Symposium: Vitamin D Insufficiency: A Significant Risk Factor in Chronic Diseases and Potential Disease-Specific Biomarkers of Vitamin D Sufficiency

Dietary Recommendations for Vitamin D: a Critical Need for Functional End Points to Establish an Estimated Average Requirement[1]

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ABSTRACT From its inaugural value in 1941, the Recommended Dietary Allowance (RDA) for adults for vitamin D has remained close to 400 IU (10 μg) level. This original recommended intake was based on the observation that the amount of vitamin D activity in a teaspoon of cod liver oil was sufficient to prevent rickets in infants. Since that time until 1997, determination of vitamin D requirements and status was more conjecture than science. In 1997, when the recommended intake level of vitamin D was set as an adequate intake value rather than an RDA, much has been learned about metabolism of vitamin D. The circulating metabolite 25-hydroxyvitamin D is the major static indicator of vitamin D status. Using its response to diet in the absence of sun exposure, a dose–response study suggests a mean requirement of at least 500 IU (12.5 μg) from which an RDA could be set. Other factors may need adjustment, such as sun exposure and body fat. However, functional indicators of status are needed. The role of vitamin D in calcium metabolism (i.e., calciotropic functions) is better understood; bone turnover and parathyroid hormone are potential indicators. Vitamin D has noncalciotropic functions arising from extrarenal synthesis of the active metabolite 1,25 dihydroxyvitamin D involving cell proliferation and immunity, from which function indicators of status may be derived. Despite gaps in our knowledge, there are data from which new dietary reference intake values for vitamin D may be set. J. Nutr. 135: 304–309, 2005.

KEY WORDS: • *vitamin D* • *requirement* • *dietary reference intakes* • *functional indicators* • *calciotropic* • *noncalciotropic*

The current (1997) recommended intake for vitamin D

Since the early 1940s, the United States and Canada have set nutrient recommendations for nutrients until the implementation of the Dietary Reference Intakes (DRI)[3] process, when, together, recommendations were made (1). Different recommended intakes for vitamin D were proposed by Canada and the United States prior to setting the current recommendations for vitamin D in 1997. **Table 1** presents recommended values for adults set by Canada and the United States (1–9) over the past 4 decades, representing the time for which metabolic pathways of vitamin D were being established. It is notable that the first recommended dietary allowance (RDA) for vitamin D for Americans in 1941 gave the value of 400 IU (i.e., the lower value of a range for infants at the time), for adults only in a footnote that stated "When not available from sunshine, [vitamin D] should be provided up to the minimal amounts recommended for infants" (10). The value of 400 IU (10 μg) was derived from an observation that this amount of vitamin D activity, found in a teaspoon of cod liver oil, was sufficient to prevent rickets (11,12). The RDA for adults for vitamin D has, for the most part, remained at or below the 400 IU (10 μg) level, with Canadian values set much lower, despite being at a higher latitude. Table 1 illustrates that

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[3] Abbreviations used: 1,25(OH)$_2$D, 1,25 dihydroxyvitamin D; 25(OH)D, 25-hydroxyvitamin D: AI, Adequate Intake; D-2, ergocalciferol; D-3, cholecalciferol; DRI, Dietary Reference Intakes; EAR, Estimated Average Requirement; PTH, parathyroid hormone; RDA, Recommended Dietary Allowance.

