The role of calcium in health and disease

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Skeletal fragility at the end of the life span (osteoporosis) is a major source of morbidity and mortality. Adequate calcium intake from childhood to the end of the life span is critical for the formation and retention of a healthy skeleton. High intakes of calcium and vitamin D potentiate the bone loss prevention effects of hormone replacement therapy in postmenopausal women. Pregnancy and lactation are not risk factors for skeletal fragility, although lactation is associated with a transient loss of bone that cannot be prevented by calcium supplementation. Low calcium intake has been implicated in the development of hypertension, colon cancer, and premenstrual syndrome, and it is associated with low intakes of many other nutrients. Encouragement of increased consumption of calcium-rich foods has the potential to be a cost-effective strategy for reducing fracture incidence later in life and for increasing patients' dietary quality and overall health. (Am J Obstet Gynecol 1999;181:1560-9.)

Key words: Bone, hypertension, lactation, osteoporosis, pregnancy

Most health professionals would agree that sufficient calcium intake is necessary for good health throughout life. There is probably less consensus, however, about what constitutes sufficient intake and the potential consequences of failing to achieve that intake. In part this disagreement results from scientific uncertainty. Although there has been substantial progress in understanding the physiologic characteristics of calcium homeostasis, calcium metabolism is both an elegant and a frustratingly complex phenomenon.

Calcium is also a threshold nutrient[1, 2]; that is, below the threshold level, an increase in dietary calcium intake results in an improved response. Above the threshold intake, however, there is little or no further improvement. This fact complicates the interpretation of many studies of the effects of calcium intake on health, because populations in which the calcium intakes straddle the threshold will exhibit a heterogeneous dose-response curve.[3]

Finally, health problems related to chronic undernutrition of calcium are in the main slowly developing and multifactorial conditions that are difficult to pin down to any single cause. It is rare for most physicians to see patients with acute pathologic conditions of calcium metabolism.

Calcium has vital functions within cells in all living creatures, predominantly as a second messenger transmitting signals between the plasma membrane and the intracellular machinery. Extracellular calcium is also an essential cofactor in clotting factors and adhesion molecules and is essential for the proper formation of bone. There is recent evidence that calcium has direct effects through a membrane-spanning calcium receptor that is coupled through G proteins to intracellular signaling. This receptor has been found in the parathyroid gland, the kidney, and the brain, among other tissues.[4-6]

More than 99% of the calcium in the human body is in the bones and teeth. In bone, calcium provides the structural strength that allows the bone to support the body's weight and anchor the muscles. Bone calcium also serves as a reservoir that can be tapped to maintain extracellular calcium concentration regardless of intake. Calcium differs from most other nutrients in that the body contains a substantial store, far in excess of short-term needs, but at the same time that store serves a critical structural role. Thus the effects of calcium deficiency may escape notice for a considerable time, until they manifest as skeletal weakness or fractures.

Among the myriad living creatures on earth the challenges presented by maintaining calcium homeostasis vary widely. Different dietary habits can provide widely

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different levels of calcium intake. For example, carnivores that feed on vertebrates and ingest significant quantities of bone have high calcium intakes. Many plant tissues contain significant calcium, so herbivores generally have moderate to high calcium intakes. In contrast, seed-eating animals, such as the psittacine avians or graminivorous rodents, have high phosphorus intakes but relatively low calcium intakes, which is reflective of the composition of most seeds.

This last observation has relevance for the human condition. Before the advent of sustained agriculture, human ancestors probably had high calcium intakes.[7] Since the advent of agriculture, the consequent increase in seed products (grains) in the human diet has resulted in a decrease in dietary calcium intake and an increase in dietary phosphate intake. Human calcium regulatory physiology may be evolutionarily adapted to conditions of high dietary calcium intake and a high calcium/phosphorus intake ratio.[7, 8] A number of the diseases of modern human beings, including bone fragility, hypertension, and colon cancer, may be caused, or at least exacerbated, by chronically low dietary calcium intake.[8]

Physiologic regulation of calcium homeostasis

Calcium homeostasis is maintained in part by complex hormonal systems that serve to keep the extracellular fluid calcium concentration within fairly narrow ranges by regulating the absorption, excretion, and redistribution of calcium and other minerals by the body. For most terrestrial organisms calcium comes in discrete packets called *food*. Thus there is also a role for motivated ingestive behaviors in maintaining calcium homeostasis.[9, 10]

