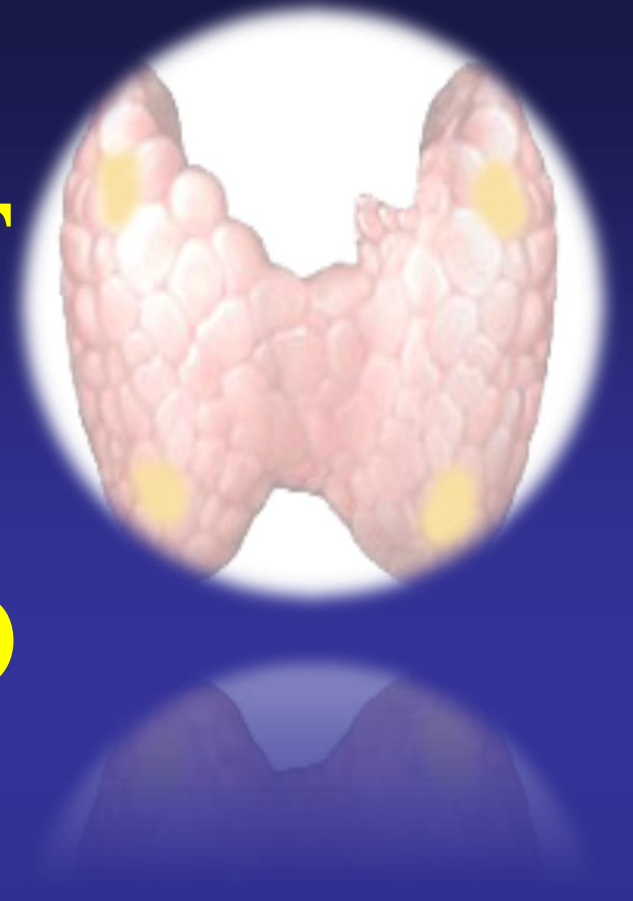


DISORDERS OF THE PARATHYROID GLANDS



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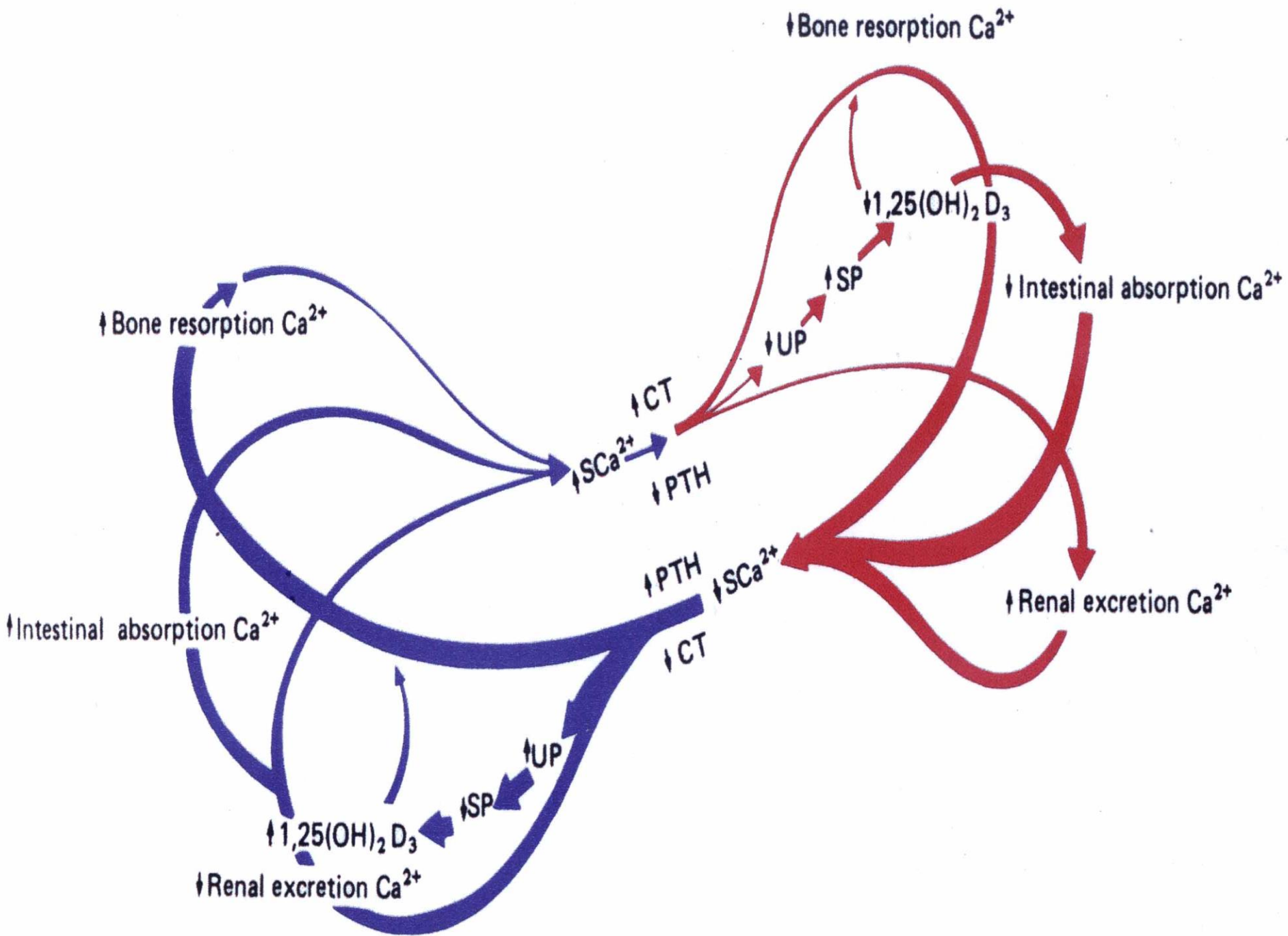
Consultant Endocrinologist

Disorders of the Parathyroid Glands

Maintenance of calcium, phosphate and magnesium homeostasis is under the influence of two polypeptide hormones; parathyroid hormone(PTH), and calcitonin (CT), as well as a sterol hormone, 1,25 dihydro-cholecalciferol ($1,25 (\text{OH})_2\text{D}_3$)

Disorders of the Parathyroid Glands

These hormones regulate the flow of minerals in and out of the extracellular fluid compartments through their actions on **intestine, kidneys, and bones.**



Disorders of the Parathyroid Glands

The PTH acts directly on the bones and kidneys and indirectly on the intestine through its effect on the synthesis of $1,25(\text{OH})_2\text{D}_3$.

Its production is regulated by the concentration of serum ionized calcium.

