Role of calcium and dairy products in energy partitioning and weight management^1^–^3^  

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ABSTRACT

Dietary calcium plays a pivotal role in the regulation of energy metabolism because high-calcium diets attenuate adipocyte lipid accretion and weight gain during the overconsumption of an energy-dense diet and increase lipolysis and preserve thermogenesis during caloric restriction, which thereby markedly accelerates weight loss. Intracellular Ca\(^{2+}\) plays a key regulatory role in adipocyte lipid metabolism and triglyceride storage; increased intracellular Ca\(^{2+}\) results in the stimulation of lipogenic gene expression and lipogenesis and the suppression of lipolysis, which results in increased lipid filling and increased adiposity. Moreover, the increased calcitriol produced in response to low-calcium diets stimulates adipocyte Ca\(^{2+}\) influx and, consequently, promotes adiposity, whereas higher-calcium diets inhibit lipogenesis, inhibit diet-induced obesity in mice, and promote lipolysis, lipid oxidation, and thermogenesis. Notably, dairy sources of calcium markedly attenuate weight and fat gain and accelerate fat loss to a greater degree than do supplemental sources of calcium. This augmented effect of dairy products relative to supplemental calcium is likely due to additional bioactive compounds, including the angiotensin-converting enzyme inhibitors and the rich concentration of branched-chain amino acids in whey, which act synergistically with calcium to attenuate adiposity. These concepts are confirmed by epidemiologic data and recent clinical trials, which indicate that diets that include \(\geq 3\) daily servings of dairy products result in significant reductions in adipose tissue mass in obese humans in the absence of caloric restriction and markedly accelerate weight and body fat loss secondary to caloric restriction compared with diets low in dairy products. These data indicate an important role for dairy products in both the prevention and treatment of obesity.  


KEY WORDS

Calcium, dairy, lipogenesis, lipolysis, obesity, vitamin D

INTRODUCTION

It is well understood that thermodynamics and energy balance are core factors involved in the obesity epidemic, with small increases in energy intake coupled with declining physical activity resulting in a net positive energy balance and progressive weight gain. It has consequently become axiomatic to reduce the obesity epidemic to a simple question of energy balance and to invoke various strategies to induce negative energy balance to address the problem. However, it is equally well understood that obesity is a complex genetic trait, with multiple genes interacting to confer relative resistance or susceptibility to positive energy balance. Similarly, specific micro- or macronutrients, dietary patterns, or both may modulate the same metabolic pathways affected by these genetic factors and thereby alter nutrient and energy partitioning.

Accordingly, whereas there can be little doubt that it is of prime importance to address issues of energy intake and energy expenditure, it is the premise of this article that it has also become critical to address nutritional strategies and dietary patterns that may alter energy partitioning and thereby reduce energy balance and the risk of overweight and obesity. This approach, if viable, becomes increasingly important as we recognize the frequent failures of individual persons and populations to adhere to strategies designed to produce negative energy balance. Indeed, we know from previous experience the value of promoting positive behaviors rather than using a prohibitive approach to accomplish a given health outcome. For example, although there is a well-established relation between salt intake and blood pressure control, the inability of most patients to comply with highly sodium-restricted diets presents a nearly overwhelming barrier to the success of these diets, not unlike the general inability of individual persons to adhere to energy-restricted weight-control diets for extended periods of time. In contrast, the DASH (Dietary Approaches to Stop Hypertension) diet presents, instead, the positive approach of increasing fruit, vegetable, and dairy intakes to lower blood pressure, and numerous studies now attest to the relative success of these less-restrictive dairy-rich or DASH-based diets in controlling blood pressure (1–3). Notably, recent evidence now indicates that these same diets play a significant role in the partitioning of dietary energy and may be helpful in the prevention and management of obesity.

