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Editorial

Vitamin D: How Much Do We Need, and How Much is Too Much?

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The bone-related nutrient that has attracted the most attention in recent years – and has aroused the most controversy – is calcium. Comparatively much less attention has been paid to vitamin D. As an example, when the Panel on Calcium and Related Nutrients of the Food and Nutrition Board (NAS) released its dietary reference intakes in 1997 [1], there were substantial questions raised about its relatively modest calcium recommendations. But almost totally ignored was the recommendation to triple the vitamin D intake of the elderly, arguably the largest increase in any intake recommendation by the Food and Nutrition Board in its entire history.

Recent issues of this journal have seen articles reviewing what is known about vitamin D requirements in the elderly [2] and describing assay-specific differences in measurement of serum 25-hydroxyvitamin D (25(OH)D) concentrations [3]. Vieth, in this issue [4], comments on both articles, asserting a consensus that the lower limit of normal 25(OH)D concentrations exceeds 100 nmol/l. Lips [5], in his reply, considers that no such consensus exists, and McKenna [6], in his, cautions against too aggressive supplementation. Whether or not a consensus exists, the questions for which the field needs answers can be listed briefly as follows: (1) What is the appropriate functional indicator of vitamin D status? (2) By what criterion are we to judge at what level that indicator reflects vitamin D sufficiency? (3) How much vitamin D must an individual synthesize and/or ingest to achieve the desired level? (4) Does the requirement change with age? (5) What is a safe upper intake limit? (6) What should be the approach to this issue by clinicians responsible for the care of elderly individuals?

The Panel on Calcium and Related Nutrients [1] attempted answers to most of these questions. However, its work is now 4–5 years old, and the field has advanced considerably in the interval. Hence it is worth evaluating and, where necessary, modifying their conclusions. Indeed, the dialog that constitutes the current correspondence [4–6] reflects just such an effort. What can be distilled from the agreements and disagreements of these leaders in this important field?

First, the functional indicator. The Panel on Calcium and Related Nutrients [1] quickly reached consensus that serum 25(OH)D was the correct functional indicator of vitamin D status. Essentially all papers recently published, and certainly those occasioning this correspondence [2,3], presume the aptness of that choice. Hence, on this point at least, there is consensus. (Notably, that was not the case as recently as 5–10 years ago.)

Second, the normal range of the indicator and the criterion by which it should be defined. Here, as Lips notes [5], there is no consensus, however much Vieth may be convinced that the data support one [4,7]. Most investigators have designated the lower limit of normal as the 25(OH)D concentration at which serum parathyroid hormone (PTH) concentration is minimized. Results range from ~80 to 120 nmol/l in various reports. Other criteria have occasionally been employed [8], and in general such findings are consistent with those based on PTH. The logic implicit in this approach is that 25(OH)D levels contribute to calcium absorption, either directly or by limiting efficiency of synthesis or activity of 1,25-dihydroxyvitamin D ($1,25(OH)_2D$). There is still considerable uncertainty about several aspects of this line of reasoning, and this is an area that requires much further research.

Parfitt [9] pointed out that mild to moderate degrees of vitamin D insufficiency produce not rickets or osteomalacia, but osteoporosis, as a result of calcium malabsorption. Thus the range of 25(OH)D values termed 'insufficiency', i.e., values between the normal range and the frankly 'deficient' (i.e., associated with osteomalacia), carries an increased risk of osteoporotic (and possibly other) morbidity. Defining at precisely

what 25(OH)D levels that risk is minimal effectively determines the lower limit of normal vitamin D status. For now, elevated serum PTH serves as a surrogate marker for insufficiency. Additionally, the distinction between deficiency and insufficiency may no longer be useful, particularly since the population burden of morbidity associated with insufficiency may well be substantially greater than that of classical vitamin D deficiency.

Finally, Vieth makes clear why the various assays in use today yield markedly different results. We cannot come to consensus on the right numbers for the requirement until we either use equivalent assays or adjust our values so as to correct for their systematic differences. He notes that much of the data used to estimate the requirement have been gathered for some other purpose, and that analytic discordances are, therefore, both understandable and excusable. But in defining the requirement it will be necessary to use assays that reflect the true serum 25(OH)D response to varying inputs of the parent vitamin.

Third, the amount of vitamin D needed to achieve given serum 25(OH)D concentrations. This is an important but still inadequately studied question. Whatever the ultimate consensus on optimal levels may be, it seems certain that most Northern European and North American adults have levels that are below even the most conservative of the current estimates. How much vitamin D must be taken or produced each day to achieve and sustain desired levels? The Food and Nutrition Board recommended 600 IU (15 μg)/day for older adults. Vieth has argued elsewhere [7] that the requirement is at least 800 IU (20 μg)/day and that it may be as high as 4000 IU (100 μg)/day.

