Serum 25-Hydroxyvitamin D Levels: Variability, Knowledge Gaps, and the Concept of a Desirable Range

Ghada El-Hajj Fuleihan,1 Roger Bouillon,2 Bart Clarke,3 Marlene Chakhtoura,1 Cyrus Cooper,4 Michael McClung,5 and Ravinder J Singh3

1Department of Internal Medicine, Calcium Metabolism and Osteoporosis Program, American University of Beirut, Beirut, Lebanon
2Department of Endocrinology and Laboratory Medicine, Katholieke Universiteit Leuven, Leuven, Belgium
3Division of Endocrinology, Diabetes, Metabolism, and Nutrition, Mayo Clinic Foundation, Rochester, MN, USA
4MRC Lifecourse Epidemiology Unit, University of Southampton, Southampton, UK
5Oregon Osteoporosis Center, Portland, OR, USA

ABSTRACT
Hypovitaminosis D is prevalent worldwide but proportions vary widely between regions, depending on genetic and lifestyle factors, the threshold to define deficiency, and accuracy of 25-hydroxyvitamin D (25OHD) assays used. Latitude, pollution, concealing clothing, sun exposure, gender, dietary habits, and lack of government regulation account for up to 50% in variations in serum 25OHD levels, whereas genetic polymorphisms in the vitamin D pathway account for less than 5%. Organizations/societies have developed guidelines for recommended desirable 25OHD levels and vitamin D doses to reach them, but their applicability across age groups and populations are still debated. This article and the accompanying online Supporting Information highlight sources of variations in circulating 25OHD levels, uncertainties and knowledge gaps, and analytical problems facing 25OHD assays, while keeping efficacy and safety data as the dominant factors when defining a desirable range for 25OHD levels. We propose a desirable range of 20 to 40 ng/mL (50 to 100 nmol/L), provided precise and accurate assays are used. Although slightly lower levels, 15 to 20 ng/mL, may be sufficient for some infants and adults, higher levels, 40 to 60 ng/mL, may still be safe. This desirable range allows physicians to tailor treatment while taking season, lifestyle, vitamin D intake, and other sources of variation into account. We reserve 25OHD measurements for at-risk patients, defined by disease or lifestyle, and the use of 25OHD assays calibrated against the recommended international standards. Most target groups reach desirable target levels by a daily intake of 400 to 600 IU for children and 800 IU for adults. A total daily allowance of vitamin D of up to 1000 IU in the pediatric age groups, and up to 2000 IU in adults, tailored to an individual patient risk profile, is probably safe over long durations. Additional data are needed to validate the proposed range and vitamin D doses, especially in children, pregnant women, and non-white populations. © 2015 American Society for Bone and Mineral Research.

KEY WORDS: DESIRABLE RANGE; VITAMIN D; KNOWLEDGE GAPS; VARIATIONS; ETHNICITIES; SAFETY; EFFICACY

Introduction

Vitamin D, a steroid hormone that controls over several hundreds of genes, amounting to around 3% of mouse and human genomes, impacts a wide range of molecular and cellular functions.1–5 Hypovitaminosis D is prevalent worldwide.1,6–11 A systematic review of 195 studies, involving over 168,000 participants from 44 countries, revealed considerable variation in mean 25OHD values. Around 37% of studies reported mean values below 20 ng/mL, proportions being higher in the Middle East and Asia.11 The beneficial effects of vitamin D on healing of rickets in children, and reducing fractures, when co-administered with calcium, and falls in elderly white populations, are, for the most part, undisputed.3,12–14 An exception is the U.S. Preventative Task Force report, which applies to younger subjects.15 A recent Cochrane systematic review of clinical trials revealed high-quality evidence for the beneficial effect of calcium and vitamin D, but not vitamin D alone, in reducing the risk of fractures. This applied to hip fracture risk, relative risk (RR) = 0.84 (95% CI, 0.74 to 0.96) from nine trials with 49,853 participants, and nonvertebral fractures RR = 0.86 (95% CI, 0.78 to 0.96) from eight trials with 10,380 participants.14

Vitamin D guidelines have been issued by major organizations worldwide:16 World Health Organization (WHO), the International Osteoporosis Foundation (IOF), the Institute of Medicine (IOM),17 the 2011 Endocrine Society (ES),18 the American...
The Association of Clinical Endocrinologists (AACE) and the European Association of Medical Doctors. The ES and IOM guidelines were formulated after an extensive review of the literature, used similar predefined outcomes of mineral metabolism, yet reached differing conclusions in terms of desirable 25OHD level, set at 30 ng/mL by ES and 20 ng/mL by IOM. They also differed in recommended doses to reach them, varying between 600 and 800 IU for IOM, and 600 and 2000 IU for ES.

The differences in desirable 25OHD levels derived by the IOM and ES may in part be explained by different target populations they addressed, the general public versus the patient in the clinic. There are, however, few arguments for maintaining higher serum 25OHD levels in the ES-defined target groups above levels recommended for the general population. Furthermore, the defined desirable 25OHD levels, and required vitamin D doses to reach them, do not take into account the wide individual variations around the mean, race, calcium intake, renal function, body mass index (BMI), and polymorphisms in key protein/enzymes involved in the vitamin D metabolism and action. Added are the concerns regarding inherent variations between 25OHD assays used, and the fact that the ES and IOM cutoffs lack strength in terms of evidence in non-white ethnic groups, children, and pregnant women. To date, the recommendations by the IOM and ES remain extensively debated and have led to substantial confusion among clinicians.

The purpose of this work is to highlight sources of variations in circulating vitamin D levels, summarize the evidence provided by the IOM and ES to derive desirable levels, and outline knowledge gaps including analytical problems facing vitamin D assays, all important considerations when defining desirable levels. We have developed a conceptual framework to derive a desirable range for circulating 25OHD levels, allowing physicians to make enlightened decisions, taking these limitations into consideration.

