CHAPTER 58

Calcium and Phosphate Physiology

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OBJECTIVES

This chapter will:
1. Analyze calcium homeostasis, absorption, and excretion in healthy adult subjects.
2. Discuss phosphate homeostasis, absorption, and excretion in healthy adult subjects.
3. Describe the physiology of vitamin D and its central role in regulating calcium and phosphate physiology.

CALCIUM METABOLISM AND HANDLING

The calcium content in a healthy adult body is 1000 to 2000 g (25,000 to 50,000 mmol). In particular, less than 2% of calcium is present in the extracellular fluid (ECF), and more than 98% is part of the mineral component of bone.[1] The calcium of the mineral phase at the surface of the crystals is in equilibrium with ECF calcium, even if only a minor fraction of the total pool (0.5%) is really exchangeable. In a given healthy individual, this value is remarkably stable over time, never deviating by more than 2% from its set point. Under normal conditions, ECF calcium concentration and body calcium content are maintained at fixed values; however, under pathologic conditions, the maintenance of ECF calcium concentration may require an alteration in calcium balance and body calcium content.[2] Furthermore, the calcium in ECF is critical for different functions, and calcium ions inside the cell play a variety of cellular functions. Most intracellular calcium is found in insoluble complexes. In addition, intracellular calcium levels are very low (0.1 mmol/L). The gradient between intracellular and plasma free calcium levels is regulated constantly, playing a critical role in the functional regulation of the single cell. These tightly regulated processes keep a constant gradient between ECF and intracellular calcium ions (10,000 : 1).[3]

Extracellular calcium activates the extracellular calcium-sensing receptor (CaSR), which is a plasma membrane-bound G protein–coupled receptor.[4] This receptor is present in different tissues, such as parathyroid glands, thyroid, intestine, kidney, bone, bone marrow, brain, skin, lung, pancreas, and heart. Once the calcium-sensing receptor is activated by calcium, it couples to a complex array of intracellular signal transduction cascades.[4]

The normal plasma levels of calcium in healthy adults range from 8.8 to 10.4 mg/dL (2.2 to 2.6 mmol/L). Plasma calcium is present in three forms: free ions (50%), ions bound to plasmatic proteins (40%), and diffusible complexes (10% primarily with citrate, phosphate, and bicarbonate). Importantly, free calcium ion concentrations may influence many cellular functions, subjecting them to tight parathyroid hormone (PTH) and vitamin D ($1,25[OH]_2D_3$) control.[5] Because most calcium ions are bound to albumin, plasma protein concentration is a very important factor when calcium ion concentration is investigated. For each 1.0 g/L decrease in serum albumin, total serum calcium decreases by 0.8 mg/dL. For each 1.0 d/dL decrease in serum globulin fraction, total serum calcium decreases by 0.12 mg/dL. The pH of plasma influences the percent of protein-bound calcium.[6] Acute alkalosis decreases the ionized calcium. For every 0.1 change in pH, ionized calcium decreases by 0.12 mg/dL. In particular, to distinguish ionized calcium from the protein-bound calcium fraction, the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines state that total calcium levels have to be adjusted for serum albumin concentration to better describe the free calcium.[7] Usually, the following formula is used:

$$\text{Corrected calcium (mg/dl, mmol/L)} = \text{Total calcium (mg/dL, mmol/L)} + 0.02 \times [40 - \text{Serum albumin (g/L)}]$$

Fig. 58.1 shows a schematic of calcium homeostasis in healthy adults. First, calcium goes into the plasma via absorption from the intestinal tract and resorption from the bone. Second, it leaves the ECF via secretion into the gastrointestinal tract, urinary excretion, deposition in bone, and losses in sweat.

Three organs create calcium flux into or outside the ECF: the intestine, the bone, and the kidney.

