REVIEW

Does calcium intake affect cardiovascular risk factors and/or events?

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Dietary intervention is an important approach in the prevention of cardiovascular disease. Over the last decade, some studies have suggested that a calcium-rich diet could help to control body weight, with anti-obesity effects. The potential mechanism underlying the impact of calcium on body fat has been investigated, but it is not fully understood. Recent evidence has also suggested that a calcium-rich diet could have beneficial effects on other cardiovascular risk factors, such as insulin resistance, dyslipidemia, hypertension and inflammatory states. In a series of studies, it was observed that a high intake of milk and/or dairy products (the main sources of dietary calcium) is associated with a reduction in the relative risk of cardiovascular disease. However, a few studies suggest that supplemental calcium (mainly calcium carbonate or citrate) may be associated with an increased risk of cardiovascular events. This review will discuss the available evidence regarding the relationship between calcium intake (dietary and supplemental) and different cardiovascular risk factors and/or events.

KEYWORDS: Dietary calcium; Supplemental calcium; Obesity; Cardiovascular risk factors; Cardiovascular events.

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INTRODUCTION

Considerable evidence indicates the role of dietary interventions in the prevention of cardiovascular disease (CVD) (1). Existing research has focused mainly on the role of macronutrients. However, micronutrients might also be important in the prevention of CVD. The possibility that a calcium-rich diet could affect energy balance, with anti-obesity effects, has attracted considerable attention (2-3). Several studies have also suggested that dietary calcium could have beneficial effects on insulin resistance (4-8), dyslipidemia (9-12), hypertension (13-18), inflammatory stress (19-20) and cardiovascular events (21-24). In this review, we discuss the evidence regarding calcium intake and cardiovascular risk factors and/or events.

CALCIUM AND OBESITY

Observational studies

The initial evidence for an inverse association between the intake of dietary calcium and/or dairy products (which are the main sources of dietary calcium) and the parameters of abdominal or total adiposity was derived from epidemiological studies in both adults and children (9,25-26). Similar results have been obtained from observational studies with fewer participants, even when a specific group of individuals was evaluated (27-30). Two studies conducted by our group observed this inverse association (28-29). In the first study (28), a higher dietary calcium intake was associated with lower total body adiposity in hypertensive patients, whereas in the second study (29), a higher dietary calcium intake was associated with lower abdominal adiposity in a group of renal transplant patients.

A global evaluation of different observational studies points to a modest negative association between dietary calcium (or dairy) and body weight. Dougkas et al. (3), based on a linear regression analysis of 18 studies, estimated that at 400 mg of calcium/day (low dietary calcium intake), a body mass index (BMI) of 25.6 kg/m^2 was predicted, while for 1,200 mg of calcium/day (adequate calcium intake), a BMI of 24.7 kg/m^2 was predicted. Thus, an increase in calcium intake of 800 mg/day was associated with a decrease in BMI of 1.1 kg/m^2.

Interventional studies

The effect of calcium supplementation on weight loss is uncertain. The results of randomized clinical trials designed to examine the effects of calcium supplementation on parameters of body fat have been ambiguous (31-36). One factor that likely contributes to the conflicting results is the lack of uniformity in the design of the studies. For example, some trials used supplemental calcium (mainly calcium carbonate or citrate) (37-40), while others used dietary calcium (derived from dairy products) (34-36). In some trials, calcium was supplemented during energy restriction (37,40), while in others, energy intake was not restricted (38-39).

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No potential conflict of interest was reported.

Among the studies without concomitant energy restriction that evaluated the effects of supplemental calcium, the majority did not observe any benefits to body weight and/or composition (38-39,41). In contrast, some studies that supplemented dietary calcium reported beneficial effects (33,42). Zemel et al. (43) compared the effects of low dairy (<1 dairy serving/day) *versus* recommended dairy (>3 servings/day) on weight maintenance and body composition subsequent to weight loss. Weight maintenance was similar in both groups. However, the recommended dairy group exhibited evidence of greater fat oxidation and was able to consume greater amounts of energy without greater weight gain compared to the low dairy group.