### Vitamin D Physiology and Sources of Individual Variations in Vitamin D Levels

#### Normal physiology

Vitamin D is a pre-hormone derived from diet or skin (sun exposure) whose active metabolite 1,25-dihydroxyvitamin D \([1,25(OH)_{2}D]\) plays a critical role in calcium and mineral homeostasis, bone modeling, and bone remodeling. Skin is the major source of vitamin D, and the vitamin D metabolic pathway is illustrated in Supporting Fig. 1. It consists of three major steps mediated by hydroxylases, all of which are cytochrome P450 enzymes that function as oxidases. Of the circulating vitamin D metabolites, 25OHD is the most abundant form, has the longest half-life, approximately 2 to 3 weeks, and reflects both skin synthesis and dietary intake. It is thus the metabolite of interest relating vitamin D nutritional status to outcomes.

#### Genetic polymorphisms and environmental modulators of serum 25OHD levels

The serum concentration of 25OHD is under marked (23% to 80%) genetic influence as demonstrated in twin studies.

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**Fig. 1.** Inflection point or plateau determined from the curves relating PTH to 25OHD levels in various ethnic groups worldwide. Data points represent the inflection point, 25OHD level below which PTH levels rise sharply, or a plateau, the 25OHD level above which PTH levels did not suppress any further. Information provided from population based studies are illustrated in upper panel, and in other studies on lower panel, by ethnicity (blue for Caucasians, green for Asians, and black for blacks). The data points include both genders unless otherwise specified. The study by Saliba et al. also included information on the plateau that was reached at a 25OHD level between 30-34 ng/mL. To convert from nmol/L to ng/mL divide by 2.496. Reproduced with permission from El-Hajj Fuleihan G, Rahme M, Bassil D. Do desirable vitamin D levels vary globally? In: Burckhardt P, Dawson-Hughes B, Weaver C, editors. Nutritional Influences on Bone Health: 8th International Symposium. London: Springer Verlag; 2013. p. 273–300. (doi:10.1007/978-1-4471-2769-7).
Two genomewide studies confirmed results from the candidate gene approach and identified polymorphisms in key genes of the vitamin D pathway.[34,35] These include: 25-hydroxylase (CYP2R1); 1-hydroxylase (CYP27B1); 24-hydroxylase (CYP24A1); and 7-dehydrocholesterol reductase (DHCR7); the D binding protein (DBP, also known as GC); and the vitamin D receptor (VDR) (see Supporting Fig. 1). Variants near genes involved in cholesterol synthesis, vitamin D hydroxylation, and transport were the most influential; however, even when combined only explain less than 5% of variations in 25OHD levels.[34]

Conversely, environmental and lifestyle factors account for more substantial variations in vitamin D status or serum 25OHD levels, amounting to 3 to 15 ng/mL. Consistent predictors of low 25OHD levels are extremes of age, gender, pregnancy, UVB/sun exposure, season, pollution, clothing style, high BMI, lower socioeconomic status, skin pigmentation, race, and ethnicity, as detailed in Supporting Information, Appendix I.[16,7,20,36]

Difficulties in predicting 25OHD level based on known genetic or lifestyle predictors

Despite characterization of genetic and lifestyle predictors of circulating serum 25OHD levels, it remains very difficult to interpret the specific impact of any one single factor because of the complex interaction between predictors, in which some instances may vary in opposing directions leading to counterintuitive findings. Modeling studies suggest that lifestyle factors combined can explain up to 50% of variability in 25OHD levels (Supporting Information, Appendix I). In a study of 664 elderly individuals vitamin D intake or supplements and baseline levels accounted for 24% of variability in serum 25OHD levels achieved.[37] Although current vitamin D guidelines by IOM and ES take age, gender, and reproductive status into consideration, none has factored in lifestyle and genetics into their recommendations for desirable levels, with the exception of the Australian guidelines that take season into account.[38]

The IOM and ES Recommended Desirable 25OHD Levels

Although the outcomes used to derive desirable 25OHD levels were similar for IOM and ES, the studies included and conclusions that were reached differed. Table 1 summarizes the prespecified outcomes and the main statements as they appeared in both reports, and in the Supporting Information, Appendix II provides evidence detailed in these reports.[16,18] The data on the PTH-25OHD inflection point is quite controversial, with a wide range for the inflection point, and therefore cannot be used with confidence. The IOM recognized the limitations of calcium absorption studies quoted, including the lack of use of the gold standard methodology for several and the lack of a clear cutoff. It nevertheless concluded there was no clear evidence for further benefit in calcium absorption at a 25OHD level above 20 ng/mL. The ES only used one publication that combined two studies with overlap in study subjects, neither of which used the gold standard method to assess absorption, and concluded a desirable level above 32 ng/mL (Table 1).[16,18] The same histomorphometric study was referenced by both organizations. It revealed that 7 of 675 individuals (1%) who had a high osteoid volume/bone volume (above 2%) had a 25OHD levels between 20 and 30 ng/mL, but serum 25OHD was measured with a poor assay on postmortem drawn blood samples. The ES concluded that the desirable 25OHD level is 30 ng/mL, because no individual above this value had osteomalacia, whereas the IOM chose 20 ng/mL; 97.5% of the subjects above this value had no osteomalacia (Supporting Information, Appendix II). BMD was not explicitly considered a parameter in the justification of the desirable 25OHD level by ES, and, although considered in the conceptual model developed by IOM linking vitamin D to bone outcomes, it was not included in their conclusions regarding desirable 25OHD levels[16] (IOM Report 2010, p. 366–7). Finally, although fractures are the most important skeletal outcomes, 25OHD levels were quite variable among trials, thus hampering the formulation of firm conclusions regarding desirable 25OHD levels for this outcome.[3,16] Out of 13 randomized controlled trials listed by the IOM, only three revealed a significant reduction in fractures (two with Ca/D, one with D alone) with mean 25OHD values ranging from 29.8 to 44.9 ng/mL (SD ranges 8 to 12 ng/mL).[16] The IOM report recognized this challenge and opted to derive needed information from several fracture observational studies. As detailed in Table 1 and in the Supporting Information, Appendix II,[16,18] these pointed to desirable levels ranging from 10 to 30 ng/mL. However, these studies are similarly limited by the fact that they used different approaches for showing significant reduction in fractures (linear versus logistic regression, using quartiles or one or more prespecified cutoffs for the latter), as well as different assays. The highest risk for fractures was in subgroups of subjects with a 25OHD level less than 16 ng/mL and up to 20 ng/mL, and the lowest risk for fracture in subjects with a 25OHD more than 25 ng/mL and up to 30 ng/mL, depending on the specific study (Table 1).[16,18] ES used two meta-analyses of randomized controlled trials (RCTs) published by the same authors, with overlap in seven studies, that showed a significant reduction in the risk of vertebral and hip fractures, at mean 25OHD level ≥42 ng/mL[39,40] (Supporting Information, Appendix II). In addition to the challenges/limitations of the evidence summarized in Table 1 and Supporting Information Appendix II, the range of serum 25OHD levels specified in the individual studies was quite high in Table 1 and Supporting Information Appendix II.[16,18] Finally, data in the pediatric age group, pregnant women and non-white populations was scarce.