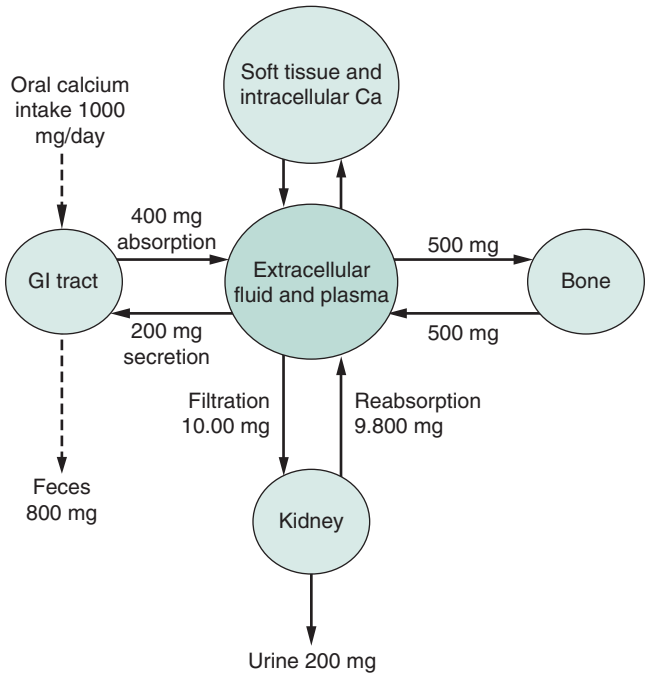

FIGURE 58.1 Calcium homeostasis. *Ca,* Calcium; *GI,* gastrointestinal.

Calcium Handling in the Gastrointestinal Tract

The average daily dietary calcium intake for most healthy adults in Western countries is about 0.6 to 0.8 g. The intake varies, depending on the amount of dairy food ingested with meals. Unfortunately, less than 50% of dietary calcium is absorbed, and an even smaller proportion with advancing age. In contrast, children and women during either pregnancy or breastfeeding usually have higher calcium absorption. However, intestinal calcium absorption after a meal does not contribute to maintenance of the serum calcium value at its set point. Nevertheless, adequate dietary calcium intake and normal intestinal calcium absorption are essential to maintaining normal calcium balance and normal bone metabolism.[8]

In the intestine, absorption efficiency can vary inversely with dietary calcium intake (chronic adaptation). Clearly, with 0.5 g of calcium intake, 50% absorption means 0.25 g; in contrast, with 1.5 g of calcium intake, the intestinal absorption will be 0.5 g (30%). Moreover, 0.1 to 0.2 g of calcium is secreted each day into the intestinal lumen constantly and independently by calcium intake and absorption. Thus, although intestinal calcium absorption cannot regulate serum calcium levels, it provides the calcium needed to keep bone calcium mass within the normal range.[3] Calcium absorption takes place almost exclusively within duodenum, jejunum, and ileum; each of these intestinal segments has an elevated absorbability capacity (i.e., function of the length of the segment and of the residence time of the food). Intestinal absorption across the gut epithelium takes place by two ways:

1. The paracellular pathway
2. The transcellular pathway

The first is a passive absorption and is the main way in the presence of high calcium concentration into the lumen, whereas the second is an active mechanism influenced by calcitriol (1,25 $[OH]_2$ Vit D).[9]

Calcium Handling in the Bone

Bone, a dynamic tissue that is remodeled constantly throughout life, controls serum calcium levels in the fasting state. In fact, to keep serum calcium levels constant, bone releases an amount of calcium identical to the amount excreted in the urine. The calcium set point is the value for which the net calcium inflow, from the bone pool to the ECF, matches the net outflow, from the ECF to the urine. This mechanism is regulated primarily by PTH, which increases the release of calcium from the bone and limits the renal loss of calcium through increased tubular resorption of filtered calcium in the ascending loop of Henle and the distal tubule.[10,11] In addition, bone provides storage for calcium and other ions necessary for homeostatic functions. In bone, the deposition of inorganic mineral is controlled by an orderly organic matrix. Importantly, the mineral phase is composed of calcium phosphate, so the serum concentration of calcium and phosphate regulate the bone formation rate.[12] Nevertheless, bone mineralization does not occur when ECF concentrations of these two ions reach a limit value and a solubility product for bone formation reaches a steady state that depends on proteins that promote or inhibit calcification. In fact, when serum calcium and phosphate values are elevated and levels of inhibitory proteins, such as fetuin-A, matrix Gla protein, osteoprotegerin, osteopontin, and pyrophosphate, are reduced, as happens in uremia, an extraskeletal process of mineralization occurs.[13,14]

