Calcium Metabolism in Health and Disease

Munro Peacock
Indiana University Medical School, Indianapolis, Indiana

This brief review focuses on calcium balance and homeostasis and their relationship to dietary calcium intake and calcium supplementation in healthy subjects and patients with chronic kidney disease and mineral bone disorders (CKD-MBD). Calcium balance refers to the state of the calcium body stores, primarily in bone, which are largely a function of dietary intake, intestinal absorption, renal excretion, and bone remodeling. Bone calcium balance can be positive, neutral, or negative, depending on a number of factors, including growth, aging, and acquired or inherited disorders. Calcium homeostasis refers to the hormonal regulation of serum ionized calcium by parathyroid hormone, 1,25-dihydroxyvitamin D, and serum ionized calcium itself, which together regulate calcium transport at the gut, kidney, and bone. Hypercalcemia and hypocalcemia indicate serious disruption of calcium homeostasis but do not reflect calcium balance on their own. Calcium balance studies have determined the dietary and supplemental calcium requirements needed to optimize bone mass in healthy subjects. However, similar studies are needed in CKD-MBD, which disrupts both calcium balance and homeostasis, because these data in healthy subjects may not be generalizable to this patient group. Importantly, increasing evidence suggests that calcium supplementation may enhance soft tissue calcification and cardiovascular disease in CKD-MBD. Further research is needed to elucidate the risks and mechanisms of soft tissue calcification with calcium supplementation in both healthy subjects and CKD-MBD patients.

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Calcium is the fifth most abundant element in the human body, with ~1000 g present in adults. It plays a key role in skeletal mineralization, as well as a wide range of biologic functions. Calcium is an essential element that is only available to the body through dietary sources. Current dietary calcium recommendations range from 1000 to 1500 mg/d, depending on age (1). In some individuals, particularly the elderly (2), calcium supplements may be needed to achieve the recommended dietary calcium intake. Calcium requirement is dependent on the state of calcium metabolism, which is regulated by three main mechanisms: intestinal absorption, renal reabsorption, and bone turnover. These in turn are regulated by a set of interacting hormones, including parathyroid hormone (PTH), 1,25-dihydroxyvitamin D [1,25$(OH)_2$D], ionized calcium itself, and their corresponding receptors in the gut, kidney, and bone.

This brief review focuses on the key mechanisms in the gut, kidney, and bone involved in the regulation of calcium metabolism in humans. It provides an overview of calcium balance and homeostasis in health. Because of the interdependent relationship between calcium and phosphorus for mineralization in bone and soft tissues, this review also discusses the interactions between calcium and phosphorus balance and homeostasis, the dysregulation that occurs in chronic kidney disease–mineral and bone disorders (CKD-MBD) (3), and the impact of calcium supplementation on phosphate homeostasis.

Correspondence: Dr. Munro Peacock, University Hospital, Room 5595, 550 North University Boulevard, Indianapolis, IN 46202. Phone: 317-274-4356; Fax: 317-274-4361; E-mail: mpeacock@iupui.edu

Calcium Distribution

Calcium plays a key role in a wide range of biologic functions, either in the form of its free ion or bound complexes. One of the most important functions as bound calcium is in skeletal mineralization. The vast majority of total body calcium (>99%) is present in the skeleton as calcium-phosphate complexes, primarily as hydroxyapatite, which is responsible for much of the material properties of bone (4). In bone, calcium serves two main purposes: it provides skeletal strength and, concurrently, provides a dynamic store to maintain the intra- and extracellular calcium pools.