Knowledge Gaps in Specific Age Groups and Populations

Vitamin D and pregnancy outcomes

Low levels of serum 25OHD are observed in pregnant women worldwide. Associations between low gestational 25OHD levels and maternal/offspring health outcomes[41] include a higher risk of developing preeclampsia or having a Caesarian section in the mothers, a higher risk of preterm birth, a higher risk of being born small for gestational age (SGA), or a higher risk of having impaired skeletal parameters for the neonates, but findings were not consistent across studies.[42–49]

Systematic reviews and meta-analyses based on observational studies show an increased risk of gestational diabetes in pregnant women with low 25OHD levels (OR varying from 1.4 to 1.7[50–52]; preeclampsia (OR varying between 1.8 and 2.8)[50,52,53]; SGA babies (OR between 1.5 and 1.9)[50,52], whereas findings on Caesarian section rates were inconsistent.[54] These findings are limited by the observational nature of studies, inconsistent adjustment for confounders, and heterogeneity in vitamin D cutoffs.

Meta-analyses based on RCTs essentially revealed negative results. One that considered five RCTs showed an OR for low
| 1. PTH inflection point | Mean/median 25OHD level range in studies: 11.26–35.2 (SD range: 5.2–15.5) | Mean/median 25OHD level range in above studies: 15–30.4 (SD range: 9–13.2) |
| 2. Vitamin D–calcium absorption relationship | For both children and adults there was a trend toward maximal calcium absorption between 25OHD levels of 30 and 50 nmol/L, with no clear evidence of further benefit above 50 nmol/L. | “When postmenopausal women who had an average blood level of 25OHD of 20 ng/ml increased their level to 32 ng/ml, they increased the efficiency of intestinal calcium absorption by 45–65%.” |
| 3. Osteomalacia in postmortem biopsies | “Data from the work of Priemel et al. (2010) have been used by the committee to support a serum 25OHD level of 50 nmol/L as providing coverage for at least 97.5 percent of the population.” | “Although they could not establish a minimum 25OHD level that was inevitably associated with mineralization defects, they did not find pathological accumulation of osteoid in any patients with circulating 25OHD above 30 ng/ml.” |
| 4. Rickets | “In the face of adequate calcium, the risk of rickets increases below a serum 25OHD level of 30 nmol/L and is minimal when serum 25OHD levels range between 30 and 50 nmol/L. Moreover, when calcium intakes are inadequate, vitamin D supplementation to the point of serum 25OHD concentrations up to and beyond 75 nmol/L has no effect.” | Not discussed |
| 5. Bone mineral density | Mean/median 25OHD level range in different ethnicities in this study: Infants: 2.4–37 (SD range: 1.6–20.8) Children and adolescents: 8.2–36.1 (SD range 2.4–30.8) Postmenopausal women and elderly men: 9.2–48.6 (SD range 2.7–15.6) | Mean 25OHD level range in different ethnicities in this study: 20–19 years: 18.7–33.1 (SD range 8–12.2) >50 years: 21–28.9 (SD range 9.4–10.4) |
| 6. Fractures | “Because available trials often administered relatively high doses of vitamin D, serum 25OHD concentrations varied considerably. Although some studies suggested that serum 25OHD concentrations of approximately 40 nmol/L are sufficient to meet bone health needs, “consistency with the threshold for hip and non-vertebral fracture prevention from a recent meta-analysis of double-blind randomized controlled trials (RCT) with oral vitamin D” |

**Table 1.** The IOM and ES Justification for the Recommended Desirable 25OHD Level

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<tr>
<td>25OHD level (ng/mL)</td>
<td>Mean/median 25OHD level range in studies: 11.26–35.2 (SD range: 5.2–15.5)</td>
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<tr>
<td>25OHD levels (ng/mL)c</td>
<td>Mean/median 25OHD level range in studies: in children: 20–33.2 (SD range: 7.8–17); in adults: 11.2–64 (SD range: 3.6–22)</td>
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<td>25OHD levels (ng/mL)d</td>
<td>Mean/median 25OHD level range: Infants: 2.4–37 (SD range: 1.6–20.8) Children and adolescents: 8.2–36.1 (SD range 2.4–30.8) Postmenopausal women and elderly men: 9.2–48.6 (SD range 2.7–15.6)</td>
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<td>Data from the work of Priemel et al. (2010) have been used by the committee to support a serum 25OHD level of 50 nmol/L as providing coverage for at least 97.5 percent of the population.</td>
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<td>Bone mineral density</td>
<td>Mean/median 25OHD level range in different ethnicities in this study: Infants: 2.4–37 (SD range: 1.6–20.8) Children and adolescents: 8.2–36.1 (SD range 2.4–30.8) Postmenopausal women and elderly men: 9.2–48.6 (SD range 2.7–15.6)</td>
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<td>Mean/median 25OHD level range in different ethnicities in this study: 20–19 years: 18.7–33.1 (SD range 8–12.2) &gt;50 years: 21–28.9 (SD range 9.4–10.4)</td>
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Table 1. (Continued)

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<td>requirements for most people, findings from other studies suggested that levels of 50 nmol/L and higher were consistent with bone health. Given that causality has been established between changes in serum 25OHD levels and bone health outcomes, information from observational studies can be useful in determining the dose–response relationship.</td>
<td>Mean/median 25OHD level range in studies: 24.8–44.9 (SD range: 7.2–14.7)</td>
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</table>

25OHD levels (ng/mL) Mean/median 25OHD level range in studies: 7.3–55 (SD range: 2.7–15.6)c

Mean/median 25OHD level range in studies: 24.8–44.9 (SD range: 7.2–14.7)

25OHD levels reported in ng/mL; for conversion into nmol/L multiply by 2.496.