Lowering of the serum calcium levels will induce an increased rate of parathyroid hormone secretion

Disorders of the Parathyroid Glands

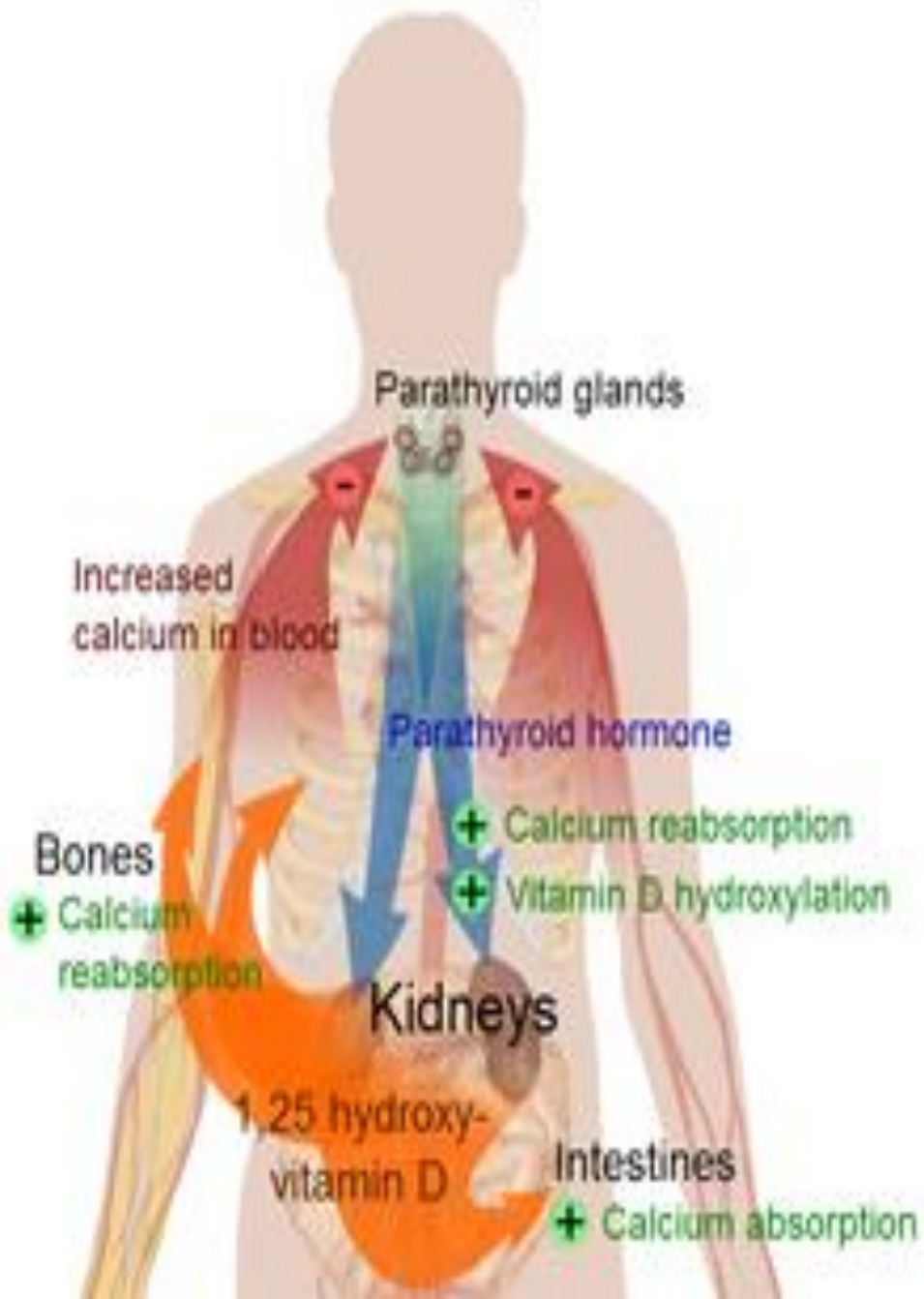
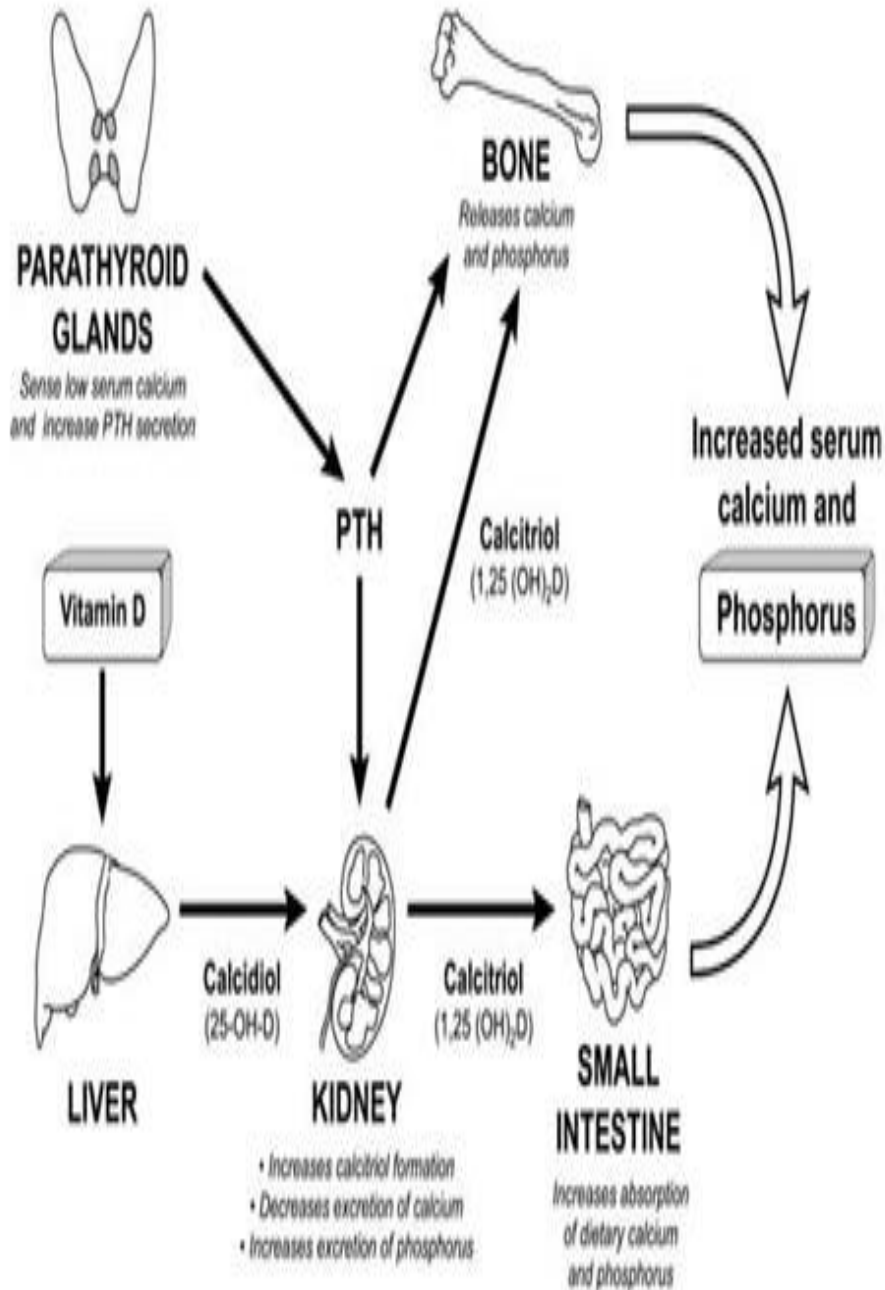
Calcitonin is released by the “C” cells (parafollicular cells in the thyroid gland) in response to small increases in plasma ionic calcium.

It acts on the kidney and bones to restore the level of calcium to just below a normal set point which in turn inhibits secretion of the hormone.

Disorders of the Parathyroid Glands

Calcitonin is therefore the physiological antagonist of PTH. The two hormones act in concert to maintain normal concentration of calcium ion in the extracellular fluid.

Calcium regulation



Disorders of the Parathyroid Function

Hyperparathyroidism

Primary hyperparathyroidism is due to **excessive production of PTH** by one or more of hyper functioning parathyroid glands.

This leads to **hypercalcemia** which fails to inhibit the gland activity in the normal manner.

Disorders of the Parathyroid Function

Hyperparathyroidism

The cause of primary hyperparathyroidism is unknown.

A genetic factor may be involved.

The clonal origin of most parathyroid adenomas suggests a defect at the level of the gene controlling the regulation and/or expression of parathyroid hormone.

Disorders of the Parathyroid Function

Hyperparathyroidism

The incidence of the disease increases dramatically after the age of 50 and it is 2-4 folds more common in women.