Importantly, the bone system corrects deviations from the calcium set point. In the fasting state, the urinary calcium level increases and the serum calcium concentration decreases. The parathyroid cells enter in the cell cycle and immediately secrete great amounts of PTH, which stimulate release of calcium from bone tissue and resorption of calcium from the kidney, allowing the serum calcium value to return to the set point. Even if bone calcium release is so rapid that it creates a fast correction of serum calcium levels, bone remodeling is a slow process because it involves the entire skeleton.[15,16]

Calcium Handling in the Kidney

Urinary calcium excretion in healthy adults with a normal calcium intake is 0.1 to 0.4 g daily. Different amounts of calcium are filtered, reabsorbed, and excreted by the kidney, and in all situations, renal calcium reabsorption is more than 95% of filtered load. When the calcium intake is less than 0.2 g daily, urinary calcium excretion is less than 0.2 g daily.[17] Moreover, the amount of calcium in the urine is usually very small compared with the quantity of calcium filtered by the glomeruli (from 6 to 10 g daily), because the rate of proximal tubular calcium reabsorption is generally high.[18] The majority of calcium reabsorption takes place along the proximal tubule (60%) and THAL (thick ascending limb of the loop of Henle) (25%). The reabsorption of calcium in the proximal convoluted tubule is a passive transport by paracellular pathway and parallels that of sodium and water. In the TALH Ca reabsorption is regulated by the CaSR located basolaterally.[19] In addition, 15% of the filtered load of calcium is reabsorbed in the distal convoluted tubule, the connecting tubule, and the initial part of the cortical collecting duct. Importantly, in this distal portion of the nephron, calcium reabsorption actively opposes the natural electrochemical gradient. The terminal nephron, although responsible for the reabsorption of only 5% to 10% of the filtered calcium load, is the major site for regulation of calcium excretion.

This active transcellular transport is regulated by PTH, $1,25(OH)_2D_3$, calcium intake, estrogens, and calcitonin. Different genes have been found to be involved in transepithelial calcium transport, of which *TRPV5* and *TRPV6* seem to play a central role.[20]

The concentration of ECF calcium depends on the balance between the amount of calcium entering into the ECF (mainly from bone) and the amount of calcium leaving the ECF (in the urine). Clearly, an increase in the ECF calcium value may result from two processes, a decrease in the renal excretion of calcium entering into the ECF or an increase in the calcium flow into the ECF.

Table 58.1 summarizes renal calcium handling in a healthy subject.

PHOSPHORUS METABOLISM AND HANDLING

In healthy adult subjects, phosphorus represents a key component not only of bone tissue but also of many other tissues and is involved in many cellular processes. About 1000 g (32 mol) of phosphorus is maintained in the body of a healthy adult, of which 850 g usually are stored in bone tissue.[1]

In a fasting plasma specimen, most of the phosphorus is present as inorganic orthophosphate in concentrations from 2.8 to 4.0 mg/dL (0.9 to 2.3 mmol/L). Serum Pi level

TABLE 58.1

Renal Calcium Handling

SEGMENT	TRANSPORT MECHANISMS	REGULATION
Glomerulus	Free filtration	Glomerulotubular feedback
Proximal tubule	Paracellular passive transport mediated by Na^+,K^+- ATPase; Na^+/calcium symport	ECF variations cause changes in Na^+ and calcium reabsorption
Loop of Henle:		
Thin loop	Permeable to calcium only in thin ascending limb, with no active transport	In thin descending limb, calcium depends on water and urea reabsorption
Thick ascending limb	Paracellular passive transport on basolateral membrane: Na^+ reabsorption	Na^+,K^+-ATPase
	On apical membrane: Calcium links to Na+ reabsorption	Na^+-K^+-$2Cl^-$ symport regulated by basolateral located CaSRs
Distal tubule	Transcellular active transport on apical membrane, calcium does not link to Na^+ reabsorption	PTH increases and acidosis reduces calcium reabsorption
Collecting tubule	Transcellular active transport against chemical and electrical gradient on apical membrane, calcium does not link to Na^+ reabsorption	PTH increases and acidosis reduces calcium reabsorption