IOM = Institute of Medicine; ES = Endocrine Society.

cMean 25OHD levels not available in the IOM or ES reports but derived from retrieving the full text of quoted studies.

dObservational and randomized controlled studies included.
neonatal outcomes were also assessed (Supporting Information, Appendix IIIa, b).

Vitamin D and bone health in children

Although the efficacy of vitamin D treatment in infants and children suffering from rickets is unequivocal, the effect of supplementation in improving bone mineral metabolism in instances of subclinical insufficiency in the pediatric age is unclear. Studies evaluating the relationship between 25OHD, PTH, and bone remodeling markers in this age group are limited by the powerful confounding effect of growth on bone modeling and remodeling. Numerous are the cross-sectional studies illustrating the direct correlation between vitamin D and BMC in the pediatric age groups, including studies from Asia, but few are the randomized trials investigating the beneficial effect of supplementation on skeletal health. In a meta-analysis, information from six studies, totaling 343 participants receiving placebo and 541 receiving vitamin D, was compiled. Vitamin D supplementation had no statistically significant effects on total body bone mineral content (BMC) or on bone mineral density (BMD) of the hip or forearm, and there was a trend to a small effect on lumbar spine BMD. In preplanned subgroup analyses, in which the mean 25OHD at entry was less than 14 ng/mL, there were significant increments in lumbar spine (LS) BMD and total body BMC. These findings were, in part, driven by data from a randomized double-blind controlled trial conducted in 179 Lebanese adolescent vitamin D–deficient girls, mean age 13 ± 2 years, and baseline vitamin D of 14 ± 8 ng/mL. Vitamin D at daily doses of 200 IU and 2000 IU improved lean mass and BMC at the hip. There was a trend for more substantial increments in a premenarcheal subgroup, underscoring the critical impact of timing of supplementation in relationship to pubertal status, as had been previously noted.

In a randomized controlled trial of vitamin D, conducted in 2000 neonates in India, vitamin D administration at 35 μg/day (1400 IU/day) significantly increased standard deviation (Z) scores for weight, length, and arm circumference, and decreased the proportion of children with stunted growth at 6 months, but had no effect on death, hospitalization, inpatient or outpatient visits. Postmenarcheal girls from India, aged 14 to 15 years, with a mean 25OHD level below 10 ng/mL, and randomized to receive 300,000 IU of vitamin D2 quarterly, experienced a 1.9% greater increase in total body BMC, but only a 0.5% greater increase in LS BMD, findings that were not significant, possibly due to sample size (n = 50). In light of the scarce number of trials, the putative beneficial effect of vitamin D in high-risk but otherwise apparently healthy children and adolescents warrants further investigation. We have identified 44 trials, 12 completed and 25 ongoing, investigating the effect of vitamin D supplementation on pediatric outcomes (ClinicalTrials.gov; accessed November 5, 2014). Supplementation doses varied between 400 and 4000 IU/day, and the outcomes included bone remodeling indices, bone density, and markers of fuel metabolism, inflammation, and infection (Supporting Information, Appendix IVa, b).

Vitamin D and musculoskeletal health in non-white subjects

Asia and the Middle and Far East represent the regions with the highest prevalence of hypovitaminosis D and of obesity worldwide, but are also the least represented in terms of inclusion of subjects from these regions in major vitamin D trials. A recent review assessing the validity for defining a single global desirable level for 25OHD examined the ethnic composition of study participants in the large vitamin D fracture and fall trials. Eleven relevant meta-analyses on RCTs on vitamin D and fractures and nine meta-analyses on vitamin D and falls were retrieved. The overwhelming majority of randomized trials included in these meta-analyses were conducted in Western countries, with an anticipated predominance of white subjects. Ethnicity was only specified in three trials, all conducted in the United States, two on fractures and one on falls. The review also examined studies available for defining desirable levels in non-whites using surrogate outcomes for calcium metabolism. There were essentially no studies on intestinal calcium absorption or bone histomorphometry. The few that attempted to define a desirable 25OHD level using the 25OHD-PTH relationship resulted in a wide range or none at all, and none of these were population-based studies (Fig. 1). Limited data from the United States reveals that lower 25OHD level may be sufficient to maintain skeletal health in blacks and that higher levels may even be harmful.

In summary, little is known today regarding the safety and efficacy of vitamin D supplementation on musculoskeletal parameters in non-white populations.

Vitamin D and nonclassical outcomes

Associations of low 25OHD with an ever expanding list of chronic diseases, cancer, and mortality have been reported but the evidence for a causal role of vitamin D on these nonclassical outcomes is lacking. Associations between polymorphisms in enzymes/proteins involved in the vitamin D pathway and several health outcomes are also beginning to emerge (Supporting Information, Appendix I). The evidence from large RCTs investigating the beneficial effect of vitamin D on nonclassical outcomes in whites, as well as all other ethnic groups, is missing. A recent review identified 15 ongoing large randomized trials evaluating the impact of high-dose vitamin D replacement on cardiovascular, renal, and hepatic health outcomes, and on survival in cystic fibrosis and chronic lymphocytic leukemia.