A single adenoma occurs in about 80% of patients with primary hyperparathyroidism.

Four glands hyperplasia account for 15-20% of cases.

A parathyroid carcinoma could be the etiology in a rare incidence of less than 1%.

Disorders of the Parathyroid Function

Clinical Features:

The two major sites of potential complications are the **bones** and the **kidneys**.

The kidneys may have renal stones (**nephrolithiasis**) or diffuse deposition of calcium-phosphate complexes in the parachyma (**nephrocalcinosis**).

Now a days such complications are seen less commonly and around 20% of patients or less show such complications.

Disorders of the Parathyroid Function

Clinical Features:

In skeleton a condition called **osteitis fibrosa cystica** could occur with sub-periosteal resorption of the distal phalanges, distal tapering of the clavicles, a “salt and pepper” appearance of the skull as well as bone cysts and brown tumors of the long bones.

Such overt bone disease even though typical of primary hyperparathyroidism is very rarely encountered.

Disorders of the Parathyroid Function

Clinical Features:

Now a days almost 90% of diagnosed cases in the developed countries are picked up by **routine screening** for calcium level using the new automated machines.

Disorders of the Parathyroid Function

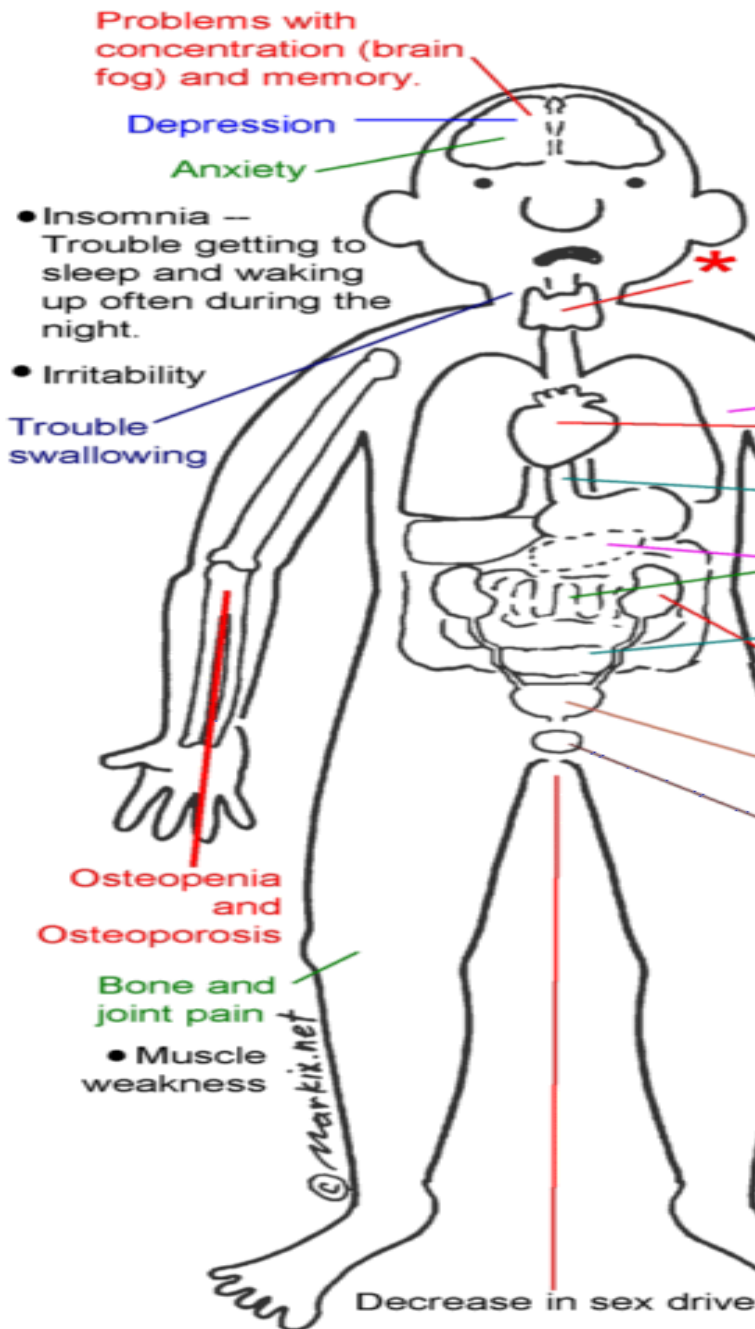
Clinical Features:

Other symptoms include muscle weakness, easy fatigability, peptic ulcer disease, pancreatitis, hypertension, gout and pseudo-gout as well as anemia and depression have been associated with primary hyperparathyroidism.

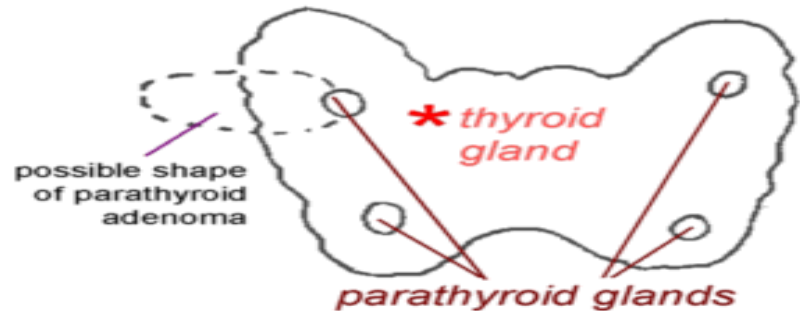
Color me

and learn all about Hyperparathyroidism.

When parathyroid glands are overactive your bones release calcium into the blood stream. High levels of calcium on blood tests (serum and ionized) are never normal. On this page you'll find just some of the symptoms associated with high calcium (hypercalcemia) and hyperparathyroidism.



- Don't feel well, but in a hard to explain kind of not well.
- Increased risk of breast cancer
- Heart palpitations (arrhythmias)
- Lack of appetite
- Heartburn, GERD
- Abdominal discomfort
- Pancreatitis
- Increased risk of colon cancer
- Low vitamin D
- Feeling tired during the day and frequently feeling like you need a nap.
- Loss of energy and a loss of interest in things you used to enjoy.
- Kidney stones
- Excessive urination
- Increased risk of prostate cancer



(Usually there are four glands located in the back side of the thyroid gland. Sometimes, however, the glands can be found in another location in the neck or even the chest area.)

These are just a few of the symptoms you can get with parathyroid disease. Please note that symptoms vary from person to person. You may have only one or all of them or even ones not listed here. Please list any additional symptoms that you want your doctor to know about on the back of this page.

Differential Diagnosis

Causes of Hyper-calcemia

Parathyroid - related

1. Primary hyperparathyroidism
 - A. Solitary adenomas
 - B. Multiple endocrine neoplasia
2. Lithium therapy
3. Familial Hypocalciuric Hypercalcemia

Vitamin D – related

1. Vitamin D intoxication
2. ↑ 1,25(OH)₂D; sarcoidosis and other granulomatous diseases
3. Idiopathic hypercalcemia of infancy

Differential Diagnosis

Causes of Hyper-calcemia

Malignancy - related

1. Solid tumor with metastases (breast)
2. Solid tumor with humoral mediation of hypercalcemia (lung kidney)
3. Hematologic malignancies (multiple myeloma, lymphoma, leukemia)

Associated with high bone turnover

1. Hyperthyroidism
2. Immobilization
3. Thiazides
4. ↑ Vitamin A intoxication

Associated with Renal Failure:

1. Severe secondary hyperparathyroidism
2. Aluminum intoxication
3. Milk alkali syndrome

Diagnosis

The presence of established hypercalcaemia in more than one serum measurement accompanied by elevated immunoreactive PTH is characteristic (iPTH)

Diagnosis

Serum **phosphate is usually low** but may be normal.