TABLE 1

Recommendations for vitamin D for adults in Canada and United States in the past 4 decades[1]

Country and date	Age groupings	Recommended value
	y	*μg (IU)*
United States		
1968	18–22	10 (400)
	22–35	10 (400)
	35–55	None given
	55–75+	None given
1974	19–22	10 (400)
	23–50	10 (400)
	51+	10 (400)
1980	19–22	7.5 (300)
	23–50	5 (200)
	51+	5 (200)
1989	19–24	10 (400)
	25–50	5 (200)
	51+	5 (200)
Canada		
1964	"Adult"	None given
1975	19–35	2.5 (100)
	36–50	2.5 (100)
	51+	2.5 (100)
1983	19–24	2.5 (100)
	25–49	2.5 (100)
	50–74	2.5 (100)
	75+	2.5 (100)
1990	19–24	2.5 (100)
	25–49	2.5 (100)
	50–74	5 (200)
	75+	5 (200)
Canada and United States (DRI)		
1997	19–30	5 (200)
	31–50	5 (200)
	51–70	10 (400)
	>70	15 (600)

[1] Values taken from references 1–9.

determination of vitamin D requirements and status has been more conjecture than science.

The current (1997) recommendations for vitamin D, also shown in Table 1, are not RDA, as were previous values, rather, they are Adequate Intake (AI) values, denoting the lack of scientific evidence needed to set an RDA (1). In the DRI process, to determine an RDA, which can serve as an amount of a nutrient that is the goal for an individual, there must be an Estimated Average Requirement (EAR), which is derived from published data. At present, in the United States and Canada, an EAR has not been established for vitamin D; instead, an AI was set, because there were not enough scientific studies defining a requirement for vitamin D (1). An AI has inherent limitations in assessing vitamin D intake adequacy of groups (13), because the AI is expected to meet or to exceed the amount needed to maintain a defined nutritional state or criterion of adequacy in essentially all members of the apparently healthy population. The 1997 AI is based on maintenance of serum 25-hydroxyvitamin D [25(OH)D] levels in the absence of sunlight at or above 27.5 nmol/L for most age groups (1). It was acknowledged that a dietary intake should maintain serum 25(OH)D above the concentration below which vitamin D deficiency rickets or osteomalacia occurs in the absence of sun exposure. Because there was not sufficient evidence to know what that dietary level should be, it was presumed that reported dietary intakes of a group of apparently healthy adults was sufficient, and this level was adjusted (multiplied by 2) for uncertainty (1).

Problems with the current recommended intakes for vitamin D

There are several constraints on the current recommended values for vitamin D. The nature of the value, i.e., that it is an AI, specifies that it has limited use. In assessment, this value can be used as a goal for an individual, similar to an RDA value. However, it cannot be used to assess prevalence of inadequacy of groups using the cut point or probability methods. Whereas some AI values may be used in comparison to mean intakes, this is not the case for vitamin D levels; these levels were not based on observed mean intakes of population groups, because should be the case when a nutrient's AI is compared with mean intake (13).

More importantly, since publication of the 1997 recommendations for vitamin D (1), much has been learned regarding the metabolism of vitamin D. Thus, a major problem is that the DRI values shown in Table 1 are out of date with respect to recent evidence, as outlined by these proceedings (12,14–17). Indeed, there is now sufficient information to set an EAR (18) and to set one that more accurately reflects the data that, without assurance of sun exposure, a requirement and a subsequent recommendation for vitamin D would be higher than that currently in place. Also, concerns about adverse effects and the level of 25(OH)D associated with toxicity have been addressed (19).

New paradigm for vitamin D metabolism

There are important new findings about vitamin D that deepen our knowledge of its role in calcium metabolism (i.e., calciotropic functions) and broaden our understanding of its roles in other pathways (i.e., noncalciotropic functions). In addition, new data show the relationships of sun exposure to status and explain the role of diet in maintaining status. Status continues to be defined primarily by the level of serum 25-hydroxvitamin (12,15) that is synthesized from vitamin D obtained either through skin synthesis or directly from ingestion (**Fig. 1**). As indicated in **Figure 2**, the exact cutoff values defining "deficiency" and "insufficiency" remain controversial (12,20,21). Having a level of 25(OH)D in the range denoted as "deficiency" only protects against development of rickets and osteomalacia, whereas a level of 25(OH)D in the range

