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Review Article

Multiple Roles of Calcium in Maintaining Human Health

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Abstract

Calcium and its salts have important roles to play in maintaining human health. It is a bone builder and plays a role in reducing the risks of cardiovascular disease, cancer, preeclampsia, cataract genesis, obesity and metabolic syndrome. Recently many new involvements of calcium in genesis of diseases were described in the literature Calcium deficiency and its precursors are discussed in this short review. Role calcium either taken by normally and/or calcium supplements, Vitamin D, and oestrogens, in pregnancy, menopause, lactose intolerance, etc. are discussed. Higher calcium intakes also suggested in lower prevalence of obesity and insulin resistance. Most of the studies suggest natural calcium diets are more effective than the supplements.

Keywords: maintaining human health; herbal; remedies; inflammation

Introduction

Calcium and its compounds are most essential ions and mineral those are required for the proper functioning of the human body. Its compounds are necessary for maintaining strong bones and teeth. Calcium is an integral part of bones and teeth and by keeping the tissues rigid, flexible and strong helps in natural body movements [1]., whereas in ionic form, it is used in functioning of nerves and muscles. It mediates blood clotting, functions of many enzymes and muscle, contraction and dilation of blood vessels, transmission of nerves, hormonal secretion and normal heart rhythm by its presence in various tissues, extracellular fluid and circulatory system [1,2]. Active transport and passive diffusion helps in the absorption of calcium present in the dietary supplements and foods across the interstitial mucosa [1,3].

Bones:

Ninety eight percent of calcium in the body is stored in bones, they act as a store house and calcium source in maintaining its homeostasis [1]. About 26-30 g of calcium is present in the body at the birth and the amount rises sharply afterwards reaching 1.2 kg in women and 1.4 kg in men by adult age

Between the ages of 9-18 years, highest calcium is needed by the body and a deficiency during this period causes bone weakening later in life. Depending on the health condition and age, men need about 1000-1200 mg of calcium daily. Calcium carbonate and calcium citrate are both good options for men, but it is important to choose a supplement that is easily absorbed by the body. Adult requirement daily to maintain a normal calcium level in the blood without affecting bone strength is 1.00-1.30 kg. For the absorption of calcium in the body, Vitamin D is also required with a daily requirement of 600 units in adults or 800 units in older adults (4).

Among men and women, calcium is more essential for women, since they have smaller bones than men and more prone to osteoporosis. The decrease in estrogen level after menopause makes their bones less protected than before. A woman having high bone density before menopause have less chances of developing osteoporosis as calcium is a bone builder [4]. The present review discusses the role of calcium, an important ion in the maintenance of good health.

For better understanding of the mechanisms (which are diverse and complex) involved in Ca^{2+} homeostasis, it is essential to understand the factors that are involved in calcium homeostasis. In maintaining homeostasis three factors are important; fluids and electrolytes, energy and nutrition, and immune response mediators. Parathyroid hormone (PTH) 1,25-dihydroxyvitamin D-3 (Vitamin D3), and calcitonin are the three primary hormones playing role in regulating transport of calcium in the bone, gut and kidneys (5).

Men and women tend to lose calcium from bones but women are more prone to the loss as they at young age and at a more rapid rate and they also have high bone resorption markers. Diseases arising due to insufficient calcium such as bone health in old people, cardiovascular disease (CVD), cancer, preeclampsia, obesity, and metabolic syndrome are discussed below.

Risk of Calcium Inadequacy

Hypocalcemia

Serum level below 8.5 mg/dL or an ionized calcium level less than 4.61 mg/dL is called hypocalcemia, which is due to deficiencies of magnesium or vitamin D, altered production of parathyroid hormone causing hypoparathyroidism, altered bone calcium resorption, critical illness, or the use of medicines like bisphosphonates, cisplatin, or proton pump inhibitors [6,7]. When mild or chronic, hypocalcemiamay be asymptomatic [7]. Low serum calcium levels cause wide signs and symptoms which are a result of effect of many organs [8]. High neuromuscular irritability, including muscle spasms, perioral numbness, and hands and feet tingling are the most common symptoms [7]. Brain calcification, congestive heart failure, cataracts, neurologic symptoms including depression and bipolar disorder, paresthesia,

renal calcification or injury, seizures and in rare cases coma are the more severe signs and symptoms [6,8].

Role of Estrogens

Estrogenis essential for bone health for both men and women, though women obviously produce more estrogen and men only a small amount. In men, conversion of testosterone to estrogen takes place for bone protection. In postmenopausal osteoporosis, by increasing serum 1,25(OH)2Dcalcium absorption improves by estrogen treatment. This result is indirectly mediated by stimulating renal 1 alpha-hydroxylase by raised serum PTH [9]. Estrogen sharply decreases and bones can be vulnerable in women in menopause and perimenopauseperiod and hence, they need to be particularly careful about their bones during this period. Osteoporosis also is the most common during this period. However, calcium supplements, hormone replacement therapy, and other medical treatment scan protect their bones luckily. Occasional bone density scan help the women in these age groups to determine whether one need additional therapies to strengthen the bones.

