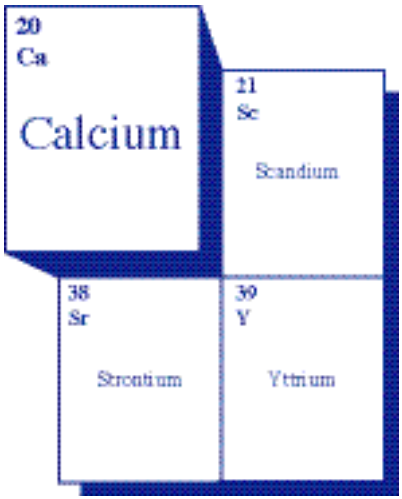

Calcium

Introduction

According to medical anthropologists, calcium intake among Paleolithic people (who ate no dairy products and little meat or fish) averaged 1,500 mg per day.[1] Actual current intakes of hunter-gatherer tribes have been calculated at 2,100-3,000 mg per day.[2] In contrast, the average daily calcium intake of the adult woman in the United States is 500 mg.[3] Several diseases, including osteoporosis, hypertension, and colon cancer have been linked to a drop in calcium intake and to increased dietary phosphorus from grains that has been occurring over the last several centuries.[4]

During the past 20 years, conflicting research in the area of calcium and osteoporosis prevention and treatment has created confusion in the scientific community. This confusion is partly due to the fact that calcium is a threshold nutrient,[5] which means that above a certain threshold there will be little, if any, improvement in response from increasing the dosage.

There are, however, several areas of clarity that have emerged from the burgeoning amount of research on calcium and bone loss. It now appears the source of calcium and its application in the female life cycle make a substantial difference. There are also indications for the use of calcium in specific types of hypertension, premenstrual syndrome, and prevention of colorectal cancer.

Pharmacokinetics

Absorption of calcium varies with age and the presence or absence of intestinal disease.[6] Although it has commonly been believed that solubility of a calcium source increases absorbability, absorption studies have not found a predictable linear relationship between solubility and absorption.[6] Absorption rates of commercially-available calcium supplements vary, with calcium carbonate as low as 22 percent[7] and calcium citrate malate (CCM) as high as 42 percent.[8] Studies looking at actual absorption of calcium supplements vary significantly based on the intra-individual differences in absorption capacity, including hydrochloric acid production.

Calcium research in the area of osteoporosis is difficult due to the complex nature of maintaining calcium balance. Twenty-five percent of the variance in calcium balance is a result of absorption differences, and absorption in menopausal women can vary as much as 61 percent. In some calcium trials, malabsorption of calcium was so common that 40 percent of women in the trials could not absorb enough calcium to stay in calcium balance even though they were ingesting 800 mg daily.[9]

Mechanisms of Action

Calcium has life-sustaining functions in all living cells, acting as a second messenger in transmitting signals between cellular plasma membranes and intracellular signal receptors. In the extracellular environment calcium is essential in promoting blood clotting and the production of cellular adhesion molecules. Recent evidence shows cell membranes in the kidney, parathyroid gland, and brain have specific receptors for calcium that initiate intracellular signals.[10]

In the kidney, calcium lowers dopaminergic activity, resulting in increased urinary volume and loss of sodium, a possible mechanism for calcium's blood pressure lowering effect.[11] Calcium supplementation also lowers levels of osteocalcin and parathormone (PTH), as well as 1,25-dihydroxy vitamin D. Both PTH and 1,25-dihydroxy vitamin D have hypertensive effects via increases in vascular tone.[12] Although the mechanism is not clear, calcium supplementation in subjects with essential hypertension appears to have an insulin-normalizing and insulin-sensitizing effect at levels of 2,000 mg daily.[13] Calcium also promotes normal histology of the colonic mucosa. It forms insoluble complexes with fatty acids and bile acids, preventing colonic hyperplasia induced by bile acids and dietary fats.[14] Calcium also appears to have direct effects on normal proliferation of colonic epithelium.[15]

