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Calcium nutrition and metabolism

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Calcium is the fifth most abundant element of the earth [1]. It is found in a variety of rocks (mostly limestone deposits) and throughout the oceans and waters of the globe. As life evolved in the oceans, ways had to be found to deal with the calcium in the surroundings. Unrestricted entry would have resulted in cell death. Early in evolution, therefore, cells were forced to develop mechanisms for restricting calcium entry. At the same time, cells developed ways to utilize phosphate for a large variety of processes including intracellular energy storage, signaling, and diverse enzymatic events, thereby preventing intracellular precipitation of calcium phosphate [2].

When organisms left the ocean and began to colonize dry land, they had to be equipped with structures that would provide support. Organisms that had developed external skeletons were in a position to do so. Ultimately, internal skeletons evolved. Both types of organisms had to evolve mechanisms for accumulating calcium and storing it in solid form extracellularly. In mammals, approximately 99% of the body's calcium is found in the skeleton. At the same time, if the calcium concentration of the blood and body fluids were to be kept from varying erratically, then mechanisms had to be evolved to regulate the rates of bone calcium deposition and resorption. The intracellular (cytosolic) calcium concentration is also fairly constant, between 50 nmol/L and 100 nmol/L. Calcium thus exists in three domains in the vertebrate body: as a solid, mostly in the chemical form of calcium phosphate, which constitutes the extracellular mineral component of the skeleton; in ionic and protein-bound form in the blood and other extracellular fluids; and intracellularly. Inside the cell, calcium is found in a variety of fixed binding sites (mitochondria, endoplasmic reticulum, and the like) or in ionic form [3]. The cytoplasmic ionic calcium constitutes less than 1% of total cellular calcium. The proportion of body fluid calcium to bone calcium is similarly low.

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Calcium nutrition

Foods rich in calcium include milk, cheese, ice cream, broccoli, custard, whole oranges [4]. Dairy products make up about 55% of the dietary sources of calcium in the United States [5], but when foods enriched with calcium (as is white flour) are included, the figure may reach 70%. The typical calcium intake of women (aged 35 to 50 years) in the United States is 500 mg (13.3 mmol) [5], less than half of the recommended daily intake [6] and much lower than that of men, which approximates 1 g/day (25 mmol/day). The increased consumption of processed foods in industrialized countries has changed food intake patterns and has affected the consumption of some food constituents such as vitamins and trace minerals. On the other hand, because of the increasing trend of supplementing processed foods with food constituents that do not normally occur in that food or in the quantity added, as in the addition of calcium to orange juice, the consumption of some food constituents may actually be higher than if the foods were not enriched.

Calcium absorption

For calcium to be absorbed, it has to be soluble (as in milk or other fluids) or undergo solubilization by the stomach acid. When chyme enters the small intestine, its pH is about 5.5 [7], but as the intestinal fluids are propelled, their pH tends to rise to alkaline levels to the point where some calcium may precipitate [8].

Calcium absorption involves two major processes: transcellular movement, predominant in the duodenum and upper jejunum; and paracellular movement through the tight junctions between intestinal cells [9].

When calcium moves paracellularly, it moves down its chemical gradient that exists between the luminal fluid and body fluids. The luminal calcium concentration after consumption of a calcium-containing meal exceeds 1 mmol/L, the maximum ionic calcium concentration of the body fluids, and may exceed 10 mmol/L [7]. Paracellular movement occurs throughout the intestine, does not require metabolic energy, and is not subject to acute regulation. Intestinal permeability in terms of tight junctions may vary somewhat in different portions of the intestine and may change with age. Intestinal sojourn time determines to a large degree the amount of calcium that is absorbed by the paracellular route, inasmuch as the rate of body fluid circulation, particularly of the blood, is so fast that virtually all calcium that diffuses through the tight junctions and on to body fluids is swept away within instants [7,10]. The total sojourn time of the luminal fluid as it is propelled along the small intestine is about 3 hours, with at least 1 hour spent in the ileum, the segment of the intestine where most of the calcium is absorbed when calcium intake is moderate to high [10]. When calcium intake is low, much of the calcium entering the intestine is absorbed transcellularly, that is, by the active transport process that resides in the

duodenum. As a result, relatively little calcium reaches the lower portion of the intestine where a more modest proportion of the total calcium intake is then absorbed paracellularly.