Hypercalcemia is common and blood alkaline phosphatase (of bone origin) is raised.

Other Diagnostic tests

Radiograph:

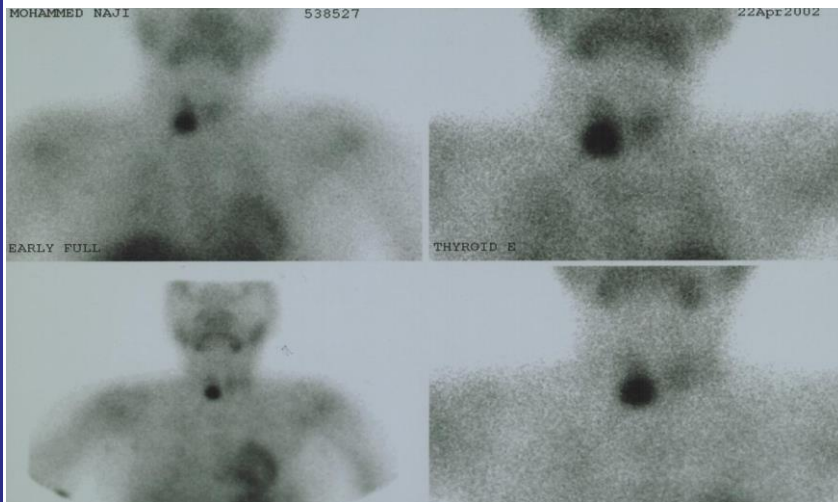
Plain X-ray of hands can be diagnostic showing **sub periosteal bone resorption** usually on the radial surface of the distal phalanx with distal phalangeal tufting as well as **cysts formation** and generalized **osteopenia**.

Other Diagnostic tests

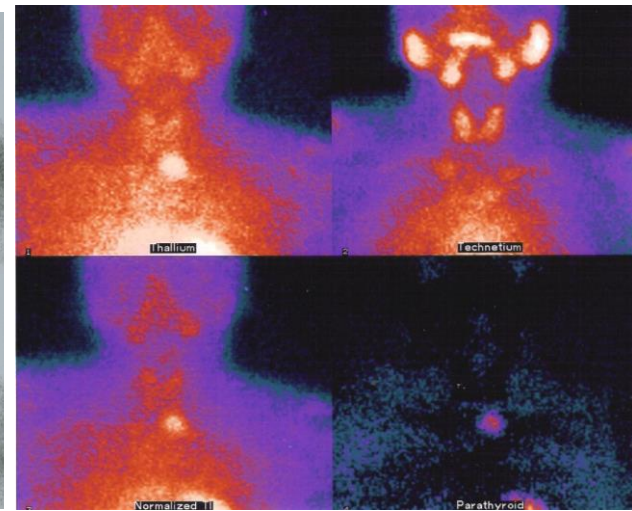
Pre-operative localization of the abnormal parathyroid gland(s):

- Ultrasonography
- MRI
- CT
- Thallium 201 – Technetium 99m scan
(subtraction study)

Parathyroid Scan



Dual phase MIBI Scan



Tc-Tl Subtraction Scan

Treatment

A large proportion of patients have *biochemical hyperparathyroidism* but with prolonged follow up they progress to overt clinical presentation.

Resection of the parathyroid lesion is curative with recurrences observed mainly in the multiple glandular disease.

Medical Treatment of the hypercalcaemia

In acute severe forms the main stay of therapy is adequate **hydration** with saline and **forced diuresis** by diuretics to increase the urinary excretion of calcium rapidly along with sodium and prevent its reabsorption by the renal tubules.

Other agents

- Glucocostroids
 - In hypercalcaemia associated the hematological malignant neoplasms
- Mythramycin
 - A toxic antibiotics which inhibit bone resorption and is used in hematological and solid neoplasms causing hypercalcaemia.

Other agents

- Calcitonin
 - Also inhibit osteoclast activity and prevent bone resorption
- Bisphosphonates
 - They are given intravenously or orally to prevent bone resorption.

Other agents

- Phosphate
 - Oral phosphate can be used as an antihypercalcaemic agent and is commonly used as a temporary measure during diagnostic workup.
- Estrogen
 - It also decrease bone resorption and can be given to postmenopausal women with primary hyperparathyroidism using medical therapy

Surgery

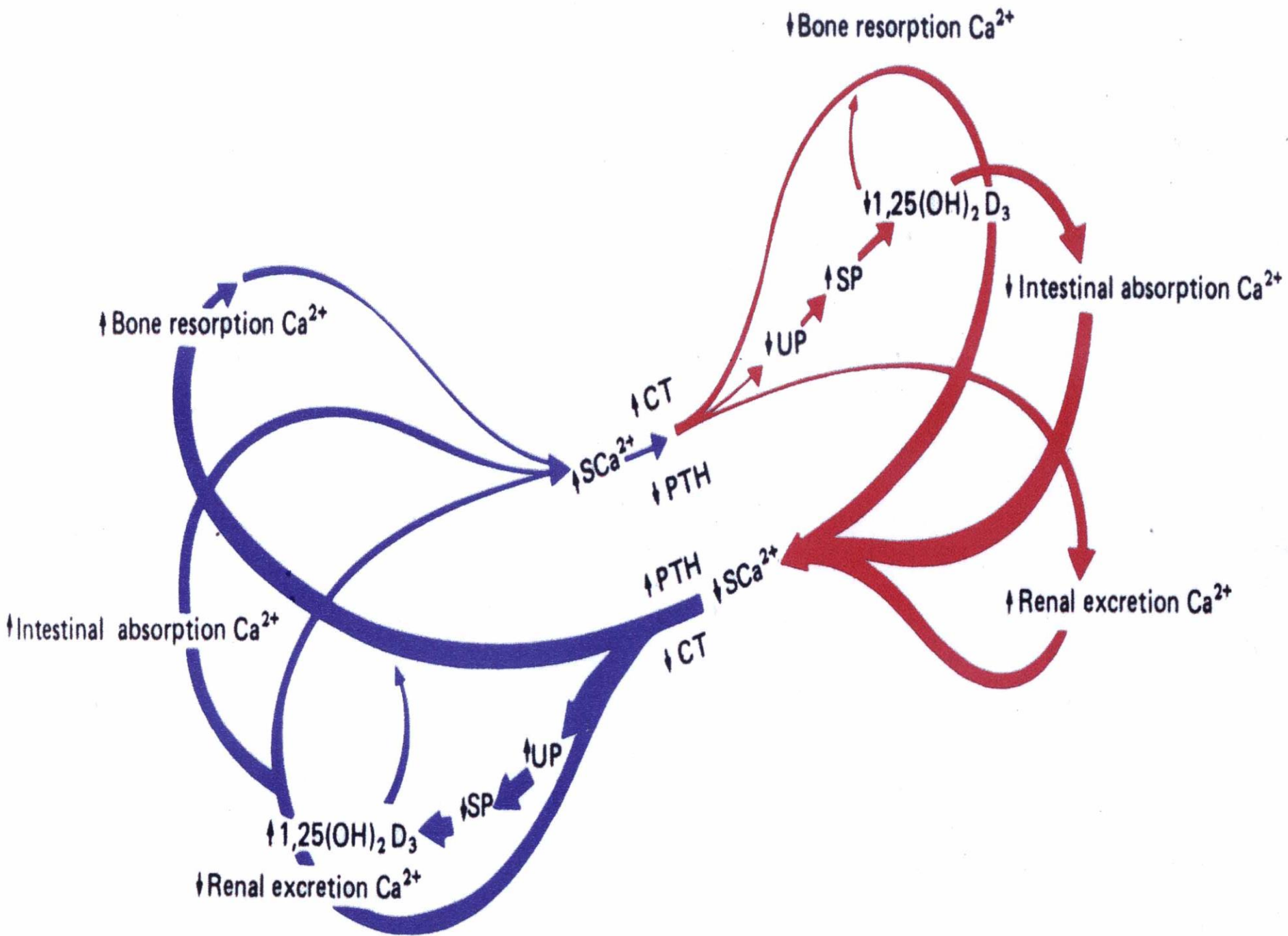
Surgical treatment should be considered in all cases with established diagnosis of primary hyperparathyroidism.