Calcium, physical exercise, and gonadal hormones are the most important factors influencing bone mass and density.[16] By decreasing circulating levels of 1,25-dihydroxy vitamin D and PTH, calcium alters the remodeling rate of bone tissue by increasing osteoblast activity, thereby increasing bone density.[17]

Clinical Indications

Premenstrual Syndrome

At midcycle, levels of serum ionized calcium in menstruating women drop significantly with a simultaneous elevation of estradiol.[18] Women with premenstrual syndrome (PMS), however, have significantly lower levels of serum ionized calcium and 25-hydroxy vitamin D and higher levels of PTH at midcycle than age-matched women who are symptom free.[19] In women with PMS there is evidence that midcycle elevations of PTH and fluctuations of serum calcium and vitamin D occur more significantly than at other times in the cycle.[18]

A randomized, placebo-controlled, double-blind study of calcium in women with PMS showed a significant relationship between PMS symptoms and calcium intake. Supplementation of 1,200 mg/day calcium in 466 women with moderate-to-severe recurrent premenstrual syndrome resulted in a 48-percent reduction of PMS symptoms after three months of use ($p< 0.001$).[18] The mechanism for calcium's benefit for PMS is not known, although the vasoactive effects of low serum calcium and elevated PTH and 1,25-dihydroxy vitamin D may play a role.

Hypertension

The effect of calcium in hypertension is seen most clearly in those with low calcium intakes, indicating a role for calcium supplementation in treating hypertension, both in children and adults who have low dietary calcium levels.[20,21] Dietary calcium and magnesium were found to be independently associated with hypertension risk in 58,218 females in the Nurses' Health Study.[22] Those with dietary intakes of less than 700 mg calcium per day were at higher risk for hypertension than those with intakes higher than 700 mg per day.[23,24] Although a recent meta-analysis of calcium and hypertension revealed only small changes in blood pressure (-1.44 mm Hg systolic and -0.84 mm Hg),[25] studies using calcium along with vitamin D have resulted in significant results. In elderly women, 1,200 mg calcium plus 800 IU vitamin D resulted in a nine-percent decrease in systolic blood pressure.[26]

It appears that baseline dietary calcium levels are also a significant factor in pregnant women and their risk for hypertension and preeclampsia. Studies with lower calcium-intake populations demonstrated significant effects on risk for hypertension.[27] A supplemental dose of 1,800 mg calcium carbonate, taken from 24 weeks to term, reduced the relative risk of preeclampsia and risk for preterm birth – each by more than 50 percent.[28]

Colorectal Cancer

Low dietary intakes of both calcium and vitamin D have been associated with increased risk for colorectal cancers. Conversely, those with higher dietary intakes are at lower risk.[29,30] A three-year intervention trial found 1,600 mg elemental calcium (4.0 grams calcium carbonate) daily was effective in reducing both adenoma growth and rectal epithelial hyperplasia in those who were cancer free, and decreasing the occurrence of new adenomas in those with a history of polyps.[31] A similar intervention trial with 1,200 mg elemental calcium (3 grams calcium carbonate) daily lead to a significantly lower risk for recurrence of colorectal adenoma.[32]

Kidney Stones

Calcium restriction has been an accepted therapy for the prevention of recurrent nephrolithiasis. Epidemiological studies, however, have found an inverse relationship between dietary calcium levels and kidney stone formation.[33,34] Although increased urinary calcium is a risk factor for kidney stone formation,[35] calcium citrate or calcium citrate malate (CCM) supplementation actually reduces risk of oxalate stone formation. Trials with 800 mg elemental calcium as citrate increased urinary citrate and reduced calcium oxalate production, decreasing risk for oxalate stone formation.[36]

Calcium citrate malate, in doses of 300 mg elemental calcium, inhibits the absorption of oxalate from the gut and consequently decreases urinary oxalate levels.[37] When 600 mg CCM was given to patients with idiopathic hypercalciuria, the urine pH and urine citrate levels rose; both urine alkalinity and elevated citric acid levels have protective effects against stone formation.[38]

