Osteoporos Int (2005) 16: 713–716
DOI 10.1007/s00198-005-1867-7

EDITORIAL

Estimates of optimal vitamin D status

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Received: 28 September 2004 / Accepted: 1 February 2005 / Published online: 18 March 2005
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Abstract Vitamin D has captured attention as an important determinant of bone health, but there is no common definition of optimal vitamin D status. Herein, we address the question: What is the optimal circulating level of 25-hydroxyvitamin D [25(OH)D] for the skeleton? The opinions of the authors on the minimum level of serum 25(OH)D that is optimal for fracture prevention varied between 50 and 80 nmol/l. However, for five of the six authors, the minimum desirable 25(OH)D concentration clusters between 70 and 80 nmol/l. The authors recognize that the average older man and woman will need intakes of at least 20 to 25 mcg (800 to 1,000 IU) per day of vitamin D_3 to reach a serum 25(OH)D level of 75 nmol/l. Based on the available evidence, we believe that if older men and women maintain serum levels of 25(OH)D that are higher than the consensus median threshold of 75 nmol/l, they will be at lower risk of fracture.

Keywords Older men and women · Serum level of 25(OH)D · Vitamin D status

This material is based in part on work supported by the U.S. Department of Agriculture, under agreement no. 58-1950-9001. Any opinions, findings, conclusions, or recommendations expressed in this publication are those of the authors and do not necessarily reflect the view of the U.S. Department of Agriculture.

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Introduction

Currently, there is no standard definition of optimal vitamin D status. The circulating 25(OH)D level needed to suppress maximally the serum parathyroid hormone (PTH) concentration has been proposed and used by several investigators. Recently, data have emerged that allow several other endpoints to be considered. This editorial will consider these possibilities and convey the current thinking of the authors on the question: What is the optimal level of serum 25(OH)D for the skeleton? It will also consider the amount of vitamin D_3 needed to reach the optimal serum level of 25(OH)D. These opinions were expressed during a round table discussion at the 5th International Symposium on the Nutritional Aspects of Osteoporosis, held in Lausanne, Switzerland, in May, 2003, and recently published [1]. Several newer findings are also included.

Defining the optimal 25(OH)D level

We will consider several criteria by which the optimal serum 25(OH)D level might be defined, including the level associated with maximal suppression of the circulating PTH concentrations, with greatest calcium absorption, highest bone mineral density (BMD),

reduced rates of bone loss, reduced rates of falling, and reduced fracture rates.

There is some disagreement as to whether PTH truly attains a lower plateau as serum 25(OH)D levels increase [2, 3]. Nonetheless, estimates of the 25(OH)D level needed for maximal suppression of PTH have been placed at 30 [4], 50 [5], 65 to 75 [6], 70 to 75 [7], 75 to 80 [8], and 99 nmol/l [9]. The studies yielding the highest estimates were cross-sectional studies [7, 8, 9]; a variety of statistical methods were used. To minimize assay-related variability, we have standardized published 25(OH)D for each method according to the mean of the Vitamin D External Quality Assurance Survey of over 100 laboratories worldwide [10, 11]. The plateau serum 25(OH)D estimates are: 30 [4], 55 [8], 75 [12], 82 [9], and 99 nmol/l [13]. These estimates of the threshold serum 25(OH)D level vary widely, but there is a cluster in the 75 to 80 nmol/l range. Notably, there are sparse data for 25(OH)D levels above this range. The inverse association of 25(OH)D with serum PTH is also present in children [14] and younger adults [2, 15] in whom the relationship appears to be more responsive to 25(OH)D than in the elderly. For example, if you are older than 70 years and desire a PTH equivalent to that of a young adult who has a serum 25(OH)D of 70 nmol/l, then your 25(OH)D level may need to exceed 100 nmol/l [2].

The effect of vitamin D on PTH is partly mediated by its effect in promoting calcium absorption. In a recent study, mean calcium absorption was 65% greater at serum 25(OH)D levels averaging 86.5 nmol/l than at levels averaging 50 nmol/l [16]. PTH suppression may also be mediated by a more direct mechanism involving metabolism of 25(OH)D to $1,25(OH)_2D$ within parathyroid tissue [17].

In elderly women, serum 25(OH)D and bone mineral density (BMD) of the hip were positively associated at 25(OH)D levels below 30 nmol/l, but not at higher 25(OH)D levels [18]. However, in a recent report, serum 25(OH)D and total hip BMD were positively associated up to 25(OH)D levels of 90 to 100 nmol/l in 13,432 men and women age 20 and older who participated in NHANES III [19]. The association was present in men and women and in Caucasians, Mexican-Americans, and African-Americans, and not dependent upon the level of physical activity. With regard to the effect of vitamin D on change in BMD, bone loss from the spine and hip was reduced during the wintertime with vitamin D supplementation that increased serum 25(OH)D levels from about 60 to 90 nmol/l [20, 21]. These studies in healthy older women demonstrated that vitamin D supplements also reduced net bone loss over 1- and 2-year periods.

There is now evidence that vitamin D alone and in combination with calcium lowers the risk of falling in older men and women. Supplementation that increased mean serum 25(OH)D levels from 30 to 65 nmol/l lowered the total number of falls occurring in very elderly institutionalized women [22]. A recent meta-analysis of five placebo-controlled vitamin D intervention trials involving 1,237 participants found that supplemental vitamin D lowered the risk of first fall by 22% [23]. All but one of the five trials used a 20-mcg dose of vitamin D or an active metabolite of the vitamin. Higher serum 25(OH)D levels have also been associated with improved lower extremity function (faster walking and sit-to-stand speeds) in older men and women [24], before and after adjustment for the level of physical activity and other factors.