Bone strength

Calcium deficiency, which reduces the strength of bones leadsto osteoporosis, which causes fragile bones and an increased risk of falling [1]. It may also result in bone disorders in adults and rickets in children, though vitamin D deficiency may be the common cause. In children with rickets, mineralization of the growth cartilage is affected leading to irreversible changes in the skeletal structure [1]. Inadults and children, Osteomalacia, or defective bone mineralization and bone softening, is another effect of chronic calcium deficiency [1]. The requirements for calcium and vitamin D for rickets and osteomalacia are interrelated, low serum Vitamin D required more calcium to prevent these diseases [10].

Menopause

Decrease in estrogen production during menopause leads to bone loss by a reduction in absorption of calcium absorption and increased loss of calcium in urine and bone resorption of calcium [1].Every year women after menopause, lose about 1% mineral density of their bone, leading to reduced bone mass and fragility of bones [1, 11]. In the US and Europe, about 30% of postmenopausal women suffer from osteoporosis and out of them around 40% get develop minimum one fragility fracture, which is seen after minor trauma [12]. The calcium daily requirement after menopause is 1.2 kg for women above 50 years (vs. 1.0 kg for younger women) to lessen bone loss [1].

Lactose intolerance

Dairy products are rich sources of calcium, avoiding them and those suffering from lactose intolerance and those with an allergy to milk have a higher risk of inadequate calcium [1,13]. In such individuals, calcium intakes can be increased by lactose-free or reduced-lactose dairy diets, which have the equal amounts of calcium as regular dairy products [1,3]. Non-dairy sources, such as some vegetables (e.g., broccoli, and Chinese cabbage [bokchoi]), canned fish with bones, or fortified foods (e.g., breakfast cereals, fruit juices, and tofu)and kale, can be used in those who wish to avoid dairy products due to allergies or other reasons [1]. However, foods fortified with calcium or supplements help better to obtain required doses [14].

Bone health in older adults

Bone is constantly being remodelled. A rapid decrease in bone mass arising in women mostly after5 years of menopause may be due to declining levels of estrogen and also due to high rates of bone resorption vs formation [7] and hence, postmenopausal women can develop osteoporosis commonly [1]. In men, age-related bone loss also leads to osteoporosis, but fracture risk usually appears in older men about 5-10 years later than in old women [1]. There is an increased risk of fractures, especially of the hip, forearms and vertebrae due toosteoporosis. To reduce the risk of osteoporosis, FDA has approved a formulation containing calcium and vitamin D supplements [15], however, many research doesn't support this claim.

Bone mineral density

Variable results were obtained on the relationship between calcium intakes and measures of bone strength in aged people [16]. In women older than 65 years of age, with average dietary calcium intake of 886 mg/day, no association between calcium intake and BMD was observed at any site, even after adjustment for such factors as age, height, physical activity, and weight [17]. Only a few clinical trials proved that supplementation of calcium can help bone health in old people. A post-hoc analysis of data found that the supplementation for a period of 5.9 years did not stop height loss after a mean follow-up [18]. On average, women lose1.28 mm/year of height in the supplementation group and 1.26 mm/year in the placebo group. However, in 500 healthy postmenopausal women daily intakes of 500 ml/day skimmed milk enriched to contain 900 mg calcium and 15 mcg (600 IU) vitamin D led to improved BMD at the femoral neck in a 2-year randomized clinical trial (RCT) [19]. Several recent and earlier studies and meta-analyses have found increases in BMD in old people after supplementation with calcium alone or a combination of calcium and vitamin D [11, 20, 21]. However, whether these BMD increases were clinically significant is not clear.

Fractures

There is a close link between increase in calcium intake and reduction in BMD loss, however, the research studies on utilization of calcium supplements to avoid fractures in aged people are variable. The fracture risk was non-significant in users of calcium supplements, though few of them used supplements of vitamin D and nonusers, even though the study observed less BMD loss with supplement use [22] and does not support the fact that the high intakes of calcium decreases the risk of fractures and falls in older age people. The results showed that calcium supplementation alone or with vitamin D had no impact on hip fracture risk, non-vertebral and vertebral fractures, or total fracture. Similar results were observed in people aged 50 and older, when calcium was supplemented with vitamin D for 2 to 7 years on the risks of total fractures or of hip fractures [23]. Hence, it is difficult to conclude that calcium supplementation alone or with vitamin D prevents fractures in men and premenopausal women and further research is needed to judge the use of supplements of calcium to help bone health and prevention of fractures in older people.

Calcium and Cancer

Calcium is a helpful in decreasing the risks of certain types of cancer, eg.,colon and rectum [1] but not in other cancers. However, inconsistent evidence is available on the association of intakes of calcium from foods or supplements and various cancers [4].

Most of the clinical trial evidences do not support the benefits of calcium supplements on cancer incidence. However, a clinical trial involving more people did find that calcium supplements decrease cancer risk [24], which was questioned due to the lack of statistical results on sample size and procedures employed for randomization [25, 26].

