Calcium intake and adiposity

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ABSTRACT  Limited epidemiologic and experimental data support the possibility that dietary calcium intake plays a role in human body weight regulation. The aim of this review was to present the data from human studies that link calcium and dairy intake to body weight, describe the existing evidence for an effect of calcium intake on body weight from animal models of obesity, present evidence of a role for intracellular calcium in the regulation of lipogenesis and lipolysis, elucidate the potential suggested relation between dietary calcium intake and intracellular calcium concentrations, and outline the effects of calcium supplementation on dietary fat absorption. We suggest that these data support the need for large, population-based clinical trials to assess the effects of supplemental calcium and other components of dairy products on human body weight.  

KEY WORDS  Calcium, dairy products, body weight, fatty acid synthase, fat absorption

INTRODUCTION

The prevalence of obesity in the United States has been steadily rising since the 1960s (1). In the past decade, the percentage of adults aged 20–74 y who are overweight or obese has increased to 61% (2). The total costs attributable to obesity-related disease approaches $100 billion annually in the United States (3), and this cost, like the prevalence of increased body mass, is rising at an alarming rate.

Although the characterization of several important obesity genes over the past 10 y has resulted in a quantum leap of insight into the pathophysiology of obesity (4), these studies have not led to any significant improvements in our ability to prevent or treat overweight. Genetic factors, it seems, have largely played only a secondary role in the rising prevalence of obesity. Rather, environmental factors affecting diet and activity appear likely to have been the most important determinants of the increasing adiposity of the US population over the past 30 y (5, 6). Studies seeking epidemiologic explanations for the phenomenon of rising adiposity have identified dietary calcium intake as one factor that is negatively correlated with body mass index (BMI; in kg/m²) (7–12).

The United States has become aware of the alarming rate of obesity and the severe costs to society related to the obesity epidemic. The prevalence of obesity in the United States has been steadily rising since the 1960s (1). In the past decade, the percentage of adults aged 20–74 y who are overweight or obese has increased to 61% (2). The total costs attributable to obesity-related disease approaches $100 billion annually in the United States (3), and this cost, like the prevalence of increased body mass, is rising at an alarming rate.

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In the following sections, we review data from human studies that link calcium and dairy intake to body weight, describe evidence of an effect of calcium intake on body weight from animal models of obesity (9, 13–16), outline the effects of calcium supplementation on dietary fat absorption (17–20), and present evidence of a role for intracellular calcium in regulating lipogenesis and lipolysis (21–23). In addition, we tried to elucidate the potential suggested relation between dietary calcium intake and intracellular calcium concentrations (9, 11, 21).

HUMAN STUDIES LINKING CALCIUM INTAKE TO BODY WEIGHT

Many epidemiologic studies have identified strong inverse correlations between adiposity and calcium intake (7–10, 12). The US Department of Agriculture’s Nationwide Food Consumption Survey from 1987 to 1988 showed that the average dietary calcium intake in the United States (24) was far below the suggested optimal calcium intake (1000 mg/d for adults and 1200 mg/d for children and young adults aged 11–24 y) (25) and that persons with the lowest calcium intakes tended to have the highest body weight. When stratified by ethnic group, the non-Hispanic black population, which has one of the highest prevalences of obesity in the United States, was also found to have a lower mean daily calcium intake (592 mg/d) than either the Hispanic white population (653 mg/d) or the non-Hispanic white population (765 mg/d). Using data from the first National Health and Nutrition Examination Survey (NHANES I), McCarron (26) found a statistically significant inverse association between calcium intake and body weight. More recently, Zemel et al (9) found a strong inverse association between the relative risk of obesity and calcium intake for participants of NHANES III (Figure 1). Zemel et al’s analysis controlled for physical activity and energy intake. They examined the relative risk of being in the highest quartile of body fat for 4 different quartiles of dietary calcium intake. The relative risk of high body adiposity was found to be greatest in those with the lowest calcium intake and was progressively lower as calcium intake increased; the relative risk was 0.75 for the 2nd quartile,

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Relative risk (RR) of being in the highest adiposity quartile on the basis of the quartile of dietary calcium intake in participants of the third National Health and Nutrition Examination Survey. Adapted from reference 9.

0.40 for the 3rd quartile, and 0.16 for the 4th quartile of calcium intake for women (n = 380; P < 0.0009). A similar inverse relation was noted in men (n = 7114; P < 0.0006). Inverse associations between calcium (or dairy) intake and adiposity have also been reported in children (7, 8), Canadian women (27), and lactose-tolerant and lactose-intolerant African American women (28).

