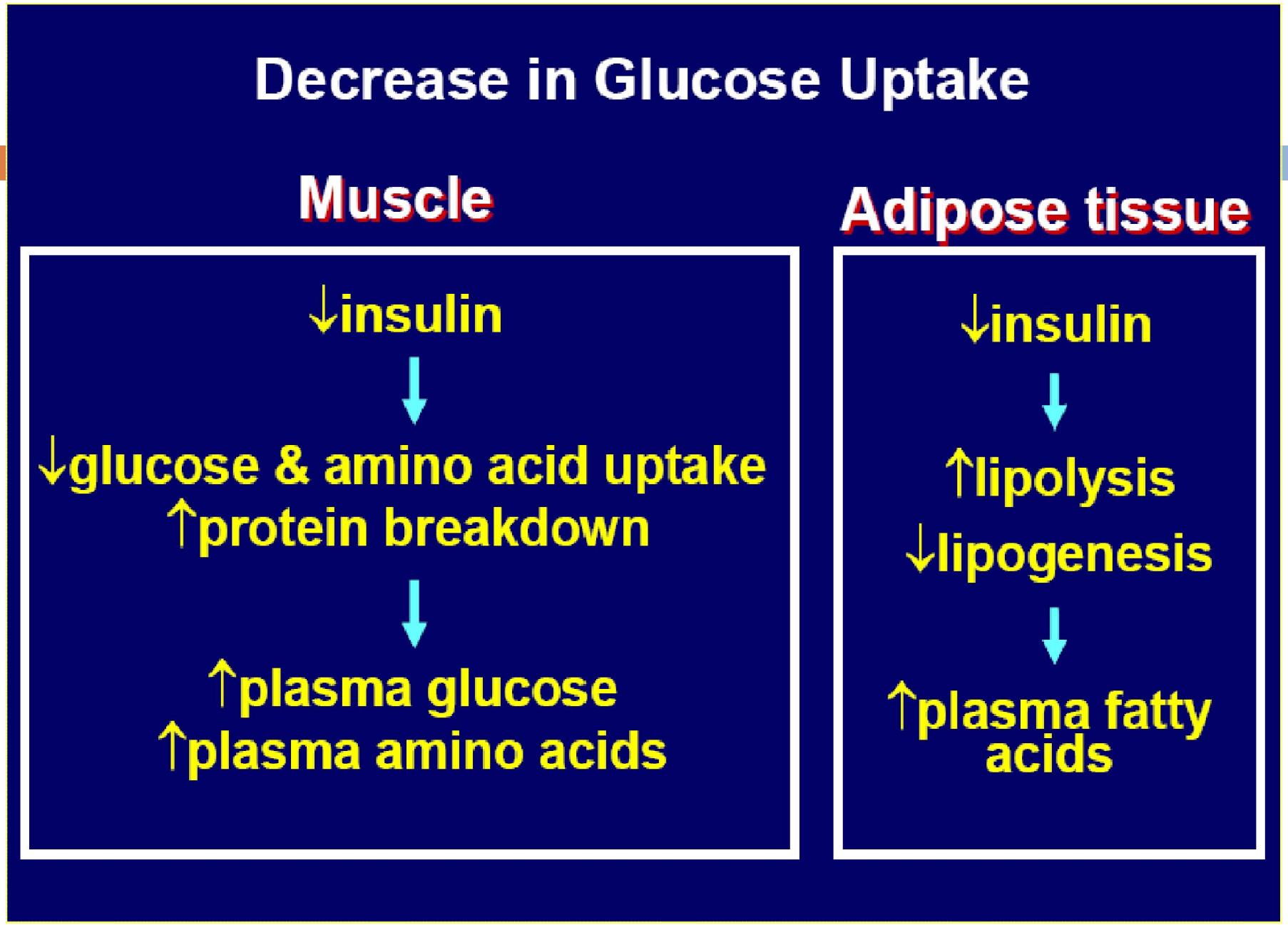
- An increase in hepatic glucose output

- A decrease in peripheral glucose uptake & utilization

Increase in Hepatic Glucose Output



Decrease in Glucose Uptake



Characteristics	Type 1	Type 2
% of diabetic popn.	5 – 10%	90%
Age of onset	Usually < 30 yr + some adults	Usually > 40 + some obese children
Pancreatic function	Usually none	Insulin is low, normal or high
Pathogenesis	Autoimmune process	Defect in insulin secretion, tissue resistance to insulin, increased HGO
Family Hx	Generally not strong	Strong
Obesity	Uncommon	Common
History of DKA	Often present	Rare except in stress
Clinical presentation	Moderate to severe symptoms: 3Ps, fatigue, wt loss and ketoacidosis	Mild symptoms: Polyuria and fatigue. Diagnosed on routine physical examination
Treatment	Insulin, Diet, Exercise	Diet, Exercise, Oral anti diabetics, Insulin

Epidemiology

- **Type 1 DM**
  - It is due to pancreatic islet β-cell destruction predominantly by an autoimmune process.
  - Usually develops in childhood or early adulthood
  - It accounts for up to 10% of all DM cases
  - Develops as a result of the exposure of a genetically susceptible individual to an environmental agent

Epidemiology

- **Type 2DM**
  - It results from insulin resistance with a defect in compensatory insulin secretion.
  - Insulin may be low, normal or high
  - About 30% of the Type 2 DM patients are undiagnosed (they do not know that they have the disease) because symptoms are mild.
  - It accounts for up to 90% of all DM cases

Risk factors

- **Type 1 DM**
  - **Genetic predisposition:** In an individual with a genetic predisposition, an event such as virus or toxin triggers autoimmune destruction of cells probably over a period of several years.

Risk factors …

- **Type 2 DM**
  - Family History
  - Obesity
  - Habitual physical inactivity
  - Previously identified IGT) or IFG
  - Hypertension
  - Hyperlipidemia

Carbohydrate metabolism

- Carbohydrates are metabolized in the body to glucose.
- CNS uses glucose as its primary energy source. This is independent of insulin.
- Glucose is taken by the muscle to produce energy (insulin required).
- Glucose is stored in the liver as glycogen and in adipose tissues as fat.
- Insulin is produced and stored by the β- cells of the pancreas

Carbohydrate metabolism …

- Postprandial glucose metabolism in normal individuals:
  - After food is ingested, blood glucose concentrations rise & stimulate insulin release.
- **Insulin action:**
  - Increase glucose uptake by the tissues
  - Increase liver glycogen formation and decrease glycogen breakdown
  - Increase lipid synthesis and inhibits fatty acid breakdown to ketone bodies
  - Promotes protein synthesis

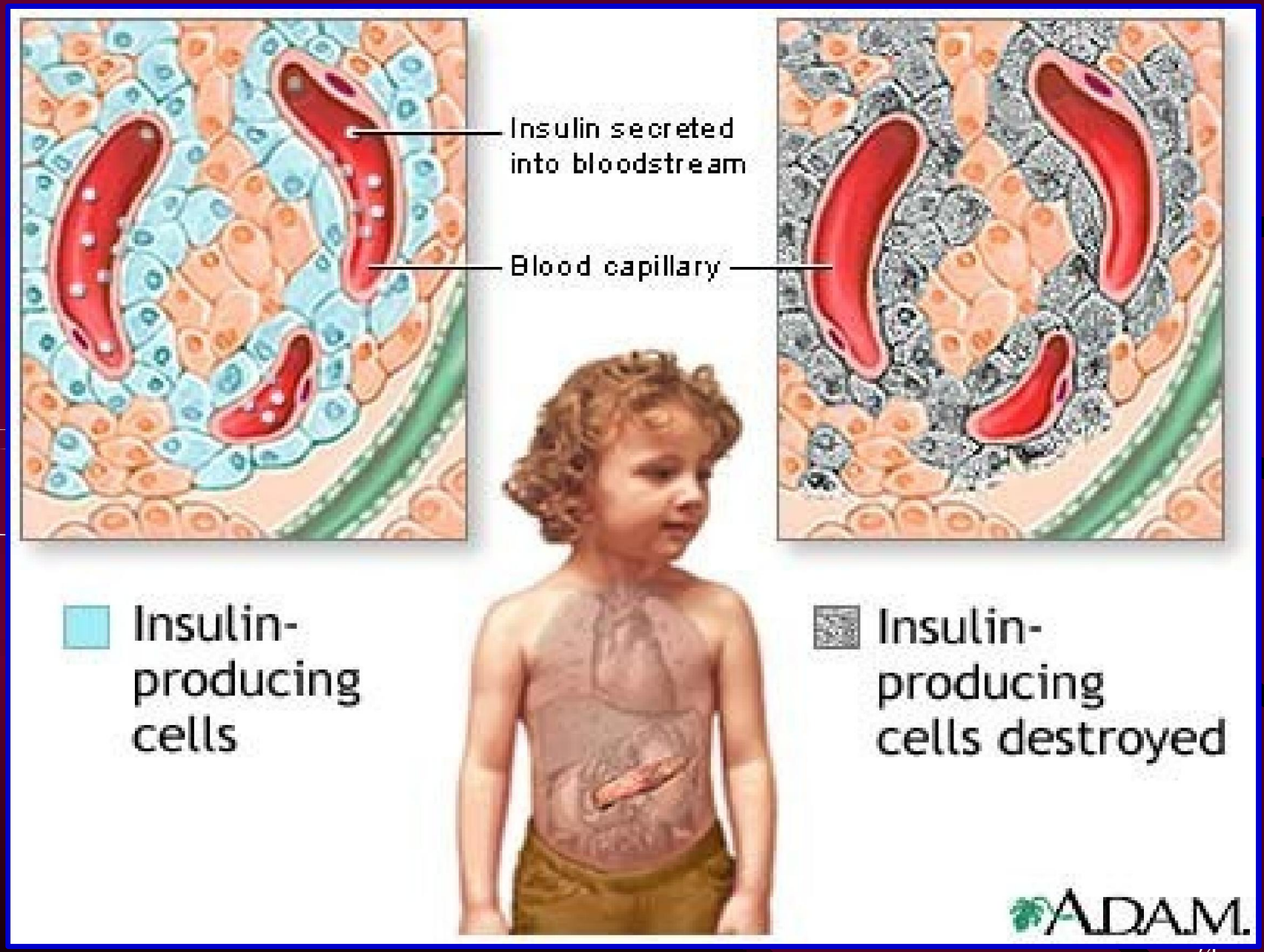
Carbohydrate metabolism …

- Fasting glucose metabolism in normal individuals:
  - Insulin release is inhibited.
  - Hormones that promote an increase in blood glucose are released:
    - Glucagon, Epi, GH, glucocorticoids, & Thyroid hormone
  - Glycogenolysis
  - Gluconeogenesis: amino acids are transported from muscle to liver and converted to glucose.
  - TG are broken down into free FAs as an alternative fuel source.

Pathophysiology of DM

- **Type 1 DM:** is characterized by an absolute deficiency of insulin due to immune- mediated destruction of the pancreatic B-cells

- In rare cases the B-cell destruction is not due to immune mediated reaction (idiopathic type 1 DM)


Insulin secreted into bloodstream
Blood capillary
Insulin-producing cells
Insulin-producing cells destroyed
A.D.A.M.

Pathophysiology of Type 1 DM …

- **There are four stages in the dev't of Type 1 DM:**
  a) Preclinical period with positive β- cells antibodies
  b) Hyperglycemia when 80-90% of the β- cells are destroyed.
  c) Transient remission (honeymoon phase).
  d) Establishment of the disease

Pathophysiology of Type 1 DM …

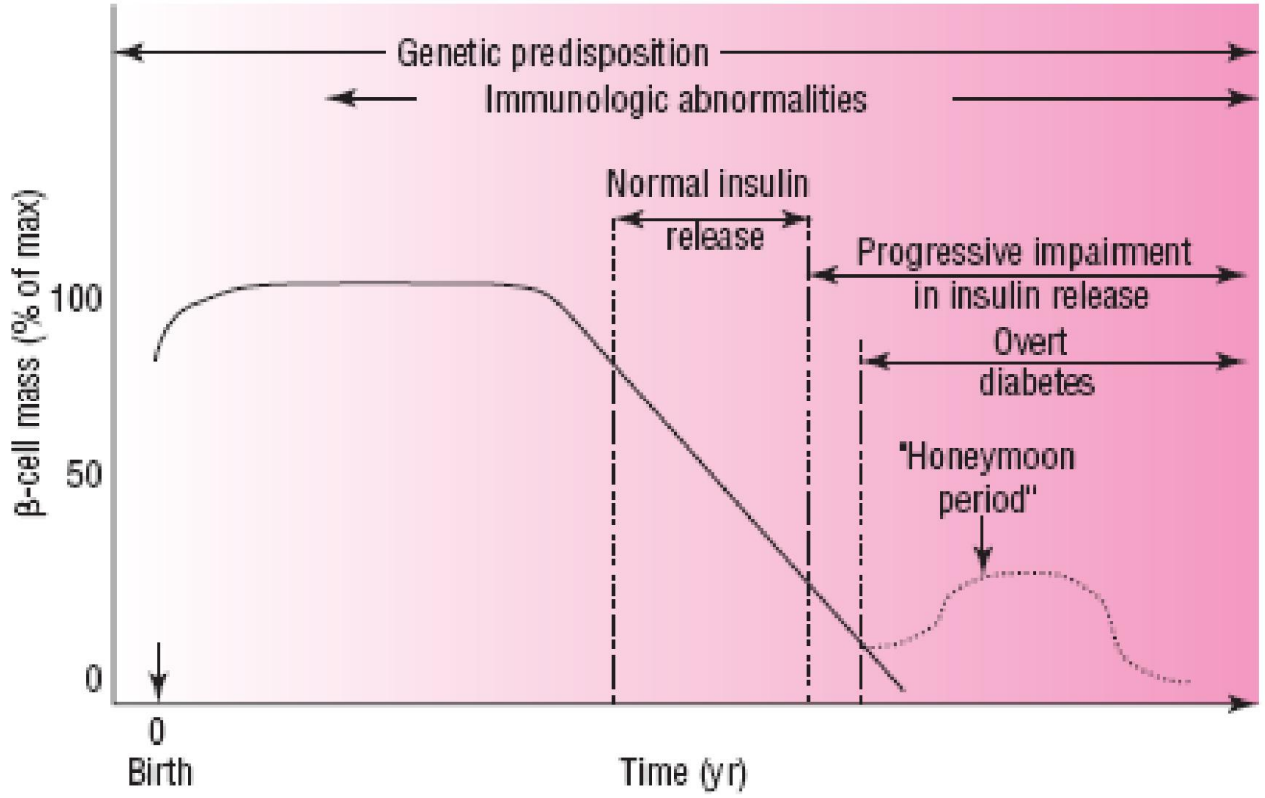


FIGURE 72–4. Scheme of the natural history of the β-cell defect in type 1 diabetes mellitus. (From ADA Medical Management of Type of 1 Diabetes, 3rd ed. 1998.)

Pathophysiology of Type 2 DM

- Insulin resistance (tissue insensitivity) and some degree of insulin deficiency or β- cell dysfunction are central to the development of type 2 DM
- Obesity is very common in type 2 DM (≥80% of patients).
- It occurs when a diabetogenic lifestyle (excessive calories, inadequate caloric expenditure and obesity) is superimposed upon a susceptible genotype.

Pathophysiology of Type 2 DM …

- In the early stages of the disorder, glucose tolerance remains near-normal, despite insulin resistance, because the pancreatic beta cells compensate by increasing insulin output.
- As insulin resistance and compensatory hyperinsulinemia progress, the pancreatic islets in certain individuals are unable to sustain the hyperinsulinemic state.

Pathophysiology of Type 2 DM …

- IGT, characterized by elevations in postprandial glucose, then develops.
- A further decline in insulin secretion and an increase in hepatic glucose production lead to overt diabetes with fasting hyperglycemia.
- Ultimately, beta cell failure ensues.

Laboratory tests

1. **Glucosuria:** to detect glucose in urine by a paper strip
   - Semi-quantitative
   - Normal kidney threshold for glucose is essential
2. **Ketonuria:** to detect ketonbodies in urine by a paper strip
   - Semi-quantitative

Laboratory tests …

3. **Fasting blood glucose**
   - Glucose blood concentration in samples obtained after at least eight hours of the last meal
4. **Random Blood glucose**
   - Glucose blood concentration in samples obtained at any time regardless the time of the last meal

Laboratory tests ….

5. **Glucose tolerance test**

   - 75 gm of glucose are given to the patient with 300 ml of water after an overnight fast
   - Blood samples are drawn 1, 2, and 3 hours after taking the glucose
   - This is a more accurate test for glucose utilization if the fasting glucose is borderline

Laboratory tests ….

6. **Glycosylated hemoglobin (HbA1C)**
   - Is formed by condensation of glucose with free amino groups of the globin component of Hgb.
   - Normally it comprises 4-6% of the total hemoglobin.
   - Increase in the glucose blood concentration increases the glycated hemoglobin fraction.
   - HbA1C reflects the glycemic state during the preceding 8- 12 weeks.

Laboratory tests ….

7. **Serum Fructosamine**

- Formed by glycosylation of serum protein (mainly albumin)
- Since serum albumin has shorter half life than hemoglobin, serum fructosamine reflects the glycemic state in the preceding 2 weeks
- Normal is 1.5 - 2.4 mmole/L when serum albumin is 5 gm/dL.

Self monitoring test

- **Self-monitoring of blood glucose**
  - Extremely useful for outpatient monitoring specially for patients who need tight control for their glycemic state.
  - A portable battery operated device that measures the color intensity produced from adding a drop of blood to a glucose oxidase paper strip.

Self monitoring …

Diagnostic Criteria

TABLE 72–3. Criteria for the Diagnosis of Diabetes Mellitus[a]

Symptoms of diabetes plus casual[b] plasma glucose concentration ≥200 mg/dL (11.1 mmol/L)
or
Fasting[c] plasma glucose ≥126 mg/dL (7.0 mmol/L)
or
2-hour postload glucose ≥200 mg/dL (11.1 mmol/L) during an OGTT[d]

- Any one test should be confirmed with a second test, most often fasting plasma glucose (FPG).
- This criteria for diagnosis should be confirmed by repeating the test on a different day.

TABLE 72–4. Categorization of Glucose Status

Fasting plasma glucose (FPG)

Normal

- FPG <100 mg/dL (5.6 mmol/L)

Impaired fasting glucose (IFG)

- 100–125 mg/dL (5.6–6.9 mmol/L)

Diabetes mellitus[a]

- FPG ≥126 mg/dL (7.0 mmol/L)

2-Hour postload plasma glucose (oral glucose tolerance test)

Normal

- Postload glucose <140 mg/dL (7.8 mmol/L)

Impaired glucose tolerance (IGT)

- 2-hour postload glucose 140–199 mg/dL (7.8–11.1 mmol/L)

Diabetes mellitus[a]

- 2-hour postload glucose ≥200 mg/dL (11.1 mmol/L)

[a]Provisional diagnosis of diabetes (diagnosis to be confirmed; see Table 72–3).

Clinical Presentation

- **Type 1 DM**

- Polyuria
- Polydipsia
- Polyphagia
- Weight loss
- Weakness
- Dry skin
- Ketoacidosis

- **Type 2 DM**

-
-
-
-
-
-
-

while performing urine glucose screening

Treatment of DM

Desired outcomes:

- Relieve symptoms
- Reduce mortality
- Improve quality of life
- Reduce the risk of microvascular and macrovascular disease complications
  - Macrovascular complications:
    - Coronary heart disease, stroke and peripheral vascular disease
  - Microvascular Complications:
    - Retinopathy, nephropathy and neuropathy

Treatment of DM …

- **How to achieve the goals?**
  - Near normal glycemic control reduce risk of developing microvascular disease complications.
  - Control of the traditional CV risk factors such as smoking, management of dyslipidemia, intensive BP control and antiplatelet therapy.

Treatment of DM …

- **General approaches**
  - Medications
  - Dietary and exercise modification
  - Regular complication monitoring
  - Self monitoring of blood glucose
  - Control of BP and lipid level

Glycemic goals of DM Treatment

TABLE 72–7. Glycemic Goals of Therapy

Biochemical Index	ADA	ACE and AACE
Hemoglobin A_{1c}	<7%[a]	≤6.5%
Preprandial plasma glucose	90–130 mg/dL (5.0–7.2 mmol/L)	<110 mg/dL
Postprandial plasma glucose	<180 mg/dL[b] (<10 mmol/L)	<140 mg/dL

[a]Referenced to a nondiabetic range of 4.0–6.0% using a DCCT-based assay. More stringent glycemic goals (i.e., a normal HbA_{1c}, <6%) may further reduce complications at the cost of increased risk of hypoglycemia (particularly in those with type 1 diabetes).

[b]Postprandial glucose measurements should be made 1–2 hours after the beginning of the meal, generally the time of peak levels in patients with diabetes.

ADA, American Diabetes Association; ACE, American College of Endocrinology; AACE, American Association of Clinical Endocrinologists; DCCT, Diabetes Control and Complications Trial.

Treatment of DM …

- **Complication monitoring**
  - Annual eye examination
  - Annual microalbuminuria
  - Feet examination
  - BP monitoring
  - Lipid profile

Treatment of DM …

- **Self monitoring of blood glucose:**
  - Frequent self monitoring of blood glucose to achieve near normal level
  - More intense insulin regimen require more frequent monitoring

Non-pharmacological Rx of DM

A. Diet:

- **For type 1:** the goal is to regulate insulin administration with a balanced diet
  - In most cases, high carbohydrate, low fat, and low cholesterol diet is appropriate
- **Type 2 DM:** patients need caloric restriction

Non-pharmacological therapy …

Diet …

- **Artificial sweeteners:**
  - e.g. Aspartame, saccharin, sucralose, and acesulfame
  - Safe for use by all people with diabetes
- **Nutritive sweeteners:**
  - e.g. fructose and sorbitol
  - Their use is increasing except for acute diarrhea in some patients

Non-pharmacological…

B. Exercise:

- Improves insulin resistance and achieving glycemic control.
- Exercise should start slowly for patients with limited activity.
- Patients with CV diseases should be evaluated before starting any exercise

Non-pharmacological…

C. Cessation of smoking

Pharmacological Rx of DM

- Insulin (Type 1 and Type 2 DM)
- Sulfonylurea (Type 2 DM)
- Biguanides (Type 2 DM)
- Meglitinides (Type 2 DM)
- Thiazolidinediones Glitazones (Type 2 DM)
- α -Glucosidase inhibitors (Type 2 DM)

Pharmacological Treatment of Type 2 DM

trategy for Controlling Hyperglycemia

Absorption from Diet

Biosynthesis in Liver

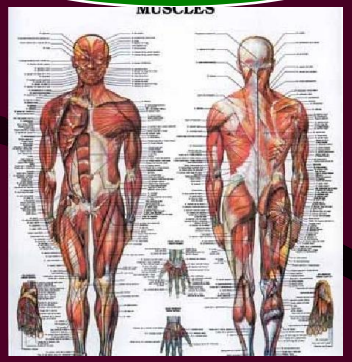
α-Glucosidase Inhibitors

Biguanides

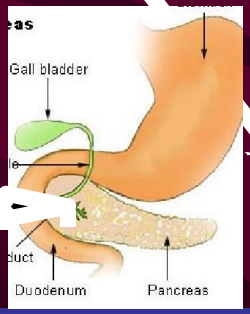
Serum Sugar

Cellular Uptake

Biguanides; thiazolidinediones



Pancreas



Insulin

Sulfonylureas

Meglitinide

1. Sulfonylureas

- Stimulate the pancreatic secretion of insulin

Classification

A. **First generation**

- e.g. tolbutamide, chlorpropamide, and acetohexamide
- Lower potency, more potential for drug interactions and side effects

1. Sulfonylureas …

B. Second generation

- e.g. glimepiride, glipizide, and glyburide
- higher potency, less potential for drug interactions and side effects

- All sulfonylurea drugs are equally effective in reducing the blood glucose when given in equipotent doses.

1. Sulfonylureas …

- **Efficacy**
  - HbA1c: 1.5 – 1.7% reduction.
  - FPG: 50 – 70 mg/dL reduction.
  - PPG: 92 mg/dL reduction.
- **Adverse effects**
  - Hypoglycemia
  - Hyponatremia (with tolbutamide & chlorpropamide)
  - Weight gain

1. Sulfonylureas …

TABLE 72–12. Drug Interactions with Sulfonylureas

Interaction	Drugs
Displacement from protein binding sites[a]	Warfarin, salicylates, phenylbutazone, sulfonamides
Alters hepatic metabolism (cytochrome P450)	Chloramphenicol, monoamine oxidase inhibitors, cimetidine, rifampin[b]
Altered renal excretion	Allopurinol, probenecid

[a] Many of these drug interactions may be metabolism-based.

[b] Inducer.

Reproduced from Gerich.[70]

2. Short-acting Secretogogues

- Repaglinide
- Nateglinide
- **Pharmacological effect:** Stimulation of the pancreatic secretion of insulin
  - The insulin release is glucose dependent and is decreased at low blood glucose
  - With lower potential for hypoglycemia (0.3%)
  - Should be given before meal or with the first bite of each meal.
  - If you skip a meal don't take the dose!

