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Metabolism

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Editorial

Dietary calcium and body weight: what's the "skinny"?

There has been growing interest in mechanisms underlying the observation that high dietary calcium intake may attenuate weight gain. Both animal and human studies have explored this association [1]. However, the metabolic alterations that explain this phenomenon remain unclear, as are the molecular mechanisms that may be at play. This month's article by Zhang et al provides new insights into this question.

Dietary calcium has been suggested to play an important role in the regulation of energy metabolism. In one study whose primary aim was to explore the relation between blood pressure and nutrient intake, a significant inverse correlation was noted between calcium intake and body weight [3]. Two other studies have shown inverse correlations between circulating ionized Ca^{2+} and body mass index in obese individuals [4,5]. Other studies found that high-calcium diets are associated with decreased lipid accretion and weight gain during periods of excessive dietary consumption, including evidence of increased lipolysis, which thereby may accelerate weight loss [1]. However, the underlying mechanisms remain largely unclear. Calcium may attenuate the direct effects of vitamin D on lipid metabolism within adipocytes, which may explain in part the effects of dietary calcium in countering obesity [6,7]. Other effects of calcium include alterations in metabolic efficiency, increased core temperature, and expression of the adipocyte uncoupling protein 2 [6]. In a 2-year prospective study of 54 normal-weight women who participated in an exercise intervention, the ratio of dietary calcium to energy was a significant negative predictor of changes in both body weight and body fat [8]. In addition, increased total calcium and dairy calcium intakes in these subjects predicted fat mass reductions independent of caloric intake for women consuming a lower-energy diet (ie, less than a mean of 1876 kcal/d). In children, a significant inverse correlation has also been reported between dietary calcium and body fat in a 5-year longitudinal study of preschool children [9]. In a final study of 780 women who participated in 5 clinical trials, significant negative associations were found between calcium intake and body weight for subjects during the third, fifth, and eighth decades of life [10]. Overall, the investigators conclude that a calcium intake of 1000 mg/d is associated with an 8-kg reduction in body weight.

The role of vitamin D in relation to this topic is important to consider. There has been interest in whether 1,25-dihydroxyvitamin D ($1,25[OH]_2D$) stimulates calcium influx within adipocytes, leading to the eventual stimulation of lipogenesis, inhibition of lipolysis, and expanded adipocyte triglyceride stores [1]. If this hypothesis were true, suppressing $1,25(OH)_2D$ concentrations through provision of dietary calcium would be assumed to inhibit adiposity and promote weight loss. What data support a relationship between $1,25(OH)_2D$ and obesity? First, vitamin D receptor gene polymorphisms (eg, D12S85) may influence insulin secretion and an individual's susceptibility to diabetes [11,12]. This polymorphism is also associated with susceptibility to obesity in patients with early-onset type 2 diabetes mellitus [13], and circulating $1,25(OH)_2D$ levels have also been reported to be elevated in obese individuals [14-16]. 1,25-Dihydroxyvitamin D–induced hyperinsulinemia may be a primary contributor to obesity, as $1,25(OH)_2D$ appears to serve as an insulin secretogogue [17-21]. Vitamin D may also function to counter resistance to both leptin and insulin that is seen in an obese individual. Although vitamin D deficiency is known to cause hyperparathyroidism, one study found the association to be present primarily in individuals with elevated leptin levels. These data suggest that leptin may be a critical important modifier of this effect, consistent with 25-OH-vitamin D–mediated inhibition of leptin [22]. Another study supported the role of vitamin D in weight management, as vitamin D3 and retinoic acid powerfully inhibited in vitro leptin secretion by human adipose tissue [23]. Leptin is well known to be a key regulator of metabolic, neuroendocrine, and immune function in humans [24,25]. Leptin's response to both calcium and vitamin D supplementation, especially in the context of obesity and weight loss, is interesting to consider.

In the article by Zhang et al [2] in this month's issue of *Metabolism*, the authors used a diet-induced obese rat model produced by feeding the rodents a high-fat diet. The study examined the expression and functional role of the signaling protein, S100A16, in the obese rats fed a diet high in both fat and calcium. Forty animals were randomly divided into 4 groups by diet, each provided for 8 weeks: normal diet; high fat, normal calcium; high fat, high calcium; and high fat, low calcium. Body weight and visceral fat were significantly attenuated in those rodents receiving the high-fat, high-calcium diet. That group of rodents also exhibited decreased serum triglyceride and total cholesterol concentrations. In addition, expression of S100A16 was significantly decreased in the high-fat, high-calcium group. Elevation of intracellular calcium via calcium ionophores led to exclusion of nuclear S100A16. In parallel experiments, overexpression of S100A16 in cultured 3T3-L1 preadipocytes enhanced adipogenesis, but a significant reduction in Akt phosphorylation was also

detected. Thus, in the 3T3-L1 adipocytes, insulin-stimulated signaling was negatively influenced by increased expression of S100A16. Taken together, these results suggest that a high-calcium diet may lead to the nuclear exclusion of S100A16 that ultimately results in inhibition of adipogenesis and enhanced insulin sensitivity. However, some questions regarding the mechanisms that mediated these findings still remain.

