Role of calcium and dairy products in energy partitioning and weight management\textsuperscript{1–3}

Michael B Zemel

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\textsuperscript{2+} plays a key regulatory role in adipocyte lipid metabolism and triacylglycerol storage; increased intracellular Ca\textsuperscript{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\textsuperscript{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 \textgeq 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. Am J Clin Nutr 2004;79(suppl):907S–12S.

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 established 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, ADIPOSY, 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," accidently, 1 From The University of Tennessee, Knoxville.
3 Address reprint requests to MB Zemel, The University of Tennessee Nutrition Institute, 1215 West Cumberland Avenue, Room 229, Knoxville, TN 37996-1920. E-mail: mzemel@utk.edu.
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 \textit{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 Ca\( ^{2+} \) ([Ca\( ^{2+} \)]\( _i \)) in regulating adipocyte lipid metabolism and triacylglycerol storage (6–13). Because [Ca\( ^{2+} \)]\( _i \) can be regulated by calcitrophic hormones, including parathyroid hormone and 1,25-dihydroxyvitamin D [1,25(OH)\( _{2} \)D\( _{3} \)], 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\( _{3} \), 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 [Ca\( ^{2+} \)]\( _i \). [Ca\( ^{2+} \)]\( _i \) 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\( _{3} \) (4, 16) stimulate rapid increases in human adipocyte [Ca\( ^{2+} \)]\( _i \); 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\( _{3} \) modulate adipocyte [Ca\( ^{2+} \)]\( _i \), a growing body of evidence indicates that 1,25(OH)\( _{2} \)D\( _{3} \) plays a pivotal role in the modulation of lipid metabolism. In support of this concept, we have shown that human adipocytes possess membrane (non-genomic) vitamin D receptors that transduce a rapid [Ca\( ^{2+} \)]\( _i \) response to 1,25(OH)\( _{2} \)D\( _{3} \) (14, 16); consequently, the treatment of human adipocytes with 1,25(OH)\( _{2} \)D\( _{3} \) 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 1α,25(OH)\( _{2} \)D\(_{3} \) in human obesity has been suggested. Polymorphisms in the nuclear vitamin D receptor (\textit{nVDR}) gene are associated with the susceptibility to obesity in humans with early onset type 2 diabetes, and 2 single nucleotide polymorphisms in \textit{nVDR} 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 \textit{BsmI} restriction site polymorphism in the \textit{nVDR} gene (18), whereas much evidence indicates increases in circulating concentrations of 1α,25(OH)\( _{2} \)D\(_{3} \) in obese humans (19, 20).

We have also shown that 1,25(OH)\( _{2} \)D\( _{3} \) acts via the classic \textit{nVDR} 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\( _{3} \) 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 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 \textit{agouti} gene in adipose tissue under the control of the \textit{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 \textit{agouti} mutants that ubiquitously overexpress \textit{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 littersmates 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...
lipogenesis, decreases in lipolysis, and accelerated increases in body weight and adipose tissue mass. In contrast, high-calcium (1.2%) diets reduced lipogenesis by 51% and stimulated lipolysis 3- to 5-fold, resulting in 26–39% reductions in body weight and adipose tissue accretion at identical ad libitum energy intakes (4). Notably, the magnitude of these effects depended on the source of dietary calcium; the effects were markedly greater when the source was dairy (nonfat dry milk) than when it was calcium carbonate (4). When the same diets were fed in combination with modest energy restriction to diet-induced, obese, transgenic mice, the low-calcium diet markedly inhibited adipose tissue lipolysis, accelerated lipogenesis, and impeded weight and fat loss secondary to energy restriction. In contrast, the high-calcium diets markedly accelerated weight and fat loss at identical levels of energy restriction, whereas dairy sources of calcium further augmented this effect by 50–70% compared with calcium carbonate (5, 23–26).

We also evaluated the effects of calcium and dairy products on the partitioning of dietary energy during refeeding after weight loss in this model. Obesity was induced by feeding a low-calcium obesogenic diet for 6 wk, after which all animals were placed on an energy-restricted high-calcium diet for an additional 6 wk to induce weight loss. The animals were then provided ad libitum access to low-calcium, high-calcium, or high dairy diets for an additional 6 wk. Although the animals fed the low-calcium diet rapidly regained all of the weight and fat that had been lost, refeeding of the high-calcium diets prevented the suppression of adipose tissue lipolysis and fat oxidation that otherwise accompanies postdieting repletion and markedly up-regulated indexes of skeletal muscle fat oxidation (27). Consequently, although the animals that were refed low-calcium diets rapidly regained all of the weight and fat that had been lost, the animals fed high-calcium diets showed a shift in energy partitioning and a 50–85% reduction in weight and fat gain. Moreover, dairy products exerted markedly greater effects than did supplemental calcium on fat oxidation and fat gain (27). These data are supported by both observational data and clinical trials, as described in the next sections.