2. Short-acting Secretogogues …

- **Adverse effect:**
  - Hypoglycemia: is very low about 0.3 %
- **Drug interactins:**
- Inducers or inhibitors of CYP3A4 affect the action of repaglinide
- Nateglinide is an inhibitor of CYP2C9

3. Biguanides

- E.g. Metformin (Glucophage)

Pharmacological effect

- Reduces hepatic glucose production
- Increases peripheral glucose utilization

3. Biguanides …

Adverse effects:

- Nausea, vomiting, diarrhea, and anorexia
- **Phenformin**: another biguanide, was taken off the market because it causes lactic acidosis in almost 50% of patients
  - As a precaution metformin should not be used in patients with renal insufficiency, CHF, conditions that lead to hypoxia

4. Glitazones (PPAR γ Agonist)

- **PPAR γ Agonists:**
  - Peroxisome proliferator-activated receptor γ agonists. E.g. Rosiglitazone, Pioglitazone
- **Pharmacological effect**
  - Reduces insulin resistance in the periphery (Sensitize muscle and fat to the action of insulin) and possibly in the liver
  - The onset of action is slow taking 2-3 months to see the full effect
  - Edema and weight gain are the most common side effects.(no hepatotoxicity)

5. α-Glucosidase Inhibitors

- E.g. Acarbose, Miglitol

Pharmacological effect:

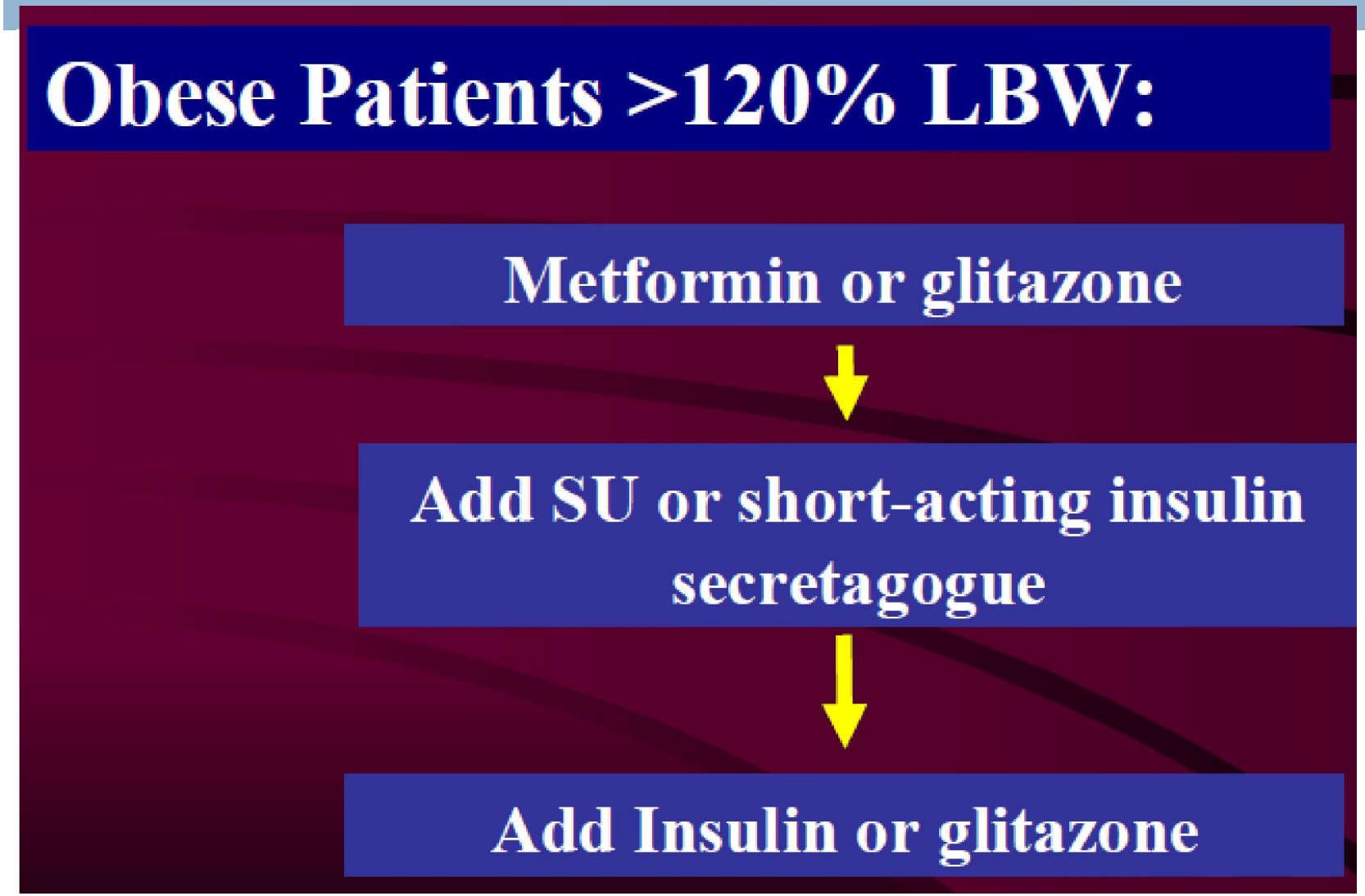
- Prevent the breakdown of sucrose and complex carbohydrates
  - net effect is to reduce postprandial blood glucose rise
  - The effect is limited to the luminal side of the intestine with limited systemic absorption. Majority eliminated in the feces.
  - FPG relatively unchanged.
  - Average reduction in HbA1c: 0.3-1.0%

Pharmacotherapy :Type 2 DM

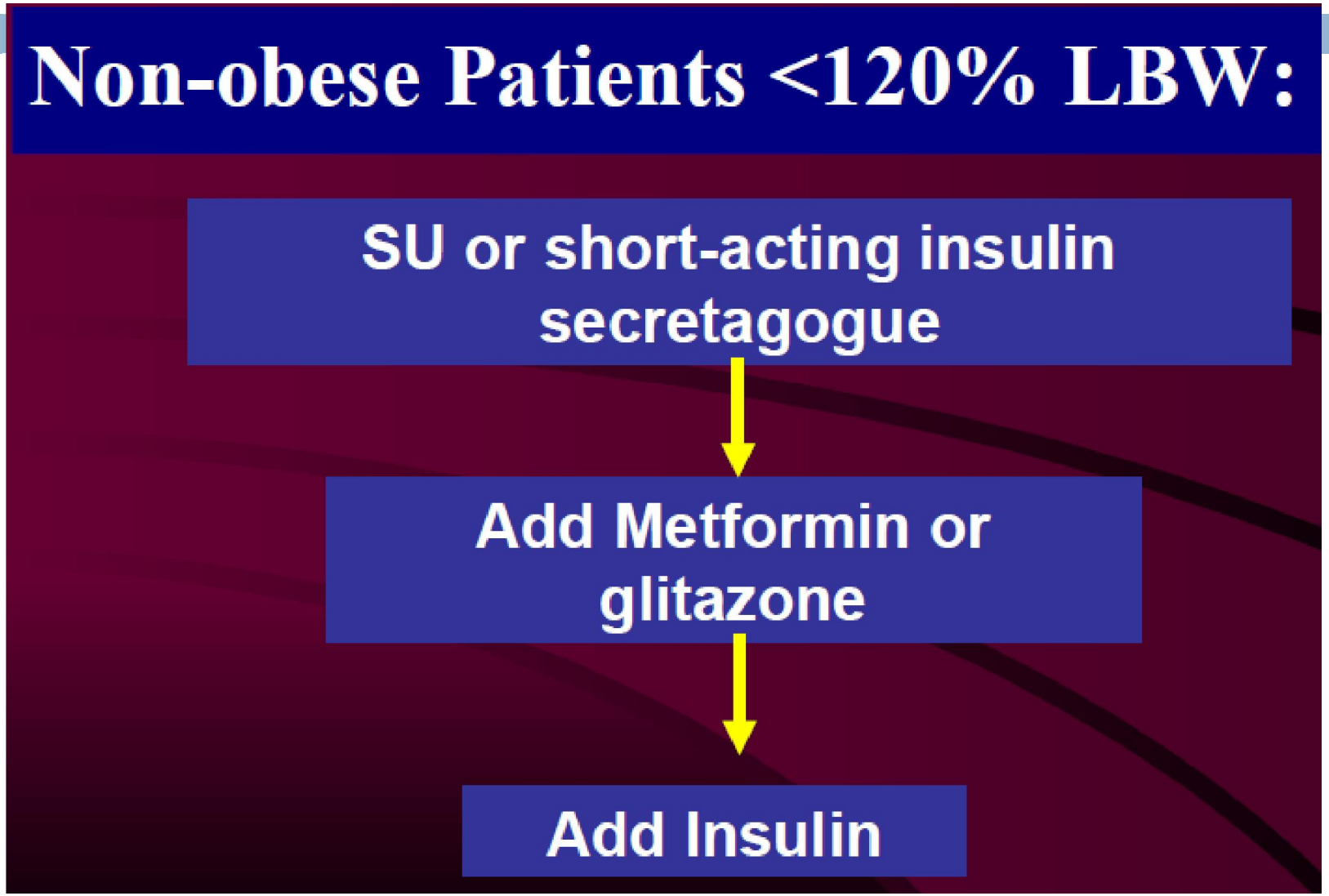
General considerations:

- Consider therapeutic life style changes (TLC) for all patients with Type 2 DM
- Initiation of therapy may depend on the level of HbA1C
  - HbA1C < 7%: may benefit from TLC
  - HbA1C 8-9%: may require one oral agent
  - HbA1C > 9- 10%: may require more than one oral agent

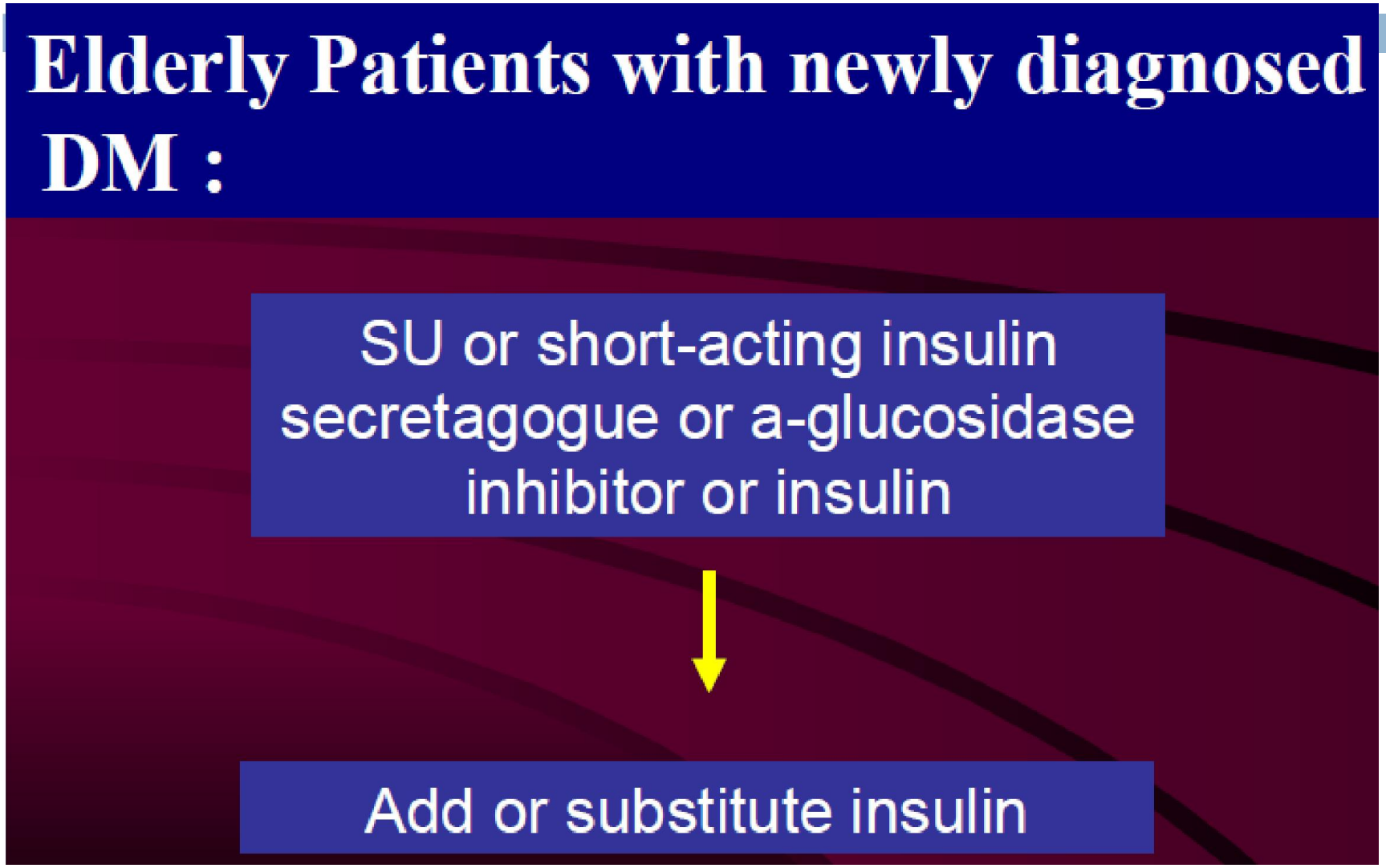
Pharmacotherapy :Type 2 DM ….



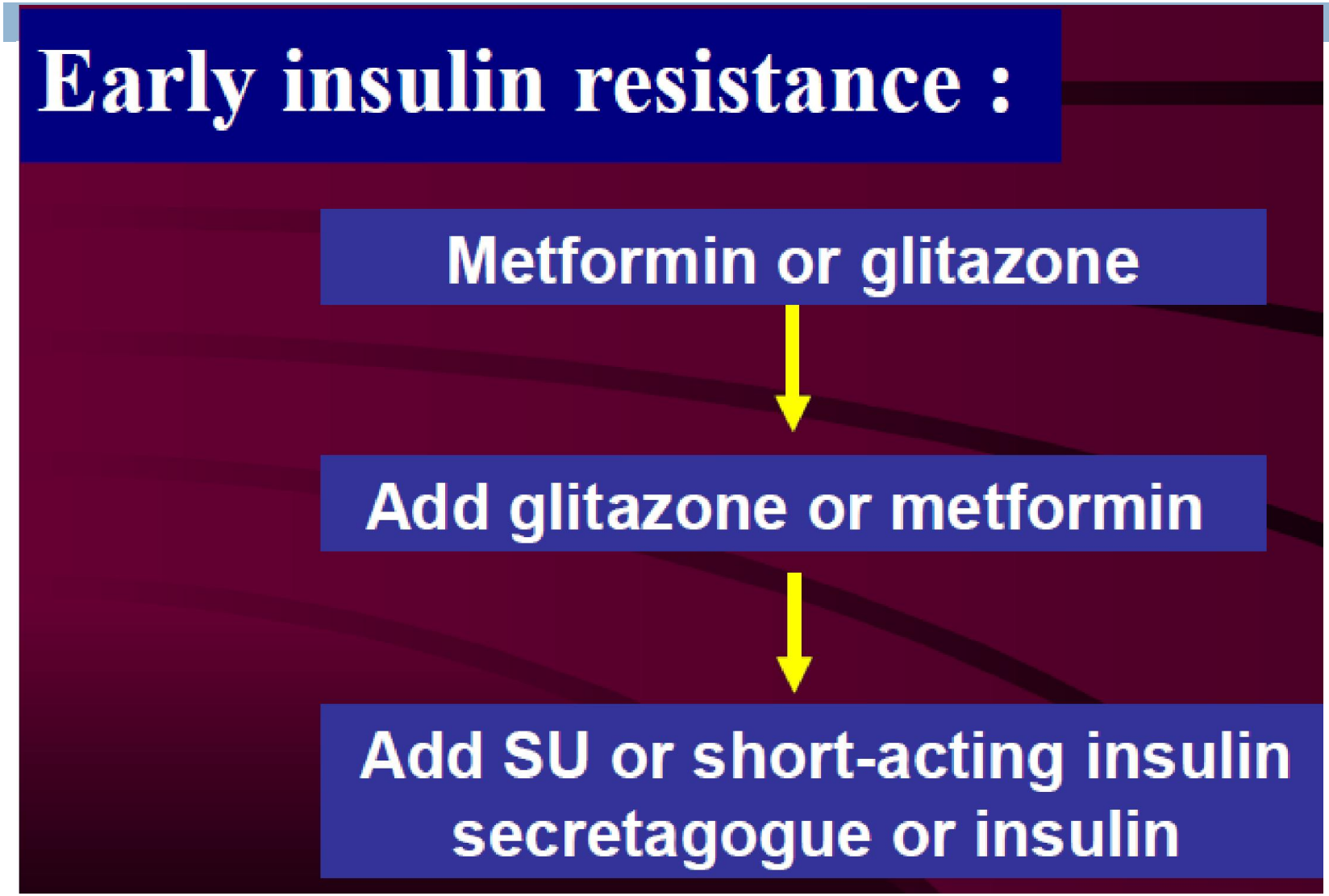
Pharmacotherapy :Type 2 DM ….



Pharmacotherapy :Type 2 DM ….



Pharmacotherapy :Type 2 DM ….



Pharmacotherapy :Type 1 DM

- The choice of therapy is simple
- All patients need Insulin

Insulin

- **Pharmacological effect:** Anticatabolic
  - Inhibits gluconeogenesis
  - Inhibits glycogenolysis
  - Inhibits lipolysis
  - Inhibits proteolysis
  - Inhibits fatty acid

Insulin …

- **Strength**
  - The number of units/ml e.g. U-100 , U-20, U-10
- **Source**
  - Pork: Differs by one amino acid
  - Beef-Pork
  - Human (recombinant DNA technology)

Onset and duration of effect

Changing the properties of insulin preparation can alter the onset and duration of action:

- **Lispro (Monomeric):** absorbed to the circulation very rapidly
- **Aspart (Mono- and dimeric):** absorbed to the circulation very rapidly
- **Regular (Hexameric):** absorbed rapidly but slower than lispro and aspart
- **Lent insulin:** Amorphous precipitate of insulin

Insulin Onset & duration of effect …

- Rapid-acting insulin
  - e.g. Insulin lispro and insulin aspart
- Short-acting insulin
  - e.g. Regular insulin
- Intermediate-acting insulin
  - e.g. NPH and Lente insulin
- Long-acting insulin
  - e.g. Insulin Glargine
- Mixture of insulin can provide glycemic control over extended period of time
  - e.g. Humalin 70/30 (NPH + regular)

Adverse effects of insulin

a. **Hypoglycemia**

Treatment:

- Patients should be aware of symptoms of hypoglycemia
- Oral administration of 10-15 gm glucose
- IV dextrose in patients with lost consciousness
- 1 gm glucagon IM if IV access is not available

b. **Skin rash at injection site**

- Treatment: Use more purified insulin preparation

c. **Lipodystrophies** (increase in fat mass) at injection site

- Treatment: rotate the site of injection

Drugs interfering with glucose tolerance

- The most significant interactions are with drugs that alter the blood glucose level:
  - Diazoxide
  - Thiazide diuretics
  - Corticosteroids
  - Oral contraceptives
  - Streptazocine
  - Phenytoin
- All these drugs increase the blood glucose concentration.
- Monitoring of BG is required

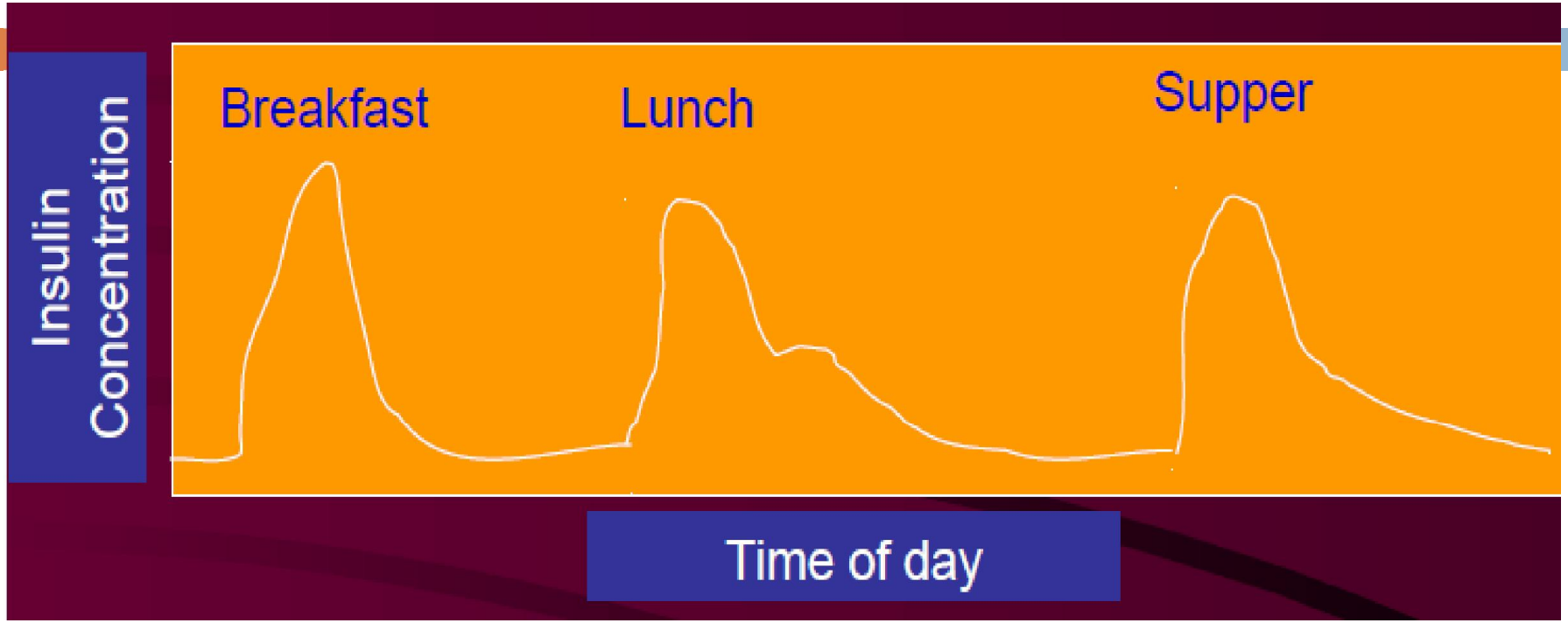
Methods of Insulin Administration

- Insulin syringes and needles
- Pen-sized injectors
- Insulin Pumps

Pharmacotherapy :Type 1 DM

- **The goal is:**
  - To balance the caloric intake with the glucose lowering processes (insulin and exercise), and allowing the patient to live as normal life as possible

Pharmacotherapy :Type 1 DM …



Normal insulin secretion during he day

- Constant background level (basal)
- Spikes of insulin secretion after eating

Pharmacotherapy :Type 1 DM …

- The insulin regimen has to mimic the physiological secretion of insulin
- With the availability of the SMBG and HbA1C tests adequacy of the insulin regimen can be assessed
- More intense insulin regimen require more intense monitoring

Pharmacotherapy :Type 1 DM …

- **Example:**

1. Morning dose (before breakfast):

   Regular + NPH or Lente

2. Before evening meal:

   Regular + NPH or Lente

- Require strict adherence to the timing of meal and injections

Pharmacotherapy :Type 1 DM …

Modification

- **NPH evening dose can be moved to bedtime**
- **Three injections of regular or rapid acting insulin before each meal + long acting insulin at bedtime (4 injections)**
- **The choice of the regimen will depend on the patient**

Pharmacotherapy :Type 1 DM …

How much insulin ?

- A good starting dose is 0.6 U/kg/day
- The total dose should be divided to:
  - 45% for basal insulin
  - 55% for prandial insulin
- The prandial dose is divided to
  - 25 %: pre-breakfast
  - 15 %: pre-lunch
  - 15 %: pre-supper

Pharmacotherapy :Type 1 DM …

- **Example:For a 50 kg patient**
- **The total dose = 0.6X50 = 30 U/day**
- 13.5 U for basal insulin (45% of dose)
  - Administered in one or two doses
- 16.5 U for prandial insulin (55% of dose)
  - The 16.5 U are divided to:
    - 7.5 U pre-breakfast (25%)
    - 4.5 U pre-lunch (15%)
    - 4.5 U pre-supper (15%)

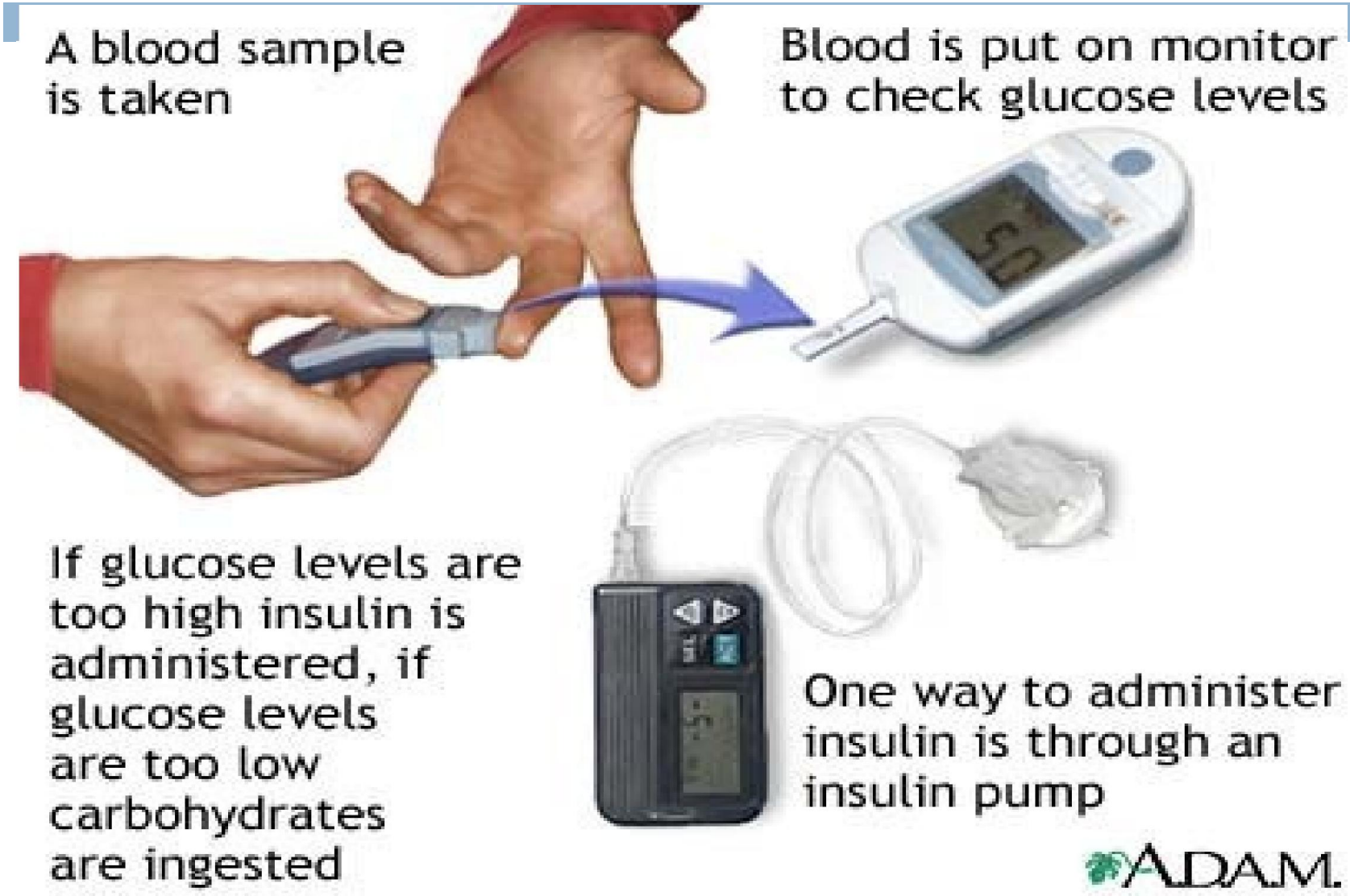
Pharmacotherapy :Type 1 DM …

- **Monitoring**

- Most Type 1 patients require 0.5-1.0 U/kg/d

- The initial regimen should be modified based on:
  - Symptoms
  - SMBG
  - HbA1C

Monitoring …

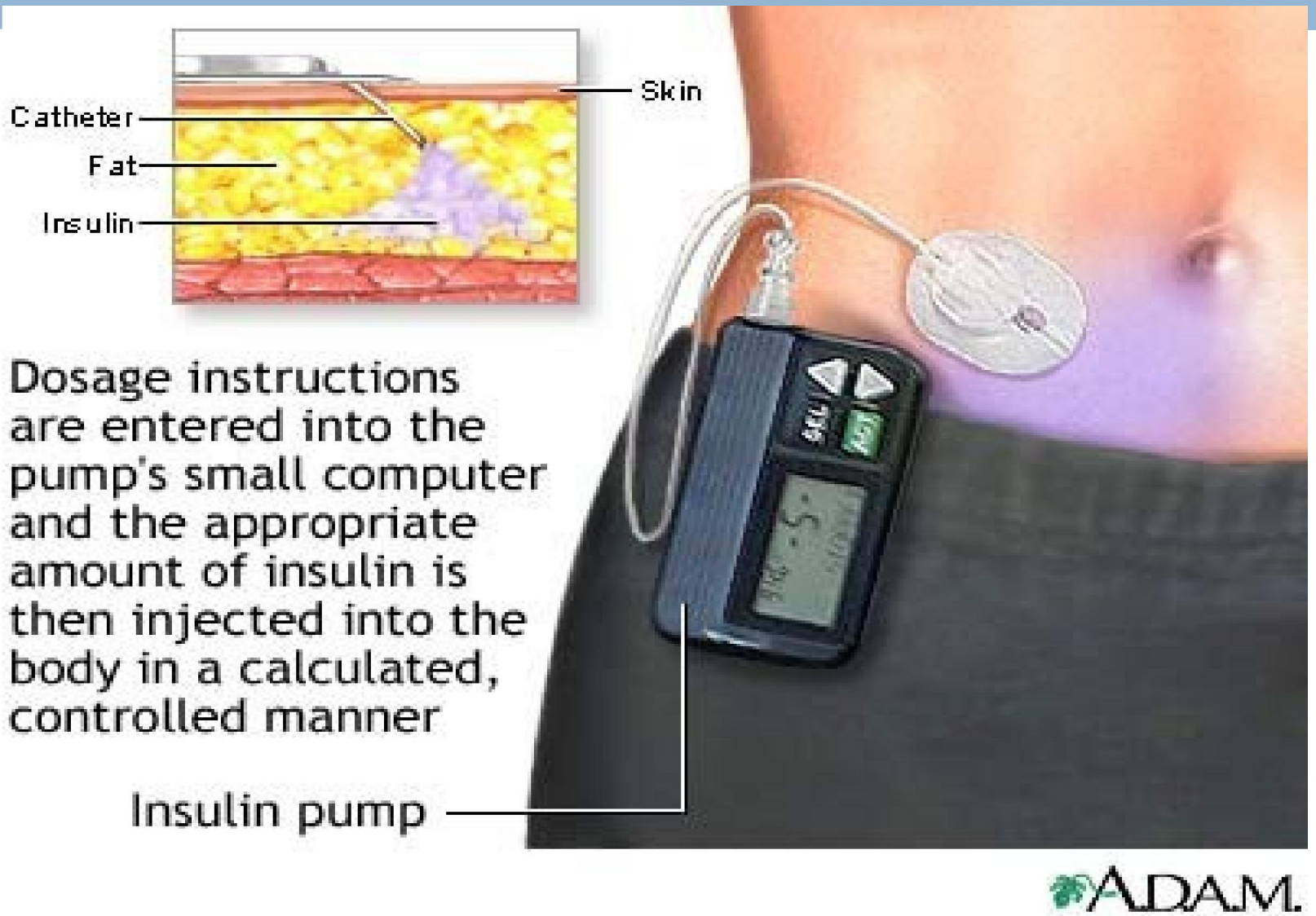

A blood sample is taken
Blood is put on monitor to check glucose levels
If glucose levels are too high insulin is administered, if glucose levels are too low carbohydrates are ingested
One way to administer insulin is through an insulin pump
A.D.A.M.