Transcellular calcium movement involves three major steps [11]: entry, mediated by a dual entry mechanism; intracellular diffusion, mediated by the vitamin D–dependent cytosolic calcium-binding protein, calbindin D_{9k}; and extrusion from the cell, mediated largely by the calcium-extruding enzyme, CaATPase. Of the three processes, extrusion is not rate limiting [9,11], but can be upregulated by vitamin D [12].

Calcium entry in the duodenal cell is mediated by a molecular structure termed CaT1 [13], which acts to prevent unhindered calcium entry. If calcium were to enter unhindered, then the cell would be severely compromised and might die. CaT1 appears to have two entry components [11]: a carrier-mediated transport that saturates at luminal calcium concentrations below 5 mmol/L, and a channel flow-like mechanism that becomes dominant when the luminal calcium concentration is high (>5 mmol/L). The channel flow is upregulated by 1,25-dihydroxyvitamin D_3, $1,25(OH)_2D_3$ [14,15], the bioactive metabolite of vitamin D, whose biosynthesis is at a maximum when calcium intake is low [16].The amount of calcium that enters by way of the channel component is regulated by the intracellular calcium concentration, with cytosolic calcium binding to a channel domain or some other molecule that acts as a channel gate.

When calcium crosses the brush border of the cell and enters the cytosol, its self-diffusion through the cell interior is enhanced up to 70 times by calbindin D_{9k}, a relatively small cytosolic molecule whose biosynthesis and concentration are directly proportional to the available amount of $1,25(OH)_2D_3$ [17]. In vitamin D deficiency, there is no synthesis of calbindin D_{9k} and virtually no transcellular calcium transport [18]. Calbindin D_{9k} acts as a mobile buffer, binding the calcium that enters the cell, and as a transporter, diffusing through the cell interior to deliver the calcium bound to it to the calcium-extruding mechanism, the CaATPase [11]. The amount of calcium transported transcellularly is directly and positively proportional to the cellular content of calbindin D_{9k} [18].

Calcium extrusion from the duodenal cell is mediated by the CaATPase [19,20]. The enzyme, located on the plasma side of the duodenal cell, contains a calcium-binding domain on the cytoplasmic side of the pump molecule, which spans the entire membrane. It also contains a calmodulin-binding domain. Calcium is extruded through a channel-like opening formed by the transmembrane elements. For this to occur, phosphorylation is thought to bring about a conformational change that causes calcium bound to the CaATPase to be propelled outwards. The estimated extrusion capacity of the enzyme appears adequate to extrude calcium, even at the highest transit rate. Nevertheless, from published data, it appears that the number of CaATPases can be increased with vitamin D treatment [12]. Enzyme biosynthesis, however, is not vitamin D dependent.

As indicated previously, the active, transcellular calcium transport process becomes functionally important when calcium intake is low. At high calcium intakes, transcellular calcium transport is downregulated and calcium absorption is largely paracellular [21]. Calcium absorption can be increased by increasing the intake of $1,25(OH)_2D_3$, but in elderly women, calcium absorption does not respond well to increased doses of the metabolite [22]. An increase in calcium intake seems to be a more effective measure.

Calcium homeostasis

Of the calcium in blood, nearly all is in the plasma, where its concentration is 2.5 mmol/L, 10 mg/100 mL, almost half of which is bound to protein (mostly albumin) [1]. The ionized calcium concentration is about 1.2 mmol/L, with some plasma calcium in the form of citrate, phosphate, and other complexes. The rate at which calcium binds to albumin is so rapid [23] that the total calcium concentration of the plasma is an adequate measure of the plasma calcium level, even though it is the ionized plasma calcium that is the signal for hormone action. There is a disparity between ionized and total calcium in some clinical conditions, but these conditions are very rare.

