Calcium and Dairy Acceleration of Weight and Fat Loss during Energy Restriction in Obese Adults

Michael B. Zemel,* Warren Thompson,† Anita Milstead,* Kristin Morris,* and Peter Campbell*

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Objective: Increasing 1,25-dihydroxyvitamin D in response to low-calcium diets stimulates adipocyte Ca^{2+} influx and, as a consequence, stimulates lipogenesis, suppresses lipolysis, and increases lipid accumulation, whereas increasing dietary calcium inhibits these effects and markedly accelerates fat loss in mice subjected to caloric restriction. Our objective was to determine the effects of increasing dietary calcium in the face of caloric restriction in humans.

Research Methods and Procedures: We performed a randomized, placebo-controlled trial in 32 obese adults. Patients were maintained for 24 weeks on balanced deficit diets (500 kcal/d deficit) and randomized to a standard diet (400 to 500 mg of dietary calcium/d supplemented with placebo), a high-calcium diet (standard diet supplemented with 800 mg of calcium/d), or high-dairy diet (1200 to 1300 mg of dietary calcium/d supplemented with placebo).

Results: Patients assigned to the standard diet lost 6.4 ± 2.5% of their body weight, which was increased by 26% (to 8.6 ± 1.1%) on the high-calcium diet and 70% (to 10.9 ± 1.6% of body weight) on the high-dairy diet ($p < 0.01$). Fat loss was similarly augmented by the high-calcium and high-dairy diets, by 38% and 64%, respectively ($p < 0.01$). Moreover, fat loss from the trunk region represented 19.0 ± 7.9% of total fat loss on the low-calcium diet, and this fraction was increased to 50.1 ± 6.4% and 66.2 ± 3.0% on the high-calcium and high-dairy diets, respectively ($p < 0.001$).

Discussion: Increasing dietary calcium significantly augmented weight and fat loss secondary to caloric restriction and increased the percentage of fat lost from the trunk region, whereas dairy products exerted a substantially greater effect.

Key words: calcium, dairy, energy restriction, fat loss, vitamin D

Introduction

Dietary calcium is now well recognized as playing an important role, beyond its key role in the maintenance of skeletal integrity, in modulating chronic disease risk. Dietary calcium modulation of blood pressure has been well established through numerous well-controlled studies over the last 20 years (1), and the practical relevance of this effect has been further established in the Dietary Approaches to Stop Hypertension trials, which have demonstrated that increasing low-fat dairy product and fruit and vegetable consumption exerts profound effects on blood pressure, with the combination of dairy and fruits and vegetables having markedly greater effects than fruits and vegetables alone (2,3). An accumulating body of recent evidence suggests that calcium-rich diets not only reduce the risk of cardiovascular disease but also play a direct role in the prevention and treatment of obesity.

We first became aware of this relationship when, during the course of conducting a clinical trial of the antihypertensive effect of calcium in obese African Americans, we noted that increasing dietary calcium from 400 to 1000 mg/d for 1 year resulted in a 4.9-kg reduction in body fat (4). Indeed, there have been several isolated reports over the last 18 years of an inverse relationship between dietary calcium and/or serum calcium and indices of obesity (5–8), but in the absence of a conceptual basis for this relationship, it was

not pursued. However, these findings have been reevaluated in light of recent work describing the role of intracellular calcium in modulating adipocyte lipid metabolism and, in turn, the role of calcitrophic hormones in regulating adipocyte intracellular calcium.

The framework for understanding an "anti-obesity" effect of dietary calcium derives from our recent studies demonstrating a key role for intracellular Ca^{2+} in regulating adipocyte metabolism. Increasing intracellular Ca^{2+} results in an increase in human adipocyte energy storage and fat mass by coordinately stimulating de novo lipogenesis and inhibiting lipolysis (9–11), whereas treatment of obesity-prone mice with a calcium channel antagonist (nifedipine) results in significant reductions in adipose tissue mass (12). Thus, adipocyte calcium appears to be a logical target for interventions to control adiposity.