Dietary Calcium, Adiposity, and Obesity Risk

Although the concept that dietary calcium and dairy products modulate energy metabolism and obesity risk has been developed over only the past 4 y, much evidence from observational, clinical intervention, and mechanistic studies now support this concept. We first observed this “antiobesity effect,” accidentally,
During a study in the 1980s that investigated the antihypertensive effect of dairy products in obese African American men (4), increasing dietary calcium from \( \approx 400 \) to \( \approx 1000 \) mg/d through the consumption of 2 cups \( (\approx 437 \) mL) of yogurt daily for 1 y produced expected decreases in blood pressure that were accompanied by an unexpected 4.9-kg reduction in body fat (4). Similarly, McCarron noted a significant inverse relation between dietary calcium and body weight in an early study of the relation between dietary calcium and blood pressure in the first National Health and Nutrition Examination Survey (NHANES I) database (5), whereas a preliminary report in 1989 showed that high calcium intakes lower body weight and reduce the rate of weight gain in Zucker rats (6). Unfortunately, in the absence of a plausible mechanism linking dietary calcium or dairy products to energy metabolism, these findings were not pursued. However, our subsequent studies of the mechanism of action of the agouti gene in regulating human adipocyte metabolism provide a theoretical framework and a compelling mechanism that has been confirmed in a series of studies described in the next section. These data support a key role for intracellular \( \text{Ca}^{2+} \) \( ([\text{Ca}^{2+}]) \) in regulating adipocyte lipid metabolism and triacylglycerol storage (6–13). Because \( [\text{Ca}^{2+}] \) can be regulated by calcitrophic hormones, including parathyroid hormone and 1,25-dihydroxyvitamin D \( [1,25(\text{OH})_{2}\text{D}] \), these cellular data provide the theoretical framework for explaining the antiobesity effect of dairy products, as described below.

**ROLE OF INTRACELLULAR Ca\(^{2+}\) AND CALCITROPHIC HORMONES IN ADIPOCYTE METABOLISM**

The calcitrophic hormones parathyroid hormone and 1,25(OH)\(_2\)D, which respond to low-calcium diets, exert coordinated regulatory effects on human adipocyte lipogenic and lipolytic systems, resulting in increased lipid storage during low-calcium diets, whereas the suppression of these hormones during high-calcium diets inhibits adiposity. These effects are mediated primarily by \( [\text{Ca}^{2+}] \). \( [\text{Ca}^{2+}] \) is a key regulator of adipocyte lipid metabolism, which serves to increase lipogenic gene expression and de novo lipogenesis and to inhibit lipolysis (4, 14–16), thereby resulting in increased lipid storage. Both parathyroid hormone (4) and 1,25(OH)\(_2\)D (4, 16) stimulate rapid increases in human adipocyte \( [\text{Ca}^{2+}] \); accordingly, the suppression of these hormones via increases in dietary calcium facilitates repartitioning of dietary energy from lipid storage to lipid oxidation and thermogenesis. Although both parathyroid hormone and 1,25(OH)\(_2\)D modulate adipocyte \( [\text{Ca}^{2+}] \), a growing body of evidence indicates that 1,25(OH)\(_2\)D plays a pivotal role in the modulation of lipid metabolism. In support of this concept, we have shown that human adipocytes possess membrane (nongenomic) vitamin D receptors that transduce a rapid \( [\text{Ca}^{2+}] \) response to 1,25(OH)\(_2\)D \(_2\) (14, 16); consequently, the treatment of human adipocytes with 1,25(OH)\(_2\)D \(_2\) results in the coordinated activation of fatty acid synthase expression and activity and the suppression of lipolysis, leading to an expansion of adipocyte lipid storage (4, 15). However, note that whereas these data provide a plausible mechanism of action based on in vitro studies in human adipocytes, the direct effect of calcitrophic hormones on human adipocyte metabolism has not yet been assessed with the use of in vivo techniques such as microdialysis. Nonetheless, a potential role of \( 1\alpha,25(\text{OH})_{2}\text{D}_3 \) in human obesity has been suggested. Polymorphisms in the nuclear vitamin D receptor \( (n\text{VDR}) \) gene are associated with the susceptibility to obesity in humans with early onset type 2 diabetes, and 2 single nucleotide polymorphisms in \( n\text{VDR} \) intron 8 and exon 9 account for a 9-kg body weight difference, or 4 kg/m\(^2\) (17). Moreover, human body weight and body mass index (BMI; in kg/m\(^2\)) have been shown to be associated with a \( BsmI \) restriction site polymorphism in the \( n\text{VDR} \) gene (18), whereas much evidence indicates increases in circulating concentrations of \( 1\alpha,25(\text{OH})_{2}\text{D}_3 \) in obese humans (19, 20).

We have also shown that 1,25(OH)\(_2\)D \(_2\) acts via the classic \( n\text{VDR} \) in adipocytes to inhibit the expression of uncoupling protein 2 (UCP2) (21), whereas the suppression of 1,25(OH)\(_2\)D \(_3\) concentrations in mice via high-calcium diets results in increased adipose tissue UCP2 expression and increased thermogenesis (15). These findings suggest that high-calcium diets may also affect energy partitioning by suppressing the 1,25(OH)\(_2\)D \(_3\)–mediated inhibition of adipocyte UCP2 expression. However, the role of UCP2 in thermogenesis is not clear, and the observed thermogenic effect may accordingly be mediated by other, as-of-yet unidentified, mechanisms. Moreover, thermogenic effects of dietary calcium or of dairy products have not yet been shown in humans. Nonetheless, in addition to inducing a mitochondrial proton leak, UCP2 serves to mediate mitochondrial fatty acid transport and oxidation, which suggests that the 1,25(OH)\(_2\)D \(_3\) suppression of UCP2 expression may still contribute to decreased fat oxidation and increased lipid accumulation with low-calcium diets (21).

