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Review Article

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Vitamin D: Clinical measurement and use

N. Binkley

Osteoporosis Research Program, University of Wisconsin, Madison, WI, USA

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Measurement of circulating 25-hydroxyvitamin D (25(OH)D) is accepted as the clinical indicator of vitamin D status[1]. Given the increasing recognition of widespread vitamin D inadequacy, clinicians are frequently obtaining 25(OH)D measurements and recommending over-the-counter or prescription vitamin D supplementation. However, the clinical measurement of 25(OH)D has been problematic and the options for correction of vitamin D inadequacy suffer from lack of standardization or limited dosing options. These issues, and current clinical approaches to correction of vitamin D inadequacy, will be reviewed.

Historically, 25(OH)D measurement was performed in research facilities using high-pressure liquid chromatography (HPLC) or competitive protein binding methods. In the 1990s, a validated radioimmunoassay (RIA) was developed. Subsequently, the increased clinical recognition of vitamin D inadequacy as a widespread problem spurred development of automated systems, one of which was problematic leading to substantial variability of results on the same serum specimen[2]. The recent clinical application of liquid chromatography mass spectroscopy (LC-MS) and HPLC technologies has improved the situation somewhat, for example, DEQAS (vitamin D External Quality Assessment Scheme)[3] data from 2006 demonstrate comparable values using RIA, HPLC and LC-MS methodologies (Figure 1a). However, even with these technologies, despite agreement of mean values, substantial variability in 25(OH)D results based upon the laboratory in which the measurement is performed continues (Figure 1b). This between laboratory variability appears likely to reflect differences in assay calibration (Figure 1c). As such, it appears probable that assay standardization could be substantially enhanced by the availability and implementation of international standard calibrators.

Despite the above noted assay variability, there is growing consensus that a serum 25(OH)D concentration above approximately 30 ng/ml constitutes optimal vitamin D status[4]. Using this cutpoint, many individuals, including approximately half of postmenopausal women receiving pharmacologic osteoporosis therapy[5], have vitamin D inadequacy. Recognizing this, clinicians are often recommending vitamin D supplementation. However, currently in the US many vitamin D preparations are sold as over-the-counter supplements and as such may have variable content. Moreover, compliance/adherence with daily therapies is often poor and has occurred even in clinical trials involving vitamin D supplementation. For example, a recent large study performed in the UK found that almost half of clinical trial participants did not reliably take their vitamin D supplement[6]. Similar non-adherence with supplementation confounds other calcium/vitamin D clinical trials[7] and may well limit the impact of population-based vitamin D supplementation recommendations. Moreover, even after hip fracture, up to 75% of patients stop calcium and vitamin D supplementation within three months[8]. Obviously, alternative strategies to provide vitamin D repletion must be sought. Examples of alternate approaches include an annual injection of "mega-dose" cholecalciferol (600,000 IU), which appears to maintain vitamin D adequacy for one year[9]. Similarly, monthly rather than daily supplementation might lead to improved adherence and a preliminary report found monthly dosing with 45,000 IU of D_3 to produce similar 25(OH)D increases as achieved with 1,500 IU daily[10]. Larger studies of longer duration are necessary to identify approaches to maintaining vitamin D adequacy. Importantly, albeit based on limited data[11], it appears that cholecalciferol (vitamin D^3) maintains circulating 25(OH)D status better than ergocalciferol (vitamin D_2)[11]. As such, routine use of D_3 seems prudent. However, the only high-dose vitamin D available by prescription in the US currently is D_2. This preparation is often dosed weekly or three times per week to treat vitamin D deficient individuals and some clinicians subsequently prescribe monthly use of 50,000 IU of vitamin D_2. However, as use of high dose D_2 reduces circulating $25(OH)D_3$[11,12], whether this approach

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Corresponding author: Neil Binkley, M.D., University of Wisconsin, Osteoporosis Research Program, 2870 University Avenue, Suite 100, Madison, WI 53706, USA
E-mail: nbinkley@facstaff.wisc.edu