Pharmacotherapy :Type 1 DM …

Insulin Pump Therapy

- This involves continuous SC administration of short-acting insulin using a small pump
- The pump can be programmed to deliver basal insulin and spikes of insulin at the time of the meals
- Requires intense SMBG
- Requires highly motivated patients because failure to deliver insulin will have serious consequences

Insulin Pump …



Surgery

- Islet transplantation has been investigated as a treatment for type 1 diabetes mellitus in selected patients with inadequate glucose control despite insulin therapy.
- Observations in patients with type 1 diabetes indicate that islet transplantation can result in insulin independence with excellent metabolic control

Special Patient Population

1. Adolescent Type 2 DM

- Type 2 DM is increasing in adolescent
- Lifestyle modification is essential in these patients
- If lifestyle modification alone is not effective, metformin the only labeled oral agent for use in children (10-16 years)

Special Patient Population …

2. Gestational DM

- Dietary control
- If not controlled by diet, insulin therapy is initiated
- One dose of NPH or NPH + regular insulin (2:1) given before breakfast. Adjust regimen according to SMBG.
- Sulfonylureas: Effective, but require further studies to demonstrate safety.

Special Patient Population …

3. Diabetic ketoacidosis

- It is a true emergency
- Usually results from omitting insulin in type 1 DM or increase insulin requirements in other illness (e.g. infection, trauma) in type 1 DM and type 2 DM
- Signs and symptoms: Fatigue, nausea, vomiting, evidence of dehydration, rapid deep breathing, fruity breath odor, hypotension and tachycardia

Special Patient Population …

3. Diabetic ketoacidosis …

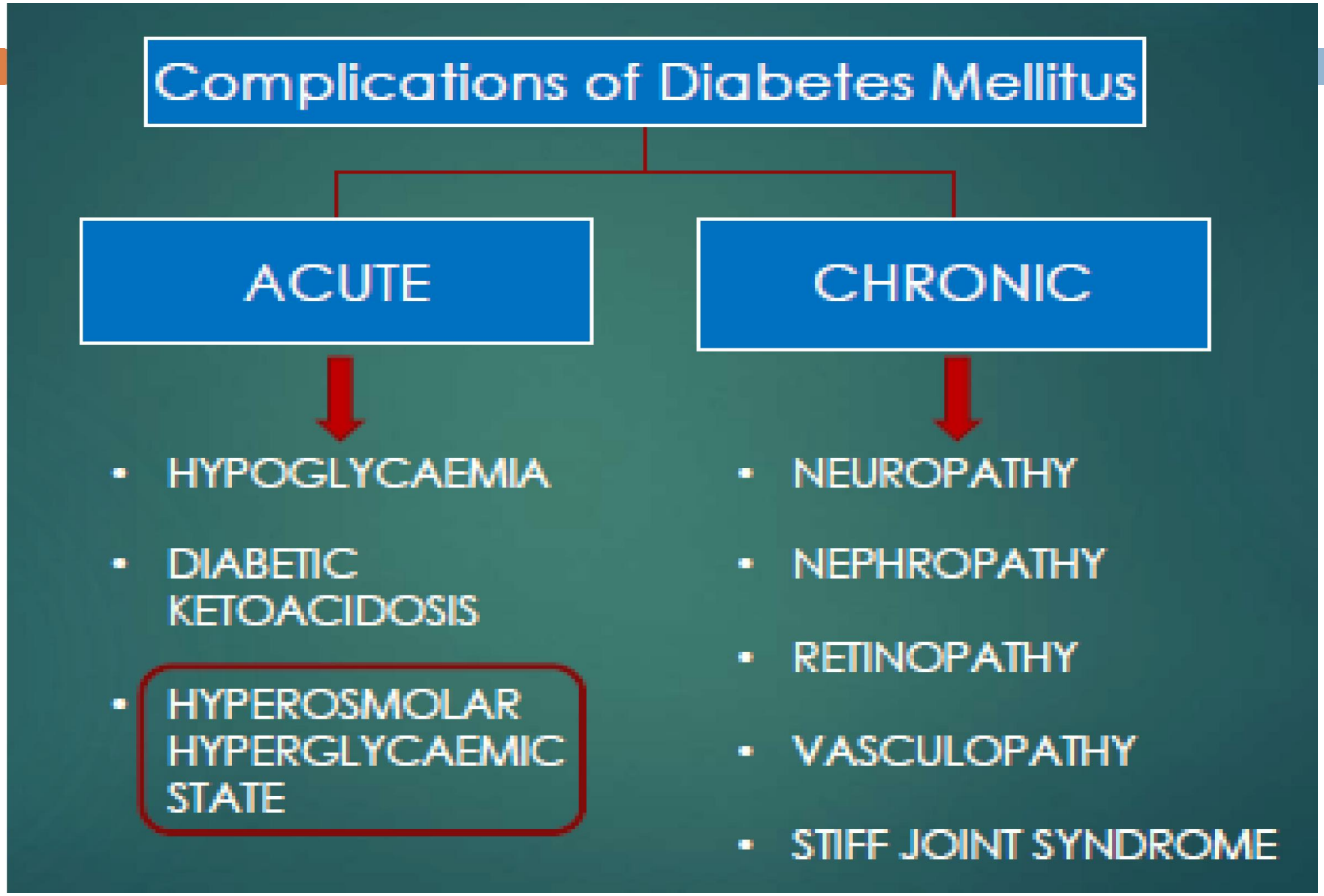
- Diagnosis
  - Hyperglycemia, acidosis, low serum bicarbonate, and positive serum ketones
- Abnormalities:
  - Dehydration, acidosis, sodium and potassium deficit
- Patient education is important

Special Patient Population …

3. Diabetic ketoacidosis …

- **Management:**
  - Fluid administration: Rapid fluid administration to restore the vascular volume
  - IV infusion of insulin to restore the metabolic abnormalities. Titrate the dose according to the blood glucose level.
  - Potassium and phosphate can be added to the fluid if needed.
- **Follow up:**
  - Metabolic improvement is manifested by an increase in serum bicarbonate or pH.

COMPLICATIONS OF DM


Complications of Diabetes Mellitus
ACUTE
CHRONIC
HYPOGLYCAEMIA
DIABETIC KETOACIDOSIS
HYPEROSMOLAR HYPERGLYCAEMIC STATE
NEUROPATHY
NEPHROPATHY
RETINOPATHY
VASCULOPATHY
STIFF JOINT SYNDROME

Acute/ short term complications of DM

Hypoglycemia In DM

- Carbohydrates (Glucose) are the first/ main calorie resource for our body
- Extra CHO are stored as glycogen in liver and muscles Or shifted to fat
- The brain and RBCs are among other tissues that relies only on glucose as a fuel

Hypoglycemia

- All episodes of an abnormally low plasma glucose concentration (w or w/o symptoms) that expose the individual to harm
- For Non Diabetic patient: Glucose value < 50 mg/dl (2.8mmo/L)
- For Diabetic patient: Glucose value < 70 mg/dl (3.9 mmo/L).

Hypoglycemia …

- Common up to 30- 60% in DM patients
- Type 1 > Type 2
- Asymptomatic in 50% + …Unawareness !
- Nocturnal …very common !

Conventional Risk Factors

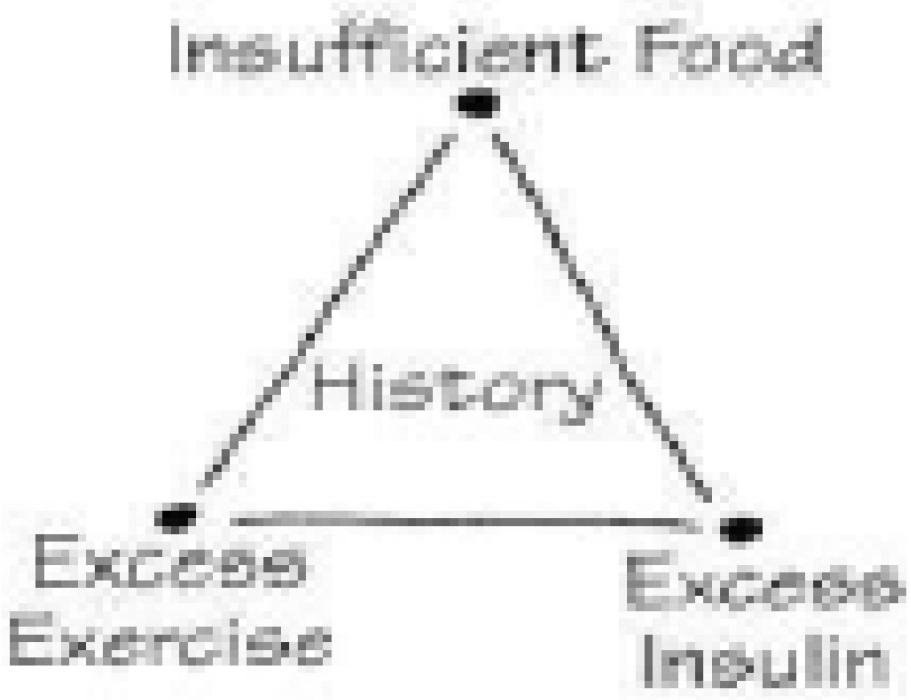
- The conventional risk factors for hypoglycemia in diabetes are identified on the basis of the premise that relative or absolute insulin excess is the sole determinant of risk.
- Relative or absolute insulin excess occurs when

1) Insulin (or insulin secretagogue) doses are excessive, ill-timed, or of the wrong type
2) The influx of exogenous glucose is reduced (e.g., During an overnight fast or after missed meals)

Conventional Risk Factors …

3) Insulin-independent glucose utilization is increased (e.g., During exercise)
4) Sensitivity to insulin is increased (e.g., With improved glycemic control, in the middle of the night, late after exercise, or with increased fitness or weight loss)
5) Endogenous glucose production is reduced (e.g., After alcohol ingestion); and
6) Insulin clearance is reduced (e.g., In renal failure).

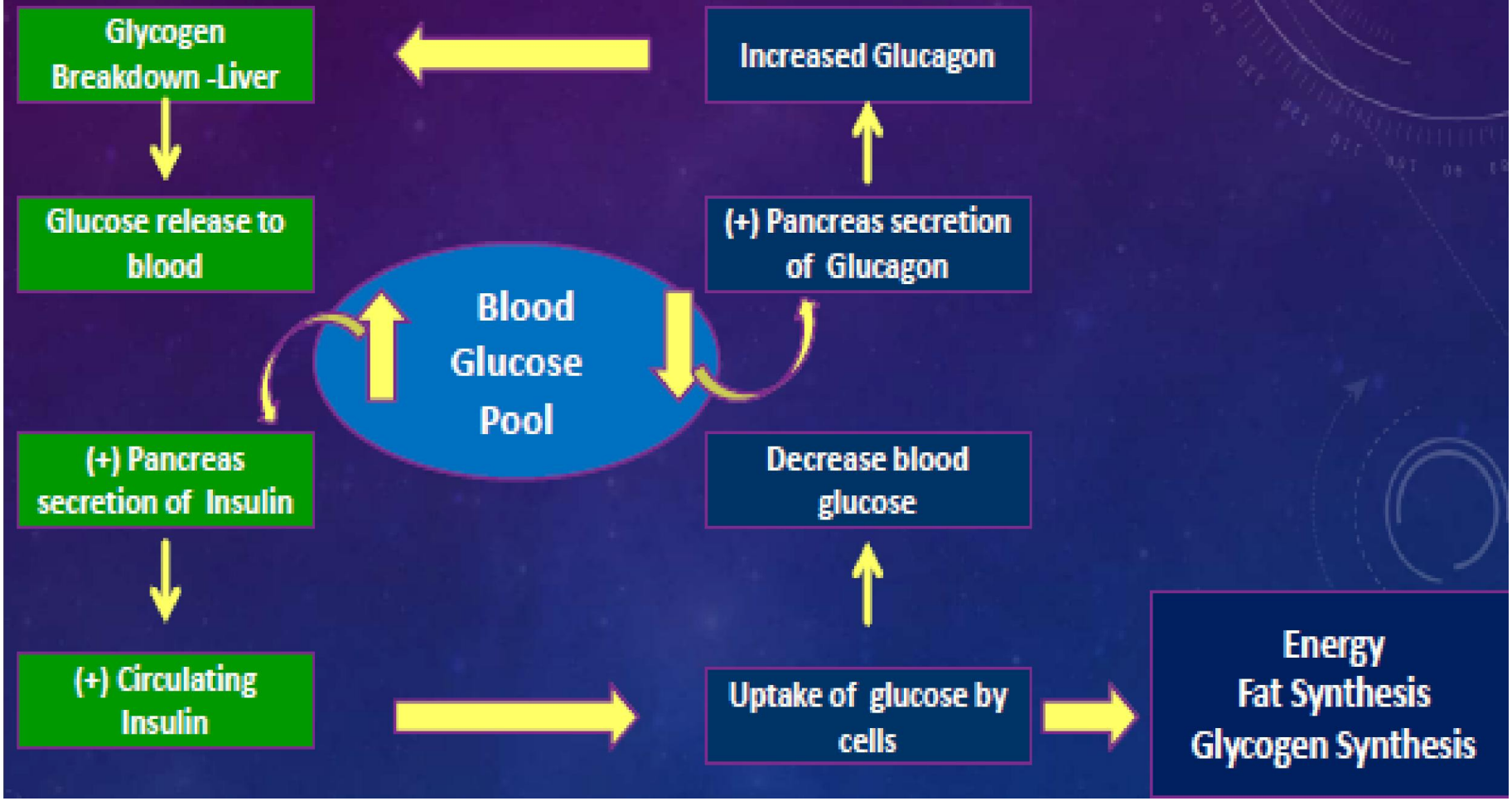
Hypoglycemia : setting / causes



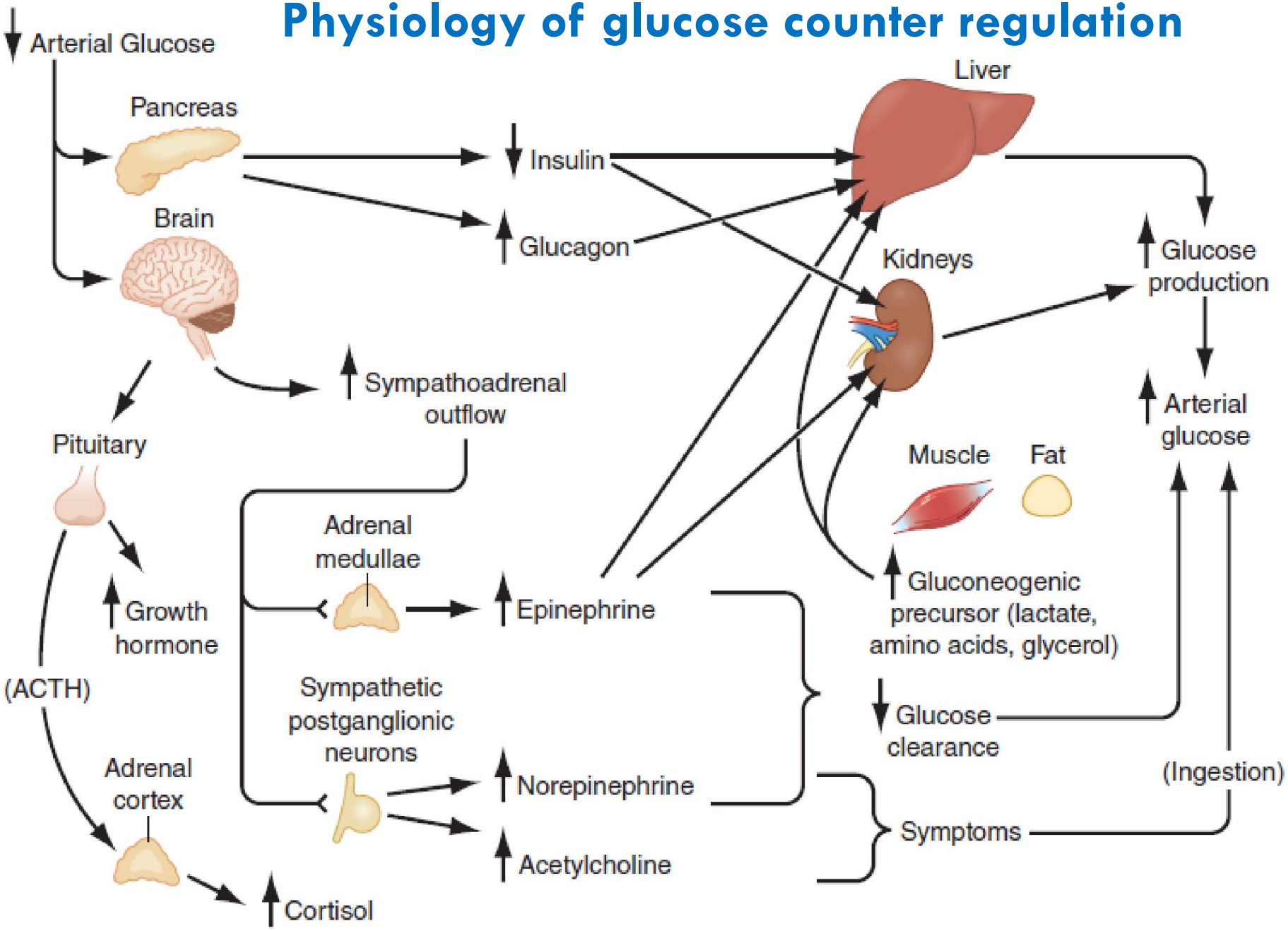
Hypoglycemia : setting / causes …

- Identification of the precipitating factors is important to prevent future events
- Common with Diabetics who are treated with Insulin releasing pills (sulfonylureas, Meglitinides,)
- Skipped or delayed meals
- Vomiting after meal & meds intake
- Wrong dose or too high a dose of medications

HYPOGLYCEMIA – PATHO-PHYSIOLOGY



Physiology of glucose counter regulation



Clinical classification of hypoglycemia

I. **Severe hypoglycemia =** Requiring assistance

II. **Documented symptomatic hypoglycemia** =Symptoms + plasma glucose ≤70 mg/dL (3.9 mmol/L)

III. **Asymptomatic hypoglycemia…Unawareness**

- No typical symptoms; but Plasma glucose ≤70 mg/dL (3.9 mmol/L)

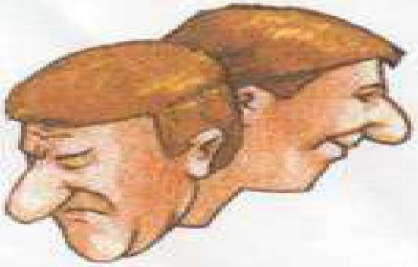
Clinical classification …

IV. **Probable symptomatic hypoglycemia:** Typical symptoms without plasma glucose determination

V. **Relative hypoglycemia:** Typical symptoms but with Plasma glucose > 70 mg/dL (3.9 mmol/L)

LOW BLOOD SUGAR
*Hypo*glycemia

SIGNS AND SYMPTOMS



Mood changes

Trembling

Paleness

Sweating

Dizziness

Blurred vision

Headaches

Extreme tiredness

Hunger

NovolinCare™

Sign & symptoms of hypoglycemia

- **Hyper-adrenergic :**
- Plasma Glucose < 70 mg/ dL (3.9 mmol/L)
  - Diaphoresis (Sweating)
  - Tachycardia /Palpitation
  - Anxiety
  - Tremor /Shaking
  - Tachypnea
  - Vomiting
  - Dizziness
  - Hunger

Sign & symptoms of hypoglycemia …

- **Neuro-glycopenic:**
- Plasma Glucose < 50 mg/dL (2.8 mmol/L)
  - Slurred speech
  - Cognitive impairment
  - Inattention and confusion
  - Focal neurologic deficits
  - Seizures
  - Irritability
  - Change in personality
  - Lack of coordination

Sign & symptoms of hypoglycemia …

- **Severe and prolonged hypoglycemia**
  - LOC/Coma
  - Irreversible brain injury

Management of hypoglycemia

- **Prevention = Education**
  - Patient education and empowerment
  - Frequent self-monitoring of blood glucose (SMBG)
  - Individualized glycemic goals
  - Professional guidance and support.
  - Keeping some sugar or sweet handy
  - Teach patient/care-giver
  - Medical alert identification
  - Glucagon Emergency kit.

Hypoglycemia treatment

- **For Conscious patient:** rapidly absorbed CHO (glucose- or sucrosecontaining foods) orally
  - E.g. fruit juice or low fat / fat-free milk, 3 glucose tablets, 1 tbsp of honey, etc
  - About 15-20 grams of glucose
- **For unconscious patient/ unable to swallow:** IV dextrose or IM glucagon
  - Give 15-20 g of 50% glucose (dextrose) intravenously
- Address underlying cause & Intervene to prevent recurrence

DIABETIC KETOACIDOSIS (DKA)

By Agazhe A.

Diabetic ketoacidosis (DKA)

- DKA is a condition in which there is a severe deficiency of insulin resulting in very high blood glucose which nonetheless is unavailable to the body tissues as a source of energy.
- Fat is therefore broken down as an alternative source of energy with ketones/ketoacids as a by-product.
- This state of severe hyperglycemia and ketone body production results in severe metabolic, fluid and electrolyte abnormalities.

DKA …..

- DKA often occurs in type 1 diabetes patients but may also occur in type 2 diabetes.
- The most common settings in which DKA occurs include:
  - ✓previously undiagnosed and untreated diabetes
  - ✓omission of anti-diabetic therapy
  - ✓stress of intercurrent illness (e.g. infection, MI, stroke, surgery, complicated pregnancy etc.).

DKA ….

- It is Biochemical triad of ketonaemia, hyperglycaemia and acidaemia.
- A medical emergency and remains a serious cause of morbidity, principally in people with type 1 diabetes
- However, an increasing number of patients presenting with DKA have underlying type 2 diabetes.
- Lack of a diabetic Hx does not exclude the diagnosis

DKA …

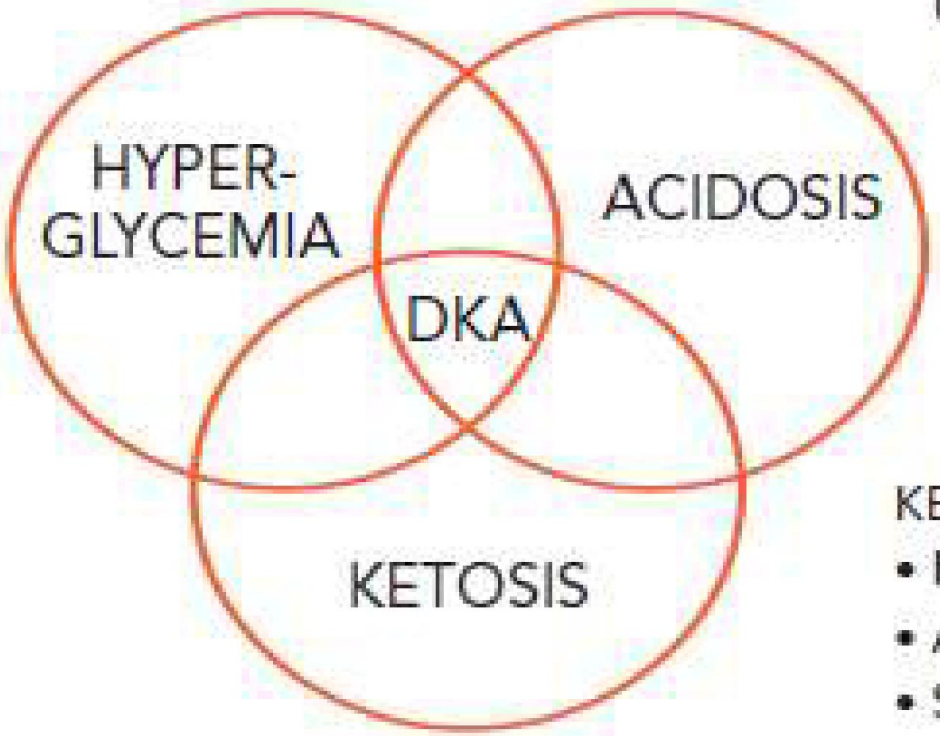
- DKA is defined as the presence of **all three of the** following:
  - Hyperglycemia (glucose >250 mg/dL)
  - Ketosis
  - Acidemia (pH <7.3).