Vitamin D in Phase III osteoporosis registration trials

The majority, if not all, pivotal phase III randomized trials included intake of calcium and vitamin D as the standard of care in both placebo and intervention arms, and several excluded subjects with low vitamin D levels at screening. However, a careful scrutiny of the information provided in the relevant publications describing these trials, detailed in Table 2, reveals the scarcity of information available regarding the subjects’ vitamin D status at trial entry, the actual average dose of vitamin D taken, mean 25OHD level achieved, and type of vitamin D assay used in the few studies that measured 25OHD level after study entry. Thus, although the efficacy of the currently approved therapies is often stated to be in light of such supplemental use, it is not clear what the vitamin D nutritional status was in subjects included in these trials. Indeed, an entry criterion for vitamin D level was mentioned in only four of 26 trials, and baseline serum 25OHD level were reported in only four. One study specified both, and a vitamin D level was not measured at study completion in any of the reported trials.

To date, little is known about the vitamin D nutritional status in the majority of subjects enrolled in the registration trials for most U.S. Food and Drug Administration (FDA)-approved osteoporosis therapies.
Table 2. Use of Vitamin D Supplements and Vitamin D Status in 26 Phase III Osteoporosis Registration Trials

<table>
<thead>
<tr>
<th>Reference (publication year)</th>
<th>Drug used</th>
<th>National or international</th>
<th>Entry 25D level criterion</th>
<th>Vitamin D dose used (IU daily)</th>
<th>Mean 25D levels at baseline</th>
<th>Mean 25D at follow-up</th>
<th>Assay type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Watts and colleagues (90) (1990)</td>
<td>Etidronate</td>
<td>International</td>
<td>NS&lt;sup&gt;a&lt;/sup&gt;</td>
<td>None stated</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>Liberman and colleagues (95) (1995)</td>
<td>Alendronate</td>
<td>International</td>
<td>NS&lt;sup&gt;b&lt;/sup&gt;</td>
<td>None stated</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>Black and colleagues (92) (1993); Black and colleagues (94) (1996)</td>
<td>Etidronate</td>
<td>International</td>
<td>&gt;25 ng/mL</td>
<td>400–450</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>Black and colleagues (92) (1993); Cummings and colleagues (95) (1998)</td>
<td>Etidronate</td>
<td>USA</td>
<td>NS&lt;sup&gt;c&lt;/sup&gt;</td>
<td>250</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Orwoll and colleagues (96) (1999)</td>
<td>Alendronate</td>
<td>International (North America)</td>
<td>&gt; 25 ng/mL</td>
<td>up to 500</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>Green and colleagues (99) (1999)</td>
<td>Risedronate</td>
<td>International</td>
<td>NS&lt;sup&gt;d&lt;/sup&gt;</td>
<td>up to 500</td>
<td>23 ng/mL (group 1); 20 ng/mL (group 2)</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>Neer and colleagues (100) (2001)</td>
<td>Risedronate</td>
<td>International</td>
<td>NS&lt;sup&gt;d&lt;/sup&gt;</td>
<td>up to 500</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>Boonen and colleagues (101) (2009)</td>
<td>Raloxifene</td>
<td>International</td>
<td>NS&lt;sup&gt;e&lt;/sup&gt;</td>
<td>400–600</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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<td>Delmas and colleagues (102) (2004)</td>
<td>Risedronate</td>
<td>International</td>
<td>NS&lt;sup&gt;f&lt;/sup&gt;</td>
<td>400–1200</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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<td>Ettinger and colleagues (103) (2001)</td>
<td>Risedronate</td>
<td>International</td>
<td>NS&lt;sup&gt;g&lt;/sup&gt;</td>
<td>400–1200</td>
<td>NR</td>
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<tr>
<td>Neer and colleagues (104) (2001)</td>
<td>Teriparatide</td>
<td>International</td>
<td>NS&lt;sup&gt;g&lt;/sup&gt;</td>
<td>400–1200</td>
<td>NR</td>
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<td>Orwoll and colleagues (105) (2001)</td>
<td>Teriparatide</td>
<td>International</td>
<td>NS&lt;sup&gt;g&lt;/sup&gt;</td>
<td>400–1200</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>Greenspan and colleagues (106) (2007)</td>
<td>PTH 1-84</td>
<td>International</td>
<td>NS&lt;sup&gt;g&lt;/sup&gt;</td>
<td>400</td>
<td>NR</td>
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<td>Black and colleagues (107) (2007)</td>
<td>Zoledronic acid</td>
<td>International</td>
<td>NS&lt;sup&gt;h&lt;/sup&gt;</td>
<td>400–800</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Lyles and colleagues (108) (2007)</td>
<td>Zoledronic acid</td>
<td>International</td>
<td>NS&lt;sup&gt;h&lt;/sup&gt;</td>
<td>400–800</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Orwoll and colleagues (109) (2007)</td>
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<tr>
<td>Meunier and colleagues (112) (2004)</td>
<td>Strontium ranelate</td>
<td>International</td>
<td>NS</td>
<td>400–800</td>
<td>NR</td>
<td>RIA (Diasorin)</td>
<td>RIA (Diasorin)</td>
</tr>
<tr>
<td>Regener and colleagues (113) (2005)</td>
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<td>International</td>
<td>NS</td>
<td>400–800</td>
<td>28 ng/mL</td>
<td>NR</td>
<td>RIA (Diasorin)</td>
</tr>
<tr>
<td>Kaufman and colleagues (114) (2013)</td>
<td>Strontium ranelate</td>
<td>International</td>
<td>NS</td>
<td>800</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Silverman and colleagues (115) (2008)</td>
<td>Basadoxifene</td>
<td>International</td>
<td>NS&lt;sup&gt;g&lt;/sup&gt;</td>
<td>400–800</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Cummings and colleagues (116) (2010)</td>
<td>Lasofoxifene</td>
<td>International</td>
<td>NS&lt;sup&gt;g&lt;/sup&gt;</td>
<td>400–800</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Cummings and colleagues (117) (2008)</td>
<td>Tibolone</td>
<td>International</td>
<td>NS&lt;sup&gt;g&lt;/sup&gt;</td>
<td>400–800</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