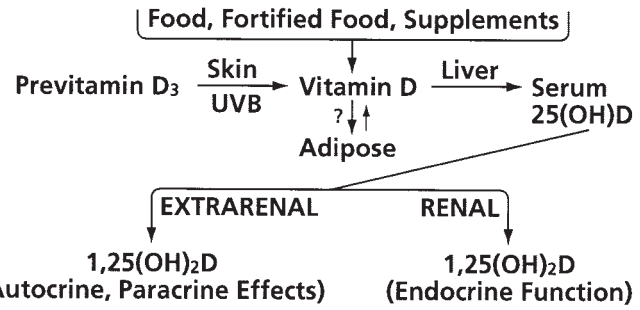

FIGURE 1 Synthesis of 25(OH)D from provitamin D-3 in skin or obtained as vitamin D in food, fortified foods, and supplements. 25(OH)D is converted to the active metabolite $1,25(OH)_2D$ by either a renal pathway or extrarenal pathways; the former is important for calciotropic functions, and the latter leads to paracrine or autocrine actions of $1,25(OH)_2D$ that are noncalciotropic.

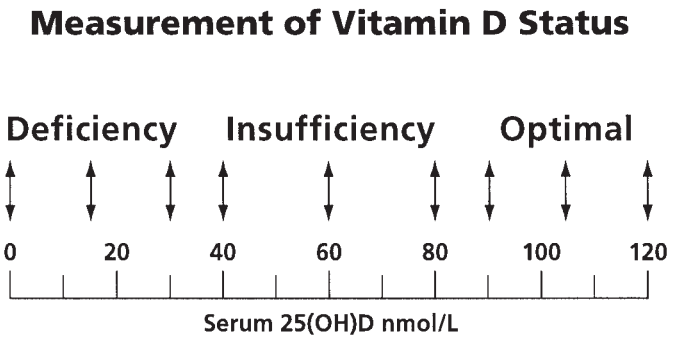

FIGURE 2 Relationship between serum 25(OH)D levels and vitamin D status. Vitamin D insufficiency has not yet been defined but resides between deficiency and optimal status.

denoted as "insufficiency" is not high enough to offer protection from many chronic diseases (**Fig. 3**) (12,16,17,20,22,23).

It is now recognized that the level of 25(OH)D must be high enough to allow for synthesis of 1,25 dihydroxyvitamin D [1,25(OH)$_2$D] in kidney by proximal renal tubule cells (the "renal" synthesis pathway) and for synthesis of 1,25(OH)$_2$D by other cells possessing the 1-hydroxylase enzyme (the "extrarenal" pathway), as depicted in Figure 1 (21). Although the metabolite 1,25(OH)$_2$D remains the active form of vitamin D for noncalciotropic functions, what has shifted in attention is recognition that there is the need for 25(OH)D to be available in sufficient quantities for the 1-hydroxylase enzyme in the nonrenal tissues that synthesize 1,25(OH)$_2$D. The shift in paradigm is away from a single renal source of 1,25(OH)$_2$D for caliotropic functions to there being endocrine, paracrine, and autocrine uses for 1,25(OH)$_2$D (21).

The renal and nonrenal production of 1,25(OH)$_2$D is illustrated in **Figure 4**. Synthesis of 1,25(OH)$_2$D occurs via the classical renal pathway (proximal tubule epithelial cells) or in several other cell types (other epithelial cells, monocytes, antigen presenting cells) (21). These cells contain the enzyme necessary to add a hydroxyl to 25(OH)D at the one position, the 1-α-hydroxylase, but differ in whether they have vitamin D receptor and inducible 24-hydroxyase (21). Availability of 25(OH)D is critical, and there are 3 conditions that may limit this. First, there must be synthesis of vitamin D in the skin, where previtamin D-3 is converted to vitamin D-3 in the presence of ultraviolet B radiation (Fig. 1). Sunscreens, staying indoors, and living at high latitudes impose a limitation of this route of synthesis. Second, availability of vitamin D from ingesting foods is quite limited in the North American diet. Vitamin D supplements, as part of multivitamins, calcium supplements, or natural products (e.g., fish oils) are other ways to obtain vitamin D. Recent data suggest that many Americans are consuming inadequate levels of vitamin D (23–25). And, finally, adipose tissue may function as a metabolic sink for vitamin D-3 and vitamin D-2, limiting their availability for conversion to 25(OH)D. The main evidence for this is from the observation that obese individuals are more likely to have a vitamin D insufficiency (26).

