CALCIUM METABOLISM

Cellular and Extracellular Calcium Metabolism

The calcium ion plays a critical role in intracellular and extracellular events in human physiology. **Extracellular** ionized Ca^{++} levels are tightly regulated within narrow physiological range to provide for proper functioning of many tissues:

Excitation-contraction coupling in the heart and other muscles, synaptic transmission and other functions of the nervous system, platelet aggregation, coagulation, and secretion of hormones and other regulators by exocytosis. The level of intracellular calcium is also tightly controlled, at levels about 10,000 fold lower than extracellular calcium, in order for calcium to serve as an **intracellular** second messenger in the regulation of cell division, muscle contractility, cell motility, membrane trafficking and secretion.

It is the concentration of ionized calcium [Ca^{++}] that is regulated in the extracellular fluid (ECF). Only about 50% of the total calcium in serum and other extra cellular fluids is present in the ionized form. The remainder is bound to albumin (~40%) or complexed with anions such as phosphate and citrate (~10%). Only the [Ca^{++}] serves a regulatory role and is under hormonal regulation.

The total calcium in ECF amounts to about 1% of total body calcium, with most of the remainder sequestered in bone (Fig. 8-1). Yet from the ECF compartment, which contains about 900 mg of calcium, 10,000 mg/d is filtered at the glomerulus and 500 mg/d is added to a labile pool in bone; and to the ECF compartment are added about 200 mg absorbed from the diet. 9800 mg reabsorbed by the renal tubule, and 500 mg from bone.

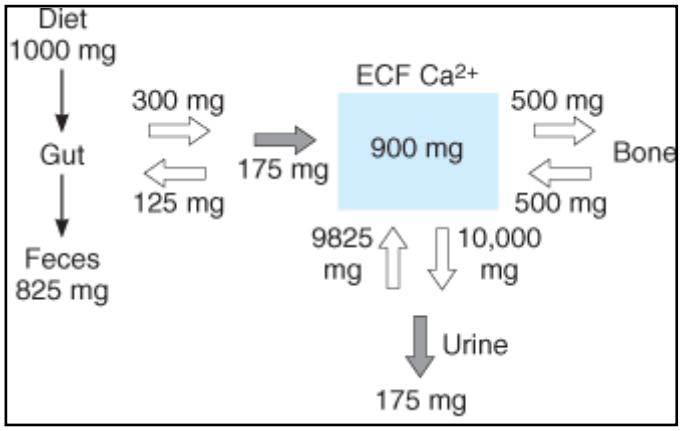


Figure 8-1. Calcium fluxes in a normal individual in a state of zero external mineral balance. The open arrows denote unidirectional calcium fluxes; the solid arrows denote net fluxes.

The challenge of the calcium homeostatic system, then, is to maintain a constant level of [Ca^{++}] in the ECF, simultaneously providing adequate amount of calcium to cells, to bone and for renal excretion, at the same time compensating, on an hourly basis for changes in daily intake of calcium, bone metabolism, and renal function. This homeostatic task requires two hormones: parathyroid hormone (PTH) and vitamin D, at the level of the gut, the bone, and the renal tubule.

The calcium gradient across the cell membrane is maintained by ATP-dependent calcium pumps and by Na^{+}-Ca^{++} exchanger. Calcium can enter cells through several types of calcium channel, some of which are voltage-operated or receptor–operated, to provide for rapid influx in response to depolarization or receptor stimulation. The cell also maintains large store of calcium in microsomal and mitochondrial pools. Calcium can be released form microsomal stores rapidly by cellular signals such as 1,4,5- inositoltriphosphate (IP_3).

Parathyroid Hormone

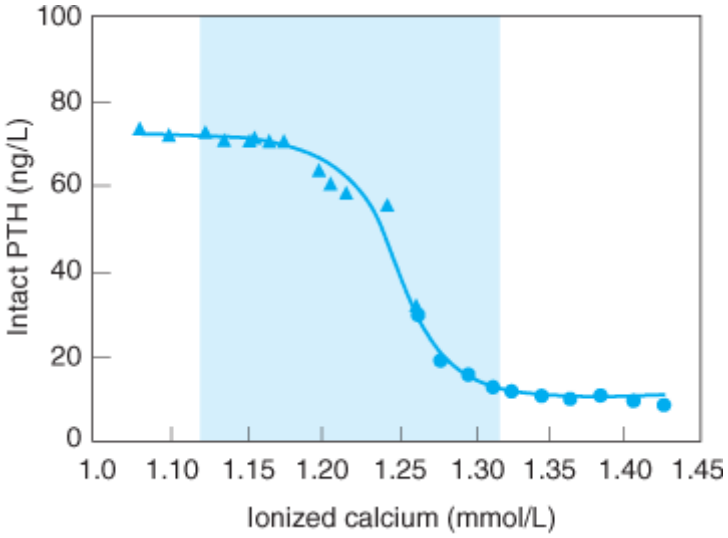
Anatomy of the parathyroid Gland

Parathyroid hormone is secreted from four glands located adjacent to the thyroid gland in the neck. The glands weigh and average of 40 mg each 12-15% of normal persons have a fifth parathyroid gland.

Secretion of PTH

In order to carry out its function to regulate the extracellular calcium concentration, PTH must be under exquisite control by the serum calcium concentration thus, the negative feedback relationship of PTH with serum [Ca^{++}] is steeply sigmoidal (Fig. 8-2)

Figure 8-2. The relationship between the serum ionized calcium level and the simultaneous serum concen-tration of intact PTH in normal humans. The serum calcium concentration was altered by the infusion of calcium (closed circles) or citrate (closed triangles). Parathyroid sensitivity to changes in serum calcium is maximal within the normal range (the shaded area). Low concentrations of PTH persist in the face of hypercalcemia.



To sense the concentration of extracellular [Ca^{++}] and there by regulate the secretion of PTH, the parathyroid cell relies on a sensor of extracellular calcium (calcium receptor). This calcium sensor is a 120-KDa G protein-coupled receptor. Calcium receptors are widely distributed in the brain, skin, growth plate, intestine, stomach, C cells, and other tissues. This receptor regulates the response to calcium in thyroid C cells, which secrete calcitonin in response to high extracellular calcium; and in the distal nephron of the kidney, where the receptor regulates calcium excretion.

The primary cellular signal by which increase extracellular calcium inhibits the secretion of PTH is an increase in intracellular ionized calcium $[Ca^{++}]_i$. the calcium receptor is directly coupled by G_q to the enzyme phospholipase C, which hydrolyzes PIP_2 to liberate the intracellular messengers, IP_3 and diacylglycerol (Fig. 3-5).

IP_3 binds to a receptor in endoplasmic reticulum that releases calcium from membrane stores. The release of stored calcium raises the [Ca^{++}]i rapidly and is followed by a sustained influx of extracellular calcium, through channels to produce a rise and a sustained plateau in $[Ca^{++}]_i$.

The initial effect of high extracellular calcium is to inhibit the secretion of preformed PTH from storage granules in the gland by locking the fusion of storage granules with the cell membrane and release of their content. In most cells, stimulation of exocytosis ("stimulus–

secretion coupling") is a calcium–requiring process, which is inhibited by depletion of calcium. The parathyroid cell is necessarily an exception to this rule, because this cell must increase secretion of PTH when the calcium level is low. In the parathyroid, intracellular magnesium appears to serve the role in stimulus–secretion coupling that calcium does in other cells. Depletion of Mg stores can paralyze the secretion of PTH, leading to reversible hypoparathyroidism.

Besides calcium, there are several regulators of PTH secretion. High Mg inhibit PTH, moderate hypomagnesemia can stimulate PTH secretion, even though prolonged depletion of Mg will paralyze it. Catecholamines, acting through β-adrenergic receptors and cAMP, stimulate the secretion of PTH.

Not only do changes in serum calcium regulate the secretion of PTH- they also regulate the synthesis of PTH at the level of stabilizing prepro PTH mRNA levels and possibly enhancing gene transcription. Transcription of the PTH gene is also regulated by vitamin D: high levels of 1,25 $(OH)_2$ D inhibits PTH gene transcription

Synthesis and processing of PTH

PTH is and 84-animo-acid peptide. The gene codes a precursor called prepro PTH with a 29-amino–acid extension at the amino terminal of the mature PTH peptide. The signal sequence in prepro PTH functions precisely as it does in most other secreted protein molecules, to allow recognition of the peptide by a signal recognition particle, which binds the nascent peptide chains as they emerge from the ribosome and guides them to the ER, where they are inserted through the membrane into the lumen (Fig.8-4).