About half of the calcium in the serum is bound to protein, predominantly albumin. A small fraction is bound to other chemicals, such as citrate, and the rest is in the free ionized state. Total serum calcium concentration can change for a number of reasons, some of which have no health consequences. In contrast, serum ionized calcium concentration is tightly regulated and is therefore the clinically important parameter to measure.[11]

The cytoplasmic calcium concentration is several orders of magnitude lower than the calcium concentration in the extracellular fluid, and this steep gradient is actively maintained. The symptoms of and treatments for hypocalcemia and hypercalcemia have been recently reviewed.[11] Briefly, when extracellular fluid ionized calcium concentration drops sufficiently below the regulated set point, hyperexcitation of cells occurs, with extreme hyperexcitation resulting in tetany and possibly death. When extracellular fluid ionized calcium concentration rises, cell firing is reduced, especially in muscle and nerve tissue. This can lead to reduced intestinal motility (constipation), lethargy, and mental confusion. Although hypercalcemia is a less acute condition than is hypocalcemia, death nonetheless may result if the condition is allowed to progress.

Calcium balance (intake minus the sum of all losses) generally is positive during growth, is essentially zero in the mature adult, and then becomes negative with advancing age.[12] Negative calcium balance can arise from low intake, poor absorption, high obligatory losses, or any combination of these factors and will inevitably lead to bone loss if not corrected.[3] There are many factors that increase the susceptibility of the older adult to negative calcium balance: Both intake and absorption decline, excretion increases, and bone resorption becomes greater than bone formation.[12, 13] The body's ability to adapt to different calcium intakes through the calciotropic hormone systems decreases with age until it is essentially nonexistent at an age of about 80 years.[13]

The absorption of bivalent ions such as calcium is less efficient than that of univalent ions such as sodium. There are 2 mechanisms of calcium absorption from the intestinal tract: (1) a paracellular, unregulated, nonsaturable mechanism that predominates at high calcium intakes and (2) a transcellular, saturable, active-transport mechanism that predominates at low calcium intakes.[14] The paracellular mechanism results in a low proportion of dietary calcium absorption, although at high intakes the absolute amount of absorbed calcium may be large. With the transcellular mechanism the total amount of calcium that can be absorbed is limited. The active calcium transport system is vitamin D dependent and involves synthesis of a calcium-binding protein.[14]

There are 3 main avenues of calcium loss: feces, urine, and dermal losses (sweat and sloughed skin cells). At calcium intakes in the range of current recommendations, fecal loss can be as high as 90% of ingested calcium. Fecal losses consist of unabsorbed dietary calcium and calcium from digestive excretions, sloughed intestinal cells, and other endogenous sources. At low calcium intakes much of the calcium excreted in feces is of endogenous origin. Dermal losses have not been accurately measured but have been estimated to be equivalent to about 30% of normal urinary losses.[15] With strenuous athletic exertion accompanied by high sweat loss, however, dermal calcium losses can be significantly higher; measurable bone loss can occur across a playing season.[16] Urinary loss of calcium is regulated through the actions of the calciotropic hormones parathyroid hormone (PTH), 1,25-dihydroxyvitamin D, and calcitonin, but it also depends on protein and sodium intake.

Diet and calcium

Several chemicals in foods have been found to affect the absorption of calcium. For example, phytates and oxalates form highly stable and largely indigestible complexes with calcium that greatly reduce calcium's bioavailability.[17, 18] The fractional absorption of calcium

from high-phytate soybean products is significantly less than that from low-phytate soybean products.[18] Spinach contains high concentrations of calcium, but because spinach also contains high concentrations of oxalates that calcium is largely unavailable.[17] Kale, in contrast, has high calcium and low oxalate concentrations, making that leafy green vegetable a good source of dietary calcium.[19] Still, it takes 4 to 5 half-cup servings of kale or broccoli to equal the calcium content of a single 8-ounce glass of milk.[20]

High sodium intake increases urinary calcium excretion in adults[21] and in elderly men and women.[22] Urinary sodium excretion is an important determinant of urinary calcium excretion in children and adolescents.[23]