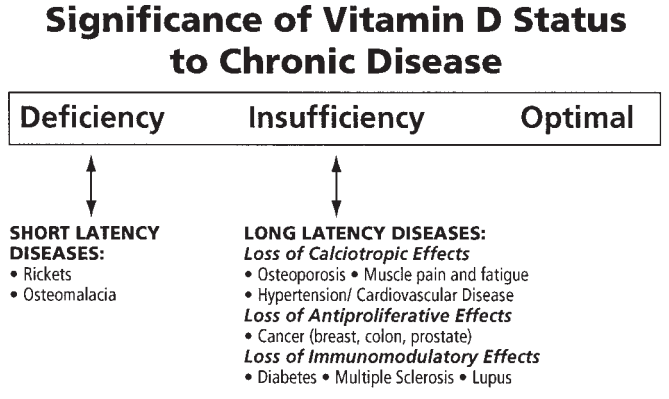

FIGURE 3 Significance of serum 25(OH)D to chronic disease. Short latency diseases are those traditionally associated with vitamin D deficiencies. Long latency diseases are those that take years to develop and may be associated with calcium metabolism, cell proliferation or the immune response (22).

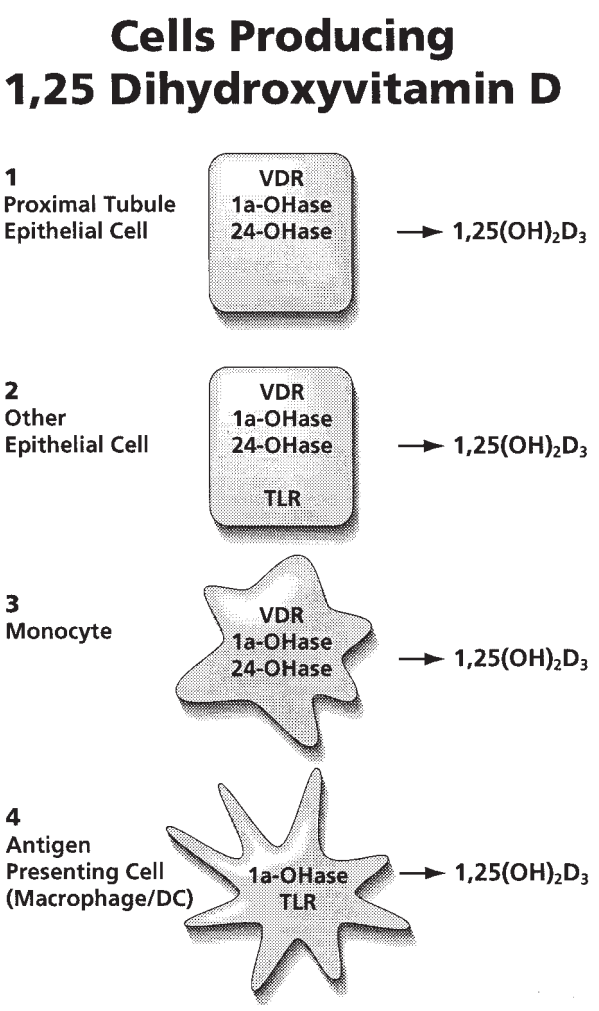

FIGURE 4 Synthesis of 1,25(OH)$_2$D by various cell types, all containing the enzyme necessary to add a hydroxyl to 25(OH)D at the one position, the 1-α-hydroxylase. Type 1, 2, and 3 contain 24-hydroxylase and have vitamin D receptor. Type 4 contains toll-like receptor (TLR). Reproduced with permission from reference (21).

