

Title: Vitamin D Round Table

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This round table discussion addressed the following two questions:

1. What is the optimal level of 25-hydroxyvitamin D [25(OH)D] for the skeleton and why?
2. How much vitamin D<sub>3</sub> (cholecalciferol) is needed to reach the optimal level of 25(OH)D?

The participants in the roundtable were: Paul Lips, M.D., Ph.D., Michael Holick, M.D., Ph.D., Robert P. Heaney, M.D., Pierre Meunier, M.D., Reinhold Vieth, Ph.D., and Bess Dawson-Hughes, M.D.

Each of the participants spent five minutes presenting his/her answers to these questions along with supporting evidence. The presentations were followed by a 45-minute general discussion with audience participation. This paper summarizes the views expressed during the round table.

- I. What is the optimal level of 25(OH)D for the skeleton and why?

The participants considered several criteria by which the optimal 25(OH)D level might be defined. These included the level needed to maximally suppress the circulating parathyroid hormone (PTH) concentration, the 25(OH)D level

associated with the highest bone mineral density (BMD), with greatest calcium absorption, with reduced rates of bone loss, and with reduced fracture rates. The issue of vitamin D status and risk of falling was addressed in the discussion.

Dr. Lips pointed out that the 25(OH)D level associated with maximal suppression of PTH in his study was 30 nmol/L (1). Several participants cited other estimates. Meunier noted that studies have placed the estimate at 75 to 80 nmol (2), 70 to 75 nmol (3), 65 to 75 nmol (4) and 50 nmol/L (5). Dr. Dawson-Hughes standardized 25(OH)D levels from several studies to DiaSorin equivalent values using the cross calibration study of Lips (6). This resulted in threshold 25(OH)D values of 55 nmol/L (2), 75 nmol/L (7), 82 nmol/L (8), and 99 nmol/L (9). Thus the estimates of 25(OH)D required for maximal PTH suppression vary widely from 30 to 99 nmol/L, and there is a cluster of estimates in the 75 to 80 nmol range. Dr. Holick noted that the inverse association in 25(OH)D and PTH is also present in healthy young adults, in whom he identified a threshold 25(OH)D level of 75 nmol/L (10). Dr. Vieth pointed out that the relationship between PTH and 25(OH)D changes with age; for example, if you are older than 70 years and desire a PTH equivalent to that of a young adult, your 25(OH)D level needs to exceed 100 nmol/L (11).

With regard to 25(OH)D levels and calcium absorption, Dr. Heaney cited his recent observation that calcium absorption increases with increasing 25(OH)D levels and that calcium absorption was 65% greater at serum 25(OH)D levels

averaging 86.5 nmol/L than at levels averaging 50 nmol/L (12). Increased absorption of calcium results in an increase in the circulating level of ionized calcium and a reduction in the circulating PTH level. Thus Dr. Heaney's finding describes the metabolic basis for the observation that increasing the 25(OH)D level to 75 to 80 nmol/L lowers the circulating level of PTH.

Dr. Lips noted that 25(OH)D and BMD of the hip are positively associated at 25(OH)D levels below 30 nmol/L, but not at higher 25(OH)D levels (13). In contrast, hip BMD increased with increasing 25(OH)D levels up to 90 to 100 nmol/L, according to an earlier presentation at the meeting by Bischoff. The latter analysis included men and women age 51 and older who participated in the NHANES III survey.

With regard to the effect of vitamin D on change in BMD, Dr. Dawson-Hughes noted that bone loss during the wintertime was reduced with vitamin D supplementation that increased serum 25(OH)D levels from about 60 to 90 nmol/L (14,15). These studies in healthy older women also demonstrated that vitamin D supplements reduced bone loss from the hip (14) and spine (15) year round.

Concerning the most important endpoint – fractures – Heaney highlighted the randomized controlled trial recently published in Great Britain in which elevating mean serum 25(OH)D from 53.4 to 74.3 nmol/L produced a 33% reduction in

typical osteoporotic fractures, over a 5-year treatment period (16). The available randomized controlled supplement studies were summarized by Dr. Meunier who noted that studies in which supplementation brought mean serum 25(OH)D levels up to the range of 74 to 112 nmol/L significantly lowered fracture rates whereas the study in which 25(OH)D increased to only 54 nmol/L per day did not significantly change fracture rates (16-21) (Table 1). Published serum 25(OH)D values and values that have been standardized to DiaSorin equivalent values are also shown in Table 1. Dr. Meunier noted that the higher supplement doses were associated with bigger decrements in serum PTH.