<sup>a</sup>Excluded patients taking >1000 IU vitamin D daily.
<sup>b</sup>Excluded patients with osteomalacia.
<sup>c</sup>Excluded patients with vitamin D deficiency.
<sup>d</sup>Excluded vitamin D deficiency. Only subjects with daily calcium intake <1000 mg day (82% of patients) received supplements.
<sup>e</sup>Severe vitamin D deficiency excluded.
<sup>f</sup>Pharmacologic doses of cholecalciferol excluded.
<sup>g</sup>≥50,000 IU/week excluded.
<sup>h</sup>If the serum 25-hydroxyvitamin D level was ≤15 ng/mL or if the level was not available, patients received a loading dose of either vitamin D3 or D2 (at a dose of 50,000 to 125,000 IU given orally or intramuscularly.)
Safety and Toxicity of Vitamin D Supplementation

Vitamin D toxicity and adverse health outcomes

Vitamin D toxicity is characterized by hypercalcemia concomitant with hypervitaminosis D, rather than by an absolute level of serum 25OHD. The reason is that hypercalcemia occurs at widely varying levels of 25OHD, although usually above 120 to 150 ng/mL. Patients may have levels of serum 25OHD above 100 ng/mL and up to 150 ng/mL without associated hypercalcemia. Vitamin D toxicity is generally rare in clinical practice in the modern era, despite use of increasingly higher doses of daily or intermittent vitamin D supplementation, and is usually the result of errors in manufacturing, formulation, or prescription, and more likely to be seen with large bolus doses (Supporting Information, Appendix I). This has been reported, both in children and adults, in the setting of an unrecognized intake that is several hundred-fold higher than allowed by the recommended daily allowance. The IOM report concluded that doses of vitamin D up to 10,000 IU/day are unlikely to be associated with toxicity in adults, whereas daily doses exceeding 50,000 IU/day for weeks to months are associated with hypercalcemia. The Drugs and Therapeutic Committee of the Pediatric Endocrine Society recently completed a review on the risk of vitamin D toxicity in children on supplementation, concluding that it was only noted at a total cumulative intake of 240,000 to 4,500,000 IU of vitamin D.

Both the IOM and Nutrition Board and the European Food Safety Authority (EFSA) set the maximum upper limit (defined as the highest dose not expected to cause adverse risks in healthy individuals) of vitamin D intake at 4000 IU/day, a conservative estimate. For the pediatric age group, it is up to 2000 IU for EFSA and between 1000 and 3000 IU for infants and children up to 8 years for IOM. For ES, the upper limit is up to 2000 IU in infants and 4000 IU in adults. These limits are mostly based on relatively short-term studies, and the long-term safety of such doses is unclear.

The prevalence of elevated serum 25OHD levels, exceeding 100 ng/mL, with or without hypercalcemia is rare, less than 1%, both in population-based and in laboratory-based databases. The increase in serum 25OHD with vitamin D supplementation varies inversely with the starting level, but the development of hypercalcemia and hypercalciuria were shown to be independent of vitamin D dose, with clear interindividual variations. The reasons behind the wide variability in both serum 25OHD and resulting hypercalcemia for any given amount of vitamin D are not completely clear.

In addition to concerns related to hypercalcemia and its complications, hypervitaminosis D may increase the risk of important health outcomes. One interventional study showed an increased risk of both falls and fractures that occurred with one bolus dose of 500,000 IU of cholecalciferol. Associations with increased mortality have also been described in several publications, at high levels and at some low levels of vitamin D, with U-shaped or J-shaped curve modeling patterns (Supporting Information, Appendix I). However, the most recent systematic review and meta-analysis of 29 trials with 71,032 participants, revealed that the mortality estimate was not adversely affected by either vitamin D, or vitamin D plus calcium, RR = 0.97 (95% CI, 0.93 to 1.01).

Safe upper 25OHD range and safe upper limit for high doses

Based on the available information, it is difficult to define a uniformly safe upper range for serum 25OHD level that will prevent hypercalcemia in all patients. Such a range can be derived from the studies outlined in section above on vitamin D toxicity, where hypercalcemia was unlikely to occur at serum 25OHD levels below 100 ng/mL. In addition, one could base it on serum 25OHD levels in normal subjects with high sun exposure, such as lifeguards, or natives living in equatorial latitude with plentiful sunshine. The mean (SD) for such subjects has been shown to range between 28 and 68 (18) ng/mL in individuals from South Africa and are lower in those from Australasia. Summer sun exposure for 20 min in a bathing suit results in synthesis of the equivalent of 15,000 to 20,000 IU of vitamin D3, but this was not observed in a more recent study. Serum 25OHD of individuals with high sun-UVB exposure, such as tanners, surfers, and outdoor workers, range between 10 ng/mL to above 65 ng/mL (Fig. 2). Similarly, mean 25OHD levels in two tribes from Tanzania, 2° to 4° South of the equator, with dark Type IV skin, revealed mean 25OHD levels of 44 and 48 ng/mL, ranging from 23 to 68 ng/mL. Finally, a recent study showed that most black subjects living in equatorial or subtropical areas have mean serum 25OHD levels of around 30 ng/mL, with few getting up to the 50-ng/mL to 60-ng/mL range. Therefore, it seems than serum 25OHD levels of 40 to 60 ng/mL are about the maximal levels reached when healthy subjects with a skin pigmentation adapted to their environment are living in natural circumstances.
Assay Variations, Impact on Care, and the Vitamin D Standardization Program

Although serum 25OHD is the best index of nutritional vitamin D status, its measurement to define desirable vitamin D levels is limited by large variations incurred by the various methodologies used to date. Such variations by far exceed the differences in desirable 25OHD levels defined by IOM and ES.

