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# Evidence-based policy on dietary calcium and vitamin D

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The Report from a committee convened by the Institute of Medicine updating the dietary reference intakes for calcium and vitamin D for the US and Canada makes a positive contribution to our understanding of the role of dietary calcium and vitamin D in bone health (1). The systematic approach to the review of the evidence base is particularly welcome. While the committee does not substantially change recommended dietary intakes for calcium and modestly increases those for vitamin D, the Report's greatest significance lies in the qualitative conclusions it reaches and in its re-examination of target levels for serum 25-hydroxyvitamin D. The key messages are that current evidence does not support non-skeletal benefits for vitamin D or calcium, that most North Americans have adequate levels of both, and that higher intakes could have adverse health consequences. These conclusions are supported by 1,000 pages of evidence, mostly drawn from two previous systematic reviews (2,3), which form a valuable reference source for people working in this area, though they are not completely up to date or comprehensive. For example, the systematic reviews did not search important, relevant databases such as Embase, and sought English language publications only. Some key randomized trials and systematic reviews in the area were not included. The Report undervalues recent systematic reviews other than those it commissioned. It makes very little reference to recently published individual patient meta-analyses (4,5) which have clinical and statistical advantages over trial level meta-analyses (6).

A recurrent theme throughout the Report is the limitations of the evidence base which underpins these recommendations. Those for calcium intake are substantially based on balance studies. In adults, in particular, it is bone balance, not calcium balance, that is critical, and the inability of the calcium balance technique to assess bone

balance has led to it being replaced by measurements of bone mineral density (BMD) in most studies in adults. While it is possible to achieve positive calcium balances with high calcium intakes, sustained increases in bone mineral density from calcium supplementation have not been demonstrable (7). The precision of the recommended average calcium requirements belies the imprecision of the balance techniques on which they are based. In the Report, postmenopausal women are said to require 200 mg/day more calcium, yet there is no evidence that an increment of this magnitude has any effect on BMD, let alone fractures. The fundamental effects of menopause on the skeleton are mediated by the fall in estrogen levels (8), and can only really be mitigated by replacement of estrogen or the use of pharmaceuticals of comparable antiresorptive potency, such as bisphosphonates. Calcium supplementation, even in large doses, is only a comparatively weak resorption inhibitor. This is reflected by the small effect of calcium supplementation on total fractures (9). Unfortunately, the Report overlooks the evidence that calcium supplement monotherapy actually appears to increase hip fracture risk (10,11), and to consider the impact of this on the balance of risk-benefit.

The appropriateness of having dietary allowances for vitamin D is open to question. The Report states that vitamin D is an essential nutrient, which is an error created by the misnaming of this compound. Most of the world's population derives very little of their vitamin D requirement from the diet, so it is more accurately regarded as a pro-hormone synthesized in the skin. Its serum levels reflect factors such as cutaneous ultraviolet light exposure, skin color, extent of skin exposed, age, obesity and exercise, as well as dietary influences. Understanding these factors leads to an understanding of who is at risk of vitamin D deficiency, and of appropriate strategies

for preventing and treating deficiency. The statement in the Report that 'vitamin D requirements could not address the level of sunlight exposure because public health concerns about skin cancer preclude this possibility' is surprising. Sunlight exposure is a normal part of most people's life and the implication that it should be universally avoided is without an evidence base. Other groups have quantified the extent of sunlight exposure which is necessary to maintain normal vitamin D status and have provided a practical recommendation as to how this can be achieved while minimizing the risk of skin cancer (12). Promulgation of such recommendations is more likely to produce optimal outcomes for both skin and bone health than an implied ban on venturing outdoors. The inappropriateness of ignoring sunlight as a vitamin D source is reflected in the fact that a minority of North Americans achieve the vitamin D intakes recommend by the committee but the majority have satisfactory serum levels of 25-hydroxyvitamin D.

The committee provides a valuable re-analysis of how vitamin D deficiency should be defined. They begin by stating that '25-hydroxyvitamin D cannot be considered a validated health outcome surrogate', a useful reminder of our limited understanding. A serum 25-hydroxyvitamin D of 50 nmol/L is described as covering the needs of 97.5% of the population, the lower end of the requirement range is set at 30 nmol/L, and 40 nmol/L represents the median population requirement, and was used as the basis for calculating the Estimated Average Requirement. The seasonal fluctuation in 25-hydroxyvitamin D of 20-30 nmol/L and the imprecision in its measurement (~10%) (13) need to be considered when implementing these guidelines. The higher level of 75nmol/L is not supported by the committee. There has been a progressive upward redefinition of cut-offs for 25-hydroxyvitamin D in recent years, which has been

substantially based on observational data. This has produced an epidemic of apparent vitamin D deficiency, leading to widespread use of vitamin D supplements in populations in whom benefits have yet to be demonstrated by randomized controlled trials. The present report provides a timely reminder of the dangers of developing public health practice in this way, and contrasts with a less critical use of the evidence base by other bodies addressing this question (14). The message that more is not necessarily better is an important product of this Report. The lack of evidence for the non-skeletal benefits from vitamin D supplementation is also an important message. Again, the suggestion that these effects might exist is mostly based on association studies, but the critical dependence of 25-hydroxyvitamin D levels on factors such as sunlight exposure, exercise and obesity, means that all association studies are potentially confounded. Such studies provide a useful basis for hypothesis generation, but not for public health policy.

In considering the safe upper limits for calcium intake, the Committee has based its conclusions on the risk of development of renal calculi, not really confronting the fact that the effects of dietary calcium and supplemental calcium on this endpoint appear to be different (15). Separate recommendations should be made for these two forms of calcium intake. They also downplay the probable cardiovascular risk associated with calcium supplements, possibly because these data have only been published very recently. They provide false reassurance by stating that the Bolland individual patient data meta-analysis of the effects of calcium supplementation without vitamin D (4) is contradicted by the trial level meta-analysis of Wang (16), whereas the Bolland analysis included all three trials in the Wang paper along with data from a further eight trials that Wang did not have access to. The Wang analysis found a

relative risk of cardiovascular events of 1.14 (0.93 – 1.41) which is quite consistent with the Bolland results. The Wang results are not significant because that analysis was underpowered. This issue is critically important, because if the cardiovascular adverse effects of calcium supplements are accepted, then the recommended calcium intakes will need to be achieved by diet alone, which is challenging. This will bring a renewed focus back on the strength of the evidence for reference intakes in this report.

In conclusion, the present Report is a welcome recall to evidence-based practice in nutrition. Wherever possible, dietary interventions need to be based on randomized trials just as other interventions are. Any bioactive entity can have unanticipated, off-target effects, so safety needs to be assessed as it would be for a pharmaceutical, particularly if supplements are used rather than sunlight or diet. Food constituents, such as calcium, may not act in the same way when re-packaged as a concentrated supplement. Finally, we should re-think the appropriateness of having dietary reference intakes for a compound like vitamin D which is not primarily derived from the diet. Perhaps the Food and Nutrition Board should share this responsibility for calciferol with another appropriate authority.

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