ATPase, Adenosine triphosphatase; *CaSR,* calcium-sensing receptor; *ECF,* extracellular fluid; *PTH,* parathyroid hormone.

is crucial for several important cellular processes (energy metabolism, bone formation, signal transduction) and as a constituent of phospholipids and nucleic acids. Contrary to calcium, of which approximately 50% is bound, only about 12% of phosphorus is bound to plasma proteins. Free dihydrogen phosphate ($H_2PO_4^-$) normally accounts for about 10% of the total phosphorus, whereas free hydrogen phosphate (HPO_4^{2-}) and sodium phosphate ($NaPO_4^-$) account for 75%. Phosphate has a pKa of 6.8, but at normal physiologic pH (7.4), it exists primarily as a divalent ion.[2] Different forms of phosphorus are present in plasma, depending on pH and other factors. In fact, children and postmenopausal women have higher phosphorus levels than the general population. Importantly, elevated total phosphorus values do not seem to depend on higher intake of phosphorus with meals. In addition, a circadian variation in levels of phosphorus during a 24-hour fast, in part mediated by the adrenal cortex, has been demonstrated. A low-phosphorus diet clearly decreases the morning fasting levels and probably reduces the enhancement and the plateau typically seen in the afternoon. Serum ionized calcium levels do not change even when serum phosphorus increases twofold.[3] Gastrointestinal absorption of phosphate takes place in the small intestine mainly in jejunum and duodenum with a minimal activity in ileum. Absorption occurs by passive (paracellular) and active (intracellular) mechanisms. Intestinal absorption of P is mediated by NaPi2b (sodium dependent P transporter), which is regulated by phosphorus intake and 1,25VitD. Phosphatonin FGF23 indirectly reduces phosphate absorption.[19] A low phosphate intake promotes a reduction in renal phosphate excretion, preventing hypophosphatemia. Clearly, renal tubular cells retain the ability to increase the phosphate tubular transport, with variability among different portions of the proximal tubules. Hypophosphatemia stimulates 25(OH)D-1α-hydroxylase, which is modulated critically by renal tubular phosphate fluxes.[21] Contrarily, hyperphosphatemia and increased renal tubular fluxes result in reduced phosphate reabsorption, increased clearance of phosphate, and suppressed activity of 25(OH)D-1α-hydroxylase.

The kidney is the major organ for control of phosphate losses. Phosphorus filtered through the glomerulus usually is reabsorbed in the proximal tubule, resulting in only 10% to 15% excretion of the filtered load. Physiologically, the proximal tubular reabsorption increases if the filtered phosphate load decreases. In contrast, phosphate clearance and renal tubular reabsorption increase if the filtered phosphate load increases. Basically, urinary phosphate excretion reflects dietary phosphate intake (Table 58.2).

In contrast to intestinal calcium absorption, phosphate is reabsorbed primarily by the gut. In fact, at levels of phosphate intake of about 2 mg per kg of body weight daily, 85% of ingested phosphorus is absorbed. Furthermore, phosphate is a key regulatory factor in parathyroid function. In fact, elevated serum phosphorus levels induce secondary hyperparathyroidism through direct (inhibition of $1,25[OH]_2D_3$ production) and indirect (subsequent reduction of calcium levels) mechanisms. Furthermore, phosphorus regulates PTH messenger RNA stability, controlling parathyroid function at a posttranscriptional level.[15] Finally, the physiologic role of phosphorus in regulating parathyroid cell growth has been well demonstrated.[16]