We have demonstrated that human adipocytes possess membrane (nongenomic) vitamin D receptors that transduce rapid intracellular Ca^{2+} responses to 1,25-dihydroxyvitamin D_3 (13); as a consequence, 1,25-dihroxyvitamin D_3 treatment of human adipocytes results in coordinated activation of lipogenic systems and inhibition of lipolysis, leading to an expansion of adipocyte lipid storage (4,13). Moreover, we have also found 1,25-dihydroxyvitamin D_3 to act using the nuclear vitamin D receptor to inhibit the expression of uncoupling protein 2 (UCP2)[1] (14), whereas suppression of 1,25-dihydroxyvitamin D_3 levels by feeding high-calcium diets to mice results in increased adipose tissue UCP2 expression and increased thermogenesis (15); this suggests that high-calcium diets may also affect energy partitioning by suppressing 1,25-dihydroxyvitamin D_3 levels, thereby permitting increased adipocyte UCP2 expression and, possibly, UCP2-mediated fatty acid transport and oxidation. Consistent with this, Melanson et al. (15) have reported recently 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. In accordance, suppressing 1,25-dihydroxyvitamin D_3 by increasing dietary calcium intake may facilitate a repartitioning of dietary energy and a reduction in adiposity.

These concepts have been validated in obesity-prone transgenic mice, in which low-calcium diets impede body fat loss, whereas high-calcium diets suppress fat accretion and weight gain on an obesity-promoting diet and markedly accelerate weight and fat loss during caloric restriction (4,16–18); notably, in each of these studies, dairy sources of calcium were shown to exert significantly greater anti-obesity effects than supplemental calcium carbonate, possibly due to the effects of other bioactive compounds in milk.

These observations are further supported by epidemiological observations from the U.S. National Health and Nutrition Examination Survey (4), the Coronary Artery Risk Development in Young Adults study (19), and the Quebec Family Study (20). Additional observational studies have found an inverse relationship between dairy and calcium intake and body fat in both younger and older women (21,22), calcium and BMI in African-American women (23), dairy products and obesity in children (24), and dietary calcium and body fat accumulation in preschool children (25). Moreover, a reanalysis of data from a series of calcium interventions originally conducted with skeletal endpoints (26) has demonstrated significant negative associations between calcium intake and body weight for all age groups and an odds ratio for overweight of 2.25 for young women in the lower one-half vs. the upper one-half of calcium intakes. Furthermore, reanalysis of a randomized controlled trial has demonstrated a calcium treatment effect of 0.325 kg weight loss/yr over 4 years with no intentional change in caloric intake (26).

Thus, accumulating data support a beneficial role for dietary calcium in weight management. However, these concepts have not yet been evaluated in a prospective clinical trial. Consequently, the present study was designed as a clinical trial to determine the effects of dietary calcium on body weight and fat loss, secondary to energy-restriction diets producing an energy deficit of 500 kcal/d, and to compare the effects of supplemental calcium carbonate and dairy calcium in augmenting weight and fat loss.

Research Methods and Procedures

Study Design

This study was designed to determine whether dairy products or calcium accelerate weight and fat loss induced by caloric restriction in 41 otherwise healthy, obese young adults. Forty-one subjects were studied for a 2-week lead-in period for baseline dietary and physiological assessment and then randomized to one of the following outpatient dietary regimens for 24 weeks: 1) a control diet providing a 500 kcal/d deficit, zero to one servings of dairy products/day, 400 to 500 mg calcium/d, and a daily placebo supplement; 2) a calcium-supplemented diet identical to the control diet, with the placebo replaced by 800 mg of calcium (as calcium carbonate), to bring total dietary calcium to 1200 to 1300 mg/d; or 3) a high-dairy diet (placebo supplemented) providing a 500 kcal/d deficit and containing three daily servings of dairy products, to bring the total calcium intake to 1200 to 1300 mg/d.

Subjects were provided individual instruction, counseling, and assessment from the study dietitian regarding dietary adherence and the development and reinforcement of

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[1] Nonstandard abbreviations: UCP2, uncoupling protein 2; HDL, high-density lipoprotein; TDEE, total daily energy expenditure; LDL, low-density lipoprotein; ACE, angiotensin-converting enzyme; 11 β-HSD-1, 11 β-hydroxysteroid dehydrogenase type 1.

strategies for continued success; although the diets were individualized to achieve a 500 kcal/person per day deficit, comparable advice was given to patients in all treatment groups, and diets were monitored weekly. All subjects maintained complete daily diet diaries throughout the study, and compliance was assessed by weekly subject interview, review of the diet diary, and pill counts. Physical activity and tobacco use were maintained at prestudy (baseline) levels throughout the study.