Nonbone calcium represents <1% of total body calcium (~10 g in an adult). However, it is in constant and rapid exchange within the various calcium pools and is responsible for a wide range of essential functions, including extra- and intracellular signaling, nerve impulse transmission, and muscle contraction (5,6). Serum calcium ranges from ~8.8 to 10.4 mg/dl (2.2 to 2.6 mM) in healthy subjects. It comprises free ions (~51%), protein-bound complexes (~40%), and ionic complexes (~9%) (7). To avoid calcium toxicity, the concentration of serum ionized calcium is tightly maintained within a physiologic range of 4.4 to 5.4 mg/dl (1.10 to 1.35 mM). Nonionized calcium is bound to a variety of proteins and anions in both the extra- and intracellular pools. The main calcium-binding proteins include albumin and globulin in serum and calmodulin and other calcium-binding proteins in the cell. The major ionic complexes in serum are calcium phosphate, calcium carbonate, and calcium oxalate.

Calcium Balance

Calcium balance refers to the state of the body stores of calcium at equilibrium over some extended time period (usu-

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ally days, weeks, or months). It results from the net effects of intestinal absorption and renal, intestinal, and sweat gland excretion on bone calcium, the dominant calcium pool. Bone balance changes throughout the normal lifespan, depending on relative rates of bone formation and resorption. Children are in positive bone balance (formation > resorption), which ensures healthy skeletal growth. Healthy young adults are in neutral bone balance (formation = resorption) and have achieved peak bone mass. Elderly individuals are typically in negative bone balance (formation < resorption), which leads to age-related bone loss. Factors that promote positive bone balance in adults include exercise, anabolic and antiresorptive drugs, and conditions that promote bone formation over bone resorption (*e.g.*, "hungry bone" syndrome, osteoblastic prostate cancer). On the other hand, immobilization, weightlessness, and sex steroid deficiency, among others, produce negative bone balance.

Bone mineral content, as measured by imaging techniques such as dual x-ray absorptiometry and computed tomography, provides good estimates of total body calcium. Measured over an extended period of time (usually >1 yr), bone mineral content measures long-term calcium balance. Bone mineral content increases throughout childhood (8), peaks in adolescence (9), remains relatively constant in early/late adulthood (10), and declines in old age (Normal Population Data Base, DPX-IQ Reference Manual, Documentation Version 5/96; Lunar Corporation, Madison, WI).

Longitudinal measurements of bone mineral content provide information on changes in calcium balance but do not assess the mechanisms involved in maintaining calcium balance. This requires calcium metabolic balance studies that quantify intake and excretion (11). When calcium balance is combined with calcium kinetics, direct measures of bone formation, bone resorption, and endogenous gut secretion can be measured (12). For example, the positive calcium balance in adolescents (*e.g.*, mean age 13 yr) is achieved by higher levels of bone formation, resorption, net bone calcium retention and absorption and lower urine calcium compared with those of young adults (*e.g.*, mean age 22 yr) in neutral balance (Figure 1A). Sex (13) and race (14) variations in calcium balance in adolescents have also been identified. This can be seen in black American adolescents, who have higher rates of calcium absorption, increased net skeletal calcium retention, and lower urine calcium than white American adolescents (Figure 1B) (14). Such differences probably explain the higher bone mass in black Americans compared with white Americans that occurs in childhood (15,16) and adulthood (17) and persists into old age (2).

Dietary calcium intake is a major determinant of calcium balance, particularly during adolescence, the period of peak bone mass accretion. Calcium supplementation to the diet of the elderly prevents age-related bone loss (18) and is established therapy for prevention of age-related osteoporosis.

