Guidelines for Preventing and Treating Vitamin D Deficiency and Insufficiency Revisited

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Vitamin D is currently a topic of intense interest to the scientific and lay communities. Recently a committee convened by the Institute of Medicine (IOM) released a report identifying dietary reference intakes; subsequently, The Endocrine Society Clinician Vitamin D Guideline was published (1, 2). Because these recommendations are not entirely congruent, in this issue of the *Journal*, we put into perspective how the goals of the guidelines differed from those of the IOM Committee.

The guideline's intent was to provide guidance for clinicians caring for patients, not to make recommendations for normal healthy populations as covered by the IOM report. It is axiomatic that the physician's role is to provide recommendations to maximize the health of their individual patient, not to provide population-based care. Thus, because the target for these recommendations differ, it is not surprising that the guidance might also differ.

It is not the intent of this commentary to revisit exhaustive data reviews. However, it is important to emphasize that the IOM report focused only on bone health (calcium absorption, bone mineral density, osteomalacia/rickets, *etc.*) and found no evidence that a serum 25-hydroxyvitamin D [25(OH)D] concentration above 20 ng/ml has beneficial effects at a population level. However, on an individual level, a salient publication by Priemel *et al.* (3) found elevated unmineralized osteoid (a hallmark of vitamin D deficiency bone disease) in 21% (six of 28) of otherwise healthy men and women whose 25(OH)D was between 20 and 30 ng/ml (3, 4) (Fig. 1) Moreover, remarkable between-individual variability of the 25(OH)D/osteoid relationship was observed. Similar variability is widely recognized for the relationship between 25(OH)D and PTH. Clearly the relationship of 25(OH)D to PTH in a given individual is the result of a complex interplay of factors including age, sex, genetics, renal function, mobility level, calcium intake, and phosphate and magnesium status, which makes selection of a single inflection point challenging at best and impossible in studies with a small number of subjects like that of Rucker *et al.* (5). For example, in a report of 33,055 women and 77,118 men, both sex and age influenced the level at which 25(OH)D caused the PTH levels to plateau. In men aged 21–30 yr, PTH levels plateaued when 25(OH)D was 35–39 ng/ml (87.5–97.3 nmol/liter), whereas in females of the same age range, the plateau was reached when 25(OH)D was 30–34 ng/ml (75–85 nmol/liter). This difference was more dramatic in men aged 41–50 yr in whom the PTH levels plateaued when the 25(OH)D reached 30–34 ng/ml (75–85 nmol/liter), whereas in females of the same age range, the PTH levels plateaued at 20–24 ng/ml (50–60 nmol/liter) (6, 7). Therefore, the target range for 25(OH)D to minimize PTH levels may be both gender and age dependent, with men requiring a higher serum 25(OH)D than women of the same age. These findings are consistent with the observa-

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in U.S.A.

doi: 10.1210/jc.2011-2601 Received September 20, 2011. Accepted February 10, 2012.
First Published Online March 22, 2012

Abbreviations: CI, Confidence interval; IOM, Institute of Medicine; 25(OH)D, 25-hydroxyvitamin D; OR, odds ration; RCT, randomized trial.

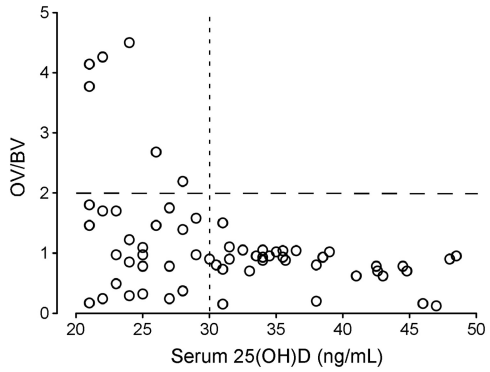

FIG. 1. 25(OH)D levels in German motor vehicle accident victims and osteoid volume. Pathological accumulations of osteoid are absent in all individuals with a 25(OH)D greater than 30 ng/ml (authors' recommendation). The IOM concluded that 99% of subjects had no evidence of pathological accumulations of osteoid when the blood level of 25(OH)D was greater than 20 ng/ml (IOM recommendation). The *horizontal line* indicates a threshold of 2% osteoid volume used in this study as a conservative histopathological border to osteomalacia. [Reproduced from M. Priemel *et al.*: Bone mineralization defects and vitamin D Deficiency: histomorphometric analysis of iliac crest bone biopsies and circulating 25-hydroxyvitamin D in 675 patients. J Bone Miner Res 25:305–312, 2010 (3), with permission. © American Society for Bone and Mineral Research.]