Body weight and waist circumference were measured weekly, with subjects wearing street clothes with no shoes, outerwear, or accessories. Body fat was measured at the beginning of the study and at weeks 12 and 24 using DXA; DXA was also utilized to ascertain regional fat loss (abdominal fat vs. other regions). Fasting levels of circulating insulin, glucose, fasting plasma lipids [triglycerides and total and high-density lipoprotein (HDL)-cholesterol], and blood pressure were measured at the same time points (baseline and weeks 12 and 24).

Subjects

Forty-one otherwise healthy, obese adults ranging in age from 18 to 60 years were initially enrolled, and 32 completed the study; there were no significant differences between completers and non-completers for any parameter studied. Of the nine subjects who did not complete the study, two were men, and seven were women. Random assignment of the original 41 subjects resulted in sample sizes of 14, 13, and 14 in the low-calcium, high-calcium, and high-dairy groups, respectively, and these three groups lost 4, 2, and 3 subjects to drop-out, respectively, resulting in final (completer) sample sizes of 10 (low calcium), 11 (high calcium), and 11 (high dairy). All subjects had an initial BMI of 30.0 to 39.9 kg/m^2, a low-calcium diet (500 to 600 mg/d, as determined by food frequency and diet history) at study entry, no more than 3-kg weight change over the preceding 12 weeks, and no recent (12 week) changes in exercise frequency or intensity. Patients were excluded from participation if they required the use of oral antidiabetic agents or insulin; used obesity pharmacotherapeutic agents and/or herbal preparations intended for the management of obesity; had a history of significant endocrine, hepatic, or renal disease; were pregnant or lactating; or suffered any form of malabsorption syndrome. Subject characteristics are summarized in Table 1. This research was approved by the Institutional Review Board of the University of Tennessee; informed consent was obtained from all subjects, and the research was conducted in accordance with the ethical standards outlined in the Helsinki Declaration.

Diets

Baseline dietary assessments (diet records) were conducted by the project dietitian during the 2-week lead-in

Table 1. Patient characteristics

	Total	Completers
Gender	34 women, 7 men	27 women, 5 men
Age (years)	46 ± 8	49 ± 6
BMI (kg/m^2)	35.0 ± 4.1	34.9 ± 4.3
Systolic blood pressure (mm Hg)	130 ± 10	130 ± 10
Diastolic blood pressure (mm Hg)	80 ± 8	79 ± 8
LDL cholesterol (mg/dL)	137 ± 33	140 ± 32
HDL cholesterol (mg/dL)	47 ± 12	46 ± 11
Triglycerides (mg/dL)	142 ± 63	133 ± 52

period to provide an initial estimate of a maintenance level of caloric intake. This was refined by calculating energy needs using World Health Organization equations for calculation of basal metabolic rate, which were then adjusted for activity level to provide an estimate of total daily energy expenditure (TDEE). TDEE was estimated as $1.3 \times$ BMR for obese patients engaged in mild daily activity and $1.5 \times$ BMR for those engaged in strenuous daily activity. Discrepancies between estimated TDEE and baseline caloric intake were resolved, if necessary, by repeat diet records reviewed by the project dietitian. Based on this initial estimate of caloric needs, a food exchange-based diet was prescribed to produce a caloric deficit of ~500 kcal/d. The diets for the treatment arms were constructed to provide comparable levels of macronutrient and fiber to approximate the average consumption in the U.S. (fat, ~35% of total kilocalories; carbohydrates, ~49%; protein, ~16%; fiber, 8 to 12 g/d). Nutritional supplements were not permitted, and caffeine intake was maintained at a constant level (individualized for each patient, based on baseline assessment). Diets were prescribed and monitored as noted above, and the key characteristics of diets achieved by subjects are shown in Table 2.