What is known about S100 proteins? These are small acidic proteins (10-13 kd in size) that possess a distinctive homo- or heterodimeric structure and 2 highly conserved calcium-binding domains. Because of their elevated expression in tumor tissue, S100 proteins are considered to be cancer biomarkers. However, altered expression of S100 proteins has been associated with a variety of diseases in addition to cancer, including psoriasis, melanoma, and neurodegenerative diseases, among others [26-28]. S100A16 is a novel member of the S100 family, with ubiquitous expression, but of unclear significance as to its physiological function within specific tissues [29,30]. Of relevance to this study, S100A16 is highly expressed in adipocytes. There is also some evidence that S100A16 interacts in immunoprecipitation assays with p53 [31], a tumor suppressor protein known to be a negative regulator of adipogenesis but a positive regulator of insulin sensitivity [32-34]. Therefore, whether increased calcium intake results in decreased interaction of S100A16 with p53 is speculated in this article and is an intriguing possibility and remains to be directly tested in future studies.

Both strengths and limitations of the study by Zhang et al [2] need to be considered. First, the authors formulate hypotheses on a subject of high interest that spans many fields and disciplines. Both basic scientists and clinical investigators are keenly interested in whether calcium intake is involved in the regulation of body weight. The animal model they developed is novel, and the experiments were rigorously designed with meticulous attention to multiple end points. Regarding limitations, the number of rats studied was small, limiting the statistical power with which conclusions could be drawn. Independent studies are needed to see if the current results can be replicated. As with any study of rodents, findings that were observed remain to be ultimately translated to human physiology. It can also be difficult in studies of rodents to determine whether the doses of nutrients (such as calcium and fat) studied in the experimental model can later be feasibly provided as part of a human diet. It is also difficult to determine whether the doses of calcium that resulted in S100A16 alterations in rodents studied will result in changes in this protein in humans. Nonetheless, the results are thought-provoking and hopefully will stimulate additional work in this area, one of particular importance given the rising incidence of obesity, insulin resistance, and the metabolic syndrome across the age spectrum.

Outside of the weight and obesity field, the topic of calcium intake and, in particular, calcium supplementation has become an area of intense controversy. Calcium is needed, in combination with vitamin D, for normal skeletal growth and repair; it is essential for normal bone turnover and remodeling [35,36]. A deficiency of calcium can lead to rickets and other metabolic bone disorders, whereas excessive consumption can lead to hypercalcemia, hypercalciuria, and, ultimately, renal stones and nephrocalcinosis. There has been recent concern that calcium supplementation may increase the risk for myocardial infarction, a topic that has spurred fierce debate. The issue under discussion is the fact that calcium may, theoretically, be harmful to blood vessels in excessive doses because it may complex with phosphorus on the endothelial surface to induce vascular calcification. In a study that has received much recent press, Bolland et al [37] suggested that an increased risk of cardiovascular events occurred in the calcium- vs placebo-supplemented adults. Their Kaplan-Meier survival curves suggested greater negative effects of calcium supplementation on cardiovascular outcomes that became more substantial with longer duration of follow-up. However, others, including a group from Western Australia, have questioned the validity of these findings. They conducted a prospective, placebo-controlled trial of 1460 women 75 years and older who were receiving calcium carbonate supplementation [38,39]. There was no risk of increased cardiovascular risk at 5 years among the outcomes studied. Opposing views related to this issue are now hotly debated, the undercurrent of the arguments being whether one would trade lower body weight for an increased risk of myocardial ischemia or other cardiovascular event! More clinical studies are needed, especially longitudinal cohort studies or trials that assess health outcomes in supplemented vs nonsupplemented individuals.

Although calcium intake is often considered in the context of bone health and osteoporosis prevention, this study suggests that dietary calcium is also of importance in the regulation of energy metabolism. These results suggest that high-calcium diets lead to inhibition of adipogenesis and enhanced insulin sensitivity via a signaling mechanism mediated by S100A16. This is an intriguing finding that will undoubtedly spur further research. At a time when the obesity epidemic is growing, dietary manipulation such as an increase in calcium intake represents a simple intervention that may result in substantial rewards on a public health level. Therefore, it will be important to continue to pursue “the skinny” on the link between calcium intake and weight control.

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0026-0495/$ - see front matter

doi:10.1016/j.metabol.2011.11.007

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