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OPINION

Toward a physiological referent for the vitamin D requirement

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Current approaches to setting nutrient intake recommendations are based in a disease-prevention paradigm. The disease to be prevented is typically the disorder classically associated with the nutrient concerned: scurvy for vitamin C, polyneuritis for thiamine, bone disease for vitamin D (D). And the method used is the randomized, controlled trial. While there is growing recognition that nutrients affect many systems, the disease-prevention approach continues, in most cases, to focus on one, or at most two, body systems. For D (cholecalciferol), that system is the skeleton [1].

In contrast, there is general recognition that most nutrients, particularly the micro-nutrients, function to sustain health basically at a molecular-biological level. Logically, the criteria for setting intake requirements should be based on the actual function of the nutrients concerned, not on diseases that they might arguably prevent. In other words, intake recommendations should be based in physiology.

A physiological approach

The particular criteria for a given nutrient would, of necessity, depend upon its specific function. Through its principal hydroxylated derivatives, D functions primarily as a part of the apparatus whereby cells access information stored in nuclear DNA. Four aspects of this role need to be understood: (i) while calcitriol is the principal active form of the vitamin, most of its production occurs intracellularly in the various tissues that are the targets for D action; (ii) serum 25-hydroxyvitamin D [25(OH)D] concentration limits the efficiency with which extra-renal cells can synthesize $1,25(OH)_2D$, the active derivative needed for unlocking the genome; (iii) genomic access is critically important for basic cell function, moment-by-moment, not just for cell replication; and (iv) the role of D is supportive rather than causative. This enabling role is illustrated in D's action in many body systems. For example, D is necessary for macrophage mobilization of defensins in response, e.g., to tuberculosis [2], but it does not by itself cause that response. Similarly, D is necessary for regulation of calcium absorption, but, without co-existing calcium deficiency, increasing D status does not itself increase calcium absorption efficiency (which is the principal reason why D has such a wide margin of safety). Another example is provided by D effects on osteoblast function. D is necessary for osteoblast production of RANK ligand, acting, as in the foregoing instances, by being a critical component of the complex that leads to expression of the corresponding gene [3]. In this way D can be said to promote bone resorption. But under other circumstances, such as severe Ca deficiency, D also is a cofactor in expression of a gene, the product of which slows matrix mineralization beneath the osteoblast [4]. The two effects, based in different genes, act in concert to decrease the severity of a hypocalcemic stress. But in neither case can D, itself, be said to be directly causal. Thus, without a biologically significant deficiency of calcium, raising D status will neither increase bone resorption nor impair mineralization of newly deposited bone.

In brief adequate D is a necessary, but not a sufficient, condition for myriad cell functions. As a result, low D status, reflected in low serum 25(OH)D concentrations, inescapably reduces the capacity of most tissues to carry out their normal functions. (This impairment can sometimes be

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as subtle as a decrease in functional reserve, highlighting the salience of using a homeostatic criterion to determine optimal nutrient intake or status [5]). The consequent, tissue-specific dysfunction is not immediately symptomatic, and is transformed into clinically evident disease only when it is severe and/or prolonged. Many years ago Szent-Gyorgi called attention to this nutrient deficiency in the gap between health and disease [6]. It is, today, a part of the explanation why a disease-avoidance approach to intake requirements yields lower values than does a physiological approach.

The challenge in setting an intake requirement based in physiology lies in identifying measurements that will reflect the extent to which cell and tissue activity is limited by nutrient status. Of the several indices that could be suggested for D, three seem particularly appropriate, i.e., the intake that: (i) does not require the organism to compensate for a prevailing intake; (ii) supports a critical physiological function such as lactation; and (iii) prevailed during the millennia when human physiology was being fine-tuned by natural selection to fit its environment.

Homeostatic compensation

Successful organisms depend upon a variety of mechanisms that allow compensation for inputs above or below optimal values. In physiology, this compensation maintains homeostasis. In nutrition, the issue is not compensation itself, but whether it is large, constant, and/or one-sided, or is, instead, minimal, intermittent, and bi-directional.