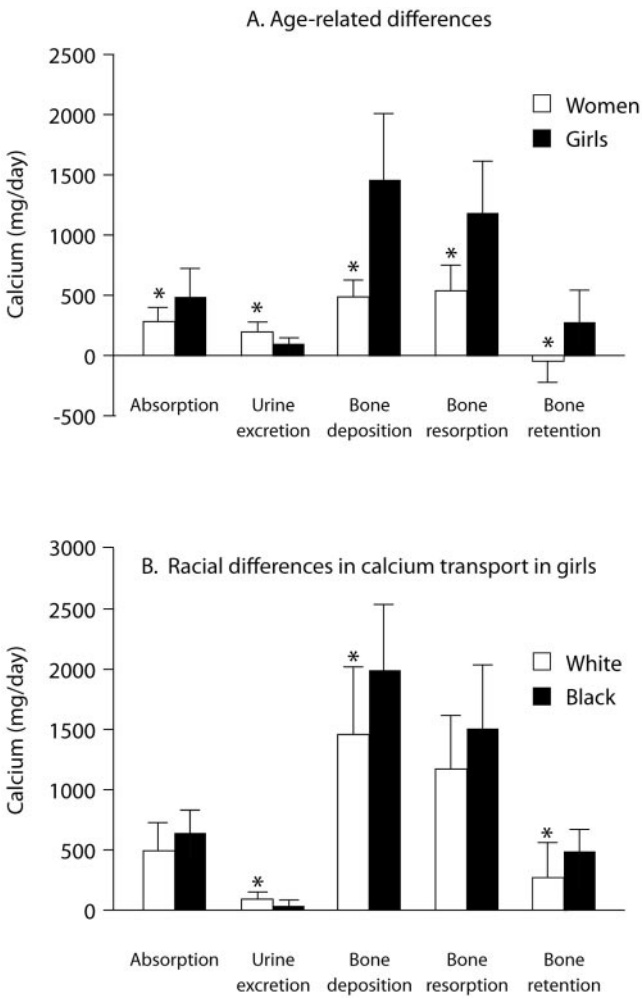

Figure 1. (A) Calcium transport in women and girls. Gut absorption, bone deposition, bone resorption, and bone retention were significantly lower, whereas urinary excretion was significantly higher in women (n = 11; mean age, 22 yr) *versus* girls (n = 14; mean age, 13 yr) (12). (B) Racial differences in calcium transport in American girls. Bone deposition and bone retention were significantly lower, whereas urinary excretion was significantly higher in white girls (n = 14; mean age, 13.7 yr) *versus* black girls (n = 14; mean age, 12.8 yr). Values are mean ± SD (mg/d). *Significant difference in mean values (14).

Calcium Homeostasis

Calcium homeostasis is largely regulated through an integrated hormonal system that controls calcium transport in the gut, kidney, and bone. It involves two major calcium-regulating hormones and their receptors—PTH and the PTH receptor (PTHR) (19) and 1,25$(OH)_2$D and the vitamin D receptor (VDR) (20)—as well as serum ionized calcium and the calcium-sensing receptor (CaR) (Figure 2) (21).

Serum calcium homeostasis has evolved to simultaneously maintain extracellular ionized calcium levels in the physiologic range while allowing the flow of calcium to and from essential stores. A decrease in serum calcium inactivates the CaR in the parathyroid glands to increase PTH secretion, which acts on the PTHR in kidney to increase tubular calcium reabsorption, and in bone to increase net bone resorption. The increased PTH also stimulates the kidney to increase secretion of 1,25$(OH)_2$D, which activates the VDR in gut to increase calcium absorption, in the parathyroid glands to decrease PTH secretion, and in

