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The Vitamin D requirement in health and disease

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Abstract

Advances in Vitamin D nutritional physiology since publication of the DRIs in 1997 are briefly summarized. Available data indicate that (1) Vitamin D's canonical function, optimizing intestinal calcium absorption, is fully expressed at serum 25-hydroxyvitamin D (25OHD) concentration of ~80 nmol/L; (2) elevated parathyroid activity, typical of aging populations, is minimized at the same 25OHD value and (3) osteoporotic fractures are reduced when serum 25OHD is raised to near 80 nmol/L. Depending upon starting value, achieving 25OHD concentrations of 80 or higher may require a daily oral intake of 2200 IU (55 μg) or more in addition to prevailing cutaneous inputs. The tolerable upper intake level (TUIL), currently set at 2000 IU (50 μg)/day, is too low to permit optimization of Vitamin D status in the general population. Actual toxicity is not seen below serum 25OHD values of 250 nmol/L, a value that would be produced only at continuing oral intakes in excess of 10,000 IU (250 μg)/day.

Keywords: Vitamin D; 25-Hydroxyvitamin D; DRI; TUIL; Calcium absorption; Parathyroid hormone; Osteoporotic fractures; Bone mineral density

1. Introduction

Although not a true nutrient for most mammals, Vitamin D shares with the other vitamins the feature that it is a trace substance and must be produced or ingested in a certain quantity if various health outcomes are to be ensured. Also, as with the other vitamins, it was early recognized that a frank deficiency results in a specific disease syndrome (in this case rickets and/or osteomalacia). Intake recommendations for Vitamin D have classically been tied to the prevention of this bone disease. The virtual eradication of rickets over the past three-quarters of a century has rightly been viewed as evidence of the success of this stratagem.

In the past three decades much has been learned about how Vitamin D operates, first for its canonical function relating to facilitation of calcium and phosphorus absorption, and more recently for its important role as a mediator of the transcription of a large number of genes in most tissues of the body, important for such diverse processes as the immune response and cell cycle regulation in most or all epithelial tissues.

This new knowledge has in one sense made the determination of the requirement easier, inasmuch as it has provided better tools than simple absence of rickets by which to judge adequacy. However, these same advances have made setting the requirement more difficult, insofar as multiple health outcomes have now to be considered and ensured.

In its 1997 recommendations for calcium and related nutrients, the Food and Nutrition Board (FNB) of the Institute of Medicine defined serum 25-hydroxyvitamin D (25OHD) as the functional indicator for Vitamin D status [1], a determination that quickly achieved worldwide consensus. However, beyond estimating the levels that constituted the rachitic threshold, the FNB was not able to link any specific level of 25OHD to particular health or disease outcomes. For example, while acknowledging the long-recognized importance of Vitamin D for calcium absorption, the FNB could provide no data relating absorptive performance to variations in Vitamin D status. Finally, while also acknowledging the importance of cutaneous production of Vitamin D, sufficient information was not then available to permit a partition of input from endogenous and exogenous sources in typical individuals.

Much has been learned in thenoted th past 10 years that closes some of these knowledge gaps, thus permitting a better definition of the requirement. In this paper I review the available evidence relating serum 25OHD concentration to various physiological processes and pathological events. (It must be noted that most of this evidence relates to the canonical

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function of Vitamin D, i.e., the calcium economy and bone health. Whether levels adequate to optimize these functions are also adequate to ensure, for example, optimal cell cycle regulation, remains to be determined.) Also, I present such data as are available with respect to the steady-state oral intake of Vitamin D needed to elevate serum 25OHD by any selected amount. Finally, I attempt to address the problem of defining an *intake* requirement for a substance that is susceptible of fully adequate *endogenous* production, and in doing so, I argue that the current tolerable upper intake level (TUIL) is set so low as to impede substantial public health improvement in Vitamin D status.