Studies that have evaluated the use of supplemental calcium during energy restriction have failed to find beneficial effects on weight loss (37,40). However, the supplementation of dietary calcium associated with energy restriction has induced significantly higher decreases in total and/or abdominal adiposity in some studies (31-33,36) but not in others (34-35). Recently, our group conducted a randomized clinical trial (36) with 50 obese subjects of both sexes, 22–55 years of age, with stable body weight and low habitual calcium intake. The participants were randomized into the following outpatient dietary regimens: (i) a low-calcium diet (<500 mg/day) or (ii) a high-calcium diet (1,200–1,300 mg/day, supplemented with non-fat powdered milk [60 g/day]). Both groups followed an energy-restricted diet (-800 kcal/day) throughout the study (16 weeks). After 16 weeks of energy restriction, the subjects on the high-calcium diet exhibited greater reductions in waist circumference ($p = 0.002$) and waist-to-hip ratio ($p = 0.0001$) than the subjects on the low-calcium diet (36).

Studies comparing the effects of supplemental *versus* dietary calcium during energy restriction have observed that calcium from dairy products has a greater effect on the reduction of body fat (31,44). According to Van Loan (45), three important elements have been present in studies showing a favorable effect of calcium and/or dairy product intake on weight loss. First, all of the individuals participating in these studies were overweight and/or obese. Second, the subjects' calcium intake levels were habitually inadequate (<600 mg/day), and an appropriate control group (<600 mg of calcium/day) was used. Third, moderate energy restriction was maintained throughout the study.

Interventional trials assessing the effects of calcium supplementation on body adiposity present inconsistent results, and further studies regarding this issue are needed.

Possible mechanisms underlying the impact of calcium on adiposity

The mechanisms underlying the possible relationship between calcium and/or dairy intake and BMI are unclear. However, a reduction in body weight can only occur if fecal energy loss, energy expenditure and/or energy intake are affected. High calcium intake has been suggested to affect all of these factors (46).

Effect of calcium on fat metabolism in adipocytes

There is evidence from *in vitro* and animal studies that increased calcium intake inhibits lipogenesis and stimulates lipolysis and thermogenesis, thereby increasing energy expenditure and lipid oxidation (46). One of the suggested mechanisms that explains these effects is that low calcium intake raises serum levels of calcitriol ($1,25(OH)_2$ vitamin D), which can stimulate adipocyte calcium influx by membrane vitamin D receptors, identified as the membrane-associated rapid response to steroids (1,25D MARRS). This increase in intracellular calcium levels ($[Ca^{2+}]i$) might promote lipogenesis and inhibit lipolysis by increasing fatty acid synthase activity and expression inhibiting hormone-sensitive lipase (2,47). Calcitriol also acts via the classical nuclear vitamin D receptors in adipocytes to inhibit the expression of uncoupling protein-2 and thus increase energy efficiency. Calcitriol regulation of uncoupling protein-2 and $[Ca^{2+}]i$ appears to exert an additional effect on energy metabolism by affecting adipocyte apoptosis (2). In contrast, an increase in calcium intake can decrease serum levels of calcitriol, consequently reducing lipogenesis and stimulating lipolysis (46).

Effect of calcium on fecal fat excretion

Although it has already been shown that both dietary and supplemental calcium can increase fecal fat excretion through the formation of insoluble complexes (soaps), there is disagreement regarding the magnitude of this effect (2,47-48). In general, the effect is relatively small (especially with supplemental calcium), and studies have used amounts of calcium that are higher than the usual intakes of different populations and also higher than the amounts of calcium used in studies evaluating the effects of calcium on adiposity (48-49).

In a recent meta-analysis (49), an increase in dairy calcium intake of approximately 1,200 mg/day resulted in an increase in fecal fat excretion of 5.2 g/day. Astrup et al. (46), assuming that increased fat excretion of 3,500 kcal/year produces weight loss of 0.45 kg/year, estimated that this would correspond to a weight change of -2.2 kg/year. According to these authors (46), this effect is sufficient to explain the differences found in observational studies but not in some interventional trials. In summary, this mechanism probably contributes to the anti-obesity effect of calcium but cannot explain it completely (2,47-48).