An audience participant raised the issue that part of the reduction in fracture rates seen with vitamin D supplementation may be related to the effect of vitamin D in lowering risk of falling. Indeed, supplementation that increased 25(OH)D levels from 30 to 65 nmol/L has been shown to lower the number of falls occurring in very elderly institutionalized women (22). This mechanism may have been a factor in the vitamin D intervention trials conducted in very elderly and D-deficient subjects, such as the trials reported by Chapuy (17,18). However, there is no evidence that it was a significant factor in a younger cohort of men and women, mean age 71 years (19). In that study the fall rate was found to be similar in the supplemented and placebo groups (19).

II. How much cholecalciferol is needed to reach the optimal level of 25(OH)D?

Dr. Vieth pointed out that at low daily doses of supplemental cholecalciferol, the increase in 25(OH)D per  $\mu\text{g}$  is 1.2 nmol/L. According to the findings of Drs. Vieth and Heaney, at higher doses, this figure drops to 0.7 nmol/L for every  $\mu\text{g}$  of cholecalciferol given as a daily oral dose (12,23). Dr. Lips noted that the increase in serum 25(OH)D following supplementation with 400 to 600 IU/d is very much dependent upon the baseline serum 25(OH)D level. He observed a large increase when baseline serum 25(OH)D was low and a small increase when it was high (24). Vitamin D<sub>2</sub>, ergocalciferol, gives a smaller increment of only 0.3 nmol/L for every  $\mu\text{g}$  (25). Dr. Holick finds that for patients with starting 25(OH)D levels over 50 nmol/L, 50,000 IU of vitamin D<sub>2</sub> twice per month will maintain their levels between 75 and 100 nmol/L. Patients with lower starting levels will need loading doses of vitamin D. Dr. Dawson-Hughes noted that of the 389 participants in her study who took 700 IU/d of cholecalciferol (together with 500 mg of supplemental calcium), 90% of the men and 87% of the women had 25(OH)D levels of 80 nmol/L or higher (measured year round) whereas only 57% of the men and 28% of the women in the placebo group had levels as high as 80 nmol/L (26). These subjects consumed an average of 200 IU of vitamin D per day in their diets. Dr. Vieth summarized the relationship between cholecalciferol dose and outcomes in fracture prevention trials (Figure 1). Fracture risk was reduced at cholecalciferol dosages of 700 and 800 IU/d, but not at lower doses.

In closing, the participants' answers to the two questions are summarized in Table 2. There is some convergence of opinion that the optimal 25(OH)D level for bone health is around 75 nmol/L and that an intake of 800 to 1000 IU of cholecalciferol is needed to attain the desired 25(OH)D level of 75 nmol/L. The group agreed with Dr. Meunier that this reappraisal of the lower limit of vitamin D sufficiency has two important clinical consequences: vitamin D insufficiency is much more common than previously believed and this is relevant to larger possibilities of vitamin D supplements for preventing fractures, particularly in elderly subjects; in addition it is important to ensure that the serum 25(OH)D level obtained after vitamin D supplementation reaches this new threshold. However, Dr. Lips expressed the view that at this time the criterion for broad-based supplementation is not fulfilled.

An audience opinion poll was taken at the beginning and again at the end of the round table. Participants were asked to vote for the 25(OH)D level that was closest to their view of optimal, given the choices of 0, 20, 40, 60, 80, and 100 nmol/L. The results of the poll are shown in Figure 2. There is a clear preference among these scientists in the general nutrition community for a 25(OH)D level of 80 nmol/L. However, we all concede 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 1. Serum 25(OH)D, PTH, and nonvertebral fracture responses to supplementation with vitamin D<sub>3</sub>

Study	Gender	Dose vit D (IU/d)	Published serum 25(OH)D values (nmol/L)	Standardized* serum 25(OH)D values (nmol/L)	Effect on PTH (%)	Preventative effect on non vert fx (hip and others)
Chapuy (17,21)	F	800	100	71	-47	++
Chapuy (18)	F	800	100	71	-33	+
Dawson-Hughes (19)	M, F	700	112	99	F -33 M -23	+
Lips (20)	M, F	400	54	54	-6	NS
Trivedi (16)	M, F	820	74	-	-	+

\*Serum 25(OH)D values standardized to DiaSorin equivalent values (i.e., HPLC followed by a competitive protein binding assay), based on a cross-calibration study (24).