2. Serum 25OHD and physiological function

It is well-established that serum parathyroid hormone (PTH) concentration varies inversely with absorbed calcium. A functional deficit of Vitamin D would, therefore, be expected to impair calcium absorptive efficiency, leading, other things being equal, to a rise in PTH production. The point along the serum 25OHD continuum at which PTH becomes constant is thus an indication of the point at which calcium absorption itself becomes constant. Calcium absorption testing is not widely available, but serum PTH is frequently measured and reported. Several investigators have provided data relating serum 25OHD to serum PTH [e.g., 2–8]. Essentially all such reports show an inverse relationship between the two variables, providing strong, but indirect evidence of a relationship between serum 25OHD and calcium absorption. Fig. 1 shows the data from one of the larger of those studies [2], splitting the subjects into two groups, those with 25OHD values above and below 80 nmol/L (32 ng/mL). As is evident from Fig. 1, at 25OHD levels above 80 nmol/L, there is no relationship between the two variables, while below that level, there is a highly significant, inverse relationship. Estimates of the inflection point for various other data sets vary from ∼50 nmol/L (20 ng/mL) [4] to ∼110 nmol/L (44 ng/mL) [8], but most investigators report figures close to

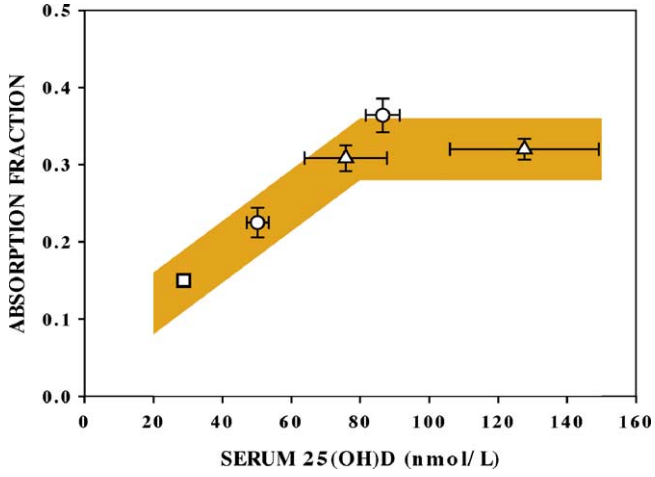

Fig. 2. Calcium absorption fraction plotted as a function of serum 25OHD concentration in three studies. The paired ◯ symbols represent the data of one study [11]; the paired △ symbols, a second [12], and the □ symbol is the estimated absorption for the subjects not treated with Vitamin D in the study of Bischoff et al. [13,14]. (Copyright Robert P. Heaney, 2003. Used with permission.)

80 nmol/L, and a recent, informal consensus of investigators active in the field settled on a value of 75 nmol/L (30 ng/mL) [9,10].

To the extent that the elevated PTH values at serum 25OHD values below ∼80 nmol/L reflect impaired absorption of dietary calcium, then one can conclude that serum 25OHD values below 80 nmol/L are suboptimal and that, therefore, the physiological normal range begins at ∼80 nmol/L.

However, as noted, serum PTH is only an indirect measure, less than optimally sensitive because many individuals with low Vitamin D status appear not to exhibit a perceptible PTH response [5]. A more salient approach would be direct assessment of absorptive efficiency at various serum 25OHD levels. Here, less evidence is available. Data from three studies [11–14], assembled in Fig. 2, show that, as expected, absorption efficiency does in fact rise as 25OHD

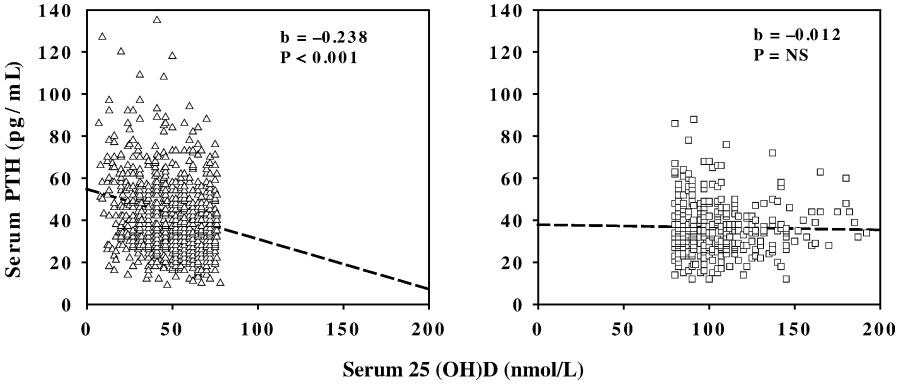

Fig. 1. Redrawing of the data of Chapuy et al. [2], derived from 1569 healthy adults living in 20 French cities. The data are split at a 25OHD value of 80 nmol/L. The left panel is for the values below 80 and the right panel for values above 80. For both panels, "*b*" is the slope of the linear regression equation. (Copyright, Robert P. Heaney, 2005. Used with permission.)

rises, and then plateaus at 25OHD levels above ~80 nmol/L, congruent with the PTH data. As just noted, the plateau region defines the range of physiological normal. Whether that plateau begins at 80 as both lines of evidence suggest, or somewhere above or below that figure, it remains important to define its lower limit as precisely as possible. Hence, more studies of absorptive efficiency as a function of serum 25OHD are needed.