Plasma calcium tends to be higher in men than in women and decreases as individuals age [24–26]. Plasma calcium is in very rapid, dynamic equilibrium with the calcium in the extracellular fluid, of which the plasma volume makes up 17% [27,28]. When calcium is injected intravenously, it expands into the extracellular fluid with a half-time of less than 1 minute. From the extracellular compartment, calcium is lost exponentially to the bone compartment, excreted into urine, and lost in the stool (endogenous fecal calcium). The calcium pool of the body is defined as all of the calcium in the extracellular volume. It turns over in 4 to 5 days [1]. In human subjects, typically 27% of the calcium that enters the pool daily is excreted in urine and stool, the remainder entering the skeleton. The calcium pool is essentially constant in size over the short term. This means that the amount of calcium that returns to the pool from the skeleton by resorption and that enters the pool by intestinal absorption must equal the amount lost to the pool by way of excretion and bone deposition. If intestinal absorption is insufficient, then resorption from bone increases, leading ultimately to a reduction in the bone calcium mass.

The plasma calcium is exquisitely well regulated, with deviations of plus or minus 20% cause for clinical concern. Only prolonged calcium deficiency will depress the plasma calcium concentration, with minute-to-minute regulation effected essentially by the bone mineral. This statement is based on the fact that when calcium tracer is injected into the blood stream, 50% of the tracer will be taken up by the skeleton, yet the calcium concentration of the blood that exits from the skeleton is unchanged [28].

Major hormonal regulation of plasma calcium is effected by parathyroid hormone [29,30], a polypeptide synthesized in and released from the

parathyroid glands. The hormone molecule consists of 84 amino acids, of which the first 34 on the N terminus exert full biologic activity. The functional role of the remainder of the molecule is not known. Ablation of the parathyroid glands leads to a rapid (<2 hour) drop of plasma calcium to about 6 mg/100 mL (1.5 mmol/L). Plasma calcium regulation is not abolished in the absence of parathyroid hormone but is less efficient. Both positive and negative calcium loads are overcome; that is, the plasma calcium returns to the preload level in the parathyroprivic animal but at a significantly slower rate than in the euparathyroid control [27,28].

Calcitonin [29], a 32–amino acid polypeptide synthesized in and released from the C cells of the thyroid gland, acts as a transient regulator of plasma calcium. It is released when plasma calcium is increasing rapidly. Calcitoninectomy does not affect steady-state plasma calcium level, because ablation of the thyroid gland (with thyroid hormone replacement) does not lower the steady-state plasma calcium [31]. Animals deprived of their supply of calcitonin, however, cannot overcome a hypercalcemic challenge as efficiently as controls [28,32].

Vitamin D, a steroidlike hormone, is the third systemic regulator of calcium homeostasis [29]. Vitamin D deficiency is associated with hypocalcemia, and administration of the active vitamin D metabolite, $1,25(OH)_2D_3$, can lead to hypercalcemia. $1,25(OH)_2D_3$ acts on all three organs that regulate calcium metabolism: intestine, kidney, and bone. A rise in the blood level of $1,25(OH)_2D_3$ will increase plasma calcium, intestinal calcium absorption, and urinary calcium reabsorption. Both intestinal absorption and renal reabsorption contribute to normalizing the plasma calcium level in overcoming vitamin D deficiency, but the increase in plasma calcium precedes the biosynthetic effects of $1,25(OH)_2D_3$ on absorption and reabsorption. The mechanism of action of $1,25(OH)_2D_3$ in raising plasma calcium is similar to that of parathyroid hormone, but the effect is slower.

Calcium in bone

Almost all calcium in vertebrate bone is in the form of one of several calcium phosphates (Table 1), with at least 90% of the crystalline solid in the form of calcium hydroxyapatite. Calcium is deposited, probably in the form of brushite, on collagen fibrils that have been synthesized in and extruded by osteoblasts, the bone-forming cells. Additional calcium phosphate is deposited by accretion. With time, the bone crystal matures, probably passing through some or all of the forms of phosphate listed in Table 1. The final stage is hydroxyapatite, the form that gets solubilized by the bone-resorbing cells, the osteoclasts.