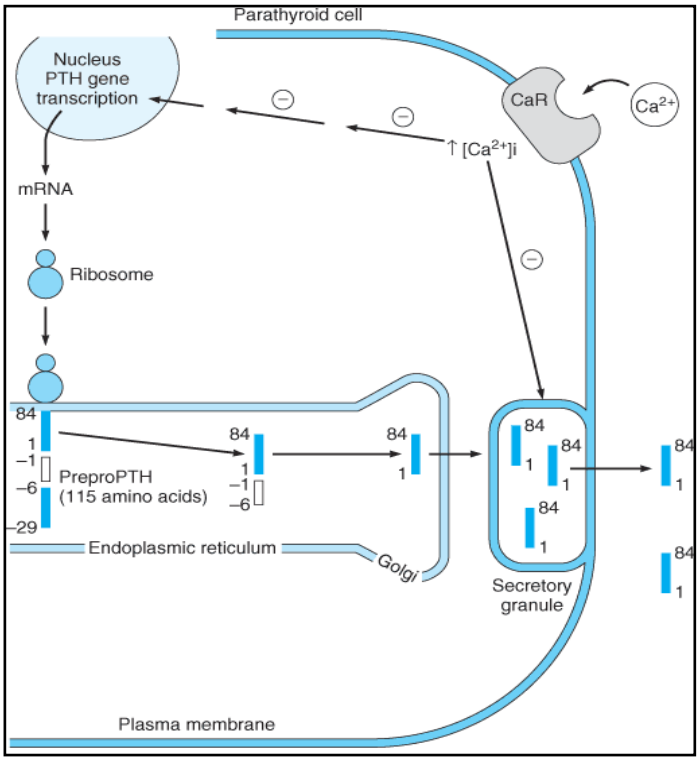


Figure 8-4. Biosynthetic events in the production of PTH within the parathyroid cell. PreproPTH gene is transcribed to its mRNA, which is translated on the ribosomes to preproPTH (amino acids -29 to +84). The pre- sequence is removed within the endo-plasmic reticulum, yielding proPTH (-6 to +84). Mature PTH(1–84) released from the Golgi is packaged in secretory granules and released into the circulation in the presence of hypocalcemia. The CaR senses changes in extracellular calcium that affect both the release of PTH and the transcription of the preproPTH gene.

In the lumen of the ER, a signal peptidase cleaves the signal sequence from pro PTH to leave pro PTH, which exit the ER lumen and travels to the Golgi apparatus, where the pro sequence is cleaved from PTH by an enzyme called furin. The processing of pro PTH is quite efficient, and pro PTH, unlike other prohormones (e.g. insulin), is not secreted. As it leaves the Golgi apparatus, PTH is repackaged into secretory granules, where it is stored to await secretion.

Biologic Effects of PTH

The function of PTH is to regulate serum [Ca^{++}] levels by concerted effects on three principal target organs: bone, intestinal mucosa, and kidney. The effect of PTH on intestinal calcium absorption is indirect, resulting from increased renal production of the intestinally active vitamin D metabolite 1,25$(OH)_2$ D. By its integrated effects on the kidney, gut, and bone, PTH acts to increase the inflow of calcium into the ECF and thus defend against hypocalcemia. Removal of the parathyroid glands results in profound hypocalcemia and ultimately in tetany and death.

In the kidney, PTH has direct effects on the tubular reabsorption of calcium, phosphate, and bicarbonate, although the bulk of calcium is resorbed from tubule fluid together with sodium in the proximal convoluted tubule fluid together with sodium in the proximal convoluted tubule. The fine tuning of calcium excretion occurs in the distal nephron. There, PTH markedly increases the reabsorption of calcium, predominantly in the distal convoluted lobule. The ability to limit renal losses of calcium is one important means by which PTH protects the serum calcium level. PTH inhibits the reabsorption of phosphate in the renal proximal tubule.

Mechanisms of Action of PTH

There are two mammalian receptors for PTH. The first receptor recognizes PTH and PTH-related protein (PTHrP) and is designated PTH-1 receptor. The PTH-2 receptor is activated by PTH only. The PTH-1 receptor in kidney and bone is a member of the G protein superfamily.

Physiologic activation of the receptor by binding of either PTH or PTHrP induces the active, GTP-bound state of two receptor- associated G proteins. Gs couples the receptor to the effector adenylyl cyclase and thereby to the generation of cAMP as a cellular second messenger. G_q couples the receptor to a separate effector system, phospholipase C, and thereby to an increase in $[Ca^{++}]_i$; and to activation of protein kinase C (Fig. 3-5). cAMP is the intracellular second messenger for calcium homeostasis and renal phosphate excretion.

PTHrP

When secreted in abundance by malignant tumors, PTHrP produces severe hypercalcemia by activating PTH / PTHrP – 1 receptor. However, the physiologic role of PTHrP is quite different from that of PTH. PTHrP is produced in many fetal and adult tissues. PTHrP is required for normal development as a regulator of the proliferation and mineralization of chondrocytes and as a regulator of placental calcium transport. In postnatal life, PTHrP appears to regulate the development of the mammary gland, skin and hair follicle. In most physiological circumstances, PTHrP carries out local rather systemic actions (autocrine or paracrine).

Calcitonin

Calcitonin is a 32-amino-acid peptide whose principle function is to inhibit osteoclast–mediated bone resorption. Calcitonin is secreted by Parafollicular C cells of the thyroid. The C cell increases secretion of calcitonin in response to hypercalcemia and shuts off hormone secretion during hypocalcemia.

The calcitonin gene is composed of six exons, and through alternative exon splicing it encodes two entirely different peptide products (Fig. 8-6). In the thyroid C cell, the predominant splicing choice generates mature calcitonin, which is incorporated within a 141-amino acid precursor. In other tissues, especially neurons of the CNS, a peptide called calcitonin gene-related-peptide (CGRP) is produced from a 128-amino-acid precursor, CGRP, is among the most potent vasodilator substance known.