tion in postmenopausal women that the prevalence of secondary hyperparathyroidism (PTH >40 pg/ml) was lowest when serum 25(OH)D was above 30 ng/ml (75 nmol/liter) (8) (Fig. 2). Although many of these women were on a bisphosphonate, which can potentially increase PTH levels, there is no evidence that vitamin D status independently influences this effect. Such variations in PTH levels could lead clinicians to conclude that a 25(OH)D concentration of 20 ng/ml does not assure optimal calcium metabolism and bone health in an individual patient. Taken together, these data suggest that a 25(OH)D concentration of 20 ng/ml does not assure optimal calcium metabolism and bone health in all individuals.

Ultimately bone health in adults relates to fracture risk. Clinicians are increasingly recognizing the importance of sarcopenia and reduced muscle strength in fracture risk evaluation as well. Because many osteoporosis-related fractures result from a fall, optimizing fracture risk reduction strategies in an individual patient necessitates consideration of fall risk (9, 10). In this regard, the IOM report concluded that vitamin D does not reduce fall risk, although their overall analysis of 12 randomized controlled trials (RCT) (n = 14,101) showed a significant benefit of vitamin D on fall prevention [odds ratio (OR) 0.89; 95% confidence interval (CI) 0.80–0.99] (1). In contrast, a recent meta-analysis of 23 trials found that vitamin D supplementation does reduce fall risk. Murad *et al.* (11) reported that vitamin D interventions were associated with a statistically significant reduction in risk of falls [OR 0.84; 95% CI 0.76–0.93; inconsistency (I^2 = 61%; 23 studies]. This effect was more prominent in patients who were vitamin D deficient at baseline. The importance of dose of supplemental vitamin D in minimizing the risk of falls was confirmed by a multidose, double-blind RCT among the 124 nursing home residents receiving 200, 400, 600, or 800 IU/d vitamin D or placebo for 5 months and by a 2009 meta-analysis (12, 13). In the multidose trial, only participants receiving 800 IU/d of vitamin D had a substantially lower rate of falls than those taking placebo or doses of vitamin D that were less than 800 IU/d (rate ratio 0.28; 95% CI 0.11–0.75) (13). Notably, in the reanalysis of the 2009 meta-analysis requested by the IOM to account for the stochastic dependencies (correlations) between the corresponding risk ratios in the multiple dosing trial by Broe *et al.* (12), there was a significant reduction in the odds of falling based on the primary analysis of the same eight trials: OR 0.73 (0.62, 0.87; $P = 0.0004$). When the model was expanded to capture the impact of both high-dose and low-dose treatment, high dose vitamin D (700–1000 IU vitamin D per day) reduced the odds of falling by 34% [OR 0.66 (0.53, 0.82), $P = 0.0002$], whereas low-dose vitamin D did not [OR 1.14 (0.69, 1.87); $P = 0.61$] (1).

These observations are consistent with the 2010 assessment by the International Osteoporosis Foundation and the 2011 assessment of the Agency for Healthcare Research and Quality for the U.S. Preventative Services Task