We also showed recently that 1,25(OH)\(_2\)D \(_2\) serves as a potent inhibitor of both murine and human adipocyte apoptosis (22). This effect is mediated, in part, via the inhibition of UCP2 expression, and a consequent increase in mitochondrial potential and in part via the 1,25(OH)\(_2\)D \(_3\) regulation of cytosolic and mitochondrial \( \text{Ca}^{2+} \) and results in marked increases in adipocyte apoptosis in mice fed diets high in calcium or high in dairy products (22). Finally, note that although these mechanisms provide a rationale for an antiobesity effect of calcium, dairy sources of calcium appear to exert markedly greater effects than does calcium per se on reducing body fat in both mice and humans. These effects must be attributable to additional mechanisms, possibly mediated by other components of dairy products, such as whey-derived bioactive components, as discussed later in this article. A summary of these mechanisms is shown in Figure 1.

**EFFECTS OF CALCIUM AND DAIRY PRODUCTS ON ADIPOSITY IN ANIMALS**

We used a transgenic mouse model of diet-induced obesity to confirm the antiobesity effects of dietary calcium and dairy products in vivo before progressing to the clinical trials discussed later (4, 15, 23–27). These mice express the agouti gene in adipose tissue under the control of the aP2 promoter and exhibit normal expression of other major known obesity-associated genes, which provides them with a human-like pattern of obesity-associated gene expression. Unlike dominant agouti mutants that ubiquitously overexpress agouti and exhibit adult-onset obesity regardless of diet, these mice are not obese when fed standard chow diets but are susceptible to adult-onset diet-induced obesity, whereas their wild-type littermates are not.

Mice placed on diets suboptimal in calcium (0.4%), high in fat, and high in sucrose for 6 wk had marked increases in adipocyte
Mechanisms of dietary calcium and dairy modulation of adiposity. 1,25(OH)_{2}D, 1,25-dihydroxyvitamin D; [Ca^{2+}], intracellular Ca^{2+} concentration; mVDR and nVDR, mouse and nuclear vitamin D receptors, respectively; RXR, retinoic acid receptor; UCP2, uncoupling protein 2; FAS, fatty acid synthase; DR-3, D response element-3.

in the predictive equation relating dietary calcium to body fat, the subsequent report represented this relation without control for BMI. Overall, in predictive equations that explain 26–34% of the variability in body fat, variations in dietary calcium explained 7–9% of the variability in adiposity (34).

Larger population studies similarly support the relation between dietary calcium and dairy products and indexes of adiposity. Epidemiologic observations from NHANES I (5), NHANES III (4), the Quebec Family Study (36), The Continuing Survey of Food Intakes by Individuals (37), the CARDIA (Coronary Artery Risk Development in Young Adults) Study (38), and the HERITAGE Family Study (39) all support an inverse relation between dietary calcium and dairy intakes and body fat, BMI, and the incidence of obesity. Pereira et al (38) evaluated the associations between dairy product intake and the incidence of the major components of the insulin resistance syndrome, including obesity, in a 10-y population-based prospective study of 3157 black and white adults. Overweight persons who consumed the most dairy products had a 72% lower incidence of insulin resistance syndrome than did those with the lowest intakes of dairy products. Moreover, the cumulative incidence of obesity in those who started the study in the overweight category was significantly reduced from 64.8% in those who consumed the least amount of dairy foods to 45.1% in those who consumed the highest amount of dairy foods. Notably, the inverse relation between dietary calcium and either the insulin resistance syndrome or the incidence of obesity in the CARDIA Study was explained solely by dairy intake and was not altered by adjustment for dietary calcium, which indicated an additional effect of dairy products beyond the mechanisms already cited for dietary calcium in modulating adiposity and obesity risk.