When osteoclasts resorb bone, their podosomes seal off a region into which the cell extrudes protons and lysosomes. This causes the bone salt to become solubilized and destroys the matrix. The resulting increase in

Table 1
Solid phases of calcium phosphate in bone[a]

Name	Formula	Molar ratio of Ca to P
Hydroxyapatite[b]	Ca_{10}-$(PO_4)_6(OH)_2$	1.66
Whitlockite	$(Ca,Mg)_3(PO_4)_2$	1.50
Amorphous $CaXPO_4$	$Ca_9(PO_4)_6$(variable)	1.30–1.50
Octacalcium phosphate	$Ca_8H_2(PO_4)\cdot 5H_2O$	1.33
Brushite	$CaHPO_4\cdot(2H_2O)$	1.00

[a] Listed in order of increasing acidity, solubility and, by inference, of decreasing calcium-binding affinity.

[b] At least 90% of the cystalline solid is hydroxyapatite, based on x-ray diffraction analysis.

From Simmons DJ, Grynpas MD. Mechanisms of bone formation in vivo. In: Hall BK, editor. Bone, vol. 1. The osteoblast and osteocyte. Caldwell (NJ): Telford; 1990. p. 218; with permission.

the calcium concentration of the fluid surrounded by the osteoclastic podosomes seems ultimately to stall the metabolism of the cell, loosening the podosome attachment and causing the fluid with the resorbed calcium to diffuse. The cell itself also seems to move to another location where it resumes its activity [33,34].

From this description of bone formation and resorption, it is evident that these processes are cascades of events that must take more time than the very rapid rates at which calcium leaves the blood plasma as it courses over bone and the equally rapid rate at which the lost calcium is replenished. The minute-to-minute regulation of plasma calcium must be by an exchange process between the plasma calcium and the various bone salts (see Table 1) with their different calcium-binding affinities [28]. It seems logical that newly deposited bone salts with relatively low calcium-binding affinity are found in association with osteoblasts, whereas mature bone salts with high binding affinity are associated with the osteoclasts. Parathyroid hormone causes osteoblasts—the only bone cells with parathyroid hormone receptors—to contract and to cease their metabolic activity, at least temporarily. When osteoblasts contract, more low-affinity calcium-binding sites are exposed and the plasma calcium concentration goes up. Only osteoclasts possess calcitonin receptors. When calcitonin interacts with osteoclasts, these cells in turn contract and diminish their metabolic activity. More sites of calcium phosphate with high calcium-binding affinity are exposed, and the plasma calcium level will go down. Cross-talk between osteoblasts and osteoclasts will also be affected so that osteoclasts become more active, covering up additional high-affinity sites when osteoblasts contract, as in response to parathyroid hormone stimulation. This process would add to the calcium that enters plasma. Contrariwise, when osteoclasts contract in response to calcitonin, osteoblasts may spread out, covering up more low-affinity sites, and less calcium would be available to enter the plasma (Fig. 1). Osteoblasts also are equipped with vitamin D receptors and respond to $1,25(OH)_2D_3$ in