During surgery the surgeon identifies all four parathyroid glands (using biopsy if necessary) followed by the removal of enlarged parathyroid or 3 ½ glands in multiple glandular disease.

Secondary hyperparathyroidism

An increase in PTH secretion which is adaptive and unrelated to intrinsic disease of the parathyroid glands is called secondary hyperparathyroidism.

This is due to chronic stimulation of the parathyroid glands by a chronic decrease in the ionic calcium level in the blood



Hypo-parathyroidism

Deficient secretion of PTH which manifests itself biochemically by hypocalcaemia, hyperphosphatemia diminished or absent circulating iPTH and clinically the symptoms of neuromuscular hyperactivity.

Major causes of chronic hypocalcemia other than hypoparathyroidism

- Deficiency of vitamin D or calcium
- Decreased intestinal absorption of vitamin D or calcium due to primary small bowel disease, short bowel syndrome, and post-gastrectomy syndrome.
- Drugs that cause rickets or osteomalacia such as phenytoin, phenobarbital, cholestyramine, and laxative.

Major causes of chronic hypocalcemia other than parathyroprival hypoparathyroidism

- States of tissue resistance to vitamin D
- Excessive intake of inorganic phosphate compounds
- Pseudohypoparathyroidism
- Severe hypomagnesemia
- Chronic renal failure

Hypoparathyroidism

Causes:

- **Surgical hypoparathyroidism**

The commonest

After anterior neck exploration for thyroidectomy, abnormal parathyroid gland removal, excision of a neck lesion.

It could be due to the removal of the parathyroid glands or due to interruption of blood supply to the glands.

Hypoparathyroidism

Causes:

- **Idiopathic hypoparathyroidism**
 - A form occurring at an early age (genetic origin) with autosomal recessive mode of transmission “multiple endocrine deficiency – autoimmune-candidiasis (MEDAC) syndrome”
 - “Juvenile familial endocrinopathy”
 - “Hypoparathyroidism – Addison's disease – mucocutaneous candidiasis (HAM) syndrome”

Hypoparathyroidism

Causes:

- **Idiopathic hypoparathyroidism**
 - Circulating antibodies for the parathyroid glands and the adrenals are frequently present.
 - Other associated disease:
 - Pernicious anemia
 - Ovarian failure
 - Autoimmune thyroiditis
 - Diabetes mellitus

Hypoparathyroidism

Causes:

- **Idiopathic hypoparathyroidism**
 - The late onset form occurs sporadically without circulating glandular autoantibodies.
- **Functional hypoparathyroidism**
 - In patients who has chronic **hypomagnesaemia** of various causes.
 - Magnesium is necessary for the PTH release from the glands and also for the peripheral action of the PTH.

Hypoparathyroidism

Clinical Features:

A. Neuromuscular

- The **rate of decrease in serum calcium** is the major determinant for the development of neuromuscular complications.
- When nerves are exposed to low levels of calcium they show abnormal neuronal function which may include decrease threshold of excitation, repetitive response to a single stimulus and rarely continuous activity.

Hypoparathyroidism

Clinical Features:

A. Neuromuscular

- Paresthesia
- Tetany
- Hyperventilation
- Adrenergic symptoms
- Convulsion (More common in young people and it can take the form of either generalized tetany followed by prolonged tonic spasms or the typical epileptiform seizures.
- Signs of latent tetany
 - Chevostek sign
 - Trousseau sign
 - Extraparalytic signs (due to basal ganglia calcification)

Hypoparathyroidism

Clinical Features:

B. Other clinical manifestation

1. Posterior-lenticular **cataract**

2. **Cardiac** manifestation:

- Prolonged QT interval in the ECG
- Resistance to digitalis
- Hypotension
- Refractory heart failure with cardiomegally can occur

Hypoparathyroidism

Clinical Features:

B. Other clinical manifestation

3. **Dental** Manifestation

Abnormal enamel formation with delayed or absent dental eruption and defective dental root formation.

4. **Malabsorption** syndrome

Presumably secondary to decreased calcium level and may lead to steatorrhoea with long standing untreated disease.

Hypoparathyroidism

Diagnosis:

In the absence of renal failure the presence of **hypocalcaemia with hyperphosphatemia** is virtually diagnostic of hypoparathyroidism.

Undetectable serum iPTH confirms the diagnosis or it can be detectable if the assay is very sensitive.

Hypoparathyroidism

Treatment:

The mainstay of treatment is a combination of oral calcium with pharmacological doses of vitamin D or its potent analogues.

Phosphate restriction in diet may also be useful with or without aluminum hydroxide gel to lower serum phosphate level.

Emergency Treatment for Hypocalcaemic

Tetany:

Calcium should be given parenterally till adequate serum calcium level is obtained and then vitamin D supplementation with oral calcium should be initiated.

*METABOLIC
BONE DISEASES*

Bone has three major functions:

1. Provide **rigid support** to extremities and body cavities containing vital organs.
2. Provide **efficient levers** and sites of attachment of muscles which are all crucial to locomotion.
3. Provide a **large reservoir of ions** such as calcium, phosphorus, magnesium and sodium which are critical for life and can be mobilized when the external environment fails to provide them