Evidences from observations and clinical trials also prove that cancer mortality is not related to higher intakes of calcium [27-29]. Supplements of calcium alone or along with vitamin D have also been tested to study mortality from all cancers. However, more research has supported the use of calcium in the prevention of adenomas and colorectal cancer or its precursor [29], though the results are variable in clinical trials on the use of supplements of calcium in preventing these cancers. [29]. However the study doesn't support the benefits of intake of calcium for rectal cancer.

Several studies observed that when the calcium comes from dairy sources, high calcium intake cause high risk of prostate cancer [30]. However, prostate cancer risks were not significantly associated with non-dairy sourced calcium intakes. The total dietary and calcium supplements intake raised the risk of prostate cancer only to an extent of 2% higher for each 400 mg/day increment observed in a systematic review and meta-analysis of nine cohort studies carried out in 750,275 men. But the risk was not associated with non-dairy and supplemental calcium intakes. [31].

Research studies have shown variable results on the association of high calcium intakes and lower breast cancer risk[32]. Further, systematic trials are necessary to conclude whether dietary or supplemental calcium intakes

increase, reduce, or no effect in reducing the risks of cancers or cancer mortality.

Calcium and Cardiovascular disease

By binding to fatty acids, calcium can reduce lipid absorption and hence, reduce the risks of cardiovascular diseases (CVD) [1,4].However, variable results were obtained on intakes of calcium in diet and supplements of calcium and reduction in risks of CVD. Some studies indicate that supplements of calcium may increase CVD risk [33]. Low calcium intakes may cause higher risk of atherosclerosis, hypertension and stroke is also indicated by several large observational studies. Women are more prone to such diseases [34]. A 13 years prospective cohort study in Australia carried out in 41,514 adults aged 40-69 years proven no link between calciumintakes of and risks of myocardial infarction or CVD mortality [35].

The research findings on the relationship between intakes of calcium and risk of stroke or related mortality were variable. [36].Diets used to reduce hypertension usually contain other nutrients like potassium and magnesium, which also reduce blood pressure, and hence, determination of independent contribution of calcium is difficult.

In contrast, no relationship between supplements of calcium and risks of CVD or outcomes of CVD was also observed in several prospective cohort studies [37]. Hence, Institute of Medicine was recommended the tolerable upper intake level (UL) values, which doesn't cause any side effects for calcium, 2.5 g for children up to 8 years of age, 3.0 g for those aged 9-18 years, 2.5 g for 19-50 years old, and 2.0 g for adults [38]. The cardio vascular associations hence, confirmed the intakes of calcium below the UL as safe for use for cardiovascular purposes.

Calcium and Preeclampsia

With all the available evidence it is shown that during pregnancy supplementation with calcium may decrease the risk of preeclampsia. Supplements of calcium to decrease the chances of preeclampsia, during pregnancy may benefit only those women, who have low calcium intakes [39, 40]. Hence, to avoid preeclampsia risk organizations like WHO recommended 1.5–2.00 g/day calcium to pregnant women [41]. Lately, Pratibha Dwarkanath et al.[42] suggested that taking 500 mg of calcium a day reduces the likelihood of developing preeclampsia in pregnant women.

Calcium in Cataractogenesis

Earlier we reported that development of human cataracts also depends oncalcium and Ca-dependent enzymes. The Ca^{2+} level in the lens epithelium controls homeostasis and growth of entire lens [43]. Steroid hormone receptors regulate the enter of Ca^{2+}into the lens epithelial cells (LEC). Activation of Ca-dependent enzymes, irreversible breakdown of important structural proteins and cell death are initiated in the LEC by the intracellular Ca^{2+} [44]. Cataract can be prevented by proper maintenance of Ca^{2+} levels by regulating activity of Ca-pumps and Ca-channels and inhibition of Ca-dependent enzymes along with calcium storage in mitochondria [45]. The opacification process in human lenses with cortical cataract may be due to the excessive Ca^{2+}, which is detrimental to cells and due to raised levels of Ca^{2+} in human lenses. Ca^{2+} plays a central role as a second messenger in cell signalling and mechanisms have evolved which give cells exquisite control over intracellular Ca^{2+}.[46]. Prevention of posterior capsular opacification can be achieved by induction of cell death in the LEC by increase in the intracellular Ca^{2+} [43]

Calcium and Weight management

Epidemiologic surveys suggestthat high intake of calcium leads to low rates of overweight or obesity, and insulin resistance. A 6-year follow-up study of the prevalence of obesity in boys was lower by 16% and in girls 18%in the high calcium intake group [47]. The prevention of weight gain or increasing fat loss by calcium supplements or increased intakes of calcium from dairy products showed variable research results [48-52].

However, a study in 4,802 adults suggested that high calcium intakes from dairy foods or calcium supplements (300 mg/day) had no effect on body weight or body fat, but when mixed with energy-restricted diet reduction in body fat was observed. [52]. Calcium supplements have also shown no effect on body weight or fat. The fact that parathyroid hormone and 1,25-hydroxy vitamin D levels get reduced due to high intake of calcium is known [53]. Intracellular calcium gets reduced due to the lower levels of these hormones, resulting in inhibition of lipogenesis and increasing lipolysis. Excretion of face al fat and increase of body temperature also takes place due to high dietary calcium [54].

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