Review

A LIGHTER SIDE OF CALCIUM: ROLE OF CALCIUM AND DAIRY FOODS IN BODY WEIGHT

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This review explains the physiological involvement of calcium in overweight/obesity (as it is understood now) and presents some of the studies where this role has been documented, as well as those reporting no effect of Ca on body weight/composition. Based on much of the presently reported data, Ca and even more so dairy foods, might help in weight reduction/maintenance when combined with energy-restricted diet. The scientific community is in agreement that there is a pressing need for large clinical trials to assess the effect of Ca on weight reduction and to investigate whether weight loss could be achieved easier with Ca supplements or dairy products. It has yet to be learned what amount of Ca would be optimal for those purposes and what influence, if any, an individual's current Ca intake and existing weight might play. Additionally, it is still hard to pinpoint which component(s) in dairy foods have a role in weight reduction and whether they act alone or in synergism with Ca. Considering the overwhelming prevalence of overweight/obesity and consequences to population health and economic burden it entails, it is of crucial importance to develop strategies to curtail the problem of obesity from all fronts and the one involving Ca seems quite promising. However, more research in this area is necessary.

KEY WORDS: *adipocytes, calcitriol, obesity, overweight, parathyroid hormone, weight reduction*

The beneficial roles of calcium in bone health, blood pressure, and colon cancer are more or less established and well supported by scientific evidence. Recently new evidence emerged about Ca role in weight reduction and management. *Zemel et al*. (1) gave a plausible conceptual framework for the cellular mechanism of Ca involvement in adiposity and how it can influence weight and/or fat tissue. Simultaneously, by evaluating National Health and Nutrition Examination Survey III (NHANES-III) data, they also showed that the risk of obesity was reduced by over 80 % in people with the highest Ca intake (approximately at the level of current recommendations).

Obesity and overweight in the United States are reaching epidemic proportions, with over 60 % of population being overweight (body mass index, BMI of 26-30 kg m^{-2}) and half of that obese (BMI >30 kg m^{-2}). Similar situation is being reported from other developed countries with the rate of obesity just slightly lower (2). Dubbed as a major health issue of the 21st century, obesity and overweight are associated with increased mortality from all causes and increased risk for about 30 morbid conditions, the most common being cardiovascular problems, type II diabetes, osteoarthritis and some kinds of cancers. Many individuals are commonly advised to engage in weight reduction regimens to alleviate obesity-related problems or even more so for the esthetic reasons. However, it is well established that weight loss leads to loss of bone and muscle (3-9), increasing risks for osteoporosis and subsequent fractures. Typically, the loss of bone and muscle during weight reduction is not recognized or adequately addressed by medical establishments when weight reduction is recommended to improve other chronic conditions. Therefore, if Ca proves to be beneficial for weight reduction and management, it might as well serve as

an excellent nutrient in preventing accompanying bone loss, particularly when older women are involved.

This paper describes the physiological involvement of Ca in overweight/obesity (as it is understood now) and presents some of the studies where its role has been documented, as well as those which did not show evidence of Ca in weight reduction or management.

Mechanism of calcium action in weight reduction/ management

The anti-obesity effect of Ca is attributed to its intracellular level and its impact on lypogenesis and lipolysis. Briefly, low Ca diets stimulate secretion of parathyroid hormone and calcitriol (1,25 dihydroxy vitamin D), which both stimulate Ca ion influx in adipocytes. Increased intracellular Ca stimulates lipogenic gene expression and lipogenesis and suppresses lipolysis resulting in increased adiposity. High Ca diets are shown to suppress this hormonal response, resulting in an up-regulation of lipolysis (10) (Figure 1). *Fujita and Palmieri* (11) called the Ca effect on weight "calcium paradox disease", paradoxical in that high cytosolic Ca caused by low dietary Ca will promote lipogenesis and conservation of fat. It is also possible that Ca contributes to weight reduction (at least to some extent) via its capacity to bind fatty acids from the intestinal tract rendering them unavailable for absorption, as reviewed recently (12).

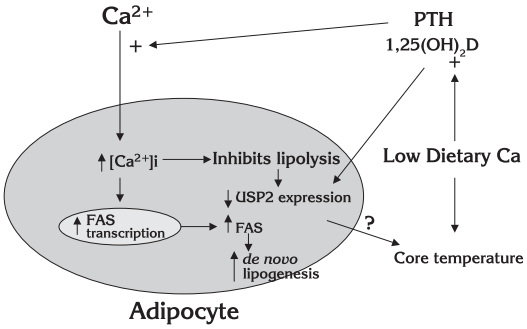

Figure 1 *Mechanism of the anti-obesity effect of dietary calcium. Adapted from Zemel (10).*
FAS = fatty acid synthase; UCP2 = uncoupling protein 2; PTH = parathyroid hormone.