Protein is necessary for bone and muscle health. Increased protein in the diet also increases the absorption of calcium from the gut[24]; however, it also increases the obligatory calcium loss.[25, 26] A doubling of protein intake with all other nutrients remaining constant results in an increase in urinary calcium loss of about 50%.[25] Part of the increase in calcium loss is due to an increased glomerular filtration rate, but high protein intake also reduces reabsorption of calcium in the distal tubules. These changes are thought to be due to the increased acid load from a high-protein diet.[27] The addition of fruits and vegetables to the diet can ameliorate this loss by buffering the acid load from protein.[28]

The functional significance of the increased obligatory calcium loss as a result of protein intake depends on the calcium intake.[26] The ratio of dietary calcium intake to dietary protein intake has been found to be positively associated with bone gain in young women.[29, 30] Current recommendations would result in a dietary calcium/protein intake ratio of 20 mg calcium/1 g protein.[26, 31] Unfortunately, the median intakes of calcium and protein for women in this country yield ratios of half that magnitude.[26] The main culprit is low calcium intake.

Theoretically, a low dietary calcium/phosphorus intake ratio could reduce intestinal calcium absorption.[32] In adults, however, this is probably a concern only for those with very low calcium intakes if at all. At normal calcium intakes a wide range of calcium/phosphorus intake ratios have been shown to have no effect on calcium absorption or balance.[33] Diets high in phosphorus and low in calcium increase serum PTH concentration[34]; however, this effect may be due solely to the low calcium intake because an identical response can be achieved with low dietary calcium intake without high dietary phosphorus intake.[35] A dietary calcium/phosphorus intake ratio >1 is associated with higher bone mass in young women[30]; however, some have suggested that the form of phosphate in the diet is more important than the quantity, with acidic phosphate leading to increased urinary calcium loss analogous to the loss associated with protein intake.[28]

Calcium interacts with iron, zinc, and magnesium.[31] Calcium inhibits iron absorption,[36, 37] but the available human data do not show any effect on iron stores.[37-39] Similarly, there is no evidence that high calcium intake compromises zinc or magnesium status.[31]

Low dietary calcium intake is associated with low intakes of many other nutrients.[40] This emphasizes the point that calcium is a nutrient and should not be treated as a pharmacologic agent. The simple addition of a calcium supplement to a low-calcium diet may not result in a healthful diet. The addition of calcium-rich foods to the diet, in contrast, could repair other nutritional deficiencies as well.

Is calcium ingestion regulated?

The existence of a hunger for sodium is well established in many species.[9, 10, 41] The importance of calcium to vertebrate species suggests that an appetite for calcium could be similarly adaptive. In a number of species (eg, rats, chickens, and macaques) a period of calcium depletion results in an increased intake of calcium salts when they are offered.[41-45] Pregnancy and lactation also increase mineral consumption, including that of calcium, in a variety of mammals.[9, 10, 41, 46] For example, the common marmoset, a New World primate, shows an especially strong preference for calcium solutions rather than water during lactation (Fig 1).[47]

The major calciotropic hormones and their receptors have been found in areas of the brain that are involved in motivating ingestion, such as the amygdala, the hippocampus, and the bed stria nucleus.[48, 49] The calcium sensor that was originally detected in the parathyroid gland has been found in many other organs, including the brain (eg, subfornical organ and hippocampus).[6] Peripheral infusion of 1,25-dihydroxyvitamin D can increase calcium ingestion in rats.[50] Thus the hypothesis that the hormones of calcium homeostasis play a role in the behavior of calcium ingestion remains reasonable.

Calcium intake worldwide

There is wide variation in calcium intake by human beings throughout the world, with average intake in many areas substantially below the US recommended dietary allowance.[51] For instance, in areas of Gambia the average calcium intake of lactating women was measured at <400 mg/d.[52, 53] These women had elevated serum concentrations of intact PTH and a fractional calcium absorption about 50% greater than that among women in Great Britain.[53]

The wide variation in habitual calcium intakes around the world and the apparent ability of the human body to adapt to a wide range of calcium intakes provide a warning that increasing calcium intake may not have as great