Three corollaries of this question relate to (1) the curvilinearity of the 25(OH)D response to a given dose, (2) the role of body weight (and specifically fat mass), and (3) the matter of whether the dose required to *sustain* (as contrasted with *achieve)* a given serum level is greater than the corresponding dose for a lower level. Available evidence indicates that the increment in serum 25(OH)D produced by a given oral dose of vitamin D is greater at low basal 25(OH)D levels than at higher values. This is what one would expect, but the precise character of the relationship needs to be better defined. The relation of body fat mass to the dose response also needs clarification. There is evidence that has been interpreted to mean that obese subjects exhibit relative resistance to standard doses of vitamin D, inasmuch as their serum 25(OH)D levels do not rise as much as those of thinner individuals. A more likely explanation is the obvious difference in volumes of distribution, with vitamin D being dissolved in body fat. This phenomenon, too, still needs more precise characterization, particularly with respect to whether the fat mass only slows the serum 25(OH)D response to oral inputs, or whether the requirement needs to be individualized by body weight (or both). Finally, whether differing inputs are needed to sustain different serum levels is essentially unknown.

Fourth, age-related change in the requirement. This question has been hard to address because the relative contributions of orally ingested and dermally synthesized vitamin D are poorly characterized, and the latter is very difficult to measure. Certainly, as they age, the elderly typically get less and less of what they need from dermal synthesis, in part because of decreased solar exposure, and in part because of an age-related decline in efficiency of the photocatalytic conversion of 7-dehydrocholesterol to pre-vitamin D. These age effects would not in themselves alter the requirement, but Slovik et al. [10] several years ago showed decreased renal conversion of 25(OH)D to $1,25(OH)_2D$ in response to standard doses of PTH, a finding that would suggest an increase in the requirement. In any event, it seems clear that there is a greater and greater dependence on oral sources of vitamin D with advancing age.

Fifth, the safe upper limit. The Food and Nutrition Board (FNB) declared 2000 IU (50 μg)/day to be the safe upper limit for intake [1], but the data available to the Upper Limits Panel of the FNB were sparse and of marginal scientific quality, and it is likely that substantially higher chronic exposures would be without harmful effect. Vieth argues forcefully for raising this limit [4,7], suggesting that optimal management of osteoporosis may require not only more than the current DRI value, but more than even this so-called safe upper intake limit. At the same time, it is clear that vitamin D intoxication is a serious problem, and whether or not he is right, McKenna's caution about not overtreating with vitamin D nevertheless reflects a commonly held conservative position. Obviously, a great deal more carefully monitored, clinical experience with doses between 1000 and 10 000 IU/day will be required before this issue will become clear.

Finally, what is a clinician to do? When ordering and interpreting serum 25(OH)D concentration, the physician needs, in virtually all cases, to ignore the laboratory's published reference range. For the moment, one can suggest that optimal levels would be above 32 ng/ml (80 nmol/l). Note that this is a fairly conservative recommendation. Vieth maintains that even 80 nmol/l is too low.

But measurement of 25(OH)D is expensive, and cannot be justified routinely, let alone in every elderly person, especially since, as Thomas et al. reported [11], the majority of middle-aged and elderly will have predictably suboptimal values. As a consequence, routine supplementation is called for. A dose of 1000 IU (25 μg)/day is certainly safe. We have recommended that intake, in addition to food sources, to all the patients in Creighton's Osteoporosis Clinic for several years, and while we have no data on clinical efficacy (because we have no simultaneous control group), we have observed that this dose is usually sufficient to maintain serum 25(OH)D levels at or above the desired lower normal limit of 80 nmol/l.

A related question concerns sources. Vitamin D is generally not available on the vitamin counters of most pharmacies in the United States. We were able to find a health food supplier (Douglas Laboratories, Pittsburgh,

PA) that makes a 1000 IU tablet containing no other vitamins or minerals. We are told that other firms offer similar products, although some effort may be required to find them. Also, quality control is a concern when dealing with these less regulated sources. Unfortunately, the United States does not have good over-the-counter vitamin D sources in desirable dose ranges and formulations. Useful alternatives to a health food source might include use of calcium supplements containing vitamin D, or the more expensive, but very effective direct oral administration of 25(OH)D itself (Calderol), in a dose of 20 μg two or three times per week McKenna advises against resort to 'activated forms' of vitamin D, but it may be that he is referring mainly to 1/α-hydroxyvitamin D and to $1,25(OH)_2D$, for both of which avoidance of toxicity must be a significant concern. By contrast, toxicity is not a problem with 25(OH)D at the dose range indicated.

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