Evidence documenting the role of calcium in weight/ body composition

Several researchers, by re-examining their data, showed an inverse relationship between calcium intake and body weight or body fat, although their original studies were designed to investigate the effects of Ca on either bone mass or blood pressure. The summaries of these findings are presented in several reviews (12-16). *Davies et al*. (13) evaluated the data from four observational (two cross-sectional, two longitudinal) and one randomized clinical trial with total of about 780 women ranging from 30 to 80 years of age. Originally, these studies were designed to examine the association of Ca intake with regard to skeletal health. In reevaluation of those data the authors found significant association between Ca intake and weight, and the odds ratio of being overweight (BMI>26) was 2.25 in individuals with the lower Ca intake. Based on the estimates from those studies, about 1000 mg Ca intake difference was associated with 8 kg difference in mean body weight and Ca intake explained about 3 % of the variance in body weight. Subsequently, *Heaney et al*. (15) extended these analyses, added reports from other related studies and another randomized clinical trial, concluding that each 300 mg increment in regular Ca intake is associated with ~1 kg less body fat in children and 2.5-3.0 kg lower body weight in adults.

Other studies suggest similar trends. *Zemel et al*. (1) demonstrated that women with the highest Ca (1300 mg per day) and dairy (3+ servings per day) intake had the lowest risk of being in the highest quartile of body fatness The authors showed that for any given level of energy intake and/or expenditure, lower Ca intake favored the increased efficiency of energy storage while higher intakes favored thermogenesis. In a prospective, two-year exercise intervention study in young women of normal weight, higher Ca intakes adjusted for energy was negatively associated with body weight and fat (17).

In reexamining our own cross-sectional and longitudinal (over two-year period) data in over 100 postmenopausal women, we found that total Ca (food and supplements) adjusted for protein or energy intake was associated with lower weight, BMI, and body fat, with Ca contributing from 2 % to 6.4 % of the variance in the multiple regression models (18). Also, repeated measures analysis of covariance (ANCOVA), with subjects divided by the ratio of median cumulative Ca (1459 mg) and protein (68.9 g) intake, (ratio 21.9 mg g^{-1}) and controlled for age and cumulative height and physical activity score, was used to examine the over-time relationship between Ca and components of body composition. Figure 2 presents the interaction between cumulative Ca/protein and energy intake on body weight (measured at a 2-year point). Subjects were divided below and above cumulative median

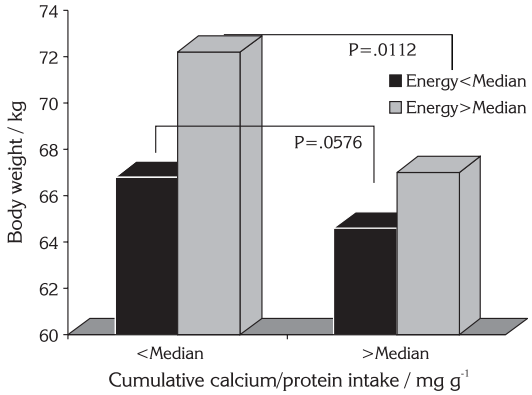

Figure 2 *Interaction between average cumulative Ca/protein and energy intake on body weight (during a two-year study period). Subjects were divided below and above cumulative median for Ca/protein and cumulative median for energy intake. Those above Ca/protein median intake had lower weight regardless of energy intake compared to those below Ca/protein median intake.*

for Ca/protein and cumulative median for energy intake. Those above Ca/protein median intake had significantly lower weight regardless of energy intake compared to those below Ca/protein median intake. The cut-off level for Ca/protein ratio was ~22 mg g^{-1}, and for Ca alone >1400 mg per day. These levels are at or slightly higher than the current recommendations for both Ca (19) and protein (20) for older adults/ women.

Based on the presented evidence, the effect of dietary or supplemental Ca on weight is very subtle and is unlikely to produce weight reduction without simultaneous energy modification. Therefore, Ca should not be viewed as a "magic bullet" in weight reduction/management issue. Additionally, the impact of Ca might be the greatest in situations when adipocytes are changing, such as during growth (21) or weight loss (10).