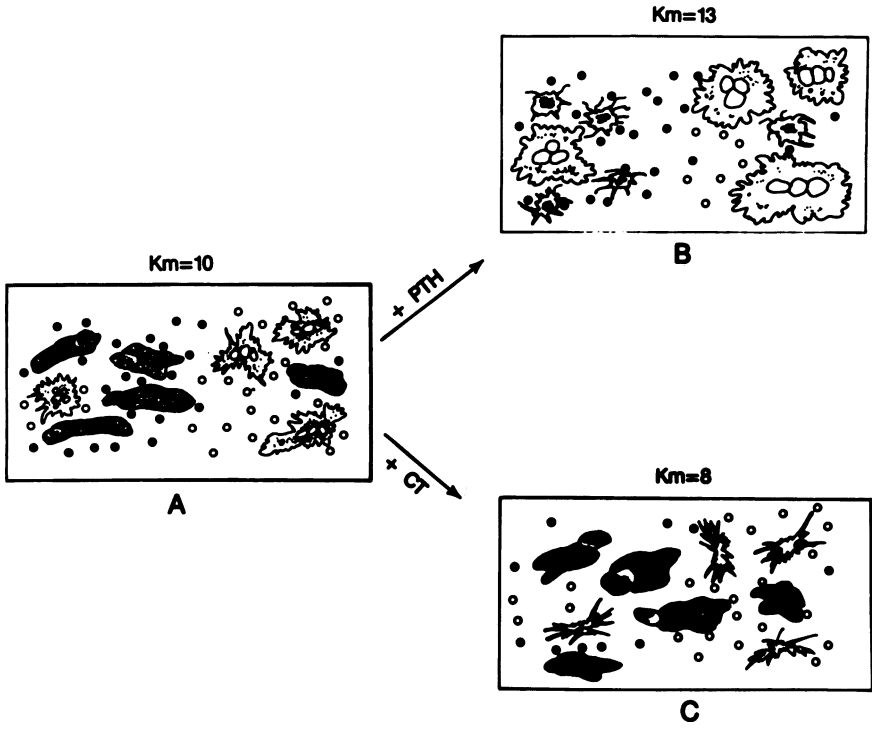

Fig. 1. Diagram representing the effect of the acute administration of parathyroid hormone (PTH) and calcitonin (CT) on the spatial relationships of osteoblasts and osteoclasts on the surface of bone. It is assumed that plasma calcium ($[Ca_s]$) is the result of instantaneous exchange between plasma calcium and the calcium-binding sites of bone and that the plasma calcium at any moment is equal to and determined by the mean average calcium-binding affinity of the bone mineral. The open and closed circles represent, respectively, the mean calcium binding values of high-affinity and low-affinity binding sites. (A) Represents a normocalcemic situation, with an equal number of high-affinity and low-affinity sites. Here, $[Ca_s]$ is 10 mg/dL. (B) Represents the result of PTH administration, where the hormone-induced contraction of osteoblasts has exposed additional low-affinity binding sites and the associated expansion of osteoclasts has blocked more high-affinity sites. As a result, $[Ca_s]$ has increased to 13 mg/dL. (C) Represents the result of CT administration, where the hormone-induced shrinkage of osteoclasts has exposed more high-affinity binding sites and the associated expansion of osteoblasts has reduced the number of low-affinity sites. As a result, $[Ca_s]$ has decreased to 8 mg/dL. Bone mineral with a high Ca/P ratio (eg, 1.66; see Table 1) is considered to have a higher affinity to bind calcium than bone mineral with a relatively low Ca/P ratio (eg, 1.0; see Table 1). (*Adapted from* Bronner F, Stein WD. Modulation of bone calcium-binding sites regulates plasma calcium: an hypothesis. Calcified Tissue Int 1992;50:483–9; with permission.)

a manner similar to their response to parathyroid hormone, but the resulting rise in plasma calcium is slower.

A third type of bone cell is the osteocyte. Whereas osteoblasts and osteoclasts are found largely on the surface of the bone mineral, osteocytes are buried fairly deep inside the lacunae of bone. They are equipped with

long, slender processes by means of which they communicate with one another and with bone cells on the surface. Their function is not fully understood. They may be involved in sensing and responding to strain in bone tissue and, thereby, contribute to adaptive modeling and remodeling of bone [35].

Bone-lining cells are flattened, metabolically inactive osteoblasts that cover the bone surfaces. Their function is not known. They may participate in calcium uptake and release by variation in the junctional spaces between them. There is no evidence that calcium moves transcellularly through them in either direction, nor is it logical to think that calcium would move in both directions in the same cell. Intermittent but not continuous treatment with parathyroid hormone has been shown to stimulate bone formation [36] and may be due to the reconversion of the metabolically inactive bone-lining cells to more active bone-forming cells [37,38].

Calcium in teeth

Teeth are the densest structures in the body, with the highest calcium content per unit volume. It has been known for many decades that teeth are privileged sites as far as calcium metabolism is concerned because their calcium does not get resorbed and does not participate in the body's calcium turnover. Indeed, tooth content of previously injected radiocalcium has been used as a measure of calcium deposition in the skeleton [39].

With the increase in longevity in industrial countries and the concurrent increase in osteoporosis and the wider awareness of metabolic bone diseases, it seems natural to raise the question of whether these conditions affect tooth health. The overall consensus is that neither osteoporosis nor most bone diseases have specific effects on tooth health.