Perhaps the best attested function of D is the promotion of the body's regulation of intestinal calcium absorption. When D status is low, calcium absorption efficiency is low as well. The body reacts by increasing secretion of parathyroid hormone (PTH), which in turn increases calcium absorption. However, this response is not invariant, in part because some individuals have sufficiently high calcium intakes to make them less dependent on D status, and in part because subclinical magnesium deficiency impairs parathyroid response to decreased calcium absorption [7]. Nevertheless, other things being equal, a population with suboptimal D status will exhibit above average PTH concentrations, inversely correlated to D status. By contrast, populations with D concentrations above some threshold value will have lower PTH concentrations, which exhibit zero correlation with 25(OH)D. This latter point—zero correlation with PTH above a threshold value—is the critical feature, as it expresses the fact that, above the threshold, D-mediated calcium absorption meets body needs and hence no compensation (i.e., PTH) is required. And since D is enabling rather than causative, further increases in D status have no effect (which is why the correlation is zero and why the safety margin for D is so broad).

This relationship has been extensively documented [8–10]; however, it has not achieved acceptance as a criterion of adequacy of D status, in part because it is not a reliable indicator in individual patients and in part because it yields optimal D status values higher than produced by a disease-avoidance approach (and hence must be "wrong"). This rejection ignores that fact, noted above, that a physiology-based approach will inevitably produce a higher requirement than a disease-avoidance approach.

In any case, as just indicated, the slope of PTH concentration on 25(OH)D is unquestionably informative at a population level. The best estimates of the threshold value at which that slope becomes zero come from healthy population databases such as NHANES in the USA, in which, in a sample of 14,681 individuals, the 25(OH)D concentration at which there was no longer an inverse correlation with PTH was 100 nmol/L [10]. Unpublished observations in 2,311 healthy individuals from the author's own laboratory revealed a similar threshold (116.5 nmol/L). Clearly, therefore, the lower end of the D status range that does not require the body to compensate for prevailing D inputs is a 25(OH)D concentration of about 100–116 nmol/L.

Support of lactation

Lactation involves production of milk of both a quantity and quality sufficient to meet the needs of the infant during the first year of life. One of those key nutrients is D. It had formerly been said that human milk did not contain much D, which was accurate, at least as measured in modern times. This is because the lactating mothers had such low D status themselves that they had little or none to give their infants [11]. Modern medicine compensates for that deficit by supplementation, generally directed at the infant. However, low D content of human milk cannot have been the case under ancestral conditions. Absence of D from milk would have jeopardized any number of systems in the growing infant, not least being impaired calcium absorption, resulting in rickets with well understood downstream consequences for reproduction.

Hollis and Wagner [11] demonstrated that 25(OH)D is not secreted into milk in sufficient quantity to be useful to the infant; whereas native D (cholecalciferol) readily enters the milk. However, for that to happen, cholecalciferol must be present in maternal blood. The concentration of cholecalciferol achieved in breast milk ranges from 28 to 44 % the concentration in maternal serum [11, 12]. Current estimates of the infant D requirement during the first year of life are in the range of 5–10 μg/day. At peak milk volume (~0.75 L/day), milk cholecalciferol concentration would have to be 6.7–13.4 ng/mL

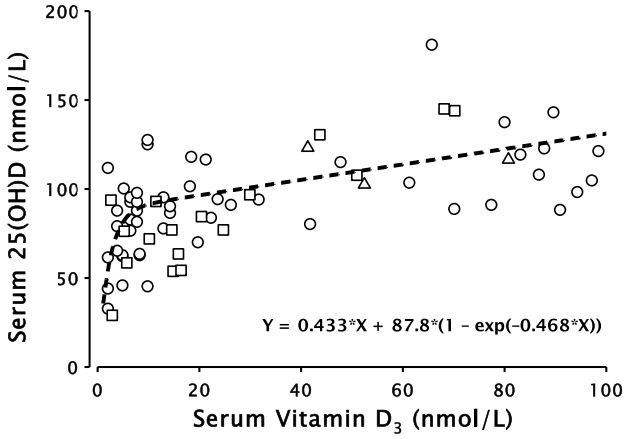

Fig. 1 Plot of the relationship of serum concentrations of 25(OH)D and cholecalciferol, redrawn from Heaney et al. [13], together with the equation for the best-fit curve through the data points. Note particularly: (i) the biphasic nature of the data, with a very steep rise of serum 25(OH)D at low cholecalciferol values (reflecting near quantitative hepatic 25-hydroxylation), and (ii) the fact that serum cholecalciferol concentration itself does not begin to rise appreciably until serum 25(OH)D reaches approximately 90 nmol/L. (Copyright, Robert P. Heaney, 2014, used with permission.)