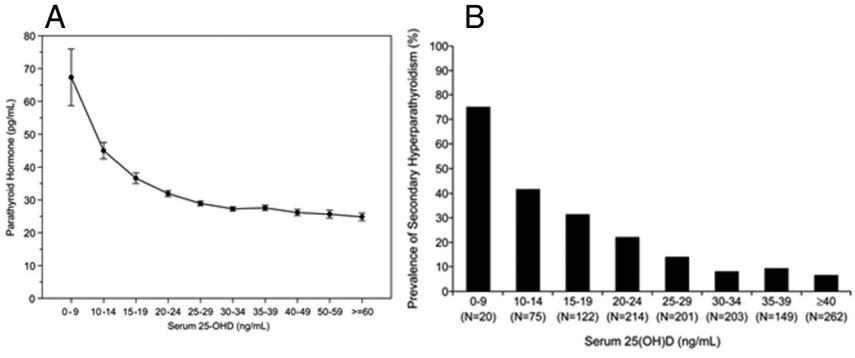

FIG. 2. A, Mean (±SE) serum PTH (picograms per milliliter) by serum 25(OH)D subgroups. Subject PTH concentrations (picograms per milliliter) relative to serum 25(OH)D concentrations sorted by subgroups delineated by predefined cutoffs for analyses of 25(OH)D inadequacy. Serum PTH values began to increase with 25(OH)D concentrations less than 29.8 ng/ml. B, Percent of subjects with secondary hyperparathyroidism by 25(OH)D level. The percent of subjects with secondary hyperparathyroidism (PTH >40 pg/ml) was sorted by subgroups with serum 25(OH)D concentrations delineated by predefined cutoffs for analyses of 25(OH)D inadequacy. [Adapted from M. Holick *et al.*: Prevalence of vitamin D inadequacy among postmenopausal North American women receiving osteoporosis therapy. J Clin Endocrinol Metab 90:3215–3224, 2005 (8), with permission. © The Endocrine Society.]

Force, both of which identified vitamin D as an effective intervention to prevent falling in older adults (14). It is well documented that severe vitamin D deficiency is associated with proximal muscle weakness, which is thought to be associated with secondary hyperparathyroidism and induced hypophosphatemia as well as possible other mechanisms (15, 16). Therefore, it is plausible that vitamin D influences bone health by fall risk reduction. Finally, there is no clinical trial in which reaching a mean 25(OH)D level of 20 ng/ml reduced fracture risk, whereas studies reaching at least 30 ng/ml have demonstrated such risk reduction (17, 18). Given the limitations of current data (and therefore potential for differing interpretations) and recognition of assay variability associated with 25(OH)D measurement combined with absence of toxicity at higher doses/circulating 25(OH)D concentrations than called for in the IOM report, it is not surprising that clinical guidelines call for higher values. Moreover, the paleolithic model of highly sun-exposed humans suggests that the ancestral normal 25(OH)D concentration ranges from approximately 20–70 ng/ml. As an example, healthy black children in South Africa were reported to have a 25(OH)D of 49 ± 4 ng/ml, similar to adult Masai herders 47 ± 10 ng/ml (19, 20)

Based on their definition of vitamin D deficiency, *i.e.* 25(OH)D less than 20 ng/mL, the IOM concluded that concerns about widespread vitamin D deficiency in North American population is not well founded. However many studies have suggested that vitamin D deficiency is a significant health problem. For example 54% of community elders in Baltimore had a serum concentration of 25(OH)D less than 10 ng/ml (21). A study in Boston, Massachusetts, of among 40 mother infant pairs reported that 76% of mothers and 81% of newborns were vitamin D deficient, even though the mothers were documented to be ingesting an average of 600 IU/d of vitamin D during their pregnancy (22). More than 40% of Hispanic and African American adolescents in Boston were found to be vitamin D deficient (23), and 48% of white preadolescent girls from Maine had a 25(OH)D less than 20 ng/ml (24). Data from the National Health and Nutrition Examination Surveys 2001–2006 showed that approximately 33% of the U.S. population had a serum 25(OH)D less than 20 ng/ml (25) (Fig. 3A). These results are similar to the observations made in Canada in which 30–50% of children and adults have been reported to be vitamin D deficient (26, 27). Indeed, vitamin D deficiency is not only common in the United States, Canada, and Europe, but it is also a global health issue (28, 29). Reports from Brazil, Australia, India, New Zealand, Mongolia, Middle East, and Africa have documented that both children and adults were at high risk for vitamin D deficiency (19, 30–41) (Fig. 3C). Therefore, this problem appears to be common in healthy individuals across the life span and even more prevalent in those with chronic disease (42–45).