HYPERGLYCEMIC STATES

- Diabetes Mellitus
- Hyperosmolar Hyperglycemic State
- Impaired Glucose Tolerance
- Stress Hyperglycemia

METABOLIC ACIDOTIC STATES

- Lactic Acidosis
- Hyperchloremic Acidosis
- Uremic Acidosis
- Drug-Induced Acidosis (eg, salicylates, methanol, ethylene glycol)



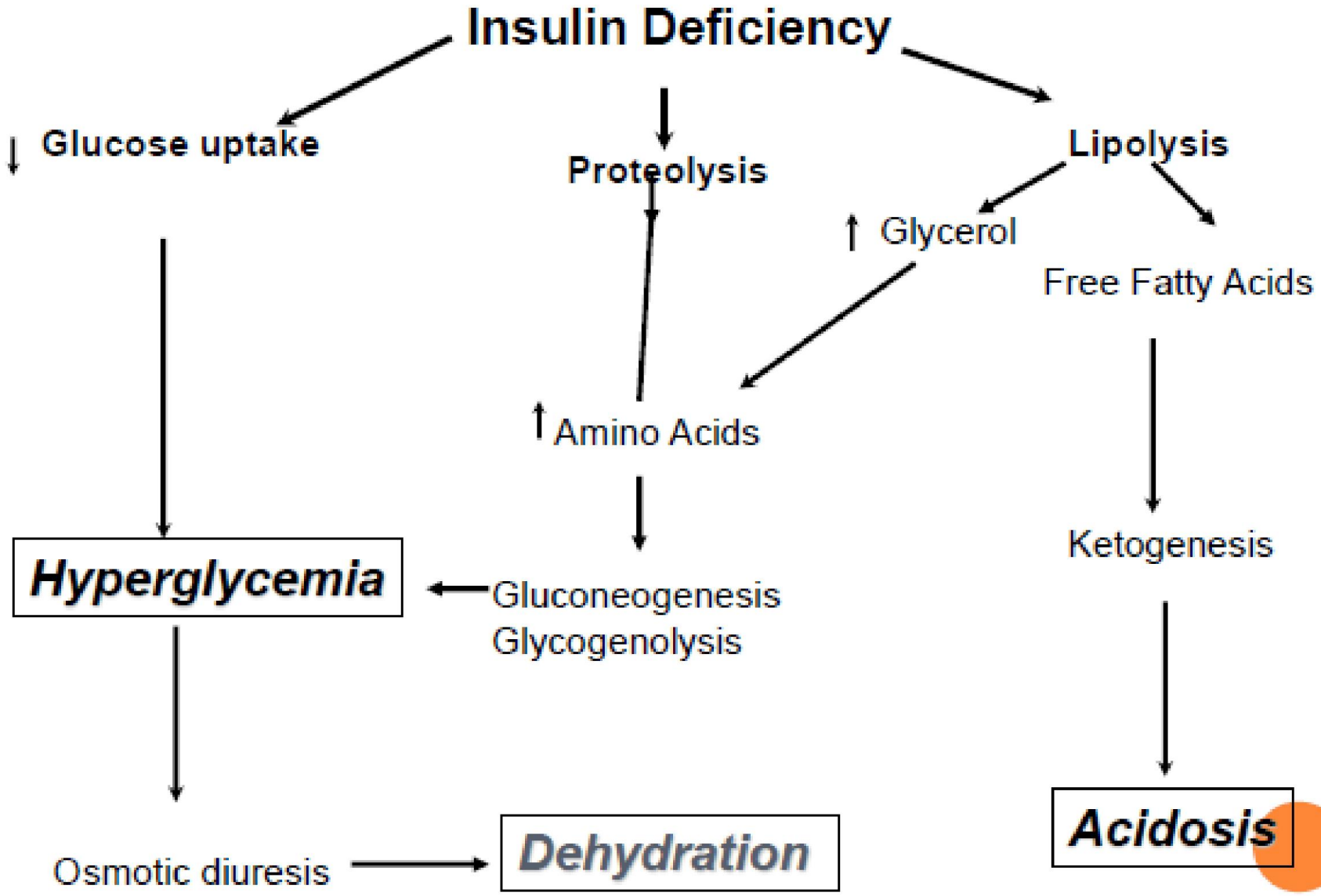
KETOTIC STATES

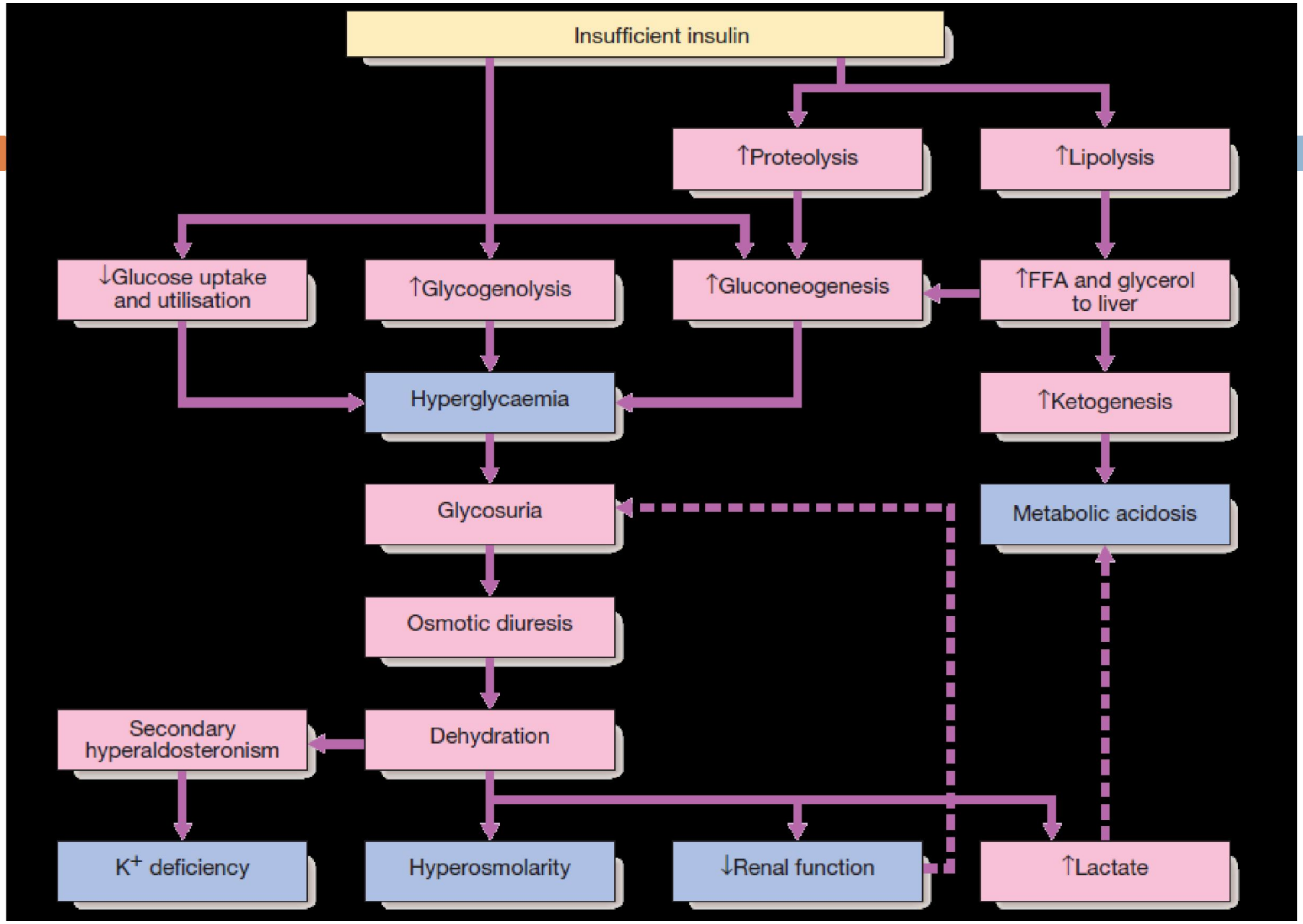
- Ketotic Hypoglycemia
- Alcoholic Ketosis
- Starvation Ketosis

Role of Insulin

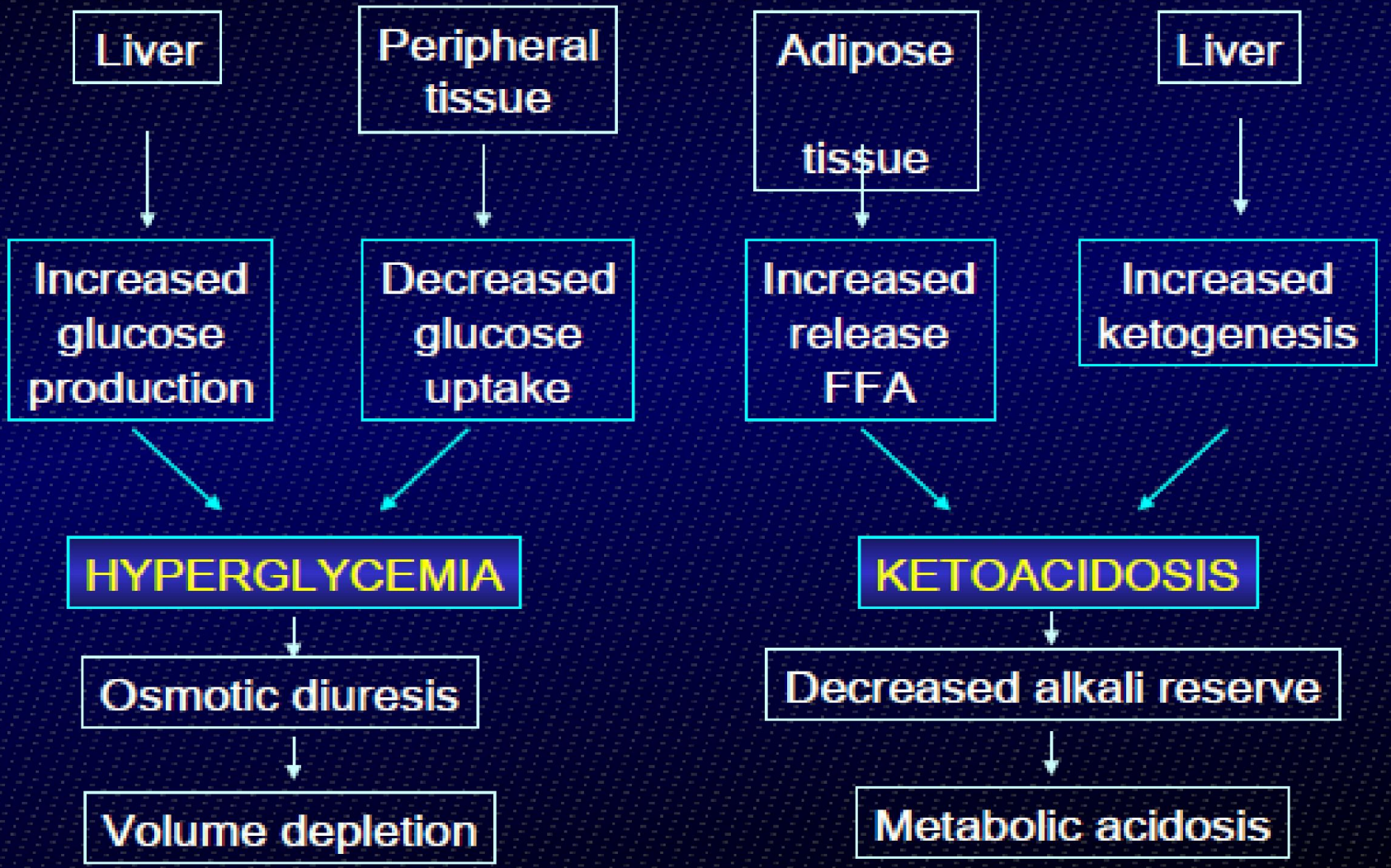
- Required for transport of glucose into Muscle, Adipose and Liver
- Inhibits lipolysis
- Absence of insulin
  - Glucose accumulates in the blood.
  - Uses amino acids for gluconeogenesis
  - Converts fatty acids into ketone bodies: Acetone, Acetoacetate, β-hydroxybutyrate

PATHOPHYSIOLOGY




Insufficient insulin
↑Proteolysis
↑Lipolysis
↓Glucose uptake and utilisation
↑Glycogenolysis
↑Gluconeogenesis
↑FFA and glycerol to liver
Hyperglycaemia
↑Ketogenesis
Glycosuria
Metabolic acidosis
Osmotic diuresis
Secondary hyperaldosteronism
Dehydration
K+ deficiency
Hyperosmolarity
↓Renal function
↑Lactate

Pathogenesis of DKA



Causes/ precipitating factors of DKA

- Stressful precipitating event that results in increased catecholamines, cortisol, glucagon.
  - Infection (pneumonia, UTI, Pancreatitis, sepsis)
  - Alcohol, Medications (steroids, cocaine)
  - Stroke, Trauma, Myocardial Infarction
  - Non-compliance with insulin
  - Inadequate insulin administration
  - Pregnancy

Clinical Presentation of DKA

Symptoms

- Nausea/vomiting
- Thirst/polyuria
- Abdominal pain
- Shortnessof breath
- Weight loss
- Weakness

Signs

- Tachycardia
- Dehydration/hypotension
- Tachypnea/kussmaul respirations/respiratory distress
- Fruity odor in breath
- Abdominal tenderness
- Lethargy/obtundation/cerebral edema/possibly coma

Initial Diagnosis of DKA

- Identify precipitating event leading to elevated glucose (Px, infection, omission of insulin, MI, etc)
- Assess hemodynamic status
- Examine for presence of infection
- Assess volume status and degree of dehydration
- Assess presence of ketonemia and acid-base disturbance

Lab investigations

- ABG's
- CBC with differential
- CMP (glucose, electrolytes, bicarbonate, BUN, Cr)
- Serum ketones/Urine ketones and sugar
- Calculate serum osmolality and anion gap
- Urinalysis and urine culture
- Consider blood culture
- Consider chest radiograph
- Cardiac enzymes
- Acid-base assessment

Lab investigations

- Venous blood
  - Urea
  - Na+/ K+
  - Glucose
  - Bicarbonate
  - Ketones
- Urine
  - Ketones
  - Leucocyte esterase
- ECG
  - Possible MI
- Infection screen
  - Full blood count
  - Blood and urine culture
  - C-reactive protein
  - Chest X-ray
- Amylase/ lipase
  - Rule out Pancreatitis

Diagnosis of DKA

- Cardinal biochemical features:
  - Hyperketonaemia (≥ 3 mmol/L) and ketonuria (>2+ on standard urine sticks)
  - Hyperglycaemia (blood glucose ≥ 11 mmol/L (~200 mg/dL))
  - Metabolic acidosis (venous bicarbonate <15 mmol/L and/or venous pH < 7.3)

Diagnostic Criteria for DKA

	DKA		
	Mild	Moderate	Severe
Plasma glucose (mg/dl)	> 250	> 250	> 250
Arterial PH	7.25 – 7.3	7.0 – 7.24	< 7.0
Anion gap	> 10	>12	> 12
Bicarbonate (mEq/l)	15 - 18	10 - <15	< 10
Urine ketones	Positive	Positive	Positive
Serum ketones	Positive	Positive	Positive
Serum Osmolality (mOsm/kg)	Variable	Variable	Variable
Mental status	Alert	Alert/drowsy	Stupor/coma

Differential Diagnosis of DKA

- Gastroenteritis
- HHNS
- MI
- Pancreatitis
- Starvation ketosis
- High anion gap metabolic acidosis:
  - Alcoholic ketoacidosis
  - Ethylene glycol intoxication
  - Lactic acidosis
  - Methanol intoxication
  - Paraldehyde ingestion
  - Rhabdomyolysis
  - Salicylate intoxication
  - Uremia

Laboratory values in DKA and HHS

	DKA	HHS
Glucose,mg/dl	250-600	600-1200
Sodium meq/L	125-135	135-145
Potassium	Normal to↑	Normal
Osmolality mosm/kg	300-320	330-380
Plasma ketones	++++	+/-
Serum bicarbonate	<15meq/L	Normal to slightly ↓
Arterial pH	6.8-7.3	>7.3
Arterial pCO_2	20-30	Normal
Anion gap	↑	Normal to slightly↑

Management of DKA

- Initial hospital management
  - Replace fluid and electrolytes
  - IV Insulin therapy
  - Watch for complications
  - Treat causes
- Once resolved
  - Convert to home insulin regimen
  - Prevent recurrence

PROTOCOL FOR MANAGEMENT OF ADULT PATIENTS WITH DKA

Initial evaluation: After history and physical examination, obtain arterial blood gases, complete blood count with differential, urinalysis, plasma glucose, BUN, electrolytes, chemistry profile, and creatinine levels STAT as well as an ECG. Chest X-ray and cultures as needed. Start IV fluid, 1.0 L of 0.9% NaCl per hour initially (15-20 ml/kg/hour).

Diagnostic criteria: DKA: blood glucose >250 mg/dl, arterial pH <7.3, bicarbonate <15 mEq/l, moderate ketonuria or ketonemia.

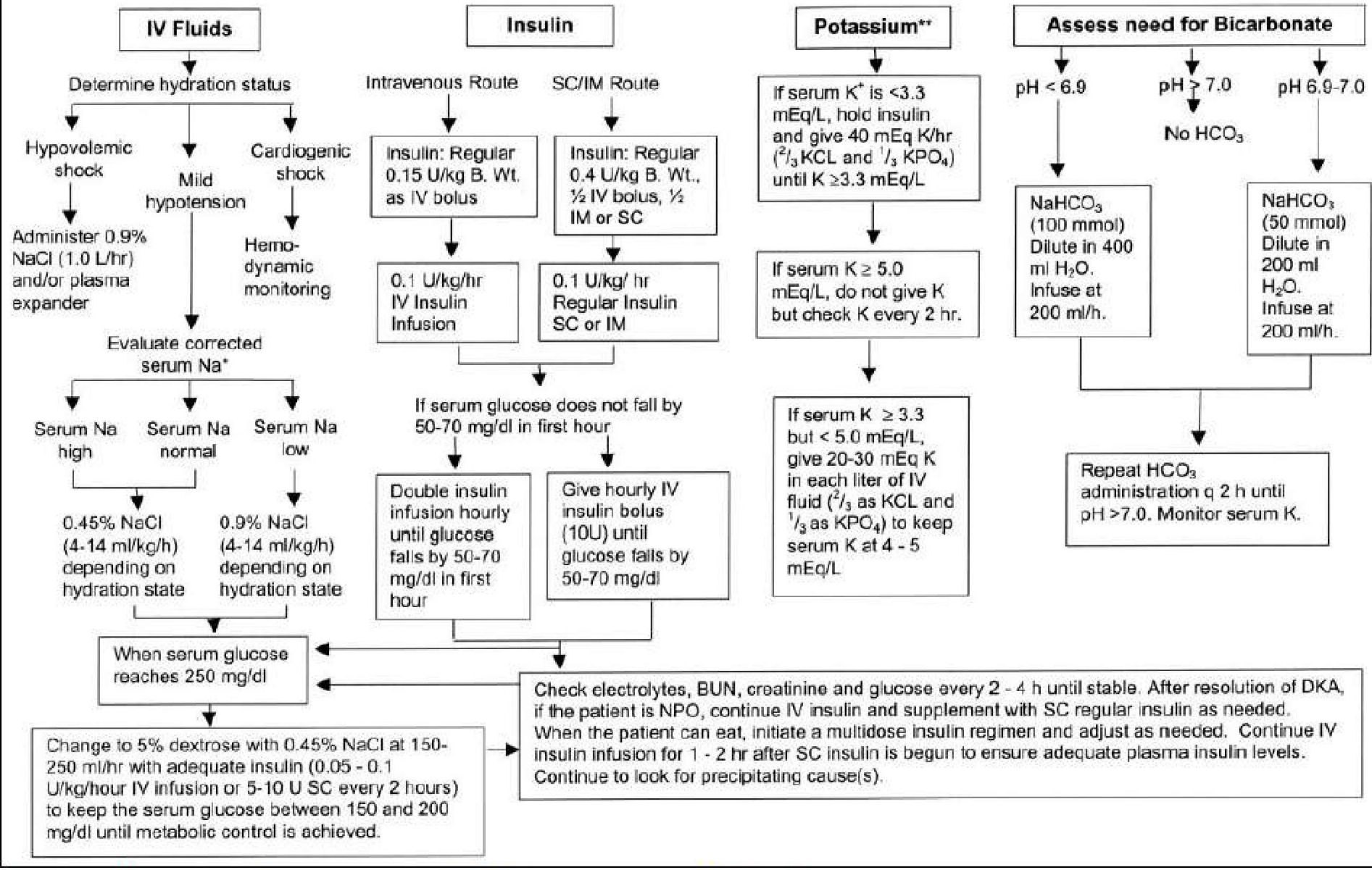


Figure 1. Protocol for Management of Adult Patients with Diabetic Ketoacidosis

Management ….

A. Hour 1: Immediate management upon diagnosis: 0 to 60 minutes.

Aims

- Commence IV 0.9% sodium chloride solution
- Fixed rate IV insulin but only after fluid therapy has been commenced
- Establish monitoring regime appropriate to patient:
  - hourly blood glucose and ketone measurement
  - at least 2 hourly serum K+ for the first 6 hours
- Clinical / biochemical assessment of the patient

Actions with in the first hr

- **Action 1:** IV access and initial investigations
  - Rapid ABC
  - Large bore iv cannula and fluid replacement
  - Vital sign, SpO2, GCS, and Full clinical examination
  - Initial investigations
  - Continuous cardiac monitoring
  - Continuous pulse oximetry
  - Consider precipitating causes and treat appropriately
  - Establish usual medication for diabetes

Actions with in the first hr …

- **Action 2**. Restoration of circulating volume
- Commence crystalloid (NS)

a. If systolic BP < 90 mmHg
   - Give 500 mL over 10–15 mins
   - Repeat if SBP< 90mmHg

b. If systolic BP ≥ 90 mmHg (for a previously well 70kg adult)
   - 1L over 1st hour
   - 1L over next 2 hours
   - 1L over next 2 hours
   - 1L over next 4 hours
   - 1L over next 4 hours
   - 1L over next 6 hours

Actions with in the first hr …

- Exercise caution in the following patients
  - Young people aged 18-25 years
  - Elderly
  - Pregnant
  - Heart or kidney failure
  - Other serious co-morbidities

Actions with in the first hr …

- **Action 3** - Commence a fixed rate intravenous insulin infusion
  - 50 U human soluble insulin in 50 mL 0.9% NaCl
  - IV infusion at 0.1 U/kg/hr (i.e. 7ml/hr if wt is 70kg)
  - Targets:
    - ↓ blood ketone by 0.5 mmol/L/hour
    - ↑ bicarbonate by 3 mmol/L/hour
    - ↓ glucose by 3 mmol/L/hour
    - K+ 4.0 - 5.0 mmol/L

Actions with in the first hr …

- **Action 4** - Potassium replacement
  - Serum K+ is often high on admission but falls precipitously upon Rx with insulin
  - Potassium replacement
    - Plasma K+ > 5.5 mmol/L Nil
    - 3.5–4.5 mmol/L 20 mmol/L
    - < 3.5 mmol/L 40 mmol/L
  - If K+ < 3.5 mmol/L, K+ replacement before insulin

Management of DKA ….

B. 60 minutes to 6 hours

- **Aims:**
  - Clear the blood of ketones and suppress ketogenesis
  - Achieve the targets
    - Fall of ketones of at least 0.5 mmol/L/hr
    - Rise of bicarbonate by 3 mmol/L/hr
    - Fall of blood glucose by 3 mmol/L/hr
  - Maintain serum K+ in normal range
  - Avoid hypoglycaemia

Actions with in 60 min to 6 hrs

- **<u>Action 1</u> – Re-assess patient, monitor vital signs**
  - Urinary catheterization if incontinent or anuric (not passed by 60 min)
  - NG tube if patient obtunded or persistently vomiting
  - Accurate fluid balance chart, minimum urine output 0.5ml/kg/hr
  - Continuous cardiac monitoring in severe DKA

Actions with in 60 min to 6 hrs …

- **<u>Action 2</u> – Review metabolic parameters**
  - Measure blood ketones and capillary glucose hourly
  - Review patient's response to fixed rate IV insulin hourly by calculating rate of change of ketone level fall (or rise in bicarbonate or fall in glucose).

Actions with in 60 min to 6 hrs …

- Assess resolution of ketoacidosis
- If blood ketones not falling by at least 0.5 mmol/L/hr increase insulin infusion rate by 1 unit/hr increments hourly until ketones falling at target rates
- If bicarbonate not rising by at least 3 mmol/L/hr increase insulin infusion rate by 1 unit/hr increments hourly

Actions with in 60 min to 6 hrs …

- If glucose is not falling by at least 3 mmol/L/hr increase insulin infusion rate by 1 unit/hr increments hourly
- *Always check the insulin infusion pump if it's working and connected and that the correct insulin residual volume is present*

Actions with in 60 min to 6 hrs …

- Measure venous blood gas for pH, bicarbonate and K+ at 60 minutes and 2 hours and 2 hourly thereafter.
- If K+ is outside the reference range, assess the appropriateness of K+ replacement and check it hourly.

Actions with in 60 min to 6 hrs …

- Continue insulin until ketones < 0.3 mmol/L, venous pH > 7.3 and/or venous bicarbonate >18 mmol/L.
- If glucose falls below 14 mmol/L (~250 mg/dl) add 10% glucose at125mls/hour with NS.
- Monitor and replace K+ as it may fall rapidly.

Actions with in 60 min to 6 hrs …

- **Action 3:** Identify & treat precipitating factors
  - Infection
  - Inadequate insulin treatment or noncompliance
  - Infarcts

Management of DKA ….

C. 6 to 12 hours

- **Aims:**
  - Ensure that clinical/ biochemical parameters are improving
  - Continue IV fluid replacement
  - Continue insulin administration
  - Assess for complications of treatment
  - Continue to treat precipitating factors as necessary
  - Avoid hypoglycaemia

Actions within 6 to 12 hours

- **Action 1** – Re-assess patient, monitor vital signs
  - If patient not improving seek senior advice
  - Ensure referral has been made to diabetes team
- **Action 2:** Review biochemical & metabolic parameters
  - At 6 hours check pH, bicarbonate, K+, blood ketones and glucose
  - Resolution: defined as ketones <0.3mmol/L, pH >7.3

Management of DKA ….

