The role of calcium in energy balance and obesity: the search for mechanisms\textsuperscript{1,2}

Arne Astrup

Observational studies almost invariably show an inverse association between the intake of dietary calcium and body fatness, which suggests that calcium influences energy balance favorably in the growing groups of people with weight problems. Most calcium intake derives from dairy products, and thus the observed association between calcium and body weight could be confounded by other components of dairy products, such as protein or bioactive peptides; alternatively, the association could be due to a healthier lifestyle among persons with a high dairy intake or to poor diet quality among those with low dairy intakes. To assess whether the association is causal, it is necessary to find plausible mechanisms that explain how calcium influences energy balance, and the effects should also be evaluated in randomized controlled trials.

The most popular hypothesis was advocated by Zemel et al (1). They proposed that dietary calcium, via its influence on plasma 1,25-dihydroxyvitamin D\textsubscript{3} (calcitriol) concentrations, regulates the concentrations of intracellular adipocyte calcium and by this means regulates fat metabolism in the adipocytes. According to this hypothesis, a low dietary calcium intake inhibits lipolysis, stimulates de novo lipogenesis, and decreases fat oxidation; through these mechanisms, a low dietary calcium intake leads to weight gain, whereas a high dietary calcium intake exerts the opposite effects. This concept has gained some support from in vitro and rodent studies. In this issue of the Journal, Bortolotti et al (2) examine the relevance of this concept to human physiology. They conducted a placebo-controlled, crossover experiment in low calcium consumers who received 800 mg dairy Ca/d for 5 wk and a similar placebo treatment after a wash-out period. Whole-body energy expenditure and fat oxidation were measured by indirect calorimetry, subcutaneous adipose tissue lipolysis was assessed by microdialysis, and gene expression studies were conducted on adipose tissue that underwent biopsy. Bortolotti et al failed to find any effect of calcium supplementation on whole-body or adipose tissue fat metabolism. They also pointed out theoretical shortcomings of the hypothesis of Zemel et al, such as the negligible role of de novo lipogenesis in fat gain in humans (2). Taking this evidence together with that from studies by Boon et al (3) and others seems to provide sufficient evidence to refute the hypothesis that dietary calcium plays an important role in human energy balance through calcium-controlled pathways in adipose tissue.

Before commenting on alternative hypotheses, it is pertinent to consider the effect of dietary calcium on body weight as assessed by intervention trials. A number of randomized trials of calcium supplementation, either from supplements or from dairy products, have been reported, but those studies did not produce a clear outcome. A systematic review that included randomized controlled trials in which calcium supplementation (supplements or dairy products) was given as treatment and body weight was reported as a final outcome measure failed to find evidence of a beneficial effect of calcium intake on body weight (4). However, of the randomized controlled trials considered in the systematic review, only one study was specifically designed and powered to examine whether calcium supplementation led to a change in body weight (5). Most of the trials were designed to examine bone health rather than changes in body fat. This point is highly relevant, because a body fat loss of \( \approx 1 \) kg/y may be extremely important in the prevention of weight gain and obesity, but large study groups are required in a randomized trial to obtain the statistical power necessary to detect such an effect over 6–12 mo. This fact is illustrated by the randomized, double-blinded, placebo-controlled trial performed in 36 282 women in the Women’s Health Initiative, who were randomly assigned to receive either 1000 mg Ca plus vitamin D or placebo daily, and whose body weight was recorded for 7 y (6). The supplement produced a small (0.13 kg) but consistent restriction in weight gain \((P = 0.001)\). After 3 y of follow-up, women with baseline daily calcium intakes of \(<1200\) mg who were randomly assigned to supplements were 11\% less likely to experience small weight gains (1–3 kg) and 11\% less likely to gain moderately more weight (>3 kg). The observed effect is probably an underestimation of the true effect of calcium, because of the lack of adherence to the supplement protocol over such a long time, but the study does not suggest that calcium supplementation plays a major role as a tool for the prevention of weight gain. In addition, both observational and interventional studies strongly suggest that dietary calcium exerts a much stronger effect on body weight than does supplementary calcium. Dietary calcium also binds some fat in the gastrointestinal tract and keeps it unavailable for absorption, which in turn reduces postprandial lipemia and increases fecal fat excretion (5). Dairy calcium may be much more effective in this respect than other forms of calcium (7).

\textsuperscript{1}From the Department of Human Nutrition, Centre for Advanced Food Studies, Faculty of Life Sciences, University of Copenhagen, Copenhagen, Denmark.

\textsuperscript{2}Reprints not available. Address correspondence to A Astrup, Department of Human Nutrition, Faculty of Life Sciences, University of Copenhagen, Rolighedsvej 30, DK-1958 Frederiksberg C, Denmark. E-mail: ast@life.ku.dk.
Another important suggestion is that the effect of calcium may be exerted mainly during energy restriction and only in persons with a low habitual calcium intake. This possibility has led to the formulation of the hypothesis that a calcium-deficient diet, which easily be experienced during an energy-restricted weight-loss diet, leads to hunger, noncompliance, and poor weight-loss outcome (5). According to Tordoff (8), “Calcium appetite is the motivation to seek out or choose calcium-containing items.” Calcium appetite may be compared with the appetite for glucose or energy, because unlike sodium homeostasis, these involve a reservoir (bone for calcium, glycogen or fat—or both—for glucose and energy) (5). Whereas a low calcium intake may be detrimental for all attempts to control weight, it may be most relevant to study its effects during weight-loss attempts, when a difference in hunger sensations is an important determinant of compliance and of weight-loss outcome.

In conclusion, there is still good evidence for a role of dietary calcium intake in human body-weight regulation, but future studies should concentrate on how calcium-deficient states during weight loss can amplify hunger and impair compliance with a diet aiming at weight control or loss. Furthermore, we still need a better mechanistic approach to elucidate both the way or ways in which dairy calcium increases fecal fat excretion and its quantitative importance for weight control.

The author is an expert member of Global Dairy Platform and of the Arla Nutrition Advisory Board, and his department receives research funding from several companies that produce dairy products and calcium supplements.

REFERENCES