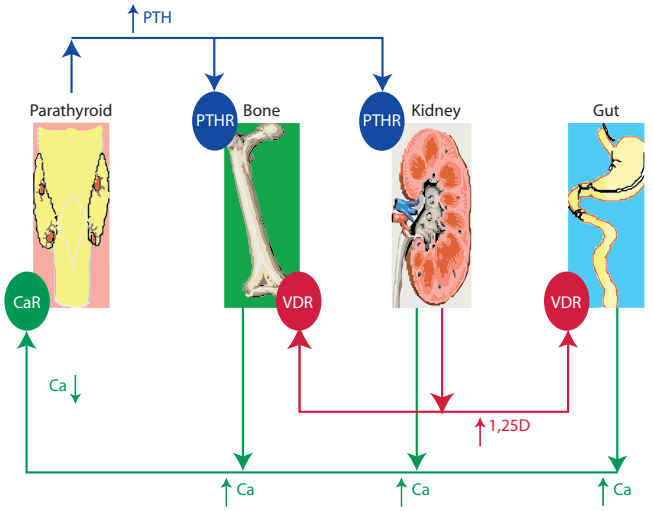

Figure 2. Regulation of serum calcium homeostasis. Serum calcium homeostasis is regulated by a rapid negative feedback hormonal pathway involving the concentration of ionized calcium in serum (Ca, green arrows) and the secretion of parathyroid hormone (PTH, blue arrows) from the parathyroid. A fall in serum calcium (↓ Ca) inactivates the calcium receptor in the parathyroid cell (CaR; green circle) and increases PTH secretion (↑ PTH), which restores serum calcium (↑ Ca) by activating the parathyroid receptor (PTHR; blue circles) in bone, to increase calcium resorption, and in kidney, to increase tubular calcium reabsorption. In kidney, the increased PTH secretion augments its calcium-restorative effect by increasing secretion of 1,25-dihydroxyvitamin D (1,25D; red arrows), which, acting on the vitamin D receptor (VDR, red circles) in gut, increases active calcium absorption and increases calcium resorption in bone.

bone to increase resorption. The decrease in serum calcium probably also inactivates the CaR in kidney to increase calcium reabsorption and potentiate the effect of PTH. This integrated hormonal response restores serum calcium and closes the negative feedback loop. With a rise in serum calcium, these actions are reversed, and the integrated hormonal response reduces serum calcium. Together, these negative feedback mechanisms help to maintain total serum calcium levels in healthy individuals within a relatively narrow physiologic range of ~10%.

Hypocalcemia and Hypercalcemia

Hypocalcemia and hypercalcemia are terms used clinically to refer to abnormally low and high serum calcium concentrations. It should be noted that, because about one half of serum calcium is protein bound, abnormal serum calcium, as measured by total serum calcium, may occur secondary to disorders of serum proteins rather than as a consequence of changes in ionized calcium. Hypercalcemia and hypocalcemia indicate serious disruption of calcium homeostasis but do not on their own reflect calcium balance. They can be classified by the main organ responsible for the disruption of calcium homeostasis, although clinically more than one mechanism is invariably involved.

Intestinal Calcium Absorption

Dietary intake and absorption are essential to provide sufficient calcium to maintain healthy body stores. Approximately 30% of dietary calcium ingested in a healthy adult is absorbed by the small intestine. Calcium absorption is a function of active transport that is controlled by $1,25(OH)_2D$, which is particularly important at low calcium intakes, and passive diffusion, which dominates at high calcium intakes. Typically, at normal calcium intake, $1,25(OH)_2D$-dependent transport accounts for the majority of absorption, whereas as little as 8 to 23% of overall calcium absorption is caused by passive diffusion (22).

Because almost all dietary calcium intake is absorbed from the upper intestine, frequent meals or oral supplements promote net calcium absorption. The bioavailability of dietary calcium can be enhanced. Aluminum hydroxide, which binds dietary phosphate (23), when taken in excess leads to hypercalciuria from increased calcium absorption (24). On the other hand, calcium absorption is lowered if the bioavailability of dietary calcium is lowered by calcium-binding agents such as cellulose, phosphate, and oxalate. A variety of diseases of the small bowel, including sprue and short bowel syndrome, can result in severe calcium malabsorption.

Absorptive hypercalcemia occurs from conditions that produce increased serum $1,25(OH)_2D$ levels as occurs in sarcoidosis, increased serum 25(OH)D levels from vitamin D poisoning, or excessive intake of calcitriol or its analogs. Absorptive hypercalcemia readily develops in children and patients with chronic kidney disease (CKD) when they receive amounts of dietary calcium that exceed the ability of their kidneys to filter and excrete the calcium load (25).

Absorptive hypocalcemia caused solely by a low dietary calcium intake is rare, because the homeostatic mechanisms are highly efficient and maintain serum calcium in the low physiologic range at the expense of calcium stores in bone. However, absorptive hypocalcemia is common in states of low, or inappropriately low, serum $1,25(OH)_2D$ as occurs in chronic vitamin D deficiency, osteomalacia, and rickets or in impaired $1,25(OH)_2D$ production as occurs in CKD.