ROLE OF DIETARY CALCIUM AND DAIRY PRODUCTS IN THE REGULATION OF HUMAN ADIPOSITY: OBSERVATIONAL STUDIES

Many recent observational studies have noted an inverse relation between dietary calcium intake and dairy products and body fat in both younger and older women (28–30), African American women (30), and children (31–33). In a 2-y prospective study of 54 normal-weight white women participating in an exercise intervention, Lin et al (28) reported that the ratio of dietary calcium to energy and the ratio of dairy calcium to energy were significant negative predictors of changes in both body weight and body fat. They reported a notable interaction between dietary calcium and energy intake in predicting changes in body fat, because calcium—but not energy—intake predicted changes in body weight and body fat for women with an energy intake below the median (1876 kcal/d), whereas energy intake alone predicted changes in weight and fat in women at higher energy intakes. Furthermore, the reported effects of calcium appeared to be specific to dairy sources, because both total calcium and dairy calcium predicted changes in body weight and fat, whereas nondairy calcium did not (28). Buchowski et al (30) reported an inverse relation between energy-adjusted dietary calcium intake and BMI in lactose-tolerant but not in lactose-intolerant African American women. Although the reason for the lack of effect in the lactose-intolerant group cannot be definitively inferred from this cross-sectional study, the lactose-intolerant group had a uniformly low calcium intake, presumably because of an aversion to dairy products. In addition, the lack of women with adequate calcium intakes in this group therefore precluded a clear relation from emerging as it did for the lactose-tolerant women.

Melanson et al (31) recently reported that calcium intake is positively correlated with whole-body fat oxidation measured in a whole-room calorimeter, with significant effects noted over a 24-h period during sleep and during light exercise. After adjustment for fat mass, fat-free mass, energy balance, and fat intake, measured calcium intake explained ≈10% of the variance in 24-h fat oxidation (31).

Most studies that have reported the relation between dietary calcium or dairy products and indexes of adiposity were conducted in adults; few studies have been conducted in children and adolescents (32–35). Phillips et al (35) recently reported no relation between dietary calcium or dietary consumption in a longitudinal assessment of adolescent females. However, they noted that dairy consumption was significantly higher in their study cohort than that reported in the Continuing Survey of Food Intakes by Individuals for a nationally representative survey of the same age group (428 compared with 269 g/d of milk and milk products). Moreover, the overall reported median dairy intake was 2.9 servings of dairy and 827 mg of dairy-derived calcium per day. Accordingly, it is possible that this cohort represented a population that consumed a diet relatively high in dairy products and, therefore, had calcium intakes that were sufficiently above formally low calcium intake, presumably because of an aversion to dairy products. In addition, the lack of women with adequate calcium intakes in this group therefore precluded a clear relation from emerging as it did for the lactose-tolerant women.

In contrast, Carruth and Skinner (33) reported a significant inverse relation between dietary calcium and body fat in a 5-y longitudinal study of preschool children studied from 2 mo of age (R² = 0.51). The same investigators recently extended these longitudinal findings to children who were 8 y of age (34). Although the initial report (33) included BMI as a controlling factor.
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 intake 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 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 trunc 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 re-
striction 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 ADIPOSITY

Data from the CARDIA Study (38), our recent clinical trials
(43–45), and rodent studies (4, 15, 23–27) all show greater ef-
fects of dairy products than of supplemental calcium in attenu-
ating adiposity. Accordingly, it is important to identify the ad-
ditional components of dairy products that may be responsible
for this augmentation. Likely candidates for this additional bio-
activity 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 pro-
tein 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 pro-
tein 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 con-
tain 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 sup-
port additional signaling pathways (47). Consequently, the abun-
dance 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 interac-
tion 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 con-
tained in whey protein may be relevant to adipocyte lipid me-
tabolism. Angiotensin II up-regulates adipocyte fatty acid syn-
thesis 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
can 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 in-
hibitor had no effect. Thus, whey components—including cal-
cium, BCAAs, ACE inhibitors, and possibly other whey com-
ponents—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 stud-
ies, 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 prod-
ucts 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 bio-
active 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 manage-
ment 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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