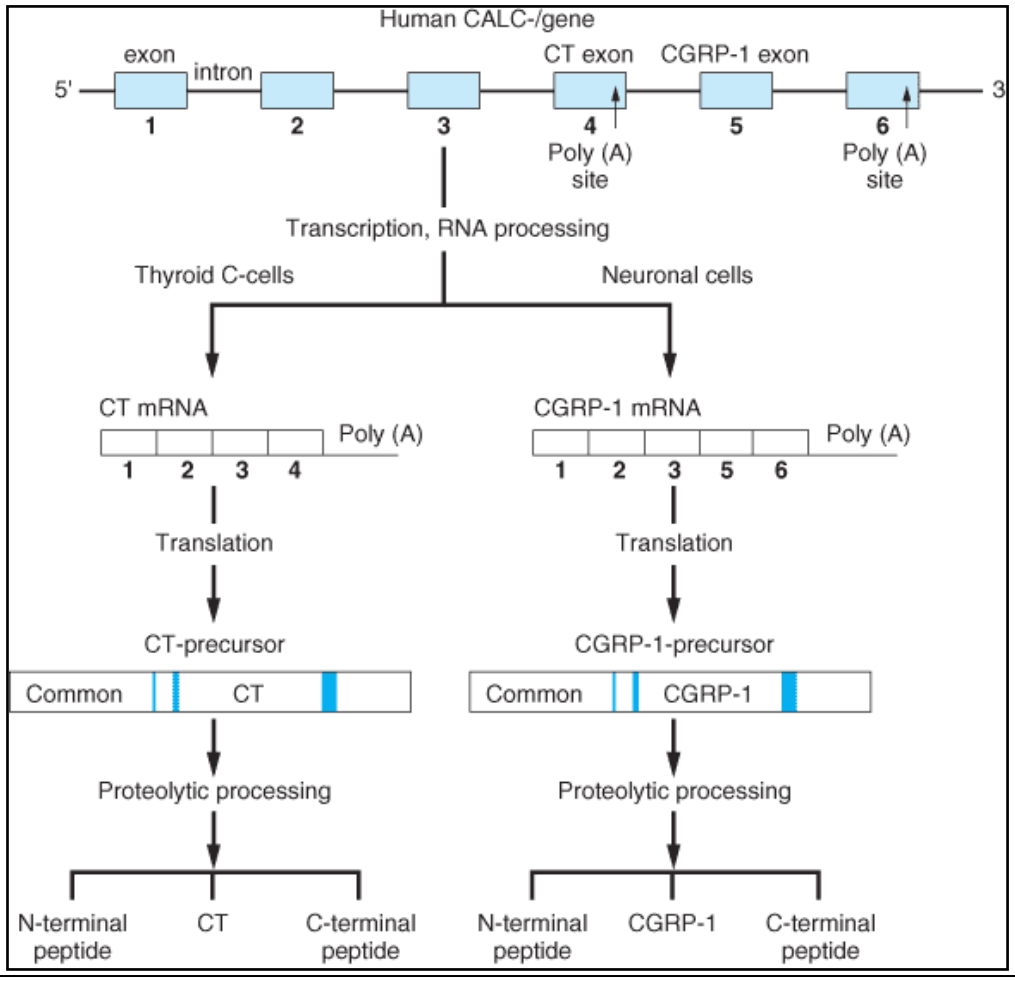


Figure 8-6. Alternative splicing of the human calcitonin (CT) gene (*CALC-I*). CT mRNA is produced by thyroid C cell, and CGRP mRNA is produced in neuronal cells by tissue-specific processing. The human *CALC-I* gene has 6 exons and 5 introns. Exons 1 and 6 are noncoding; exons 2 and 3 comprise the amino terminal peptide that is shared by the CT and the CGRP precursors. Exons 4 and 5 encode CT and CGRP, respectively.

When administered intravenously, calcitonin produces a rapid and dramatic decline in levels of serum calcium and phosphate, primarily through actions on bone. The major effect of the hormone is to inhibit osteoclastic bone resorption. Calcitonin has also renal effects. At the kidney, calcitonin inhibits the reabsorption of phosphate, thus promoting renal phosphate excretion.

Although its secretory control by calcium and its antiresorptive actions enable calcitonin to counter PTH in the control of calcium homeostasis, it is actually unlikely that calcitonin plays an essential physiological role in human. This is supported by two lines of residence. First, removal of the thyroid gland-the only known source of calcitonin in mammals – has no impact on calcium handling or bone metabolism. Second, secretion of extremely high

calcitonin levels by thyroid carcinoma, a malignancy of the C cell, like wise has no apparent effect on mineral homeostasis calcitonin plays a much more obvious homeostatic role in salt-water fish.

Calcitonin is of clinical interest for two reasons. First, calcitonin is important as a tumor marker in medullary thyroid carcinoma. Second, calcitonin has found several therapeutic uses as an inhibitor of osteoclastic bone resorption. Calcitonin can be administrated either parenterally or as a nasal spray and is used in the treatment of Paget's disease of bone, hypercalcemia and osteoporosis.

Vitamin D

The term vitamin D (calciferol) refers to two steroids: vitamin D_2 (ergocalciferol) and Vitamin D_3 (cholecalciferol) (Fig. 8-8). Vitamin D_2 is the principle form of vitamin D available for pharmaceutical purpose other than as dietary supplements. Vitamin D_3 is produced from 7-dehydrocholesterol, a precursor of cholesterol found in high concentration in the skin. Vitamin D_2 and D_3 are nearly equipotent in humans. Both are converted to 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D_3.

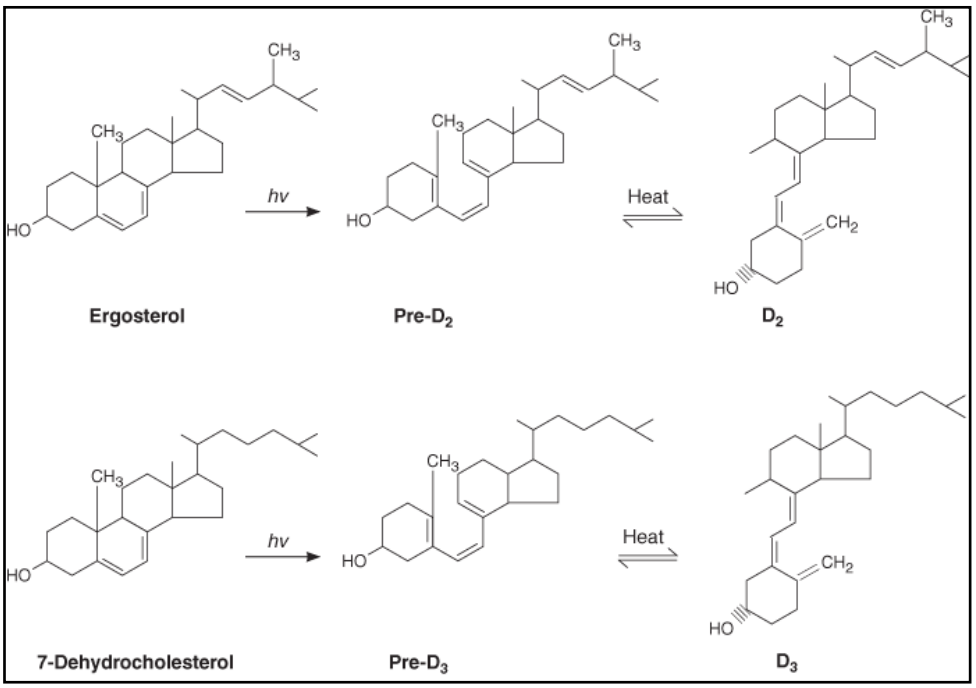


Figure 8-8. The photolysis of ergosterol and 7-dehydrocholesterol to vitamin D_2 (ergocalciferol) and vitamin D_3 (cholecalciferol), respectively. An intermediate is formed after photolysis, which undergoes a thermal-activated isomerization to the final form of vitamin D. The rotation of the A-ring puts the 3β-hydroxyl group into a different orientation with respect to the plane of the A-ring during production of vitamin D.

Since vitamin D can be formed in vivo (in the epidermis) in the presence of adequate amounts of U.V. light, it is more properly considered a hormone (or prohormone) than as a vitamin. To be biologically active, vitamin D must be metabolized further. The liver metabolizes Vitamin D to its principal circulating form, 25(OH) D. the kidney and other tissues metabolize 25(OH) D to 1,25(OH) D_3 and 24,25$(OH)_2$ D.

Synthesis of Vitamin D

Vitamin D_3 is formed in the skin from 7-delydrocholesterol, which is distributed throughout the epidermis, and dermis but has its highest concentration in the lower layers of the epidermis. This step requires U.V. light. Vitamin D_3 is carried in the bloodstream primarily bound to vitamin D-binding protein (DBP), an α-globulin, produced in the liver.

Dietary Source and Intestinal Absorption

Dietary sources of vitamin D are chemically important because exposure to UV light may not be sufficient of maintain adequate production of vitamin D in the skin. Vitamin D is found in high concentration in fish oils, fish liver, and eggs. Vitamin D is absorbed from the diet in the small intestine with the help of bile salts. Vitamin D is taken up rapidly by the live and is metabolized to 25(OH) D. little vitamin D is stored in the liver. Excess vitamin D is stored in adipose tissue and muscle.