PHYSIOLOGY OF VITAMIN D

Vitamin D is not a "vitamin" but rather a hormone. Vitamin D plays a pivotal role in calcium homeostasis and skeletal metabolism throughout life. Classical vitamin D deficiency causes rickets in children and osteomalacia in children and adults. Vitamin D is also important for the functioning of many other systems, such as the immune, cardiovascular, and reproductive systems.[22,23,24] Classically, the metabolic control for activation of vitamin D is regulated by liver and kidney, and the target tissues for vitamin D are the bone and the gut. Calcium, phosphate, PTH, and other peptides regulate renal vitamin D handling (Fig. 58.2).

The vitamin D precursors, cholecalciferol, typical of animal life (vitamin D_3), and ergocalciferol, typical of vegetal life (vitamin D_2), derive from dietary sources (animal and fish liver, eggs, fish oils). However, cholecalciferol also is produced in the skin from 7-dehydrocholesterol (pre-vitamin D_3), through the nonenzymatic effect of the ultraviolet B rays of sunlight (UVB; wavelengths 295–305 nm). Cholecalciferol and ergocalciferol are hydroxylated enzymatically at carbon 25 in the liver and at carbon 1 in renal tubules.[21]

The monohydroxylated metabolite, 25-hydroxycholecalciferol ($25[OH]D_3$), is 500 times less active than $1,25(OH)_2D_3$, but its serum concentration is the best indicator of vitamin

TABLE 58.2

Renal Phosphorus Handling

SEGMENT	TRANSPORT MECHANISMS	REGULATION
Glomerulus	Free filtration	Glomerulotubular feedback
Proximal tubule	Na^+,K^+-ATPase; Phosphate transporters NaPi-2a and -2c are responsible for transepithelial transport Na^+ and PO_4^- reabsorption	ECF variations cause changes in Na^+ and PO_4^- reabsorption Transepithelial transport is regulated by P load, PTH, FGF23/Klotho: last two inhibit PT phosphate reabsorption PTH induces PO_4^- excretion
Loop of Henle		
Thin loop	Permeable to PO_4^- only in thin ascending limb, with no active transport	In thin descending limb, PO_4^- depends on water and urea reabsorption
Thick ascending limb	Extremely low PO_4^- reabsorption	—
Distal tubule	On apical membrane, PO_4^- reabsorption depends on PTH but does not link to Na^+ reabsorption	Increased PTH inhibits PO_4^- reabsorption and enhances PO_4^- excretion Reduced serum PO_4^- levels suppress PTH and increase PO_4^- reabsorption
Collecting tubule	On apical membrane, PO_4^- reabsorption depends on PTH but does not link to Na^+ reabsorption	Increased PTH inhibits PO_4^- reabsorption and enhances PO_4^- excretion Reduced serum PO_4^- levels suppress PTH and increase PO_4^- reabsorption

ATPase, Adenosine triphosphatase; *ECF,* extracellular fluid; *FGF23,* fibroblast growth factor 23 (phosphatonin produced by osteocytes and osteoblasts); *Klotho,* transmembrane protein of FGF23 for its receptors; *PO_4^-,* phosphate; *PTH,* parathyroid hormone.