Consistent with the finding of rising absorptive efficiency at 25OHD levels below 80 nmol/L is a report of a reduction in fracture risk across essentially the same range of 25OHD concentrations [15]. A 5-year, randomized, placebo-controlled, Vitamin D trial in the elderly in the UK, raised serum 25OHD from 53 to 74 nmol/L, and produced a 33% reduction in typical osteoporotic fractures, relative to placebo. Thus, both for calcium absorption and for fracture resistance, serum 25OHD concentrations in the range of 80 nmol/L are much more "healthy" than values in the range of 50 nmol/L, although both sets of values fall well within the usual laboratory reference ranges.

Whether 80 nmol/L is itself high enough is unclear. Bischoff et al. [16], in an analysis of the NHANES-III data, reported rising bone mineral density (BMD) values as a function of serum 25OHD up to levels well above 100 nmol/L.

The foregoing studies relate more or less directly to Vitamin D's canonical function. However, not all skeletal benefits of a nominally adequate Vitamin D status can be unambiguously attributed to its effects on the calcium economy. Bischoff et al. [13] in a controlled trial, showed that improving Vitamin D status rapidly and substantially reduced fall propensity, suggesting a neuromuscular effect of the nutrient. Similar effects have been reported in other studies [17], but not in all [18]. The data from these studies are not adequate to define a threshold for adequacy for this outcome variable, but analysis of NHANES-III data showed that lower extremity neuromuscular functional indices rose with serum 25OHD, continuing to improve at values well above 80 nmol/L [19].

In must be noted that both sets of NHANES data, being cross-sectional in nature, are susceptible of an alternative interpretation, i.e., healthier individuals exercise more and get outdoors more, thereby ensuring more bone mass, better muscle function and reflexes, and, incidentally, higher 25OHD levels. More controlled trials will be needed to establish a causal connection for a neuromuscular outcome.

Nevertheless, the fall-protective effect in the randomized, controlled trial of Bischoff et al. [13] was so striking that, if it can be confirmed, it could well explain some or all of fracture risk reduction found in the UK controlled trial [15]. In either event, whether Vitamin D is acting through its well understood effect on calcium absorption, or through a still poorly understood effect on neuromuscular function, the evidence indicates: (1) that recipients of supplemental Vitamin D in the UK trial experienced a significant health benefit; (2) that values within the reference range are associated with functional impairment (calcium malabsorption, falls and fractures) and (3) that this disease burden is reduced at 25OHD values of ~80 nmol/L.

Accumulating evidence from many fields indicates that Vitamin D functions in a variety of other systems and syndromes. These include conditions as varied as seasonal affective disorder, multiple sclerosis, various other autoimmune disorders, gingivitis, insulin resistance and many cancers, particularly of the breast, colon and prostate. The relationship of serum 25OHD to cancer will be treated extensively in other papers in this supplement, and will not be discussed further here. However, given this broad spectrum of activity, it is clearly vital to determine what levels of 25OHD may be required to ensure physiological normality not just for the calcium economy, but for the *whole* person.