Effect of calcium on appetite regulation

Recently, it was suggested that calcium intake could interfere in the regulation of appetite. However, this effect was evaluated in a very small number of studies, and this hypothesis is not confirmed (3,46). In humans, only two studies have been conducted (50-51). Major et al. (50) found that daily supplementation of 1,200 mg of calcium + 10 mcg of vitamin D for 15 weeks in subjects with low habitual calcium intake (<600 mg/day) resulted in decreased *ad libitum* lipid intake. These authors speculated that the co-occurrence of fats and calcium in an abundance of food, especially dairy foods, could influence subjects with habitual low calcium intake toward the selection of high-fat foods (50). In contrast, Lorenzen et al. (51) found that acute ingestion of dietary and/or supplemental calcium has no effect on postprandial appetite, the levels of hormones involved in the regulation of appetite or energy intake at subsequent meals.

Effect of calcium on abdominal obesity

Observational studies (27,29) and randomized clinical trials (31-33,36) have indicated that a high-calcium diet is associated with a significantly greater decrease in abdominal obesity, suggesting body fat redistribution. The exact

mechanism by which dietary calcium intake induces abdominal obesity reduction is still not clear, although recent studies describing the role of adipose tissue autocrine cortisol production could provide a plausible explanation (2). Human adipose tissue expresses 11b-hydroxysteroid dehydrogenase-1, which catalyzes the conversion of cortisone to cortisol. Recently, it was demonstrated that calcitriol stimulates the expression of 11b-hydroxysteroid dehydrogenase-1 and cortisol production by human adipocytes. Because high-calcium diets suppress calcitriol levels, it has been suggested that the decrease in central obesity seen with these diets could be partly explained by the suppression of calcitriol levels, leading to a reduction of adipocyte cortisol production (52).

CALCIUM AND INSULIN RESISTANCE

The association is relatively consistent between low calcium (and/or dairy) intake and the increased prevalence of type 2 diabetes and/or insulin resistance (4) and has been found in several observational cohort studies (5-8). Pittas et al. (5) followed 83,779 women participating in the Nurses' Health Study for 20 years and identified a multivariate relative risk of type 2 diabetes of 0.79 (95% CI 0.70 – 0.90; $p<0.001$) when comparing the highest category of calcium intake with the lowest category (dietary + supplemental). In prospective data from 41,254 men taking part in the Health Professionals Follow-up Study who were followed for 12 years, intake of dairy products was associated with a modestly lower risk of type 2 diabetes (6).

Despite the epidemiological findings, there is only limited evidence regarding the effects of calcium supplementation on insulin sensitivity (4). The results of studies with supplemental calcium appear to have been influenced by the level of insulin sensitivity at baseline. In a study by Pittas et al. (53), combined daily supplementation of vitamin D (700 IU) + calcium (500 mg) for three years only produced a significant improvement in insulin sensitivity in subjects with impaired glucose tolerance at baseline.

The exact mechanism by which calcium modulates insulin resistance is not known (4). There is evidence that an increase in $[Ca^{2+}]i$ in adipocytes and other insulin target cells, induced by a low-calcium diet, can result in insulin resistance via phosphorylation of glucose transporter type 4 (GLUT-4) and other substrates sensitive to insulin, rendering glucose uptake mediated by insulin less efficient (54).

CALCIUM AND DYSLIPIDEMIA

The effects of calcium on lipid profiles have not yet been elucidated. Some studies using dietary or supplemental calcium have found significant reductions in total cholesterol and low-density lipoprotein (LDL) cholesterol or increases in high-density lipoprotein (HDL) cholesterol (10-12), while other studies have not found such benefits (39,55).

In the gut, saponification of free fatty acids by calcium reduces the intestinal absorption of lipids; this mechanism can explain the effects of calcium on lipid profiles (10,12). This reduction in the absorption of fatty acids, especially saturated fatty acids, could reduce serum cholesterol levels by decreasing the production of very low-density lipoprotein (VLDL) and by increasing the uptake of LDL cholesterol by the liver. Calcium can also bind to bile acids, increasing fecal excretion and thus favoring the conversion of cholesterol into bile acids (56).

