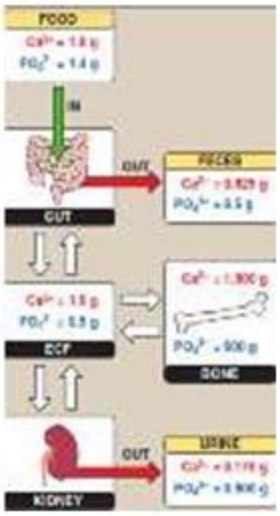
Al muthanna University **Pharmacy college**

Lecturer Dr. Zainab sattar Ali **Theo.** ***physiology lec.6***

Calcium:



Plasma calcium, normally at a concentration of around 10 mg/dL, is partly bound to protein and partly diffusible. It is the free, ionized calcium (Ca^{2+}) in the body fluids that is a vital second messenger and is necessary for blood coagulation, muscle contraction, and nerve function. Large quantities of Ca^{2} and PO_4^{3} are stored in bone (think of bone as a Ca^{2} bank depository). This large Ca^{2} source can be mobilized (withdrawn) during bone resorption in a process mediated by osteoclasts. Alternately, Ca^{2} can be actively stored (deposited) within bone during bone deposition in a process mediated by osteoblasts. Besides storage and release, Ca^{2} balance is maintained by Ca^{2} excretion from the kidney and Ca^{2} intake by the GI system. PO_4^{3} intake, excretion, and storage sites are similar to those of Ca^{2}.

The free, ionized calcium Ca^{2+} exerts a net excitatory effect on nerve and muscle cells. A decrease in extracellular Ca caused hypocalcemic tetany, characterized by extensive spasms of skeletal muscle, involving especially muscles of the extremities and the larynx. Laryngospasm can become so severe that the airway is obstructed and fatal asphyxia is produced. Other electrolytes and pH also affect free Ca. For example, symptoms of tetany appear at higher calcium levels if the patient hyperventilates, thereby increasing plasma pH. Plasma proteins are more ionized when the pH is high, providing more protein anions to bind with Ca^{2+}.

The calcium in bone is of two types: a readily exchangeable reservoir and a much larger pool of stable calcium that is only slowly exchangeable. The absorbed Ca is delivered to the basolateral membrane of the epithelial cell, from where it can be transported into the bloodstream by a Na^{2+}\Ca^{+2}-dependent ATPase. The overall transport process is regulated by 1,25-dihydroxycholecalciferol. As Ca^{2+} exchanger (NCX1) or a Ca uptake rises, 1,25-dihydroxycholecalciferol levels fall in response to increased plasma Ca^{2+}.

Plasma $Ca^{2+}$is reabsorbed occurs in the proximal tubules and ascending limb of the loop of Henle and the distal tubule. Distal tubular reabsorption depends on the TRPV5 channel, which is regulated by PTH.

Phosphate:

Total plasma phosphorus is about 12 mg/dL, with two-thirds of this total in organic compounds and the remaining inorganic phosphorus (Pi) mostly in, HPO_4^{2-}, and H_2PO_4.

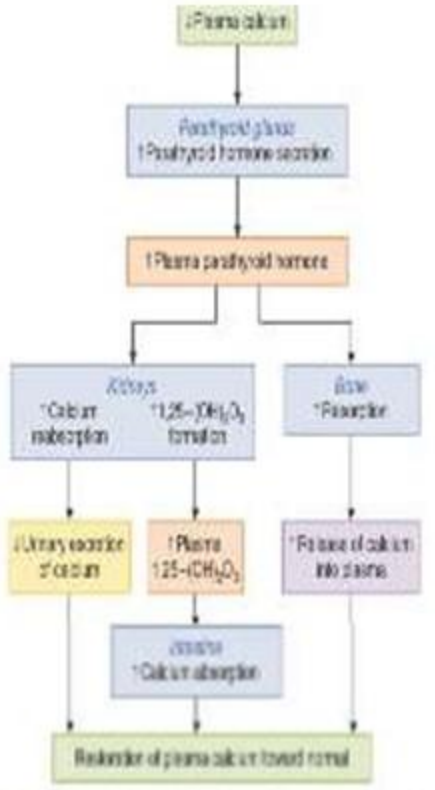
Pi in the plasma is filtered in the glomeruli, is reabsorbed in the proximal tubule involves to related sodium-dependent Pi cotransporters. NaPi-IIa cotransporters is powerfully inhibited by PTH, causing a reduction in renal Pi reabsorption.