Metabolism

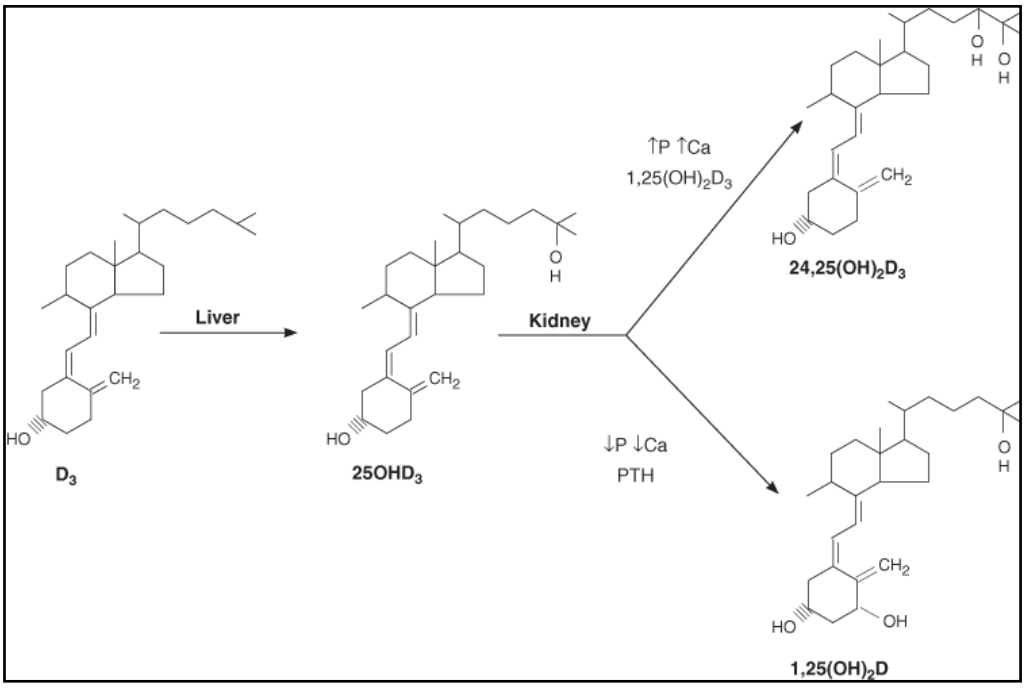


Figure 8-9. The metabolism of vitamin D. The liver converts vitamin D to 25(OH)D. The kidney converts 25(OH)D to $1,25(OH)_2D$ and $24,25(OH)_2D$. Control of metabolism is exerted primarily at the level of the kidney, where low serum phosphorus, low serum calcium, and high parathyroid hormone (PTH) levels favor production of $1,25(OH)_2D$ whereas FGF-23 inhibits $1,25(OH)_2D$ production.

The conversion of vitamin D to 25(OH) D occurs principally in the liver (Fig. 8-9). Both mitochondria and microsomes have the capacity to produce 25(OH) D. Control of vitamin D metabolism is exerted principally in the kidney (Fig. 8-9). $1,25(OH)_2$ D_3 and $24,25(OH)_2$ D are produced by cytochrome mixed function oxidase in mitochondria of the proximal tubules. The kidney remains the principal source for circulating $1,25(OH)_2$ D_3. Production of $1,25(OH)_2$ D_3 in the kidney is stimulated by PTH and is inhibited by high blood levels of calcium and phosphate.

Mechanism of Action

The main function of vitamin D metabolites is the regulation of calcium and phosphate homeostasis, which occur in conjunction with PTH. The gat, the kidney and bone are the principal target tissues for this regulation. The major pathologic complication of Vitamin D deficiency is rickets (in children) or osteomalacia (in adults), which in part results from a deficiency in calcium and phosphate required for bone mineralization. $1,25(OH)_2$ D_3 is the most biologically active of not the only vitamin D metabolite involved in maintaining calcium and phosphate homeostasis.

Most of cellular processes regulated by $1,25(OH)_2$ D_3 involve the nuclear vitamin D receptor (VDR). The VDR-retinol X receptor (RXR) complex then binds to specific regions within the regulatory portions of the genes whose expression is controlled by $1,25(OH)_2$ D_3 (Fig. 8-10). The regulatory regions are called vitamin D response elements (VDREs).

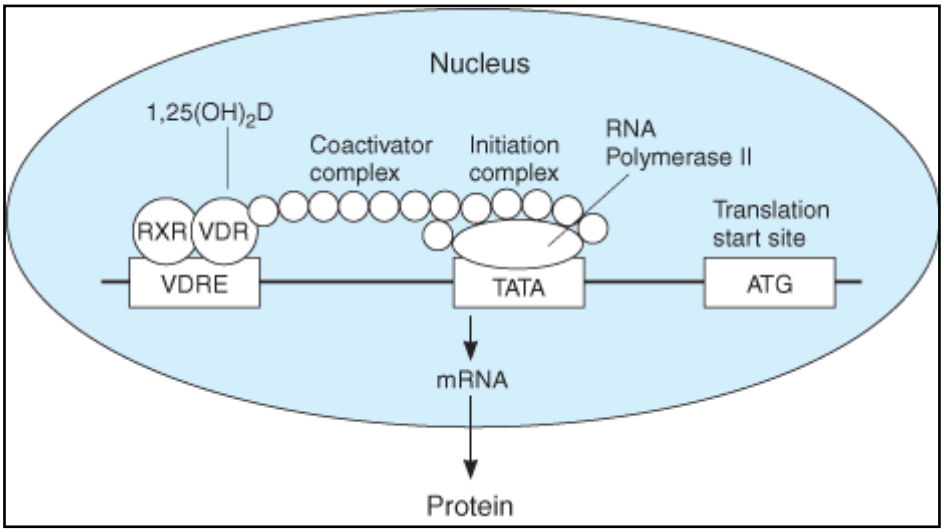


Figure 8-10. $1,25(OH)_2D$-initiated gene transcription. $1,25(OH)_2D$ enters the target cell and binds to its receptor, VDR. The VDR then heterodimerizes with the retinoid X receptor, RXR. This increases the affinity of the VDR/RXR complex for the vitamin D response element (VDRE), a specific sequence of nucleotides in the promoter region of a vitamin D responsive gene. Binding of the VDR/RXR complex to the VDRE attracts a complex of proteins termed coactivators to the VDR/RXR complex which span the gap between the VDRE and RNA polymerase II and other proteins in the initiation complex centered at or around the TATA box (or other transcription regulatory elements). Transcription of the gene is initiated to produce the corresponding mRNA, which leaves the nucleus for the cytoplasm to be translated to the corresponding protein.

A. Intestinal Calcium Transport

Calcium transport through the intestinal epithelium proceed by a least three distinct steps: (1) entrance into the cell from the lumen across the brush border membrane down a steep electrochemical gradient; (2) passage through the cytosol; and (3) removal from the cell against a steep electrochemical gradient at the basolateral membrane. Each of these steps is regulated by $1,25(OH)_2$ D_3. At the brush border, $1,25(OH)_2$ D_3 induces a change in the binding of calmodulin to brush border myosin 1, a unique form of myosin found only in the intestine. The calmodulin- myosin 1 complex may provide the mechanism for removing calcium from the brush border after it crosses the membrane

into the cell. Recent studies indicate that a newly described calcium channel (CaT1) in the brush border membrane may be induced by $1,25(OH)_2\ D_3$. This channel may be the major mechanism by which calcium enters the intestinal epithelial cell. The transport of calcium through the cytosol requires a vitamin D-inducible protein called calbindin. At the basolateral membrane, calcium is removed from the cell by an ATP-driven pump, the Ca^{++}-ATPase, a protein also induced by $1,25(OH)_2\ D_3$.

B. Actions of Vitamin D in Bone

The critical role of $1,25(OH)_2\ D_3$ in regulating bone formation and resorption is evidenced by the development of rickets in children who lack the ability to produce $1.25(OH)_2\ D_3$ (Vitamin D-dependent rickets type 1) or who lock a functional VDR (Vitamin D-dependent rickets type 2 or hereditary$1,25(OH)_2\ D_3$-resistant rickets). The former have mutations in the 1-hydroxylase gene and can be treated successfully with calcitriol as well as to vitamin D [calcitriol is $1,25(OH)_2\ D_3$].

C. Actions of Vitamin D in Kidney

The kidney expresses VDR, and $1,25(OH)_2\ D_3$ stimulates calbindin and Ca^{++}-ATPase in the distal tubule as well as $24,25(OH)_2$ D production in the proximal tubule. However, the role of $1,25(OH)_2\ D_3$ in regulating calcium and phosphate transport across the renal epithelium remains controversial. 25(OH) D may be more important than $1,25(OH)_2\ D_3$ in acutely stimulated calcium and phosphate reabsorption by the kidney tubules. In vivo studies are complicated by the effect of $1,25(OH)_2\ D_3$ on other hormones, particularly PTH.

Integrated Control of Mineral Homeostasis

If calcium and phosphate intake is low, the net absorption of calcium falls sharply, causing a transient decrease in the serum calcium level. The homeostatic response to this transient hypocalcemia is led by an increase in PTH, which stimulates the release of calcium and phosphate from bone and the retention of calcium by the kidney. The phospaturic effect of PTH allows elimination of phosphate, which is resorbed from bone together with calcium. In addition, the increase in PTH, along with the fall in serum calcium and serum phosphorous, activates renal $1,25(OH)_2\ D_3$ increases the fractional absorption of calcium and further increases bone resorption.

