Dietary Calcium and Dairy Modulation of Adiposity and Obesity Risk
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Dietary calcium plays a key role in the regulation of energy metabolism and obesity risk. This appears to be mediated primarily by dietary calcium modulation of circulating calcitriol, which in turn regulates adipocyte intracellular calcium ([Ca^{2+}]_{i}). Increased [Ca^{2+}]_{i} stimulates lipogenic gene expression and activity and inhibits lipolysis, resulting in increased adipocyte lipid accumulation. Since calcitriol stimulates adipocyte Ca^{2+} influx, low calcium diets promote adiposity, while dietary calcium-suppression of calcitriol reduces adiposity. These concepts are confirmed in controlled rodent studies as well as by epidemiologic and clinical trial data, all of which confirm protection from obesity with high calcium intakes. Moreover, dairy sources of calcium exert markedly greater effects which are most likely attributable to additional bioactive compounds in dairy which act synergistically with calcium to attenuate adiposity.

Key words: dairy, calcium, adiposity, obesity

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Introduction

Over the last 4 years, a substantial body of evidence has emerged in support of an “antiobesity” effect of dietary calcium and dairy products.1–7 Increasing dietary calcium without restricting energy appears to cause a re-patterning of dietary energy from adipose tissue to lean body mass, which results in a net reduction in fat mass in both mice and humans.1,8 Furthermore, increasing dietary calcium intake during energy restriction results in a markedly augmented body weight loss and fat loss in both mice and humans.3,5,6,9–12 When dairy is the source of the calcium, these effects are more pronounced, suggesting that additional components of dairy contribute to this effect. These findings are supported by epidemiologic observations from the National Health and Nutrition Examination Survey (NHANES III), The Quebec Family Study,13 The Continuing Survey of Food Intake by Individuals (CSFII),14 the CARDIA study,15 and the HERITAGE Family Study.16

Data from NHANES III show that, in women, after controlling for age, energy level, activity level, race, and ethnicity, the odds ratio (OR) of being in the highest quartile of body fat was reduced from 1.00 in the first quartile of calcium intake (mean intake of 25 mg/day) to 0.16 for the fourth quartile of calcium intake (mean intake of 1346 mg/day); a similar inverse relationship between calcium intake and adiposity was found for men (P < 0.0009).1 A comparable relationship was noted in a recent analysis of CSFII, which noted a highly significant inverse relationship between body mass index (BMI, kg/m^2) and calcium consumption, and a dose-response reduction in obesity prevalence among women as calcium intake increased from the first tertile (<453 mg/day) to the second (453–712 mg/day) and third (≥712 mg/day) tertiles of calcium intake.14 Similarly, data from the CARDIA study demonstrate a significant inverse relationship between dairy consumption and each of the components of the insulin resistance syndrome (IRS), including obesity, during a 10-year follow-up of young adults who were overweight (BMI ≥25) at baseline. In this group, the odds of developing IRS reduced by 72% in overweight individuals in the highest versus the lowest category of dairy consumption. Moreover, the cumulative incidence of obesity was significantly reduced from 64.8% in those consuming the least amount of dairy foods to 45.1% in those in the group consuming the highest amount of dairy food (P < 0.001).15

Jackmain et al.13 examined the relationship between calcium intake and body composition in adults participating in Phase 2 of the Quebec Family study and found that body weight, body fat, BMI, waist circumference, and total abdominal adipose tissue were significantly...
greater in adults consuming <600 mg calcium per day than in those consuming higher levels of calcium. In the HERITAGE Family study, the strongest inverse relationship between dietary calcium and adiposity occurred in black men and white women. Black men in the highest calcium tertile were significantly leaner than those in the low calcium group, whereas white women exhibited a significant inverse relationships between calcium intake and BMI, percent body fat, and total abdominal fat area.16