Role of dairy foods in weight/body composition

It has been noted by some researchers that dairy foods have a greater role in weight reduction/ management than could be predicted from their Ca content alone (22) and greater than Ca supplements (23). One of the rare clinical studies designed to actually compare the effects of dairy and supplemental Ca on weight reduction was published just recently. Women on reduced energy intake lost about 26 % and 70 % more weight on Ca supplements and dairy products, respectively (total Ca ~1200-1300 mg per day in both groups) than controls consuming similar energy levels (24). This effect is attributed to either synergistic or separate influence of some of the bioactive components of milk, including possibly whey peptides (25), conjugated linoleic acid (26), and branched chain amino acids (27).

Other studies, although not designed to compare the effectiveness of dairy products vs. Ca supplements on weight reduction, point to the same direction. *Summerbell et al*. (28) compared three dietary regimens for weight reduction during a 4-month intervention: standard, 3348 kJ (800 kcal) per day diet; 3348 kJ (800 kcal) per day diet derived mostly from dairy products; and 5441 kJ (1300 kcal) per day diet derived from dairy products and one additional food of choice. The highest weight reduction was achieved on 3348 kJ (800 kcal) per day dairy diet (-11.2 kg), followed by 5441 kJ (1300 kcal) per day dairy+food diet (-8.2 kg), and the least, on the standard 3348 kJ (800 kcal) per day diet (-3 kg). At that time, the authors did not contribute the weight loss achieved on two dairy regimens to the effects of Ca and/or dairy products, but rather to the novelty of their diets and consequent better compliance. An earlier study (29) compared severely energy-restricted diets of 1381 kJ (330 kcal) per day with milk-based diet of 3264 kJ (780 kcal) per day over a 6-month period. There was no difference in achieved weight loss, although the milk-based diet was more than double in kcal and there was more loss of fat and less loss of lean tissue on the latter diet. All the above evidence points to better effectiveness of weight reduction programs and easier weight loss in the presence of calcium, but especially dairy products.

Studies reporting negative or no effect of calcium on weight/body composition

There are also studies with conclusions opposite to the ones stated above (30-33) and as reviewed by *Barr* (34). According to that review (34), in seven out of nine studies in which dairy products were supplemented to increase Ca intake, there was no significant difference in weight or body composition change, while in other two, a significant increase in body weight in the dairy supplemented group was noted compared to the control. Similarly, only one out of 17 randomized clinical trials with Ca supplements showed significantly higher weight loss in supplemented versus control group. However, none of those studies were designed or powered to examine the effects of Ca from dairy products or supplements on weight/body composition.

In some, dietary assessments of unknown validity and reliability were used. Additionally, in many of those studies, energy and protein intake, or physical activity were not accounted for, all of which are important for controlling for confounding and removing extraneous variations.

Kamycheva et al. (30) reported no influence of Ca on body mass index (BMI) in women and positive influence on BMI in men. The study was a cross-sectional assessment in over 19,000 men and women aged 24-70 years from an epidemiological survey carried out in Tromso, Norway. However, dietary vitamin D was an independent predictor for obesity and was inversely related to BMI in both men and women in the study. The authors could not quite explain their findings regarding Ca, but since they did not have the information about energy and protein intake of the subjects, it was not possible to control for those two crucial items that might override or mask the influence of Ca. Additionally, as much as epidemiological studies provide strong statistical analyses due to large sample sizes, a drawback is that there is not much control in data collection, particularly when dietary intakes are in question.

In a longitudinal, observational study in about 900 peri- and early postmenopausal women, *MacDonald et al*. (31) also found no relationship between Ca intake and weight or weight change. In a pooled analysis of three separate 25-week randomized, placebo controlled trials of weight loss intervention, Ca supplements did not affect weight or body fat in a supplemented group of postmenopausal women compared to a group that received placebo. The placebo group lost about 6 kg and the supplemented group about 7 kg during 25-week intervention, but there was no significant difference between them (32).

Despite the controversies, many agree that although Ca intake explains probably less than 10 % of the variance in individual body weight, the relationship is such that in a steady adult state, for each 300 mg increment in Ca intake, there is a decrement of 2-3 kg of body weight. Currently, there is a consensus in the scientific community that there is a pressing need for controlled clinical trials to assess the effect of Ca on weight reduction and to investigate whether weight loss could be achieved easier with Ca supplements or dairy products (12, 13, 16). It has yet to be learned what amount of Ca would be optimal for those purposes and whether the level of accustomed Ca intake before the weight reduction intervention has any role in the process.