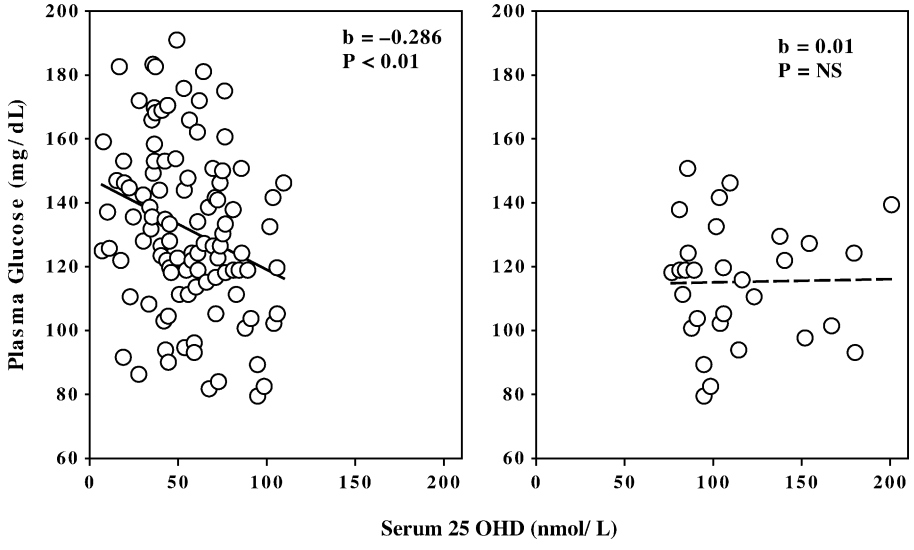

Fig. 3. Blood glucose values in non-diabetic individuals 60 min after a standard oral glucose load, expressed as a function of serum 25OHD. Split regression lines are depicted, as for the data of Fig. 1. Redrawn from the data of Chiu et al. [20]. (Copyright Robert P. Heaney, 2005. Used with permission.)

The data that are available for these non-skeletal disease benefits of Vitamin D are largely observational in character and, for many endpoints, measurements of the outcome variable are not available across the full spectrum of 25OHD values (as is the case for calcium absorption, see Fig. 2). However, one recent study [20] showed that insulin sensitivity in non-diabetic individuals was inversely associated with Vitamin D status across a wide range of serum 25OHD values. Fig. 3 replots the data from this study for blood glucose at 60 min after a standard oral glucose load, superimposing two best fit regression lines on the data (as was done for the data of Fig. 1). The inflection point in this case, i.e., the point where no further lowering of glucose is found, was at a serum 25OHD of ∼114 nmol/L (46 ng/mL), but the confidence interval around this estimate is broad. Similar significant inverse relations were found in this study for blood glucose at the 0, 90 and 120 min time points as well, indicating substantially better glucose handling overall at the higher 25OHD levels.

In brief, the bulk of the prevailing evidence indicates that physiologically optimal Vitamin D status requires serum 25OHD levels of at least 80 nmol/L (32 ng/mL), and very possibly higher.

3. Achieving desired levels of serum 25OHD

The Vitamin D input needed to achieve optimal serum 25OHD obviously depends upon both the starting value and the chosen target level. For the sake of this discussion, I shall use a target of 80 nmol/L and attempt to define the input needed to reach it. Obviously, if a higher figure turns out to be physiologically more advantageous, then larger inputs will be needed. (In this discussion I use the word “input” advisedly, meaning both oral intake and cutaneous synthesis.)

My colleagues and I have approached this issue by defining the rise in serum 25OHD produced by a broad range of controlled, oral intakes [21,22]. A portion of the results from one such study is shown as Fig. 4. Healthy adult men with low food Vitamin D intakes, not taking supplements, and studied at 41°N latitude, were given controlled oral doses of cholecalciferol for 4–5 months over the winter (when cutaneous Vitamin D synthesis is minimal). Fig. 4 plots the induced rise in serum 25OHD at equilibrium as a function of measured daily Vitamin D intake. The slope of the regression relationship is 0.7 nmol/(L μg day). This value, taken by itself, means that to raise serum 25OHD from 50 (e.g.) to 80 nmol/L, one would need an additional daily oral input of 30/0.7, or 43 μg (1720 IU) of cholecalciferol.

To our knowledge, ours are the only studies that have attempted a systematic quantification of the change in serum 25OHD in response to specific inputs of Vitamin D in healthy subjects. However, numerous recent treatment studies [e.g., 15,22,23] have provided data on the changes produced by the particular treatment regimens employed. For example, the British fracture intervention trial [15], with

