Estimation of optimal serum concentrations of 25-hydroxyvitamin D for multiple health outcomes[1–3]

Heike A Bischoff-Ferrari, Edward Giovannucci, Walter C Willett, Thomas Dietrich, and Bess Dawson-Hughes

ABSTRACT

Recent evidence suggests that vitamin D intakes above current recommendations may be associated with better health outcomes. However, optimal serum concentrations of 25-hydroxyvitamin D [25(OH)D] have not been defined. This review summarizes evidence from studies that evaluated thresholds for serum 25(OH)D concentrations in relation to bone mineral density (BMD), lower-extremity function, dental health, and risk of falls, fractures, and colorectal cancer. For all endpoints, the most advantageous serum concentrations of 25(OH)D begin at 75 nmol/L (30 ng/mL), and the best are between 90 and 100 nmol/L (36–40 ng/mL). In most persons, these concentrations could not be reached with the currently recommended intakes of 200 and 600 IU vitamin D/d for younger and older adults, respectively. A comparison of vitamin D intakes with achieved serum concentrations of 25(OH)D for the purpose of estimating optimal intakes led us to suggest that, for bone health in younger adults and all studied outcomes in older adults, an increase in the currently recommended intake of vitamin D is warranted. An intake for all adults of ≥1000 IU (40 μg) vitamin D (cholecalciferol)/d is needed to bring vitamin D concentrations in no less than 50% of the population up to 75 nmol/L. The implications of higher doses for the entire adult population should be addressed in future studies. *Am J Clin Nutr* 2006;84:18–28.

KEY WORDS 25-Hydroxyvitamin D, vitamin D intake, bone density, lower-extremity strength, colorectal cancer

INTRODUCTION

Current efforts to assess optimal serum concentrations of 25-hydroxyvitamin D [25(OH)D] generally focus on bone health in older white persons, and the common definition of the optimal 25(OH)D concentration has been the concentration that maximally suppresses serum parathyroid hormone (PTH). This is a useful criterion because PTH promotes bone loss, but fluctuations related to diet (1, 2), time of day (3), renal function (1), and physical activity (4) raise concerns with respect to this approach. Estimates of optimal 25(OH)D concentrations reached by using the PTH suppression criterion vary widely, from 20 to 110 nmol/L (9–38 ng/mL; 5–10), and a consensus has not been reached. Serum 25(OH)D concentrations have also been related to calcium absorption, but those studies did not allow for estimation of a precise threshold (11, 12).

This review draws together recent work by the authors and places it in the context of other research to estimate the optimal 25(OH)D concentration for multiple health outcomes. Specifically, we examine several alternative endpoints to the maximal suppression of PTH or optimal calcium absorption, including bone mineral density (BMD) in younger and older adults of different racial or ethnic backgrounds and antifracture efficacy, as ascertained in a recent meta-analysis of double-blind randomized controlled trials (RCTs; 13). We also evaluated optimal 25(OH)D concentrations for nonskeletal outcomes of public health significance, including lower-extremity function, falls, dental health, and colorectal cancer prevention. Finally, our goal was to ascertain the optimal 25(OH)D concentrations and the corresponding vitamin D intakes throughout adult life that best enhance health (14).

MATERIALS AND METHODS

This review summarizes the evidence for optimal serum 25(OH)D concentrations. The endpoint selection for this review was based the strongest evidence to date—ie, that from RCTs, consistent evidence from prospective and cross-sectional epidemiologic studies, and strong mechanistic evidence or dose-response relations. BMD, fracture prevention, lower-extremity function, falls, oral health, and colorectal cancer met these criteria. Weaker evidence exists of a beneficial effect of vitamin D on other diseases, including multiple sclerosis (15), tuberculosis (16), insulin resistance (17, 18), cancers other than colorectal (19–22), osteoarthritis (23, 24), and hypertension (25–27), but these diseases are not considered here.

We reviewed studies that evaluated threshold concentrations for 25(OH)D regarding the above outcomes. The most recent

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studies designed by some of the authors of this review to define such thresholds are shown as figures and are the focus of this review and data synthesis (28–31).

Concentrations of 25-hydroxyvitamin D and bone health

Background

In a large part of the population, including younger persons and nonwhite racial-ethnic groups, BMD may be a better endpoint than serum PTH for the estimation of optimal 25(OH)D concentrations with respect to bone health. In the elderly, BMD is a strong predictor of fracture risk (32), and evidence from several RCTs suggests a positive effect of vitamin D supplementation on BMD (33–35). Moreover, BMD integrates the lifetime effect of many influences on the skeleton, including PTH.

Optimal 25-hydroxyvitamin D concentrations for BMD

A threshold for optimal 25(OH)D and BMD has been addressed only recently (28). The association between serum 25(OH)D and hip BMD among 13 432 subjects of the third National Health and Nutrition Examination Survey (NHANES III), including both younger (20–49 y) and older (≥50 y) persons with different ethnic-racial backgrounds was examined by some of the authors of this review (28). Compared with subjects in the lowest quintile of 25(OH)D, those in the highest quintile had mean BMD that was 4.1% higher in younger whites (P for trend < 0.0001), 4.8% higher in older whites ($P < 0.0001$), 1.8% higher in younger Mexican Americans ($P = 0.004$), 3.6% higher in older Mexican Americans ($P = 0.01$), 1.2% higher in younger blacks ($P = 0.08$), and 2.5% higher in older blacks ($P = 0.03$). In the regression plots, higher serum 25(OH)D concentrations were associated with higher BMD throughout the reference range of 22.5 to 94 nmol/L in all subgroups (**Figure 1**). In younger whites and younger Mexican Americans, higher 25(OH)D was associated with higher BMD, even that >100 nmol/L.