Additional studies have found an inverse relationship between dairy and calcium intake and body fat in both younger and older women,17,18 between calcium and BMI in African-American women,19 between dairy products and obesity in children,20 and between dietary calcium and body fat accumulation in preschool children.21 Davies et al.22 evaluated the relationship between dietary calcium and body weight in a reanalysis of data from a series of calcium interventions originally conducted with skeletal endpoints. This reanalysis of 780 women who participated in five trials (four observational and one double-blind, placebo-controlled, randomized trial) demonstrated significant negative associations between calcium intake and body weight for all age groups, and an OR for overweight of 2.25 for young women in the lower half versus the upper half of calcium intakes.22 Moreover, data from the randomized, controlled trial demonstrated a calcium treatment effect of 0.325 kg weight loss per year over 4 years with no intentional change in caloric intake. Overall, the relationships derived from this reanalysis indicate that a 1000 mg/day difference in calcium intake is associated with a corresponding 8 kg difference in body weight. This value is consistent with our previous observation of a 4.9 kg reduction in body fat resulting from increasing the calcium intake of obese African-American adults from 400 to 1000 mg/day for 1 year.1

The source of dietary calcium has a substantial impact on the magnitude of calcium’s effect on adiposity, with dairy sources of calcium producing 50% to 70% greater effects on fat loss during energy restriction in both mice and humans. Consistent with this observation, analysis of NHANES III data demonstrates a significantly stronger inverse relationship between dietary calcium and adiposity when the number of dairy servings is included in addition to the level of calcium consumption.1 Moreover, the inverse relationship between dietary calcium and IRS in the CARDIA study was explained solely by dairy intake, whereas the inverse association between dairy consumption and IRS was not altered by adjustment for calcium, indicating an effect of dairy consumption independent of calcium intake.15

Mechanisms
A compelling mechanism for the antiobesity effect of dietary calcium was provided by studies of the mechanism of action of the agouti gene in regulating murine and human adipocyte metabolism.23–29 These studies demonstrated a key role for intracellular Ca2+ in the regulation of adipocyte metabolism, that of modulation of adipocyte triglyceride stores. Because intracellular Ca2+ can clearly be regulated by calcitrophic hormones, including 1,25-(OH)2-D3 and parathyroid hormone, suppression of these hormones by increasing dietary calcium may facilitate repartitioning of dietary energy from adipose tissue to lean body mass and thermogenesis. In support of this concept, we have demonstrated that human adipocytes possess membrane (nongenomic) vitamin D receptors that transduce a rapid intracellular Ca2+ response to 1,25-(OH)2-D3.12 Consequently, 1,25-(OH)2-D3 treatment of human adipocytes results in coordinated activation of fatty acid synthase expression and activity and suppression of lipolysis, all of which lead to an expansion of adipocyte lipid storage.1,30 Moreover, 1,25-(OH)2-D3 acts via the adipocyte nuclear vitamin D receptor to inhibit the expression of uncoupling protein 2 (UCP2),31 while suppression of 1,25-(OH)2-D3 levels from feeding high-calcium diets to mice causes increased adipose tissue UCP2 expression and increased thermogenesis.5 This suggests that high-calcium diets may also affect energy partitioning by suppressing 1,25-(OH)2-D3-mediated inhibition of adipocyte UCP2 expression (Figure 1).31

Effects of Calcium on Adiposity in Animals
We have confirmed the antiobesity effect of dietary calcium and dairy products in a series of studies con-
ducted in transgenic mice that express the agouti gene in adipose tissue under the control of the aP2 promoter, which is similar to the human pattern of expression of agouti and other obesity-associated genes.\(^1,5,9,10,32–34\) These mice are not obese when fed standard chow diets but are susceptible to adult-onset, diet-induced obesity. These mice respond to low-calcium diets with accelerated weight gain and fat accretion, while high-calcium diets markedly inhibit lipogenesis, accelerate lipolysis, increase thermogenesis, and suppress fat accretion and weight gain in animals maintained at identical caloric intakes.\(^1\) Further, low-calcium diets impede body fat loss while high-calcium diets markedly accelerate weight and fat loss in transgenic mice subjected to identical levels of caloric restriction.\(^5,9,10,32,33\) Additional studies in other animal models (Zucker lean and obese rats, Wistar rats, and Spontaneously Hypertensive rats) confirm the observation that increased calcium intake lowers body weight and fat content.\(^35–37\)