CALCIUM AND HYPERTENSION

An inverse relationship between calcium and/or dairy intake and blood pressure has been reported in various epidemiological studies, typically showing that reduced intake of calcium is associated with higher blood pressure and/or an increased risk of developing hypertension (13-16).

The randomized clinical trials that have evaluated the effects of calcium supplementation have identified modest reductions in blood pressure (17-18). vanMierlo et al. (17) performed a meta-analysis of 40 randomized controlled trials evaluating the effects of calcium supplementation (mean daily dose: 1,200 mg) and found significant reductions in systolic (-1.86 mm Hg) and diastolic (-0.99 mm Hg) blood pressure. Calcium supplementation has a greater hypotensive effect on: (i) subjects regularly consuming small amounts of calcium (17); (ii) hypertensive individuals or groups at a higher risk of developing hypertension, such as individuals with sub-Saharan African ancestry, salt-sensitive persons and pregnant women (57); and (iii) studies using dietary calcium (18).

Reid et al. (39) conducted a randomized controlled trial of calcium supplementation in 323 generally healthy men over a period of two years. The subjects were assigned to groups taking a placebo, 600 mg of calcium/day, or 1,200 mg of calcium/day. There were downward trends in systolic and diastolic blood pressures within the calcium-supplemented groups, but there were no significant treatment effects over the entire trial period ($p>0.60$). In a *post hoc* analysis of those subjects with baseline calcium intakes less than the median value (785 mg/day), their blood pressures exhibited borderline treatment effects ($p = 0.05–0.06$ for changes at two years in those subjects who received 1,200 mg of calcium/day compared with those taking a placebo: systolic, -4.2 mm Hg; diastolic, -3.3 mm Hg).

To date, the evidence available provides the basis for the argument that a diet containing the recommended amounts of dairy products can reduce the risk of hypertension (57). The protective effect of calcium on blood pressure can be partly explained by the influence of calcitriol on $[Ca^{2+}]i$. An increase of $[Ca^{2+}]i$ in vascular smooth muscle cells can result in vasoconstriction and a consequent rise in blood pressure (58-59).

CALCIUM AND INFLAMMATORY STRESS

Some studies have suggested that calcium intake can facilitate the suppression of the inflammatory state associated with obesity (19-20). Few studies have been conducted in humans (20,60), and these studies have evaluated only the effects of dietary calcium. Zemel et al. (20) conducted a study to assess the acute effects of a diet rich in dairy products on inflammatory stress in obese and overweight subjects in the absence of changes in adiposity. In this randomized, blinded, crossover trial, normocaloric diets were supplemented with dairy or soy over two periods of 28 days, separated by a washout period of 28 days. The diet supplemented with dairy products resulted in significantly lower levels of inflammatory markers (tumor necrosis factor-α, interleukin-6 and monocyte chemotactic protein-1) and significantly increased levels of adiponectin (20%) (20).

The modulation of inflammatory stress by calcium is likely mediated, in part, by a reduction in body fat. However, it has been shown that calcium could have additional effects via the suppression of calcitriol (20). Elevated serum levels of calcitriol, in addition to increasing $[Ca^{2+}]i$, appear to increase the production of reactive oxygen species (ROS) through the modulation of mitochondrial uncoupling. These two mechanisms modulate the production and release of cytokines (19-20).

ADDITIONAL BIOACTIVE COMPONENTS OF DAIRY PRODUCTS

Dairy products have other bioactive components (in addition to calcium) that can have beneficial effects on adiposity and/or cardiovascular risk factors, such as leucine and the peptides that inhibit angiotensin-converting enzyme (ACE) (2). The high concentrations of leucine present in dairy products can contribute to the anti-obesity effects of these foods by stimulating muscle protein synthesis, inhibiting muscle degradation, and suppressing the energy storage of adipose tissue (61). The peptides that inhibit ACE, found in dairy whey, could contribute to the beneficial effects of dairy products on adiposity, blood pressure and inflammatory stress (2,20).

CALCIUM AND CARDIOVASCULAR EVENTS

The relationship between calcium intake and the risk of cardiovascular events has been explored in some studies (21-24,62-65). The results of studies evaluating dietary calcium differ from studies evaluating supplemental calcium. Thus, these studies will be discussed separately.