Hypercalcemia

Clinical Features

A number of symptoms and signs accompany the hypercalcemic state: CNS effects such as depression, psychosis; neuromuscular such as weakness, myopathy, hypertonic; cardiovascular effects such as hypertension, bradycardia, and shortened QT intervals; renal effects such as stones, decreased glomerular filtration, polyuria; gastrointestinal effects such as nausea, vomiting, constipation, and anorexia.

Mechanisms

Although many disorders are associated with hypercalcemia, they can produce hypercalcemia through only a limited number of mechanisms; (1) increased bone resorption, (2) increased gastrointestinal absorption of calcium, or (3) decreased renal excretion of calcium. The common feature of virtually all hypercalcemic disorders is accelerated bone resorption.

The central feature of defense against hypercalcemia is suppression of PTH secretion. This reduces bone resorption, reduces renal production of $1,25(OH)_2$ D_3 and thereby inhibits calcium absorption, and increases urinary calcium losses. The kidney plays a key role in the adaptive response to hypercalcemia as the only route of net calcium elimination, and the level of renal calcium excretion is markedly increased by the combined effects of an increased filtered load of calcium and the suppression of PTH. The only alternative to the renal rout for elimination of calcium from the ECF is deposition as calcium phosphate and other salts in bone and soft tissues. Soft tissue calcification is observed with massive calcium load, with massive phosphate loads and when renal function is markedly impaired. Hyperparathyroidism is by far the most common cause of hypercalcemia. Thus the first step in the differential diagnosis is determination of PTH (Figure 8-13).

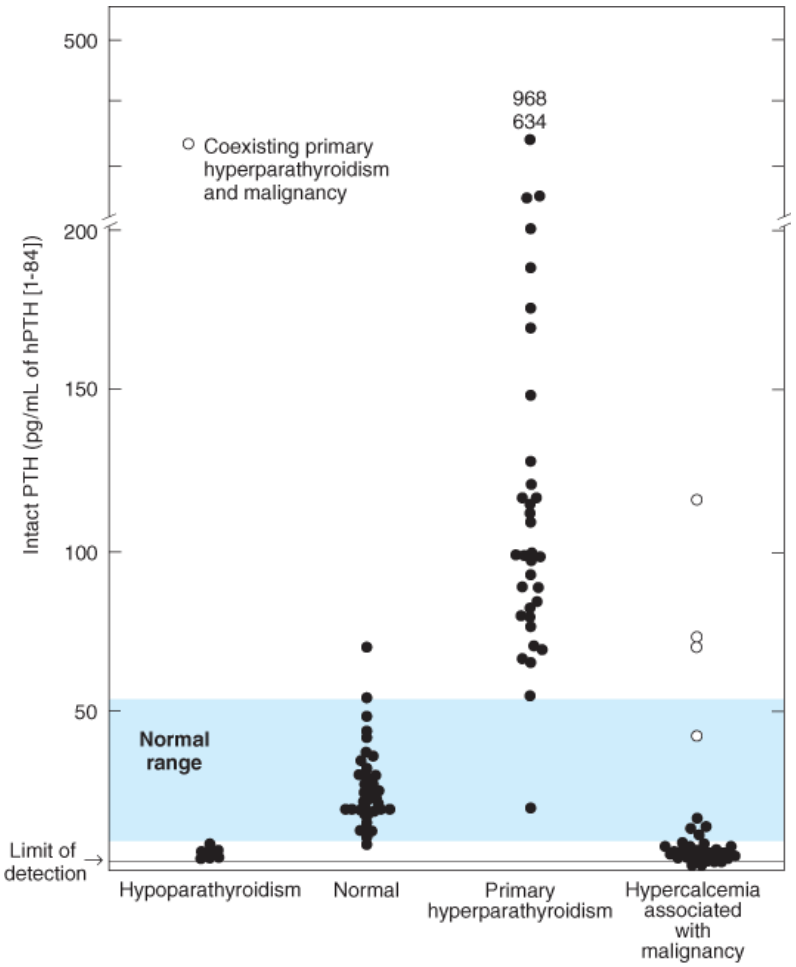


Figure 8-13. Clinical utility of immunoradiometric assay for intact PTH.

Disorders Causing Hypercalcemia

1. Primary Hyperparathyroidism

Primary hyperparathyroidism is a hypercalcemic disorder that results from excessive secretion of PTH. It is 2-3 times as common in women as in men.

Etiology and pathogenesis: primary hyperparathyroidism is caused by a single parathyroid adenoma in about 80% of cases and by primary hyperplasia of the parathyroids in about 15%. Primary hyperparathyroidism can occur as part of at least

three different familial endocrinopathies. All of them are autosomal dominant traits causing four-gland parathyroid hyperplasia.

Clinical features: as the disease is detected increasingly by screening that includes determination of serum calcium levels, there has been a marked reduction in the frequency of the classic signs and symptoms of primary hyperparathyroidism, renal disease -renal stones, decreased renal function- and the classic hyperparathyroid bone disease osteitis fibrosa cystica. In fact, about 85% of patients presenting today have neither bony nor renal manifestation of hyperparathyroidism and are regarded as asymptomatic or minimally symptomatic.

The other important consequence of hyperparathyroidism is osteoporosis (predominant loss of cortical bones). Kidney stones may occur in less than 15% cases. They are usually calcium oxalate stones. Chronic hypercalcemia can also compromise the renal concentrating ability, giving rise to polydipsia and polyuria. The definitive treatment of primary hyperparathyroidism is parathyroidectomy leaving a remnant sufficient to prevent hypocalcemia. surgery is recommended (1) if the serum calcium is markedly elevated (above 11.4-12 mg/dL, normal 8.5-10.5 mg/dl); (2) if there has been a previous episode of life-threatening hypercalcemia; (3) if the creatinine clearance is reduced below 70% of normal; (4) if a kidney stone is present; (5) if the urinary calcium is markedly elevated (> 400 mg/24hr, normal 175 mg/24hr); (6) if bone mass is substantially reduced; (7) if the patient is young (under 50 year of age, particularly premenopausal women).

2. Malignancy–Associated Hypercalcemia

Malignancy–associated hypercalcemia is the second most common form of hypercalcemia.

3. Sarcoidosis

Hypercalcemia is seen in up to 10% of subjects with sarcoidosis. This is due to inappropriately elevated $1,25(OH)_2$ D_3 levels. Lymphoid tissue and pulmonary macrophages from affected individuals contain 25(OH) D 1α-hydroxylase activity which is not seen in normal individuals. 1α-Hydroxylase activity in these cells is not readily inhibited by calcium or $1,25(OH)_2$ D_3 indicating a lack of feedback – inhibition.

4. Endocrinopathies

Mild hypercalcemia is found in about 10% of patients with thyrotoxicosis. Thyroid hormone has direct bone–resorbing properties causing a high-turnover state, which often eventually progresses to mild osteoporosis. Hypercalcemia can be a feature of acute adrenal insufficiency.

5. Endocrine Tumors

Hypercalcemia is found occasionally in pheochromocytoma, where it appears to result from secretion of PTHrP by the tumor.

6. vitamin D and Vitamin A

Hypercalcemia may occur in individuals ingesting large doses of vitamin D or vitamin A.

Hypocalcemia

Both PTH and 1,25$(OH)_2$ D_3 function to maintain a normal serum calcium and are thus central to the defense against hypocalcemia. Chromic hypocalcemia can result from a failure to secrete PTH, a failure to respond to PTH, a deficiency of vitamin D or a failure or respond to vitamin D.

Clinical Features

Clinically, the hallmark of severe hypocalcemia is tetany. Tetany is a state of spontaneous tonic muscular contraction. Other manifestations of hypocalcemia include delay in repolarization of cardiac muscles, excitation–contraction coupling may be impaired and congestive heart failure is sometime observed. Ophthalmologic effects include cataract, its severity is correlated with the duration and level of hypocalcemia. Dermatologic effects include dry skin, flaky and brittle nails.

Causes of Hypocalcemia

1. **Hypoparathyroidism**
   Hypoparathyroidism may be surgical, autoimmune, familial, or idiopathic. The most common cause of hypoparathyroidism is surgery of the neck, with removal or destruction of the parathyroid gland. The operation most often associated with hypoparathyroidism is cancer surgery, total thyroidectomy, and parathyroidectomy.

2. **Pseudohypoparathyroidism**
   Pseudohypoparathyroidism is a heritable disorder of target-organ unresponsiveness to parathyroid hormone. The PTH level is elevated and there is a markedly blunted response to the administration of PTH.