Assessment

Body weight was measured with a calibrated scale (Detecto, Webb City, MO) and height measured with a wall-mounted stadiometer (Seca, Vogel & Halke, Hamburg, Germany) with subjects in street clothes with no outerwear or shoes. BMI was calculated using the standard equation (kilograms per meters squared). Waist circumference was measured in the standing position, with measurements obtained midway between the lateral lower rib margin and the iliac crest. The measurements were taken midexhalation, and the average of two readings was recorded.

Table 2. Diet characteristics

	Low calcium	High calcium	High dairy
Calcium intake (mg/d)	430 ± 94	1256 ± 134	1137 ± 164
Energy intake (kcal/d)	1309 ± 253	1186 ± 155	1370 ± 216
Energy from fat (%)	32 ± 6	32 ± 5	31 ± 5
Energy from protein (%)	17 ± 2	17 ± 2	18 ± 1
Energy from carbohydrate (%)	52 ± 4	50 ± 7	51 ± 6

Total fat mass and percent lean and fat mass were assessed using DXA (Hologic Model QDR 2000; Hologic, Bedford, MA) at baseline and at weeks 12 and 24 of the study. The instrument was calibrated, and a spine phantom was assessed daily to determine whether any drift had occurred; spine phantom variation was <1.8% throughout the study.

Blood pressure and heart rate measurements were taken with the subject seated in an upright position in a chair for at least 5 minutes with the arm supported at heart level. Blood pressure was measured with an appropriately sized cuff using a standard, calibrated sphygmomanometer on the same arm for every measurement. Two readings, at least 1 minute apart, were taken and the average value reported.

A standard 75-g oral glucose tolerance test was administered at baseline and weeks 12 and 24 of the study, with blood sampled for glucose and insulin at 0, 15, 30, 60, 90, and 120 minutes.

Plasma glucose was determined using a glucose oxidase method and insulin and leptin using standard, commercially available radioimmunoassay kits (Linco Research, Inc., St. Charles, MO). Fasting lipid profiles [cholesterol, low-density lipoprotein (LDL)- and HDL-cholesterol, and triglycerides] were assessed using standard clinical techniques.

Statistics

Data were assessed by multivariate ANOVA using SAS software (Version 9, SAS Institute, Cary, NC) to facilitate evaluation of both the repeated measures and independent group comparisons inherent to this study design. Only subjects who completed the entire study ($n = 32$) were included in the data analysis. All data are presented as mean ± SE.

Results

As expected from the experimental design, all participants lost body weight and body fat due to the daily energy deficit of 500 kcal/d. However, both weight and fat (measured by DXA) loss were markedly increased on the high-dairy diet, with intermediate, but still significant, effects on the high-calcium diet. Table 3 summarizes the weight and fat loss data. Participants on the low-calcium control diet lost 6.4 ± 2.5% of their body weight. This was increased by 26% (to 8.6 ± 1.1%) on the high-calcium diet and by 70% (to 10.9 ± 1.6%) on the high-dairy diet ($p < 0.01$, Table 3). Fat loss followed a similar trend. Patients lost 8.1 ± 2.3% of their body fat on the low-calcium control diet. This was increased to 11.6 ± 2.2% on the high-calcium diet and to 14.1 ± 2.4% fat loss on the high-dairy diet ($p < 0.01$,

Table 3. Effects of dietary treatments on body weight and body fat

	Treatment		
	Low calcium	High calcium	High dairy
Initial body weight (kg)	103.1 ± 6.1[a]	99.8 ± 4.5[a]	101.6 ± 6.8[a]
Initial body fat (kg)	59.4 ± 4.7	48.4 ± 5.3*	50.7 ± 5.0*
Initial trunk fat (kg)	26.0 ± 1.7[a]	22.8 ± 3.1[a]	26.7 ± 3.0[a]
Initial waist circumference (cm)	104.6 ± 3.3[a]	100.6 ± 4.8[a]	103.4 ± 2.8[a]
Weight change (kg)	6.60 ± 2.58[a]	8.58 ± 1.60[b]	11.07 ± 1.63[c]
Weight change (% of initial)	6.4 ± 2.5[a]	8.6 ± 1.1[b]	10.9 ± 1.6
Fat change (kg)	4.81 ± 1.22[a]	5.61 ± 0.98[b]	7.16 ± 1.22[c]
Trunk fat change (kg)	1.38 ± 0.60[a]	2.94 ± 0.73[b]	3.74 ± 0.64[c]

Non-matching letter superscripts in each column denote significant differences ($p < 0.01$).