Other information on vitamin D metabolism has been determined. The 2 forms of vitamin D, cholecalciferol (D-3) and ergocalciferol (D-2), have, until recently, been considered equivalent in humans. However, new data from a controlled trial suggest that the D-2 form is less well utilized as D-3 (27). While this remains controversial, with a dissenting observation reported recently (28), there will be a need to evaluate studies in light of this possibility. Also important are conditions that may influence the need for vitamin D. Calcium intake can influence vitamin D status. A high intake of cal-

cium, through its action on suppression of parathyroid hormone (PTH), reduces vitamin D turnover; conversely, a low calcium intake increases metabolic turnover of vitamin D metabolites (20). Other determinants of PTH may similarly influence vitamin D requirements.

Chronic diseases associated with vitamin D deficiency and insufficiency

The newly described roles for $1,25(OH)_2D$ resulting from its extrarenal production have allowed researchers to understand how vitamin D may be involved in more than calcium and phosphorus metabolism. The production of $1,25(OH)_2D$ in the kidney remains the important source of this active metabolite for intestinal absorption of calcium and phosphate and for bone turnover (i.e., the calciotropic functions). There are convincing arguments to view diseases associated with inadequate vitamin D as short latency and long latency (Fig. 3) (22), and calciotropic functions of vitamin D may be associated with the long latency diseases osteoporosis, hypertension, and sarcopenia (29).

Extrarenal synthesis of $1,25(OH)_2D$ is linked to modulation of immune response, and the regulation of cell differentiation, proliferation, and apoptosis (21). Significant extrarenal 1-hydroxylase activity has been found in skin, hair follicles, adrenal medulla, lymph, brain, pancreatic islets, and colon (21). Hewison and colleagues (21) have hypothesized that the noncalciotrophic actions of vitamin D may be those functions for which vitamin D was originally needed in early evolution, i.e., functions related to immune defense, including provisions of barrier integrity for immune surveillance. These newly discovered functions help explain the association between 25(OH)D levels and/or sunlight exposure and many chronic diseases not normally associated with calciotropic functions of vitamin D, such as type I diabetes, type 2 diabetes, cancer, and multiple sclerosis (12,16,17,29,30).

Studies have demonstrated the important effects of race and ethnicity to significantly lower serum 25(OH)D levels in adults over a range of latitudes in North America and over different seasons (23). Despite a low 25(OH)D status, black men and women have a very well-established higher bone mass and a reduced rate of bone fracture compared with whites of comparable age and gender. In sharp contrast to their white counterparts, however, blacks have a much higher incidence and mortality of specific types of aggressive cancers and autoimmune diseases, including type I diabetes, that may be related to their lower levels of serum 25(OH)D (16,17). Thus, functional indicators for vitamin D should include indicators of its noncalciotropic functions.

There is a surprisingly high prevalence of vitamin D insufficiency in healthy adults living in Canada and the United States, 2 countries that have many foods fortified with vitamin D (23). Median vitamin D intakes of Americans indicate that there is an insufficient amount of vitamin D in foods as typically consumed (24,25). Recent studies showing suboptimal serum levels of 25(OH)D confirm the adverse effects of seasonality and latitude on serum 25(OH)D in healthy younger individuals, findings that previously had only been reported in elderly homebound or institutionalized subjects, and in hospital outpatients in North America (15,23). Therefore, it is critical to set EAR and RDA values for vitamin D to facilitate planning and nutrition education initiatives.