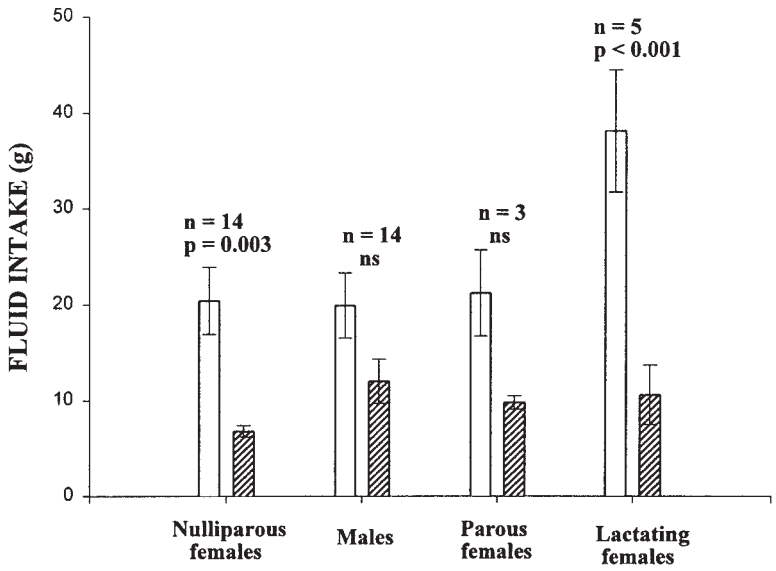

Fig 1. Voluntary intake of 2% calcium lactate solution *(open bars)* versus deionized water *(striped bars)* by common marmosets. *Bar heights* represent mean; *error bars* represent SE. *ns,* Not significant. [Modified with permission from Power ML, Tardif SD, Schulkin J. Ingestion of calcium solutions by common marmosets (*Callithrix jacchus*). Am J Primatol 1999;47:255-61.]

a public health benefit as might be hoped.[54] However, the increase of life expectancies worldwide has resulted in a fast-growing population of elderly people who not only have a greatly reduced capability to physiologically adapt to low calcium intakes but, by virtue of their longer lives, will face a greater probability of bone fragility if bone loss is not attenuated. Also, epidemiologic evidence suggests that low calcium intakes are associated with other diseases in addition to bone pathologic conditions, such as hypertension and colon cancer.[8] It is far from certain that calcium intakes sufficient to maintain bone in young adults will necessarily result in good health throughout life.

Bone

Bone is continually being remodeled, with osteoclasts resorbing bone and osteoblasts replacing the absorbed bone. In general, these 2 processes are in equilibrium. Bone remodeling serves to repair microdamage and to allow bone to respond and adapt to mechanical stress. Older bone becomes more brittle and thus more susceptible to fracture. Bone remodeling also aids in maintaining extracellular fluid calcium homeostasis.

At any given time some fraction of the bone surface contains resorption cavities. This "missing bone," from which calcium has been released into the extracellular fluid, is termed the *remodeling space.*[55] If the bone remodeling rate increases, the remodeling space increases and total bone mineral content decreases. If the bone remodeling rate decreases, the opposite happens. This is reversible bone mineral loss or gain.[55] Estrogen, the calciotropic hormones, and dietary calcium intake have substantial effects on the bone remodeling rate, as do such pharmacologic agents as bisphosphonates.

In the mature adult, bone formation often does not replace 100% of the resorbed bone. This imbalance between resorption and formation is dependent on age, hormones, and calcium intake. For example, the number of osteoblasts decreases with age, whereas low estrogen level and low dietary calcium intake both increase osteoclast formation. Low estrogen concentration also increases the depth of the resorption cavity, which can lead to perforation and disconnection of trabeculae. This latter type of bone loss is irreversible and has serious negative consequences for bone strength.

Osteoporosis

Osteoporosis is characterized by bone fragility such that fractures can occur under conditions of minimal trauma, including the normal stresses of living. Osteoporosis is generally a disease of older adults because the cumulative effects of slow bone mineral loss take time to deplete the skeleton. The dramatic increase in elderly populations worldwide and their expected continued increase mean that an epidemic of disease related to bone fragility may be in the offing.[56] Treatment of established osteoporosis is difficult, and the public health emphasis has therefore been placed on prevention.