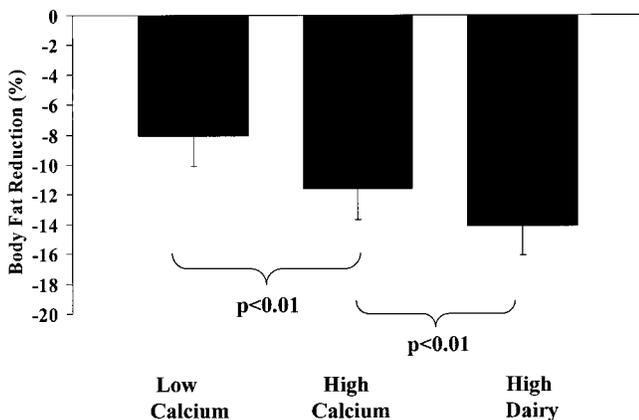* Denotes significant difference ($p < 0.05$) in initial body fat.

Figure 1: Effects of dietary treatments on body fat reduction. Changes in body fat are expressed as a percentage of original body fat measured by DXA as described in "Research Methods and Procedures." Fat loss on each diet is significantly different from the other two diets ($p < 0.01$).

Figure 2: Effects of dietary treatments on fat loss from the trunk region. Trunk fat loss is calculated as the change in trunk fat divided by the change in total body fat and is expressed as a percentage of total fat lost. Trunk fat loss on each diet is significantly different from the other two diets ($p < 0.01$).

Figure 1). Subjects on the low-calcium control diet exhibited a significantly higher fat mass than the other two groups ($p < 0.05$); nonetheless, this group lost the least amount of body fat during energy restriction, indicating that these findings are not confounded by "regression to the mean" secondary to this difference because the greatest fat loss would have been predicted for the group with the greatest initial body fat. Circulating leptin followed a pattern similar to that observed for body fat. All three groups exhibited significant decreases in plasma leptin levels ($p < 0.01$). Patients on the high-dairy diet exhibited a 51% decrease, vs. 19% and 33% in the low-calcium and high-calcium groups, respectively ($p < 0.01$ vs. high dairy).

An unexpected finding was a marked change in the distribution of body fat loss (Figure 2). Patients on the low-calcium diet lost $5.3 \pm 2.3\%$ of their trunk (abdominal region) fat on the low-calcium diet. This was increased to $12.9 \pm 2.2\%$ on the high-calcium diet and $14.0 \pm 2.3\%$ on the high-dairy diet ($p < 0.025$ vs. low-calcium and high-calcium diets). As a consequence, fat loss from the abdominal region represented $19.0 \pm 7.9\%$ of the total fat lost on the low-calcium diet, and this was increased to $50.1 \pm 6.4\%$ of the fat lost on the high-calcium diet ($p < 0.01$) and $66.2 \pm 3.0\%$ on the high-dairy diet ($p < 0.01$). These changes are reflected in corresponding differences in waist circumference changes ($p < 0.01$, Figure 3).

Glucose tolerance was not significantly different among the groups at baseline (Figure 4A); however, the high-dairy group exhibited a significant improvement in glucose tolerance after 24 weeks on the diet, whereas the other two groups exhibited no change (Figure 4B). As a consequence, there was a 27% decrease in the area under the glucose curve for the high-dairy group ($p < 0.01$), whereas there was no significant change for the low- or high-calcium
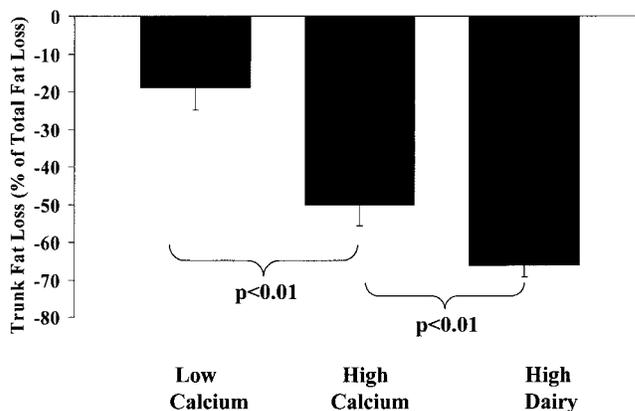
groups. Fasting glucose levels were unaffected by diet, but there was a 44% decrease in plasma insulin levels in patients on the high-dairy diet ($p < 0.01$, Figure 5), although the area under the insulin curve after the glucose tolerance test was unaffected by diet.