D. 12 to 24 hours

- **Expectation**: By 24 hours ketonaemia and acidosis should have resolved
- **Aims:**
  - Ensure clinical/ biochemical parameters improving/ have normalized
  - Continue IV fluids if not eating and drinking.
  - Continue to treat precipitating factors as necessary
  - Subcutaneous insulin if patient is eating and drinking normally

Actions within 12 to 24 hours

- **Action 1** – Re-assess patient, monitor vital signs
- **Action 2** – Review biochemical and metabolic parameters
  - At 12 hours check pH, bicarbonate, K+, blood ketones and glucose
  - Resolution is defined as ketones <0.3mmol/L, venous pH>7.3

Management of DKA ….

E. Conversion to subcutaneous insulin.

- When biochemically stable
  - Glucose <200 mg/dl
  - Anion gap <12 meq/L
  - Bicarbonate >18 meq/L
  - Ketones < 0.3
  - pH > 7.3
- And the patient is ready and able to eat

Management of DKA ….

- Overlap between the insulin infusion and first injection of fast acting insulin of 1- 2 hours
- Abrupt discontinuation may lead to acute fall in insulin, recurrence of hyperglycemia and/ or ketoacidosis.
- If unable to take oral nutrition, continue IV insulin
- In insulin-naïve patients, a multi- dose insulin at a dose 0.5- 0.8 U/ kg including a bolus

Complications of DKA mgt

1. Cerebral oedema

- More common in children than in adults
- Occurs within first 24 hours of initiation of treatment
- **Risk factors:**
  - Younger age
  - New-onset diabetes
  - Longer duration of symptoms
  - Severe acidosis
  - Low initial bicarbonate level
  - Low sodium level
  - High glucose level at presentation
  - Rapid hydration

Complications …..

- Signs of cerebral edema that require immediate evaluation:
  - Headache
  - Persistent vomiting
  - Hypertension
  - Bradycardia, Lethargy
- **Treatment**:
  - Mannitol (20% 0.5-1 g/kg over 10-15 minutes) or
  - Hypertonic saline (3% 2.5-5 ml/kg over 10-15 minutes)

Complications …..

2. Acute circulatory failure

- Due to hypovolemia
- May cause acute renal failure
- Corrected by NS
- May need ionotropes in severe hypotension
- Sepsis treated by antibiotics

Complications …..

3. Acute gastric dilatation

- Vomiting and abdominal distension
- Auscultation: Succusion splash
- Abdominal Xray: ground glass appearance
- Treated with NG aspiration

Complications …..

4. Pulmonary Edema

- Occurs within a few hours of initiation due to rapid infusion of crystalloids over a short period of time
- Elderly patients and those with impaired cardiac function are at particular risk
- Monitoring of Central venous pressure (CVP) should be considered.

Complications …..

5. Hypokalaemia and hyperkalaemia

6. Hypoglycemia

7. Acute renal failure

8. Shock: If not improving with fluids r/o MI

Clinical Errors

- Fluid shift and shock
  - Giving insulin without sufficient fluids
  - Using hypertonic glucose solutions
- Hyperkalemia
  - Premature K+ administration before insulin has begun to act
- Hypokalemia
  - Failure to administer potassium once levels falling
- Recurrent ketoacidosis
  - Premature discontinuation of insulin and fluid when ketones still present
- Hypoglycemia: Insufficient glucose administration.

Strategies to Prevent Diabetic Ketoacidosis

Diabetic education

Blood glucose monitoring

Sick-day management

Home monitoring of ketones or beta-hydroxybutyrate

Supplemental short-acting insulin regimens

Easily digestible liquid diets when sick

Reducing, rather than eliminating, insulin when patients are not eating

Guidelines for when patients should seek medical attention

Case monitoring of high-risk patients

Special education for patients on pump management

Fluid Therapy

- Assume 10-15% dehydration
- Begin with a 10-20 ml/kg bolus of NS
- Replace calculated deficit evenly over 36 hours - generally 1.5 x maintenance for the next several hours is appropriate
- Do not exceed 40ml /kg in the initial 4 hours
- Double bag system
  - NS at 1.5 x M until glucose below 300 mg/dl
  - D10 NS to be mixed with NS to achieve desired glucose concentration

Hyperglycemic Hyperosmolar State (HHS)

Introduction

- HHS is a metabolic emergency that occurs in diabetic patient usually Type 2 DM
- Characterised by uncontrolled hyperglycemia that induces hyperosmolar state and dehydration without significant ketoacidosis.
- High blood sugars cause severe dehydration, increases in osmolarity (relative concentration of solute) and a high risk of complications, coma and death.

Diagnostic features of HHS

- According to American Diabetes Association, **diagnostic features of HHS may include the following:**

1. Plasma glucose level of 600 mg/dL or greater
2. Effective serum osmolality of 320 mOsm/kg or greater
3. Profound dehydration, up to an average of 9L with elevated BUN-to- Cr ratio
4. Serum pH greater than 7.30
5. Bicarbonate concentration greater than 15 mEq/L
6. Small ketonuria and absent-to-low ketonemia
7. Some alteration in consciousness

DKA Vs HHS

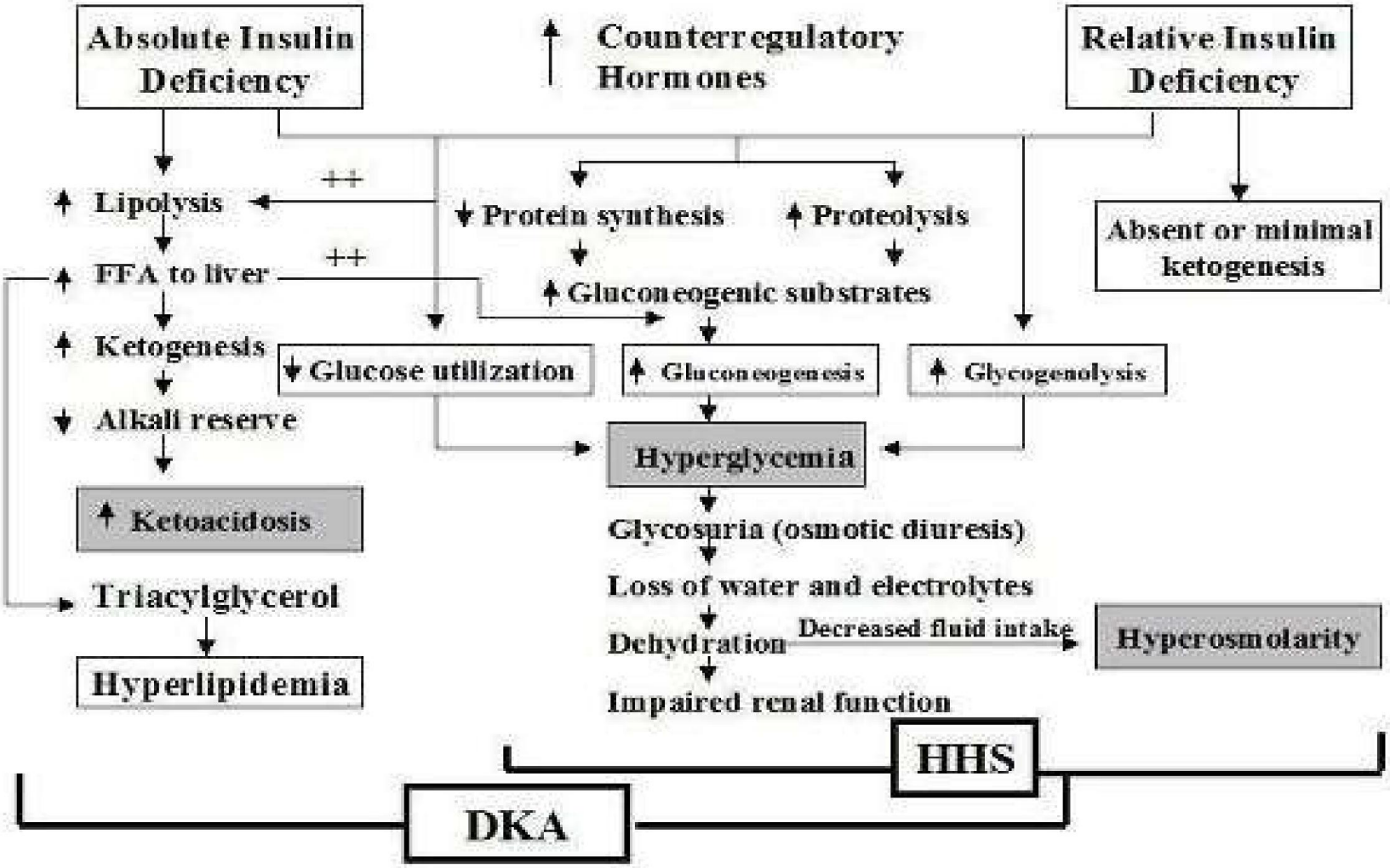
	DKA	HHS
Glucose	250-600	>600
Sodium	125-135	135-145
Potassium	Normal/inc	Normal
Bicarbonate	<15meq/l	Normal/slightly reduced
Arterial pH	<7.3	>7.3
Anion gap	Increased	Normal/slightly increased
pCO_2	20-30	Normal
Osmolality	300-320	>320

Causes and risk factors of HHS

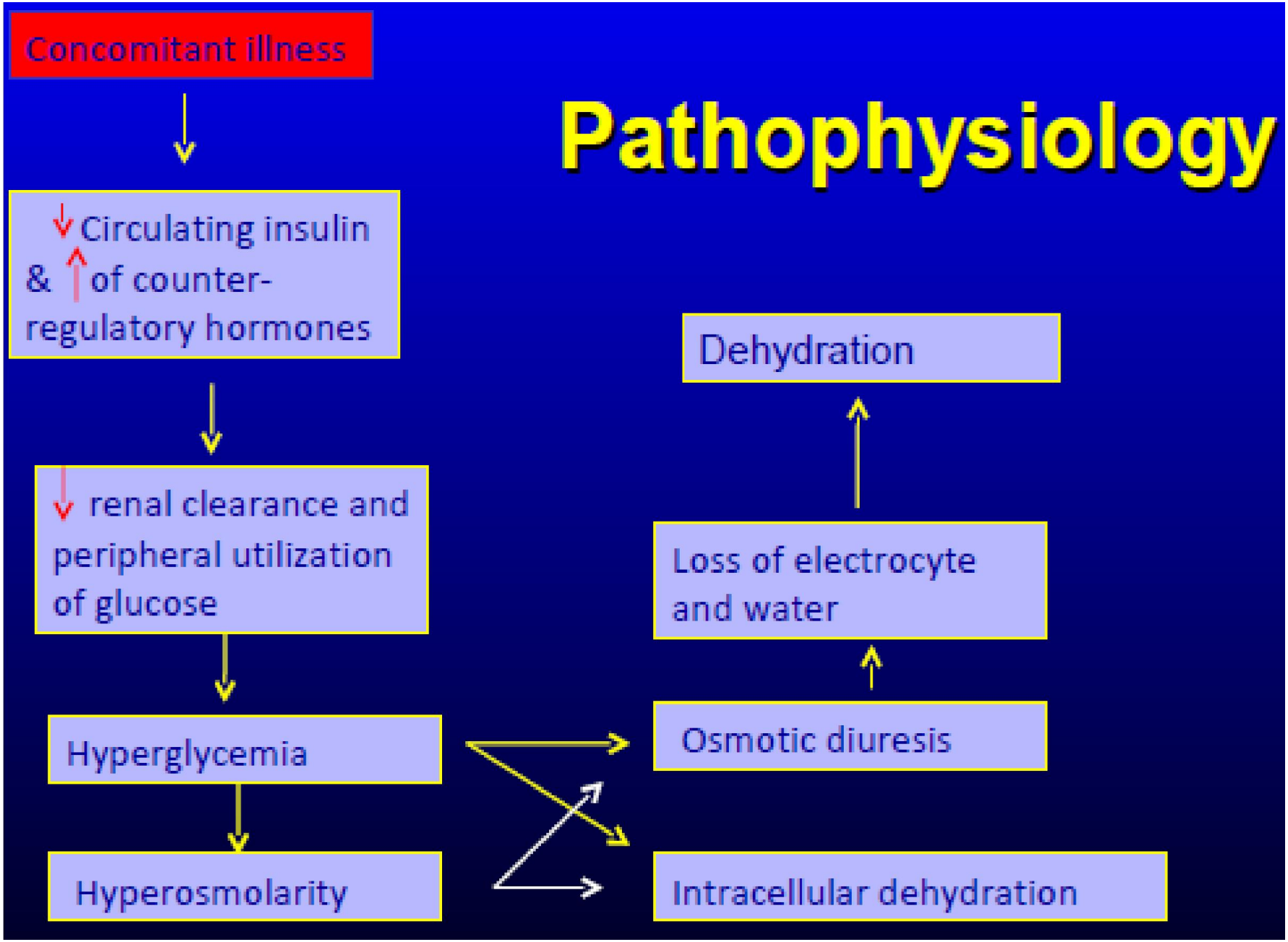
- Why HHS happens?
  - Infection
  - Non-compliance to OHA or insulin therapy
  - Dialysis
  - Dehydration
  - Total parenteral nutrition (TPN)
  - Diuretics
  - B-Blockers
  - Alcoholism, etc

Pathogenesis of DKA and HHS

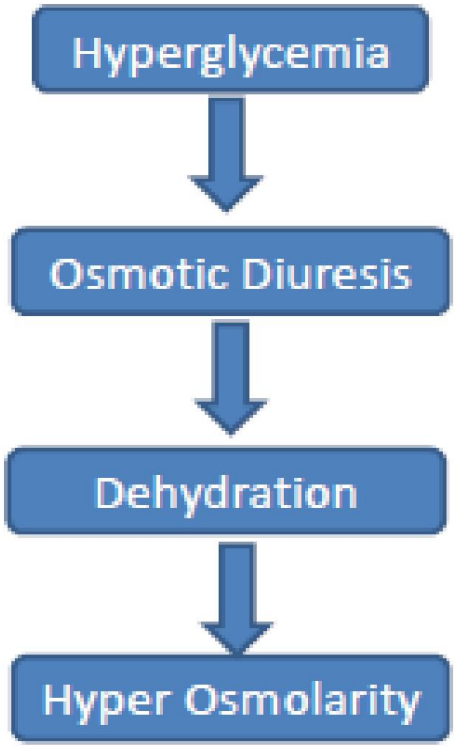
Stress, Infection and/or Insufficient Insulin

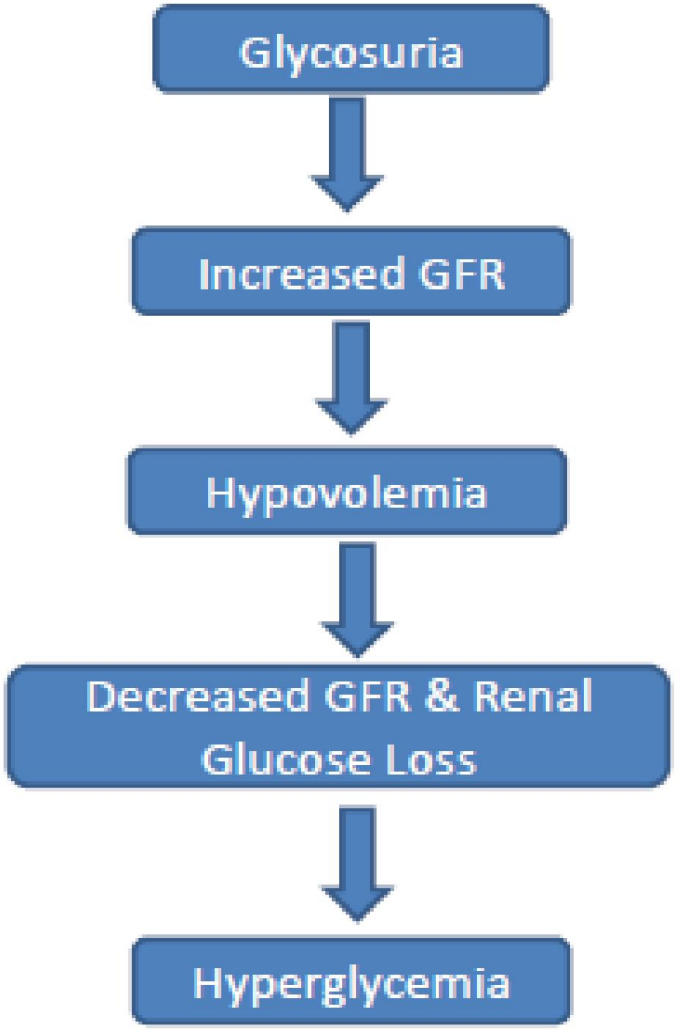


Pathophysiology



Dehydration & Hyperosmolarity:





Clinical features of HHS

History and presentation:

- Known history of diabetes mellitus (DM), usually type 2
- Patients may complain of increasing thirst, polydipsia, polyuria, weight loss, and weakness
- A wide variety of focal and global neurologic changes may be present, including drowsiness and delirium to hemiparesis and coma

Clinical features of HHS …

Physical examination:

- Examine the patient for evidence of HHS, focusing on hydration status, mentation(skin tugor), and signs of possible underlying causes, such as a source of infection.
- Tachycardia is an early indicator of dehydration; hypotension is a later sign suggestive of profound dehydration due to volume loss secondary to osmotic diuresis.
- Body weight is the single most important measurement in assessing the degree of hydration.
- For every 1 L of body fluids lost, 1 kg of body wt is lost.

Lab studies

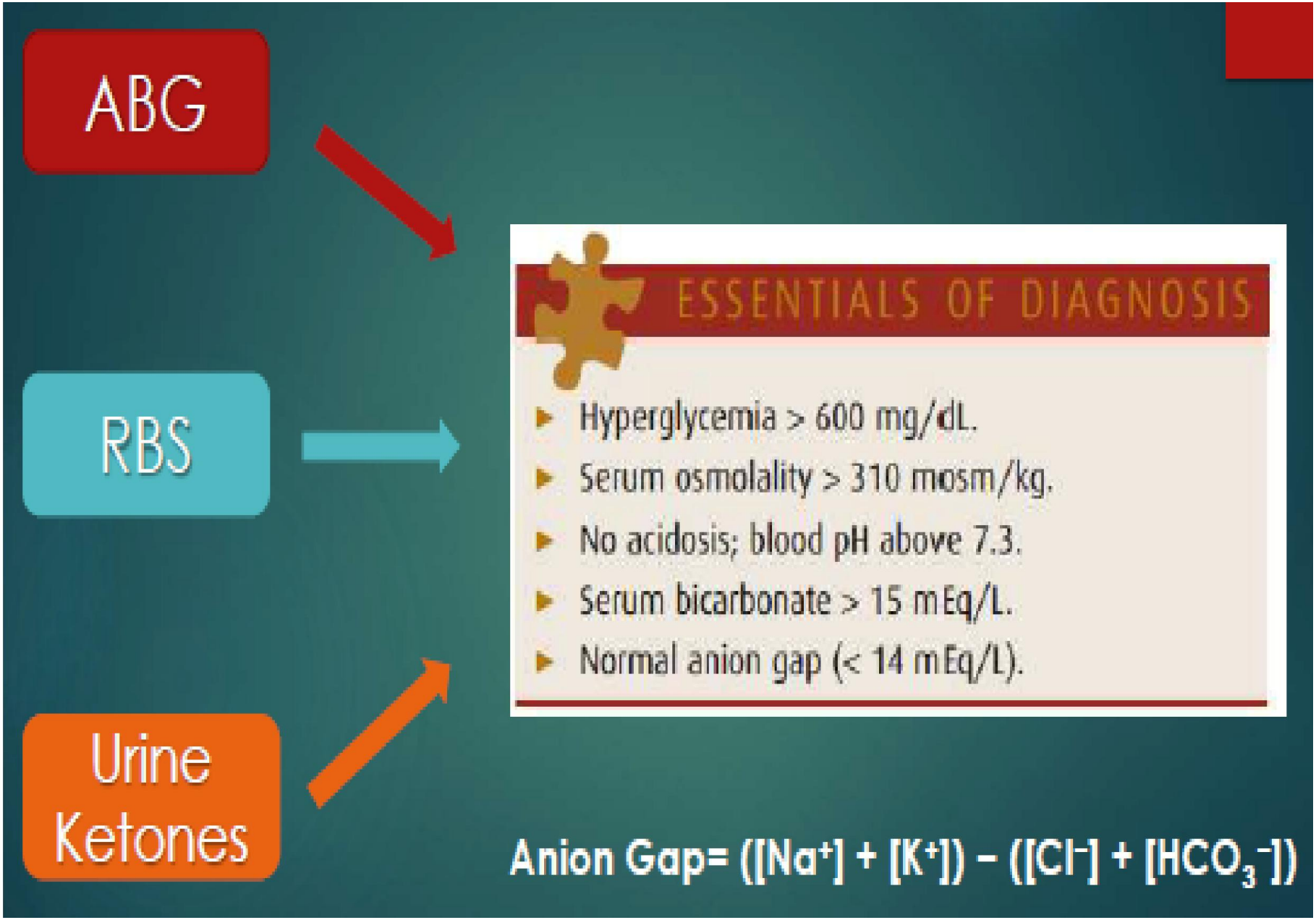
- Plasma glucose: CBG : > 600 mg/dl
- ABG: PH> 7.3, HCO3>15 mmol/l
- Serum osmolality: >320 mmol/l
- Urine-analysis
  - Exclude UTI
  - Proteinuria
- Plasma ketone, Plasma electrolyte
- Renal function test(Creatinine &BUN)
- CBC
- Creatine kinase

Laboratory findings:

- Severe hyperglycemia is present, with blood glucose values ranging from 600 mg/dL to 2400 mg/dL.
- In mild cases, where dehydration is less severe, dilutional hyponatremia as well as urinary sodium losses may reduce serum sodium to 120-125 mEq/L, which protects to some extent against extreme hyperosmolality.
- However, as dehydration progresses, serum sodium can exceed 140 mEq/L, producing serum osmolality readings of 330-440 mosm/kg.
- Ketosis and acidosis are usually absent or very mild.
- Prerenal azotemia is the rule, with serum urea nitrogen elevations over 100 mg/dL being typical.

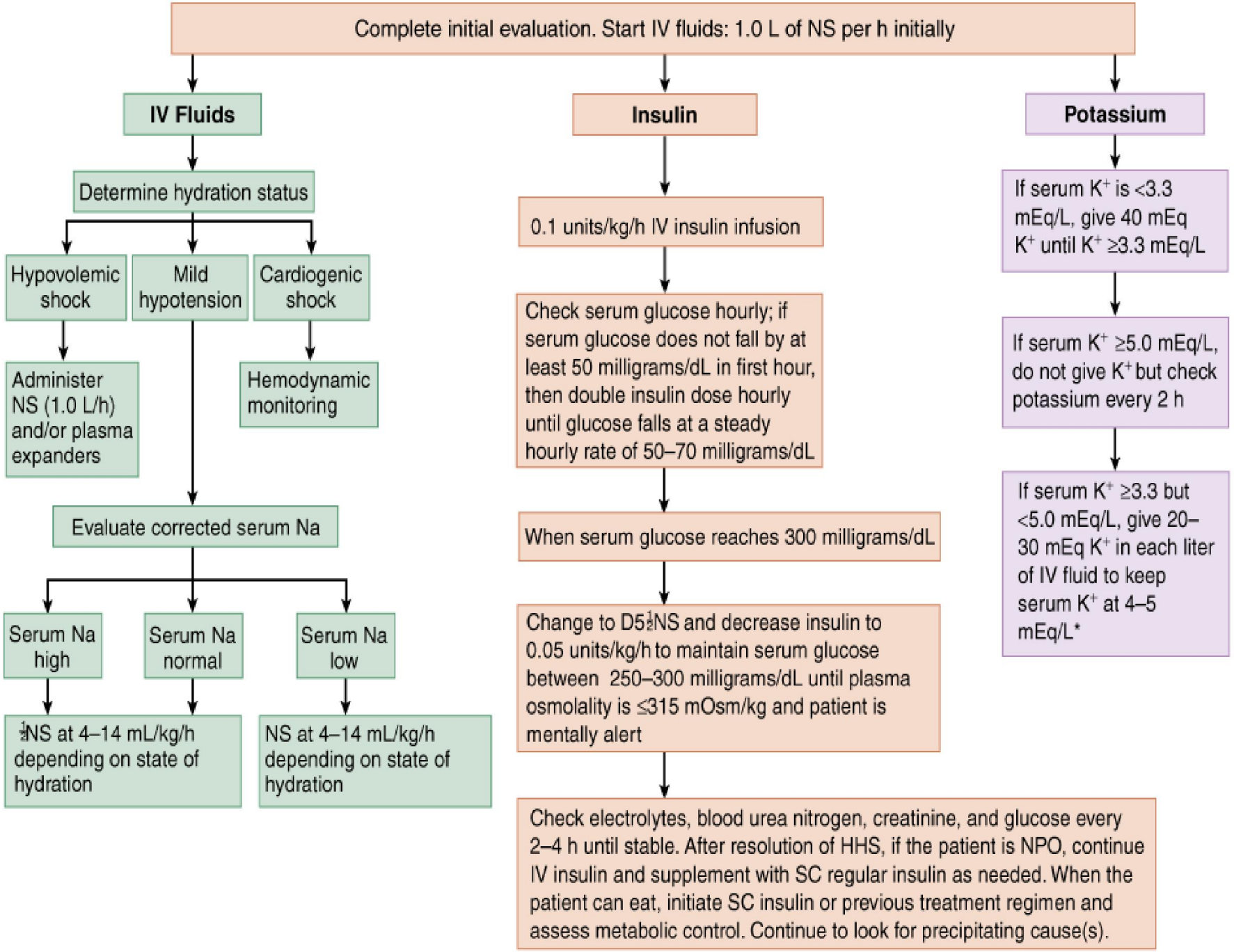
Imaging studies

- Chest radiograph
  - Exclude pnuemonia
  - Cardiomegaly
- CT scan of the head
  - Exclude haemorrhagic stroke, subdural haematoma
  - Look for cerebral edema


ABG
RBS
Urine Ketones
ESSENTIALS OF DIAGNOSIS
Hyperglycemia > 600 mg/dL.
Serum osmolality > 310 mosm/kg.
No acidosis; blood pH above 7.3.
Serum bicarbonate > 15 mEq/L.
Normal anion gap (< 14 mEq/L).
Anion Gap= ([Na+] + [K+]) – ([Cl-] + [HCO3-])

Management of HHS

- **Treatment Goals:**
  - Correction of hypovolemia
  - Identify and treating underlying cause
  - Correcting electrolyte abnormalities
  - Gradual correction of hyperglycemia and osmolarity
  - Frequent monitoring


Complete initial evaluation. Start IV fluids: 1.0 L of NS per h initially
IV Fluids
Determine hydration status
Hypovolemic shock
Mild hypotension
Cardiogenic shock
Administer NS (1.0 L/h) and/or plasma expanders
Hemodynamic monitoring
Evaluate corrected serum Na
Serum Na high
Serum Na normal
Serum Na low
½NS at 4–14 mL/kg/h depending on state of hydration
NS at 4–14 mL/kg/h depending on state of hydration
Insulin
0.1 units/kg/h IV insulin infusion
Check serum glucose hourly; if serum glucose does not fall by at least 50 milligrams/dL in first hour, then double insulin dose hourly until glucose falls at a steady hourly rate of 50–70 milligrams/dL
When serum glucose reaches 300 milligrams/dL
Change to D5½NS and decrease insulin to 0.05 units/kg/h to maintain serum glucose between 250–300 milligrams/dL until plasma osmolality is ≤315 mOsm/kg and patient is mentally alert
Check electrolytes, blood urea nitrogen, creatinine, and glucose every 2–4 h until stable. After resolution of HHS, if the patient is NPO, continue IV insulin and supplement with SC regular insulin as needed. When the patient can eat, initiate SC insulin or previous treatment regimen and assess metabolic control. Continue to look for precipitating cause(s).
Potassium
If serum K+ is <3.3 mEq/L, give 40 mEq K+ until K+ ≥3.3 mEq/L
If serum K+ ≥5.0 mEq/L, do not give K+ but check potassium every 2 h
If serum K+ ≥3.3 but <5.0 mEq/L, give 20–30 mEq K+ in each liter of IV fluid to keep serum K+ at 4–5 mEq/L*

Complications:

- **Cerebral edema may occur from rapid lowering of glucose levels and an ensuing** rapid drop in plasma osmolarity
- **Acute respiratory distress syndrome, PE, MI, or pneumonitis that has worsened with** rehydration-rapid correction of hyperglycemia and hyperosmolarity gives rise to pulmonary edema
- Vascular complications like **hypotension and hyperviscosity of the blood, both of** which predispose patients to thromboembolic disease of the coronary, cerebral, pulmonary, and mesenteric beds

Patient Education:

- **Warning signs that the patient should keep in mind:**
  - Dry, parched mouth
  - Extreme thirst
  - Warm, dry skin that does not sweat
  - High fever
  - Sleepiness or confusion
  - Loss of vision
  - Hallucinations (seeing or hearing things that are not there)
  - Weakness on one side of the body

Prognosis of HHS

- The overall mortality rate of HHS is more than **ten times that of DKA**, chiefly because of its higher incidence in older patients, who may have compromised cardiovascular systems or associated major illnesses and whose dehydration is often excessive because of delays in recognition and treatment.
- When prompt therapy is instituted, the mortality rate can be reduced from nearly 50% to that related to the severity of coexistent disorders.

