Vitamin D and Bone Health – Discussion Points Following the Recent Institute of Medicine Recommendations

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Abstract

The 2011 Institute of Medicine recommendations for vitamin D – both the recommended daily amount (RDA) and the vitamin D status judged adequate for bone health – are too low. Calcium absorption, osteoporotic fracture risk reduction and healing of histological osteomalacia all require values above 30 ng/ml, and probably even 40 ng/ml. Furthermore, the proposed RDA (600 international units per day up to the age of 70) is not compatible with the blood level of 25-hydroxyvitamin D (i.e., 20 ng/ml) recommended in the same report. Concerns regarding adverse consequences of higher intakes or status levels can be dismissed, in view of our extensive experience with outdoor summer workers (who regularly have values of 60 ng/ml or more) and the virtual certainty that human physiology evolved in – and is attuned to – an environment providing 10,000 IU/day or more.

Keywords

Osteoporosis, fracture, calcium absorption, osteomalacia, 25-hydroxyvitamin D

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At the outset, it is important to understand that the 2011 Institute of Medicine (IOM) recommendations for vitamin D[1,2] can be taken at three levels of applicability. The first is the level of my own decision, for my own intake, informed not just by whim, but by my reading of the appropriate science. The second level is what I, as a physician, might recommend to patients who come to me for advice. And the third level is what policy-makers decide with respect to the population in general, many, perhaps most, of whom would be ignorant of the topic entirely and not able to make an informed decision for themselves.

Clearly, the needed level of certainty (the strength of the evidence – for whatever recommendations may be made) rises as one moves up from the first to the third level. In theory, I might disagree with the IOM recommendations with regard to my own intake, or even with regard to what I recommend to my patients, and at the same time accept the recommendations for the public at large.

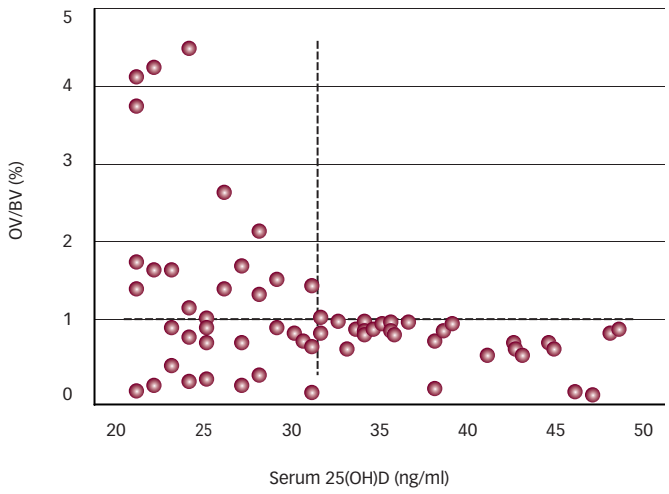
It is important to note that the IOM's recommendations actually apply only to the general public and are explicitly predicated on a healthy population. They are not intended for patients with various medical disorders, either current or potential. Thus, they apply only in a very limited way to the advice that physicians give to their patients and, while it is useful for a physician to be aware of them, they do not constitute guidelines for his or her practice. A good example of that distinction is found in the vitamin D guidelines for physicians issued by The Endocrine Society[3] just a few months after the IOM recommendations were formally released and by yet another set of guidelines, soon to be released, developed by the American Geriatrics Society (AGS). There is a sharp contrast between, for example, the IOM's recommended intake for the general public up to the age of 70, set at 15 µg (600 international units [IU]) per day, and the Endocrine Society's recommendation, set at up to 50 µg (2,000 IU) per day. Similarly, the Endocrine Society's safe upper level (UL) for adults is 250 µg (10,000 IU) per day, while the IOM's UL is 100 µg (4,000 IU) per day. Even larger differences will be evident when the AGS guidelines are published.

A further point of note is that the current IOM recommendations are explicitly intended to deal with skeletal endpoints only. The panel required evidence from multiple randomised trials to conclude that a particular health outcome was due to vitamin D status and, while they acknowledged that there may be some extra-skeletal benefits, they did not find evidence they considered sufficient to allow them to specify intakes that might produce such benefits. Thus there is nothing in the IOM recommendations that would be specifically applicable for practitioners in the fields of psychiatry, obstetrics, oncology, infectious disease, and other disciplines.