There were no significant effects of any of the diets on diastolic pressure or circulating lipids (Table 4), whereas the patients on the high-dairy diet exhibited a modest (4.8 ± 2.1 mm Hg) reduction in systolic pressure ($p < 0.02$).

Discussion

Data from this study demonstrated that increasing dietary calcium accelerated weight and fat loss secondary to energy
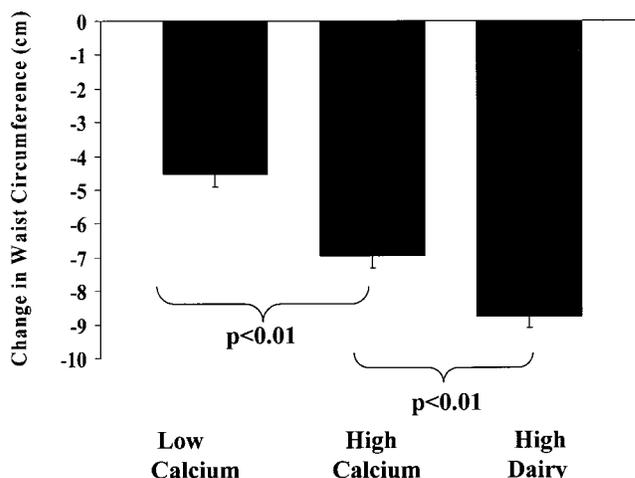

Figure 3: Effects of dietary treatments on waist circumference. Waist circumference was measured in the standing position, as described in "Research Methods and Procedures."
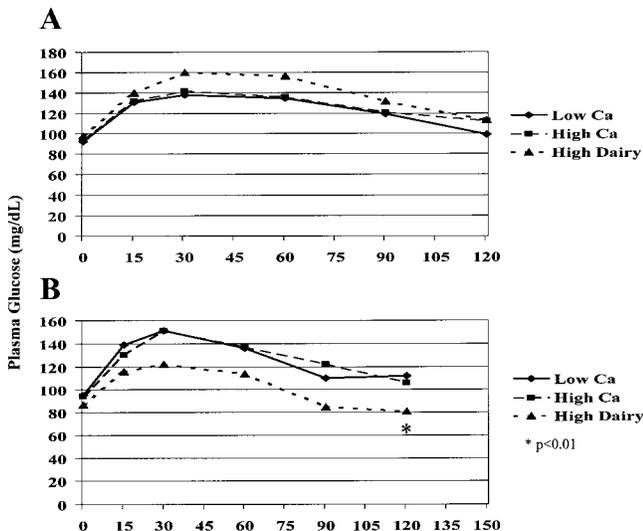
A

B

Figure 4: Effects of dietary treatments on glucose tolerance. Glucose tolerance was measured using an oral glucose-tolerance test as described in "Research Methods and Procedures." (A) Depiction of glucose tolerance at study initiation. (B) Depiction of glucose tolerance after 24 weeks of dietary treatment.