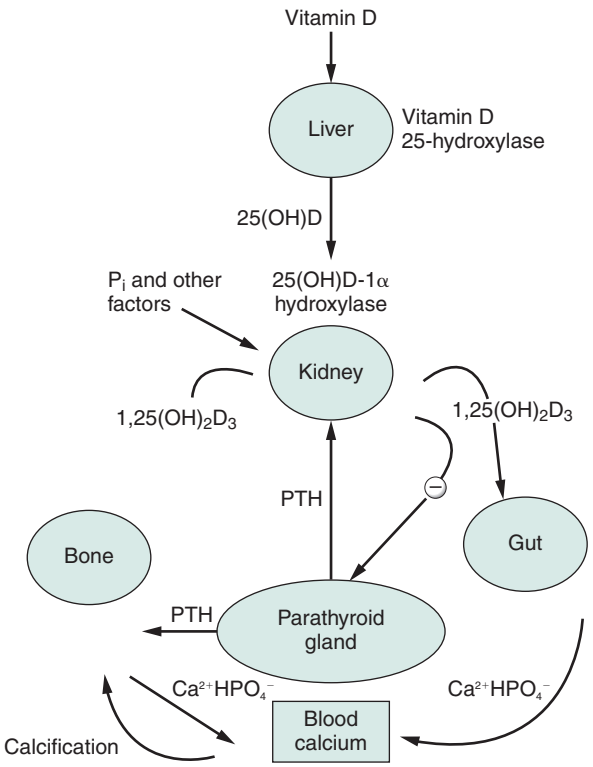

FIGURE 58.2 Vitamin D physiology. *P_i,* Inorganic phosphate; *PTH,* parathyroid hormone.

D body stores. Optimal levels of 25(OH)$_2$D$_3$ are not defined unanimously; most experts agree that values below 20 ngL(50 nmol/L) indicate deficiency, values between 21 and 30 ng/L indicate insufficiency, and levels above 30 ng/mL (75 nmol/L) indicate sufficiency.[25] In spite of its low affinity for the vitamin D receptor (VDR), 25(OH)D$_3$ maintains some biologic effects, because its serum concentrations are 1000 times higher than those of 1,25(OH)$_2$D$_3$, thus compensating for the low affinity for VDR.[2] Furthermore, lower 25(OH)D$_3$ serum concentrations are associated with higher risk of fracture and low bone mineral density at different bone sites in young and elderly healthy individuals of both genders. Conversely, excessively high 25(OH)D$_3$ levels are associated with low bone turnover. The need to maintain normal vitamin D stores suggests that an unknown vitamin D metabolite in addition to 1,25(OH)$_2$D$_3$ may have a beneficial effect on bone and parathyroid metabolism.[26]

The α-hydroxylation of 25(OH)D takes place in the kidney and in extrarenal tissues via the 1α-hydroxylase enzyme CYP27B1 to 1,25(OH)2D. The 1,25(OH)2D produced in the kidney and transported bound to DBP to tissues involved in Ca-P metabolism acts as an endocrine modulator of calcium and phosphate homeostasis.[27] The final product, 1,25-dihydroxycholecalciferol (1,25[OH]$_2$D$_3$), is the active metabolite of vitamin D, although its serum concentration does not correlate with vitamin D stores. It has been demonstrated that 1,25(OH)$_2$D$_3$ promotes active and passive intestinal absorption of calcium and phosphate and, consequently, bone mineralization. The actions of 1α,25(OH)2D3 on the osteoblast (bone formation) and cross-talk with the osteoclast result in bone resorption and overall bone remodeling.[22] Conversely, 1,25(OH)$_2$D$_3$ suppresses PTH synthesis and parathyroid cell proliferation through a genomic activity.[28] The genomic effect of 1,25(OH)$_2$D$_3$ is modulated by specific cytosolic vitamin D receptors (VDRs) in target cells. VDR forms a heterodimer with the retinoid X receptor that enables the complex 1,25(OH)$_2$D$_3$–VDR to bind with high affinity to the vitamin D response element (VDRE) on the transcription promoters of vitamin D–sensitive genes. VDR has been detected in vitamin D–sensitive tissues (bone, intestine, kidney, and parathyroid glands) and even in tissues in which vitamin D activity is still unclear (myocardium, brain, pancreas, and testis). In addition to the genomic effect, a rapid nongenomic effect of 1,25(OH)$_2$D$_3$ has been found in intestinal cells.[2] This rapid effect is mediated with the interaction with the classic VDRs associated with