Concerning the most important endpoint—fractures—the results of several randomized controlled supplement trials are summarized in Table 1. Both published and standardized [10] serum 25(OH)D values of the subjects taking vitamin D supplements are shown in this table. Studies in which supplementation brought mean serum 25(OH)D levels up to 71 to 99 nmol/l (standardized values) found significantly lowered fracture rates (25, 26, 27, 28, 29), whereas the study in which 25(OH)D increased to 54–62 nmol/l did not [30, 31]. In these studies, fracture risk was reduced at vitamin D_3 dosages of 17.5 and 20 mcg/d [25, 26, 27, 28, 29], but not at the lower dose of 10 mcg/d [30]. As expected, the higher supplement doses were associated with larger decrements in serum PTH. The calcium supplementation in several of these studies probably also played a role in the PTH decrease and fracture prevention.

Table 1 Serum 25(OH)D, PTH, and non-vertebral fracture responses to supplementation with vitamin D_3. From Dawson-Hughes et al. [1], with permission

Study	Gender	Dose vitamin D_3 (/d)	Published serum 25(OH)D values (nmol/l)	Standardized[a] serum 25(OH)D values (nmol/l)	Effect on serum PTH (%)	Preventative effect on non-vertebral fracture (hip and others)
Chapuy [25, 26]	F	20 [b]	100	71	–47	+ +
Chapuy [27]	F	20 [b]	100	71	–33	+
Dawson-Hughes [28]	M, F	17.5 [b]	112	99	–23 [c] –33 [c]	+
Trivedi [29]	M, F	20.5	74	–	–	+
Lips [30]	M, F	10	54	54	–15 [d]	NS

[a]Serum 25(OH)D values standardized to all laboratories mean data on the DEQAS proficiency survey [10]
[b]Supplemental calcium also given
[c]The decrease was 33% in females and 23% in males
[d]Difference between vitamin D and placebo groups after 1 year [31]

Vitamin D_3 intake needed to reach the optimal serum 25(OH)D level

It is generally recognized that the increment in serum 25(OH)D in response to a given oral dose of vitamin D_3 is inversely related to the starting level of 25(OH)D [3, 32]. The average increment in serum 25(OH)D has been estimated at 1.2 nmol/l for every mcg (40 IU) of vitamin D_3 given as a daily oral dose at low starting serum 25(OH)D levels and only 0.7 or less nmol/l at the higher starting level of 70 nmol/l [2, 33]. Vitamin D_2 gives a smaller increment of only 0.3 nmol/l for every mcg [34, 35]. In healthy young and middle-aged adults, 25 mcg of vitamin D_3/d corrected vitamin D deficiency and maintained serum 25(OH)D levels between 80 and 100 nmol/l [36]. In adults with serum 25(OH)D levels under 60 nmol/l, a weekly dose of 700 mcg (28,000 IU) of vitamin D_3 produced an average 25(OH)D level above 70 nmol/l in all subjects [37]. As an alternative approach to replacement, Holick notes that for patients with starting serum 25(OH)D levels over 50 nmol/l, a dose of 1,250 mcg (50,000 IU) of vitamin D_2 twice per month will maintain their levels between 75 an 100 nmol/l. Patients with lower starting levels will need loading doses of vitamin D. The level of calcium intake does not appear to modify the impact of oral vitamin D_3 on the serum 25(OH)D level [38].

Conclusion

Our individual answers to the question of optimal serum 25(OH)D level and the amount of vitamin D_3 needed for the average adult to reach that level are summarized in Table 2. There is a common opinion that the optimal serum 25(OH)D level for bone health is between 50 and 80 nmol/l, with five of the six estimates clustered between 70 and 80 nmol/l. A daily intake of 15 mcg (600 IU) of vitamin D_3 is needed to reach a mean serum 25(OH)D level of 50 nmol/l and at least 20–25 mcg (800–1,000 IU) is needed to attain a mean level of 75 nmol/l. This reappraisal of the lower limit of vitamin D sufficiency has two important clinical implications: vitamin D insufficiency is much more common than previously believed, and this presents the possibility that vitamin D supplements may prevent many fractures, particularly in the elderly. To achieve this benefit, it is important to ensure that the serum 25(OH)D level obtained after vitamin D supplementation in individual patients reaches this new threshold. However, Lips expressed the view that at this time the criterion for broad-based supplementation in the general population is not fulfilled, except for in high-risk groups, such as the elderly, nursing home residents, and all other persons with negligible exposure to sunshine. Meanwhile, more data are needed on the utility of vitamin D doses beyond 20 mcg/day, and studies are needed to determine whether the use of any amount of vitamin D prior to the age of 50 might affect the development of osteoporosis. We all agree that the questions addressed in this workshop are not yet fully answered and will require ongoing evaluation of data from a variety of studies.

Table 2 Estimates of the minimum serum 25(OH)D levels optimal for fracture prevention and the doses of vitamin D_3 needed to achieve them. From Dawson-Hughes et al. [1], with permission

Investigator	Optimal 25(OH)D level, nmol/l	Oral vitamin D_3 dose needed to reach average optimal 25(OH)D level[a]	
		μg/d	IU/d
Lips	50	10–15	400–600
Holick	75	25	1,000 [b]
Heaney	80	40	1,600
Meunier	75	20	800
Vieth	70	25	1,000
Dawson-Hughes	80	25	1,000

[a]Estimated dose to deliver the average 25(OH)D levels given in the table (equivalent to an estimated average requirement).
[b]Consistent with the recent observation that 1,000 IU of vitamin D_3/d in orange juice maintained an average 25(OH)D level of 94 ± 20 nmol/l [35]

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