restriction, with a substantially greater effect exerted by dietary (dairy) sources of calcium when compared with a supplemental (calcium carbonate) source. Previous epidemiological and experimental data have suggested such a relationship, with numerous isolated reports over the past 18 years of an inverse relationship between dietary calcium and/or serum calcium and indices of obesity (5–8), although the lack of a theoretical basis for this relationship minimized interest in pursuing further study. However, we have demonstrated that 1,25-dihydroxyvitamin D_3 is a potent mediator of human adipocyte lipid metabolism that exerts a coordinated stimulation of lipogenesis and inhibition of lipolysis, thereby resulting in an expansion of adipocyte
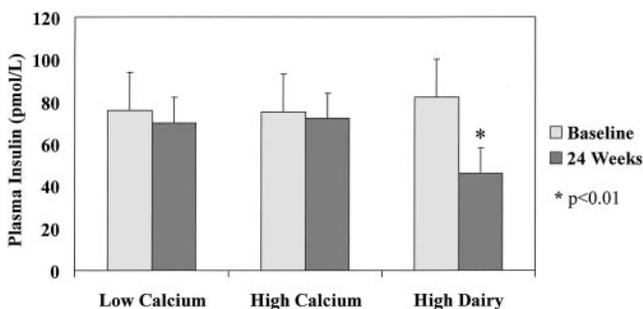

Figure 5: Effects of dietary treatments on plasma insulin. The light-shaded bars show insulin levels at study initiation, and the dark-shaded bars show insulin levels after 24 weeks of dietary treatment.

Table 4. Effects of dietary treatments on circulating lipids*

	LDL cholesterol (mg/dL)	HDL cholesterol (mg/dL)	Triglycerides (mg/dL)
Low calcium	148 ± 8	46 ± 4	136 ± 32
High calcium	147 ± 18	47 ± 4	143 ± 54
High dairy	130 ± 13	46 ± 4	114 ± 24

* No significant treatment effects.

triglyceride stores and adipose tissue mass (4,13,14). As a consequence, suppression of 1,25-dihydroxyvitamin D_3 with high-calcium diets would be anticipated to reduce adipocyte intracellular Ca^{2+}, decrease lipogenesis, and increase lipolysis, thereby exerting an anti-obesity effect.

This concept was validated in obesity-prone transgenic mice, in which low-calcium diets impeded body fat loss, whereas high-calcium diets suppressed fat accretion and weight gain on an obesity-promoting diet and markedly accelerated weight and fat loss during caloric restriction (4,16–18). Notably, dairy sources of calcium exerted significantly greater anti-obesity effects than supplemental calcium carbonate in each of these studies, consistent with the clinical results presented here. Although the additional factor(s) in dairy responsible for this effect have not been identified yet, milk is recognized as a rich source of bioactive compounds (27) that may act independently or synergistically with the suppression of 1,25-dihydroxyvitamin D_3 to favorably affect nutrient portioning, metabolic efficiency, and fat loss. For example, milk proteins contain significant angiotensin-converting enzyme (ACE) inhibitory activity (28,29), and recent data demonstrate that adipocyte lipogenesis is regulated, in part, by angiotensin II and that adipocytes have an intact paracrine/autocrine renin-angiotensin system (30). Moreover, ACE inhibition mildly attenuates obesity in rodents, and limited clinical observations support this concept in hypertensive patients treated with ACE inhibitors (reviewed in 30). Thus, dairy-based ACE inhibitory activity may explain, in part, the significantly greater effect of the high-dairy vs. high-calcium diet in augmenting weight and fat loss in the present study. Consistent with this, we recently found a whey-derived ACE inhibitor to augment the effect of dietary calcium on weight and fat loss in energy-restricted aP2-*agouti* transgenic mice (31); 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. For example, Layman (32) has

proposed recently 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. In accordance, 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.

It is also possible that a portion of the anti-obesity effects of dietary calcium may be due to an increase in fecal fatty acid excretion, because clinical studies demonstrate that substantial (2- to 4-gram) increases in dietary calcium result in statistically significant, but modest, increases in fecal fat losses (33–35). A supplement of 2 grams of calcium (as calcium carbonate) has been shown to result in an increase in fecal fat excretion from 6.8% to 7.4% of total fat intake (34). Although this will contribute to a net negative energy balance, this effect is too small to explain the anti-obesity effects found in the present study. For example, to provide a clinically meaningful contribution to weight loss, orlistat produces an ~30% inhibition of total dietary fat absorption, vs. the ~1% seen with large supplements of calcium. Thus, although calcium inhibition of fat absorption may contribute to its anti-obesity actions, this effect is too small to be primarily responsible; instead, the primary effects are likely to result from inhibition of 1,25-dihydroxyvitamin D_3 effects on energy storage and use, with additional contributions deriving from dairy-derived bioactive compounds discussed above and from inhibition of fat absorption.

