Calcium Metabolism in Health and Disease

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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.

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, 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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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 anti-resorptive 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.

**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)2D 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)2D, which activates the VDR in gut to increase calcium absorption, in the parathyroid glands to decrease PTH secretion, and in

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**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).
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.

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 phosphatonin (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 II 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 (\( \downarrow \)) decreases secretion of FGF-23 (\( \downarrow \)), which restores serum P by acting on the type 2 sodium-phosphate renal tubular transporters (NaPi-II) to increase (\( \uparrow \)) phosphate reabsorption (TmP; red squares) and by increasing secretion (\( \uparrow \)) of renal 1,25-dihydroxyvitamin D (1,25D; purple hexagons) to increase phosphate gut absorption. A rise (\( \uparrow \)) in serum P increases (\( \uparrow \)) FGF-23 secretion, which restores serum P by lowering (\( \downarrow \)) phosphate reabsorption (TmP; red squares) and by lowering secretion (\( \downarrow \)) 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-II 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.](image-url)
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 phosphate 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 rea-
soned 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 reten-
tion, 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 osteopo-
rosis 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 cal-
cium 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 hyperparathyroid-
ism and the osteomalacic component of the metabolic bone
disease. Recently, there has been increasing interest in main-
taining 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 popula-
tion 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 supplemen-
tation 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 vita-
mín D supplementation have not been adequately established.
A large clinical trial in healthy postmenopausal women re-
cently 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 mor-
tality. 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, adoles-
cents, or young to middle-aged adults. However, these inves-
tigators do caution that, in patients at high risk of cardiovas-
cular 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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References

1. Institute of Medicine Standing Committee on the Scientific
Evaluation of Dietary Reference Intakes Food and Nutri-
tion Board: Dietary Reference Intakes for Calcium, Phosphorus,
Magnesium, Vitamin D, and Fluoride, Washington, DC, Na-
tional Academy Press, 1997
2. McCabe LD, Martin BR, McCabe GP, Johnston CC, Weaver
CM, Peacock M: Dairy intakes affect bone density in the
in bone and dissolution insensitivity of bone mineral.
Biointerphases 1: 106–111, 2006
5. Campbell AK: Calcium as an intracellular regulator. Proc
6. Bootman MD, Collins TJ, Peppiatt CM, Prothero LS, Mac-
Kenzie L, De Smet P, Travers M, Tovey SC, Seo JT, Ber-
ridge MJ, Ciccolini F, Lipp P: Calcium signalling—an
7. Robertson WG, Marshall RW: Calcium measurements in
serum and plasma—Total and ionized. CRC Crit Rev Clin
Lab Sci 11: 271–304, 1979
8. Lu PW, Triody JN, Ogle GD, Morley K, Humphries IR,
Allen J, Howman-Giles R, Sillence D, Cowell CT: Bone
mineral density of total body, spine, and femoral neck in
children and young adults: A cross-sectional and longitudi-
9. Bailey DA, Martin AD, McKay HA, Whiting S, Mirwald R:
Calcium accretion in girls and boys during puberty: A


