

## Calcium and obesity: effect size and clinical relevance

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The connection between calcium intake and body weight was first described by McCarron et al.,<sup>1</sup> who found an inverse relationship between these two variables in the National Health and Nutrition Examination Survey (NHANES) data. This observation was largely ignored for the next 16 years, until Zemel et al.<sup>2</sup> described the weight-loss effect of calcium supplementation in a hypertension trial and suggested a cell biologic basis for the action of calcium in adipocytes. Since that time, there have been well over 100 reports of both experimental and observational studies evaluating the role of calcium intake in energy balance and body composition in humans. As summarized in 2009 in this journal,<sup>3</sup> most of these studies found that increased calcium intake augmented the weight loss of energy-restricted diets, protected lean body mass, and reduced age-related weight gain, or that it had null effect. A very few reported negative findings (i.e., high calcium intakes were associated with weight gain), but the preponderance of the evidence tilted clearly toward the side of calcium intake favoring weight loss.

In the present issue of this journal, Onakpoya et al.<sup>4</sup> present yet another meta-analysis of this topic, with the results also favoring calcium. They report a highly significant, positive effect of calcium supplementation on total body weight loss and a somewhat larger effect on fat loss (suggesting some protection of lean tissue mass, which is a frequent casualty of energy-restricted weight-loss regimens). However, the authors seem concerned to characterize the effect as “small” and of “uncertain clinical relevance.” Many other authors writing on this topic have also waffled, characterizing the issue of calcium and weight as “controversial.” (The term “confused” might be better.) There is actually very little that is controversial about the facts. Where there is conflict, it is between the very different expectations that investigators, the general public, and nutritional policy bodies bring to the data. This most recent meta-analysis affords an opportunity to clarify some of the confusion surrounding this issue.

Onakpoya et al.<sup>4</sup> report a mean weight-loss difference of 0.74 kg in trials, most of which were of 6 months’

duration, for an annualized rate of loss of about 1.5 kg. To a woman weighing 140 kg and hoping to lose 70 kg, that rate of loss would, indeed, have very limited interest; however, for a population confronting secular weight gain (e.g., otherwise healthy women at mid-life), this same weight effect is huge. This contrast between individual responses and population-level effects of nutrients was clearly elucidated by Rose<sup>5</sup> in an insightful, if widely ignored, essay on precisely this seeming paradox.

The population-level effect of calcium intake on weight is shown clearly in a study by Davies et al.,<sup>6</sup> who described weight gain at mid-life amounting to 0.27 kg/year, continuing for at least 20 years. They further reported an inverse association between calcium intake and the rate of gain, with the best estimate of the intake associated with zero weight gain on the order of 1,500 mg/day,<sup>7</sup> an intake that would have been reached for most of the participants in the trials analyzed by Onakpoya et al.<sup>4</sup> Even if the 6-month data of Onakpoya et al.<sup>4</sup> reflected the best that could be realized at 1 year, that rate of loss is still larger than typical mid-life weight gain and could be enough to prevent such gain. This congruence between observational and experimental results is reassuring in its own right. And, more to the point, the magnitude of the effect, when viewed from the perspective of a population gaining weight over time, must be recognized as of high clinical relevance and interest.

In this context, it is useful to recall that secular weight gain typically follows from an energy balance of as little as +50 kcal/day; clearly, this is a very small difference, but one that, when extended over many years, nevertheless produces outspoken obesity. Even a moment’s reflection should suffice to convince one that an energy balance that small is extremely difficult to detect in clinical studies. It is to be expected, therefore, that counteracting that small positive energy balance (as with high calcium intakes) would be equally hard to detect. Thus, it is hardly surprising that there are many null (as contrasted with negative) trial reports for calcium and weight. In brief, mid-life

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weight gain is quantitatively small, and counteracting of that gain is also necessarily small, yet of high clinical relevance.

Apart from the issue of weight, we must ask ourselves the following question: Is it realistic, or even appropriate, to expect a large effect size for nutrients – that is, any nutrient and any effect? For the most part, the answer must be “no.” The early victories over beriberi and pellagra, which were seemingly large (at least in impact), were the low-hanging fruit in the nutrient orchard. Without those victories, nutrition as a science might never have been born, for a century ago the idea that *not* eating something might make one sick was utterly foreign to medicine. However, those early nutrient successes must be recognized as exceptions. For the most part, nutrient effects are, as just noted for calcium, small in size, even if large in cumulative impact. Moreover, they typically involve multiple body systems, each with a distinct, if small, effect. They thereby exert a broad range of effects, many of which can be clinically important. Nutrients, however, are not drugs, and they should not be thought of as drugs. Nor can they be appropriately tested or meta-analyzed as if they were drugs.<sup>8,9</sup>

Yet another instance of this same apparent discrepancy between effect size and importance is found in the matter of calcium intake and blood pressure control. Multiple meta-analyses have confirmed a blood-pressure-lowering effect of adequate calcium intake. As with weight, though, the average decrease is small (1–5 mmHg), and in one of the meta-analyses<sup>10</sup> the authors went so far as to write “. . . the effect is too small to support the use of calcium . . . for preventing or treating hypertension.” Such a statement is at best misguided, as population data show that each decrement of 1 mmHg can reduce the prevalence of hypertension by as much as 5% (or more).<sup>5,11</sup> Yet, in an individual patient with high blood pressure, a drop of just a few mmHg is indeed a small effect. The problem, as noted earlier, lies entirely in the expectations we bring to the issue.

So, what can responsibly be said about calcium and body weight (or, *mutatis mutandis*, calcium and blood pressure)? Simply this: Other things being equal, a generous dietary calcium intake 1) will reduce or eliminate the gain in weight that commonly occurs in mid-life (as one such effect); 2) should be a component of any weight-loss regimen, as it augments the weight loss of a caloric deficit while protecting lean body mass; 3) is not a substitute for control of an energy intake/output imbalance; and 4) is not a drug and is certainly not a magic bullet.

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