Vitamin D: criteria for safety and efficacy

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The functional status indicator for vitamin D, for both safety and efficacy, is serum 25-hydroxyvitamin D concentration. Efficacy for several health endpoints requires levels of 80 nmol/L or higher. Toxicity occurs at levels of 500 nmol/L or higher. The input needed for efficacy, in addition to typical food and cutaneous inputs, will usually be 1000–2000 IU/day of supplemental cholecalciferol. Toxicity is associated only with excessive supplemental intake (usually well above 20,000 IU/day).

INTRODUCTION

Since the publication of the dietary reference intakes for the bone-related nutrients in 1997,[1] the fundamental criterion for both the safety and efficacy of vitamin D has been accepted worldwide to be the serum concentration of 25-hydroxyvitamin D [25(OH)D]. 25(OH)D serves 1) as a sensitive indicator of vitamin D nutritional status; 2) as the principal form of vitamin D storage in the body under typical vitamin D inputs; and 3) as the precursor for the autocrine synthesis of tissue-level calcitriol. Because inputs of vitamin D come from cutaneous synthesis, from natural and fortified foods, and from vitamin supplements, and because the proportions from these sources vary widely, it is not particularly useful to base the definition of levels for safety or efficacy on oral inputs, unlike the situation for most nutrients. But for similar inputs, all three sources produce apparently identical effects on serum 25(OH)D. Thus, serum 25(OH)D is not only a useful measure, it is also the only practicable measure to use as a criterion for safety or efficacy. The task of establishing such criteria amounts simply to defining serum levels as follows: 1) at or above the level at which toxicity is likely to occur (for safety); and 2) the level below which the desired physiological effects are suboptimal (for efficacy).

The classical endocrine function of vitamin D, mediated prototypically through circulating calcitriol concentrations, is the facilitation of intestinal calcium absorption. But vitamin D also functions as a ubiquitous second messenger linking a broad variety of extracellular signals to the gene transcription needed for the appropriate responses in the cells of many, perhaps most, tissues. Such effects have been demonstrated extensively for the immune response and for oncogenesis, among others.[2] These functions have recently been reviewed in detail elsewhere,[3] and it is beyond the scope of this brief review to attempt to define efficacy criteria for the large, and still growing, array of functions putatively impaired by low vitamin D status. It is important to note that, for most or all of them, there is an extensive, concordant body of basic science from animal models and cell biologic systems.

SAFETY

Excessive inputs of vitamin D produce a syndrome known as vitamin D intoxication, which is characterized by hypercalcemia, renal stones, and renal calcification, with kidney failure and death. Except for infrequent cases of accidental or intentional poisoning, this syndrome is rarely seen today. The mechanism for hypercalcemia, which is generally considered the initial expression of toxicity, is unclear. It is usually assumed to be based in one of two mechanisms. The first is a direct effect of the extremely high serum levels of either 25(OH)D or of vitamin D itself. Despite being very weak ligands for the vitamin D receptor, these metabolites may nevertheless be present in sufficient quantities to override usual physiological controls, thus directly producing high intestinal

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calcium absorption and bone resorption, ultimately in excess of the kidney's ability to handle the calcemic load. The second is a possible elevation of free $1,25(OH)_2D$, caused by displacement of this active form of the vitamin from circulating D-binding protein by high levels of 25(OH)D.

Both the intoxication literature and the recent controlled dosing studies have been reanalyzed by Hathcock et al.[4] These authors show that essentially no cases of confirmed intoxication have been reported at serum 25(OH)D levels below 500 nmol/L. Correspondingly, the oral intakes needed to produce such levels are in excess of 20,000 IU/day in otherwise healthy adults and, more usually, above 50,000 IU/day. These findings led Hathcock et al.[4] to select 10,000 IU/day as the tolerable upper intake level (TUIL, or UL), with considerable confidence. It is likely that a higher intake could be defended, but little good would be served by doing so, as 10,000 IU/day is substantially more than is apparently needed for any recognized efficacy endpoint.

Incidentally, it is worth noting that one minimum erythema dose of total body solar exposure, such as might be achieved in a few minutes on a summer day at the beach or pool, produces a vitamin D input in the range of 10,000–20,000 IU, depending upon skin type.[5,6] Thus, frequent summer exposure produces inputs of the same magnitude as the Hathcock UL, which can thus be characterized as a "physiological" input. Moreover, despite such cutaneous inputs, there has never been a case of vitamin D intoxication reported as a result of sun exposure.[6]

EFFICACY

Efficacy is harder to define than safety, as vitamin D acts in multiple body systems, and there is no general agreement as to appropriate endpoints. For some systems, vitamin D functions as a threshold nutrient; in fact, a threshold may be a feature of most of the systems in which the nutrient operates, although current data are not adequate to resolve this issue.

Bone

Classically, vitamin D has been related to the prevention of rickets through promotion of active intestinal calcium transport. Clinical rickets or osteomalacia will be common at serum 25(OH)D levels below 20 nmol/L. These levels can typically be achieved by oral vitamin D inputs in the range of 200–400 IU/d, and this fact serves as the basis for the current intake recommendation.[1] Absence of clinical evidence of rickets or osteomalacia has been taken as presumptive evidence of vitamin D adequacy, but this position is no longer defensible.