(17.4–34.5 nmol/L) in order to meet the infant's needs, and, accordingly, maternal serum cholecalciferol concentrations must be about two to four times those values.

Serum cholecalciferol is a research measure and is almost never available clinically. While cholecalciferol unquestionably enters the bloodstream (either from the skin or the gut), it is rapidly 25-hydroxylated, and its serum concentration does not rise appreciably until the 25-hydroxylation reaction in the liver is approximately saturated. Figure 1 plots the relationship between serum 25(OH)D and cholecalciferol concentrations under continuous daily dosing and shows the 25(OH)D values that are achieved when administered cholecalciferol begins to accumulate in serum after 25-hydroxylase saturation has occurred [13]. Briefly, maternal cholecalciferol concentration does not reach levels needed for human milk until maternal needs for D have themselves been approximately met. As the figure shows, the maternal 25(OH)D concentrations that ensure adequate milk content of cholecalciferol are in the range of 100–150 nmol/L.

Ancestral values

Human physiology developed over a thousand millennia in East and Southeast Africa, an environment that would have provided abundant sun exposure, year-round. Arguably, our physiology is adapted to a D status characteristic of such equatorial regions. Incomplete adaptation, requiring continuous compensation, would have been metabolically costly, and natural selection would have worked to minimize that cost. There is no fossil evidence that could illuminate that ancestral status. However, serum 25(OH)D in contemporary Africans who follow ancestral lifestyles (Masai and Hadza) averages 115 nmol/L [14]. Like ancestral humans, these contemporary Africans have pigmented, glabrous skin, and there is no reason to believe that their 25(OH)D concentrations are appreciably different from ancestral values. Coincidentally, these findings attest to the safety of a vitamin D status centered around 25(OH)D concentrations of 115 nmol/L. Manifestly, also, this level is automatically adequate to support lactation.

Comment

There is a quite remarkable degree of convergence in the estimates for optimal D status provided by these approaches, i.e., 100–130 nmol/L. These serum values require total, all-source inputs ranging from 100 to 150 μg (4,000–6,000 IU)/day [12]. The criteria of minimizing need for compensation and of matching ancestral values might be considered discretionary, i.e., a governmental health authority could arguably choose to state that such levels, while perhaps desirable, were not required for everyone. Such a decision would be harder to defend for the human milk criterion. Any nutritional policy agency that tells an adult woman that a 25(OH)D concentration of 50 nmol/L is adequate for her health [1] must also tell her that it is not adequate if her milk is to ensure her infant's health.

Clinical application

An individual with a serum 25(OH)D value of 50 nmol/L should receive sufficient D to reach a 25(OH)D value of at least 100 nmol/L. There is very wide variation in individual response to D supplementation [12]; nevertheless, the mean response is an increase in 25(OH)D of about 1 nmol/L for each additional 1 μg of D oral intake [12]. Thus, the foregoing individual would need a daily oral dose of ≥50 μg (≥2,000 IU). High-dose, intermittent therapy e.g., 1,00,000 IU orally once every 1–3 months, is not to be recommended, as it does not maintain steady serum concentrations of either D or 25(OH)D during the inter-dose interval. Such constancy is crucial for lactation and may be important for other D-related functions as well [11, 12].

Conclusion

In brief, a 25(OH)D value between 100 and 130 nmol/L is the status best suited for fully normal human physiology.

Such a level is safe [15] and automatically ensures the skeletal, immune, developmental, anti-carcinogenic, cardiovascular, lactational, and myriad other benefits that flow from optimizing cell-level physiology.

Conflict of interest None.

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