Historical perspective on calcium intake

The current recommendations for Ca are set with skeletal health as an endpoint. However, it is well established that the evolution of contemporary humans occurred in high Ca nutritional environment and that our physiology is still adapted to the Paleolithic dietary regimen, since our genome has not changed much from that time. According to the anthropologic evidence and studies of bony remains from that time, ancient humans were consuming at least twice as much calcium as the contemporary humans (35, 36). Ca intake (obtained mostly from seeds, nuts and other plants) was a marker of the overall food/energy intake. When food and subsequently Ca intake were low, both parathyroid hormone and calcitriol rose, possibly as a physiological adaptation to low energy intake. Therefore, those two hormonal systems might be responding to low Ca as a proxy to overall low energy consumption, because they were programmed to conserving energy and promoting weight gain. It might be that the prevalence of obesity, at least partly, is another response to the overall, chronic, suboptimal Ca intake.

As *Heaney* (14) points out, the effect of chronic low Ca intake on obesity prevalence might be "as large as, or larger than, the corresponding effect on osteoporosis prevalence" at least in northern hemisphere. In that line, *Heaney* (14) gives an elegant population perspective on the prevalence of obesity, suggesting that the overweight/obesity in women could be reduced by 60-80 % by increasing Ca intake via dairy products to the recommended level of 1000-1200 mg per day. As an irony, in many weight reduction protocols, patients are discouraged of consuming dairy products and additional Ca (16). It is important to note however, that energy imbalance still remains to be the main and the strongest underlying cause of overweight.

Conclusions

Considering the overwhelming rise of overweight/obesity and consequences to population health and economic burden it entails, it is of crucial importance to develop strategies to curtail this problem from many fronts. The physiological explanation for the mechanism of Ca involvement in adipocytes is plausible and much of the reported data so far give

a promising notion that Ca might help in weight reduction/maintenance in combination with energy restriction. However, the scientific community is in agreement that large clinical trials must be conducted to assess the effect of Ca on weight reduction and to investigate whether weight loss could be achieved easier with Ca supplements or dairy products (12, 13, 16), the studies on the latter being basically non-existent. It yet has to be learned what amount of Ca would be optimal for those purposes, since the current recommendations for Ca are set with skeletal health as an endpoint. Additionally, it is unknown whether the individuals' accustomed Ca intake before the weight reduction might have some influence and whether initial body weight plays any role.

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Sažetak

LAKŠA STRANA KALCIJA: UTJECAJ KALCIJA I MLIJEČNIH PROIZVODA NA TJELESNU TEŽINU

U preglednom radu prikazane su dosadašnje spoznaje o ulozi kalcija u nastanku prekomjerne tjelesne težine te navedeni rezultati istraživanja gdje je taj utjecaj dokazan, kao i nalazi gdje ta uloga kalcija nije potvrđena. Na temelju većine dosad objavljenih radova može se zaključiti da kalcij, a pogotovo mliječni proizvodi, zajedno sa smanjenim energetskim unosom, mogu pridonijeti smanjenju tjelesne težine i/ili održavanju niže tjelesne težine. Međutim treba istaknuti da su postojeći podaci u literaturi nedostatni za konačnu prosudbu utjecaja kalcija na smanjenje tjelesne težine. Nužna su velika klinička istraživanja kojima bi se utvrdilo da li se smanjenje tjelesne težine može lakše i učinkovitije postići suplementiranjem preparatima kalcija ili mliječnim prerađevinama. Nije poznato ni kolika bi količina kalcija bila optimalna u tu svrhu, ni kakav utjecaj može imati uobičajeni unos kalcija i postojeća težina osobe. Također se još ne zna koji bi sastojak ili sastojci u mliječnim prerađevinama mogli imati aktivnu ulogu u smanjenju težine te je li ta uloga izolirana ili je u kombinaciji s kalcijem. S obzirom na golem porast pojave prekomjerne tjelesne težine u ljudi, što ima štetne i zdravstvene i ekonomske posljedice, nužno je razviti mjere za suzbijanje pretilosti i debljine na svim razinama. Strategija koja bi uključivala unos kalcija u hrani čini se razumnim i realnim rješenjem, ali su potrebna daljnja istraživanja kojima bi se konačno potvrdila ta pretpostavka.

KLJUČNE RIJEČI: *kalcitriol, masne stanice, mršavljenje, paratiroidni hormon, pretilost*

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