Parfitt[7] defined three grades of vitamin D deficiency osteopathy, with rickets and osteomalacia being simply the most severe, but he was not able to tie these grades to specific levels of serum 25(OH)D; however, using histomorphometric criteria, Need et al.[8] recently showed significant impairment of osteoblast function across the seasons, from summer to winter, corresponding to a drop in mean serum 25(OH)D from 61 to 51 nmol/L. These values are well within the usual reference range for 25(OH)D and are substantially above the levels found in clinical osteomalacia. Vitamin D supplementation has been shown in several controlled trials to reduce osteoporotic fractures.[9,10] In meta-analyses of these studies,[11] the benefit is confined to trials in which the achieved serum 25(OH)D reached 75 nmol/L or higher. In studies that failed to achieve such a level, or used oral doses of 400 IU or less, no reduction of fracture risk could be demonstrated.[11]

The canonical function of vitamin D, i.e., promotion of active calcium absorption from the intestine, has been shown in two independent studies to rise substantially as serum 25(OH)D levels rise through the nominal reference range,[12,13] with an apparent plateau being reached at about 80 nmol/L. Thus, by bone histology, by calcium absorptive performance, and by fracture risk reduction, a criterion of 80 nmol/L can be taken as the boundary between vitamin D inadequacy and normalcy, at least with respect to those endpoints.

Falls and neuromuscular function

Controlled trials and subsequent meta-analyses established that raising serum 25(OH)D concentration in the elderly reduces fall risk, in some instances by as much as half.[14,15] Lower extremity neuromuscular function in older adults in NHANES-III was inversely correlated with serum 25(OH)D, with the bulk of the improvement occurring up to serum 25(OH)D concentrations of ~40 nmol/L.[16] However, continued, though less dramatic, improvement was noted up to levels above 80 nmol/L. In the Amsterdam Longitudinal Aging Study, lower extremity function was also significantly related to serum 25(OH)D, with appreciable improvement occurring all the way up to serum 25(OH)D values of 75 nmol/L.[17] (There were too few individuals with higher values to permit assessment of the association at levels above 75 nmol/L).

Cancer

Carcinogenic response to standard stimuli is substantially enhanced in vitamin D-deficient or in vitamin D receptor knock-out animal models, and can be reduced by vitamin D supplementation.[18] A large body of epidemiological

evidence points to a counterpart situation in humans. There is an inverse relationship between serum 25(OH)D and risk for such cancers as lung, colon, breast, prostate, pancreas, and lymphoma, and both breast and all-cancer mortality are inversely related to UV-B exposure (probably the principal source of vitamin D in most individuals).[19–23] In several of the reported studies, antecedent values for serum 25(OH)D had been obtained, and the available evidence indicates a dose-related, linear decrease in risk as serum 25(OH)D rises to levels of at least 80 nmol/L.[20] As with lower extremity function, it is not possible to extend the association to higher 25(OH)D values, because such small fractions of the populations at risk have vitamin D levels above 80 nmol that the required data are not available. While most of the human data are of an observational character, there is one very recently published, randomized, controlled trial with a cancer endpoint. Lappe et al.[24] showed that raising serum 25(OH)D from a mean of 71 nmol/L to a mean of 96 nmol/L decreased all-cancer risk in 1169 postmenopausal women by approximately 60% in a 4-year trial ($P < 0.01$).

Immune function

There is an extensive body of basic science dealing with the role of vitamin D in various aspects of the immune response.[2,3] At a clinical level, it has long been recognized that rickets in children was associated with increased risk of respiratory infection, and that the cause of death in rachitic children was commonly pneumonia. Two recent, randomized, controlled trials help to extend these observations to adult humans. In one, Nursyam et al.[25] showed a highly significant improvement in response to standard anti-tubercular therapy in a group of patients with pulmonary tuberculosis who were randomly allocated to receive a placebo or 10,000 IU vitamin D per day, a dose that would typically produce a serum 25(OH)D level in the range of 200–220 nmol/L.[26] Aloia et al.,[27] in a randomized controlled trial of 208 African American women, showed a 70% reduction in the occurrence of serious respiratory infections (including influenza) in the group treated with up to 2000 IU vitamin D per day. In these women, serum 25(OH)D was raised from 46.9 to 86.9 nmol/L.

Insulin response

As with cancer and the immune response, there is a large body of epidemiological evidence implicating vitamin D inadequacy in the risk of developing type I diabetes mellitus, but there are, as yet, no randomized trials to confirm the results of the observational studies. However, in NHANES-III[28] both fasting blood sugar and response to a standard glucose challenge were inversely correlated with serum 25(OH)D, with the available data suggesting that the response plateaued at values between 100 and 120 nmol/L. Similar results have been reported for other adult cohorts.[29]

CONCLUSION

The functional criterion for both safety and efficacy for vitamin D is the circulating serum concentration of 25(OH)D. Toxicity is almost never observed at serum levels below 500 nmol/L, corresponding to oral intakes in excess of 20,000–50,000 IU/day. 10,000 IU/day can be taken, with considerable confidence, as the safe upper intake level. The criteria for efficacy depend upon the body systems evaluated. For calcium absorption, the system is not optimized until a level of 80 nmol/L or higher is reached, and for fractures, falls, cancer, immune function, and insulin sensitivity, the efficacy criterion is less well established, but is at least as high as for calcium absorption, and perhaps as high as 120 nmol/L.

Because vitamin D is essential for facilitating the body's response to both physiological and potentially harmful stimuli, low vitamin D status increases the risk of many chronic diseases. We will not know the true burden of those diseases until we restore population-level vitamin D status to the Paleolithic levels that prevailed during the evolution of human physiology.

Acknowledgment

Declaration of interest. The author has no relevant interests to declare.

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