Davies et al (29) reviewed results from 5 clinical studies (30–33) of calcium intake, including an ongoing unpublished study (RP Heaney, Osteoporosis Research Center, Creighton University, Omaha), all of which were designed to assess the effects of dietary calcium on bone mineral. Depending on the study, age ranged from the third to the eighth decades of life. Taken together, the total population was 780 women. Significant negative associations between calcium intake and weight were found for all age groups, and the odds ratio for being overweight (BMI > 26) was 2.25 for women in the lower half of calcium intakes in their respective study groups (P < 0.02). For young women in the third decade of their lives, a significant negative association was found when baseline BMI was plotted against the ratio of dietary calcium to protein intake (Figure 2).

The 2 longitudinal observational studies mentioned above also enabled Davies et al (29) to examine how the change in body weight (in kg/y) was related to the initial dietary calcium intake. In each study the slope was significantly negative. In pooled data from the 2 studies (Figure 3), weight change was negatively related to calcium intake (P = 0.008). Another trial (34), not reviewed by Davies et al (29), noted that of 54 normal-weight young women participating in a randomized exercise intervention trial, subjects with higher dairy calcium intakes corrected for total energy intake gained less weight and body fat over a 2-y period.

To date, there have been no large trials designed primarily to examine the effects of dietary calcium supplements on body weight change. However, in one large trial of the effect of calcium supplementation on bone, in which elderly women were randomly assigned to take either placebo or 1.2 g elemental Ca/d as carbonate (33), the data have been retrospectively analyzed for changes in body weight (29). Although both study groups lost some weight over the nearly 4 y of observation, the mean (±SEM) weight change, weighted for duration of the study, was greater in the calcium-supplemented group (−0.671 ± 0.112 kg/y) than in the placebo-control group (−0.325 ± 0.110 kg/y), for an estimated calcium treatment difference of 0.346 kg/y (P < 0.025). This change in body weight was consistent with the predicted change found in the longitudinal observational studies reviewed by Davies et al (29). Because body-composition studies were not reviewed in this
DAIRY INTAKE AND ADIPOSITY

Some recent findings in animals (9, 15, 16) and in humans (37) suggest that there may be greater effects on body weight from dairy-containing foods than might be predicted from their calcium content alone. Although a full discussion of these data are beyond the scope of this review, a few selected epidemiologic and human experimental studies supporting these findings are presented. A recently published multicenter, population-based, prospective observational study (12) found that increased dairy consumption had a strong inverse association with the 10-y cumulative incidence of obesity (ie, BMI = 30) and with the insulin-resistance syndrome in overweight adults (BMI ≥ 25 at baseline; n = 923). The odds of obesity, abnormal glucose homeostasis, and elevated blood pressure were 20% lower at each additional daily occasion of dairy consumption, whereas the odds of developing the insulin-resistance syndrome were lower by 21%. A recent study, published in abstract form (37), compared the relative effects of supplemental calcium and dairy products for 24 wk on weight loss during energy restriction in 32 obese adults. Body weight loss was 26% greater in the high-calcium group (control diet: 400–500 mg Ca/d supplemented with 800 mg elemental Ca/d) but was 70% greater in the high-dairy group (total elemental calcium intake: 1200–1300 mg/d) than in the placebo control group (total elemental calcium intake: 400–500 mg/d) (P < 0.01). When compared with the low-calcium diet, fat loss (by dual-energy X-ray absorptiometry) with the high-calcium and the high-dairy diets was augmented by 38% and 64%, respectively (P < 0.01). The subjects who consumed the high-calcium diet and the high-dairy diet also showed a significantly greater (P < 0.001) fat loss in the trunk area than did those who consumed the low-calcium diet. Another abstract (39) reported that women with the greatest intake in dietary calcium (primarily in the form of dairy products) had significantly greater weight losses than did those with lower calcium (dairy) intakes as a result of a 6-mo behavioral weight-loss program (n = 181 overweight women aged 24–45 y). The mechanisms explaining the greater effects of dairy products relative to calcium supplementation remain unclear. The bioavailability of calcium from dairy sources is not considered to be greater than that of calcium supplied as nondairy foods, except for calcium from a few plant sources with a high phytate or high oxalate content, which can interfere with calcium absorption (40, 41). It is therefore possible that dairy products contain other components unrelated to calcium that affect body weight (11, 34). Thus, future studies should determine the effects on body weight of the components of dairy products other than calcium.