Differences in the effects of dietary vs. supplemental calcium on biological responses are not unprecedented; they have been noted previously with regard to the effects of calcium on blood pressure regulation. Although dietary calcium modulation of blood pressure has been well established through numerous well-controlled studies over the last 20 years (for review, see Ref. 1), recent meta-analyses indicate a considerable heterogeneity in the blood pressure response to dietary calcium (1,36). Because a statistically significant heterogeneity has been noted when conducting meta-analysis for all trials and for trials of supplemental calcium, but not when analysis is restricted to trials of dietary sources of calcium, this heterogeneity may be explained, in part, by the sources of dietary calcium utilized. Moreover, studies examining dietary calcium have exhibited nearly twice the antihypertensive effect as those utilizing calcium supplements (1,36), similar to the differences we have noted between dietary and supplemental sources of calcium in the modulation of adiposity. Consistent with this, patients on the high-dairy diet in the present study exhibited a modest, but significant, reduction in systolic pressure (4.8 mm Hg), whereas those on the high-calcium diet did not.

Participants in the high-dairy diet exhibited a significant increase in insulin sensitivity, as indicated by reductions in both circulating insulin and the area under the glucose tolerance curve. Unfortunately, it is not possible to discern whether these are direct effects of the high-dairy diet or are secondary to the greater weight and fat loss found on this diet, which would also have been predicted to improve insulin sensitivity. However, increased intracellular calcium may result in diminution of insulin signal transduction (37); as a consequence, suppression of 1,25-dihydroxyvitamin D_3 may decrease intracellular calcium in insulin target tissue and, thereby, augment insulin sensitivity, suggesting that the observed increase in insulin sensitivity on the high-dairy diet may result from the greater weight loss on that diet and from suppression of circulating 1,25-dihydroxyvitamin D_3 levels. Alternatively, it should be noted that the high-dairy group exhibited a significantly higher initial area under the glucose tolerance curve, such that a regression to the mean may have also contributed to the observed improvement on the high-dairy diet.

Finally, both the high-calcium and high-dairy diets resulted in striking changes in the distribution of body fat loss during energy restriction, with a marked augmentation of body fat loss from the trunk region. Although these data cannot distinguish between visceral and subcutaneous fat, the greater loss of fat from the trunk is highly suggestive of increased mobilization and loss of visceral fat. Thus, increasing dietary calcium not only accelerates weight and fat loss, secondary to caloric restriction, but also appears to shift the distribution of fat loss to a more favorable pattern, with more fat lost from the abdominal region on the high-calcium diet. Although the mechanism of this effect is not clear, recent studies describing the role of autocrine production of cortisol by adipose tissue provide a plausible explanation. Human adipose tissue expresses significant 11 β-hydroxysteroid dehydrogenase type 1 (11 β-HSD-1), which acts as a reductase to regenerate cortisol from cortisone (38,39). Further, visceral adipose tissue exhibits greater expression of 11 β-HSD-1 than subcutaneous adipose tissue, and there is greater activation of 11 β-HSD-1 in adipose tissue of obese humans (39). Moreover, transgenic mice overexpressing 11 β-HSD-1 selectively in adipose tissue develop visceral obesity (40). We have demonstrated recently that increasing intracellular Ca^{2+} using a variety of agonists, including 1,25-dihydroxyvitamin D_3, results in a marked augmentation of human adipocyte cortisol production (41). Therefore, one may reasonably expect that suppression of adipocyte intracellular Ca^{2+} levels on high-calcium diets may result in reduced adipose tissue cortisol production, which may, thereby, explain the preferential loss of visceral adipose tissue.

In summary, a high-calcium diet and a high-dairy diet enhanced the efficacy of an energy-restricted diet in weight control, with a significantly greater effect of dairy vs. a nondairy (supplemental) source of calcium. Furthermore, both diets had a particularly beneficial effect on central

obesity. Further study of the mechanisms for the enhanced effect of dairy products over calcium alone may provide further insight into the prevention and treatment of obesity.

Acknowledgment

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