Pi is absorbed in the duodenum and small intestine. Uptake occurs by a transporter related to those in the kidney, NaPi-IIb cotransporters. Many stimuli that increase Ca^{2+} absorption, including 1,25 dihydroxycholecalciferol, also increase Pi absorption vi

increased NaPi-IIb activity.

CALCITONIN

Calcitonin is a small peptide hormone produced by thyroid parafollicular C cells. Calcitonin is released in response to high plasma Ca^2 concentrations, and its primary effect is to block osteoclast-mediated bone resorption and Ca^2 mobilization. Calcitonin is not thought to play any significant role in Ca_2 homeostasis in humans, but it can be used as a biomarker for thyroid cancer, and its physiologic effects can be exploited therapeutically. Plasma Ca^2 and PO_4^3 levels are regulated primarily by PTH and vitamin D derivatives.



Parathyroid Hormone and Vitamin D:
PTH and vitamin D together regulate Ca^2 and PO_4^3. The major targets of regulation are the GI system (absorption), kidneys (reabsorption), and bone (deposition and resorption).

THE PARATHYROID GLANDS

Humans usually have four parathyroid glands embedded in the poles of the thyroid gland. The abundant chief cells synthesize and secrete PTH.

Parathyroid hormone:

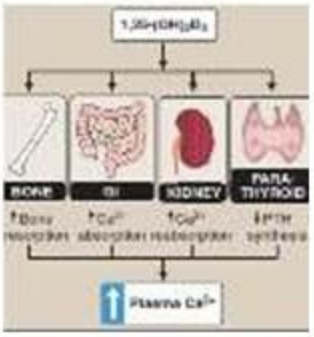
PTH is released from parathyroid glands in response to a decline in circulating Ca^2 and Mg^2 levels. PTH actions are geared toward increasing Ca^2 availability.

Regulation: Parathyroid cells express a specialized GPCR that functions as a Ca^2 sensor. When plasma Ca^2 levels are high, the receptor tonically inhibits PTH secretion. The relationship between free Ca^2 and PTH release is sigmoidal, with the steepest portion of the curve being in the physiologic range of plasma Ca^2. PTH release is similarly dependent on plasma free Mg^2

Function: PTH increases circulating Ca^2 levels by two principal mechanisms:

First, it stimulates bone resorption by binding to receptors on the surface of osteoblasts, which then recruit osteoclasts precursors to a bone resorption site.

Second, it stimulates Ca^{2} reabsorption by the renal tubule. Proximal tubule reabsorption of PO_4^{3} is decreased by PTH. Although this increases PO_4^{3} excretion, it does not significantly alter circulating plasma PO_4^{3} levels because PTH also increases PO_4^{3} liberation from the bone. PTH also indirectly increases circulating Ca^{2} by its stimulatory effects on 1,25-dihydroxyvitamin D_3 [1,25-(OH)2D3] synthesis.



Vitamin D derivatives:

Vitamin D is functionally related to PTH. Vitamin D and its derivatives are hydrophobic and transported in the blood primarily by vitamin D-binding protein. The primary active vitamin D derivative is $1,25\text{-}(OH)_2D_3$, which increases Ca^{2} and PO_4^{3} absorption by the small intestine. The synthesis of $1,25\text{-}(OH)_2D_3$ from vitamin D2 or D3 involves a multistep process that includes both the liver and the kidney. The major regulatory enzyme for $1,25\text{-}(OH)_2D_3$ synthesis is $25(OH)D_1$--hydroxylase. Vitamin D3 can be synthesized in the skin by keratinocytes via interaction with UV light with 7-dehydrocholesterol, and vitamin D2, and D3 can also come from dietary sources.

Regulation: The primary factor that regulates $1,25\text{-}(OH)_2D_3$ is PTH. PTH increases the activity of $25(OH)D_1$-hydroxylase and decreases the activity of $25(OH)D_{24}$-hydroxylase in the kidney. This shifts the reactions toward the production of $1,25\text{-}(OH)_2D_3$. Low levels of both Ca^{2} and PO_4^{3} as well as hormones, such as growth hormone, prolactin, and estrogen, also increase $1,25\text{-}(OH)_2D_3$ levels.