Supplemental calcium and cardiovascular events

The results of studies assessing the effects of supplemental calcium on cardiovascular events are inconsistent. Supplemental calcium is widely recommended for postmenopausal women to prevent osteoporosis. The effects of this supplementation on bone mineral density and fracture risk have been investigated in numerous studies. Secondary analyses of the data from a few of these studies suggest that supplemental calcium (with or without co-administered vitamin D) might be associated with an increased risk of cardiovascular events, especially acute myocardial infarction (63-64,66). Bolland et al. (63) conducted a randomized clinical trial to evaluate the effects of calcium supplementation (1 g of elemental calcium daily, as citrate) on myocardial infarction, stroke, and sudden death in healthy postmenopausal women. The study included 1471 women (mean age of 74 years old): 732 were randomized to calcium supplementation and 739 to placebo. The composite end points of myocardial infarction, stroke, and sudden death were more common in the calcium group ($p = 0.008$). The authors concluded that calcium supplementation in postmenopausal women is associated with upward trends in cardiovascular risk.

Despite the potential harmful effects of supplemental calcium observed in the studies cited above, other authors do not agree with this point of view (67-69). Several studies have found no increased risk of CVD with calcium supplementation (with or without vitamin D) in postmenopausal women (65,70-74).

Lewis et al. (65) found no increased risk of atherosclerotic CVD with daily calcium supplementation of 1,200 mg. Mursu et al. (70) assessed the use of vitamin and mineral supplements in relation to total mortality in 38,772 older women in the Iowa Women's Health Study; the mean age was 61.6 years old at baseline in 1986. Supplement use was self-reported in 1986, 1997, and 2004. Through December 31, 2008, a total of 15,594 deaths (40.2%) were identified. Supplemental calcium was inversely correlated with total mortality rate (hazard ratio, 0.91; 95% CI, 0.88-0.94; absolute risk reduction, 3.8%); however, no clear dose-response relationship was observed.

Shah et al. (71) investigated the long-term cumulative effects of calcium and vitamin D supplementation on cardiovascular outcomes and death in older women. An observational cohort study using a UK electronic primary care records database was referenced; 9,910 women aged 60–89 years old were studied who began calcium and vitamin D supplementation between 2000 and 2005, with no heart disease or stroke history and who survived disease-free for two years after supplement initiation. Two years after initiation, the women who consistently received supplementation with calcium and vitamin D did not experience more cardiovascular events or deaths than the women who received minimal supplementation.

The proposed mechanism for the increased risk of atherosclerotic disease is the acute rise in serum calcium that can be induced with supplemental calcium (but not with dietary calcium). There is epidemiological evidence that serum levels of calcium in the upper limit of the normal range are a risk factor for vascular disease (62).

Dietary calcium and cardiovascular events

In a series of studies, it has been observed that high intake of milk and/or dairy products is associated with a reduction in the relative risk of CVD (21-24). In a recent meta-analysis, Elwood et al. (22) observed that the relative risks for stroke and coronary heart disease in individuals with high intake levels of milk and dairy products were 0.84 (95% CI 0.76-0.93) and 0.79 (95% CI 0.75-0.82), respectively, compared with subjects with low intakes.

FINAL CONSIDERATIONS

Epidemiological studies indicate an inverse association between calcium intake and total or abdominal adiposity, insulin resistance, and blood pressure. In contrast, the effects of calcium supplementation (either dietary or supplemental) on obesity and cardiovascular risk factors have not been proven. The most consistent findings indicate modest benefits of dietary calcium (especially in individuals with low habitual intake of this mineral) in the reduction of adiposity during periods of energy restriction and in the reduction of blood pressure.

The relationship between calcium intake and cardiovascular events is uncertain. High levels of intake of milk and/or dairy products have been associated with a reduction in the relative risk of CVD in a series of studies. However, supplemental calcium has been associated with increased risk of cardiovascular events in some trials. Further studies are needed to define the effects of calcium intake on cardiovascular risk factors and/or events.

AUTHOR CONTRIBUTIONS

Torres MR and Sanjuliani AF conceived and designed the study and were also responsible for the references, analysis and interpretation, manuscript drafting and approval of the final version of the manuscript.

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