Some reports indicate a correlation between bone health and periodontal disease. For example, Klemetti and collaborators [40] concluded from their study of 227 healthy postmenopausal women, aged 48 to 56 years, that individuals with high mineral content of their bones seemed to retain teeth with deep periodontal pockets more easily than those who had osteoporosis. Subsequent studies have, on the whole, confirmed this finding (eg, [41–44]). Although osteoporosis and osteopenia affect trabecular bone more than cortical bone, support of the teeth by the jaw bone is lessened in both of these conditions and, therefore, the effects of deep pockets and bacterial infection may be enhanced [62]. On the other hand, in an earlier study [35], no significant differences were found in mandibular radiographic measurements of women with mild-to-moderate osteoporosis compared with normal controls, and there also was no correlation between skeletal and mandibular bone measurements.

Nishida and colleagues [45] studied the role of dietary calcium intake as a contributing risk factor for periodontal disease, measured by attachment

loss. Their subjects were in the Third National Health and Nutrition Survey. It was concluded that low dietary intake of calcium results in more severe periodontal disease.

Oshiro and colleagues [46] investigated the mechanisms by which roots of deciduous teeth are resorbed and concluded that "the cellular mechanisms of physiological root resorption appear to be quite similar to those of osteoclastic bone resorption." Again, this is not surprising because the basic composition of tooth roots is similar to calcified extracellular matrix.

Certain bone diseases have dental correlates. Osteogenesis imperfecta has been associated with imperfect tooth formation [47]. In hypophosphatasia, a hereditary disorder transmitted by a recessive gene, when manifest after 6 months of age, the teeth are crowded and lost early [48,49]. In hypoparathyroidism the teeth erupt late and are lost early [50]. Forbes [51] reported changes in the lamina dura and enamel in one case of hypoparathyroidism, and enamel hypoplasia, thickening of the lamina dura, and pulp calcification in another case. Snapper [52] stated that the lamina dura frequently disappears in the course of hyperparathyroidism, but that the teeth are unaffected. Teeth may, however, fall out due to resorption of the jaw bone. Cementosis (ie, hyperplastic deposition of cement on the dental roots), because rare in other bone diseases, may justify a diagnosis of Paget's disease [52].

Calcium excretion

Urine

Less than 0.1% of the calcium that circulates in the body is excreted by way of urine [1]. For example, an adult who weighs 70 kg would have a plasma volume of about 2.5 L that contains 6.25 mmol (250 mg) calcium. Between 20% and 25% of cardiac output is presented to the kidney, about half of which is filtered through the glomerulus, with the other half entering the tubules. Thus, the nephron of a 70 kg person may handle approximately 2100 mmol (84 g) calcium per day, with only about 0.3% of the filtered load, or 6.3 mmol (252 mg) calcium, excreted. Actual calcium excretion is a complicated function of calcium intake, vitamin D and nutritional status, sex, reproductive status in women, and age.

Calcium that is filtered into the renal tubule, like calcium in the intestine, is subject to two reabsorptive processes: active and passive. Approximately 60% of calcium that enters the tubule is reabsorbed in the proximal tubule, mostly by a passive mechanism, although perhaps 20% of the calcium reabsorbed in the proximal tubule may be moving transcellularly against an electrochemical gradient. Very little calcium that enters the thin limbs of the loop of Henle is reabsorbed, but reabsorption becomes significant again as calcium reaches the thick and convoluted segments of the renal tubule.

Active transcellular transport in the convoluted tubule is mediated by calbindin D_{28k} (a molecule similar to calbindin D_{9k}, but larger), equipped with four calcium-binding sites. Calbindin D_{28k} is a separate gene product and functions in the cells of the distal convoluted tubule like calbindin D_{9k}; that is, as a buffer and transporter [53]. In the absence of calbindinD_{28k}, as in severe vitamin D deficiency, very little if any calcium is reabsorbed in the distal convoluted tubule, and the relative calcium loss in the urine is greater than in the vitamin D–replete state, notwithstanding the hypocalcemia characteristic of vitamin D deficiency.