**Role of Additional Dairy-derived Compounds**

Dairy products consistently exert markedly greater effects in attenuating weight and fat gain on obesity-promoting diets and in accelerating fat loss during energy restriction compared with identical levels of inorganic calcium sources. Although the additional components of dairy products responsible for the differential effects between calcium and dairy products are not yet known, current work is underway to determine their identity. At present, preliminary data suggest that this additional activity resides in the whey fraction of milk. Whey is recognized as a rich source of bioactive compounds that may act independently or synergistically with the calcium to attenuate lipogenesis, accelerate lipolysis, and/or affect nutrient partitioning between adipose tissue and skeletal muscle. Notably, whey proteins have recently been reported to contain significant angiotensin-converting enzyme (ACE) activity.\(^38\) Although ACE inhibitory activity may appear to be more relevant to an antihypertensive effect than to an obesity effect of dairy, recent data demonstrate that adipocytes have an autocrine/paracrine renin-angiotensin system (RAS), and that adipocyte lipogenesis is regulated, in part, by angiotensin II.\(^38\) Thus, activation or suppression of the adipocyte RAS may exert corresponding effects on adipocyte lipid metabolism independent of the circulating RAS. Indeed, inhibition of the RAS mildly attenuates obesity in rodents, and limited clinical observations support this concept in hypertensive patients treated with ACE inhibitors. These observations suggest that whey-derived ACE-inhibitory activity may contribute to the antiobesity effect of dairy products. Consistent with this proposed mechanism, we recently found a whey-derived ACE inhibitor augmented the effect of dietary calcium on weight and fat loss in energy-restricted aP2-agouti transgenic mice\(^33\); however, the combination of calcium and ACE inhibitor was still significantly less potent than milk or whey in reducing body fat, indicating that other whey bioactive compounds may contribute or, alternatively, that a synergistic effect of multiple factors, along with the aforementioned effects of the calcium, are responsible.

Dairy protein in total may play a role in the antiobesity effect of dairy. Moderate- or high-protein diets in general \((\geq 25\%\) of total energy) appear to enhance weight loss efforts,\(^39\) or at least to improve body composition during energy restriction.\(^40,41\) These benefits may derive from direct physiologic pathways, such as effects on thyroid hormone\(^40\) or muscle protein synthesis,\(^42\) or indirect effects mediated through displacement of dietary carbohydrate.\(^43,44\) Animal proteins such as dairy and meat, which are rich in essential amino acids and branched-chain amino acids, may be particularly effective in terms of weight management and optimizing body composition.\(^38,39\)

**Role of Whey Proteins**

High-protein diets have long been touted as beneficial in weight loss efforts, but only recently has a significant body of scientific literature emerged to support this position. These studies were reviewed recently.\(^39\) High-protein diets that also restrict carbohydrate intake have been the subject of much debate in the nutrition community. Two recently published studies in the *New England Journal of Medicine*\(^45,46\) compared the efficacy of high-protein, high-fat, low-carbohydrate diets with standard low-fat, hypocaloric diets and found that, in fact, people did lose more weight and significantly improved their health profile on Atkins-type diets, for at least up to 6 months. However, the long-term safety and adequacy of these essentially unbalanced diets has been questioned. More moderate protein-based diets appear to provide some of the advantages of high-fat diets in terms of satiety, glucose homeostasis, and triglycerides without severely restricting carbohydrate intake. A number of studies using diets comprising between 25 and 30% of total energy as protein have been published recently. This level of protein intake is consistent with the high end of the range of dietary protein intakes recommended in the Dietary Reference Intakes for macronutrients. These studies report enhanced weight loss, enhanced fat loss, muscle-protein sparing, improved glucose regulation, and triglyceride reduction in response to moderately high-protein diets.\(^40,41\)

There are several reasons why diets that emphasize protein may result in greater weight loss. Dietary proteins require more energy to be metabolized than fat and carbohydrate and are therefore less calorically efficient.
Protein is also significantly more satiating than other macronutrients, so overall energy intake is likely to be lower on high-protein diets.\textsuperscript{30} Benefits in terms of glucose regulation and triglyceride reduction are likely related to the decrease in carbohydrate intake that accompanies increased protein intake and, perhaps, provision of leucine and other essential amino acids.\textsuperscript{30} Another indirect benefit of displacing carbohydrate with protein is restoration of the oxidation of body fat, which is inhibited on high-carbohydrate diets.\textsuperscript{43} In one study, substitution of dietary protein for carbohydrate in an energy-restricted diet maintained levels of thyroid hormones T3 and T4 and reduced the insulin response to a test meal.\textsuperscript{40} These changes in the endocrine profile would likely promote higher rates of lipolysis.