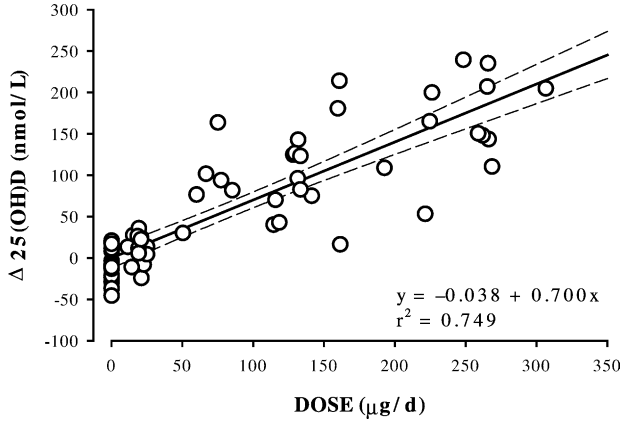

Fig. 4. Regression of the treatment-induced equilibrium increment in serum 25(OH)D_3 concentration on analyzed daily cholecalciferol dose in 67 healthy men treated for 4–5 months across winter [21]. (Copyright Robert P. Heaney, 2003. Used with permission.)

an average daily dose of 800 IU (20 μg), produced a mean rise of 21 nmol/L, i.e., ∼1 nmol/(L μg day); and most others have yielded estimates between 0.6 and 1.2 nmol/(L μg day). We had previously shown [22] that the rise produced by a given steady-state oral dose is an inverse function of baseline 25OHD level, and that, from very low starting values, the rise may be as much as 2 nmol/(L μg day). The precise character of this relationship must still be worked out, but a non-linear response requires that dose quantification take starting value into consideration. Accordingly, if one takes plausible slopes of 2.0, 1.2 and 0.7 nmol/(L μg day) for groups with baseline values of ∼20, ∼40 and ∼60 nmol/L, one can calculate the approximate daily oral dose needed to reach or maintain 80 nmol/L, as set forth in Table 1 . As is immediately evident, all the values in Table 1 except that for replete subjects (who need no oral intake at all) are above the recommended intakes (AIs) in the 1997 DRIs [1].

Another approach to this issue is to estimate the oral input needed to prevent the winter fall in 25OHD [24]. As inspection of Fig. 4 indicates, the regression line through the data has a small negative *Y*-axis intercept, reflecting the widely documented trans-winter drop in serum 25OHD. The zero change value from Fig. 4, i.e., the dose needed just to prevent the winter drop, is ∼12.5 μg/day (500 IU/day). However, simply maintaining starting levels, most of which are below the target value, does nothing toward achieving optimal status, which for the subjects in our study required additional oral inputs close to the value given in Table 1 for a 60 nmol/L baseline.

Table 1
Estimated daily oral doses needed to reach and maintain a serum 25OHD value of 80 nmol/L

Baseline (nmol/L)	Daily oral dose
20–40	55 μg (2200 IU)
40–60	45 μg (1800 IU)
60–80	29 μg (1160 IU)
> 80	0 μg (0 IU)

The values given in Table 1 must be considered approximations, in part because of poor standardization of 25OHD assay around the world [25,26], (a factor that may influence reported slope estimates). Nevertheless, the high degree of consistency of the data from varied sources indicates that these estimates cannot be far from correct.

4. The problem of setting a requirement in a situation with multiple inputs

The term "requirement", when applied to nutrients, generally relates to an oral intake. As noted earlier, Vitamin D is synthesized in the skin, a factor that strongly influences the oral requirement. The data from our controlled dosing study during winter [21] indicated a daily metabolic utilization of ∼75–100 μg (3000–4000 IU), the vast majority of which had to have come from stores accumulated over the preceding seasons when cutaneous synthesis was active. Plainly, therefore, cutaneous input accounts for the bulk of daily utilization in healthy individuals. In our subjects, who had combined food and supplement intakes of no more than 5 μg (200 IU)/day, cutaneous sources accounted for better than 90% of total utilization.

Various studies report that one minimal erythema dose of UV-B radiation to the whole body produces between 10,000 and 25,000 IU (250 and 625 μg) of cholecalciferol [27]. Thus, frequent sun exposure during the summer months is capable of generating a substantial reserve, the size of which will depend upon latitude, clothing practices, and outdoor activity. Skin color is also an important determinant, as melanin, whether constitutive or as a result of tanning, absorbs the critical UV wave lengths and hence reduces the rate of cutaneous synthesis of pre-vitamin D. Even so, dark-skinned agricultural workers in the tropics commonly have 25OHD values of ∼150 nmol/L (60 ng/mL) or higher [28]. Hence, by no means is skin pigmentation an absolute barrier to endogenous input. Time in the sun makes up for a slower rate of synthesis.