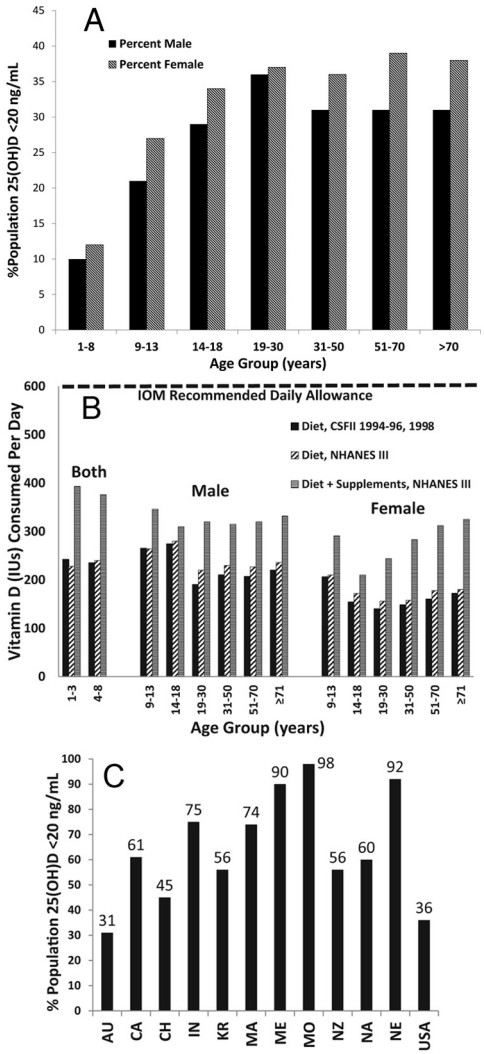

FIG. 3. A, Prevalence at risk of vitamin D deficiency defined as a 25(OH)D < 20 ng/ml by age and sex: United States, 2001–2006. [Adapted from Looker *et al.*: Vitamin D status: United States, 2001–2006. *NCHS Data Brief* 1–8, 2011 (25), with permission. © Centers for Disease Control and Prevention.]. B, Mean intake of vitamin D (IU) from food and food plus dietary supplements from Continuing Survey of Food Intakes by Individuals (CSFII) 1994–1996, 1998, and the Third National Health and Nutrition Examination Survey (NHANES III) 1988–1994. [Adapted from Moore *et al.*: Vitamin D intake in the United States. *J Am Diet Assoc* 104: 980–983, 2004 (46), with permission. © Elsevier.]. C, Reported incidence of vitamin D deficiency defined as a 25(OH)D < 20 ng/mL around the globe including Australia (AU), Canada (CA), China (CH), India (IN), Korea (KR), Malaysia (MA), Middle East (ME), Mongolia (MO), New Zealand (NZ), North Africa (NA), Northern Europe (NE), United States (USA).

The IOM concluded that dietary and supplemental vitamin D intake is adequate to satisfy both children and adults. However, Moore *et al.* (46) estimated the vitamin D intake in U.S. men, nonpregnant, and nonlactating women, and non-breast-feeding children aged 1 yr and older and found that in more than 9000 female teenagers and adults, the estimated vitamin D intake range from food was 156–208 IU/d and including that received from

supplements, 244–324 IU/d. For male teenagers and adults and children of both sexes between the ages of 1 and 8 yr, the estimated vitamin D intake from food was 208–320 and 228–240 IU/d, respectively, and with supplements 308–392 and 376–392 IU/d, respectively. Based on the recommendation by the IOM that all children and adults (1–50 yr) require 600 IU/d, the study of Moore *et al.* (46) suggested that neither children nor adults in the United States are obtaining the new recommended daily allowance for vitamin D (Fig. 3B). The IOM suggests one can obtain one's vitamin D requirement from the diet. However, the major dietary source is from vitamin D-fortified dairy and orange juice, and because there is only 100 IU per 8 oz of milk or orange juice, this would require children and adults to drink 6 glasses a day, which is unrealistic. Other foods rich in vitamin D such as fatty fish are not staples in diets of most people.