EFFECTS OF DIETARY CALCIUM ON BODY WEIGHT AND ADIPOSITY IN ANIMAL MODELS

Studies in the 1980s in spontaneous hypertensive rats found a lower net weight gain in the rats fed a high-calcium diet (2.8%, wt:wt) than in the rats fed a low-calcium diet (0.4%, wt:wt): 9.1 ± 1.8 and 27 ± 2 g, respectively (13). Shortly afterward, it was observed that diets high in both dietary calcium and sodium induced favorable changes in the total body fat content of spontaneous hypertensive rats and its normotensive genetic control, Wistar-Kyoto rats (14). More recently, Zemel et al (9, 15, 16) studied transgenic mice with an overexpression of the agouti gene (42), specifically in adipocytes. In one of these studies (9), Zemel et al examined the effects of various calcium intakes on weight gain over 6 wk (Figure 4). Weight change in the low-calcium group (0.4% Ca) was compared with that in 3 calcium-supplemented groups in which calcium was given as either dietary calcium carbonate (1.2% Ca) or as dairy products (nonfat dry milk, either 1.2% or 2.4% Ca). Weight gain and fat-pad mass were reduced by 26% with the 1.2%-Ca diet (P < 0.04 compared with the 0.4%-Ca diet), by 29% with the 1.2%-Ca diet (P < 0.04 compared with the 0.4%-Ca diet), and by 39% with the 2.4%-Ca diet (P < 0.04 compared with all other diets). These data suggest that, at least for mice expressing excess agouti protein in the adipocytes, an increase in dietary calcium decreases body weight gain. When adipocyte function in fat cells isolated from such transgenic animals was examined, high-calcium diets were associated with a 51% inhibition of adipocyte fatty acid synthase (EC 2.3.1.85) expression and activity (P < 0.002) and a 3.4- to 5.2-fold (P < 0.015) augmentation of basal lipolysis. When energy-restricted transgenic mice with an overexpression of the agouti gene were studied (15), a significantly greater reduction in body weight, fat-pad mass, and basal intracellular calcium concentrations in the adipocytes was seen after consumption of a high-calcium or high-dairy diet; the decrease in total body weight and fat pad mass was greater with the high-dairy diet. The rate of lipogenesis was suppressed, whereas that of lipolysis was stimulated, more in the high-dairy group than in the high-calcium group, whereas the results in both groups were significantly different from those in the basal energy-restricted group.

Although these data relate only to animals with an overexpression of the agouti gene in their adipocytes, the observed changes...
in intracellular calcium in their adipocytes suggest that changes in intracellular calcium concentrations may be an important part of the effect of calcium and dairy intakes on adiposity in humans. A brief summary of some of the actions of intracellular calcium in adipocytes is given in the next section.

**ROLE OF INTRACELLULAR CALCIUM IN HUMAN ADIPOCYTE LIPID METABOLISM**

Intracellular calcium ([Ca$^{2+}$]i) concentrations are determined by complex interactions between the flux through voltage-dependent and receptor-stimulated calcium channels, by sequestration with binding proteins, by storage of free Ca$^{2+}$ in intracellular compartments such as the endoplasmic reticulum, and by active gradient-maintaining ion pumps (43). [Ca$^{2+}$]i appears to play an important role in the metabolic derangements associated with obesity, hypertension, and insulin resistance (21, 44, 45). Factors important in obesity, such as insulin (44) and the agouti protein (22, 46)—normally expressed in human adipocytes (47)—have been shown to trigger an increase in [Ca$^{2+}$]i in human adipocytes (Figure 5). Obese persons have a greater [Ca$^{2+}$]i than do nonobese age- and sex-matched control persons (44). [Ca$^{2+}$]i was also found to regulate both lipogenesis and lipolysis in human adipocytes (21). High [Ca$^{2+}$]i stimulates the expression and activity of fatty acid synthase, a key enzyme in de novo lipogenesis (21). When potassium chloride is used to increase [Ca$^{2+}$]i in human adipocytes, agonist-stimulated lipolysis is inhibited through activation of phosphodiesterase 3B (EC 3.1.4.17), thereby reducing cyclic AMP concentrations and thus decreasing hormone-sensitive lipase phosphorylation (23).