Table 2. Round table participants' views of the optimal 25(OH)D levels and the doses of cholecalciferol needed to achieve those levels

Participant	Optimal 25(OH)D	Oral cholecalciferol dose needed to	
	level, nmol	reach average optimal 25(OH)D level, µg/d	IU/d
Lips	50	10-15	400-600
Holick	75	25	1000
Heaney	80	40*	1600*
Meunier	75	20	800
Vieth	70	25**	1000
Dawson-Hughes	80	25	1000

\*Based on data in the Trivedi paper (16).

\*\*Estimated dose to deliver an *average* 25(OH)D level of 70 nmol/L is given in the table, but the dose needed to provide the level of 70 nmol/L for practically all healthy adults (criterion for an RDA) would be 100 mcg/day.



Figure 1.

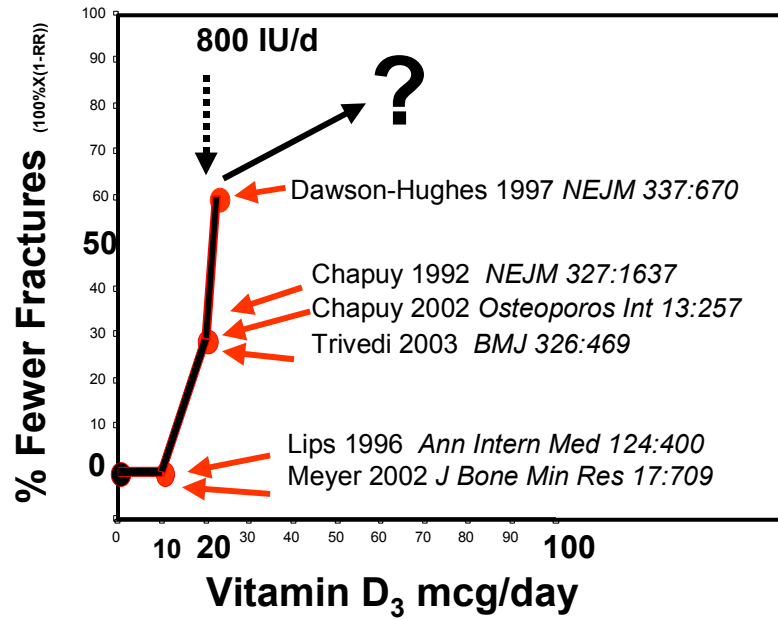
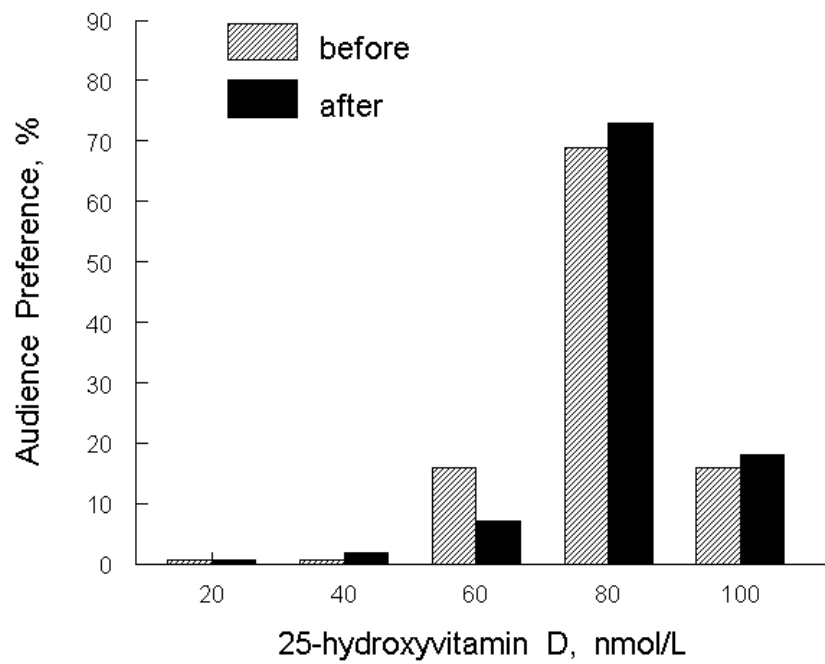




Figure 2.



## Figure Legends

Figure 1. Fracture prevention studies with Vitamin D<sub>3</sub>

Figure 2. Scientific audience views of optimal 25(OH)D levels for bone health.  is their view at the beginning and  is their view at the end of the round table discussion.

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