Long term complications of DM

By: Agazhe Aemro

Diabetic neuropathy

- Diabetic neuropathy is a syndrome comprising a series of separate clinical disorder that affects distinct components of the peripheral nervous system.
- **Prevalence**

  ✓66% for type I and 59% for type II

Risk factors

- Hyperglycemia
- Duration of diabetes
- Age
- Hypertension
- Smoking

Pathogenesis

- Increased aldose reductase activity.
- Auto oxidation of glucose
- Non enzymatic glycation of protein(AGE)
- Activation of protein kinase C
- Oxidative stress
- Decrease essential fatty acid
- Reduced serum levels of nerve growth factor
- Nerve ischemia/hypoxia.

Classification

1) Impaired glucose tolerance and hyperglycemic neuropathy

2) Generalized neuropathies:

- -Sensorimotor
- -Acute painful
- -Autonomic
- -Acute motor

Classification ….

3) focal and multifocal neuropathies:
   - Cranial
   - Thoracolumbar
   - Lumbosacral radiculoplexus
   - Focal limb
4) Superimposed CIDP
5) hypoglycemic neuropathy

Staging

- No-no symptoms or signs of neuropathy
- N1-asymptomatic,signs of neuropathy
- N2-symptomatic neuropathy
- N3-disabling polyneuropathy.

Neuropathy related to IGT and hyperglycemia

- Sensory symptoms are described in poorly controlled DM.
- Neuropathy can be the presenting feature of IGT.
- Prevalence of IGT in patients with idiopathic neuropathy is 25-35%.
- Neuropathy is likely to be painful.
- GTT is an important investigation for a patient with painful neuropathy.

Distal symmetrical sensorimotor polyneuropathy

- Most common form of diabetic neuropathy
- DSDP is a mixed neuropathy with small and large fiber sensory, autonomic and motor involvement in various combinations.
- DSDP can easily be diagnosed when other complications such as retinopathy and nephropathy are present.
- In a patient with DM ,if there are clinical autonomic abnormalities, a DSDP is invariably present.
- DSDP has insidious onset and progressive course.

Symptoms

- Numbness or feeling of walking in cotton
- Sharp shooting or stabbing pain
- Dull constant or boring pain.
- Tingling pins & needles
- Hot or cold sensation
- Allodynia
- Cramps

Signs

- Significant distal weakness is uncommon but EDB weakness may be there.
- Ankle reflexes are absent .
- Sensory loss in a length related distribution with the toes and feet being most affected.
- Loss or impairment of all sensory modalities with vibration sense often the first to go.
- As the sensory loss extends proximally from a sock to stocking distribution the finger tips become involved.

Investigations

- Urinalysis for protein/glucose/microscopy- for evidence of nephropathy.
- HbA1c/glucose
- Urea and electrolytes
- LFT including GGT
- Thyroid function tests
- Serum protein electrophoresis
- Vitamin B 12 levels.

Clinical features suggesting a non diabetic etiology

- F/H/O neuropathy
- Abrupt onset
- Asymmetrical
- Motor>sensory
- Large>small fiber involvement
- Selective small fiber involvement
- Pes cavus and hammertoes
- Monoclonal gammopathy in serum
- CSF protein>100 gm/dl
- Elevated ESR,+ RF or ANA

Acute painful neuropathy

- Ellen berg followed by archer & co described this entity.
- Weight loss and severe pain often accompanied by depression and impotence.
- Two circumstances

  -prior to diagnosis of DM

  -after institution of treatment

Acute painful neuropathy…

- Pain is of rapid onset , severe and superficial described as burning , stinging or electrical shock like.
- Begins distally & spreads proximally.
- Sensory loss on examination is minimal , weakness is absent.
- Complete resolution is the rule.

Autonomic neuropathy (AN)

- Prevalence is difficult to ascertain.
- Affects CVS , GIT , urogenital , sudomotor , respiratory & pupillary function.
- Correlates with poor glycemic control.
- Prevalence increases with the duration of DM.
- When severe, it has adverse effects on survival.

C/M of Autonomic neuropathy

System	Presentation
CVS	Increased heart rate Impaired cardiac function Painless MI Orthostatic hypotension
GIT	Abnormal esophageal motility Gastroparesis Diarrhea & constipation

C/M of Autonomic neuropathy …

System	Presentation
Urogenital:	Erectile dysfuction Impaired testicular pain Retrograde ejaculation
Sudomotor function	Anhidrosis Gustatory sweating
Respiratory	Sleep apnea
pupillary function	Small, unreactive pupil

Management of AN

DYSFUNCTION	MANAGEMENT
Diarrhea	Tetracycline Loperamide Clonidine
Gastro paresis	Metaclopramide Bethanacol Mozapride Domperidone Erythromycin

Management …

dysfunction	management
Orthostatic hypotension	High salt diet Fludrocortisone Desmopresine Midodrine Sildenafil
Erectile impotence	Papverin injection Prosthesis

Cranial neuropathy

- Isolated neuropathies of extra ocular nerves (III,IV,VI) & facial nerves(VII) occur at an increased rate in diabetic patients
- Occulomotor nerve palsy
  - abrupt onset
  - retro orbital pain
  - ptosis & opthalmoplegia with sparing of pupillary function
  - CT/MRI is indicated when there is III rd cranial nerve palsy with pupil involvement.

Cranial neuropathy ….

-VI N palsy:

-abrupt onset & usually painless

-full recovery in 3-5 months

-VII N palsy:

-lower incidence of impaired taste sensation

-IV N palsy:

-less common

Truncal radiculoneuropathy

- Abrupt onset
- Pain over a focal area of chest/abdomen
- Worse at night
- Characteristically thoracic & upper lumbar roots are involved.
- Focal anterior abdominal wall weakness pseudo hernia
- Weight loss
- Diagnosis is often clinical
- EMG study shows e/o paraspinal /abd wall denervation
- Spontaneous recovery over months

Lumbosacral radiculoplexus neuropathy (bruns garland syndrome)

- Distinct entity , more common in men with DM 2 in middle to late adult life
- Onset :severe aching pain in one or both legs or in lower back.
- Followed by lower limb muscle weakness often proximal & unilateral , when bilateral it is asymmetrical.
- Knee jerk is depressed or absent.
- Ischemic nerve injury is secondary to microvasculitis.

Contd……

- Clinical diagnosis is often straight forward
- Ensure the markers of systemic inflammation are normal.
- when doubtful consider:
  - CT pelvis
  - MRI
  - CSF
  - EMG/NCS

Treatment

- Pain control
- Treatment of secondary depression
- Good diabetic control
- Physiotherapy

spontaneous recovery over months.

often carries good prognosis with full recovery.

Compressive neuropathy

- Incidence of compressive neuropathy is higher in diabetics.
- Carpal tunnel syndrome
- Ulnar neuropathy at the elbow
- Peroneal neuropathy at the fibular head

Treatment

- Similar to nondiabetics
- Surgery is indicated when there is significant deficit

Electrophysiological Testing

- Nerve conduction study & electromyography may aid in clinical evaluation of diabetic neuropathy.

  1) Confirmation of clinical disease

  2) Identification of a pattern characteristic of diabetes.

  3) Monitoring of progression/remission of disease

  4) Detection of asymptomatic cases.

Electrophysiological Testing ..

- EPS cannot specifically diagnose diabetic neuropathy and no features are pathognomic.
- Asymptomatic-distal slowing of conduction
- Overt neuropathy-features of both demyelination and axonal regeneration.

Treatment

- Correcting the underlying pathogenetic mechanism.
  - Normalization of blood glucose
  - Antioxidant therapy
  - Aldose reductase inhibitor
  - Growth factor analogue

Symptomatic treatment

Physical approach

- Proper footwear
- Foot care
- Nocturnal splint
- physiotherapy

Pharmacological

- NSAIDS
- Antidepressants
- Anticonvulsants
- others-capsaicin

Alpha lipoic acid

- Antioxidant
- 600 mg/day iv for 5 days ×14 days.
- Improves neuropathic symptoms including pain.
- Clinical trials has consistently shown benefit over placebo.

Aldose reductase inhibitor

- Tolrestat , epalrestat , ranirestat, fidarestat are available.
- Potentially slow or reverse progression of neuropathy.
- Clinical trials fail to show any benefit over placebo.

Antidepressants

- Amitriptyline, nortriptyline, imipramine, paroxetine, duloxetine are commonly used.
- Efficacy is similar within the class.
- Useful when secondary depression coexists.
- Side effects are bothersome in elderly.
- Duloxetine hydrochloride
    - Dual uptake inhibitor
    - Dose: 20-60 mg/day
    - Nausea, sedation &sleepiness

Anticonvulsants

- Carbamezipine , Gabapentin , pregabaline are often used.
- Used alone or as add on therapy to tricyclics.
- Well tolerated.
- Carbamezipine:200-600 mg/day
- Gabapentin:900-3600 mg/day
- Pregabaline:75-300 mg/day

Refractory neuropathic pain

- Mexiletine
- Iv lidocaine
- Phenothiazines
- Tramadol
- Local nerve blocks
- TENS
- Acupuncture

Conclusion

- DSDP is the most common form of diabetic neuropathy encountered in clinical practice.
- GTT is an important tool to uncover IGT associated neuropathy.
- Prevention is the best form of treatment.
- Normoglycemia is the cornerstone of therapy.

DIABETIC RETINOPATHY (DR)

Introduction

- Diabetic retinopathy is a chronic progressive sight-threatening disease of retinal microvasculature
- Associated with prolonged hyperglycaemia & other conditions linked to diabetes such as hypertension.

Prevalence

- ✓ The total number of people with diabetes is projected to rise from 285 million in 2010 to 439 million in 2030.
- ✓ Diabetes remains a leading cause of legal blindness between the ages of 25-65 years in the western world.
- ✓ It is responsible for 1.8 million of the 37 million cases of blindness throughout the world (4.9%).
- ✓ 33% of patients with diabetes have signs of diabetic retinopathy.

Risk factors of DR

1) **Duration of diabetes**
   - It's the best predictor of diabetic retinopathy.
   - In patients diagnosed with DM before the age of 30 years, the incidence of DR after 10 years is 50%, and after 30 years 90%
   - After 20 years of diabetes, nearly 99% of patients with type I DM and 60% with type II have some degree of diabetic retinopathy.
     - This is because PDR is a result of very high average blood glucose levels that are more likely to be in DM type I than type II.

Risk factors of DR …

2) Poor glycaemic control

- The severity of hyperglycemia is the key alterable risk factor associated with the development of diabetic retinopathy.
- Tight blood sugar control, particularly when instituted early, can prevent or delay the development or progression of DR.

Risk factors of DR …

3) Pregnancy

- Sometimes associated with rapid progression of DR.
- Key factors are:
  - Greater pre-pregnancy severity of retinopathy
  - Poor pre-pregnancy control of diabetes
  - Control exerted too rapidly during early Px stages
  - Development of pre-eclampsia and fluid imbalance

Risk factors of DR …

4) Hypertension

- According to **"Appropriate Blood-pressure Control in Diabetes (ABCD) Trial"**, target BP should be <140/80.
- Tight control of BP appears to be particularly beneficial in type II diabetics with maculopathy.
- The **"EURODIAB Controlled Trial of Lisinopril in Insulin Dependent Diabetes (EUCLID)"** showed lowered rates of development of retinopathy in diabetics taking lisinopril for anti-hypertensive medication as compared to placebo.

Risk factors of DR …

5) Nephropathy

- Nephropathy, if severe, is associated with worsening of DR.
- Conversely, treatment of renal disease (ACE inhibitors and Angiotensin II receptor antagonists) may be associated with improvement of retinopathy.

Risk factors of DR …

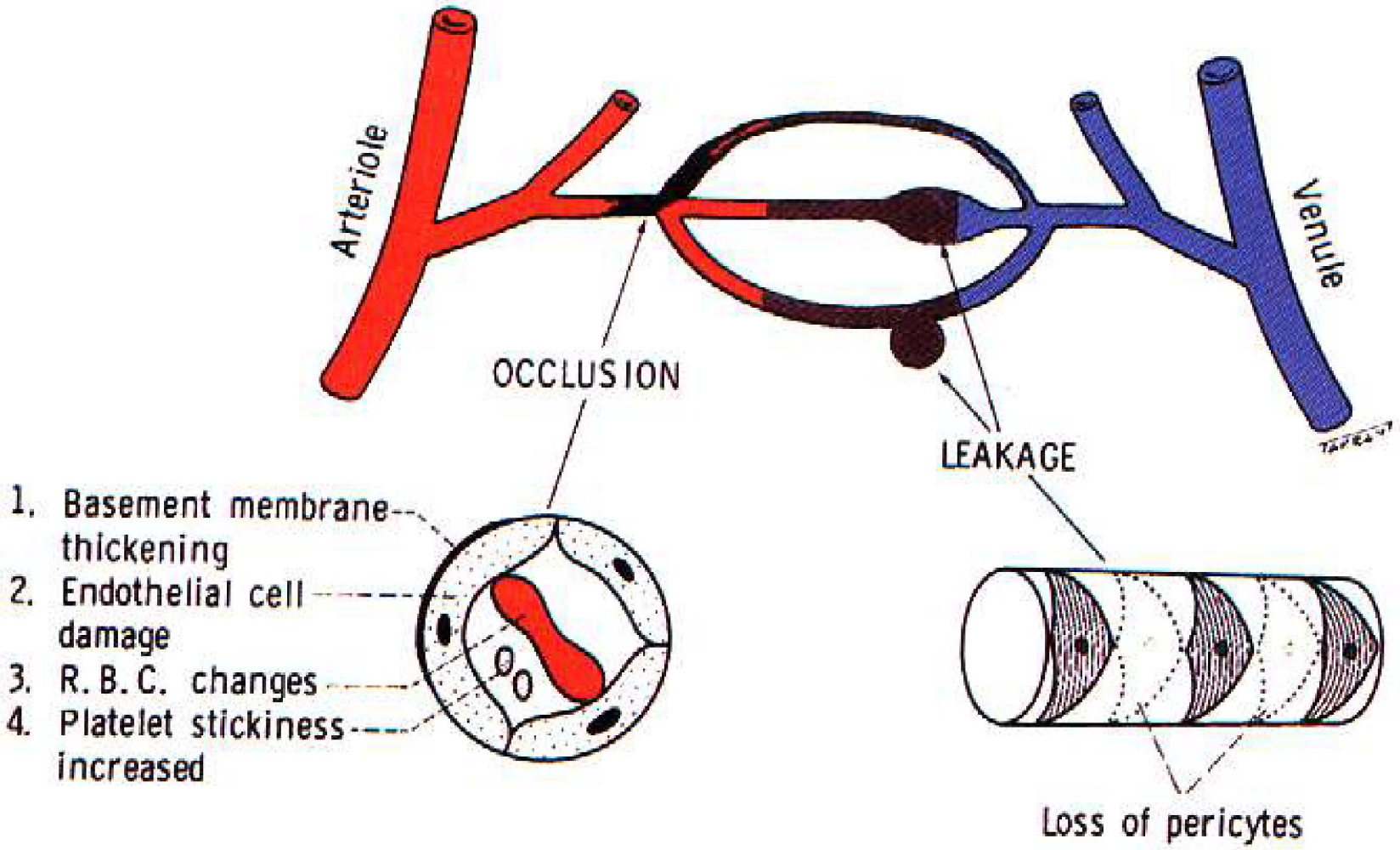
6) Other risk factors

- Smoking
- Sex : M > F
- Hyperlipidemia (TG, LDL)
- Cataract surgery
- Obesity
- Anemia (leading to hypoxia)
- Carotid artery occlusive disease
- Alcohol ???

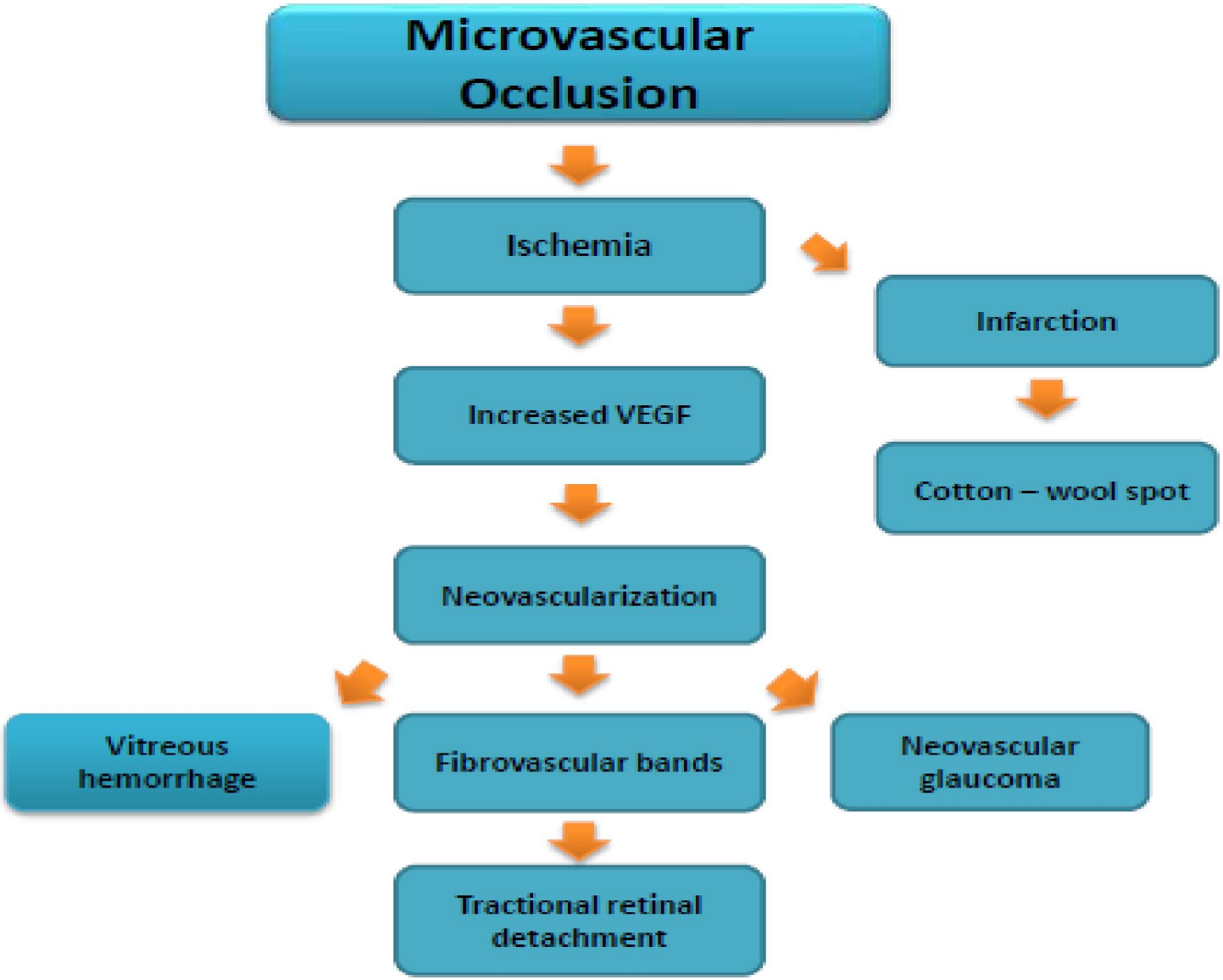
Pathogenesis of DR

- It is a microangiopathy caused by effect of hyperglycemia on small blood vessels leading to:
  - ✓ Retinal capillary occlusion
  - ✓ Retinal capillary leakage

Pathogenesis of DR…



Pathogenesis of DR…



Classification of DR

- Non proliferative diabetic retinopathy (NPDR)
- Proliferative diabetic retinopathy (PDR)
- Diabetic maculopathy
- Advanced diabetic eye disease

Non proliferative diabetic retinopathy (NPDR)

A. **Mild**: at least one microaneurysm must be present

B. **Moderate :**

- ✓ Microaneurysms or retinal hemorrhages in 2/3 quadrants
- ✓ Mild Intraretinal microvascular abnormalities (IRMA)
- ✓ hard or soft exudates may or may not be seen
- ✓ venous beading in not more than 1 quadrant

Non proliferative DR …

C. **Severe :** (any one of the following)

- ✓ microanuerysms and intraretinal hemorrhages in 4 quadrants
- ✓ venous beading in 2 or more quadrants
- ✓ moderate IRMA in 1 quadrant

D. **Very severe:** ≥ 2 of the criteria for severe

Proliferative diabetic retinopathy (PDR)

- **Early PDR:**
  - New vessels on the disc (NVD) Or
  - New vessels elsewhere (NVE) without any high risk characteristics
- **High risk:**
  - NVD ¼ - 1/3 of disc area with or without vitreous hemorrhage (VH) or preretinal hemorrhage (PRH)
  - NVD < ¼ disc area with VH or PRH
  - NVD > ½ disc area with VH or PRH

Advanced diabetic eye disease

- Persistent vitreous hemorrhage
- Tractional retinal detachment
- Neovascular glaucoma

Symptoms of DR

- DR is asymptomatic in early stages of the disease.
- As the disease progresses symptoms may include:
  - ✓ Blurred vision
  - ✓ Floaters and flashes
  - ✓ Fluctuating vision
  - ✓ Distorted vision
  - ✓ Dark areas in the vision
  - ✓ Poor night vision
  - ✓ Impaired color vision
  - ✓ Partial or total loss of vision

Diagnostic testing

- Screening
- Investigations :
  - urine examination
  - blood sugar, HbA1C
  - RFT
  - lipid profile
  - FFA
  - Ocular coherence tomography (OCT)

Treatment of DR

- **Indications of treatment:**
  - NVD > 1/3 disc in area
  - Less extensive NVD + hemorrhage
  - NVE > 1/2 disc in area + hemorrhage

Treatment of underlying disorders

- Glycemic control – Insulin, OHG
- BP control – Anti-hypertensive medications
- Cholesterol control – Statins, Fibrates
- Support renal function – ACEI, ARB
- Lifestyle modification – Smoking and alcohol cessation, exercise ,weight control

Rx of DR …

- Laser therapy
- Surgical Rx:
  - Pars plana vitrectomy

DIABETIC NEPHROPATHY

Diabetic nephropathy

- Diabetic nephropathy is characterized by:
  - Persistent albuminuria (>300 mg/24 hr)
  - Presence of diabetic retinopathy
  - Absence of clinical or laboratory evidence of other kidney or renal tract disease.
  - Declining GFR

Pathology of DN in Patients with Type 1 DM and Proteinuria

Always present

1. Glomerular basement membrane thickening.
2. Tubular basement membrane thickening
3. Mesangial expansion with predominance of increased mesangial matrix.
4. Interstitial expansion with predominance of increased extracellular matrix material.