Variability between methods and impact on patient care

The most common types of assays used today in clinical laboratories are the antibody-based methods that use a kit, the increasingly more popular rapid high-output automated platforms, and high-performance liquid chromatography (HPLC)-based methods with either UV or mass spectrometric (MS)-detection (Supporting Information, Appendix I). Potential source of variability between assays include differences in method of vitamin D metabolite extraction from DBP; cross-reactivity to 25OHD$_2$, 3-epi-25-OHD$_3$ and other vitamin D metabolites, and matrix interferences. The wide variations between methods remains to be a significant problem, and is apparent from scrutinizing reports issued by the Vitamin D External Quality Assessment Scheme (DEQAS) (Fig. 3A), and as reported by investigators. Clinically, the wide differences in measured serum 25OHD levels within and between assays would result in underestimation or overestimation of the actual 25OHD level dependent on the assay used and on the type of supplement used by the patient (vitamin D2 or vitamin D3). A study comparing 25OHD values obtained using an RIA and a platform fast assay in 494 patient samples revealed that serum values measured in parallel with both assays could vary between −38 and +19 ng/mL, a bias that was independent of the serum 25OHD level. The implications of such wide variability on the interpretation and comparison of trial results, systematic reviews, and meta-analyses, on the relevance and applicability of guidelines/recommendations, be it at the public health level or at the individual level in the clinics, are substantial.

Assay standardization and the Vitamin D Standardization Program

Challenges in all of the above assay methods are clear, and a high level of technical expertise is required for performing manual test and designing any vitamin D method. External proficiency testing schemes (USA), or external quality assessment schemes (UK), such as DEQAS, and the vitamin D quality assessment service offered by the College of American Pathologists (CAP), are primarily based on the methodology being used in the respective laboratories, and results obtained vary widely. Examination of the quarterly reports issued by DEQAS that are based on data received from around 1000 laboratories, measuring four unknown samples, reveal wide variations in the mean serum 25OHD level derived by each specific methodology for the same sample of 8 to 16 ng/mL (Fig. 3A). The histogram also reveals a consistent trend for the interassay differences between the mean for methodologies reported, varying between 2.5 and 16 ng/mL. The closest to target value were those values obtained by LC-MS/MS, followed by HPLC (DEQAS; Fig. 3A). The above-reported 25OHD levels derived with each methodology are based on means values obtained from a few dozen to several hundred laboratories, and underestimate variations on individual patient measurements. At present, there exist no practical regulated and reference procedures for clinical measurement of serum 25OHD level. The choice of a particular method by a laboratory more often depends on available expertise, economics, and profitability.

There is a pressing need for harmonization and standardization of vitamin D assays.

The Vitamin D Standardization Program (VDSP) is an international collaborative venture that was organized in 2010 by the Office of Dietary Supplements (ODS) of the National Institutes of Health. The goal of the VDSP is to promote standardized laboratory measurement of total 25OHD, in order to improve decision making to inform clinical and public health practice worldwide. It calibrates vitamin D measurements to National Institute for Standards and Technology (NIST) reference standards and does not mandate a specific analytic approach. VDSP targets an accuracy of $\pm$5%, a goal that is hard to consistently achieve with any methodology to date. More recently, DEQAS has become an accuracy-based scheme, and results are assessed against those obtained by the NIST reference standards. Figure 38 shows that mean 25OHD values obtained for four circulated unknown samples with the various assay methodologies differ widely from the NIST standard for most methods. LCMS and HPLC were the only two methodologies that consistently approached an accuracy of $\pm$10%, but neither fulfilled the desirable accuracy of $\pm$5% on all four samples (Fig. 3B).

In conclusion, assay variability undermines pooling of results from different studies to define dose-response and desirable 25OHD levels. This is a major obstacle to developing evidence-based clinical guidelines and puts into question the applicability of desirable levels derived from means of studies, as currently applied, to the individual patient.

The Concept of a Desirable Range for Level and Dose

In summary, differences between the recommended desirable 25OHD level by IOM of 20 ng/mL, and ES of 30 ng/mL, and the doses to reach them, are best interpreted in the context of all challenges and limitations outlined above, sources of variability in vitamin D levels, and the target age group of interest. Furthermore, the above desirable levels were often based on mean 25OHD levels, with large SDs of 10 to 15 ng/mL, and on information relating mean 25OHD values to endpoints in studies conducted mostly in Western populations. The variations imposed by genetic differences may be the most modest, amounting to a mean of 3 to 4 ng/mL, whereas those incurred by environmental and lifestyle factors and assay differences vary between 5 and 15 ng/mL. Mean differences also underestimate variations between individual patients. Thus, the concept of a desirable range is needed; a range that takes into account efficacy and safety considerations, sources of variations, and incurred differences on both ends of the derived desirable range.

Desirable range for serum 25OHD level

We anchor the lower limit of the desirable range by taking into consideration efficacy data, based on serum 25OHD levels and musculoskeletal outcomes, and an upper limit considering efficacy and safety data. The beneficial effects on fall and fracture risk occurred at mean levels above 20 ng/mL with the upper confidence limits of about 40 ng/mL, with no additional
Fig. 3. Histogram for mean serum 25(OHD) level in nmol/L (A) and percent bias from NIST target values (B), for each of unknown samples prepared from serum donations, measured by participating laboratories, and as provided by the Vitamin D External Quality Assessment Scheme (DEQAS) report for the July 2014 cycle. (A) Each bar graph represents the specific method mean ± 1SD (for eg, LC-MS or HPLC) for serum 25OHD by each of the 10 different measurement methods, used by 989 participating laboratories for that cycle, as specified in the table below the figure, along with number of laboratory participants for each method (for eg, n = 146 for LCMS). The ALTM stands for the altered mean, that is the mean derived from results provided by all 989 participating laboratories, and the target value stands for the corresponding reference value for each unknown sample using reference measurement procedures (RMP) developed by the National Institute of Standards and Technology (NIST) and Ghent University. The target value is the sum of 25OHD2, 25OHD3 and the 3epi-25OHD3 measured according to RMP by NIST. Reproduced with permission from DEQAS. For details on DEQAS see http://www.deqas.org or http://deqas.kpmd.uk (B) Each bar graph represents the specific method mean percent deviation from NIST standard for serum 25OHD by each of the different methods used by participating labs for that cycle. Only methods with 10 or more results returned are plotted. Reproduced with permission from Graham Carter, DEQAS.

