CHAPTER 5

Optimal Serum 25-Hydroxyvitamin D Levels for Multiple Health Outcomes
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Abstract
Recent evidence suggests that higher vitamin D intakes beyond current recommendations may be associated with better health outcomes. In this chapter, evidence is summarized from different studies that evaluate threshold levels for serum 25(OH)D levels in relation to bone mineral density (BMD), lower extremity function, dental health, risk of falls, admission to nursing home, fractures, cancer prevention and incident hypertension. For all endpoints, the most advantageous serum levels for 25(OH)D appeared to be at least 75 nmol/l (30 ng/ml) and for cancer prevention, desirable 25(OH)D levels are between 90-120 nmol/l (36-48 ng/ml). An intake of no less than 1000 IU (25 mcg) of vitamin D3 (cholecalciferol) per day for all adults may bring at least 50% of the population up to 75 nmol/l. Thus, higher doses of vitamin D are needed to bring most individuals into the desired range. While estimates suggest that 2000 IU vitamin D3 per day may successfully and safely achieve this goal, the implications of 2000 IU or higher doses for the total adult population need to be addressed in future studies.

Introduction
Current efforts to assess optimal levels of serum 25(OH)D levels generally focus on bone health in older Caucasian persons and the common means to define optimal 25(OH)D has been the level that maximally suppresses serum parathyroid hormone (PTH). This is a useful criterion because PTH promotes bone loss, but concerns related to this approach are several, such as fluctuations related to diet,^{3,4} time of day,^{4} renal function^{5} and physical activity.{^{6}} Estimates of optimal 25(OH)D levels using PTH suppression vary widely from 20 to 110 nmol/l (9 to 38 ng/ml)\(^6^{11}\) and a consensus has not been reached.

Thus, this chapter examines several alternative endpoints to the maximal suppression of PTH for bone health, including BMD in younger and older adults of different racial/ethnic backgrounds and antifracture efficacy based on a recent meta-analysis of double-blind randomized controlled trials (RCTs).^{12} In addition, optimal 25(OH)D levels for nonskeletal outcomes of public health significance are evaluated, including lower extremity function and falls, nursing home admission, dental health, cancer prevention and hypertension. Finally, the optimal 25(OH)D levels and corresponding vitamin D intakes throughout adult life that best enhance health are discussed.

25(OH)D Levels and Bone Health

Background
BMD may be a better endpoint than serum PTH for the estimation of optimal 25(OH)D levels in regard to bone health for a large part of the population, including younger individuals

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and non-Caucasian ethnicities. In the elderly, BMD is a strong predictor of fracture risk, and evidence from several RCTs suggest a positive effect of vitamin D supplementation on BMD. Furthermore, BMD integrates the lifetime impact of many influences on the skeleton, including PTH.

**Optimal 25(OH)D Levels for BMD**

A threshold for optimal 25(OH)D and hip BMD has been addressed among 13,432 individuals of NHANES III (The Third National Health and Nutrition Examination Survey) including both younger (20-49 years) and older (50+ years) individuals with different ethnic racial background. Compared to the lowest quintile of 25(OH)D the highest quintile had higher mean BMD by 4.1% in younger whites (test for trend; p < 0.0001), by 4.8% in older whites (p < 0.0001), by 1.8% in younger Mexican Americans (p = 0.004), by 3.6% in older Mexican Americans (p = 0.01), by 1.2% in younger blacks (p = 0.08) and by 2.5% in older blacks (p = 0.03). In the regression plots higher serum 25(OH)D levels were associated with higher BMD throughout the reference range of 22.5 to 94 nmol/l in all subgroups (Figs. 1A and B). In younger whites and younger Mexican Americans, higher 25(OH)D was associated with higher BMD even beyond 100 nmol/l.

**Optimal 25(OH)D Levels for Fracture Prevention Efficacy**

A meta-analysis of primary prevention high-quality RCTs published in 2005, evaluated the antifracture efficacy of oral vitamin D supplementation in older persons (all trials used cholecalciferol). Five RCTs for hip fracture (n = 9294) and seven RCTs for nonvertebral fracture risk (n = 9820) were included. There was heterogeneity among studies for both hip fracture and nonvertebral fracture prevention, which disappeared after pooling RCTs with low dose vitamin D (400 IU/day, 10 mcg/day) and higher dose vitamin D (700-800 IU/day; 17.5-20 mcg/day) separately. 700-800 IU vitamin D per day reduced the relative risk (RR) of hip fracture by 26% (pooled RR = 0.74; 95% CI [0.61, 0.88]) and any nonvertebral fracture by 23% (pooled RR = 0.77; 95% CI [0.68, 0.87]) compared to calcium or placebo. No significant benefit was observed for RCTs with 400 IU vitamin D per day (pooled RR for hip fracture was 1.15; 95% CI [0.88, 1.50] and for any nonvertebral fracture 1.03; 95% CI [0.86, 1.24]). The most recent Women’s Health Initiative (WHI) trial comparing 400 IU vitamin D plus 1000 mg calcium to placebo among 36,282 postmenopausal women confirm the findings of the earlier meta-analysis indicating no benefit of low dose vitamin D on hip fracture risk (RR = 0.88; 95% CI [0.72, 1.08]).

From left to right, Figures 2 A and B indicate increased antifracture efficacy with higher achieved 25(OH)D levels in the treatment group for both hip (2A) and any nonvertebral fracture (2B), which reached significance in meta-regression analyses. From Figures 2 A and B optimal fracture prevention appeared to occur in trials with achieved mean 25(OH)D levels of at least 74 nmol/l. This level was reached only in trials that gave 700-800 IU cholecalciferol starting from mean baseline levels between 44 and 77 nmol/l. Thus optimal fracture prevention may require more than 700-800 IU vitamin D in populations with baseline 25(OH)D levels below 44 nmol/l and baseline levels may depend on latitude, type of dwelling, and fortification of dairy products with vitamin D. Low baseline levels plus low compliance may in part explain why two recent trials from the UK, which were not included in the 2005 meta-analysis, did not achieve antifracture efficacy with 800 IU cholecalciferol per day.

In the Record Trial, starting from a mean of 38 nmol/l (15.2 ng/ml), the achieved mean 25(OH)D levels were 62 nmol/l in the vitamin D treatment group. This is, according to the 2005 meta-analysis, not enough for fracture prevention. The small increase in 25(OH)D levels despite the 800 IU vitamin D intervention dose may be explained by the low compliance in the trial: 60% at 12 months and 47% at 24 months among persons who returned the 4-monthly questionnaire and even lower if all participants were considered. In the second UK trial 800 IU vitamin D by Porthouse and colleagues 25(OH)D levels were not reported. Limitations of the Porthouse trial were the open design plus low compliance. In addition, instructions given to the control group regarding adequate calcium and vitamin D intake may have biased the result towards the null. Still, the authors report an effect size for hip fracture prevention with vitamin D that is similar to...