Pathology of DN in Patients with Type 1 DM and Proteinuria …

Often or usually present

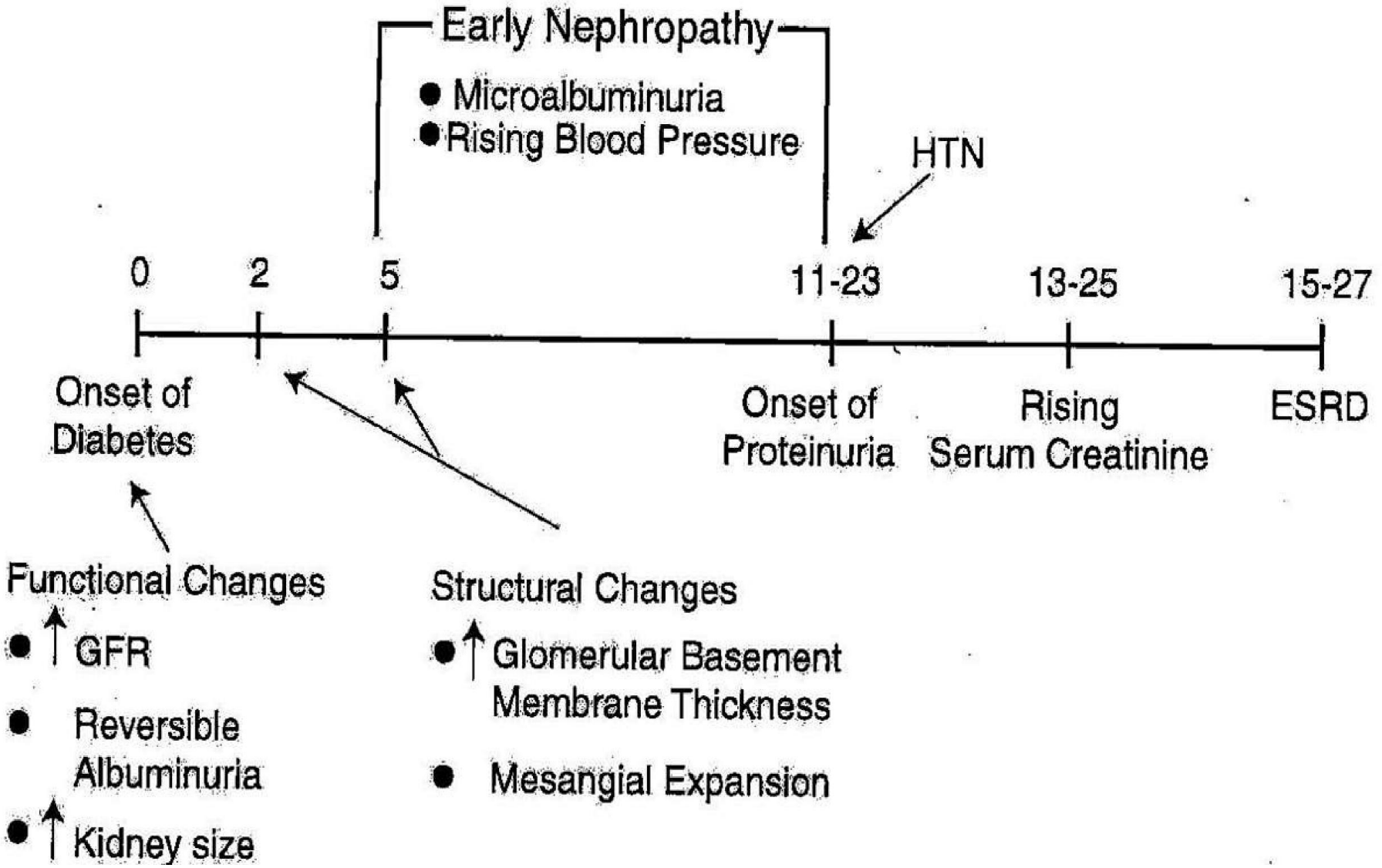
1. Kimmelstiel-Wilson nodules (nodular glomerulosclerosis)
2. Global glomerulosclerosis
3. Focal segmental glomerulosclerosis
4. Atubular glomeruli
5. Foci of tubular atrophy
6. Afferent and efferent arteriolar hyalinosis

Pathology of DN in Patients with Type 1 DM and Proteinuria …

Sometimes present

1. Hyaline caps or fibrin caps (Highly characteristic of diabetic nephropathy)
2. Capsular drops (Highly characteristic of diabetic nephropathy)
3. Atherosclerosis
4. Glomerular micro-aneurysms

Natural history of diabetic nephropathy (DN)



Natural Hx of diabetic nephropathy

Five stages

Stage 1: Hyperfiltration

- Increased GFR (GFR >90ml/min)
- Concomitant renal hypertrophy (glomerular & tubular)
- Various factors contributing are:
  - Intra renal hemodynamic abnormalities
  - TGF-β
  - Increased salt absorption
  - Osmotic load and toxic effect of high sugar levels on kidney cells

Stage 2 : The Silent Stage

- The GFR has returned to normal with no evidence of albuminuria
- Glomerular damage occurs in the form of basement membrane thickening and mesangial expansion.
- Ambulatory BP monitoring studies have shown modest rise in BP and absence of nocturnal dip

Stage 3: Incipient nephropathy /Microalbuminuria

- Urine AER has increased to 30 to 300 mg/24 hrs
- Renal functions could be normal or reduced
- 30-50% of patients may show reversal of microalbuminuria
- Persistent microalbuminuria , if untreated, will progress to end-stage renal disease (ESRD).
- Therefore, all diabetes patients should be screened for microalbuminuria on a routine basis.

Stage 4 : Macroalbuminuria/Overt Nephropathy

- The urine AER is more than 300 mg of albumin in a 24-hour period.
- Over two thirds of patient in this stage have Hypertension .
- If untreated a vicious cycle of progressive renal impairment develops leading to ESRD.

Stage 4 : Macroalbuminuria/Overt Nephropathy

- The urine AER is more than 300 mg of albumin in a 24-hour period.
- Over two thirds of patient in this stage have Hypertension .
- If untreated a vicious cycle of progressive renal impairment develops leading to ESRD.

Stage 5: Uremia

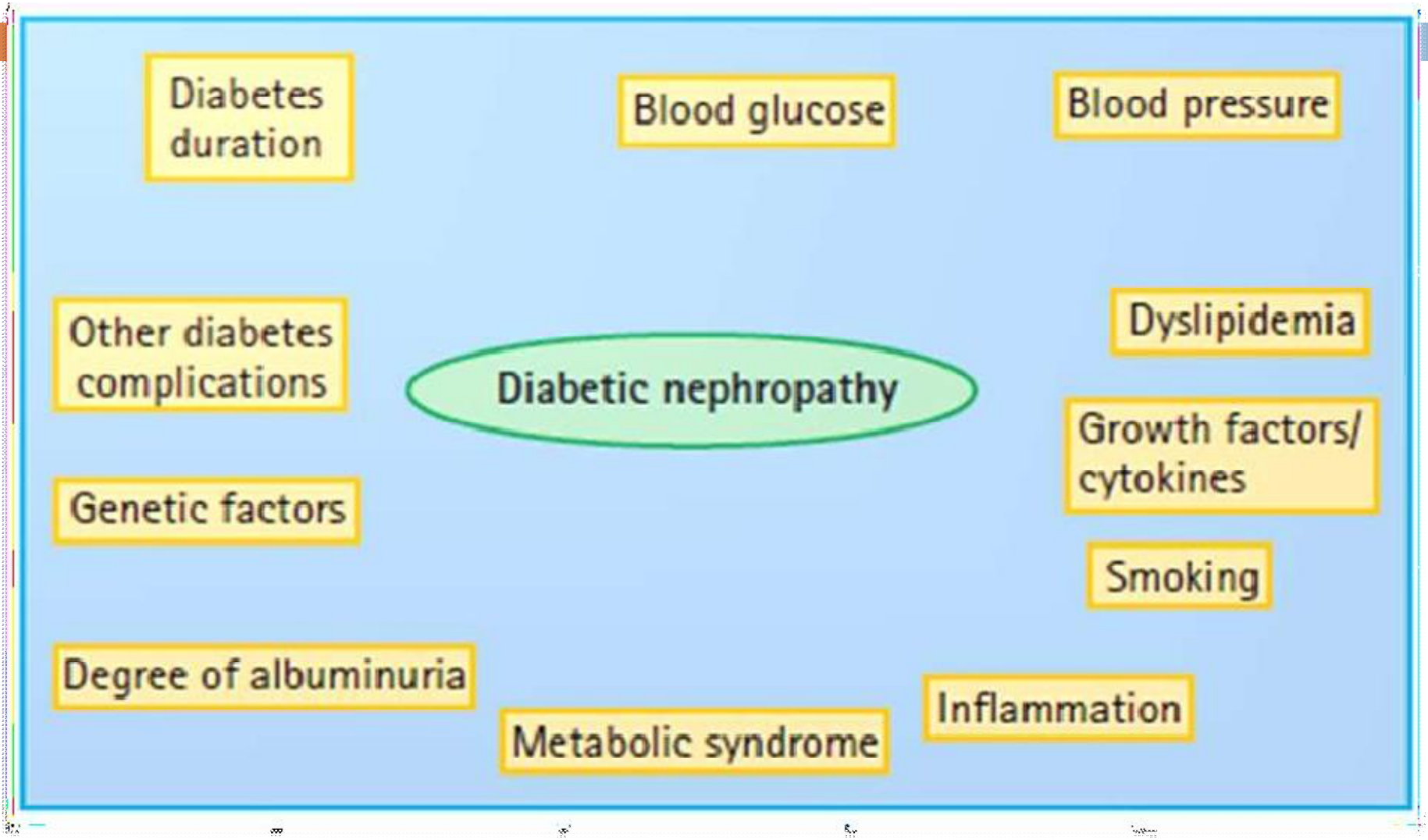
- GFR has fallen to **<15 ml/min** and renal replacement therapy (i.e., haemodialysis, peritoneal dialysis, kidney transplantation) is needed.

Diabetic nephropathy is a clinical syndrome characterized by:

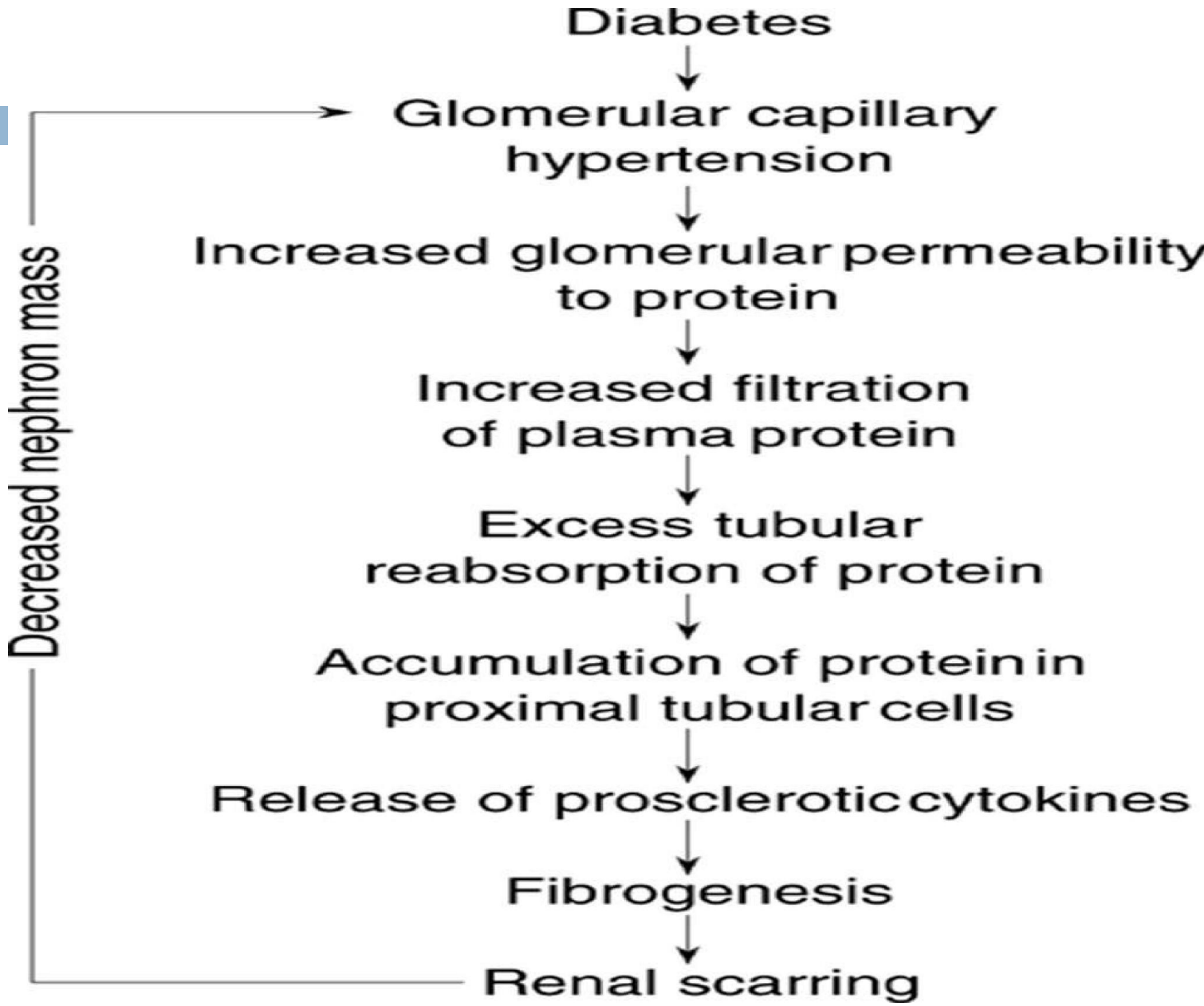
- Persistent albuminuria
- Decline in GFR
- Raised arterial BP
- Enhanced cardiovascular morbidity and mortality

- Albuminuria is the first sign and peripheral edema is the first symptom of diabetic nephropathy

Risk factors associated with progression



Proteinuria induced renal damage



Screening and diagnosis of DN

- Diabetes should be screened annually with serum creatinine and eGFR and urine alb:creatinine (ACR)
  - Starting 5 yrs after diagnosis of type 1
  - Starting at the diagnosis of type II
- Elevated urine ACR confirmed ≥ 2 times and not in setting of UTI ,acute febrile illness, vigorous exercise, uncontrolled hypertension, and heart failure
  - Microalbuminuria: ACR 3-30 mg/mmol
  - Macroalbuminuria: ACR >300 mg/mmol

Albuminuria categories in CKD

Category	AER (mg/24 hours)	ACR (approximate equivalent) (mg/mmol)	ACR (approximate equivalent) (mg/g)	Terms
A1	<30	<3	<30	Normal to mildly increased
A2	30-300	3-30	30-300	Moderately increased*
A3	>300	>30	>300	Severely increased**

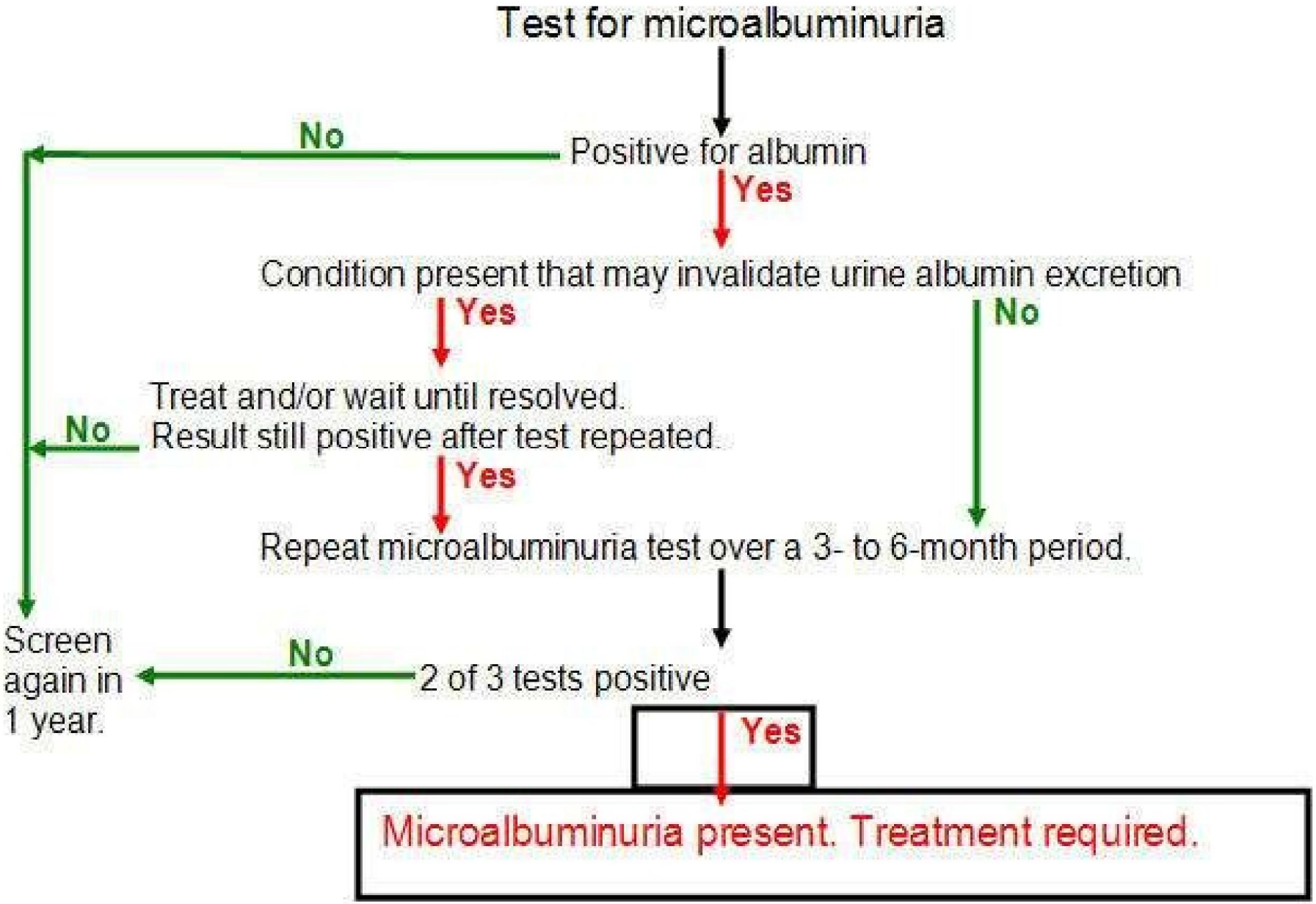
Abbreviations: AER, albumin excretion rate; ACR, albumin-to-creatinine ratio; CKD, chronic kidney disease.

*Relative to young adult level.

**Including nephrotic syndrome (albumin excretion usually >2200 mg/24 hours [ACR >2220 mg/g; >220 mg/mmol]).

Factors affecting urinary albumin excretion

Increased AER	Decreased AER
▪ Strenuous exercise ▪ Poorly controlled DM ▪ Heart failure ▪ UTI ▪ Acute febrile illness ▪ Uncontrolled HPT ▪ Hematuria ▪ Menstruation ▪ Pregnancy	▪ NSAIDs ▪ ACE inhibitors


Test for microalbuminuria
Positive for albumin
No
Yes
Condition present that may invalidate urine albumin excretion
Yes
No
Treat and/or wait until resolved.
Result still positive after test repeated.
No
Yes
Repeat microalbuminuria test over a 3- to 6-month period.
Screen again in 1 year.
No
2 of 3 tests positive
Yes
Microalbuminuria present. Treatment required.

Cont …

- Screening should be done when the person is free from acute illness and with stable glucose levels
- Early morning urine sample is preferred
- Serum Cr level should also be measured annually
- Recently serum Cystatin C – a naturally circulating protein, freely filtered by glomerulus has been suggested as an alternative to Cr measurement

Treatment

- **Major therapeutic interventions include:**
  - Glycemic control
  - Control of BP to near normal level
  - Antihypertensive treatment
  - Lipid lowering therapy, e.g. statins
  - Restriction of dietary proteins
  - Cessation of smoking

Treatment goal for lipids in diabetic nephropathy

- LDL <2.6 mmol/L (100 mg/dL)
- HDL >1 mmol/L (40 mg/dL) in men, >1.3 mmol/L (50 mg/dL) in women
- Triglycerides <1.7 mmol/L (150 mg/dL)

Dietary Protein Restriction

- A low protein diet reduces urinary albumin excretion and hyperfiltration independent of changes in glucose control and blood pressure.

KDIGO GUIDELINE FOR PROTIEN INTAKE

- Lowering protein intake to 0.8 g/kg/day in adults ± diabetes and GFR<30 ml/min/ 1.73 m2(GFR categories G4-G5) with appropriate education.
- Avoiding high protein intake (>1.3 g/kg/day) in adults with CKD at risk of progression

Diabetic foot ulcer

Introduction

- Diabetic foot, Is a spectrum of pathological entities that affect the foot of a diabetic patient as a result of its complications
- Diabetic foots are common throughout the world
- Resulting in high morbidity, mortality and major economic burden
- Management of diabetic foot is multi-disciplinary
- Diabetic foot ranges from foot at risk to frank gangrene

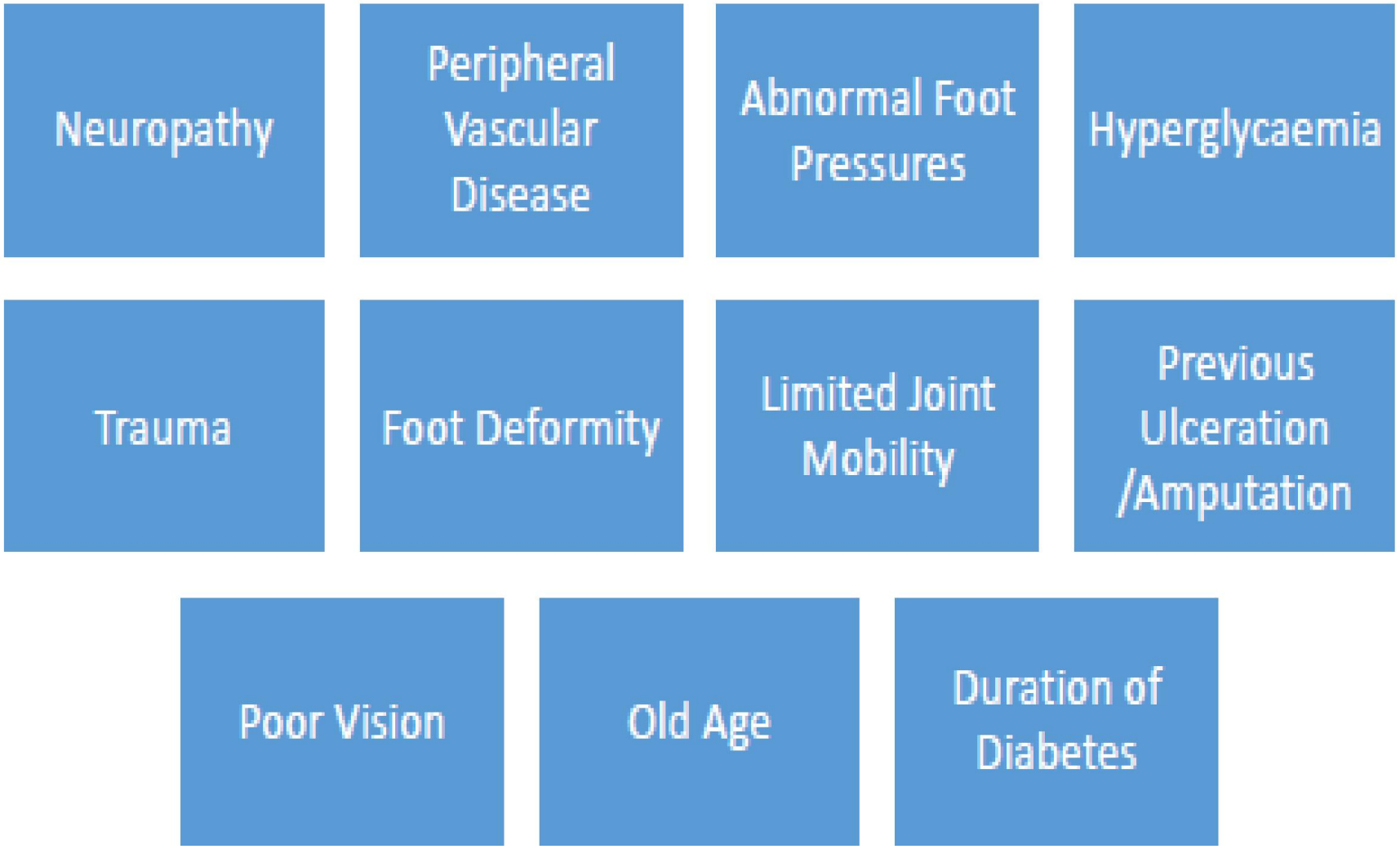
Diabetic foot ulcer

- A non healing or poorly healing, break in the skin, below the ankle in an individual with diabetes, critical in the natural history of the diabetic foot.

Epidemiology

- Diabetic foot , affect 15% of all diabetic globaally, 15– 20% may require amputation
- DFU account up to 24% mortality in patients with DM
- About 41.5% of DM patients have foot at risk
- Type II diabetes account for 98.1%
- Mean duration before development of DF is 10.8yrs
- Neuropathy was the commonest risk factor 76%

Risk factors

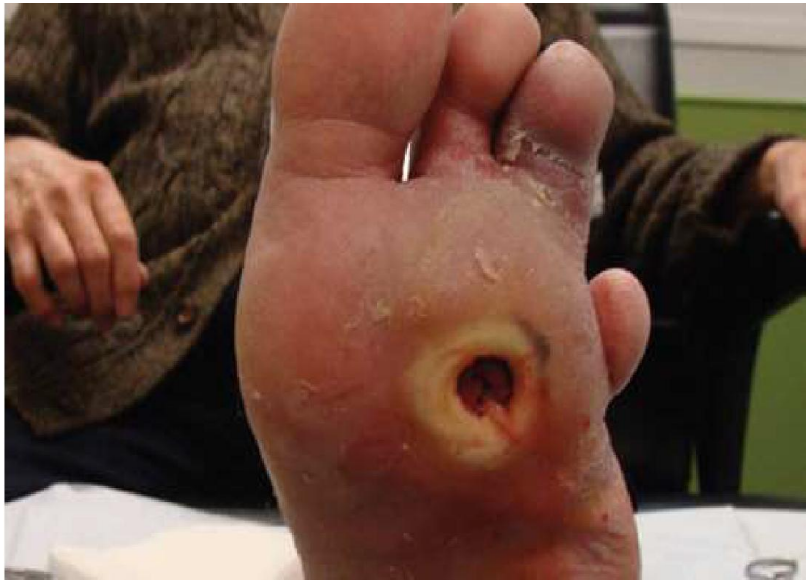


Pathogenesis

- Diabetic foot result from either;

1.Peripheral Neuropathy 80 - 90%

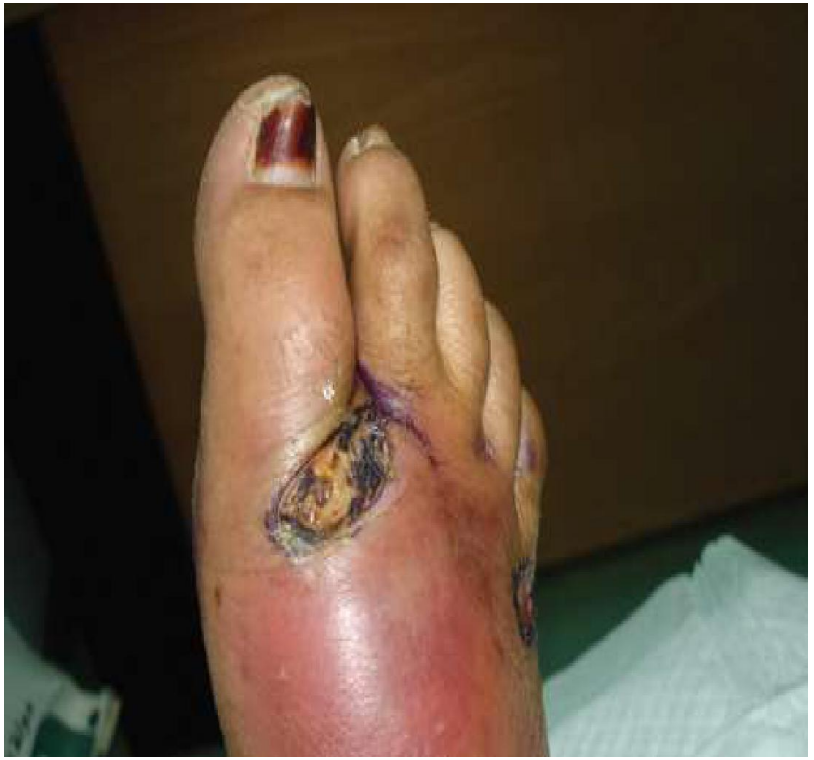
- leads to skin dryness and cracks, foot deformity and loss of protective sense in the foot



Pathogenesis ….