Types of Bone

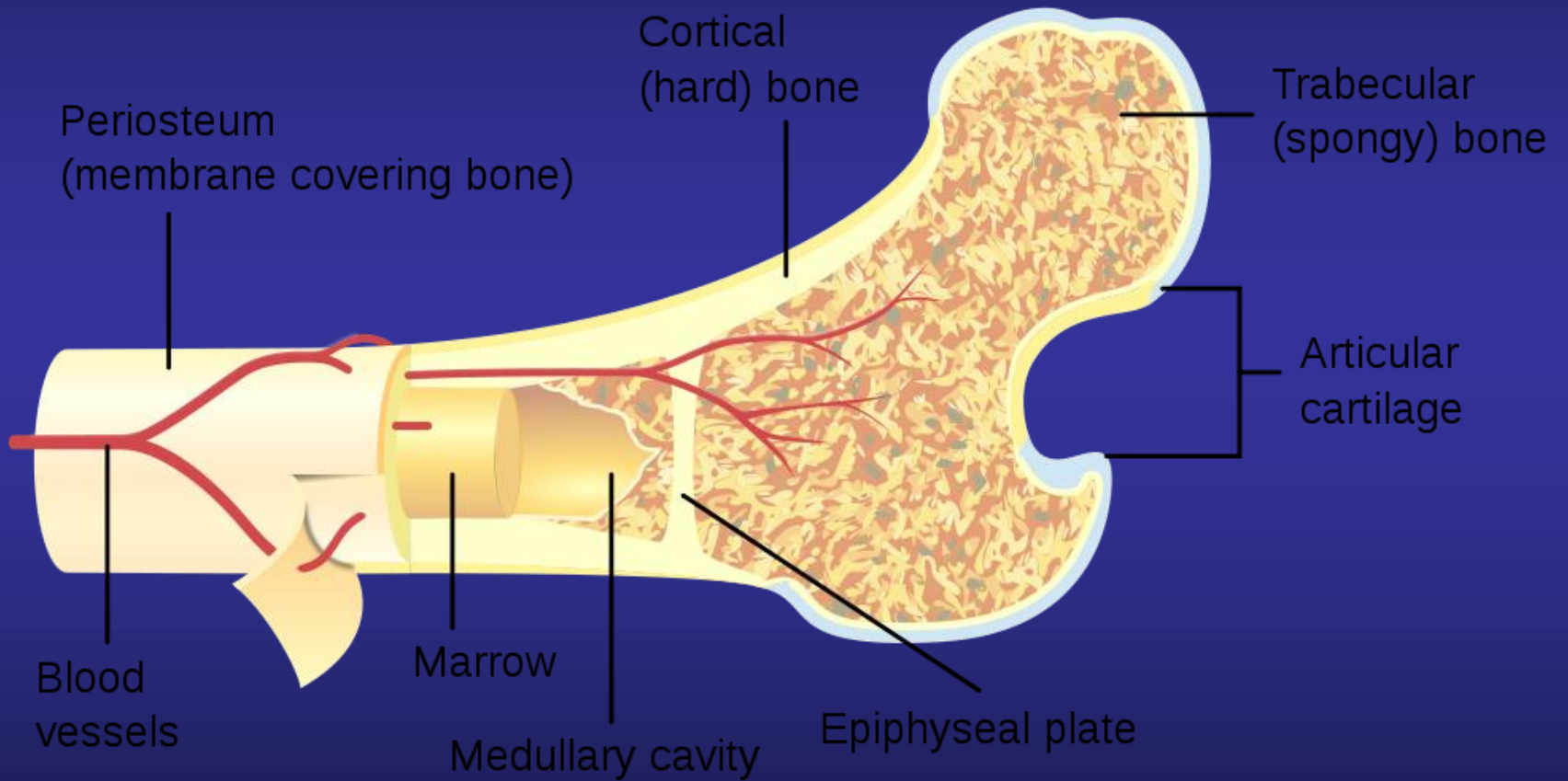
I. Cortical Bone:

The compact bone of Haversian systems such as in the shaft of long bones.

II. Trabecular Bone:

The lattice – like network of bone found in the vertebrae and the ends of long bones.

The difference pattern of bone loss affecting trabecular and cortical bone results in two different fracture syndrome.



Disorders in which **cortical bone** is defective or scanty lead to **fractures of long bones** whereas disorders in which **trabecular bone** is defective or scanty lead to **vertebral fractures** and also may help in fractures of long bones because of the loss of reinforcement.

Bone is resorbed and formed continuously throughout life and these important processes are dependent upon three major types of bone cells.

I. Osteoblasts:

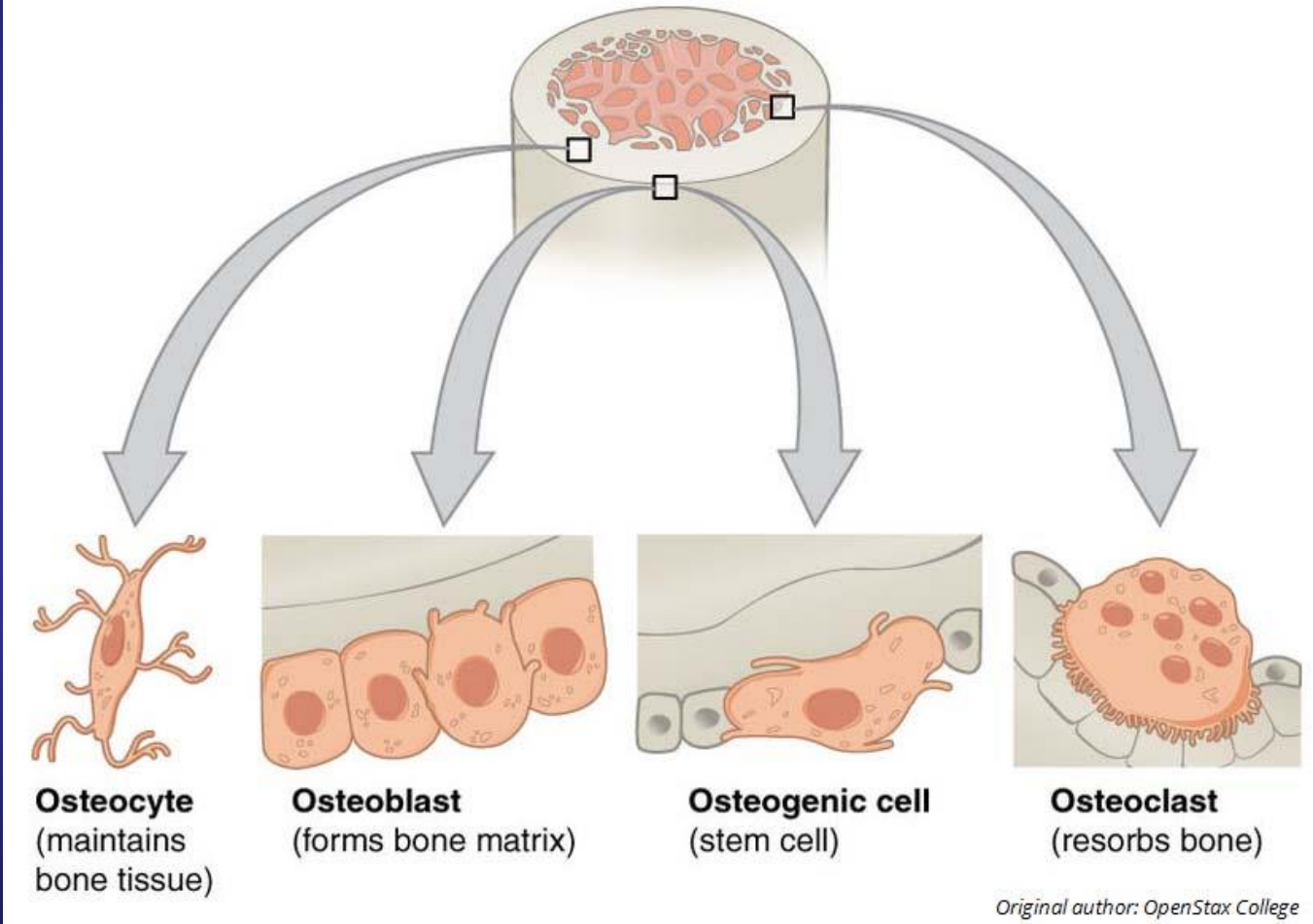
The **bone forming cells** which are actively involved in the synthesis of the matrix component of bone (primarily collagen) and probably facilitate the movement of minerals ions between extracellular fluids and bone surfaces.

II. Osteocytes:

The are believed to act as a cellular syncytium that permits translocation of mineral in and out of regions of bone removed from surfaces, as well as **signaling between different bone cells**.

III. Osteoclasts:

The **bone resorption cells**.