The morbidity and mortality associated with osteoporosis are related to fractures. The increased incidence of fractures in the elderly population arises from a number of different factors, but skeletal fragility is certainly important. Bone strength can be negatively affected by reduced bone mass, poor bone architecture (eg, reduced

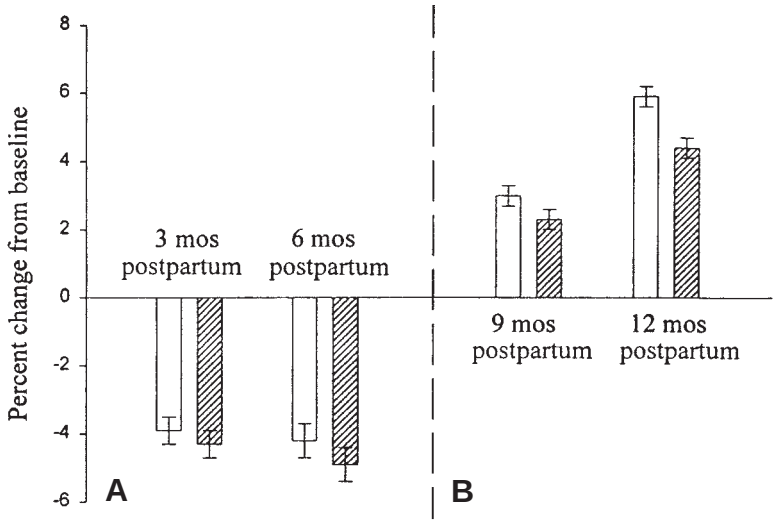

Fig 2. Effects of lactation, weaning, and calcium supplementation on bone density at lumbar spine in 2 groups of healthy women. **A,** Change in bone mineral density at lumbar spine from prepartum measurement in lactating women receiving calcium supplement *(open bars)* and placebo *(striped bars)*. **B,** Change in bone mineral density at lumbar spine in women receiving calcium supplement *(open bars)* and placebo *(striped bars)* from approximately 6 months post partum (before weaning) through 12 months post partum. Weaning occurred on average at about 7 months post partum. *Bar heights* represent mean; *error bars* represent SE. (Data from Kalkwarf HJ, Specker BL, Bianchi DC, Ranz J, Ho M. The effect of calcium supplementation on bone density during lactation and after weaning. N Engl J Med 1997;337:523-8.)

trabecular connectivity), and accumulating fatigue damage.[3] All are multifactorial conditions; however, low calcium intake can be a key element.[3]

Exercise to improve muscle strength and balance and other interventions to encourage a healthier lifestyle also can reduce fracture rates.[3] Bone mineral content can be affected by exercise; however, physical activity appears to increase bone mass only at calcium intakes >1000 mg/d,[57] providing further evidence of calcium's threshold nature.

Bone mass in old age is determined by peak bone mass and the subsequent rate of bone loss. Osteoporosis is increasingly being viewed as a pediatric disease with geriatric consequences. This view stems from the facts that ≥90% of bone mass is attained before age 20 years and that bone mass generally peaks before the age of 30 years.[29] Deposition of calcium into bone in women decreases markedly after menarche.[58] Dietary calcium intake, especially early in life, is positively associated with bone mass.[59, 60] Maximizing the likelihood of individuals' attaining their genetically determined peak bone masses is an important step in reducing the incidence of osteoporosis.[3] However, there are few studies on the effects of calcium intake on bone growth during childhood or of the long-term consequences.

Bone loss is normally minimal until the age of 40 years, after which it gradually increases with age. Bone loss in older adults is associated with low calcium intake, vitamin D insufficiency, and low androgen status.[3] In women there is a dramatic increase in bone loss during the 5 years immediately after menopause.[3] This high rate of bone loss is only minimally affected by calcium supplementation. Hormone replacement therapy can prevent this loss, especially if combined with calcium and vitamin D supplementation.[61] More than 5 years after menopause (or after cessation of hormone replacement therapy), the rate of bone loss decreases; at this time calcium supplementation has been shown to be effective at reducing bone loss,[62] especially in conjunction with vitamin D supplementation.[63, 64] Bisphosphonates have also been shown to reduce bone loss.[65] Combination therapies that include calcium, vitamin D, and, for women, hormone replacement therapy are the most efficacious at reducing or even reversing bone loss in older adults.[61]