Optimal 25-hydroxyvitamin D concentrations for fracture prevention efficacy

In a recent meta-analysis, we evaluated the antifracture efficacy of oral vitamin D supplementation in older persons (all trials used cholecalciferol) (13). Five RCTs of hip fracture ($n = 9294$) and 7 RCTs of nonvertebral fracture risk ($n = 9820$) were included. There was heterogeneity among studies of both hip fracture and nonvertebral fracture prevention, which disappeared after RCTs with low-dose vitamin D (400 IU/d; 10 μg/d) were pooled and evaluated separately from the pooled group of RCTs with higher-dose vitamin D (700–800 IU/d; 17.5–20 μg/d). Vitamin D intakes of 700–800 IU/d 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 with calcium or placebo. No significant benefit was observed in RCTs with intakes of 400 IU vitamin D/d (pooled RR for hip fracture was 1.15; 95% CI: 0.88, 1.50; that for any nonvertebral fracture was 1.03; 95% CI: 0.86, 1.24). The most recent Women's Health Initiative (WHI) trial, which compared 400 IU vitamin D plus 1000 mg calcium with placebo in 36 282 postmenopausal women, confirmed the findings of the earlier meta-analysis by indicating no benefit of low-dose vitamin D for hip fracture risk (RR = 0.88; 95% CI: 0.72, 1.08; 36).

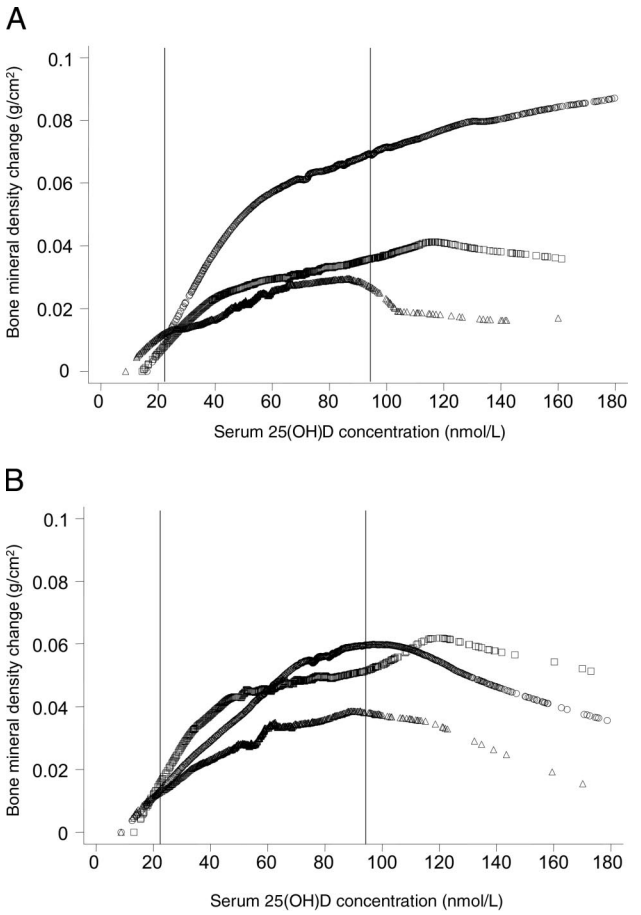

FIGURE 1. Regression plot of difference in bone mineral density by 25-hydroxyvitamin D [25(OH)D] concentrations in younger (20–49 y; A) and older (≥50 y; B) adults after adjustment for sex, age, BMI, smoking, calcium intake, estrogen use, month of vitamin D measurement, and poverty income ratio. Whites, ○; Mexican Americans, □; African Americans, △. The intercept was set to 0 for all racial-ethnic groups to focus on the differences in bone mineral density by 25(OH)D concentrations, rather than the differences by race-ethnicity. The reference range of the 25(OH)D assay (22.5–94 nmol/L) is marked by vertical lines. The reference range of the Diasorin assay (Diasorin, Stillwater, MN) was provided by the company and was established by using 98 samples from apparently healthy volunteers that were collected in the Southwestern United States (high latitude) in late autumn (www.fda.gov/cdrh/pdf3/k032844.pdf). Weighting accounts for sampling weights, stratification, and clustering (from the third National Health and Nutrition Examination Survey. Adapted from Bischoff-Ferrari HA, et al. Positive association between 25-hydroxy vitamin D levels and bone mineral density: a population-based study of younger and older adults. Am J Med 2004; 116(9):634–9. Copyright © (2004), America Journal of Medicine. All rights reserved (28).

Greater antifracture efficacy with higher achieved 25(OH)D concentrations in the treatment group for both hip and any nonvertebral fracture, a difference that reached significance in metaregression analyses, is shown in **Figure 2**). It appears that optimal fracture prevention occurred in trials with mean achieved 25(OH)D concentrations of ≈100 nmol/L. These concentrations were reached only in trials that gave 700–800 IU cholecalciferol/d to subjects with mean baseline concentrations between 44 and 77 nmol/L. Thus, optimal fracture prevention may require intakes of >700–800 IU vitamin D/d in populations with baseline 25(OH)D concentrations <44 nmol/L, and baseline concentrations may depend on latitude (44), type of dwelling