Age, too, is a substantial factor influencing the oral requirement. Skin content of 7-dehydrocholesterol (the immediate precursor of pre-vitamin D) drops by 50% from age 20 to age 80 [29], and the same dose of UV-B radiation evokes a smaller rise in serum cholecalciferol levels in older individuals than in the young [30]. Nevertheless, like pigmentation, age too is not an absolute barrier. A recent report from Japan (at a latitude of ∼40°N) indicated that spending time outdoors daily raised serum 25OHD level in a group of elderly stroke patients from ∼20 to ∼50 nmol/L, while an indoors, control group had further deterioration in their already very low serum 25OHD levels [31].

Thus, not only is the problem of setting a requirement complicated by multiple inputs, but cutaneous input, usually the larger of the two, is far from constant across the general population, varying by large amounts with latitude, occupation, clothing practices, skin pigmentation, and age. How does one go about setting an oral intake requirement when some members of a population (e.g., young, outdoor, athletic persons) may need nothing by mouth at all, while others (e.g., the shut-in elderly) may need as much as 75–100 μg/day (3000–4000 IU/day)? The key lies in careful definition of the tolerable upper intake level (TUIL).

A single oral intake value for everyone, sufficient to ensure that the total needs of most individuals are met, will provide more than enough for many. Hence, it is important to ascertain the safety of total inputs when they fall above the specified average requirement. The FNB in its 1997 recommendations established 2000 IU/day (50 μg/day) as the TUIL [1], without tying that dose to serum 25OHD. The Vitamin D content experts on the Upper Limits Panel objected to this 2000 IU/day figure (R. Heaney, M. Holick, personal communication) on the grounds that extensive clinical experience had established the safety of substantially higher inputs. The problem the Panel dealt with was that this experience was largely unpublished, for the obvious reason that safety studies on essential nutrients are virtually never performed or published until that safety is questioned. Furthermore, the single paper used to establish the lowest observed adverse effect level (LOAEL) [32] has itself been challenged by Vieth [28], and several other investigators have called for upwards revision of the TUIL.

Since 1997 several studies have demonstrated the essential safety of continuous daily dosing with 4000, 5000 and 10,000 IU/day (100, 125 and 250 μg/day) for up to 16 weeks, and of 50,000 IU (1250 μg)/day for 8 weeks, all without evidence of toxicity [21,22,33]. Indeed, a continuing daily oral intake of 10,000 IU produces a mean serum 25OHD value approximating what is seen naturally after extensive summer sun exposure at mid latitudes [12].

Revision is indicated also because, as noted earlier, at the time it was defined, the TUIL was not tied to serum 25OHD. Using newer data, such as those used to generate Table 1, 2000 IU (50 μg/day), given as a steady daily input to an already replete individual (i.e., with a serum 25OHD value of 80 nmol/L), would raise serum 25OHD by no more than 35 nmol/L, i.e., to 115 nmol/L, a value well within the range currently found in healthy younger individuals. Even giving twice the TUIL would raise 25OHD in already replete individuals to only 150 nmol/L, a value typical of healthy outdoor workers. Manifestly, for starting values less than 80 nmol/L, 2000 IU daily would produce and sustain lower values still. Also, as Table 1 shows, more than 2000 IU would actually be required to bring individuals with starting values between 20 and 40 nmol/L up to the physiologically optimal range.

For sun-deprived individuals, particularly the homebound elderly, the optimal oral intake may well be as much as 3000–4000 IU (75–100 μg)/day. Clearly, therefore, the 1997 TUIL constitutes a significant policy barrier. It would be difficult to make a policy recommendation to provide the amounts needed for a major sector of the population in the face of a TUIL that remained as low as 2000 IU.