The two major regulators of urinary calcium excretion are vitamin D and parathyroid hormone [54]. Vitamin D regulates the biosynthesis of calbindin D_{28k}. Parathyroid hormone causes diminished urinary calcium output, probably acting by way of the cyclic adenosine monophosphate system in the distal tubule. It also causes an increase in the biosynthesis of 1,25-dihydroxyvitamin D, and this may contribute to the increased reabsorption of calcium. The action of the hormone on the biosynthesis of the vitamin D metabolite, however, is relatively slow, yet its effect on urinary calcium reabsorption is longer lasting than the relatively rapid action by way of the cyclic adenosine monophosphate system. In addition to its effect on calcium excretion, parathyroid hormone also causes an increase in phosphate excretion, probably by way of its action in the proximal tubule.

In summary, urinary calcium excretion represents less than 1% of the calcium that is circulated to the kidney. Most of the calcium filtered by the kidney is reabsorbed, much of it by passive, paracellular transport, with active reabsorption occurring almost entirely in the distal convoluted tubule where intracellular movement is mediated by calbindinD_{28k}.

Stool

Calcium in the feces comes from two sources: unabsorbed food calcium and endogenous calcium secreted into the intestine by way of the bile, the *succus entericus*, or originating in sloughed-off cells. In general, the fraction of unabsorbed dietary calcium varies inversely with calcium intake, plateauing between 15% and 20% when calcium intake is high (>1200 mg/day) [55].

In humans, the amount of endogenous fecal calcium is approximately equal to the urinary output [1]. A precise determination of the amount requires a balance study combined with a tracer (radiocalcium or a stable calcium isotope) that is injected intravenously at the same time that a stool marker is ingested. Endogenous fecal calcium output does not seem to contribute to the regulation of calcium metabolism, inasmuch as there is no evidence that endogenous fecal output varies significantly with calcium nutriture. To be sure, endogenous calcium is mixed with exogenous (food) calcium in the intestine and, therefore, is subject to absorption. When absorption is high, there is a tendency for endogenous calcium to be low,

and vice versa; however, this merely reflects the response of absorption to the level of calcium intake.

Calcium and osteoporosis

Fig. 2 shows the age-dependent changes in bone mineral density, an index of the whole bone mass and its extracellular calcium content. Peak bone mass is the resultant of genetic factors and calcium intake, because a deficiency in calcium intake will prevent bone mass from attaining its genetically programmed maximum. The age-dependent decrease in bone mass that begins in the fourth decade of life decreases at a fairly invariable rate. If the peak mass is low, as in populations on a low-calcium intake, then the age-related decrease will obviously reach a low value sooner than if the peak value is higher, with fractures more likely at the low-bone mass values [56]. An adequate calcium intake, therefore, particularly in the first two decades of life, is the surest way of minimizing the chances of the occurrence of osteoporosis between the ages of 60 and 80 years. This is particularly true for girls and young women in the United States whose calcium intake tends to average 600 mg/day, which is only about half of the recommended daily allowance [57].

In men, as shown in Fig. 2, the bone mass decreases fairly uniformly from 30+ years on, at the rate of 0.2% per year [58]. There is greater relative loss of trabecular bone, inasmuch as trabecular bone turns over faster than cortical bone. In women, however, there is a much greater loss in the first decade after menopause, a loss that affects trabecular bone much more than cortical bone. As a result, the physical signs of bone loss and their functional effects are much more pronounced in women as they enter their eighth decade than in men, even though thereafter the rate of bone loss is fairly comparable in both sexes. As men live on, they develop osteoporosis or at least osteopenia, usually in their ninth decade.

Treatments for osteoporosis and osteopenia have multiplied in recent years, thus permitting treating physicians to individualize treatment. Hormone replacement therapy, with estrogen and progesterone, is still considered the "gold standard" for treating women. An alternative treatment omits progesterone, with estrogen taken daily throughout the month. Because of concern with an increased risk of breast cancer, two estrogen-related molecules have been approved for treatment: raloxifene and tamoxifen. These selective estrogen-receptor modulators compete with estrogen for high-affinity binding to the same ligand-binding domain of the estrogen receptor; this antagonizes estrogen actions in the breast and uterus. As far as their action on bone is concerned, these estrogen-receptor modulators have the same general effects as estrogen, although definitive clinical studies have not yet been completed, especially with respect to tamoxifen. Phytoestrogens have been recommended and tried, but there is