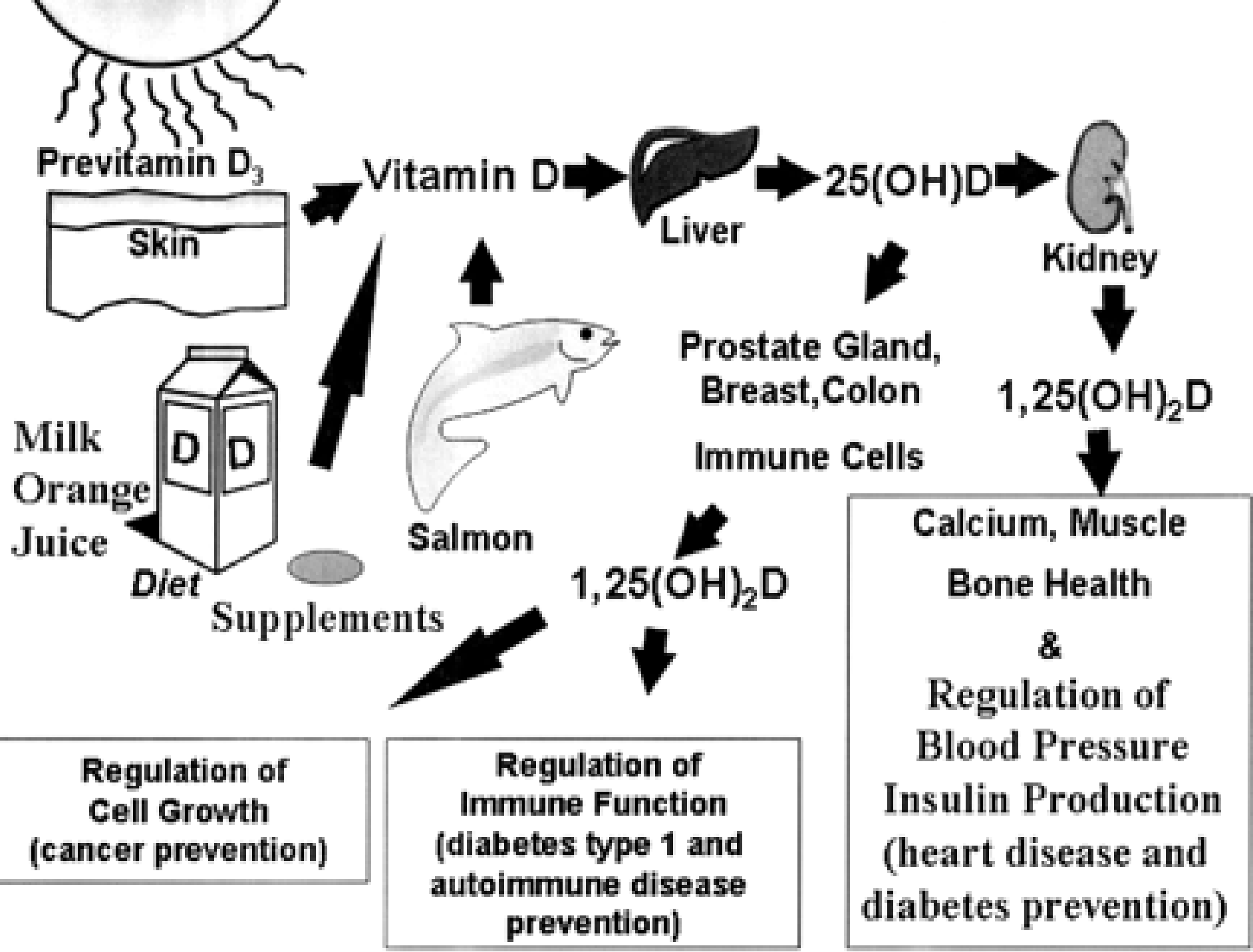
Osteomalacia

Failure of organic matrix (osteoid) of bone to mineralize normally.

A number of factors are critical for normal bone mineralization. An absence or a defect in any one of them may lead to osteomalacia, the most common biochemical causes are a decrease in the product of concentrations of calcium and phosphate in the extra-cellular fluid so that the supply of minerals to bone forming surfaces is inadequate.

Osteomalacia

Other causes include abnormal or defective collagen production and a decrease in the PH at sites of mineralization.



Etiology of Osteomalacia

Vitamin D deficiency:

1. **Inadequate sunlight exposure** without dietary supplementation.
 - House- or institution bound people.
 - Atmosphere smog.
 - Long term residence in far northern & far southern latitudes.
 - Excessive covering of body with clothing.
2. **Gastrointestinal diseases** that interrupts the normal enterohepatic recycling of vit. D & its metabolites, resulting in their fecal loss.
 - Chronic steatorrhea (pancreatic)
 - Malabsorption (gluten-sensitive enteropathy)
 - Surgical resection of large parts of intestine.
 - Formation of biliary fistulas.

Etiology of Osteomalacia

Vitamin D deficiency:

3. Impaired synthesis of 1,25(OH)₂D₃ by the kidney.

- Nephron loss, as occurs in chronic kidney disease
- Functional impairment of 1,25(OH)₂D₃ hydroxylase (eg. In hypoparathyroidism)
- Congenital absence of 1,25(OH)₂D₃ hydroxylase (vit. D-dependency rickets type I).
- Suppression of 1,25(OH)₂D₃ production by endogenously produced substance (cancer).

4. Target cell resistance to 1,25(OH)₂D₃

e.g. absent, or diminished number of 1,25(OH)₂D₃ receptors, as in vit.D-dependency rickets type II.

Etiology of Osteomalacia

Phosphate deficiency:

Dietary

- Low intake of phosphate.
- Excessive ingestion of aluminum hydroxide.

Impaired renal tubular reabsorption of phosphate

- X-linked hypophosphataemia.
- Adult-onset hypophosphataemia.
- Other acquired & hereditary renal tubular disorders associated with renal phosphate loss (Fanconi's syndrome, Wilson's disease).
- Tumor-associated hypophosphataemia

Etiology of Osteomalacia

Systemic Acidosis:

- Chronic renal failure
- Distal renal tubular acidosis
- Ureterosigmoidostomy
- Chronic acetazolamide & ammonium chloride administration

Drug induced Osteomalacia:

Laboratory & Radiological Findings

Patients with osteomalacia go through phases of developments characterized by unique changes in the *serum concentration of calcium, phosphate, PTH and vit D3* levels and the radio graphically assessed bone lesions.

Laboratory & Radiological Findings

The underlying defect leading to these changes is the decrease in the production of 1,25(OH)₂D₃ which is due to diminished availability of the major circulating metabolites of vit D 25OHD₃.

The decreased 1,25(OH)₂D₃ results in decreased intestinal calcium absorption, decreased bone resorption, hypocalcaemia, increased PTH secretion and hypo phosphataemia .

Laboratory & Radiological Findings

The **decreased Ca x Pho. Product** in serum is insufficient for the normal mineralization of bone and the **osteomalacic process** is initiated.

The **increased PTH** secretion and **hypo phosphataemia** occur at the expense of osseous demineralization caused by hyperparathyroidism.

Clinical Features

The clinical manifestations of osteomalacia in adults usually go unrecognized because of the **non-specific skeletal pain and muscular weakness**. Only when the disease is extensive, **deformities** occur with fractures of ribs, vertebrae and long bones.

Clinically patients with osteomalacia have a characteristic **waddling gait**, that is due to the **proximal muscle weakness and to the pain** and discomfort during movements of the limbs.

Some patients have severe **muscular hypotonia** and paradoxically **brisk deep tendon reflexes**.

Treatment

Patients with osteomalacia due to simple dietary deficiency of vit D or lack of exposure to sunlight will respond well to small daily doses of **vit D and calcium**.

Administration of oral doses of ergocalciferol(D2) or cholecalciferol (D3)(2000 IU daily) for several months will heal the bone disease and restores biochemical and hormonal values to normal in most cases.

1,25(OH)₂D₃ (calcitriol) has also been successful in the treatment of simple osteomalacia.

Treatment

It is important to administer calcium to provide adequate calcium for bone mineralization (1-2 gm of elemental calcium daily).

Serum ALP and PTH decrease slowly over several weeks but improvement in radiological appearances may take several months.

Other forms of osteomalacia may need different preparations and doses of treatment e.g., osteomalacia secondary to malabsorption may require huge doses of vit D (200,000 IU orally) because of the poor absorption of the drug or even I.V./I.M. vit D (40,000-80,000 IU).