Bone Calcium Remodeling

Bone continuously remodels by coordinated cellular mechanisms to adapt its strength to the changing needs of growth and physical exercise (26). Old, damaged, and unneeded bone is removed by resorption, and new bone is subsequently deposited by formation. Diseases affecting either or both of these processes lead to disturbed calcium homeostasis.

Remodeling hypercalcemia results from increased net bone resorption as occurs in osteoclastic metastatic bone cancer, primary hyperparathyroidism, and vitamin D poisoning. In CKD patients with adynamic bone disease, hypercalcemia is readily produced because the bone is unable to take up calcium by formation (27).

Remodeling hypocalcemia results from increased net bone formation as occurs in postparathyroidectomy "hungry bone syndrome" and osteoblastic metastatic bone cancer. It has been hypothesized that bone can release to, and remove calcium from, the circulation by active mechanisms separate from the

remodeling system (28). However, although bone acts as a temporary buffer to take up and release serum calcium, the mechanism is largely passive and driven by the serum calcium concentration itself.

Renal Calcium Excretion

Renal calcium excretion is regulated by two main mechanisms: tubular calcium reabsorption and filtered calcium load (29). Disruption of either or both of these mechanisms leads to abnormal calcium homeostasis. In CKD, disturbances in calcium homeostasis are common and, as GFR decreases, disturbances in calcium homeostasis increase (30).

Tubular reabsorptive hypercalcemia arises from a sustained increase in tubular calcium reabsorption as occurs in primary hyperparathyroidism, sodium depletion, thiazide medications, and inactivating mutations in the CaR.

Tubular reabsorptive hypocalcemia arises from a sustained decrease in tubular calcium reabsorption as occurs in postsurgical hypoparathyroidism, abnormalities in the PTHR complex, and activating CaR mutations.

GFR hypercalcemia develops when the input of calcium to the circulation exceeds its removal by the kidney's filtration rate independent of the tubular calcium reabsorption rate (29). This readily occurs in children and patients with CKD (25). In states of reduced GFR, even a normal input of calcium into the circulation from gut or bone can result in hypercalcemia. It is also important to note that hypercalcemia itself is deleterious to kidney function, and reduced GFR is often an important component of any hypercalcemia.

Calcium–Phosphate Interactions

Calcium and phosphate (inorganic phosphorus) interact in several fundamental processes. In the skeleton, calcium and phosphate metabolism work in cohort with osteoblasts, osteocytes, and extracellular matrix proteins (31) to mineralize osteoid as it is deposited. On the other hand, in nonskeletal tissues, there is a less understood regulatory system that prevents the harmful deposition of calcium-phosphate complexes in soft tissue (32,33). In CKD, soft tissue calcification is common. Calcification in blood vessels is associated with increased mortality (34), which can be predicted from the levels of serum phosphate and calcium-phosphate product (35).

There have been fewer phosphate balance studies than calcium studies, in part because phosphorus isotopes are less amenable to kinetic studies and also because phosphorus was previously regarded as a passive companion of the calcium fluxes at gut and bone. The understanding of the regulation of phosphate homeostasis has also lagged behind that of calcium. However, with the elucidation of the role of phosphatonins (36) and the sodium-dependent phosphate transporters (37) in phosphate metabolism, the regulation of serum phosphate and its interaction with calcium homeostasis has become clearer. The hormonal system regulating phosphate homeostasis involves two main hormones: fibroblast growth factor 23 (FGF-23) and the FGF/Klotho receptor complex and PTH and PTHR (Figure 3).

An increase in serum phosphate stimulates FGF-23 secretion from bone, which acts on the Na/Pi II co-transporters in proximal tubular cells of the kidney to decrease phosphate reabsorption (38). Concurrently, FGF-23 reduces renal secretion of $1,25(OH)_2D$, which decreases intestinal phosphate absorption. The overall effect is to reduce serum phosphate to normal levels. A reduction in serum phosphate has the opposite actions and, by reducing serum FGF-23, leads to restoration of serum phosphate.