Function: $1,25\text{-}(OH)_2D_3$ is very effective in aiding the absorption of Ca^{2} and PO_4^{3} from the GI tract and reabsorption of these ions from the renal tubule.

A- Ca^{2} absorption is improved by:

1- $1,25\text{-}(OH)_2D_3$ via increased synthesis of apical, basolateral, and cytosolic transport proteins.
2- 1,25-(OH)2D3 binds to a nuclear vitamin D receptor that complexes with an RXR and induces transcription from the vitamin D response element. Thus, most of the effects of 1,25 (OH)2D3 are genomic, but there are some faster effects mediated by a cell mediated by a cell membrane vitamin D receptor.
3- $1,25\text{-}(OH)_2D_3$ decreases PTH through negative feedback in addition to the negative feedback provided by increases in circulating Ca^{2} due to increased intestinal absorption

B-PO_4^{3} absorption is also improved by $1,25\text{-}(OH)_2D_3$ effects on apical Na-PO_4 cotransporter synthesis.

Effects of Other Hormones & Humoral Agents On Calcium Metabolism

a) Glucocorticoids lower plasma Ca levels by decrease bone formation by inhibiting protein synthesis in osteoblasts. They also decrease the absorption of Ca^{2} and PO_4^{3} from the intestine and increase their renal excretion. The decrease in plasma Ca^{2} concentration also increases the secretion of PTH, and bone resorption is facilitated.

b) Growth hormone increases Ca^{2} excretion in the urine, but it also increases intestinal absorption of Ca^{2}, and this effect may be greater than the effect on excretion, with a resultant positive calcium balance.

Insulin-like growth factor I (IGF-I) stimulates protein synthesis in bone.

c) Thyroid hormones may cause hypercalcemia, hypercalciuria, and some instances,

d) osteoporosis.

Estrogens prevent osteoporosis by inhibiting the stimulatory effects of certain cytokines

e) on osteoclasts.

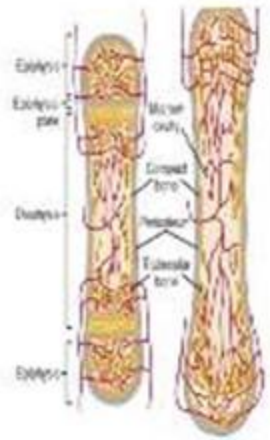
Insulin increases bone formation, and there is significant bone loss in untreated diabetes.

f)

BONE PHYSIOLOGY

Bone is a special form of connective tissue, is well vascularized, with a collagen framework impregnated with Ca^{2+}, PO_{43-} salts, particularly hydroxyapatites. Bone is also involved in overall Ca and PO4 homeostasis. It protects vital organs, and the rigidity it provides permits locomotion and the support of loads against gravity. Old bone is constantly being resorbed and new bone formed; permitting remodeling that allows it to respond to the stresses.

During fetal development, most bones are modeled in cartilage and then transformed into bone by ossification. During growth, specialized areas at the ends of each long bone (epiphyses) are separated from the shaft of the bone by a plate of actively proliferating cartilage, the epiphysial plate. The bone increases in length as this plate lays down new bone cell on the end of the shaft. The epiphyses of the various bones close in an orderly temporal sequence, after puberty.

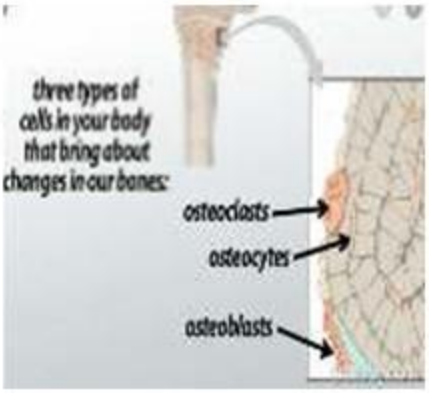


The periosteum is a dense fibrous, vascular, and innervated membrane that covers the surface of bones. This layer consists of an outer layer of collagenous tissue and an inner layer of fine elastic fibers that can include cells that have the potential to contribute to bone growth. The periosteum covers all surfaces of the bone except for those capped with cartilage (eg, at the joints) and serves as a site of attachment of ligaments and tendons. As one ages, the periosteum becomes thinner and loses some of its vasculature. The cells responsible for bone formation are osteoblasts and the cells responsible for bone resorption are

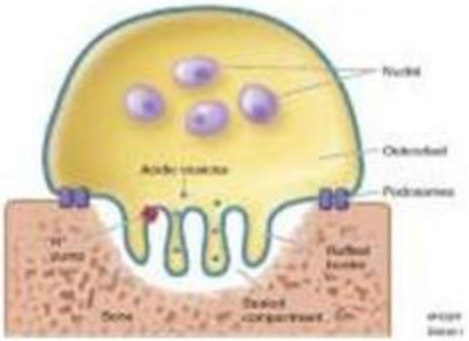
osteoclasts.