Age-related Osteoporosis

Emphasis on building peak bone mass is the most crucial step in osteoporosis prevention. More than 90 percent of bone mass is acquired before age 20 and acquisition of peak bone mass ends by age 30.[17] If peak bone density in young adults reaches one standard deviation above normal levels for that age group, a 15-percent loss of total bone mass during menopause will not result in negative consequences. Studies with adolescents given 500 mg calcium citrate malate per day in addition to approximately 1,000 mg calcium from dietary sources resulted in additional bone growth equal to 1.3 percent of the total skeleton per year.[39] If this growth was sustained through adulthood, the total gain would ensure protection against menopausal bone loss. Further studies in adolescents have repeated these findings and support the need for a re-evaluation of the National Institutes of Health (NIH) guidelines for calcium intake in this age group. Optimal gains in bone mass were achieved with total calcium intakes of an average of 1,600 mg daily.[40]

During the first 5-7 years of menopause, bone loss is under hormonal control and researchers in the field have agreed calcium supplementation alone is not able to alter the average of 15 percent bone loss that occurs, nor is calcium alone able to reduce risk of spinal fracture.[17] However, in three separate meta-analyses of calcium's effect in reducing bone loss prior to and after menopause in women and in men over 40, calcium had a significant effect in preventing bone loss. In postmenopausal populations calcium was effective in preventing the one-percent bone loss per year that occurs as the average postmenopausal bone-mass decline.[41-43]

Relative risk of fracture is the most sensitive and accurate way to assess the efficacy of treatments for osteoporosis. Studies with CCM in combination with vitamin D (500 mg CCM and 700 IU vitamin D) in menopausal women reduced non-vertebral fracture risk by 50 percent,

equivalent to hormone replacement therapy.[44] Another large trial using a calcium triphosphate and vitamin D3 combination protocol has replicated this research.[45]

Glucocorticoid-induced Osteoporosis

Glucocorticoids have an immediate effect on bone metabolism by impeding formation and accelerating resorption of bone, inhibiting calcium absorption, suppressing circulating estrogen, and increasing urinary calcium levels. Glucocorticoid-induced osteoporosis is the most devastating side effect of long-term glucocorticoid therapy and the second most common form of osteoporosis seen in subspecialty clinics.[46] It is recommended that those receiving long-term (more than six months) treatment with glucocorticoids at doses over 7.5 mg/day be monitored every 6-12 months for bone loss.[47] Studies support the use of calcium and vitamin D in these patients as a means to maintain and increase bone density (in some trials). Dosages of 800-1,000 mg calcium carbonate and 250-500 IU vitamin D daily have stabilized lumbar and hip bone density in those on low-dose prednisone (11-15 mg).[48,49]

Drug-Nutrient Interactions

Inhibition of Drug Absorption

Calcium interferes with absorption of some drugs, including bisphosphonates for osteoporosis, quinilone antibiotics (ciprofloxacin, gatifloxacin, etc.), and tetracycline.[50] Calcium carbonate was found to decrease absorption of levothyroxine, while increasing serum thyrotropin levels.[50] Calcium supplements should be taken at a different time of day than these medications.

Inhibition of Calcium Absorption

Absorption of calcium can be inhibited by H_2 blockers (cimetidine, ranitidine, etc.), proton pump inhibitors, inositol hexaphosphate, sodium alginate, and oxalate- and phytic-acid rich foods.[50] Calcium may also be depleted by the use of thiazide diuretics.[51]

Enhancement of Calcium Absorption

Absorption of calcium is enhanced by consumption of vitamin D, vitamin D analogs (calcitriol, alfacalcidol), and fructooligosaccharides.[50]

Side Effects and Toxicity

Dosages up to 2,500 mg per day are considered safe in healthy adults.[2] People with idiopathic hypercalciuria, hyperparathyroidism, vitamin D intoxication, milk-alkali syndrome, and sarcoidosis may need special consideration.

Dosage

Dosages for calcium vary with individual age, gender, and condition. Federal guidelines for calcium intake are sex- and age-specific and vary from 1,000-1,300 mg per day.[17] As indicated by research in adolescent women, higher doses, in the range of 1,500 mg daily, may be a better recommendation.[40]

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