Serum PTH level, which is central to calcium homeostasis, also plays a key role in phosphate homeostasis. Increased serum PTH acting on renal Na/Pi ll co-transporters (39) decreases renal phosphate reabsorption and serum phosphate, whereas decreased PTH increases renal phosphate reabsorption and serum phosphate. It should be noted that PTH has an

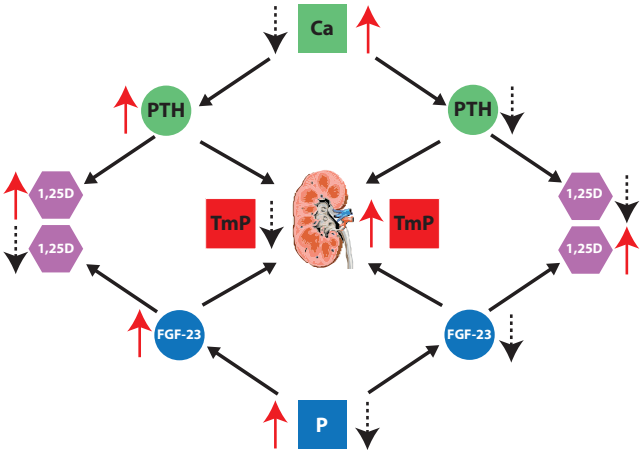

Figure 3. Regulation of serum phosphate (P) homeostasis: interface with serum calcium (Ca) homeostasis at the kidney. Serum phosphate homeostasis is regulated by a negative feedback hormonal pathway (black arrows) involving the concentration of phosphate in serum (P, blue square) and the secretion of fibroblast growth factor 23 (FGF-23; blue circles) from bone cells. A fall in serum P (↓) decreases secretion of FGF-23 (↓), which restores serum P by acting on the type 2 sodium-phosphate renal tubular transporters (NaPi-II) to increase (↑) phosphate reabsorption (TmP; red squares) and by increasing secretion (↑) of renal 1,25-dihydroxyvitamin D (1,25D; purple hexagons) to increase phosphate gut absorption. A rise (↑) in serum P increases (↑) FGF-23 secretion, which restores serum P by lowering (↓) phosphate reabsorption (TmP; red squares) and by lowering secretion (↓) of renal 1,25-dihydroxyvitamin D (1,25D; purple hexagons) to decrease phosphate gut absorption. Changes in the Ca–PTH homeostatic system also have major effects on serum P, but not through a negative feedback pathway, because serum P does not directly regulate PTH secretion. Ca-induced changes in PTH secretion (green circles) induce changes in serum P by regulating tubular phosphate reabsorption (TmP; red squares) through the activity of the NaPi-ll renal tubular transporters. It should be noted that, although both FGF-23 and PTH have the same action on renal tubular reabsorption (TmP; red squares), these hormones have opposing effects on renal 1,25-dihydroxyvitamin D (1,25D; purple hexagons) secretion; the P-FGF23 homeostatic system is more slowly acting than the Ca-PTH homeostatic system; and the receptor for serum P remains to be discovered.

effect on $1,25(OH)_2D$ secretion opposite to that of FGF-23. Increased PTH stimulates $1,25(OH)_2D$ secretion, whereas increased FGF-23 decreases $1,25(OH)_2D$ secretion. Conversely, decreased PTH reduces $1,25(OH)_2D$ secretion, whereas decreased FGF-23 increases $1,25(OH)_2D$ secretion.

Thus, a sophisticated coordination exists between calcium and phosphate homeostasis. The disruption of this coordination by disease (such as CKD) has important implications in the regulation of serum calcium and phosphate and on the propensity to develop ectopic tissue calcification.