**CLINICAL TRIALS OF THE MODULATION OF ADIPOSY WITH CALCIUM AND DAIRY PRODUCTS**

Davies et al (40) conducted a series of calcium intervention studies that were originally designed with primary skeletal endpoints, but recently retrospectively reevaluated these studies with a body weight endpoint. In this reanalysis of 4 observational studies and one double-blind, placebo-controlled randomized trial, they noted significant negative associations between calcium intake and body weight for all age groups studied (third, fifth, and eighth decades of life) and odds ratio for being overweight of 2.25 for young women with below-median calcium intakes compared with those with above-median calcium intakes. In the randomized trial of 216 older women who received either a placebo or 1200 mg supplementary Ca daily over 4 y, both groups lost weight. However, the calcium-treated group lost an additional 0.325 kg/y over the 4 y with no intentional change in energy intake. Overall, the relations derived from these reanalyses indicate that an increase in calcium intake of 1000 mg/d is associated with an 8-kg reduction in body weight, a relation that is reasonably consistent with our initial observation of a 600-mg/d difference in calcium intake (from dairy products) being associated with a 4.9-kg reduction in body fat (4).

Heaney et al (41, 42) subsequently summarized data from 9 studies, including 3 controlled trials and 6 observational studies, of calcium intake in which body weight could be assessed as a secondary outcome. Overall, increases in calcium intake were consistently associated with reduced indexes of adiposity (body weight, body fat, and weight gain); the aggregate effect was each 300-mg increase in daily calcium intake associated with a 3-kg lower weight in adults and a 1-kg decrease in body fat in children. Consequently, they suggested that a 600-mg/d increase in calcium intake (2 standard dairy servings) could reduce the risk of overweight by as much as 70%.

We conducted several clinical trials that evaluated the modulating effects of calcium and dairy products on adiposity in persons consuming energy-restricted or eucaloric diets (43–45). In the initial trial (43), 32 obese adults were maintained on balanced calorie-deficit diets (500 kcal/d deficit) and then randomly assigned to a control diet (0–1 servings/d and 400–500 mg Ca/d supplemented with placebo), a high-calcium diet (control diet supplemented with 800 mg Ca/d), or a diet high in dairy products (3–4 servings of milk, yogurt, or cheese daily; total calcium intake of 1200–1300 mg/d). Control subjects lost 6.4% of their body weight over the 24-wk study, and this loss was increased by 26% with the high-calcium diet and by 70% (to 10.9%) with the diet high in dairy products (P < 0.01). Fat loss (measured by dual-energy X-ray absorptiometry) followed a similar trend; the high-calcium diet and the diet high in dairy products augmented the fat loss that occurred with the low-calcium diet by 38% and 64%, respectively (P < 0.01). An unexpected finding was a marked change in the distribution of body fat loss (43). Fat loss from the trunk region represented 19% of the total fat lost with the low-calcium diet, and this loss increased to 50% of the fat lost with the high-calcium diet and to 66% of the fat lost with the diet high in dairy products (P < 0.001). These findings show that an increase in dietary calcium from suboptimal to adequate amounts can enhance the efficacy of an energy-restricted diet in achieving weight and fat losses. Furthermore, these effects are markedly greater when dairy foods rather than calcium supplements are consumed (43).

We confirmed these findings in a follow-up clinical trial in 34 obese subjects who consumed a diet supplemented with 3 servings of yogurt compared with a placebo control group who consumed a balanced calorie-deficit diet (500 kcal/d deficit) for 12 wk (44). Dietary macronutrient and fiber intakes were held constant at the US average, and the control group maintained a calcium intake of 400–500 mg/d, whereas the yogurt group achieved an intake of 1100 mg Ca/d. Both groups lost weight, but the yogurt group lost 61% more fat and 81% more trunk fat than did the control group (P < 0.001). Similar to the first clinical trial, the fraction of fat lost from the trunk was markedly higher with the yogurt diet than with the control diet (60.0% compared with 26.4%). Moreover, there was a significant 31% reduction in the loss of lean tissue mass during energy restriction in the yogurt group compared with the control group. No adverse effects on any serum lipid fraction were observed in either of these trials, and an improvement in insulin sensitivity, glucose tolerance, and blood pressure were observed in the dairy product groups in both trials.

We also recently showed that increases in dairy intakes result in improvements in body composition in the absence of energy deficits. Isocaloric substitution of 3 daily servings of dairy products into the diets of obese African American adults maintained on eucaloric diets for 6 mo resulted in a 5.4% reduction in total body fat and a 4.6% decrease in trunk fat (P < 0.01 for both) in the absence of any change in body weight. The control group maintained on a low-calcium, low-dairy diet with an identical macronutrient composition showed no significant changes in total body fat or trunk fat (45). Accordingly, it appears that the
use of dairy products to attain an optimal calcium intake during energy restriction results in a marked augmentation of weight loss, a loss of total fat and trunk fat, and a relative preservation of lean body tissue compared with the same degree of energy restriction with a low-dairy diet. Further incorporation of dairy products in the absence of energy restriction appears to result in a repartitioning of dietary energy from adipose tissue to lean body mass, resulting in a net reduction in fat mass (43–45).

