Vitamin D — Baseline Status and Effective Dose

Robert P. Heaney, M.D.

There has been more ink spilled over the efficacy of vitamin D than over that of most nutrients, with the possible exception of sodium. Why is this? Dozens of randomized, controlled trials have been conducted — some large, and many small. Unfortunately, their results have been inconsistent — some positive, some null, and the odd one or two actually negative. Even the many available meta-analyses on the topic have yielded inconsistent results. If vitamin D is actually efficacious, why is there this inconsistency?

In this issue of the *Journal*, in yet another meta-analysis, Bischoff-Ferrari et al.[1] suggest several explanations, including differences in study inclusion criteria and in the handling of adherence to the trial supplement. An even more salient reason is failure to consider the dose–response relation that vitamin D shares with most nutrients. Figure 1 shows that in persons whose baseline values differ, an identical nutrient intake may or may not produce a measurable response. Unfortunately, most of the randomized, controlled trials of vitamin D that have been published to date have paid little attention to baseline status. Among the 31,022 patients whose results were analyzed by Bischoff-Ferrari et al., data on baseline concentrations of 25-hydroxyvitamin D were available for only 4383 patients (barely 14%). Instead, the studies focused almost exclusively on the assigned dose.

Figure 1 makes it clear that giving additional amounts of a nutrient to persons who already have enough, or not giving enough to push a person with a deficiency up onto the ascending limb of the response curve, is likely to produce a null response. In this regard, as in several other respects, nutrients are unlike drugs.[2] Once an adequate concentration has been achieved, additional intake has no effect. This truism is little more than a restatement of a long-standing skepticism among clinicians about the purported benefits of many nutrient supplements[3] and is the explicit basis for the recommendations of the Institute of Medicine.[4]

Despite the consensus that more is not better, we have continued to conduct trials (and include them in meta-analyses) without regard to ensuring the presence of two key features: baseline status and dose adequacy. For example, two large, randomized, controlled trials[5,6] tested the effect of supplemental calcium on the risks of preeclampsia or fracture in patients whose baseline calcium intakes were already at the recommended levels for adequacy. Both trials had null outcomes. But both failed to address the underlying hypothesis that low calcium intake increased the risk of preeclampsia or fracture because neither trial included a group with low calcium intake. Nevertheless, both trials were included in the systematic review[7] used by the Institute of Medicine in formulating its intake recommendations for calcium.[4] Because of their relatively large samples, both trials heavily weighted the aggregate effect toward the null hypothesis in the corresponding meta-analysis.

The second of the two key considerations, adequacy of dose, was specifically addressed by Bischoff-Ferrari et al., who used individual adherence data to modify the assigned dose. They found that fracture risk was reduced only among persons who were assigned to receive doses of 800 IU per day or higher — a finding that would be more persuasive if it were accompanied by data on the baseline concentration and induced change in the level of 25-hydroxyvitamin D, but very few of the included studies provided this information. Nevertheless, such an intake is consistent with the guidelines for adults that have been issued by the Endocrine Society (1500 to 2000 IU per day).[8]

The question of how much vitamin D is enough is likely to remain muddled as long as meta-analyses focus on trial methodology rather than on biology. For example, the trial by Sanders et al.,[9] which used a single yearly dose (500,000 IU) and was included in the meta-analysis by Bischoff-Ferrari et al., was methodologically sound. Biologically, however, that trial was seriously flawed, with an intertreatment interval that was 12 times as long as the half-life of the agent in the body and a dose that almost certainly induced transient vitamin D intoxication in the 2 to 3 weeks after its administration. If there is a parallel between nutrient repletion and thyroid-replacement therapy, which are both daily matters, then this *Stosstherapie* (i.e., massive

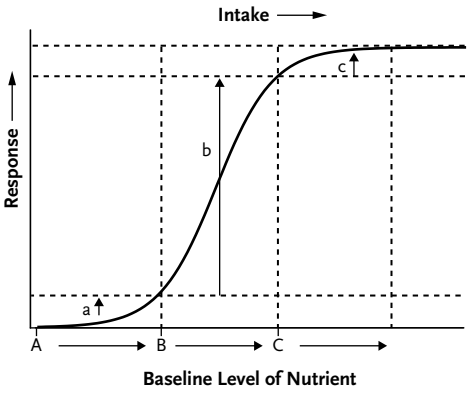

Figure 1. Intake–Response Curve for a Typical Nutrient.
The curve shows the response expected (a, b, or c) for the same intake of a nutrient at three different baseline levels (A, B, or C). For the same intake increment, a person with a baseline level of "A" has the response designated "a," for baseline level "B", the response is "b", and so on.

single doses of the vitamin) is not the way to evaluate vitamin D efficacy.

Given the congruence of the findings of this latest meta-analysis with the guidelines from the Endocrine Society, it would appear to be prudent, and probably helpful as well, to ensure an intake at the upper end of the range at which Bischoff-Ferrari et al. found a reduction in fracture risk.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

From the Osteoporosis Research Center, Creighton University Medical Center, Omaha, NE.

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