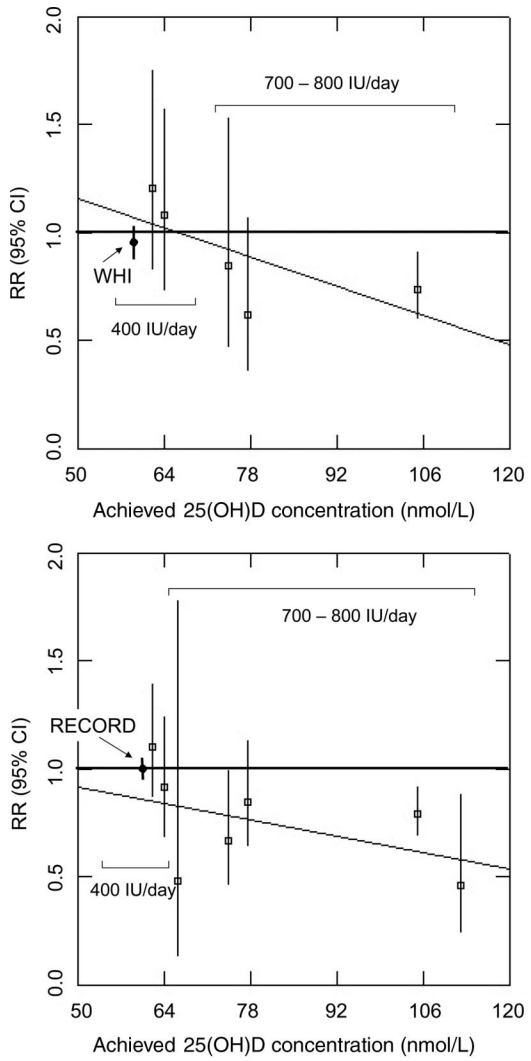

FIGURE 2. Relative risks (RRs; □) of hip fracture (A) and nonvertebral fracture (B) between subjects who took vitamin D and control subjects. A: All trials identified for the primary analysis are included (from left to right): Lips et al (38), Meyer et al (39), Trivedi et al (40), Decalyos II (41), and Decalyos I (34). Error bars represent 95% CIs. The trend line is based on a series of effect sizes (□). A meta-regression including 9294 subjects indicated a significant inverse relation between higher achieved 25-hydroxyvitamin D [25(OH)D] concentrations in the treatment group and hip fracture risk ($\beta = -0.009$, $P = 0.02$), which meant that the log RR of hip fracture is estimated to decrease by 0.009 per 1-nmol/L increase in 25(OH)D. We added the result of the Women's Health Initiative (WHI) that compared 400 IU vitamin D plus 1000 mg Ca with placebo. The WHI achieved serum 25(OH)D concentrations of 59 to 62 nmol/L in the treatment group (estimated 28% increase from baseline according to the nested case-control study data) with an RR of 0.88 (95% CI: 0.72,1.08; 36). B: All trials identified for the primary analysis are included (from left to right): Lips et al (38), Meyer et al (39), Pfeifer et al (37), Trivedi et al (40), Decalyos II (41), Decalyos I (34), and Dawson-Hughes et al (33). Error bars represent 95% CIs. The trend line is based on series of effect sizes (□). A meta-regression including 9820 subjects indicated a significant inverse relation between higher achieved 25(OH)D concentrations in the treatment group and any nonvertebral fracture risk ($\beta = -0.006$, $P = 0.03$), which meant that the log RR of nonvertebral fracture is estimated to decrease by 0.006 per 1-nmol/L increase in 25(OH)D achieved in the treatment group. Diasorin equivalent values [Diasorin, Stillwater, MN (42)] are Lips (50): 54 nmol/L; Meyer (39): as reported, Diasorin equivalent values were not available (43); Pfeifer (37): as reported, Diasorin equivalent values were not available; Decalyos II (41): 63 nmol/L; Decalyos I (34): 75 nmol/L; Trivedi (40): 74 nmol/L; and Dawson-Hughes (33): 99 nmol/L. Adapted from Bischoff-Ferrari HA, et al. Fracture prevention with vitamin D supplementation: a meta-analysis of randomized controlled trials. JAMA 2005;293(18):2257–64. Copyright © (2005), American Medical Association. All rights reserved (13).

(45, 46), and fortification of dairy products with vitamin D (47). Low baseline concentrations may in part explain why 2 recent trials from the United Kingdom (UK), which were not included in our meta-analysis, did not achieve antifracture efficacy with 800 IU cholecalciferol/d (48, 49). The UK has little sunshine, and food is not commonly fortified with vitamin D. In the Randomized Evaluation of Calcium or Vitamin D (RECORD Trial; 48), starting from a mean concentration of 15.2 ng/mL (38 nmol/L), the achieved mean 25(OH)D concentrations were only 62 nmol/L in the vitamin D treatment group. This is, according to our meta-analysis, not enough for fracture prevention (Figure 2B). Moreover, the increase in mean 25(OH)D concentrations by 24 nmol/L is small for an intake of 800 IU/d and was observed with an intake of 400 IU vitamin D/d in another European population (50). This suggests that participants in the RECORD Trial were not sufficiently compliant. In fact, the documented compliance rate was 60% at 12 mo and 47% at 24 mo in persons who returned the 4-mo questionnaire, and even lower if all participants were considered. In addition, the RECORD Trial was a secondary prevention trial, whereas the meta-analysis (Figure 2) included only primary prevention trials. In the second UK trial, by Porthouse et al (49), 25(OH)D concentrations were not reported. Furthermore, the open design and instruction of the control group to ensure adequate calcium and vitamin D intakes may have biased the result toward the null. Still, those authors reported an effect size for hip fracture prevention with vitamin D that is similar to the result of the meta-analysis (RR = 0.75; 95% CI: 0.31, 1.78), although surrounded by a large CI. Thus, the data for bone health, based on BMD in younger and older adults and on the prevention of hip and any nonvertebral fractures in older adults, suggest that serum 25(OH)D concentrations between 90 and 100 nmol/L are desirable.

25-Hydroxyvitamin D and lower-extremity function

Background

The protective effect of vitamin D on fractures has been attributed primarily to the established benefit of vitamin D for calcium homeostasis and BMD (33, 35, 51–53). However, muscle weakness is also a prominent feature of the clinical syndrome of vitamin D deficiency (54, 55) and may plausibly mediate fracture risk through greater susceptibility to falls (54, 56–60).