The criteria needed to set an EAR

An EAR is best set using both a static indicator and a functional indicator. The static indicator generally measures the concentration of a nutrient or its metabolite, and the measurement directly or indirectly measures storage of the nutrient. For example, leukocyte concentrations of vitamin C directly measure vitamin C storage in a functional tissue, whereas serum magnesium is a measure of transport of this intracellular nutrient, which is a indirect measure of its stores. As shown in **Table 2**, several EARs set for vitamins have used both static and functional indicators (31–33); however, some EARs were set with only 1 type of indicator.

For vitamin D, it would be best to have a static level of the vitamin and an indicator that shows when function of the vitamin has been compromised. For the static measure, there is agreement that serum 25(OH)D is not only the transport form of vitamin D but a direct measure of stores. Yet there is a debate about the level of 25(OH)D to select as the cutoff for vitamin D status (12,15,18,20). What is needed to set an EAR is a dose–response study, and one has recently been published (18). This innovative study measured the amount of dietary vitamin D needed to maintain levels of 25(OH)D levels in a situation of restricted sunlight exposure (18). In the absence of sun exposure, the oral dose of vitamin D that sustains 25(OH)D levels in subjects who have excellent stores of vitamin D from sun exposure is 12.5 μg per day (500 IU) in young adults (18); however, it must be recognized that body stores are also being used during this time. Nevertheless, this value of 12.5 μg (500 IU) is corroborated in a recent study where a 500 IU supplement was sufficient to prevent the winter-time drop in

TABLE 2

Examples of indicators used to set EARs for vitamins (adult values)[1]

Nutrient	Static indicator of transport or stores	Indicator of function
Vitamin C	Near maximal leukocyte levels	
Vitamin E		Prevention of hydrogen peroxide-induced hemolysis
Folate	Erythrocyte folate, serum folate	Plasma homocysteine and
Vitamin B-12	Serum B_{12} levels	Maintenance of hematological status
Vitamin B-6	Women: plasma pyridoxal-phosphate levels	Men: xanthurenic acid and other metabolites following a tryptophan load; plasma homocysteine concentrations
Thiamin	Urinary thiamine	Erythrocyte transketolase
Riboflavin	Urinary riboflavin	Erythrocyte glutathione reductase
Niacin	Urinary excretion of methyl-nicotinamide	
Vitamin A	Adequate liver vitamin A stores	

[1] Information taken from references 29–31.

25(OH)D levels and the accompanying increase in bone turnover and loss of adults living in Germany (34).

To set an RDA from an EAR, the variation in the requirement estimate (SD) is needed, 2 SD are added to the EAR to obtain the RDA. For most micronutrients, a standard estimate of variance of 20% has been applied (where 1 SD = 10%) (30–32). The resulting RDA for vitamin D would be a value > 12.5 μg (500 IU). In setting this higher recommendation, it should be noted that concerns about vitamin D toxicity have been alleviated. Vieth and colleagues (19) initially reported that no adverse effects could be seen at levels twice the current upper level of 50 μg (2000 IU) (1). Heaney et al. (18) extended dosing to 250 μg (10,000 IU) and found no adverse effects in men treated for 5 mo.

It is well established that serum 25(OH)D is the best static indicator of vitamin D, because levels of vitamin D itself, from skin synthesis or absorbed from diet is rapidly cleared from blood within 24 h (12,29). Circulating levels of serum $1,25(OH)_2D$ are largely synthesized in the kidney, under the control of PTH, are influenced by serum calcium and phosphorus levels, and are independent of cutaneous synthesis or intake of vitamin D. What remains controversial is the level at which the cutoff for serum 25(OH)D represents deficiency and insufficiency (Fig. 2). Heaney (22) has provided a useful perspective on this, arguing that, historically, the level of serum 25(OH)D has depended on the level needed to prevent the index diseases rickets and osteomalacia. For those short latency diseases (Fig. 3), a cutoff of 27.5 nmol/L indicates deficiency. In consideration of long latency diseases, such as osteoporosis, diabetes, and cancer, the cutoff for serum 25(OH)D is much higher, perhaps as high as 80 nmol/L. Further, he and others argue that one should not view the cutoff for this metabolite as the level determined using normal ranges, because these may be determined in persons apparently disease free but possibly with inadequate vitamin D status (12,20).