**ROLE OF ADDITIONAL DAIRY COMPONENTS IN MODULATING ADIPOSY**

Data from the CARDIA Study (38), our recent clinical trials (43–45), and rodent studies (4, 15, 23–27) all show greater effects of dairy products than of supplemental calcium in attenuating adiposity. Accordingly, it is important to identify the additional components of dairy products that may be responsible for this augmentation. Likely candidates for this additional bioactivity include the high branched-chain amino acid (BCAA) content of dairy protein and the specific nonessential bioactive components of dairy foods.

Although considerable interest in the role of high-protein diets in weight management has recently emerged, studies showing an antiobesity effect of dairy products in both rodents and humans have maintained constant protein intakes. Accordingly, the protein content of dairy products per se is unlikely to be responsible for its specific additional bioactivity and will not be addressed in this article. However, the amino acid composition of dairy protein may play a role. Our preliminary data in mice isolate most of the additional bioactivity of dairy products to the whey fraction (26). Whey proteins have a high protein-quality score and contain a high proportion (~26%) of BCAAs (46, 47). In addition to supporting protein synthesis, BCAAs (leucine, isoleucine, and valine) play specific metabolic roles as energy substrates and in the regulation of muscle protein synthesis, and their potential to participate in these additional metabolic processes is limited by their availability, the first priority being provided to new protein synthesis (recently reviewed by Layman; 47). Accordingly, only diets that provide BCAAs in general, and leucine specifically, at levels that exceed requirements for protein synthesis can fully support the intracellular leucine concentrations required to support additional signaling pathways (47). Consequently, the abundance of leucine in whey is of particular interest because it plays a distinct role in protein metabolism and plays a pivotal role in the translation initiation of protein synthesis (48).

Notably, a BCAA mixture has been reported to match the anabolic effects of a complete amino acid mixture in rodents (49), suggesting a primary role of BCAA in protein synthesis (recently reviewed in 50), whereas milk proteins were reported to elicit a greater increase in BCAAs than were soy proteins in peripheral tissues in humans (51). Accordingly, the high concentration of BCAAs, and leucine in particular, in dairy products may be an important factor in the repartitioning of dietary energy from adipose tissue to skeletal muscle. This suggests that an interaction between the high amounts of calcium in dairy products in combination with the BCAA content of dairy protein, possibly in concert with other dairy product–derived bioactive compounds, may work in synergy to minimize adiposity and maximize lean mass.

In addition to its calcium and BCAA content, whey contains many bioactive compounds, which may act independently or synergistically to affect lipogenesis, lipolysis, lipid oxidation, and energy partitioning. Of these compounds, the significant angiotensin-converting enzyme (ACE) inhibitory activity contained in whey protein may be relevant to adipocyte lipid metabolism. Angiotensin II up-regulates adipocyte fatty acid synthase expression (reviewed in 14), and ACE inhibition mildly attenuates obesity in both mice and in hypertensive patients. Consequently, because adipose tissue has an autocrine renin-angiotensin system, it is likely that a whey-derived ACE inhibitor may contribute to the antiobesity effects of dairy products.

In support of these concepts, we showed that a whey-derived ACE inhibitor augmented the effects of dietary calcium on weight and fat loss in energy-restricted ap2-agouti transgenic mice (26). However, the combination of the calcium and ACE inhibitor was markedly less potent than was either milk or whey in reducing body fat; moreover, milk and whey both substantially preserved skeletal muscle mass during energy restriction, whereas calcium and the combination of calcium and ACE inhibitor had no effect. Thus, whey components—including calcium, BCAAs, ACE inhibitors, and possibly other whey components—appear to exert a synergistic effect on adiposity and energy partitioning.

**CONCLUSIONS**

An antiobesity effect of dietary calcium and dairy foods is now evident from animal studies, observational and population studies, and clinical trials. Although there is a strong theoretical framework in place to explain the effects of dietary calcium on energy metabolism, the precise mechanisms whereby dairy products exert substantially greater effects than do equivalent amounts of calcium are not yet clear. However, these additional effects are likely to be mediated, in part, by whey-derived bioactive compounds, including ACE inhibitors, and by the high concentration of BCAAs in whey protein. These data provide the framework for the development of an effective weight management strategy—based on the use of dairy products in a DASH-based diet—for the prevention of overweight and obesity and for the control of energy balance.

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