Osteoblasts: are able to lay down type 1 collagen and form new bone.

Osteoclasts: erode and absorb previously formed bone. They become attached to bone via integrins in a membrane extension called the sealing zone. This creates an isolated area between the bone and a portion of the osteoclast. Throughout life, bone is being constantly resorbed and new bone is being formed. The resorbed mechanism:



Osteoclasts are bone-destroying cells.



1- Proton pumps (H-dependent ATPases) then move from endosomes into the cell membrane apposed to the isolated area, and they acidify the area to approximately pH 4.0.
2- The acidic pH dissolves hydroxyapatite, and acid proteases secreted by the cell break down collagen, forming a shallow depression in the bone.
3- The products of digestion are then endocytosed and move across the osteoclast by transcytosis, with release into the interstitial fluid.

Bone remodeling is mainly a local process carried out in small areas by populations of cells called bone-remodeling units. First, osteoclasts resorb bone, and then osteoblasts lay down new bone in the same general area. This cycle takes about 100 days. Modeling drifts also occur in which the shapes of bones change. About 5% of the bone mass is being remodeled. The remodeling is related in part to the stresses. The bone remodeling process is primarily under endocrine control. The circulating leptin can increase bone mass through osteoblast and preosteoblast cell signaling pathways. More generally, PTH accelerates bone resorption, and estrogens slow bone resorption by inhibiting the production of bone-eroding cytokines.

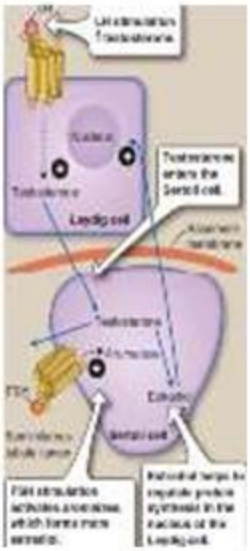
HYPOTHALAMIC–PITUITARY–TESTICULAR AXIS

The male gonads are the testes. The testes are under endocrine axis control.

Hypothalamus and pituitary gland:

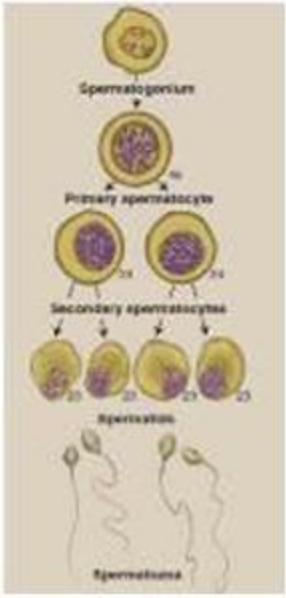
The hypothalamic areas involved in testicular control are identical to those that regulate ovaries. GnRH is also secreted into the hypophyseal portal system, binding to anterior pituitary gonadotropes cell. There, GnRH stimulates GnRH receptors to secrete the peptide hormones LH and FSH, as occurs in females. Gender differences are confined to the target organ (i.e., testis).

Testis



The testis contains Leydig cells that produce testosterone; blood vessels; and seminiferous tubules, which produce sperm and house Sertoli cells. The testicular endocrine functions reside in Leydig cells and Sertoli cells, which work cooperatively in a similar manner to theca and granulosa cells in female, to synthesize testosterone and, to a lesser extent, estradiol.