As renal function decreases and CKD develops, increased phosphate retention results in a rise in serum phosphate and FGF-23 levels (40). Meanwhile, a reduction in calcium absorption caused by decreased $1,25(OH)_2D$ secretion leads to a fall in serum calcium and a rise in PTH. Thus, the tendency to develop hyperphosphatemia in CKD is delayed for a time by high levels of FGF-23 and PTH, which compensate by decreasing renal phosphate reabsorption and reducing gut phosphate absorption. Eventually, however, as renal function continues to decrease, frank hyperphosphatemia develops. The risk of ectopic calcification and a raised calcium-phosphate product remains relatively low as long as serum calcium remains low. However, any increase in serum calcium levels caused by conditions such as the development of tertiary hyperparathyroidism or overtreatment with calcium and vitamin D supplementation greatly increases the risk of ectopic calcification.

Phosphorus Balance

Phosphorus balance includes both the organic and inorganic forms. Phosphorus balance, like calcium, is also maintained by intestinal absorption, renal excretion, and bone accretion. However, there are several important differences between phosphorus and calcium balance. Phosphorus absorption is rarely limited. Dietary phosphorus, which parallels dietary protein, is present in abundance in most foods; this is in contrast to calcium, which is restricted to a few dietary items. Dietary phosphorus is absorbed almost twice as efficiently as dietary calcium. Thus, phosphorus absorption, unlike calcium, is rarely a nutritional problem. Indeed, in CKD, in which renal phosphate excretion is compromised, reduced dietary phosphorus absorption is needed to avoid hyperphosphatemia.

Bone is the major store for both phosphorus and calcium. However, there are much larger stores of phosphorus than calcium in soft tissues, reflecting the central role of phosphorus in energy metabolism, intracellular signaling, and cell structure. A healthy adult has ~1400 mg of phosphorus in the diet. Of this, >900-mg net is absorbed. In neutral balance, >200 mg of phosphorus enters bone and an equal amount leaves as formation and resorption, respectively, with 900 mg excreted in the urine.

Phosphate Homeostasis

Phosphate homeostasis has several noteworthy differences from calcium homeostasis. First, a receptor that senses the level of serum phosphate has not, as yet, been identified. Second, changes in serum phosphate concentration are readily tolerated; the physiologic range is wide, there is a marked fluctuation in serum levels with meals, and children have much higher values than adults. Finally, the dose response between serum phosphate and FGF-23 concentrations is much less rapid than that between calcium and its regulating hormones. On the other hand, renal excretion of phosphate is as closely regulated as calcium, and the kidney is the main organ that regulates both calcium (29) and phosphate homeostasis (41).

Hypophosphatemia and Hyperphosphatemia

Like calcium, hyperphosphatemia and hypophosphatemia do not reflect phosphorus balance. These can be classified by the main organ responsible for the disruption of homeostasis.

Intestinal Phosphate Absorption

Hyperphosphatemia and hypophosphatemia are rarely absorptive in origin, because the bulk of phosphorus is absorbed passively and not by the $1,25(OH)_2D$-dependent active transport system. However, bioavailability of phosphorus can be reduced by excessive use of compounds that bind dietary phosphate, such as aluminum hydroxide (23), and can result in symptomatic hypophosphatemic osteomalacia.

Bone Phosphate Remodeling

Bone remodeling abnormalities are dominated by changes in calcium homeostasis and rarely give rise to clinically relevant disturbances in phosphate homeostasis.

Renal Phosphate Excretion

Renal phosphate excretion is regulated by tubular reabsorption and filtered phosphate load. Similar to calcium, alteration in either of these mechanisms results in abnormal phosphate homeostasis.

Reabsorptive hyperphosphatemia occurs in diseases with decreased PTH secretion, including various forms of hypoparathyroidism, and is usually asymptomatic. In contrast, in hereditary diseases in which the FGF-23 receptor/Klotho receptor complex is disrupted (36), hyperphosphatemia is marked and leads to ectopic soft tissue calcification.

Reabsorptive hypophosphatemia occurs in diseases with increased PTH secretion, including primary and secondary hyperparathyroidism. The hypophosphatemia is usually mild and asymptomatic. In diseases with increased serum FGF-23, including oncogenic osteomalacia and various forms of hereditary osteomalacia, hypophosphatemia is symptomatic and causes mineralization failure in bone.