The IOM as well as The Endocrine Society Guidelines recognized that vitamin D toxicity is a rare event and recommended that much higher intakes of vitamin D can be tolerated in children and adults without concern for toxicity. However, the sporadic reports suggesting that blood levels of 25(OH)D greater than 30 ng/ml may have detrimental health effects including increased risk for breast, pancreatic, and prostate cancer, and mortality was of concern for the IOM. However, the association of vitamin D deficiency with a 50% increased risk of having a myocardial infarction (44), more than 100% increased risk of dying of the event (45), and an increased risk for colorectal cancer (43, 47) was dismissed as not being supported by RCTs. The IOM noted that low 25(OH)D levels less than 15 ng/ml were associated with increased risk of mortality and that some but not all studies observed increasing blood levels of 25(OH)D above 30 ng/ml were associated with increased mortality including the report by Melamed *et al.* (48). The major cause for mortality was due to cardiovascular disease. However, Melamed *et al.* (48) concluded that there was a lower risk of mortality for 25(OH)D levels of 30–49 ng/ml and levels greater than 50 ng/ml were associated with a higher risk of mortality in women but not men. The same authors also reported a strong inverse association with peripheral vascular disease and serum 25(OH)D levels (49). A recent meta-analysis for the U.S. Preventative Services Task Force regarding vitamin D supplementation concluded that for each 4 ng/ml increase in blood 25(OH)D levels was associated with a 6% (95% Cl 3–9%) reduced risk for colorectal cancer but no statistically significant dose-response relationships for prostate and breast cancer (50).

Given the imperfect nature of the evidence and the differing goals of the IOM and The Endocrine Practice Guidelines Committee, it is not at all surprising that their recommendations differed. At this time, the existing guidelines provide reasonable recommendations for clinical care. It is to be expected that these guidelines, as well as the IOM recommendations, will require reconsideration in the future as additional data from ongoing longitudinal studies become available.

In summary, vitamin D deficiency is not rare; many patients of all races, from young to old age in North America and throughout the world, are at high risk to be vitamin D deficient. With the exception of patients who have a chronic granulomatous disorder or lymphoma, the task force agreed that the potential benefits of increasing the vitamin D intake of children and adults to the recommended levels in the guidelines outweigh any potential risks (2). It is also important to note that the availability of both sets of guidelines ensures that all are considered, including both individuals who are healthy, as well those afflicted with chronic disease.

Acknowledgments

Financial disclosures of the task force include the following: Michael F. Holick, Ph.D., M.D. (chair), financial or business/organizational interests: Merck, Novartis, Nichols-Quest Diagnostics, Bayer, Aventis, Warner Chilcott, Amgen, UV Foundation, Mushroom Council and Dairy Management, Inc.; significant financial interest or leadership position: none declared; Neil C. Binkley, M.D., financial or business/organizational interests: American Society for Bone and Mineral Research, International Society for Clinical Densitometry; significant financial interest or leadership position: none declared; Heike A. Bischoff-Ferrari, M.D., Dr.P.H., financial or business/organizational interests: none declared; significant financial interest or leadership position: none declared; Catherine M. Gordon, M.D., M.Sc., financial or business/organizational interests: none declared; significant financial interest or leadership position: codirector, Clinical Investigator Training Program (Harvard/Massachusetts Institute of Technology with Pfizer/Merck); David A. Hanley, M.D., F.R.C.P.C., financial or business/organizational interests: Canadian Society of Endocrinology and Metabolism, Osteoporosis Canada, International Society for Clinical Densitometry; advisory boards: Amgen Canada, Merck Frosst Canada, Eli Lilly Canada, Novartis Canada, Warner Chilcott Canada; significant financial interest or leadership position: past president of Canadian Society of Endocrinology and Metabolism; Robert P. Heaney, M.D., financial or business/organizational interests: Merck, Procter & Gamble; significant financial interest or leadership position: none declared. M. Hassan Murad, M.D., financial or business/organizational interests: KER Unit (Mayo Clinic); significant financial interest or leadership position: none declared. Connie M. Weaver, Ph.D., financial or business/organizational interests: Pharmavite; significant financial interest or leadership position: National Osteoporosis Foundation.

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