2. Peripheral vascular disease 30-40%

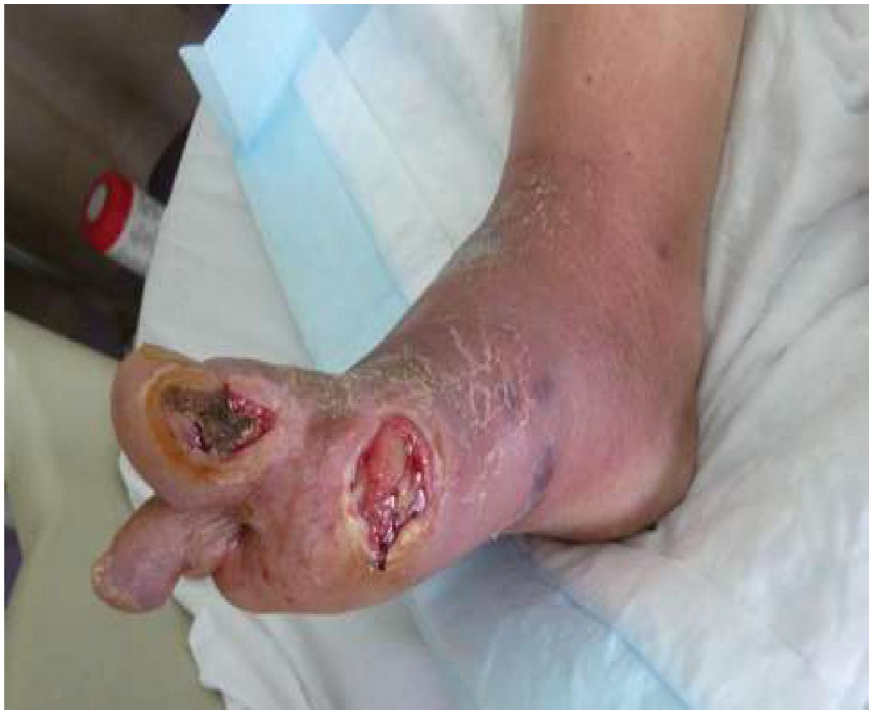
- Micro/Macro angiopathy
- lead to poor blood supply to the toes and foot and then ulcerate easily



Pathogenesis ….

3. Neuroischaemic foot

- is the commonest



Pathology

- The natural history of diabetic foot was studied
- It was explained by the following stages
- **STAGE 1- Normal foot**

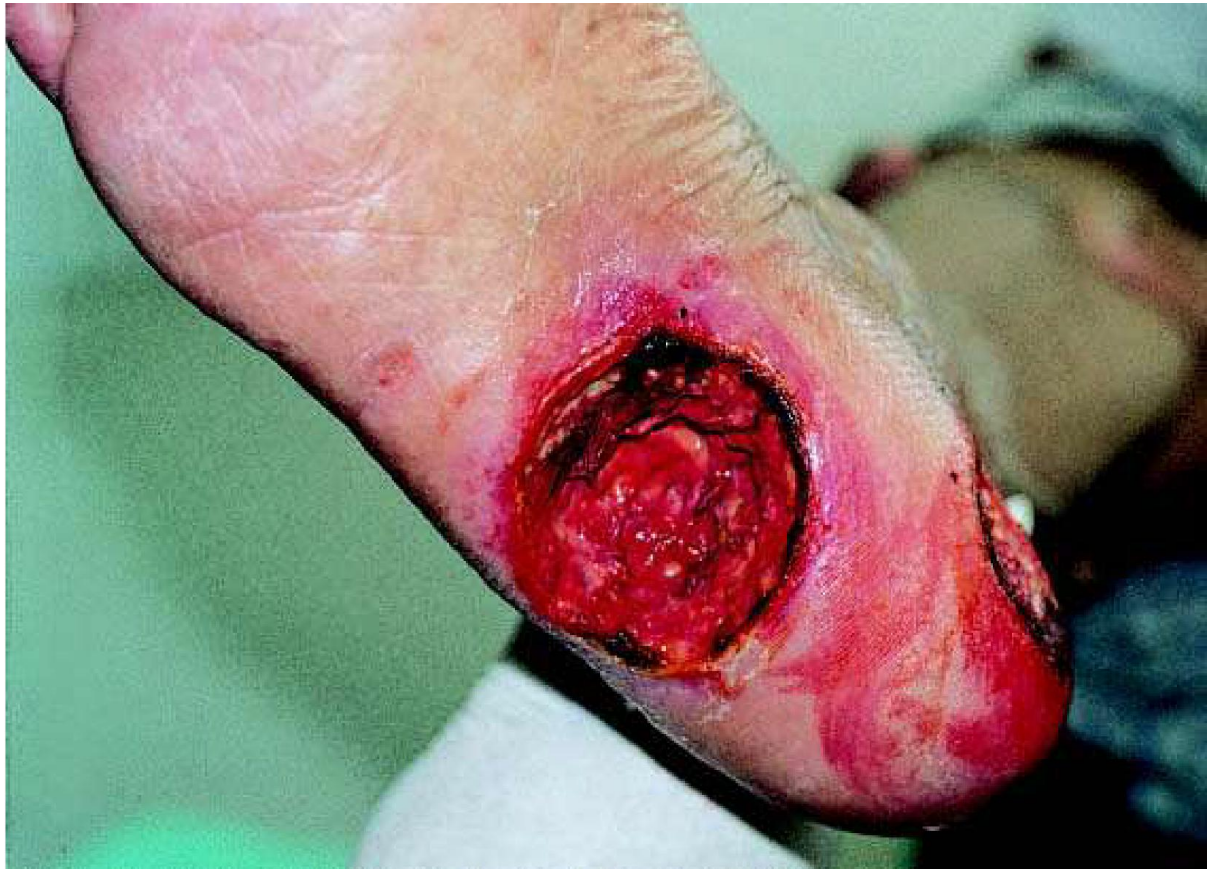
Pathology ….

Stage 2 : High risk foot

- Duration of diabetes >10yrs
- Poor glycemic control
- Neuropathy
- PVD
- Foot deformity, dryness and callousity
- Decreased immunity
- Previous healed ulceration
- Previous amputation
- Retinopathy

Pathology ….

Stage 3 : Ulcerated foot



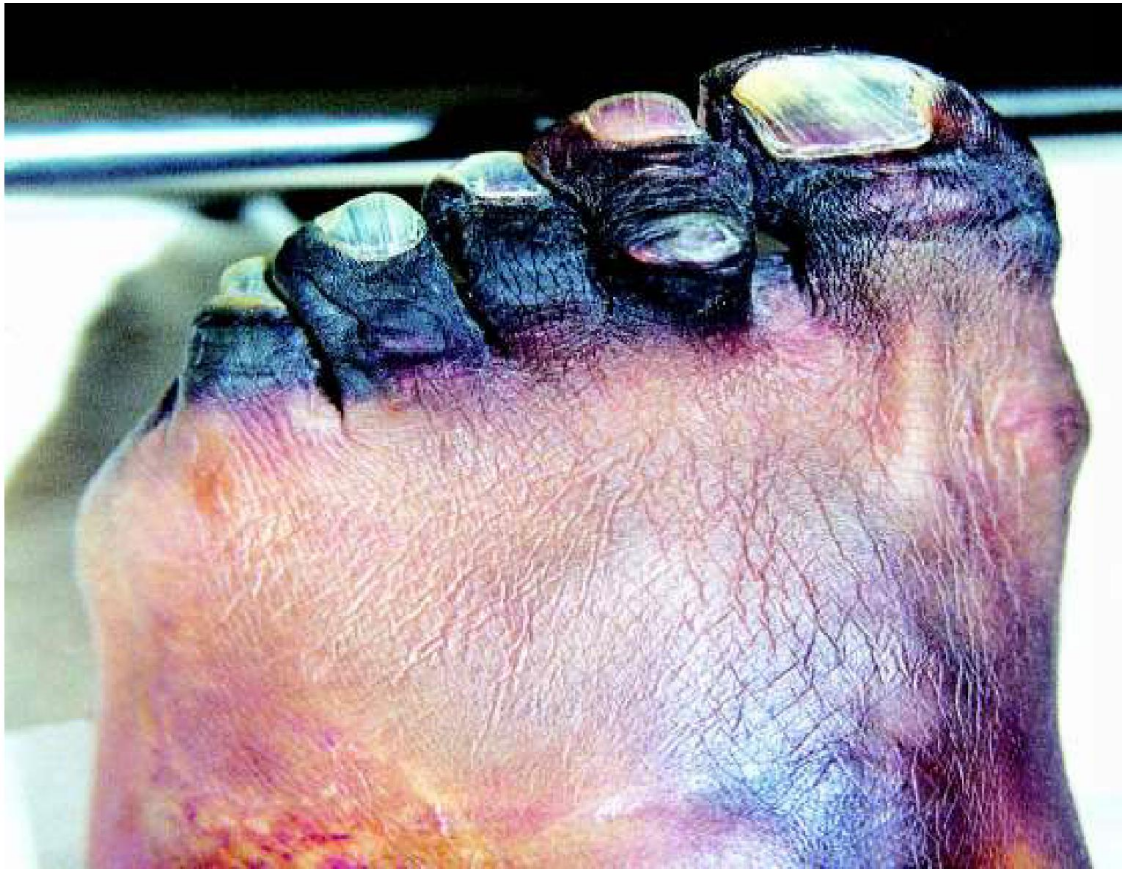
Pathology ….

Stage 4 : Infected foot

- Cellulitis
- Abscess
- Osteomylitis

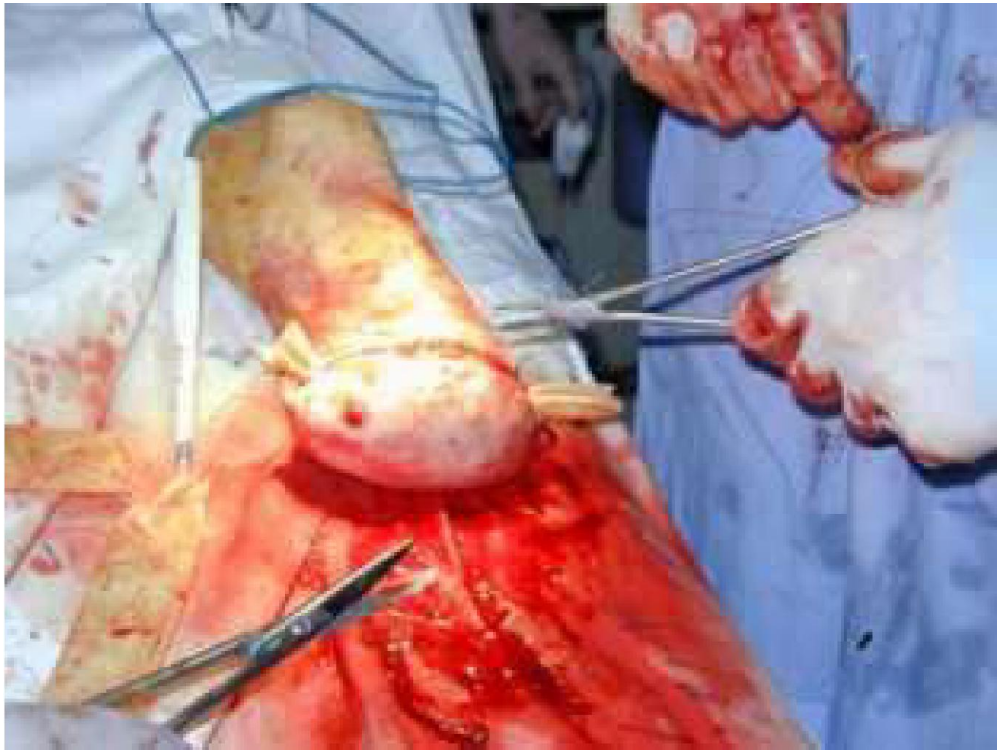
Pathology ….

Stage 5 : Necrotic foot



Pathology ….

Stage 6: Unsalvageable



Classification

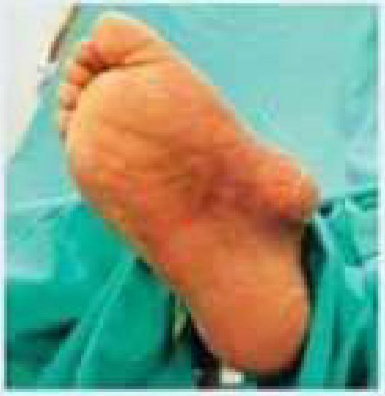
Wagner's Classification of Diabetic Foot Ulcers[81]

Grading	Features
0	Pre-ulcer. No open lesion. May have deformities, erythematous areas of pressure or hyperkeratosis.
1	Superficial ulcer. Disruption of skin without penetration of subcutaneous fat layer.
2	Full thickness ulcer. Penetrates through fat to tendon or joint capsule without deep abscess or osteomyelitis.
3	Deep ulcer with abscess, osteomyelitis or joint sepsis. It includes deep plantar space infections, abscesses, necrotizing fascitis and tendon sheath infections.
4	Gangrene of a geographical portion of the foot such as toes, forefoot or heel.
5	Gangrene or necrosis of large portion of the foot requiring major limb amputation.

Wagner's ….

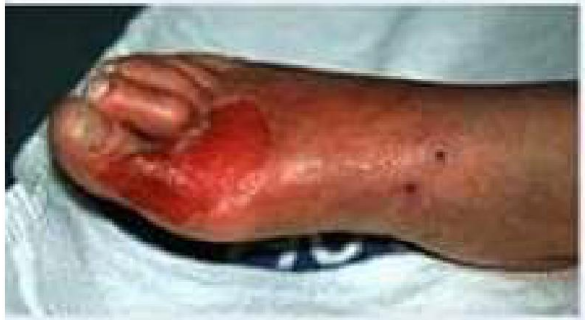
Grade 0

No ulcer in a high-risk foot



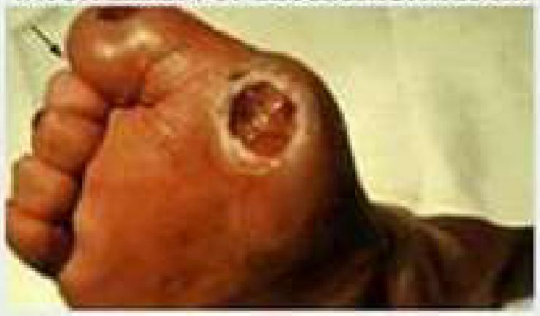
Grade 1

Superficial ulcer involving the full skin thickness but not underlying tissues



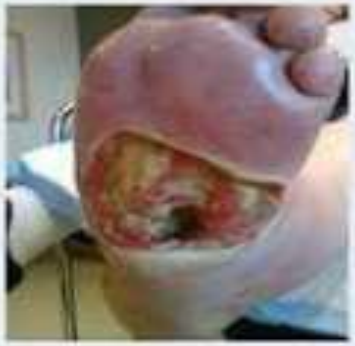
Grade 2

Deep ulcer, penetrating down to ligaments and muscle, but no bone involvement or abscess formation



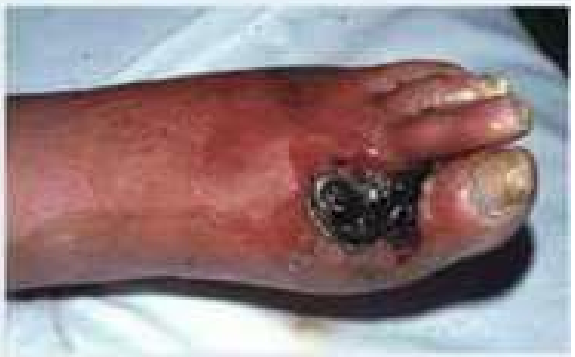
Grade 3

Deep ulcer with cellulitis or abscess formation, often with osteomyelitis



Grade 4

Localized gangrene



Grade 5

Extensive gangrene involving the whole foot

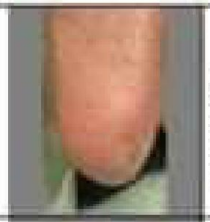
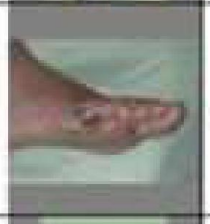
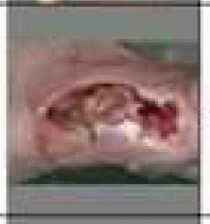
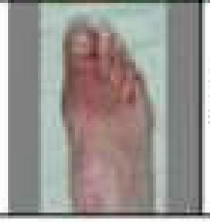
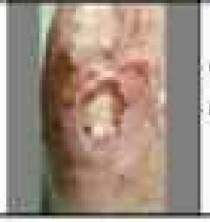
Classification

University of Texas

Table 2.3 'The University of Texas classification system for diabetic foot wounds'

Stage	Grade 0	1	2	3
A	Pre- or post-ulcerative lesion completely epithelialized	Superficial wound not involving tendon, capsule or bone	Wound penetrating to tendon or capsule	Wound penetrating to bone or joint
B	With infection	With infection	With infection	With infection
C	With ischemia	With ischemia	With ischemia	With ischemia
D	With infection and ischemia	With infection and ischemia	With infection and ischemia	With infection and ischemia

The University of Texas Classification System for Diabetic Foot Wounds

Stage/Comorbidities "Is the wound infected, ischemic or both?"	Grade/Depth "How deep is the wound?" 0	1	2	3
A	Pre- or post ulcerative lesion completely epithelialised 	Superficial wound not involving tendon, capsule or bone 	Wound penetrating to tendon or capsule 	Wound penetrating to bone or joint 
B	With infection 	With infection 	With infection 	With infection 
C	With ischemia 	With ischemia 	With ischemia 	With ischemia 
D	With infection and ischemia 	With infection and ischemia 	With infection and ischemia 	With infection and ischemia 

Clinical presentation

- Soft tissue infections (superficial to deep tissue infection e.g. cellulitis, necrotizing fasciitis, etc.)
- Osteomyelitis (bone infection)
- Septic arthritis (joint infection)
- Gangrene (dry or wet)
- Chronic non-healing ulcer
- Combination of more than one of the above mentioned condition

Assessment

- History
- Examination

Assessment …

- **History**
  - Diabetic history
  - Previous ulcer or amputation
  - Symptoms of peripheral neuropathy
  - Symptoms of peripheral vascular/ischemic problem
  - Contributing factors
  - Other complications of diabetes (eyes, kidney, heart etc).
  - Current ulcer

Assessment …

- **Examination**
  - Previous amputation/ulcer
  - Deformity and footwear
  - Inspect web spaces - signs of infection or wound
  - Hypercallosity or nail deformity or paronychia
  - Present of peripheral neuropathy with tuning folks, also mono filament and position sense.
  - Peripheral pulses - peripheral vascular disease
  - Ankle-brachial index (ABSI)
  - Other relevant systems (renal, eye, heart etc)

Investigations

- Blood Sugar / long term control - RBS , FBS, Glycated HB
- Wound Swab, Tissue biopsy for M/C/S
- Doppler / Duplex USS
- X- rays
- Angiography
- Others: U, E & Cr, CXR, ECG

Management

Objectives:

1. Control infection
2. Ulcer/wound management
3. Prevent amputation
4. Maintain pre-morbid foot/lower extremity function as much as possible
5. Prevent recurrent ulcer

Management …

VIPS

- **V**= **V**ascular supply is adequate
- **I**= **I**nfection control is achieved
- **P**= **P**ressure offloading
- **S**= **S**harp\surgical debridement

Management …

➢ **Operative**

- Debridement
  - Indications : grade 3 or greater ulcers, Infected wound
  - The benefits are:
    - removal of necrotic\sloughy tissue and callus
    - drainage of secretions and pus
    - stimulating healing, and reducing pressure

Management …

➢ **Operative …**

- Surgical Mgt to reduce or remove bony prominences and/or improve soft tissue cover
  - A structurally deformed foot may give rise to high-pressure areas causing ulcers that do not heal with off loading treatment or therapeutic footwear.
  - Examples are correction of hammertoes, excision of exostoses, bunions and tendo-achilles lengthening

Management …

➢ **Non-operative**

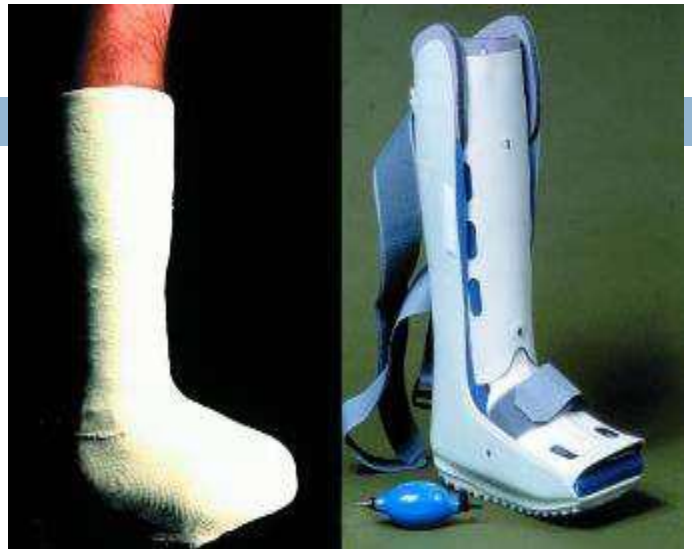
- Wound care
  - provide moist environment
  - absorb exudate
  - act as a barrier
  - off-load pressure at ulcer
- Reduction of plantar pressure (offloading)
  - Involves reducing the pressure to the diabetic foot ulcer, thus reducing the trauma to the ulcer and allowing it to heal.

Management …

- Reduction of plantar pressure (offloading) …
- Methods: (pics please)
  - Total non-weight bearing.
  - Total contact cast (GOLD STANDARD)
  - Foot cast or boots
  - Removable walking braces with rocker bottom soles
  - Total contact orthoses – custom walking braces
  - Patellar tendon bearing braces
  - Half shoe or wedge shoes

Management …

- Reduction of plantar …
  - Healing sandal - surgical shoe with molded plastizote insole
  - Accommodative dressing: felt, foam, felted-foam, etc
  - Shoe cutouts (toe box, medial, lateral or dorsal pressure points).
  - Assistive devices: crutches, walker, cane, etc.



Management …

- **Contraindications of total contact cast:**
  - Ischemia
  - Infected DFUs
  - Osteomyelitis

Management …

- **Others**
  - Infection
  - Vascular management of ischemia
  - Medical management of comorbids
  - Reduce risk of recurrence

Management …

- Infection control and local wound care (Antibiotics & wound dressing)
- **Local signs of wound infection**
  - Granulation tissue becomes increasingly friable
  - Base of ulcer becomes moist & changes from healthy pink granulations to yellowish/grey tissue
  - Discharge changes from clear to purulent
  - Unpleasant odour is present

General principles of bacterial management

- At initial presentation of infection it is important to assess its severity, take appropriate cultures and consider need for surgical procedures.
- Optimal specimens for culture should be taken after initial cleansing and debridement of necrotic material.
- Patients with severe infection require empiric broad-spectrum antibiotic therapy, pending culture results. Those with mild (and many with moderate) infection can be treated with a more focused and narrow-spectrum antibiotic.
- Patients with diabetes have immunological disturbances; therefore even bacteria regarded as skin commensals can cause severe tissue damage and should be regarded as pathogens when isolated from correctly obtained tissue specimens.

General principles of bacterial management

- Gram-negative bacteria, especially when isolated from an ulcer swab, are often colonizing organisms that do not require targeted therapy unless the person is at risk for infection with those organisms.
- Blood cultures should be sent if fever and systemic toxicity are present.
- Even with appropriate treatment, the wound should be inspected regularly for early signs of infection or spreading infection.

General principles of bacterial management

- Clinical microbiologists/infectious diseases specialists have a crucial role; laboratory results should be used in combination with the clinical presentation and history to guide antibiotic selection.
- Timely surgical intervention is crucial for deep abscesses, necrotic tissue and for some bone infections.

Bacterial management ….

- **Duration of antibiotic treatment**
  - 1-2 weeks course for mild to moderate infections
  - more than 2 weeks for more serious infections
  - For osteomyelitis, if infected bone is not removed, antibiotics are given for 6 - 8weeks, depending on culture results
  - If all infected bone is removed, a shorter course (1-2 weeks) of antibiotics, as for soft tissue infection, maybe adequate.

ANTIBIOTIC TREATMENT FOR TREATING DIABETIC FOOT INFECTION[185]

Severity of infection	Recommended	Alternatives
Mild / Moderate (Oral for entire course)	- Cephalexin (500 mg qid) - Amoxcillin/Clavulanate (875/125 mg bid) - Clindamycin (300 mg tid)	- Ofloxacin (400 mg bid) ± Clindamycin (300 mg tid) - Cotrimoxazole (2 DS bid)
Moderate / Severe (IV until stable, then switch to oral)	- Ampicillin / Sublactam (3.0g tid) - Clindamycin (450 mg qid) + Ciprofloxacin (750 mg bid)	- Trovofloxacin (500 mg qid) - Metrodinazole (500 mg qid) + Ceftazidime (2 gm tid)
Life threatening (Prolonged IV)	- Imipenem / Cilastin (500 mg qid)- - Clindamycin (900 mg tid) +Tobramycin ($5.1\ mg\ kg^{-1}\ d^{-1}$) + Ampicillin (500 mg qid)	- Vancomycin (1 gm bid) + Aztreonam (2.0 gm tid) + Metronidazole ($7.5\ mg\ kg^{-1}$ qid)

Prevention of diabetic foot ulcer (DFU)

Diabetic foot-care

- ✓ Foot inspection - minimally once a day
- ✓ Use lukewarm, not hot water to wash feet
- ✓ Use gentle soap to bath/wash feet
- ✓ Apply moisturizer to avoid dry feet
- ✓ Proper nail cutting, avoid cutting too close
- ✓ Wear clean, dry socks (NEVER use heating pad or hot water bottle) to keep foot warm
- ✓ Avoid walk barefooted.

Diabetic foot-care …

- ✓ Wear comfortable well fitting shoe (not too tight or too loose).
- ✓ Shake out shoes and feel the inside before wearing
- ✓ Good diabetic control
- ✓ Stop smoking
- ✓ Periodic foot examination by relevant personals
- ✓ Keep the blood flowing to feet (elevate, wiggers toes, moving ankle) , avoid cross-leg

References

1) Harrison's Principles of Internal Medicine; 19th edition , 2015
2) Williams Textbook of Endocrinology; 14th edition
3) Brunner & suddarths textbook of medical surgical nursing; 12th edition
4) Google

THANK YOU !!

For any information, you can contact me at: agazhe1049@gmail.com