With regard to calcium homeostasis, the calcium-regulating hormones vitamin D and parathyroid hormone (PTH) have both been shown to stimulate a significant and sustained increase in [Ca$^{2+}$]i concentrations in primary cultures of human adipocytes (9). In addition 1α,25-dihydroxyvitamin D$_3$ [1α,25(OH)$_2$D$_3$] treatment results in a marked (83%) inhibition of forskolin-stimulated lipolysis in human adipocytes and a 35% reduction in basal lipolysis (48). Shi et al (48) suggested that there are rapid nongenomic actions of 1α,25(OH)$_2$D$_3$ via a putative membrane vitamin D receptor that play a significant role in vitamin D–induced increases in [Ca$^{2+}$]i. Shi et al found that 1α,25-dihydroxymisterol 3, a specific agonist for the membrane vitamin D receptor, increased [Ca$^{2+}$]i, fatty acid synthase activity and glycerol-3-phosphate dehydrogenase (EC 1.1.1.94) expression and inhibited lipolysis in human adipocytes, whereas the specific membrane vitamin D receptor antagonist 1β-hydroxyvitamin D$_3$ blocked vitamin D–stimulated increases in [Ca$^{2+}$]i. PTH treatment, although it does increase [Ca$^{2+}$]i, exerts little effect on lipolysis, possibly as a result of the concurrent activation of adenylate cyclase (EC 4.6.1.1) by PTH (9).

**RELATION BETWEEN DIETARY AND INTRACELLULAR CALCIUM**

The 2 preceding sections outlined the diametrically opposed effects of increases in [Ca$^{2+}$]i and increases in dietary calcium. Greater [Ca$^{2+}$]i stimulates lipogenesis and inhibits lipolysis. Greater dietary calcium appears to have opposite effects. If the mechanism through which dietary calcium affects body weight is primarily related to the actions observed within the adipocytes of agouti-expressing mice exposed to greater dietary calcium intakes, there must be a physiologic basis for the dissociation between [Ca$^{2+}$]i concentrations and dietary calcium intake. One possible explanation that would link greater dietary calcium to less [Ca$^{2+}$]i is the effect of dietary calcium on the hormones regulating calcium balance. Dietary calcium supplementation in humans has

**FIGURE 4.** Weight gain in transgenic mice expressing the agouti gene, specifically in adipocytes, who were fed diets with different calcium contents. *Significantly different from the 0.4%-Ca diet, $P < 0.04$. **Significantly different from all other diets, $P < 0.04$. Adapted from reference 9.

**FIGURE 5.** Suggested role for the agouti protein, insulin, and intracellular calcium in lipogenesis in human adipocytes. FAS, fatty acid synthase (EC 2.3.1.85). Adapted from reference 21.
been shown to cause significant suppression of intact PTH, 1α,25(OH)2D3, and the [Ca2+]i in erythrocytes and platelets (49). Thus, increased calcium intakes lower blood concentrations of calcitropic hormones, such as 1,25-dihydroxyvitamin D [1,25(OH)2] and PTH, whereas, as is well known, diets deficient in calcium stimulate the production and release of 1,25(OH)2 and PTH. Bell et al (50) previously reported significantly higher concentrations of immunoreactive PTH and 1,25(OH)2 in obese (106 ± 6 kg; n = 12) white subjects than in normal-weight (68 ± 2 kg; n = 14) control subjects, whereas elevated concentrations of these hormones were previously reported in obese children compared with age-matched control subjects (51). Thus, lower dietary calcium intakes (as found epidemiologically for obese subjects) can lead to increased concentrations of 1,25(OH)2 and PTH, which in turn may increase adipocyte [Ca2+]i (Figure 6). These elevated intra adipocyte calcium concentrations might then increase the rate of lipogenesis and inhibit lipolysis, consequently leading to increased adiposity. An increased dietary calcium intake would be proposed to prevent this cascade from developing by keeping the calcitropic hormone concentrations low, therefore lowering [Ca2+]i and ultimately the lipid content in adipocytes.