Some of the authors of this review addressed the effect of vitamin D on the risk of falling in older persons in a recent meta-analysis (61). Combined evidence from 5 RCTs ($n = 1237$) showed that vitamin D reduced the risk of falling by 22% (pooled corrected OR = 0.78; 95% CI: 0.64, 0.92) compared with calcium or placebo (37, 50, 57, 62, 63). Subgroup analyses suggested that the reduction in risk was independent of the type of vitamin D, duration of therapy, and subject's sex. However, the results from one trial suggested that 400 IU vitamin D/d may not be clinically effective in preventing falls in the elderly (50), whereas 2 trials that used 800 IU vitamin D/d plus calcium showed a lower risk of falling (37, 57). For the 2 trials with 259 subjects using 800 IU cholecalciferol/d, the corrected pooled OR was 0.65 (95% CI: 0.40, 1.00; 61). A recent double-blind RCT comparing the long-term effect of 700 IU vitamin D plus 500 mg calcium with placebo confirmed a beneficial effect on falls in 246 community-dwelling older women: the odds of falling declined by 46% [odds ratio (OR): 0.54; 95% CI: 0.30, 0.97; 64). Fall reduction was most pronounced in less active women (OR: 0.35;

95% CI: 0.15, 0.81), whereas the effect in community-dwelling older men ($n = 199$) was neutral (OR: 0.93; 95% CI: 0.50, 1.72).

A physiologic explanation for the beneficial effect of vitamin D on muscle strength is that 1,25-dihydroxyvitamin D ($1,25(OH)_2D$), the active vitamin D metabolite, binds to a vitamin D–specific nuclear receptor in muscle tissue (65–67), which leads to de novo protein synthesis (54, 58), muscle cell growth (58), and improved muscle function (29, 37, 55, 57). Higher serum 25(OH)D concentrations increase the substrate concentration for intracellular, tissue-specific 1-α-hydroxylases, thereby permitting intracellular concentrations of $1,25(OH)_2D$ to rise in muscle and other tissues (68).

Optimal 25-hydroxyvitamin D concentrations and lower-extremity function

A threshold for optimal 25(OH)D and lower-extremity function has only recently been addressed (29). Some of the authors of this review examined the association between serum 25(OH)D concentrations and lower-extremity function in 4100 ambulatory older adults in NHANES III (29). Functional assessments included the 8-foot-walk test and the sit-to-stand test (69, 70). Both tests depend on lower-extremity strength, and they mirror functions needed in everyday life.

The association between 25(OH)D concentrations and lower-extremity function is shown in **Figure 3**. In both tests, performance speed continued to increase throughout the reference range of 25(OH)D (ie, 22.5–94 nmol/L); most of the improvement occurred at 25(OH)D concentrations from 22.5 to ≈40 nmol/L. Further improvement was seen at concentrations in the range of 40 to 94 nmol, but the magnitude was less dramatic. Results of the 8-foot-walk test in the subjects in the highest quintile of 25(OH)D were 5.6% lower than the results in subjects in the lowest quintile of 25(OH)D (P for trend < 0.001). Results of the sit-to-stand test in the subjects in the highest quintile of 25(OH)D were 3.9% lower than the results in the subjects in the lowest quintile of 25(OH)D (P for trend $= 0.017$).

Results were similar in subgroups of active and inactive persons, men and women, 3 racial-ethnic groups (whites, African Americans, and Mexican Americans), and persons with higher (>500 mg/d) and lower (≤500 mg/d) calcium intakes. Only for the sit-to-stand test did there appear to be a decline in performance speed at the highest 25(OH)D concentrations (>120 nmol/L), but this was based on a relatively small number of observations.

Thus, the data for lower-extremity strength suggest that serum 25(OH)D concentrations of ≥40 nmol/L are desirable, but those of 90 to 100 nmol/L are best. This finding is supported by data from the Longitudinal Aging Study Amsterdam that included 1351 Dutch men and women aged ≥65 y (71). In that study, a physical performance score (chair stands, a walking test, and a tandem stand) showed the greatest improvement from very low concentrations of serum 25(OH)D up to 50 nmol/L and had less pronounced but continuous improvement at concentrations >50 nmol/L (65).

25-Hydroxyvitamin D and periodontal disease

Background

Periodontal disease is a common chronic inflammatory disease in middle-aged and older persons that is characterized by the loss of periodontal attachment, including the periodontal ligaments and alveolar bone. Periodontal disease is the leading cause of tooth loss, particularly in older persons (72–75), and tooth loss is an important determinant of nutrient intakes and quality of life (76–78). Several epidemiologic studies have reported positive associations between osteoporosis or low bone density and alveolar bone and tooth loss, which indicate that poor bone quality may be a risk factor for periodontal disease (79–85). In one RCT, supplementation with vitamin D (700 IU/d) plus calcium (500 mg/d) significantly reduced tooth loss in older persons over a 3-y treatment period (OR: 0.4; 95% CI: 0.2, 0.9), whereas serum 25(OH)D concentrations increased from 71 to 112 nmol/L (86). Vitamin D may also reduce periodontal disease through its anti-inflammatory effect (87, 88).

Optimal 25-hydroxyvitamin D concentrations and periodontal disease

Apart from the above-mentioned RCT that successfully tested vitamin D plus calcium in relation to the prevention of tooth loss in ambulatory elderly men and women (86), little direct evidence that vitamin D status is an important determinant of periodontal disease has appeared in the literature. Some of the authors of this review therefore evaluated the association between 25(OH)D concentrations and alveolar attachment loss, a measure of periodontal disease, in 11 202 ambulatory subjects aged ≥20 y in NHANES III (30). That analysis found that 25(OH)D status was not significantly associated with attachment loss in younger men and women (aged 20–50 y), but, in persons aged > 50 y, a significant association between 25(OH)D and attachment loss was observed in both sexes, independent of race-ethnicity (P for trend $= 0.001$ in men and 0.008 in women). The quintiles of 25(OH)D concentrations in relation to the degree of attachment loss are shown in **Figure 4**. The BMD of the total hip region was not associated with attachment loss, and adjustment for that did not attenuate the association between 25(OH)D and attachment loss, which suggests that vitamin D, independent of bone, may play a role in attachment loss. Thus, although data vitamin D and dental health outcomes are limited, available evidence suggests that serum 25(OH)D concentrations between 90 and100 nmol/L are desirable.