<table>
<thead>
<tr>
<th>Method</th>
<th>Sample 456</th>
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<td>78.0</td>
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<td>99.4</td>
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<td>93.4</td>
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</table>

Reproduced with permission from DEQAS.
benefit for any bone health outcome in subjects with serum 25OHD level above 40 ng/mL. Serum levels of up to 60 ng/mL are reached in healthy subjects exposed to natural sunlight in certain latitudes, but concerns regarding deleterious effects of levels above 50 to 60 ng/mL have been raised from observational studies. Patients with well-documented vitamin D toxicity usually have serum 25OHD levels above or well above 100 ng/mL. Thus, our proposed desirable range, set for now at 20 to 40 ng/mL, takes into account the currently available evidence, put in the context of common sources of variations and uncertainties, and avoids the use of a single cutoff. Although slightly lower levels (15 to 20 ng/mL) may be sufficient for some infants and adults, higher levels (40 to 60 ng/mL) may still be safe. Additional data would be needed to validate this range, especially in children, pregnant women and non-white populations.

The desirable range should be interpreted in individual patients in the context of specific assay used, season, sun exposure, and intake of vitamin D. For example, if an individual patient has a serum 25OHD level in the summer of 21 ng/mL, when measured with the most accurate assay, the patient’s real value would fall below the desirable range in the winter. Additional adjustments are needed for methods that systematically overestimate or underestimate the true values, using standardization and calibration information derived from VDSP.

Recommendations for serum 25OHD measurements

Both IOM(16) and ES(18) and several other societies and organizations, such as Osteoporosis Canada,(149) the National Osteoporosis Society in the UK,(150) AACE,(151) and the U.S. Preventive Task Force recommend against the routine measurement of serum 25OHD levels. In light of the problem of assay variation, the assay cost, and the fact that healthy persons respond to the IOM recommended doses by raising serum 25OHD to desirable levels, we believe this is most appropriate approach. Testing should therefore be confined to patients at risk, including those with osteoporosis and other metabolic bone disorders or medical conditions, or on medications known to affect vitamin D metabolism, and conditions known to improve with vitamin D treatment. Measurements should be performed in laboratories with rigorous quality assurance protocols, partaking in external proficiency testing, such as the VDSP and DEQAS, and that are calibrated to NIST standards.

Recommended daily allowance and maximum daily allowed intake

Because routine measurement of serum 25OHD is not recommended, physicians are provided guidance on the recommended vitamin D intake to reach desirable vitamin D levels in over 97.5% of the population. Such recommendations run from as low as 200 IU/day in some European countries, to as much as 4000 IU/day, for the Vitamin D Council.(152) The recommended daily intake for adults is 600 to 800 IU for IOM,(16) USPTF,(15) and AACE,(151), 1500 to 2000 IU for ES,(18) 800 to 2000 IU for IOF(153), and 800 to 1000 IU below age 50 years and 800 to 2000 IU for those over age 50 years for Osteoporosis Canada Updated guidelines.(149) The recommended daily intake for the pediatric age group beyond infancy is 600 IU for IOM,(16) 400 to 1000 IU for ES,(18) and none to 400 IU for EFSA.(122) The differences between the IOM(16) and ES(18) is that the former targets nondiseased individuals of all ages in the United States and Canada only, whereas the ES addresses high-risk individuals. The latter definition of high risk would apply to certain populations, such as in the Middle East and Asia, where some of the lowest 25OHD levels are recorded. In such high-risk groups, dose requirements may indeed differ(20) as shown in dose-ranging RCTs conducted in the Middle East and Asia.(10) Specifically, RCTs using daily equivalent doses of up to 2000 IU in children from Lebanon, Iran, and India, and 4000 IU in adults from Japan and India for up to 1 year, failed to meet IOM RDA definition for vitamin D dose.(20,154,155) Because of the variability in the dose-response curve with vitamin D, the various moderators that may vary by season, age, BMI, and calcium intake, it is also difficult to determine a single recommended daily vitamin D dose, and certainly more so across populations and ethnicities.20)

A dose of 400 to 600 IU/day for infants and children and 600 to 800 IU/day is sufficient for otherwise healthy Caucasian adults and elderly. In some populations with different risk stratification such as low baseline vitamin D status, obesity, or higher metabolic rate of vitamin D, higher levels may be needed (1000 and 2000 IU/day in children and adults, respectively) as to achieve the desirable target levels. These recommendations fall within the conservative upper limit level set by IOM. Meta-analyses and meta-regressions using results of ongoing randomized trials in pregnant women, children, and other ethnic groups, would help refine age-specific and ethnic-specific recommended doses, as has been done for European recommendations.156,157

Research Agenda

The number of vitamin D publications has exponentially risen over the last two decades, yet many questions linger, and debates continue. There is a pressing need for vitamin D assay standardization to derive a unified desirable vitamin D range that overcomes the major obstacle of assay performance. Evidence remains to be gathered to guide preventive practices at the public health level for several age and ethnic groups.

Areas of ongoing investigation, or needed investigations, to fill knowledge gaps include implementation of the VDSP and rigorous trials investigating:

1. Effect of vitamin D on maternal and fetal-neonatal outcomes;
2. Effect of vitamin D on musculoskeletal parameters in children and adolescents;
3. Effect of vitamin D on musculoskeletal outcomes in non-whites;
4. Effect of vitamin D on nonclassical outcomes in all ethnic groups;
5. Gene-environment interaction and impact of enzymatic polymorphisms on baseline levels and response to therapy to define desirable levels in various populations; and
6. Impact of genetic polymorphism in vitamin D pathways on disease expression in various ethnic groups.

Disclosures

All authors state that they have no conflicts of interest.

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Authors’ roles: GEHF developed the general concept for the review, and wrote the manuscript. All authors contributed to various sections of the manuscript and approved the final version.

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