Calcium metabolism during pregnancy

The term human fetus contains approximately 30 g calcium, all of which must come from maternal sources and most of which is transported during the last trimester. Calcium metabolism during pregnancy differs from that of the nonpregnant state in important ways; however, some of the data are contradictory and our understanding is far from complete. Maternal and fetal calcium metabolism has been recently reviewed.[66]

Maternal total serum calcium concentration falls during pregnancy, but that change can be accounted for by the fall in serum albumin concentration and thus a fall in protein-bound calcium concentration. Serum ionized calcium concentration, the physiologically important parameter, remains unchanged.[67] During pregnancy, in-

testinal absorption of calcium is markedly increased, probably in response to a significant increase in circulating levels of 1,25-dihydroxyvitamin D,[68, 69] some of which is placental in origin.[66] Urinary excretion of calcium is increased, reflecting the increased absorption and also the increased renal plasma flow related to the expanded plasma volume during pregnancy.[68, 69] Serum calcitonin level is elevated, which may serve to protect the maternal skeleton from excessive resorption of calcium.[66] Early studies found that serum PTH concentration was increased during pregnancy.[67] More recent studies with more specific assays for serum concentration of intact PTH cast doubt on this result, finding either a lower difference or no difference in serum PTH concentration between pregnant and nonpregnant women.[68-70] Some longitudinal studies suggest that the serum concentration of intact PTH does increase from the first to the third trimester,[71, 72] but others do not support this.[69] Thus pregnancy is not a state of secondary hyperparathyroidism.[66] Serum PTH-related peptide levels increase during pregnancy, but the source and role of PTH-related peptide during pregnancy remain unclear.[66]

The fetus is hypercalcemic relative to the maternal serum and has lower serum concentrations of PTH and 1,25-dihydroxyvitamin D and a higher serum calcitonin concentration.[66] Serum 25-hydroxyvitamin D concentration is correlated with maternal levels. The mechanism for maintaining the calcium gradient between fetus and mother is not understood, but PTH-related peptide may play a role.[66] Maternal hyperparathyroidism can suppress the fetal parathyroid glands and lead to neonatal hypocalcemia.[66] Maternal hypoparathyroidism can cause fetal parathyroid hyperplasia and increased resorption in the fetal skeleton.[66]

During pregnancy a biphasic pattern of bone remodeling is seen, with bone loss during early pregnancy followed by restoration in late pregnancy.[73] Thus, in general, pregnancy is not a risk factor for low bone mass or fractures.[74, 75] The increased absorption of dietary calcium would appear sufficient to provide the necessary calcium for the fetus in vitamin D–sufficient women. However, osteoporosis related to pregnancy is a documented, although rare, finding of uncertain pathogenesis,[76] although some have suggested that it may be related to subclinical vitamin D deficiency, low dietary calcium intake, and elevated PTH concentration.[77]

Calcium, lactation, and bone

Lactating women secrete approximately 210 mg/d calcium in breast milk.[78] Breast milk contains sufficient minerals to support bone growth in term infants but may not provide adequate vitamin D, especially if mothers are not receiving adequate sun exposure or dietary vitamin D.[79] If the infant is receiving adequate sun exposure, however, this should protect against vitamin D deficiency in the infant. Breast milk is not sufficient for proper bone growth and development in premature infants because it provides inadequate phosphorus.[80]

Intestinal calcium absorption during lactation decreases from the elevated level during pregnancy and is essentially the same as in the nonreproductive state.[68, 69, 81, 82] Urinary excretion of calcium, however, is significantly reduced relative to both pregnant and nonpregnant levels.[69] Thus renal calcium conservation does play a role in meeting the calcium requirements of lactation. However, the published data strongly support the hypothesis that the calcium demands of lactation are largely met by an increase in bone resorption.[52, 83-86] The loss of bone mineral can exceed 7% in 6 months, a higher rate of bone loss than that seen immediately after menopause. In rare instances this bone loss may result in fractures.[66]