25-Hydroxyvitamin D concentrations and colorectal cancer

Background

Five lines of evidence suggest that higher 25(OH)D concentrations may contribute to lower rates of colorectal cancer. First, a strong latitudinal gradient exists for colorectal cancer, in which rates rise with increasing distance from the equator (89, 90). Second, most studies that examined circulating 25(OH)D concentrations and subsequent risk of colorectal cancer or adenoma, the cancer precursor, found a lower risk associated with higher 25(OH)D concentrations (31, 91–97), although some exceptions occurred (98). Third, when the relations between colorectal cancer and dietary or supplementary vitamin D have been investigated in cohorts of men (99, 100), women (31, 93, 101–103), and both sexes (104, 105) and in case-control studies (106–113), most studies suggested inverse associations of vitamin D intake

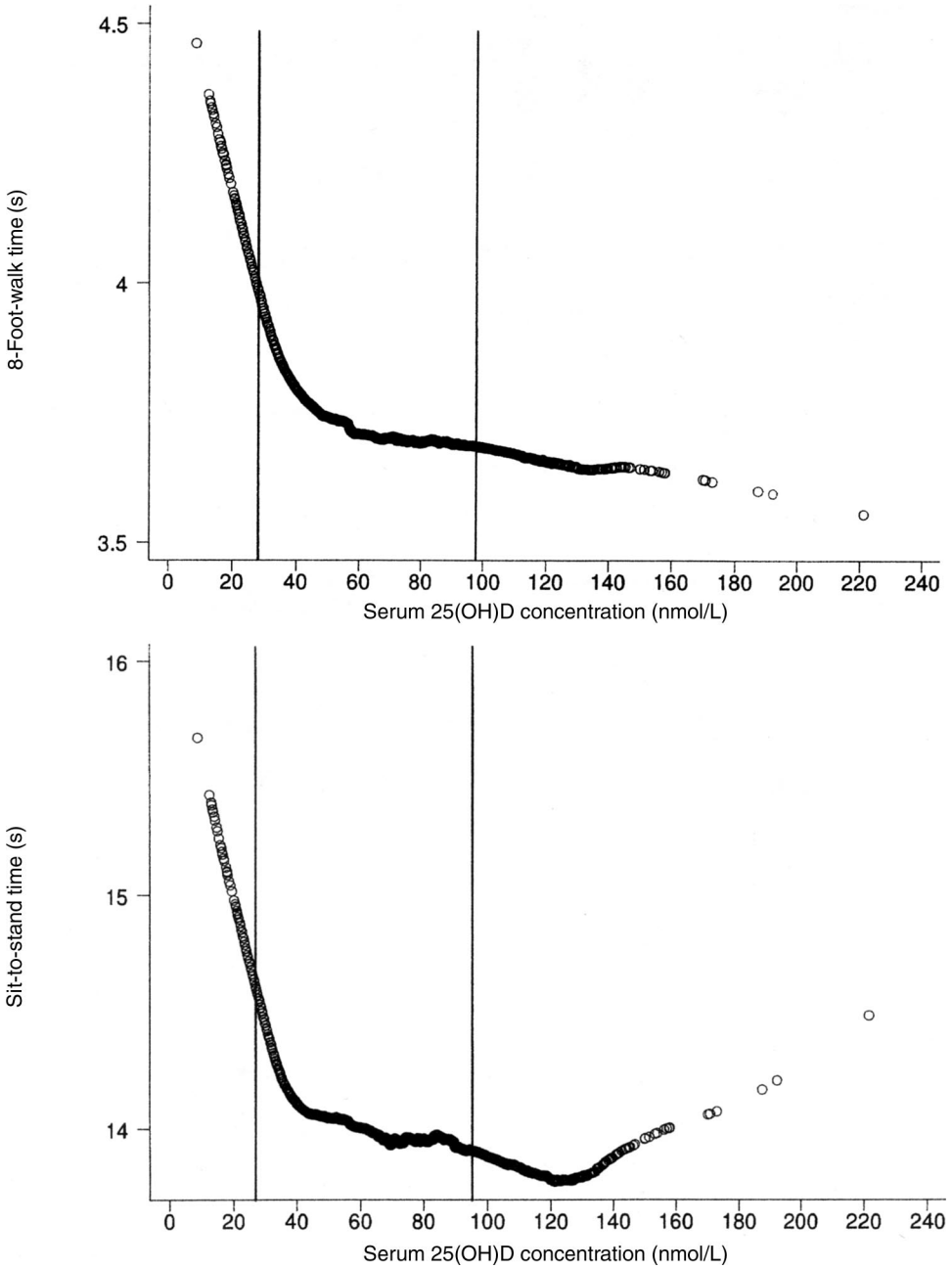

FIGURE 3. The relation between 25-hydroxyvitamin D [25(OH)D] concentrations and lower-extremity function, as tested by the 8-foot walk and sit-to-stand tests. Both analyses were controlled for sex, age (5-y categories), race-ethnicity, BMI, poverty income ratio, daily calcium intake, number of medical comorbidities, use of a walking device, self-reported arthritis, and activity level. In addition, the model was controlled for month of vitamin D measurement to adjust for seasonal changes in vitamin D concentrations (9). Mean (±SD) age of the total population was 71.4 ± 7.9 y, 49% of the population was female, and 25% were classified as inactive. Adapted from reference 29.

with colon or rectal cancer or both (99–102, 105, 107, 109, 111, 112). Most important, all of the studies of colorectal cancer that took into account supplementary vitamin D reported an inverse association (9100–102, 105, 112–114). Fourth, after vitamin D supplementation, circulating 25(OH)D concentrations are inversely associated with the size of the proliferative compartment in the colorectal mucosa in humans (115). Fifth, the vitamin D–colorectal cancer hypothesis is supported by the ability of $1,25(OH)_2D$ or 25(OH)D to reduce proliferation and increase differentiation in vitro for colorectal cancer cells (116–119).