While only several studies employing high-protein diets show greater weight loss relative to standard hypocaloric diets, almost all demonstrate sparing of lean tissue or muscle mass. This benefit likely relates to the abundance of branched-chain amino acids, and leucine in particular, which serves as a key regulatory signal in muscle protein synthesis.\textsuperscript{47}

For example, Layman\textsuperscript{40} recently proposed that the rich concentration of leucine in whey protein may play a significant anabolic role in skeletal muscle and thereby contribute to greater maintenance of skeletal muscle mass during weight loss. Accordingly, the high concentration of leucine and other branched-chain amino acids in dairy products may also be an important factor in the repartitioning of dietary energy from adipose tissue to skeletal muscle. Thus, dairy proteins in combination with dairy calcium, possibly other dairy minerals, and yet to be determined bioactive components derived from dairy, may work in synergy to minimize body fat and maximize lean mass.

### Clinical Data

We recently confirmed the utility of calcium-rich diets in accelerating fat loss during a 6-month clinical trial in obese patients.\textsuperscript{11} Obese adults (\textit{n} = 32) were maintained for 24 weeks on balanced deficit diets (500 kcal/day deficit) and randomized to the following groups: control (0–1 serving/day and 400–500 mg Ca/day supplemented with placebo), high-calcium (control diet supplemented with 800 mg Ca/day), or high-dairy (3–4 servings of low-fat dairy products/day, total Ca intake of 1200–1300 mg/day). Control subjects lost 5.4% of their body weight, which was increased by 26% on the high-calcium diet and by 70% (to 10.9%) on the high-dairy diet (\textit{P} < 0.01). Fat loss (via DEXA) followed a similar trend, with the high-calcium and high-dairy diets augmenting the fat loss found on the low-calcium diet by 38 and 64%, respectively (\textit{P} < 0.01).

An unexpected finding was a marked change in the distribution of body fat loss.\textsuperscript{11} Subjects on the low-calcium diet lost 5.3% of their trunk (abdominal region) fat on the low-calcium diet. This was increased to 12.9% on the high-calcium diet and 14.0% on the high-dairy diet (\textit{P} < 0.025 vs. low-calcium and high-calcium diets). Consequently, fat loss from the abdominal region represented 19.0% of the total fat lost on the low-calcium diet, and this was increased to 50.1 ± 6.4% of the fat lost on the high-calcium diet (\textit{P} < 0.001) and 66.2% on the high-dairy diet (\textit{P} < 0.001). We have confirmed these findings in a follow-up clinical trial in 34 obese subjects consuming a diet supplemented with three servings of yogurt compared with a placebo control group on a balanced calorie deficit (–500 kcal/day) for 12 weeks.\textsuperscript{12} Dietary macronutrients and fiber were held constant at the U.S. average, and the control group maintained a calcium intake of 400 to 500 mg/day, whereas the yogurt group achieved an intake of 1100 mg calcium/day. Both groups lost weight, but the yogurt group lost 61% more fat and 81% more trunk fat than the control group (\textit{P} < 0.001); this was reflected in a markedly greater reduction in waist circumference (–3.99 cm vs. –0.58 cm, \textit{P} < 0.001). Further, the fraction of fat lost from the trunk was markedly higher on the yogurt diet than on the control (60.0 vs. 26.4%, \textit{P} < 0.005). No adverse effects were observed on any serum lipid fraction in either of the two clinical trials, and there was an improvement in insulin sensitivity, glucose tolerance, and blood pressure in the dairy groups in both trials. Thus, increasing dietary calcium not only accelerates weight and fat loss secondary to caloric restriction, but also shifts the distribution of fat loss to a more favorable pattern, with more fat lost from the abdominal region on the high-calcium diet. Moreover, dairy products exert a substantially greater effect on both fat loss and fat distribution compared with an equivalent amount of supplemental calcium. Consistent with this, Melanson et al. recently reported that higher calcium intakes are associated with higher rates of whole-body fat oxidation measured in a whole-room calorimeter, with significant effects noted over a 24-hour period, during sleep and during light exercise.\textsuperscript{48} We have also recently demonstrated that isocaloric substitution of three daily servings of dairy products into the diets of obese African-American adults maintained on eucaloric diets for 6 months results in a 5.4% reduction in total body fat and a 4.6% decrease in trunk fat (\textit{P} < 0.01 for both) in the absence of any change in body weight, whereas the control group maintained on a low-calcium/low-dairy diet with identical macronutrient composition exhibited no significant changes in total body fat or trunk fat.\textsuperscript{8}