3. **Vitamin D Deficiency.**
   Vitamin D deficiency result from one or a combination of three causes: inadequate sunlight exposure, inadequate nutrition, and malabsorption. Although the human skin is capable of producing sufficient amounts of vitamin D if exposed to sunlight of adequate intensity, institutionalized patients frequently do not get adequate exposure. Furthermore, the fear of skin cancer has led many to avoid sunlight exposure or apply protective agents that block the UV sunlight.

   Heavy pigmented and elderly individuals have less efficient production of Vitamin D. The supplementation of dairy products has reduced the incidence of vitamin D deficiency. Individuals with a variety of small intestine diseases, partial gastrectomy, pancreatic diseases, and biliary tract disease have reduced capacity to absorb the vitamin D in the diet.

4. **Vitamin D–Dependent Rickets Type I**
   Also known as pseudovitamin D deficiency, in which there is a low level of 1,25$(OH)_2$ D_3 but normal levels of 25(OH) D and rickets. The disease is due to mutation in the 25(OH) D 1α-hydroxylase gene. Calcitriol is a preferred treatment.

5. **Vitamin D–Dependent Rickets Type II**
   It is a hereditary 1,25$(OH)_2$ D_3 resistant rickets with very high levels of 1,25$(OH)_2$ D_3. The disease is caused by inactivating mutations in the vitamin D receptor (VDR) gene. These patients are treated with large doses calcitriol and dietary calcium.

Bone Anatomy and Remodeling

Function of Bone

Bone has three major functions:

(1) It provides rigid support to extremities and body cavities containing vital organs. In disease situation in which bone is weak or defective, erect posture may be impossible, and vital organ function may be compromised. An example is cardiopulmonary dysfunction that occurs in patients with vertebral collapse.

(2) Bones are crucial to locomotion in that they provide efficient levers and sites of attachment for muscle, with bony deformity, these levers become defective, and severe abnormalities of gait develop.

(3) Bones provide a large reservoir of ions, such as calcium, phosphorus, magnesium, and sodium that are crucial for life and can be mobilized where the external environment fails to proved them.

Structure of Bone

Bone is not only rigid and resists forces but is also light enough to be moved by muscle contraction. Cortical bone, composed of densely packed layers of mineralized collagen, provides rigidity and id the major component of tubular bones (Fig. 8-19). Trabecular (cancellous) bone is spongy in appearance, provides strength and elasticity. Two–thirds of the weight of bone is due to mineral; the remainder is due to water and type1 collagen.

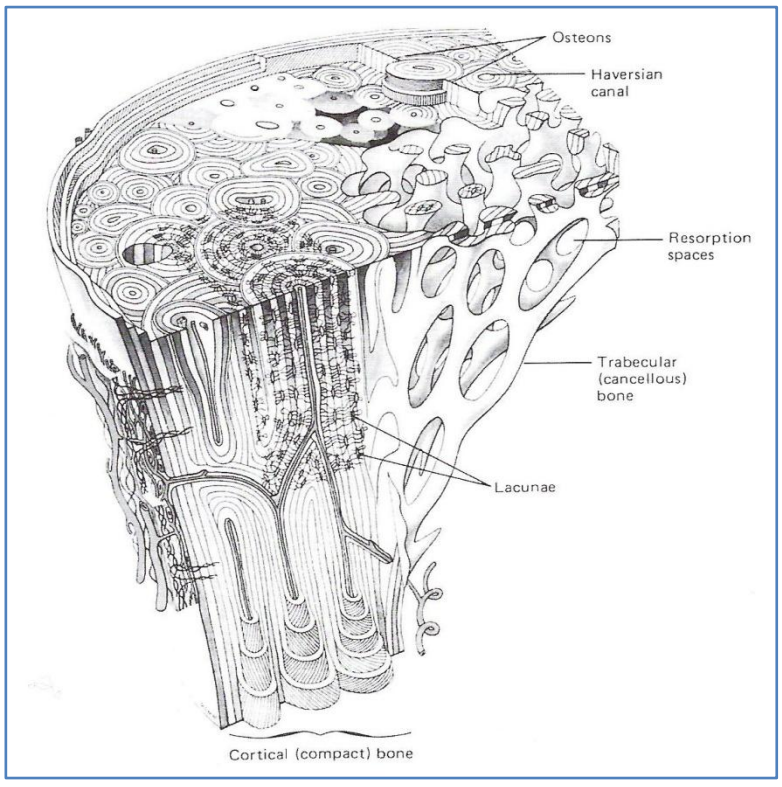
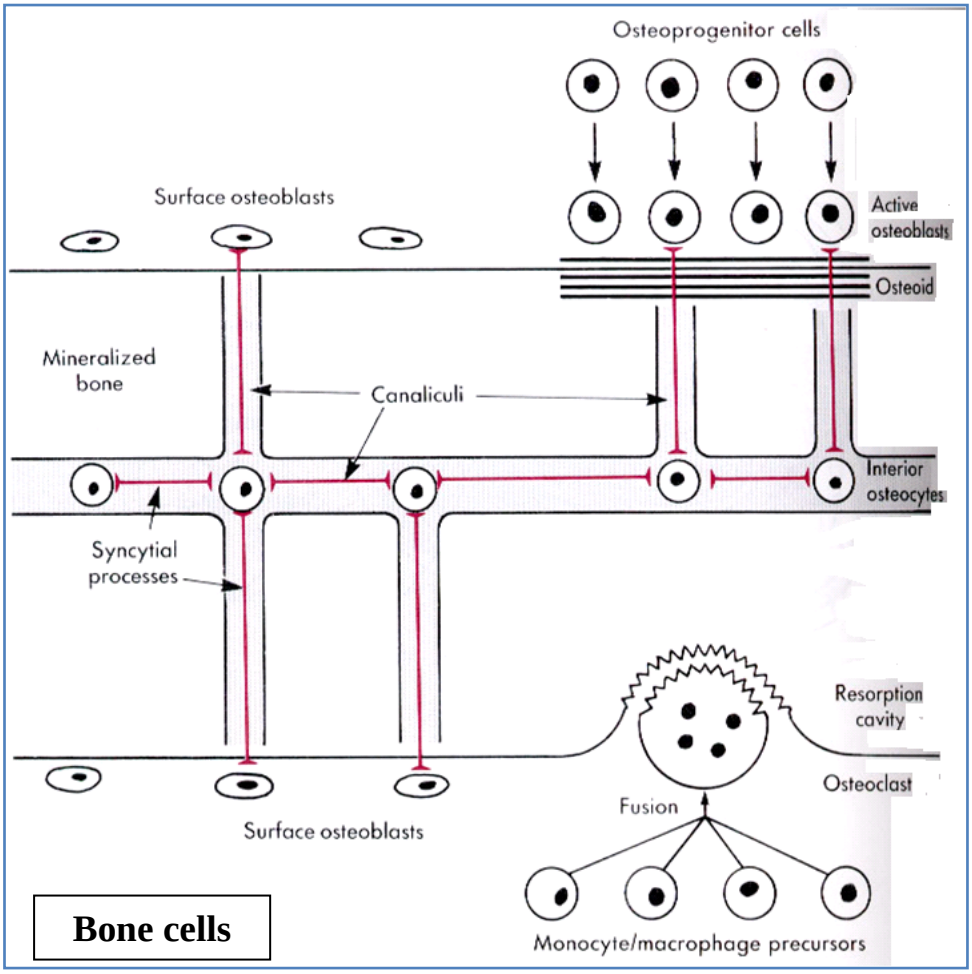


Figure 8-19. Diagram showing features of the microstructure of mature bone seen in both transverse (top) and longitudinal section. Areas of cortical (compact) and trabecular (cancellous) bone are included.

Bone Mineral

The mineral of bone is present in two forms. The major form consists of hydroxyapatite in crystals of varying maturity. The remainder is amorphous calcium phosphate, has a lower calcium/phosphate ratio than pure hydroxyapatite, occurs in regions of active bone formation, and is present in large quantities in young bone.

Bone cells



Bone is composed of three types of cells: the osteoblast, the osteocyte, and the osteoclast.