Optimal 25-hydroxyvitamin D concentrations for colorectal cancer prevention

Until recently, studies of 25(OH)D concentrations and colorectal cancer risk have been too small to identify a threshold for 25(OH)D. In the first small US study, involving 34 cases, persons with concentrations >50 nmol/L had an RR of 0.3 (which was statistically significant) relative to those with lower concentrations (91). In a study of 146 cases conducted in Finland that compared the lowest (<24.5 nmol/L) with the highest (>48.3

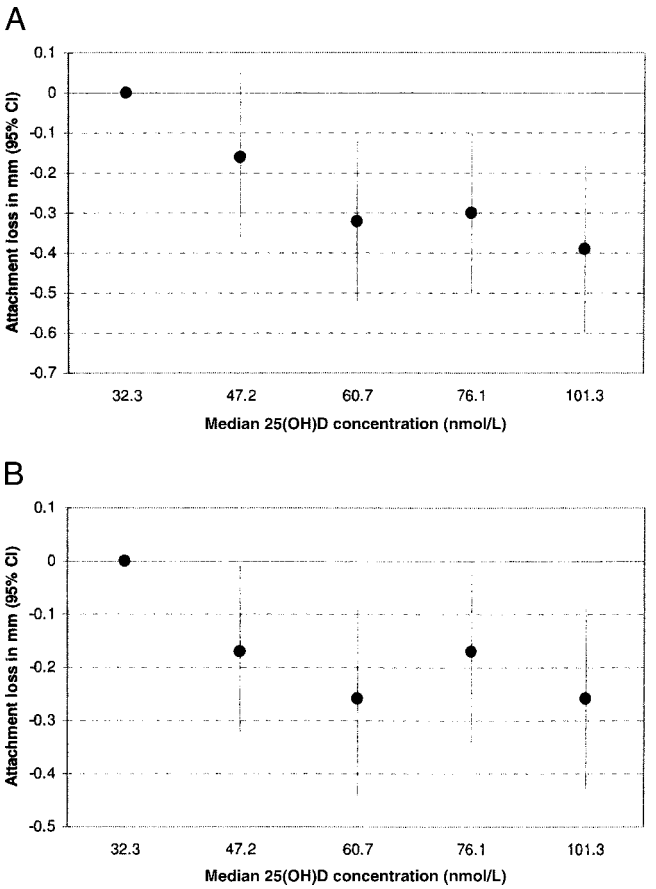

FIGURE 4. The relation of 25-hydroxyvitamin D [25(OH)D] concentrations and attachment loss in men (A) and women (B) ≥50 y old. Analyses were controlled for age, race-ethnicity, smoking, diabetes, calcium intake, BMI, estrogen use among women, poverty income ratio, gingival bleeding, survey phase, and dental examiner. Compared with men in the lowest quintile of 25(OH)D, men in the highest 25(OH)D quintile had, on average, 0.39 mm (95% CI: 0.17, 0.60 mm) less mean attachment loss. Women in the highest 25(OH)D quintile had, on average, 0.26 mm (95% CI: 0.09, 0.43 mm) less mean attachment loss than did women in the lowest quintile. Adapted from Tables 2 and 3 in reference 30.

nmol/L) quintile, the RR was 0.6 (95% CI: 0.3, 1.1; 92). In the recent analysis in the Nurses' Health Study involving 193 incident cases, serum 25(OH)D concentrations were inversely related to colorectal cancer risk (31). As shown in **Figure 5**, the RR decreased monotonically across quintiles of 25(OH)D concentrations; the RR was 0.53 (95% CI: 0.27, 1.04) for quintile 5 (median: 88 nmol/L) as compared with quintile 1 (median: 38 nmol/L; *P* for trend = 0.02).

The several studies that have examined circulating vitamin D concentrations and the risk of colorectal adenoma, a cancer precursor, also suggested an inverse association with 25(OH)D (93–96, 120). In one of these studies (93), a monotonic inverse association was observed across quintiles of 25(OH)D (reference: <35.6 nmol/L, top category: >79.5 nmol/L), and the respective RRs were 1.0, 0.99, 0.86, 0.74. In another of these studies (94), with each 25 nmol/L increase in serum 25(OH)D, the RR of adenoma decreased by 26% (RR = 0.74; 95% CI: 0.60, 0.92). In the most recent of these studies, a 13% decrease in adenoma risk (RR = 0.87; 95% CI: 0.75, 1.01) was found for each 25 nmol/L increase in serum 25(OH)D (120). This relation was observed only in women, whose risk decreased monotonically across quintiles (reference: <48 nmol/L; quintile 5: >91.5 nmol/L; RR = 0.27; 95% CI: 0.11, 0.69).

Some studies have examined vitamin D intakes in relation to risk of colorectal cancer. In those that have taken into account supplementary vitamin D, an inverse association has invariably been observed (100–102, 105, 112–114). In these studies, the cutoff for the top category was 500–600 IU/d, with an average of ≈700–800 IU/d in this category. The risk reduction in the top category compared with the bottom category was as follows: 46% (101), 34% (100), 58% (102), 24% (114), 30% (112), 29% in males and 0% in females (105), and 50% in males and 40% in females (113).