The IOM's recommendations related to skeletal endpoints in adults can be briefly summarised as follows:

- the serum 25-hydroxyvitamin D (25(OH)D) level that demarcates the lower end of the 'normal' or 'healthy' range is 20 ng/ml (50 nmol/l);
- the daily intake sufficient to meet the needs of 97.5 % of the population up to the age of 70 (i.e., the recommended daily amount [RDA]) is 15 µg (600 IU); and
- the tolerable upper intake level (TUIL, or simply the UL) is 100 µg/day (4,000 IU/day). (I stress that this is not a limit, but a tolerable level. The IOM states that it is uncertain about whether there would be any benefits from such an intake but, by specifying

Figure 1: Osteoid Volume Expressed as a Function of Serum 25(OH)D Concentration



25(OH)D = 25-hydroxyvitamin D; BV = bone volume; OV = osteoid volume. Data shown are from those individuals in Priemel et al.'s study[25] with serum 25(OH)D values of 20 ng/ml or higher (i.e. the level proposed by the Institute of Medicine as 'adequate'). The horizontal dashed line demarcates normal values for osteoid volume, and the vertical dashed line demarcates the 25(OH)D boundary between those individuals with and without abnormal osteoid volume. Source: redrawn from the data from Priemel, et al., 2010[25] (copyright Robert P Heaney, 2011. All rights reserved. Used with permission).

100 µg/day as the UL, it provides explicit assurance that there would be no harm.)

Completeness requires me to note also that, relative to the 1997 dietary reference intakes (DRIs), the IOM panel did produce quite substantial elevations in its recommendations. For adults up to the age of 50, the daily intake recommendation was tripled from 5 to 15 µg (200 to 600 IU); for adults aged 50–70, it was increased from 10 to 15 µg (400 to 600 IU); and for adults aged over 70, it was increased from 15 to 20 µg (600 to 800 IU). Further, in the 1997 DRIs, the UL was 50 µg/day (2,000 IU/day) and it was doubled to 100 µg/day (4,000 IU/day).

There is general agreement that these moves were in the right direction. Still, most working vitamin D scientists have concluded that the IOM did not go far enough, and many of them have publicly expressed their dissent from the IOM position both on skeletal and non-skeletal endpoints. (See, for example, a series of letters to the ditor in *Public Health Nutrition*[4–12] as well as further dissents in other journals.[13,14]) While nutrient intake recommendations are often a contentious subject, it appears that the reaction to the IOM's 2011 DRIs for vitamin D is of an order of magnitude more vocal and widely shared than had previously been elicited by any comparable set of IOM recommendations.

Since the focus of this review is explicitly bone health, and since the calcium intake recommendations were little changed from the 1997 values, I shall confine my analysis and comment to the IOM recommendations for vitamin D and specifically to those that relate to calcium homeostasis and skeletal endpoints.

Are Serum 25-hydroxyvitamin D Values Above 20 ng/ml Adequate for Skeletal Health?

Three lines of evidence converge on the conclusion that 20 ng/ml is not adequate to achieve the skeletal and calcium metabolic benefits of vitamin D. These are:

- randomised controlled trials (RCTs) with fracture endpoints and meta-analyses of such trials;
- physiological studies of calcium absorption; and
- studies of bone histology with emphasis on osteoid volume.

Anti-fracture Trials

One of the earliest of the reported trials involved 2,686 older British individuals in a five-year, double-blind, placebo controlled study and used a dose of 100,000 IU of vitamin D every four months (averaging 820 IU/day).[15] Serum 25(OH)D was raised from 21 ng/ml to 30 ng/ml, and osteoporotic fractures combined were reduced by 33 % in the vitamin D-treated group, relative to placebo. Not all trials, to be sure, have shown such a positive result,[16–18] but, in most of the null studies, compliance was so poor or the dose so low (often both) that the achieved dose of vitamin D was too low to test a hypothesis of benefit.[16–18] That was certainly the case in the Women's Health Initiative, where, taking compliance into consideration, the actual dose was only about 200 IU/day.[18] In a series of meta-analyses of published trial results, with particular emphasis on achieved 25(OH)D levels, Bischoff-Ferrari et al. showed that fracture reduction is either small or barely detectable at achieved serum 25(OH)D levels <32 to perhaps 40 ng/ml.[19–22] Thus, there is strong positive evidence that raising achieved serum 25(OH)D values above 20 ng/ml produces substantial reduction in osteoporotic fracture risk, and that trials failing to raise serum 25(OH)D appreciably will not alter fracture risk.

Studies of Calcium Absorption

Facilitation of calcium absorption is the canonical effect of vitamin D. Strangely, only two studies testing the response of calcium absorption as a primary outcome to additional vitamin D have been performed to date in humans.[23,24] Both showed an increase in calcium absorption when baseline 25(OH)D values averaging 20 ng/ml were elevated, in one case to 35 ng/ml and in the other to 29 ng/ml. Furthermore, the slope of that rise on the change in 25(OH)D was virtually identical in the two studies. These data show that, just as with anti-fracture trials, serum 25(OH)D values of 20 ng/ml are not adequate to insure a physiologically appropriate response of calcium absorption to vitamin D. Higher values are simply better, at least up to 30 or 32 ng/ml. (Since vitamin D itself does not cause calcium absorption, but only enables the body to regulate it, the fact that extra vitamin D allowed calcium absorption to rise in both studies strongly suggests that baseline values for 25(OH)D had limited the participants' ability to respond adequately to their own calcium need.)