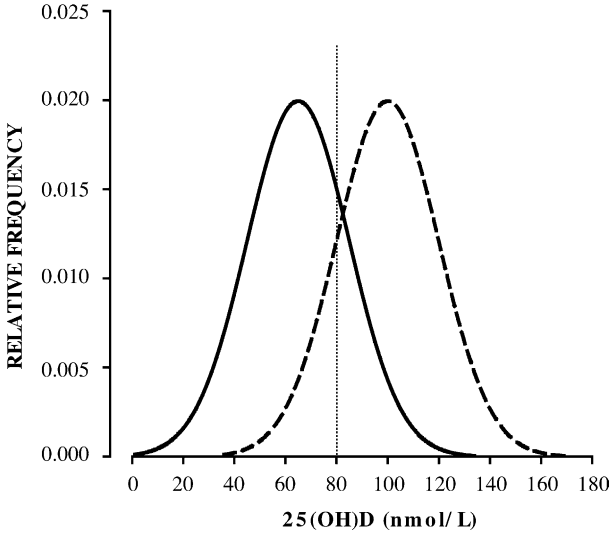

Fig. 5. Gaussian frequency distributions for serum 25OHD values in women age 60–79, from the NHANES-III database, based upon published parameters [34,35]. The solid curve is constructed from observed data, while the dashed curve reflects the effect of a 35 nmol/L rise in everyone, produced by a population-wide increase in Vitamin D intake of 2000 IU/day. The dotted vertical line at 80 nmol/L serves to give a visual cue to the proportion of both distributions with serum 25OHD values below the target figure. (Copyright Robert P. Heaney, 2005. Used with permission.)

DRIs generally, and the TUIL specifically, apply to populations, not to individuals. A physician with a patient (or group of patients) whose 25OHD concentrations are ∼50 nmol/L, can rationally give 2000 IU/day with the assurance that serum 25OHD will rise just above the lower limit of the optimal range, and with no fear of toxicity. But what if we were to recommend 2000 IU for everyone, as a statement of nutritional policy? Perhaps the best way to answer that question is to fall back on such data as those of NHANES-III. Fig. 5 shows two frequency distributions for serum 25OHD in women aged 60–79 based upon data from NHANES-III. The first is constructed from the parameters published by Looker et al. [34,35], and the other by shifting that distribution to the right by 35 nmol/L (the rise calculated above that would be produced in a healthy individual with a steady-state daily oral dose of 2000 IU). The upper tail of the higher distribution has only 0.6% of its members above 150 nmol/L, and none above 200 nmol/L. More importantly, the shifted distribution, despite an additional intake equal to the current TUIL, still has 15% of its members below the target value of 80 nmol/L.

Fig. 5 must be understood to be primarily illustrative of the type of approach that needs to be taken when evaluating the risk of pushing people already replete into a possibly unhealthy range. Because of seasonal sampling issues, NHANES-III values tend to overestimate the year-round national values. Also, the calculation used for Fig. 5 assumes a uniform increase, irrespective of baseline, whereas it is likely that lower starting values would be raised to a greater extent (see above), hence compressing the second distribution somewhat. Neither of these problems would exaggerate the estimate of numbers of individuals above any given *high* value of 25OHD. However, the approach taken in Fig. 5 also assumes a normal distribution, while the true distribution is almost certainly skewed somewhat to the right, and so will have more members in the upper tail than would be the case for a truly Gaussian distribution. Even so, there would be at least a 50 nmol/L safety margin before reaching serum 25OHD values at which toxicity might be a consideration (i.e., above 250 nmol/L).

5. Tentative adult recommendations

Against the background of the foregoing considerations, it is possible to develop tentative recommendations for both the RDA and the TUIL. Taking 80 nmol/L as the desired target, using the NHANES-III distributional data [34,35], and taking the dose–response rise to be ∼1.0 nmol/(L μg day) at the low end of the distribution and 0.6 nmol/(L μg day) at the upper end, it can be shown that it would require ∼2600 IU/day (65 μg/day) to move 97% of women over age 40 to values above 80 nmol/L. If an RDA is defined as the intake that would meet the needs of 97% of the population, then 2600 IU/day is the RDA. As an extra oral intake, 2600 IU/day would be safe even for individuals with starting 25OHD values two standard deviations above the NHANES mean (i.e., ∼140 nmol/L), since it would raise their values to only ∼180 nmol/L.

Using some of the same factors, but taking, for example, 250 nmol/L as the safe upper limit of serum 25OHD, the TUIL value would be ∼10,000 IU/day (250 μg/day) for replete individuals (i.e., at ∼80 nmol/L prior to raising intake), and ∼6700 IU/day (167 μg/day) for individuals already at two standard deviations above the NHANES mean.

The foregoing estimates are dependent upon the actual distributional values of 25OHD in the US population and on the dose–response relationships discussed in the foregoing. Hence, the figures given, while defensible in their own right, must be understood to be primarily illustrative of the process involved in setting an RDA and a TUIL.

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