A final note is a concern regarding the measurement of 25(OH)D. There are 2 commonly used commercial methods: a radioimmunoassay method and the competitive protein binding assay. Although both methods claim to recognize the D-2 and D-3 isomers of 25(OH)D, the competitive protein binding assay method yields values that are ~30% higher than the radioimmunoassay method, because protein binding assays are nonspecific (35). Therefore, the cutoff values for 25(OH)D used to define vitamin D status must be defined in terms of appropriate assay methods.

Having functional indicators for vitamin D would make setting an EAR more precise and would allow determination of tissue needs beyond those of the skeleton. **Table 3** provides a list of candidate functional indicators that could be considered for setting the EAR for vitamin D. These include the calciotropic indicators PTH (12,15,20), calcium absorption (33,36), fracture risk (37), blood levels of calcium, phosphorus, and bone turnover markers (38). The most common responsive functional indicator examined to date is the suppression of secondary hyperparathyroidism, based on the calciotropic function of vitamin D in providing enough calcium through active intestinal absorption to suppress PTH levels. Thus, calcium absorption itself can also serve as a functional indicator; Heaney et al. (36) have shown that calcium absorption is 65% higher when serum 25(OH)D is raised from 50 nmol/L to 80 nmol/L. A number of studies suggest strong correlations between serum 25(OH)D and the various bone markers; however, the responses are variable, making them less desirable candidates to serve as functional markers for vitamin D requirements (38). Muscle strength is poor when 25(OH)D levels are low, and the rationale for this has been the provision of adequate phosphate to muscles, a calciotropic function; however, other mechanisms are possible (39). Functional indicators of noncalciotropic function of vitamin D are less well understood (Table 3); however, research is rapidly progressing in determining the role of vitamin D at the cellular and subcellular level.

In summary, vitamin D has emerged as a critical nutrient for which there is a compelling health need to establish adequate dietary guidelines in North America and worldwide given the increasing evidence of vitamin D deficiency and insufficient links to risk of chronic disease. We strongly argue

TABLE 3

Potential candidates as functional indicators for setting the EAR for vitamin D

Indicator	How vitamin D influences function	Indicator of suboptimal status
Calciotropic function		
Parathyroid hormone	By ensuring active transport of calcium, vitamin D restores PTH level to an nonstimulated level	Stimulated level of PTH
Calcium absorption	Optimizes calcium absorption	Percentage absorption of calcium improves when vitamin D provided
Fracture risk	By ensuring active transport of calcium, vitamin D restores PTH level to an nonstimulated level thereby reducing bone turnover	Increase in fracture risk relative to adequate vitamin D status
Muscle strength[1]	By ensuring active transport of phosphate and reduction in PTH to prevent phosphate loss, vitamin D maintains phosphate levels in muscle	Muscle strength tests
Serum calcium and phosphorus	Maintenance of normal serum levels	Relative hypocalcemia and hypophosphatemia
Bone turnover markers	May reduce bone turnover but results to date are highly variable	Increased bone resorption and decreased bone formation
Noncalciotropic function		
Immunomodulatory function	Maturation of antigen-presenting cells	Increase in T-cell proliferation; decrease in killer cells
Cell proliferation	Decrease cell proliferation	More cells in G1 phase of cell cycle compared with G2 or S-phase
Metabolic function	Glucose tolerance and pancreatic beta-cell function are normalized	Glucose clearance rates

[1] Muscle strength may be unrelated to calcium and phosphorus metabolism (39).

that now there are enough data to consider setting an estimated average requirement for vitamin D and to recognize the crucial need for more research to determine the role of vitamin D in noncalciotropic functions and prevention of chronic diseases.

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