Although there have now been several clinical studies evaluating the effects of the Dietary Approaches to Stop Hypertension (DASH) diet on blood pressure reg-
ulation and on related cardiovascular risk factors, there have thus far been no studies of the effects of this dietary pattern (as opposed to the effects of calcium and/or dairy per se, as summarized above) on body weight regulation. However, Newby et al. recently reported a prospective evaluation of the effects of five identified dietary patterns on changes in BMI and waist circumference in the Baltimore Longitudinal Study of Aging. Of the five non-overlapping eating patterns defined, one (defined in the study as “Healthy”) was defined similar to the DASH eating pattern. This pattern was associated with a significantly lower annual increase in BMI (0.05/year) compared with the other four identified eating patterns (mean changes of 0.1–0.3/year) (P <.01). Similarly, the mean annual change in waist circumference was reduced by 50 to 75% in the group following the “healthy” (DASH) eating pattern compared with those following the other four dietary patterns (P <.05). Similarly, data from a recent cross-sectional assessment of dietary patterns in a Spanish Mediterranean population showed that men and women in the highest tertile of dairy product consumption have significantly lower BMIs than those in the lowest tertile of dairy product consumption (24.3 vs. 25.6, P <.05), although both groups exhibited similar levels of energy intake.

Overall, the mechanistic, animal, clinical, and epidemiologic data collectively provide compelling support for an effect of the calcium and the dairy foods component of the DASH diet on body weight regulation, body fat, and obesity risk. However, no clinical or population data are yet available regarding the role of dairy products in weight maintenance following successful weight loss. We have recently demonstrated that ad libitum refeeding of high-calcium diets to previously energy-restricted aP2-agouti transgenic mice prevented the suppression of adipose tissue lipolysis and fat oxidation that otherwise accompanies such refeeding, and markedly up-regulated skeletal muscle fat oxidation. Consequently, although animals refed low-calcium diets rapidly regained all of the weight and fat that had been lost, animals fed high-calcium diets exhibited a shift in energy partitioning and a 50 to 85% reduction in weight and fat gain; moreover, dairy exerted markedly greater effects than supplemental calcium on fat oxidation and fat gain.

Conclusions
A substantial body of evidence supporting a beneficial role of dietary calcium and dairy foods in the partitioning of dietary energy has rapidly emerged over the last several years. Increasing dietary calcium intake from the prevailing low levels to levels in the currently recommended range of intakes results in reductions in body fat in the absence of energy restriction and acceleration of weight and fat loss during periods of modest energy restriction. Notably, dairy sources of calcium appear to exert markedly greater effects than supplemental or fortified sources. Although there is a strong theoretical framework in place to explain the effects of dietary calcium on adipocyte metabolism and lipid storage, the mechanism(s) whereby dairy products augment these effects are not yet clear. Preliminary evidence suggests that bioactive compounds in whey, including ACE inhibitory activity, may play a role but cannot fully explain the greater effect of dairy versus calcium. However, the high concentration of branched-chain calcium in dairy proteins, and especially in whey protein, appears likely to contribute to the repartitioning of dietary energy from adipose tissue to skeletal muscle, resulting in greater preservation of skeletal muscle mass during weight loss.

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