A. Osteoblasts: the osteoblast is the principal bone-forming cell. It arises from a pool of mesenchymal precursor cells in the bone marrow which as they differentiate, acquire PTH and vitamin D receptors; surface expression of alkaline phosphatase; and expression of bone matrix protein genes –type I collagen (90-95%), osteocalcin (1-2%, rich in γ-carboxylglutamic acid that binds hydroxyapatite with high affinity), ect. Differentiated osteoblasts are directed to the bone surface, where they line regions of new bone formation, laying down bone matrix (osteoid) in orderly lamellae and inducing its mineralization (Fig. 8-20). In the mineralization process, hydroxyapatite crystals are deposited on the collagen layers to produce lamellar bone. Mineralization requires an adequate supply of extracellular calcium and phosphate as well as the enzyme alkaline phosphatase which is secreted in large amount by active osteoblasts.

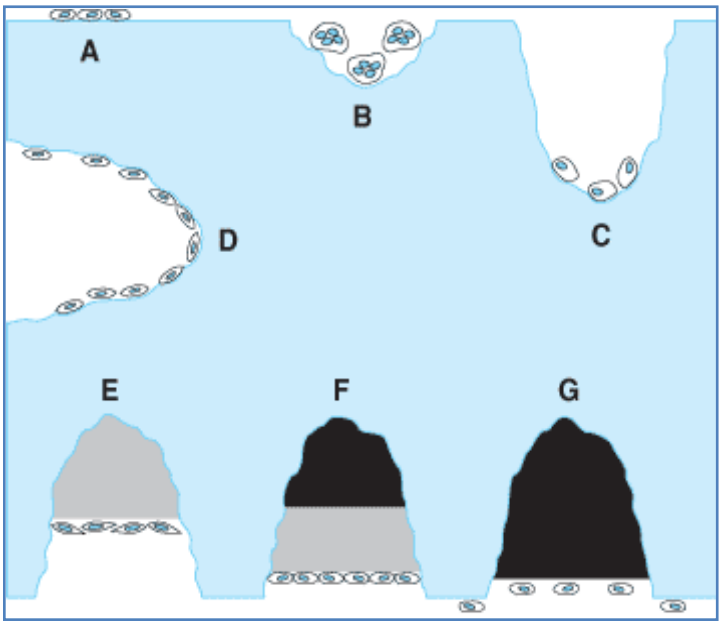


Figure 8-20. The remodeling cycle. ***A:*** Resting trabecular surface. ***B:*** Multinucleated osteoclasts dig a cavity of approximately 20 microns. ***C:*** Completion of resorption to 60 microns by mononuclear phagocytes. ***D:*** Recruitment of osteoblast precursors to the base of the resorption cavity. ***E:*** Secretion of new matrix (gray shading) by osteoblasts. ***F:*** Continued secretion of matrix, with initiation of calcification (black areas). ***G:*** Completion of mineralization of new matrix. Bone has returned to quiescent state, but a small deficit in bone mass persists.

B. Osteocytes: osteoblasts that are trapped in cortical bone during the remodeling process become osteocytes. Protein synthetic activity decreases markedly, and the cells develop multiple processes that reach out through lacunae in bone tissue to communicate with nutrient capillaries. The physiological importance of osteocytes is controversial, but they are believed to act as a cellular syncytium that permits translocation of mineral in and out regions of bone removed for surface.

C. Osteoclasts: the osteoclast is a multinucleated giant cell that is specialized for resorption of bone. To resorbe bone, the motile osteoclast seals off an area by forming an adhesive origin. Having isolated an area of bone surface, the osteoclast develops above the surface an elaborately invaginated plasma membrane structure called the **ruffled border** (Fig. 8-22). The ruffled border acts as a huge lysosome that dissolves bone mineral by secreting acid onto the isolated bone surface and simultaneously breaks down bone matrix by secretion of proteases. Bone resorption can be controlled in two ways: by regulating the number of osteoclasts or the activity of the mature osteoclasts.

Bone Remodeling

Bone remodeling is a continuous process of breakdown and renewal that occurs throughout life. Each remodeling event is carried out by individual "bone remodeling units" (BMUs) on bone surfaces throughout the skeleton (Fig. 8-20). Normally, about 90% of these surfaces lie dormant, covered by a thin layer of lining cells. Following physical or biochemical signals, precursor cells from bone marrow migrate to specific loci on the bone surface, where they fuse into multinucleated bone-resorbing cells – osteoclasts- that dig a cavity into the bone.

Bone remodeling does not absolutely require systemic hormones except, to maintain intestinal absorption of minerals and thus ensure an adequate supply of calcium and phosphorous. Systemic hormones use the bone pool as a source of minerals for regulation of extracellular calcium homeostasis. When they do, the coupling mechanism ensures that bone is replenished. For example, when bone resorption is activated by PTH to provide calcium to correct hypocalcemia, bone formation will also increase, tending to replenish lost bone. One probable mechanisms of coupling has to do with the apparent absence of PTH receptors and

VDRs on osteoclasts. This means that other bone cells that have receptors for these hormones, such as osteoblasts, must receive the hormonal signals and pass along to the osteoclast. This would allow for bone formation to be activated along with bone resorption.

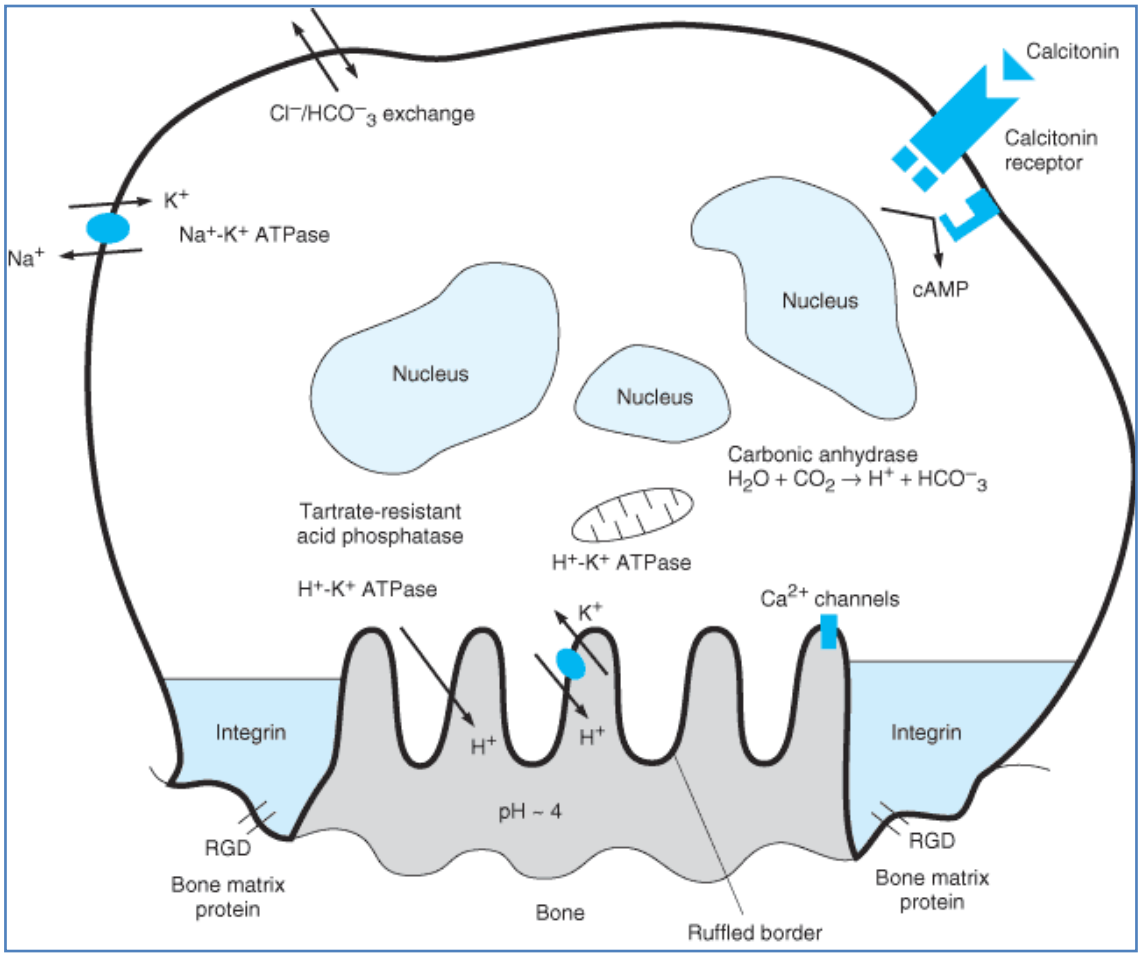
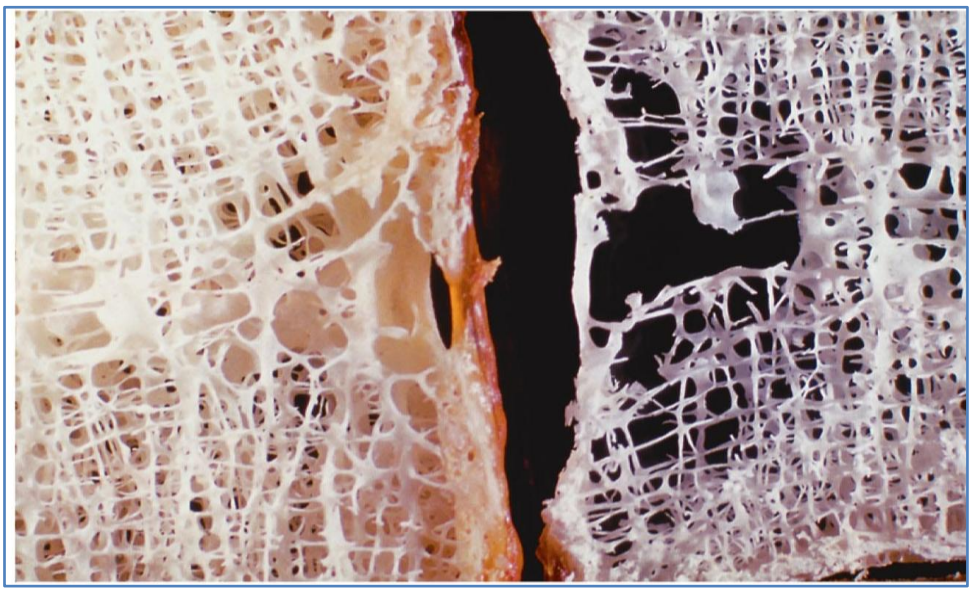