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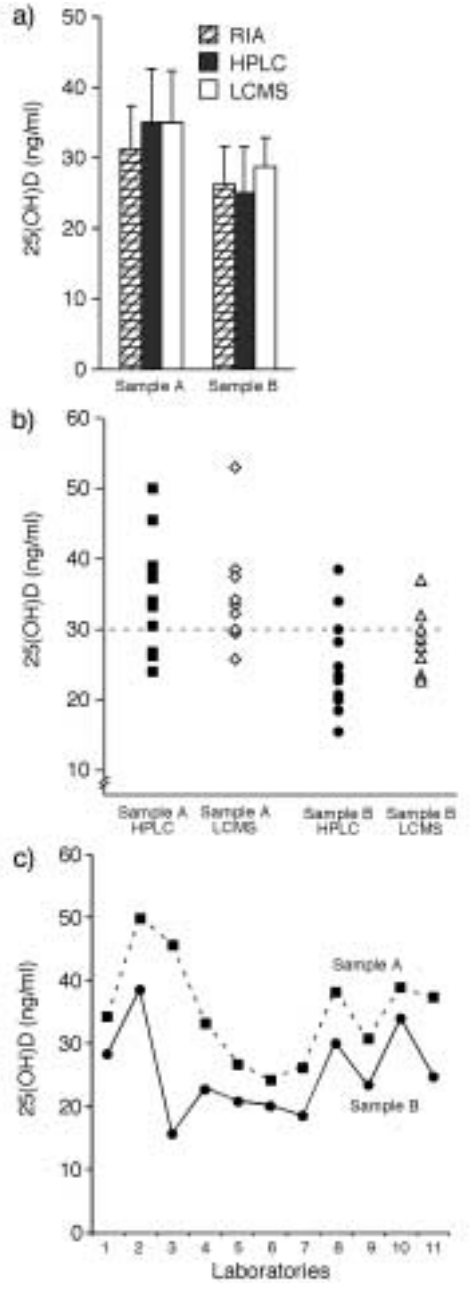

Figure 1a-c. Agreement of 25(OH)D measurements. Data from the DEQAS specimens of spring 2006 reveal that, on average (Figure 1a), there is good agreement between laboratories utilizing the Diasorin radioimmunoassay (RIA), high-pressure liquid chromatography (HPLC) and liquid chromatography-mass spectroscopy (LCMS). Data as mean (SD); number of participating laboratories using RIA, HPLC and LCMS is 54, 11 and 9, respectively. However, as demonstrated in Figure 1b, individual specimens have substantial variability using either HPLC or LCMS. As such, the possibility persists that an individual patient's vitamin D status could be classified as insufficient or optimal depending upon the laboratory utilized to measure 25(OH)D. Figure 1c indicates that the individual differences between laboratories appear to primarily reflect differences in assay calibration. In fact, if laboratory 3 is excluded, the values obtained for samples 1 and 2 are highly correlated (r2=0.87). As such, provision of standard calibrators should substantially enhance standardization of 25(OH)D results.

might be counter-productive requires clarification.

As an alternative approach to enhancing vitamin D status, routine exposure to sunlight or ultraviolet B (UVB) radiation could be advocated. However, even high amounts of sun or UVB exposure does not guarantee vitamin D adequacy on an individual basis[13,14]. Finally, the goal 25(OH)D concentration to achieve with high dose vitamin D supplementation has not been clearly defined. In this regard, in highly sun-exposed populations, it does not appear possible to obtain a circulating 25(OH)D status above approximately 70 ng/ml[15]. As such, supplementation with high-dose vitamin D to attain levels greater than this does not seem physiologically sound.

In summary, progress has been made in 25(OH)D measurement, however further standardization is desirable. Additional definition of potential approaches to maintenance of optimal vitamin D status and improved standardized options for vitamin D supplementation/prescription are necessary.

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