The release of bone calcium into the blood does not appear to be regulated by the calciotropic hormones.[87] Concentrations of neither PTH nor 1,25-dihydroxyvitamin D differ from nonpregnant levels.[69, 87] PTH-related peptide concentration is elevated, however, and PTH-related peptide is suspected of playing a role in the bone loss.[66, 87] Recent investigations in animal models have suggested that increases in cytokines, such as interleukin 6, induced by decreases in estrogen concentration result in increased osteoclast activity and simultaneous decreased osteoblast recruitment.[88] Bone resorption mediated by estrogen withdrawal may have evolved as a means of ensuring a supply of calcium for milk regardless of diet. Thus menopausal osteoporosis may represent in part the unfortunate consequences of an adaptive reproductive physiologic mechanism that continues to operate for some time beyond the reproductive years.[66]

Unlike postmenopausal bone loss, the loss of bone caused by lactation is transient (Fig 2). After weaning, the intestinal calcium absorption increases, urinary calcium excretion remains low, and the rate of bone remodeling decreases.[69, 83, 86] There is evidence that these changes are linked to the resumption of menses.[86] The loss of bone mineral has largely been reversed by 1 year post partum, even if a second pregnancy occurs during that period.[89, 90]

Calcium supplementation during lactation does not appear to have any effect on bone loss during lactation and has only a mild effect on bone mineral recovery after weaning.[86] Even in women with chronic low calcium intakes, calcium supplementation during lactation appears to be without effect. For example, calcium supplementation was not found to have any measurable effects on calcium content of milk or bone mineral loss during lactation in Gambian women but was observed to increase urinary calcium loss.[52, 53]

Table I. Recommended daily intakes of calcium for women at different ages and life stages

Age or life stage	*Recommended intake (mg/d)*
9-18 y	1300
18-51 y	1000
51 y to end of life	1200
Pregnant or lactating, 14-18 y	1300
Pregnant or lactating, >18 y	1000

Data are drawn from reference 31. Note that the recommended intake varies with age but is not increased by either pregnancy or lactation.

Calcium and hypertension

Epidemiologic evidence implicates low calcium intake in the increased incidence of both hypertension and preeclampsia. An inverse relationship between dietary calcium intake and blood pressure status has been found in many studies (reviews can be found in Hamet[91] and Morris and Reusser[92]). Hypertension is often associated with hypercalciuria.[93] The calciotropic hormones may also play a role. For example, seasonal changes in blood pressure correlate with seasonal changes in vitamin D status.[91]

There are many proposed mechanisms by which low calcium intake would result in increased vascular resistance, but none have been confirmed. Low serum calcium concentration has been suggested to increase intracellular calcium concentration in vascular smooth muscle cells, which in turn increases vascular resistance.[94] The calciotropic hormones PTH and 1,25-dihydroxyvitamin D have vascular activity. At pharmacologic doses PTH acts as a vasodilator, but that may be a result of its binding to the same receptor as PTH-related peptide, which is known to be a potent vasodilator. At physiologic doses PTH does not appear to be able to modulate vascular reactivity, although there is an association between high serum concentration of intact PTH and hypertension.[95]

Recent evidence suggests that diets high in low-fat dairy products, fruits, and vegetables and thus moderate to high in calcium content are efficacious in reducing blood pressure and preventing hypertension.[96] Calcium supplementation decreased diastolic blood pressure in African American adolescents.[97] The effect was greater among those subjects with lower habitual calcium intakes.[97] If dietary calcium intake does reduce blood pressure, this might have additional beneficial effects on offspring because maternal blood pressure and low calcium intake are risk factors for hypertension in children.[98]

Until recently, the only empiric evidence that low calcium intake was associated with a greater risk of preeclampsia came from epidemiologic studies and small trials with insufficient discriminatory power. A meta-analysis of those trials[99] concluded that calcium supplementation did have a beneficial effect. However, the results of the Calcium for Preeclampsia Prevention trial dispute that conclusion.[100] That study found no significant effect of calcium supplementation on pregnancy-related hypertension, preeclampsia, or other pregnancy-related outcomes, although the incidences of hypertension and preeclampsia were numerically lower in the calcium-supplemented group. The Calcium for Preeclampsia Prevention study has a large enough sample size (>4500 women) that any effect would be expected to be seen. However, the Calcium for Preeclampsia Prevention population was healthier than the general US population and also had higher calcium intakes. Many of the women in the Calcium for Preeclampsia Prevention study had habitual calcium intakes above the threshold intake for maximal calcium balance. Thus the hypothesis that preeclampsia is associated with low calcium intake probably either (1) is false, as the Calcium for Preeclampsia Prevention study would indicate, (2) is true for certain populations (eg, women with "salt-sensitive" hypertension or women with very low calcium intakes), in which case the lack of significance in the Calcium for Preeclampsia Prevention study was the result of a heterogeneous response by the sample population, or (3) is partially true, but the mechanisms linking calcium, hypertension, and preeclampsia are not direct.