Findings from the WHI appear to contrast with the epidemiologic data described in this review (121). However, 2 critical issues are dose and duration of supplementation. In the Nurses' Health Study, a significant reduction in colorectal cancer in connection with higher vitamin D intake emerged only at doses >550 IU/d in consistent users for >10 y (RR = 0.42; 95% CI:

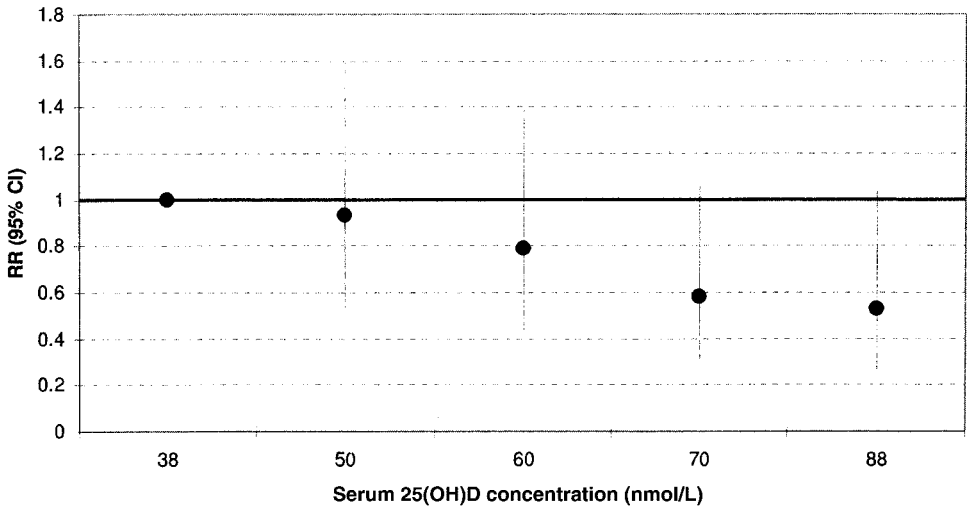

FIGURE 5. The relative risk (RR) of colon cancer by quintiles of 25-hydroxyvitamin D [25(OH)D]. The 25(OH)D concentrations given are the median of each quintile. *P* for trend = 0.02. Adapted from Table 2 in Feskanich D, et al. Plasma vitamin D metabolites and risk of colorectal cancer in women. Cancer Epidemiol Biomarkers Prev 2004;13:1502-8 (31).

0.19, 0.91; 96). In the WHI, median follow-up was only 7 y. Furthermore, similar to the most recent findings on 25(OH)D concentrations and risk of colorectal cancer in the Nurses' Health Study (Figure 5; 31), a significant ($P = 0.02$) inverse trend between lower baseline serum 25(OH)D concentrations and a greater risk of colorectal cancer was observed in the WHI participants.

Thus, epidemiologic data for colorectal neoplasia, based on cancer and adenomas, are generally consistent with a protective effect of a higher 25(OH)D concentration and higher vitamin D intake**.** It has been suggested that there may be a local effect on colonic epithelial cells with increasing 25(OH)D concentrations leading to less cell proliferation and greater cell differentiation (122). Estimated optimal serum 25(OH)D concentrations were ≥90 nmol/L. This conclusion is supported by a 2004 National Institutes of Health–sponsored symposium at which the role of vitamin D in cancer chemoprevention and treatment was discussed (123–125).

Vitamin D intake needed to achieve optimal 25-hydroxyvitamin D concentrations

Currently recommended intakes of vitamin D are 200 IU/d for young adults, 400 IU/d for those aged 51–70 y, and 600 IU/d for those aged >70 y (126). The vitamin D intake needed to bring the concentrations in a large majority of adults to the desirable 90–100 nmol/L 25(OH)D range has not been defined precisely and depends to some extent on the starting intake. Studies in older persons show that 25(OH)D concentrations could be increased by ≈10–40 nmol/L to means of ≈60 nmol/L with an intake of 400 IU vitamin D/d (43, 127, 128), by 31 nmol/L to means of 79 nmol/L with 600 IU (129), or by 50–65 nmol/L to means of 100 nmol/L with 800 IU vitamin D/d (33, 34). Mean concentrations of 75 to 100 nmol/L are achieved with intakes of 700 to 1000 IU/d in groups of young and older adults (130–132). In young men and women (aged 41 ± 9 y), 4000 IU vitamin D/d (100 μg/d) may increase 25(OH)D concentrations by 56 nmol/L to means of 125 nmol/L (133).

DISCUSSION

In this review, we examined optimal blood 25(OH)D concentrations for BMD and fracture risk reduction, lower-extremity function, dental health, and colorectal cancer prevention. For all endpoints, as summarized in **Figure 6**, the data suggested that the most advantageous target concentration of 25(OH)D begins at 75 nmol/L (30 ng/mL) and that the best concentrations are between 90 and 100 nmol/L (36–40 ng/mL). Thus, reaching the optimal 25(OH)D range for bone health, which is the most widely acknowledged benefit of adequate vitamin D status, is expected to provide additional benefits with respect to lower-extremity function, oral health, and colon cancer prevention. The target of ≥75 nmol 25(OH)D/L for optimal health is supported by several experts and a recent conference on the role of vitamin D in cancer prevention (124, 125, 134–138).

Our group's recent meta-analysis (13) indicated that intakes of 700–800 IU vitamin D/d (with or without calcium) could prevent approximately one-fourth of all hip and nonvertebral fractures in both ambulatory and institutionalized older persons. Given the high cost of fracture treatment and the personal burden of disability after fractures, especially hip fractures, this finding has significant public health implications (139, 140). Notably,

