

## Lessons for nutritional science from vitamin D<sup>1,2</sup>

Robert P Heaney

The compound we call vitamin D can no longer properly be considered a vitamin, and for most mammals, it is not in any sense even a nutrient. Nevertheless, vitamin D resembles true vitamins inasmuch as humans—who are cut off from the critical solar ultraviolet wavelengths by reason of latitude, clothing, or shelter—depend on an exogenous source of the substance just as they do for the true essential nutrients. In any event, vitamin D is inextricably imbedded in nutritional science and the matter of discerning how much we need for health offers instructive general lessons for the setting of nutrient requirements.

Rickets and osteomalacia were recognized as being caused by vitamin D deficiency ≈75 y ago; their prevention and cure with fish liver oil constituted one of the early triumphs of nutritional science. The requirement for vitamin D has been pegged to these disorders ever since. Despite the explosion in understanding how vitamin D operates, vitamin D sufficiency continues, implicitly at least, to be equated with the absence of rickets or osteomalacia. Many developments have made it clear that that is no longer a tenable position. The shift away from this approach is reflected, for example, in the tripling of the vitamin D recommendation for the elderly in the most recent dietary reference intakes from the Food and Nutrition Board of the Institute of Medicine (1), arguably the largest increase in the history of dietary recommendations.

There is now a consensus that serum 25-hydroxyvitamin D [25(OH)D] concentration is the correct functional indicator. What is less certain is what the optimal concentration of 25(OH)D should be and how much we must produce or ingest to achieve it. In this issue of the *Journal*, Vieth (2) marshalls an impressive array of evidence relating to both questions. Vieth stresses that early humans would have produced far more vitamin D daily than the amount needed simply to prevent rickets or osteomalacia—production on the order of several thousands of IUs per day. And although this abundance has reassuring implications for safety, it also raises questions about the functional significance of this seeming surplus.

Parfitt (3), building on the expansion of knowledge in bone biology in the past 40 y, has characterized the disorder due to insufficient vitamin D as “hypovitaminosis D osteopathy” (HVO) (3). He divides HVO into 3 stages along a scale of increasing severity. In HVOi there is malabsorption of calcium accompanied by physiologic evidence of an attempt to compensate (eg, elevated parathyroid hormone production and high bone remodeling); the result is bone loss, ie, osteoporosis. In HVOii, bone mass is also low, calcium malabsorption continues, and bone remodeling is either high or drops back into the normal range; now, histolog-

ic examination of bone reveals subclinical, early osteomalacia. In HVOiii, clinical rickets or osteomalacia is present and bone remodeling is reduced or absent entirely (partly because of the dependence of bone resorption on 1,25-dihydroxyvitamin D [1,25(OH)<sub>2</sub>D] and partly because bony surfaces covered with unmineralized osteoid serve as barriers to osteoclastic erosion). The prevalence of each degree of HVO is unknown but environmental vitamin D availability seems sufficient to prevent HVOiii in most North Americans. Therefore, most vitamin D deficiency does not manifest itself as clinical rickets or osteomalacia.

As Vieth notes, total daily intake, production, or both, amounting to 2.5–5 μg (100–200 IU) and serum 25(OH)D concentrations >20–25 nmol/L, suffice to prevent HVOiii. But the mere absence of clinical rickets can hardly be considered an adequate definition either of health or of vitamin D sufficiency. This is particularly important in view of the worldwide epidemic of osteoporosis which, although a multifactorial disorder like hypertension and coronary artery disease, can nevertheless also be produced by milder degrees of vitamin D insufficiency (ie, HVOi and HVOii).

The key questions then are as follows: What serum 25(OH)D concentration is needed to prevent HVOi? How much vitamin D must we make (or ingest) each day to reach that concentration? Clearly, the laboratory reference ranges are of no help here. Vitamin D insufficiency is prevalent in higher latitudes (4); hence, population distributions, although undoubtedly typical, cannot be considered normative. Published lower reference values are in the range of 40–45 nmol/L, but Vieth argues for a lower limit of 100 nmol/L and there is a well-established body of evidence extending back over 20 y that has pointed to a value ≥80 nmol/L (5). Moreover, Dawson-Hughes et al (6) and Kinyamu et al (7) reported recently that the evidence of HVOi persists with serum 25(OH)D concentrations as high as 100–120 nmol/L. Not all studies support values that high and the reasons for discrepancies between them are not always clear [although analytic differences in measurement of serum 25(OH)D have been a factor]. Thus, careful studies are still needed to define the optimal 25(OH)D concentration. Nevertheless, it will almost certainly be higher than was previously thought. Vieth makes a point that should help us with the needed mental adjustment: individuals exposed

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<sup>1</sup>From Creighton University Medical Center, Omaha.


<sup>2</sup>Reprints not available. Address correspondence to RP Heaney, Creighton University Medical Center, 601 North 30th Street, Suite 4841, Omaha, NE 68131.

to the sun for much of the year in lower latitudes always have blood 25(OH)D concentrations values >100 nmol/L. So, if the true lower limit of the acceptable normal range is, in fact,  $\approx$ 100 nmol/L, it could hardly be considered "high."

The issue of how much vitamin D must be ingested to reach 100 or even 80 nmol/L will require even greater conceptual readjustment as well as careful studies specifically designed to answer the question. Part of the difficulty here lies in the fact that the response to orally administered vitamin D is nonlinear (8); the achieved increment in serum 25(OH)D per unit dose varies as some inverse function of the baseline 25(OH)D concentration. Vieth's estimate of the daily requirement from all sources is 100  $\mu$ g (4000 IU), an order of magnitude higher than the current dietary reference intakes. Whatever the value turns out to be, it seems inescapable that it will be substantially higher than the current values and possibly higher than nutritional policymakers may be prepared to accept. Nevertheless, the adequacy of even the newly elevated dietary reference intakes, still released only in draft form, has already been questioned (9).

The experience with vitamin D may offer several lessons for nutrition generally. Significant dysfunction occurs at exposures far short of those needed to evoke the index disease. It would be surprising if something similar were not to occur with other nutrients.

Far from being a "chronic condition" that may be helped by intake of a nutrient above the requirement, osteoporosis occurring as HVOi and HVOii is as truly a deficiency disease as is scurvy or beriberi. The fact that it takes 30 or more years to manifest itself makes it no less a deficiency condition than a disorder that develops in 30 d. It is easy to understand how long-period deficiency diseases could never have been recognized in the early days of nutritional science, but with modern methods and a better grasp of the relevant physiology, failing to recognize a slowly developing condition as a true deficiency state can no longer be justified.

Finally, better understanding of the prevailing availability of various nutrients during hominid evolution challenges the privileged position accorded to contemporary exposures. Primitive environmental availability of a nutrient does not ipso facto establish the requirement, but primitive exposures would have influenced the evolution of the relevant physiology and such concentrations should at least be considered presumptively acceptable. Rather than have all the burden fall on establishing their efficacy, one would think that the burden would be on establishing the safety and adequacy of the often much lower contemporary exposures. 

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