GFR hyperphosphatemia occurs in CKD because of the inability of the kidney to excrete the dietary phosphorus load independent of the tubular phosphate reabsorption rate and occurs in the face of increased serum concentrations of both PTH and FGF-23.

Calcium and Vitamin D Supplementation

Calcium Supplementation

Dietary reference intakes, developed in 1997, recommend calcium intakes of 1000 to 1500 mg/d in healthy individuals, depending on age (1). These values represent the minimum amount of calcium needed to achieve maximal retention based

on calcium balance studies in various age groups. It was reasoned that achieving maximal retention should optimize bone mass during peak bone growth in childhood, promote bone consolidation in adulthood, and minimize bone loss in old age. The prevailing beliefs are that any calcium in excess of the maximal retention intake would achieve no increase in retention, offer no additional benefit, and would not be detrimental.

Calcium supplements with or without vitamin D have long been used to slow bone loss and the development of osteoporosis in adults (42). This is particularly common in the elderly, whose diets are frequently insufficient to meet the dietary reference intakes. Calcium supplementation that reverses calcium insufficiency decreases bone loss in older individuals (2,42). In CKD-MBD, calcium supplements used as phosphate binders (23) are thought to be also beneficial to bone health. However, there are few measures from clinical trials or calcium balance studies that show calcium supplementation improves bone mass in CKD-MBD patients. Such studies are needed to determine the effects of increased dietary calcium specifically in these patients.

Vitamin D Supplementation

The use of $1,25(OH)_2D$ and its analogs in CKD-MBD are well established in the management of secondary hyperparathyroidism and the osteomalacic component of the metabolic bone disease. Recently, there has been increasing interest in maintaining serum 25(OH) vitamin D levels above the insufficiency range (*i.e.,* 10 to 30 ng/ml) to prevent loss of bone mass in the healthy elderly population. Because patients with CKD-MBD are likely to be in the vitamin D insufficiency range from lack of sunlight and poor dietary vitamin D intake, there has been great interest by nephrologists in supplementing this population with oral vitamin D for its potential effect on both bone mass and general health (43). However, there are few studies to support this approach (44). Thus, there is a pressing need to establish the necessity and degree for vitamin D supplementation in CKD-MBD patients.

Calcium Benefits/Risks

Despite the small but clear benefits of calcium and vitamin D supplementation on bone mass in the elderly, it is appropriate to consider their possible adverse effects. The risks of vascular and soft tissue calcification associated with calcium and vitamin D supplementation have not been adequately established. A large clinical trial in healthy postmenopausal women recently reported an association between calcium supplementation and increased rates of cardiovascular events (45). The need for studies is even more pressing in CKD patients who are at risk of hypercalcemia and hyperphosphatemia and in whom soft tissue calcification is a major risk factor for increased mortality. Numerous studies of calcium-based *versus* calcium-free phosphate binders in patients with renal failure suggest a link between calcium use and soft tissue calcification, especially coronary vascular calcification (46). In addition, the choice of phosphate binder continues to generate ongoing debate, and more evidence is needed from randomized clinical trials to confirm the cardiovascular risks associated with calcium used as a phosphate binder in patients with CKD (47,48).

Until a consensus of data from clinical studies establishes the most appropriate use of calcium in both non-CKD and CKD patients, it is judicious to carefully weigh the relative benefits and risks of high calcium intake. It has been suggested (49) that no changes in calcium intakes are needed in children, adolescents, or young to middle-aged adults. However, these investigators do caution that, in patients at high risk of cardiovascular disease (those >70 yr of age), calcium supplementation should be limited to prevent total dietary intake in excess of the dietary reference intakes (*i.e.,* dietary sources of calcium other than from supplements should be taken into account). It is appropriate to consider similar precautions when determining calcium intake in CKD patients but with the additional caveat that further sources of calcium, including diet, dialysate, and phosphate binders, must also be included.

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