Studies of Bone Histology

Osteomalacia is the adult bone disease classically related to vitamin D deficiency. Its histological hallmark is widened osteoid seams and increased coverage of trabecular surfaces with unmineralised osteoid on bone biopsy. The quantitative relationship of these bone changes to vitamin D status had essentially not been studied until recently when, in a report of 675 autopsies, osteoid volume was measured as a function of serum 25(OH)D concentration.[25] A portion of the results from this study are presented in *Figure 1*.

The figure shows the osteoid volume values for individuals with 25(OH)D values of 20 ng/ml or higher – i.e., the level judged 'adequate' by the IOM. There is a visually evident (and highly significant) trend toward lower osteoid volume as serum 25(OH)D rises above 20 ng/ml. It is also clear that no individual with a 25(OH)D value above 32 ng/ml had an osteoid value greater than 1 %

of bone volume, which we can thus take as the upper limit of normal for this measure. It is clear also that, in the 25(OH)D range between 20 and 32 ng/ml, fully half of the individuals included had elevated osteoid volume, some more than four times the upper limit of normal – i.e., they exhibited histological evidence of osteomalacia. The IOM panel was aware of this study and nevertheless judged this prevalence of osteomalacia to be 'acceptable' at a population level.

Concordant findings had earlier been published showing greater osteoid volume in winter than in summer in the biopsies of the studied women.[26] In this study, winter 25(OH)D values averaged 20.4 ng/ml, and summer values 24.4 ng/ml. Thus, in both studies, which involved very different populations, patients with 25(OH)D values of 20–32 ng/ml still exhibit histological evidence of osteomalacia, which does not disappear until 25(OH)D values rise appreciably.

Convergent Evidence

Thus all three lines of evidence converge on the conclusion that a 25(OH)D value of 20 ng/ml is not 'healthy', and that preventable disease or dysfunction (fracture, calcium malabsorption, and histological osteomalacia) persists until serum 25(OH)D is at least 30 or perhaps even 40 ng/ml.

Daily Requirement

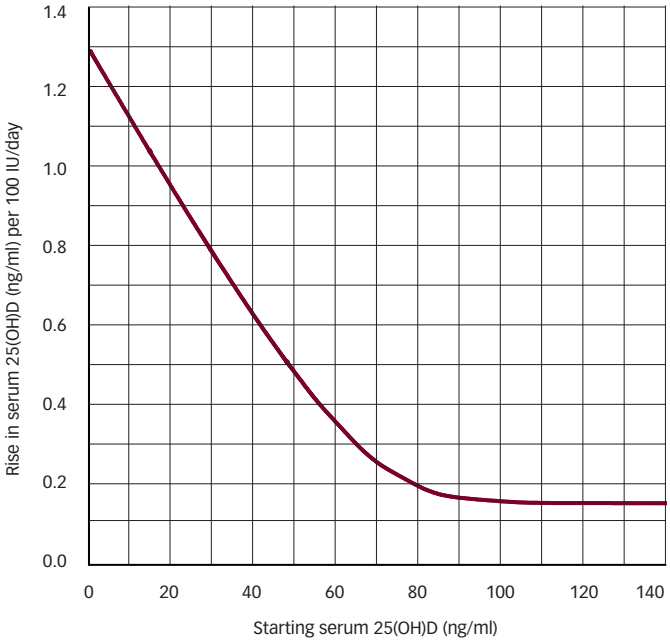
Thousands of clinicians worldwide using vitamin D in their deficient patients know from personal experience that the IOM's recommended dietary allowance (600 IU/day for individuals up to the age of 70) is not close to sufficient to produce the stated 'normal' 25(OH)D value of 20 ng/ml or higher. Even if patients start with values above 10 ng/ml, 600 IU would still not be enough for most of them. *Figure 2* sets out the best available estimates of the expected rise in serum 25(OH)D for each 100 IU daily dose, plotted as a function of the starting 25(OH)D value. (The data in *Figure 2* were derived from a study of over 3,500 adults ingesting daily vitamin D doses ranging from zero to 50,000 IU.)[27] Once again, as most clinicians have discovered, and as the figure demonstrates, the absolute value of the rise in 25(OH)D in response to a given dose declines as baseline status rises. What *Figure 2* does is to put numbers to this experience.