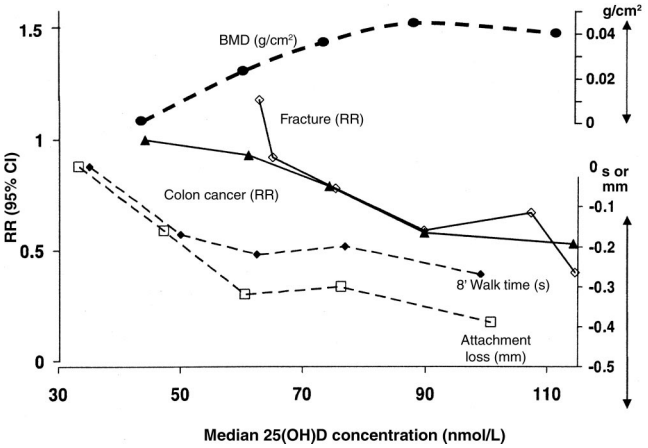

FIGURE 6. Relative risks (RRs) of fracture (for more detail, *see* Figure 2) and colon cancer (for more detail, *see* Figure 4). Solid lines relate to the left axis, and dashed lines relate to the right axis. 25(OH)D, 25-hydroxyvitamin D. For bone mineral density (BMD), the example of older whites was chosen (for more detail, *see* Figure 1), and the unit is shown in the upper part of the right *y* axis. For lower extremity, we chose the 8-foot walk test (8' walk time), which is shown in more detail in Figure 3A; the unit is seconds, as shown on the lower half of the right *y* axis. Attachment loss (for more detail, *see* Figure 4) is given in millimeters for older men, as shown in the lower part of the right *y* axis. This summary of all outcomes indicates that a desirable serum 25(OH)D concentration for optimal health begins at 75 nmol/L, and the best concentration is 90–100 nmol/L.

across all trials, a significant positive association was found between the higher 25(OH)D concentrations achieved in the treatment group and fracture prevention efficacy. Furthermore, because the positive association between 25(OH)D concentrations and BMD in younger adults (28; Figure 1) is consistent with the concept that higher concentrations of serum 25(OH)D may contribute to peak bone mass, maintenance of high 25(OH)D concentrations in younger adulthood could further protect against fractures at older ages (141).

According to a recent national survey in the United States, only 31% of whites aged 20–49 y, <9% of older whites, and an even smaller fraction of Mexican American and African American adults have serum 25(OH)D concentrations of ≥90 nmol/L (28). Most vulnerable to low vitamin D concentrations are the elderly (45, 142), persons living in northern latitudes where the winters are prolonged (9, 143), obese persons (144), and African Americans of all ages (28, 145, 146). Other groups with dark skin pigmentation living in northern latitudes will also be at high risk of low vitamin D status. Thus, a large majority of the US population could benefit from vitamin D supplementation, which is a simple, highly affordable, and well-tolerated strategy that could reduce osteoporosis and fractures and could probably reduce falls associated with lower-extremity weakness, could improve dental health, and reduce the incidence of colorectal cancer in older adults.

Our review also estimated the vitamin D intakes that may be required to achieve the optimal concentration of 25(OH)D. Studies suggest that 700–1000 IU vitamin D/d may bring 50% of younger and older adults up to a concentration of 90–100 nmol/L (130–132). Thus, to bring most adults to the desirable range of 90–100 nmol/L, vitamin D doses higher than 700–1000 IU would be needed. The current intake recommendation for older persons (600 IU/d) may bring concentrations in most subjects to

50–60 nmol/L, but not to 90–100 nmol/L, and, for younger adults, the current recommendation of 200 IU/d (5 μg/d) is unlikely to be adequate (28). According to studies in younger adults, intakes as high as 4000–10 000 IU/d (250 μg/d) are safe (127, 133), and those of 4000 IU may bring concentrations in 88% of healthy young men and women to ≥75 nmol/L (133). Heaney (124) and Heaney et al (127), in a study of healthy men, estimated that 1000 IU cholecalciferol/d is needed during the winter months in Nebraska to maintain the concentration of 70 nmol/L that subjects had in late summer, whereas persons with baseline concentrations between 20 and 40 nmol/L may require a daily dose of 2200 IU vitamin D to reach and maintain concentrations of 80 nmol/L (124, 127).

If 75–100 nmol/L were the target range of a revised recommended daily allowance (RDA), the new RDA should meet the requirements of 97% of the population (147). The dose-response calculations of ≈1.0 nmol/L (1 μg/d) at the lowest end of the distribution and of 0.6 nmol/L (1 μg/d) at the highest end, proposed by Heaney (124), suggest that a daily oral dose of 2000 IU (50 μg/d), the safe upper intake limit as defined by the National Academy of Science (126), may shift the NHANES III distribution so that only ≈10–15% of persons had concentrations < 75 nmol/L. This calculation may result in a shift of 35 nmol/L in already-replete persons from concentrations between 75 and 140 nmol/L (NHANES III distribution) to concentrations of 110–175 nmol/L, which are observed in healthy outdoor workers [ie, farmers: 135 nmol/L (148) and lifeguards: 163 nmol/L (149)]. Thus, 2000 IU may be a safe RDA even at the higher end of the normal 25(OH)D serum concentration distribution, and, at the lower end, it may be conservative. As a first sign of toxicity, only serum 25(OH)D concentrations of >220 nmol/L have been associated with hypercalcemia (150, 151).

Because of seasonal fluctuations in 25(OH)D concentrations (9), some persons may be in the target range during the summer months. However, these concentrations will not be sustained during the winter months, even in sunny latitudes (129, 137). Thus, even after a sunny summer, winter supplementation with vitamin D is needed. Furthermore, several studies suggest that many older persons will not achieve optimal serum 25(OH)D concentrations during the summer months, which suggests that vitamin D supplementation should be independent of season in older persons (142, 152, 153).

On the basis of this review, we suggest that, for bone health in younger adults and all outcomes in older adults, including antifracture efficacy, lower-extremity strength, dental health, and colorectal cancer prevention, an increase in the current recommended intake of vitamin D may be warranted. To bring concentrations in ≥50% of the population up to 75 nmol vitamin D/L, we recommend that intakes for adults should be ≥1000 IU vitamin D/d in all racial-ethnic groups. Given the low cost, the safety, and the demonstrated benefit of higher 25(OH)D concentrations, vitamin D supplementation should become a public health priority to combat these common and costly chronic diseases.

The review was planned by HAB-F, B D-H, and WCW. All authors evaluated the review and contributed their comments. HAB-F wrote the manuscript; EG contributed the section on colon cancer. None of the authors reported a personal or financial conflict of interest.

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