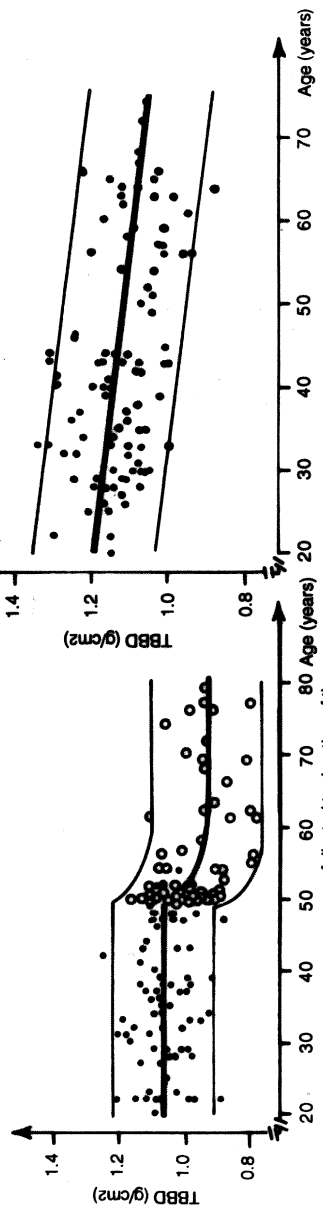

Fig. 2. Total body bone density (TBBD) as a function of age in women (A) and men (B). TBBD was obtained by measuring total bone mineral content of the body by gadolinium 153 scanning, normalized to skeletal surface area. (*From* Gotfredsen A, Hadberg A, Nilas L, et al. Total body bone mineral in healthy adults. J Lab Clin Med 1987;110:362–8; with permission.)

considerable uncertainty as to whether they have an effect, except perhaps at very high doses.

An entirely different class of compounds are the bisphosphonates. In appropriate doses they inhibit osteoclast action and thereby cause bone resorption to be markedly slowed. They tend to be deposited on the bone surfaces underlying osteoclasts and, when administered in large quantities, also on other bone mineral surfaces. According to Fleisch and collaborators [59], there are two general classes of bisphosphonates: those that are metabolized within the cell to form toxic analogs of adenosine triphosphate (ie, clodronate and etidronate) and those that inhibit the enzyme farnesyl diphosphate synthase (alendronate, pamidronate). The precise molecular pathways by which the farnesyl diphosphate enzyme, with its effect on cholesterol synthesis, inhibits osteoclast activity is still under study. Osteoclast changes include alterations in the cytoskeleton and disruption of the ruffled border. Clinically, the bisphosphonates have led to short-term improvements in bone mineral density and, over the long term, have at least slowed the decrease in bone mineral density.

Fluoride has been used to treat osteoporosis. According to Ringe [60], there can be little doubt that pharmacologic doses of fluoride stimulate osteoblastogenesis and increase bone mass. The therapeutic window for fluoride treatment, however, is quite narrow (between 10 mg and 20 mg daily of bioavailable fluoride ions). Also, fluoride compounds are relatively inexpensive, causing pharmaceutic firms to shy away from the expense of conducting appropriate clinical trials.

There has been interest in dietary calcium supplementation as a means of combating osteoporosis. Heaney [61] has concluded there is virtually no evidence that calcium supplementation alone, in any quantity, will lead to substantial bone calcium gain in persons who already have osteoporosis. Heaney has recommended, however, substantial calcium supplementation in combination with other regimens, for example, hormone replacement therapy or bisphosphonate treatment.

Summary

An adequate calcium intake throughout life is essential for maintenance of the skeleton, by far the largest body reservoir of calcium. Appropriately high calcium intake is particularly important in the first two decades, when the body calcium mass increases to near maximum. In subsequent decades, because calcium absorption is relatively modest, typically 25% or less, calcium intake must be kept near 1000 mg per day in order to minimize the possibility that the skeleton will be mined for its mineral content. The amount of calcium needed for signaling and to maintain the extracellular calcium constant is relatively small; however, skeletal turnover is enhanced in calcium deficiency, the increased turnover representing the body's attempt to preserve skeletal calcium.

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