Other diseases

Although healthy young adults appear able to adapt to low calcium intake and still maintain bone, evidence suggests that chronic calcium undernutrition may have adverse health consequences unrelated to bone.[8, 101] In addition to the possible associations with hypertension and preeclampsia discussed previously, low calcium intake and low vitamin D status together are a risk factor for colon and rectal cancers.[102-105] Daily calcium intakes of 1200 mg reduce colonic epithelial cell proliferative activity.[106] Low dietary calcium intake and low vitamin D intake together increase the susceptibility of rats to induced mammary neoplasia.[107] However, high calcium intake has recently been noted to be associated with an increased risk for prostate cancer,[108] possibly as a result of a reduction in the circulating level of 1,25-dihydroxyvitamin D, which is thought to have an antitumor effect on the prostate.[109, 110] Higher bone density in women has been found to be a risk factor for breast cancer,[111] but this is thought to relate to a longer lifetime exposure to estrogen and not to calcium intake.

Women who exhibit common symptoms of premenstrual syndrome have lower serum concentrations of ionized calcium and 25-hydroxyvitamin D and higher concentrations of intact PTH than do symptom-free women.[112] Calcium supplementation has been shown to reduce the symptoms of premenstrual syndrome.[113, 114] Women with premenstrual syndrome also have lower bone mass.[115, 116] Thus premenstrual syndrome could serve as an indicator of subclinical vitamin D deficiency,

low calcium intake, and a higher risk for low bone mass and eventual osteoporosis.[117] An increase in calcium intake among women with premenstrual syndrome might have significant health benefits beyond the simple reduction of premenstrual syndrome symptoms.

Hypercalciuria is a risk factor for nephrolithiasis and is associated with increased absorption of calcium from the intestine, decreased calcium reabsorption from the renal tubules, and increased bone turnover.[118, 119] High calcium intake, however, is not a risk factor for renal stones. In fact, high calcium intake from foods is associated with a decreased risk of stone formation in both men and women.[119, 120] This is hypothesized to result from a decreased intestinal absorption of oxalates because of their binding with calcium. However, these same studies have shown a small increase in the risk of stone formation with the intake of calcium supplements. This is possibly because the supplements were not taken with food or were taken at meals with low oxalate content.

Comment

In this article we provide an overview of areas in which calcium intake has the potential to affect health. In some instances the health benefits are well established, such as the positive effects of calcium, especially in conjunction with vitamin D supplementation and (in women) hormone replacement therapy, on bone mass in older adults.[61, 63, 64] In other instances, for example, during lactation, calcium supplementation would appear to provide minimal if any benefits.[86] Indeed, the current scientific evidence indicates that pregnancy and lactation do not increase a woman's calcium requirement (Table I).

On the basis of the existing scientific evidence, should health professionals encourage women to increase calcium intake? Many women currently consume considerably less than the recommended amount of calcium,[121] far below the threshold intake that would maximize calcium balance.[2] A growing body of evidence suggests that calcium has a protective effect for colon and rectal cancer, hypertension, and premenstrual syndrome. The evidence is overwhelming that low calcium intake can compromise bone. An increase in calcium consumption by women whose intakes are <1000 mg/d would probably result in a significant decrease in the future risk of fracture. However, other interventions, such as pharmacologic and behavioral interventions, can also decrease fracture risk. The multifactorial disease of osteoporosis is best treated through a multifaceted approach.

Proper nutrition is important to health. Good dietary habits need to be established at a young age and reinforced throughout life. Because there has been much recent publicity about calcium,[122] it is likely that calcium is a nutrient that most women will associate with health. Thus calcium could serve health professionals as an avenue to open a discussion of nutrition and health. Although calcium supplements are appropriate for some patients, encouraging the consumption of low-fat dairy products and other calcium-rich foods could increase the general overall quality of the diet and provide health benefits in addition to those offered by increased calcium intake alone.

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