To apply the information in *Figure 2*, note that, for a starting 25(OH)D value close to zero (i.e., 'unmeasurable' in many assays), each 100 IU predicts a rise of about 1.1 ng/ml or, for 600 IU, an aggregate rise of about 7 ng/ml – certainly not 20 ng/ml or higher. In fact, to reach 20 ng/ml requires an all-source, daily input (cutaneous plus oral) averaging about 1,800 IU/day and, to reach 32 ng/ml, the required input averages close to 4,000 IU/day – a figure confirmed in a previously reported, long-duration dose-ranging study.[28]

Prudential Caution

One possible reason for the surprisingly low recommendations from the IOM is a concern not to do more harm than good. If, for example, the lower end of the normal range had been set at 30, or even 40 ng/ml, and the RDA set at 2,000 IU/day (figures many experts would consider fully justifiable), given the inevitable Gaussian distribution of values, some individuals might conceivably be pushed into a potentially toxic range. That would not be formal vitamin D intoxication to be sure – as the raised UL (4,000 IU/day) assures us – but possibly some of the other ostensible benefits would disappear or unanticipated negative effects would develop. Concern for such unintended outcomes is entirely appropriate and would be expected of such a policy-making body. However, action taken on such concern must depend heavily on the quality of the evidence suggesting untoward effects – in this case, at 25(OH)D concentrations above 40 or 50 ng/ml (specifically cited in the IOM report).

Figure 2: Expected Rise in Serum 25(OH)D for Each 100 IU of Additional Vitamin D_3, Expressed as a Function of the Basal Value



25(OH)D = 25-hydroxyvitamin D; IU = international unit. Source: redrawn from the data from Garland, et al., 2011[27] (copyright Robert P Heaney, 2011. All rights reserved. Used with permission).

A single study suggesting such harm used 500,000 IU once yearly, and showed an actual increase in falls and fractures,[29] certainly a concern if applicable. However, it is questionable whether any weight at all should be given to this particular study in view of the fact that, with once yearly dosing, it employed an extremely unphysiological approach to replacement therapy. A comparable approach in the field of clinical endocrinology would be to treat hypothyroid patients with a single dose of 12,000 µg l-thyroxine once every three months. Such a regimen would be both ineffective and dangerous. As the half-life of 25(OH)D is approximately four times that of thyroxine, the two regimens just described (yearly for vitamin D and quarterly for thyroxine) are exactly equivalent. It is not surprising, therefore, that the outcomes of such a vitamin D study are not representative of the outcomes that would have been produced by the same dose had it been given on a daily basis (which would have averaged about 1,370 IU/day).

In a similar vein, the IOM panel undoubtedly noted that, for certain endpoints (mostly non-skeletal), apparent benefit waned at the highest percentiles of a particular population's distribution of 25(OH)D values – and, in some reports, even reversed.[30,31] Vieth has insightfully explained that this is due to wide annual variations in serum 25(OH)D concentrations, and has shown why this oscillation nullifies any apparent benefit.[32] Exactly such wide annual oscillation also would have been the case in the study using 500,000 IU once yearly.[29] Vieth noted that annual oscillations of more than a few ng/ml are unphysiological and described its effect well in advance of the IOM panel's deliberations, but whether the panel was aware of his work is not clear.

The panel certainly should, however, have been aware of the fact that both outdoor summer workers in temperate latitudes and people living in the tropics have 25(OH)D values in the range the IOM considered suspect (40–60 ng/ml), and yet do not exhibit any apparent untoward effects. In fact, one of the most powerful arguments for requirements higher than those currently recommended by the IOM is that, during the evolution of human physiology, daily vitamin D inputs from solar UV-B radiation would certainly have been in excess of 10,000 IU, with serum 25(OH)D values well above 40 ng/ml. Since these are the conditions to which human physiology has been adapted by natural selection, it has been argued that such values should be taken as the starting point in setting recommendations for the intake of contemporary humans, with the burden of proof shifted to those who propose that lower values are either adequate or safe.[12]

In summary, the IOM recommendations are internally inconsistent, and both the RDA and the 25(OH)D blood level declared by the IOM to be 'adequate' are low, in the first case by approximately six-fold and in the second by about two-fold. Further, the panel's insistence on evidence from RCTs to establish particular benefits is itself inappropriate.[33,34] This may seem a retrogressive statement in today's climate, which applies indiscriminately the criteria of evidence-based medicine to all interventions, but nutrients are not drugs, and consuming them at levels plausibly available from the environment is not an intervention. All nutrients are efficacious, i.e., essential for health – by definition. Inadequate intake of a particular nutrient leads to dysfunction or disease. This much is given. To associate a particular nutrient with a particular disease is equivalent to stating that low intake produces or worsens the disease concerned. Such a hypothesis cannot ethically be tested in humans using the RCT design. Even if a particular association turns out not to be causal, the control group in such a trial will have received an inadequate intake and hence will have experienced some disease or dysfunction, if not the one being specifically tested. Continued insistence on RCT-level evidence will guarantee not certainty, but stagnation. ■

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