Figure 8-22. Osteoclast-mediated bone resorption. The osteoclast attaches to the bone surface via integrin-mediated binding to bone matrix bone proteins. When enough integrin binding has occurred, the osteoclast is anchored and a sealed space is formed. The repeatedly folded plasma membrane creates a "ruffled" border. Secreted into the sealed space are acid and enzymes forming an extracellular "lysosome."

If the replacement of reabsorbed bone matched the amount that was removed, remodeling would lead to no net change in bone mass. However, small bone deficits persist on completion of each cycle, reflecting inefficiency in remodeling dynamics. Consequently, lifelong accumulation of remodeling deficits underlies the well-documented phenomenon of age-related bone loss, a process that begins shortly after growth stops. Alterations in remodeling activity represent the final pathway through which diverse stimuli such as dietary insufficiency, hormones and drugs affect bone balance. A change in whole body remodeling rate can be brought about through distinct perturbations in remodeling dynamics. Changes in hormonal milieu often increase the activation of remodeling units. Examples include hyperthyroidism, hyperparathyroidism, and hypervitaminosis D. Other factors may impair osteoblastic functional adequacy, such as high doses of glucocorticoids or ethanol. Yet other perturbations, such as estrogen deficiency, may augment osteoclastic receptive capacity.

Osteoporosis

Osteoporosis is a condition of low bone mass and microarchitectural disruption that results in fractures with minimal trauma. Osteoporosis fractures are a major public health problem for older women and men. The consequences of vertebral deformity are less readily measured, but chronic pain, inability to conduct daily activities and psychological depression may be devastating.



Normal bone (left) and bone loss in osteoporosis (right)

The term "primary osteoporosis" denotes reduced bone mass and fractures in postmenopausal women (postmenopausal osteoporosis) or in older men and women (“senile” osteoporosis). "Secondary Osteoporosis" is bone loss resulting from specific clinical disorders, such as thyrotoxicosis or hyperadrenocortisolism. States of estrogen-dependent bone loss, such as exercise-related amenorrhea or prolactin–secreting tumors, are conventionally treated as special cases of primary osteoporosis.

At any age, women experience twice as many osteoporosis-related fractures as men do. Estrogen deprivation promotes bone remodeling by releasing constraints on osteoblastic production of skeletally active cytokines (mainly interleukin-6, IL-6) which in turn, stimulate the proliferation of osteoclast precursors.

With accelerated bone turnover, delivery of calcium from bone to the circulation increases, and the resultant subtle increase in plasma calcium concentration suppresses the secretion of PTH thereby enhancing calciuria, suppressing renal production of $1,25(OH)_2$ D_3, and reducing intestinal calcium absorption efficiency. At menopause, loss of endogenous estrogen promotes an increase in daily calcium loss from 20 mg to about 60 mg, reflecting a relative increase in bone resorption over formation activity. Women who receive estrogen replacement as they enter menopause, show calcium balance and rates of mineral turnover similar to those of premenopausal women. To accommodate changes in calcium by dietary means alone, a rise in daily calcium intake from 1000 mg to about 1500 mg would be necessary.

Osteomalacia and Rickets

Osteomalacia and Rickets are caused by the abnormal mineralization of bone and cartilage. Osteomalacia is a bone defects in which the epiphysial plates have closed (i.e. in adults). Rickets occurs in growing bone affects the transformation of cartilage into bone at the zone of provisional calcification. Growth is retarded by the failure to make new bone.

The best–known cause of abnormal bone mineralization is vitamin D deficiency. Vitamin D, through its biologically active metabolites, ensures that the calcium and phosphate concentration are adequate for mineralization.

Vitamin D may also permit osteoblasts to produce a bone matrix that can be mineralized and then allows them to mineralize the matrix in a normal fashion. Phosphate deficiency can also cause defective mineralization, as in disease in which phosphate is lost in the urine or poorly absorbed in the intestine.

Osteomalacia or rickets may develop despite adequate levels of calcium, phosphate and vitamin D if the bone matrix cannot undergo normal mineralization as a result of enzyme deficiencies such as decreased alkaline phosphate; or in the presence of inhibitors of mineralization such as aluminum (Al) or fluoride (F).

Paget's Disease of Bone (Osteitis Deformans)

Paget's disease is a focal disorder of bone remodeling that leads to greatly accelerated rates of bone turnover, disruption of the normal architecture of bone, and sometimes to gross deformities of bone which might be due to virus infection of bone. Paget's disease is highly prevalent in northern Europe, particularly in England and Germany. Abnormal osteoclastic bone resorption is the probable initiating event in Paget's disease. The rate of bone resorption is often increased by as much as 10-20 fold.

Renal Osteodystorphy

Renal disease results in reduced circulating levels of both $1,25(OH)_2$ D_3 and $24,25(OH)_2$ D_3. With the reduction in $1,25(OH)_2$ D_3 levels, intestinal calcium absorption falls, and bone resorption appears to become less sensitive to PTH a result that leads to hypocalcemia. Phosphate excretion by the diseased kidney is decreased, resulting in hyperphosphatemia. The fall in serum calcium combined with the phosphatemia with the low levels of $1,25(OH)_2$ D_3 results in hyperparathyroidism (Fig. 8-34).

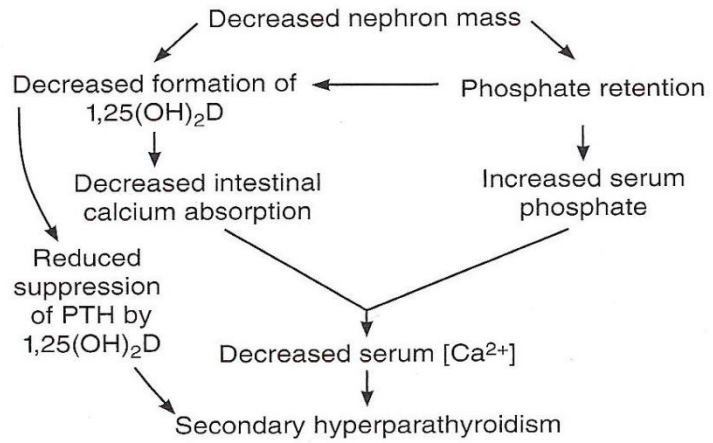


Figure 8–34. Schema for the pathogenesis of renal osteodystrophy.