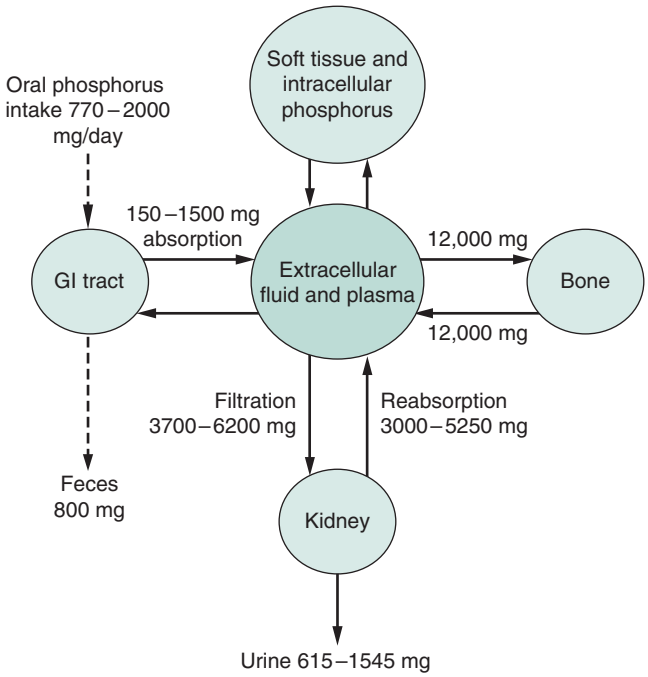

FIGURE 58.3 Phosphate homeostasis. *GI,* Gastrointestinal.

caveolae present in the plasma membrane of these cells.[29] Vitamin D receptors are diffusely present in the intestine, bone, kidney, skin, breast, parathyroid gland, brain, gonads, pituitary gland, skeletal muscle, circulating monocytes, and activated lymphocytes of healthy adults. Clearly, $1,25(OH)_2D_3$ controls the proliferation of fibroblasts and keratinocytes, stimulates keratinocyte differentiation, and enhances interleukin-1 synthesis by monocytes. Importantly, $1,25(OH)_2D_3$ suppresses PTH synthesis and secretion and controls parathyroid cell proliferation in renal insufficiency, maintaining a central role in the pathogenesis and treatment of secondary hyperparathyroidism.[1]

The 1,25(OH)2D produced in extrarenal target tissues acts locally in an autocrine or paracrine fashion and generally does not reach the circulation. The function of 1,25(OH)2D in cells of the calcium-phosphate homeostatic system and other target tissues is to induce genomic and nongenomic responses mediated through its interaction with VDRs.[22,30] Modification of serum calcium levels is the major physiologic mechanism that regulates $1,25(OH)_2D_3$ production, PTH secretion, and phosphate homeostasis (Fig. 58.3).

CONCLUSION

In healthy subjects, the calcium and phosphate balance may be positive, normal, or negative in the absence of any overt abnormality in either serum calcium or phosphate concentration. Therefore simply measuring serum calcium and phosphate concentrations is not much help in predicting calcium and phosphate balance. Anyway, if treatment is initiated assuming an initial condition of low serum calcium or high serum phosphate levels, a subsequent increase in PTH synthesis and secretion, accompanied by a rapid parathyroid gland hyperplasia, occurs. Target tissues for PTH are bone, kidney, and gut. The effects on bone are to enhance bone to increase serum calcium and phosphate levels. The effects on the kidneys are to increase calcium reabsorption but produce phosphate excretion, with an enhancement in active vitamin D. Active vitamin D increases calcium and phosphate reabsorption from the gut. Finally, higher calcium levels suppress PTH secretion through negative feedback.

Key Points

1. Calcium and phosphate physiology is regulated by the intestine, bone, kidney, and the parathyroid gland.
2. Parathyroid hormone and vitamin D are the two key hormones that control calcium and phosphate handling.
3. Renal calcium and phosphate transport is regulated differently along the proximal and distal tubules.
4. Serum calcium and phosphate concentrations poorly predict calcium and phosphate balance.
5. Vitamin D receptors and calcium-sensing receptors are expressed widely in the body, and both types of receptors biologically regulate calcium and phosphate homeostasis.

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A complete reference list can be found online at ExpertConsult.com.

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