Osteoporosis

**“THE SILENT
THIEF”**

Definition

Decrease in *bone mass* and *strength* associated with an increased tendency to *fractures*

Clinical Features

It is usually an asymptomatic disease until fractures occur. The first manifestation of reduced bone mass is usually a **wrist fracture** or a vertebral crush fracture caused by a small amount of force which produces severe localized pain.

Subsequent **vertebral fractures** may contribute to chronic back pain.

In well established osteoporosis dorsal Kyphosis and loss of height occurs.

Hip fractures with its fatal complications also occur commonly as osteoporosis become more severe.

Type I: Osteoporosis (Post Menopausal)

Fractures of bones composed mainly of Trabecular bone.

e.g., Distal Radius	-	Colle's fracture
Vertebra	-	Crush & Wedge fractures

Usually affects woman within 15 years of menopause.

Type II: Osteoporosis (Senile)

Fractures of bones composed of both cortical & Trabecular bone.

e.g., Hip - Femure neck fracture

Usually affects individual over age of 70 years.

Laboratory & Radiological Findings

ALP and PTH are within normal in patients with osteoporosis due to sex hormones deficiency and aging.

X-rays of skeleton do not show a decrease in osseous density until at least 30% of bone mass has been lost.

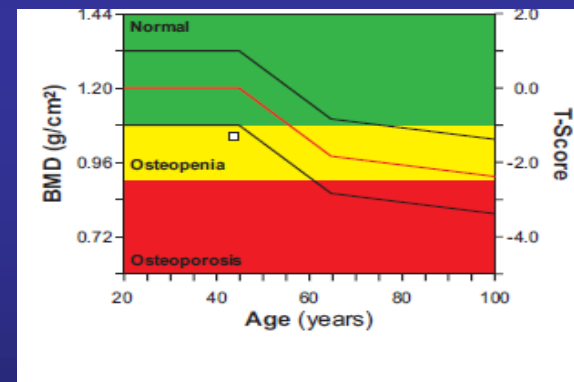
Assessment of bone mass available methods

- Single-Photon absorptiometry SPA
- Dual-Photon absorptiometry DPA
- Computed Tomography CT
- Dual-Energy X-ray Absorptiometry DEXA

Measure bone mass by the ability of the tissue to absorb the photons emitted from the radionuclide source or the X-ray tube.

Age related bone loss particularly trabecular bone in the spine begins in women before menopause.

Lumbar spine
Femoral neck



Bone densitometry scanner

WHO Osteoporosis criteria 1994

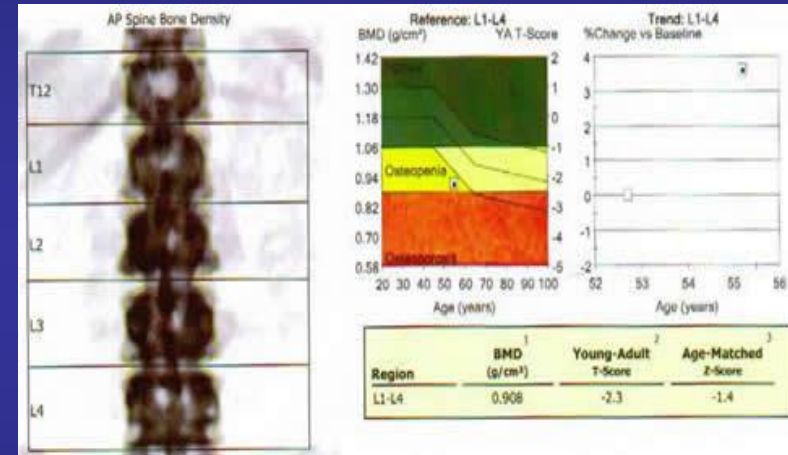
Definition based on BMD

Normal : greater than or equal to -1 SD

Osteopenia: BMD which lies between - 1 and -2.5 SD

Osteoporosis : less than or equal to - 2.5 SD

Severe osteoporosis :
osteoporosis with 1 or more
fragility fractures



It is appropriate to begin to look for risk factors that predispose a person to osteoporosis and develop a rational prevention program tailored to person's risk before the menopause.

e.g., Women with thin light frame, history of low calcium intake, decreased physical activity, high alcohol or caffeine consumption, smoking, family history of osteoporosis, history of prior menstrual disturbances or history of drug like antiepileptics or steroids are all high risk groups and in the presence of one or more of such risk factors measurement of BMD provides further information to the risk of fractures.

Strategy for Management of Osteoporosis

- Prevent Osteoporosis
- Detect and treat early to decrease further progression
- Limit disability and provide rehabilitation

Treatment

The Adolescent Female (Peak bone mass attainment)

“Senile Osteoporosis is a pediatric disease”.

- Adequate calcium intake of 1200 mg/day is recommended.
- Adequate sun exposure or vit D supplementation to ensure adequate level.
- A reasonable exercise program is recommended.
- ? Genetic influence on peak bone mass attainment.

Treatment

The Premenopausal Female (Maintenance of bone mass)

- A. Adequate calcium intake; 1000-1500 mg/day disease.
- B. Adequate sun exposure or vit D supplementation
- C. A reasonable exercise program is recommended, but not to the point of amenorrhea.
- D. Avoidance of osteopenia-producing conditions/medications/lifestyles:
 1. Smoking & excessive alcohol intake, excessive caffeine/protein intake.
 2. Amenorrhea/oligomenorrhea.
 3. Cortisone, excessive thyroid hormone replacement (?), loop diuretics, prolonged heparin exposure.

Treatment

The Immediately Postmenopausal Female
(Prevention of bone mass loss)

Consideration of estrogen replacement
therapy

**If intact uterus, consideration of
medroxy progesterone**

Treatment

The Immediately Postmenopausal Female (Prevention of bone mass loss)

Other modalities of therapy

1. Bisphosphonates
2. SERMS (Selective estrogen receptor modulators) e.g., Evista, Livial
3. Protelos (strontium ranelate)
4. Forteo (Teripratide)
5. Prolia (Denosumab)

Treatment

The elderly postmenopausal female with low bone mass but no compression fractures (Prevention of bone mass loss & restoration of bone mass previously lost)

- A. Adequate calcium intake: 1000-1500 mg/day
- B. Adequate supply of vit D (1000-2000IU)
- C. A reasonable exercise program with physical therapy instruction in para spinous muscle group strengthening exercise.
- D. Avoidance of osteopenia-producing conditions/medications/lifestyles:
 - 1. Smoking & excessive alcohol intake, excessive caffeine/protein intake.
 - 2. Cortisone, excessive thyroid hormone replacement (?),

Treatment

Other modalities of therapy

1. Bisphosphonates
2. SERMS (Selective estrogen receptor modulators) e.g., Evista, Livial
3. Protelos (strontium ranelate)
4. Forteo (Teripratide)
5. Prolia (Denosumab)

Treatment

The elderly (age>62) postmenopausal female with fractures (spine &/hip)
(Prevention of further fractures.)

Treatment

The male or female with corticosteroid induced osteopenia

(Prevention of bone mass loss & restoration of bone mass previously lost)

- A. Bone mass measurement if possible to identify bone mass loss
- B. Lowest possible dose of corticosteroids: ?
Deflazacort
- C. A program of reasonable calcium intake (1000-1500 mgm daily, depending upon urinary calcium), exercise, & avoidance of other osteopenia-producing situations is indicated.

Treatment

The male or female with corticosteroid induced osteopenia

(Prevention of bone mass loss & restoration of bone mass previously lost)

Adequate intake of vit D (1000-2000 IU)

Other modalities of therapy

1. Estrogen (Females), testosterone (males)
2. Bisphosphonates
3. Forteo

**Education is not the learning
of facts, but the training
of the mind to think.**

~Albert Einstein