RELATION BETWEEN DIETARY CALCIUM AND DIETARY FAT ABSORPTION

A second mechanism by which dietary calcium intake might affect body adiposity is an effect on the absorption of triacylglycerol from the gastrointestinal tract. Denke et al (18) studied the effect of dietary calcium on fecal fatty acid excretion and serum lipids in a randomized, single-blind, metabolic study of 13 men with moderate hypercholesterolemia. In this study, a low-calcium diet (410 mg elemental Ca/d) was compared with a high-calcium diet (2200 mg elemental Ca/d) using calcium citrate maleate as a source for the supplemental calcium for 10 d. Calcium fortification increased the percentage of dietary saturated fat excreted in 72-h fecal collections from 6% to 13% per day. The high-calcium diet also significantly reduced total cholesterol by 6%, LDL cholesterol by 13%, and apolipoprotein B concentrations by 7% when compared with the low-calcium diet (P < 0.05). A 1-y randomized controlled trial in postmenopausal women using 1 g elemental Ca (as calcium citrate) also found a 19% increase (P = 0.0009) in the HDL-LDL ratio compared with the placebo group (52). This suggests that the effects of increased calcium intake on lipids may be long lasting. Welberg et al (19) studied the effects of calcium supplementation on quantitative and qualitative fecal fat excretion in 24 subjects consuming a controlled diet (1450–1880 mg Ca/d) that was supplemented with 0, 2, or 4 g elemental Ca/d (given as calcium carbonate). Calcium increased fecal fatty acids in a dose-dependent fashion. Total fat excretion increased from 6.8 ± 0.9% of total fat intake with no calcium supplementation to 7.4 ± 1.0% with 2 g Ca and 10.2 ± 1.4% with 4 g elemental Ca (P = 0.03). Increased fat excretion was due to greater fatty acid excretion; the excretion of neutral fat remained changed. Other studies found similar effects (20).

These studies of calcium’s effects on fecal fat excretion predict small effects on total-body lipid flux. The degree of fecal fat loss induced by 2 g elemental Ca in Welberg et al’s (19) study is only ≈3% of that induced by lipase inhibitors such as orlistat (53–55). A person consuming a 2500-kcal diet containing one-third of energy from fat who took an additional 2 g elemental Ca/d as calcium carbonate might be expected to excrete an additional 1% of energy from fat per day and would be anticipated to lose ≈12.6 MJ/y (3010 kcal/y) in the stool. Because a 14.64-MJ (3500 kcal) excess or deficit is often quoted as the energy gained or lost when body weight changes by 0.45 kg (1 lb), this amount of lost energy might indeed explain a change in body weight of ≈0.4 kg/y. Thus, these data suggest that supplemental calcium–induced fecal fatty acid excretion may have accounted for much (if not all) of the observed weight loss in the calcium-supplemented subjects of Davies et al’s randomized trial (29). However, the effects of calcium on fat excretion are not sufficient to explain the much greater weight differences suggested by some animal and human studies, particularly those supplying calcium in the form of dairy products (9, 15, 37).

SUMMARY

In this article, we reviewed the evidence supporting a role for dietary calcium and possibly dairy intake in the regulation of body adiposity. With regards to dietary calcium, epidemiologic and limited experimental data from some studies suggest that differences in calcium intake may be associated with changes in body weight of ≈0.35 kg/y (29). The binding of fatty acids in the gut by dietary calcium can decrease fat absorption sufficiently to account for a similar weight change. More recent data, however, point to a much greater magnitude of weight loss with the calcium supplementation of energy-restricted adults, especially when calcium supplementation is achieved through dairy sources (37). Such findings may indicate an independent effect of another component of dairy products (11, 34), but the mechanism for the augmented weight losses from dairy consumption remains unclear.

Limited data from the animal models of obesity described above also suggest that dietary calcium intake may conceivably affect the regulation of lipogenesis and lipolysis within adipocytes.
Dietary calcium might alter lipid flux by lowering plasma concentrations of calcitropic hormones (vitamin D and PTH), which are known to modulate human intraadipocyte calcium concentrations and thereby affect the rate of lipogenesis and lipolysis.

Regardless of the actual mechanism involved, most of the available cross-sectional, longitudinal, observational, and small controlled trials in humans and the available animal studies support the conclusion that dietary calcium may play a role in body weight regulation and lend credence to the hypothesis that increasing dietary calcium or dairy intake may diminish future weight gain. So far, only small clinical trials designed specifically to examine the effects of either dietary calcium or dairy intake on body weight or adiposity have been done. Given the increasing prevalence of obesity along with its significant medical consequences, the importance of environmental factors in the rapid rise in the prevalence of obesity, and the relative cost-effectiveness and safety profile of calcium and dairy supplementation, we believe that well-designed, population-based clinical trials should be carried out to determine whether the body weight of overweight adults can be altered by either dietary calcium or dairy product supplementation.

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