1. **Leydig cells:** transport cholesterol, and cholesterol provides the initial structure for steroid-hormone synthesis. LH binds to surface membrane LH receptors, which activate and produce steroid hormone synthetic enzymes such as side-chain cleavage enzyme complex. The end product of this pathway is testosterone. Testosterone diffuses out of the Leydig cell with a portion entering the circulation, and a portion migrating to nearby Sertoli cells.
2. **Sertoli cells**: Adjacent Sertoli cells form tight junctions to create a functional blood–testis barrier. This barrier is selectively permeable for substances like testosterone but inhibits passage of many other substances. Sertoli cells primarily express FSH cell surface receptors. FSH receptors are in the GPCR superfamily and primarily work through cAMP second messenger system to stimulate synthesis of enzymes such as aromatase, inhibins for FSH negative feedback, and various growth factors. Sertoli cells rely on Leydig cells for testosterone. Aromatase activation facilitates the conversion of testosterone into estradiol, which regulates much of the protein synthesis in both Sertoli and Leydig cells. Sertoli cells secrete androgen binding protein (ABP) along with testosterone into the seminiferous tubular lumen.



Spermatogenesis:

The primitive germ cells next to the basal lamina of the seminiferous tubules, mature into primary spermatocytes beginning during adolescence. The primary spermatocytes undergo meiotic division, reducing the number of chromosomes. They divide into secondary spermatocytes and then into spermatids, which contain the haploid number of 23 chromosomes. The spermatids mature into spermatozoa (sperm). The formation of a mature sperm from a primitive germ cell by spermatogenesis takes approximately 74 days.

Each sperm is made up of a head of chromosomal material and a flagellum tail for motility. Covering the head like a cap is the acrosome, a lysosome-like organelle rich in enzymes involved in sperm penetration of the ovum. The motile tail of the sperm is wrapped in its proximal portion by a sheath holding numerous mitochondria. Spermatids mature into spermatozoa in the cytoplasm of Sertoli cells. Mature spermatozoa are released from the Sertoli cells and become free in the lumen of the tubules. The Sertoli cells contain aromatase, the enzyme responsible for conversion of androgens to estrogens, and they can produce estrogens. Spermatogenesis is regulated by testosterone, and testosterone level is maintained by ABP probably functions to maintain a high, stable supply of androgen in the tubular fluid. FSH and androgens maintain the gametogenic function of the testis. Spermatozoa continue their maturation and acquire motility during their passage through the epididymis. Spermatogenesis requires a temperature considerably lower than that of the interior of the body. The testes are normally maintained at a temperature of about 32°C, through blood circulating around the scrotum and likely by heat exchange in a countercurrent manner between the spermatic arteries and veins.

Tissue	Effect
Bone	↑ Growth of bone and connective tissue
Muscle	↑ Growth of muscle and connective tissue
Reproductive organs	↑ Growth and development of testes, prostate, seminal vesicles, and penis ↑ Growth of facial, axillary, and pubic hair ↑ Growth of larynx ↑ Spermatogenesis
Skin	↑ Sebaceous gland size and secretions

Semen: The fluid that is ejaculated, contains sperm and the secretions of the seminal vesicles, prostate, Cowper glands, and urethral glands. Reduction in sperm production is associated with infertility 50% of men. The presence of many morphologically abnormal or immotile spermatozoa also correlates with 30% infertility.

Ejaculation: of the spermatozoon involves contractions of the vas deferens "the duct which conveys sperm from the testicle to the urethra". Once ejaculated into the female, the spermatozoa move up the uterus to the isthmus of the fallopian tubes, where they slow down and undergo capacitation in preparation for fertilization.

TESTOSTERONE:

is produced from the conversion of androstenedione via 17β-hydroxysteroid dehydrogenase. In addition to direct usage of testosterone, some target tissues convert testosterone into dihydrotestosterone (DHT) via 5α-reductase. Similar to estrogens, testosterone has a high binding affinity to sex steroid-binding globulin SSBG and, to a lesser extent, albumin. The liver produces SSBG and also inactivates and processes testosterone. Testosterone and byproducts are secreted in the urine and feces.

Function : Testosterone and DHT have a number of androgen effects for adrenal androgens. Once testosterone binds the receptor, a homodimer is formed that translocates to the testosterone- response element. The functional effects are dependent on the target tissue.

The pathways regulating testosterone secretion are similar to those regulating the ovaries.

1. **Testosterone:** Testosterone secreted from Leydig cells exerts negative feedback on both the hypothalamus to decrease GnRH and the anterior pituitary to decrease both LH and FSH. Testosterone also stimulates Sertoli cells to release inhibins.

2. **Inhibins:** Inhibin B provides negative feedback to the anterior pituitary in males, where it decreases secretion of FSH.