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Editorial

14th Vitamin D Workshop consensus on vitamin D nutritional guidelines☆

As background information, the reader should appreciate that at the 13th Vitamin D Workshop in 2006 it was agreed that about half of elderly North Americans and Western Europeans and probably also two thirds of the rest of the world are vitamin D deficient as judged by their inability to maintain a healthy bone density [1–3]. It was also generally agreed that the serum concentration of 25(OH)D in normal subjects is the best indicator for judging the vitamin D status in patients with vitamin D-related disease states [4].

The 14th Workshop on Vitamin D, held in Brugge, Belgium, October 4–8, 2009 was attended by 419 scientists from 35 countries who were privileged to listen and participate in a Vitamin D Roundtable that was held in order to allow presentation and broad discussion of two distinct views of and approaches to worldwide vitamin D nutritional status. One Roundtable position is that an absolute minimum 25(OH)D level of 20 ng/ml (50 nmol/l) is necessary in all individuals in order to support and maintain all the classic actions of vitamin D on bone and mineral health and that, according to this criterion, a large proportion of the world's population is vitamin D deficient. Those who hold this position further believe that the huge effort needed to ameliorate this deficiency must be undertaken as soon and actively as possible and that the target 25(OH)D levels of >20 ng/ml should be obtained in the majority of the target population. The second Roundtable position is that newer data showing associations between vitamin D status and prevalence of several diseases such as cardiovascular disease, hypertension, colon and breast cancer, multiple sclerosis as well as the involvement of vitamin D in muscle strength and immune functions [5], indicates that target levels of 25(OH)D should be 30–40 ng/ml (75–100 nmol/l) at the minimum. As a basis for policy decision making, these two positions are incompatible with one another. However, through consideration of the aspects of vitamin D nutrition upon which the proponents of the two views agree, as well as acknowledging differences in opinion, consensus on how to proceed in the near term can emerge. This was the goal of the Vitamin D Roundtable.

The Roundtable, chaired by Anthony Norman (USA) and Christopher Gallagher (USA), began with 15-min presentations from Robert Heaney (USA) and Reinhold Vieth (Canada), both proponents of 25(OH)D > 40 ng/ml, followed by presentations by Roger Bouillon (Belgium) and Paul Lips (Netherlands), who advocate minimum 25(OH)D levels of 20 ng/ml. A selected group of experts from around the world, Bess Dawson-Hughes (USA), John Pettifor (South Africa), Peter Ebeling (Australia), and Christine Lamberg-Allardt (Finland), then joined the four presenters and the chairs on the panel for further discussion. Finally, there was open discussion with questions and comments from the floor.

The main points made by Dr. Heaney in favor of targeting minimal 25(OH)D levels of 40 ng/ml were as follows: (i) average 25(OH)D levels of about 60 ng/ml are seen in outdoor summer workers without hypercalcemia, indicating that the human body can and does achieve these levels from sunlight exposure alone without ill effect [6]; (ii) 20 ng/ml is not sufficient to reduce fracture risk [7,8]; (iii) in several specific studies the best results for both the classical physiological functions such as calcium absorption as well as risk reduction for major diseases are seen at serum 25(OH)D levels greater than 30 ng/ml [9]; (iv) although much of the data supporting an association between increased serum 25(OH)D levels and risk reduction are from association studies, still there are more than 20 randomized controlled trials (RCTs) demonstrating vitamin D benefits for non-skeletal endpoints and most are positive and, none of the data is negative (i.e. indicating harm from the higher levels); and (v) different vitamin D-dependent endpoints likely require different threshold 25(OH)D levels and the highest level should be chosen to cover them all.

Dr. Vieth, who also supports 25(OH)D levels > 30 ng/ml as preferable to the proposed minimum level of 20 ng/ml, covered three main points in his talk: (i) the dosage levels of vitamin D in many clinical trials are too low to elicit positive responses, while in the clinical trials that do demonstrate fracture prevention, average 25(OH)D values exceeded 30 ng/ml [10]; (ii) several studies showing response as a function of serum 25(OH)D concentration indicate that 20 ng/ml does not give the maximal response; (iii) a study in MS patients showed tolerability, as assessed by serum and urinary calcium, of the administration of very high (40,000 IU/day) vitamin D doses [11]. In addition, Dr. Vieth suggested that perhaps it is the instability of 25(OH)D levels due to seasonal variations, rather than average concentrations, that are responsible for the increased disease risk seen in people at northern latitudes [12].

Dr. Bouillon, who supports targeted 25(OH)D levels of >20 ng/ml began his presentation that only randomized controlled trials should be used to define the optimal vitamin D status with regard to bone health, and especially the hard endpoint as the number of fractures (per person per time) and surrogate (or soft) measures such as PTH levels, calcium absorption and bone turnover markers [13]. He presented studies indicating that the threshold level of 25(OH)D for these three measures is approximately 20 ng/ml. Raising 25(OH)D by vitamin D administration above 20 ng/ml has no effect on Ca^{2+} absorption or bone mineral density. As for the hard endpoint of fracture incidence, a serum 25OHD level < 20 ng/ml was

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identified as a risk factor for hip fracture in the Women's Health Initiative and intervention studies. Dr. Bouillon then presented studies of the association between 25(OH)D levels and diseases such as cancer and multiple sclerosis [11] which show that the greatest risk is seen at levels of <20 ng/ml. Although in these studies there is a trend for an even lower risk at higher levels, it is Dr. Bouillon's belief that this association evidence is not a sufficient basis for establishing levels of greater than 20 ng/ml as a target for all populations [14].

Dr. Lips, who also supports 25(OH)D levels of 20–25 ng/ml began by stating that the targeted level should be based on clinical trials and prospective cohort studies [15]. He then presented data showing that fractures and falls are the endpoints for which evidence from clinical trials is available to support a beneficial effect of vitamin D. When bone markers are used, clinical vitamin D deficiency occurs at <8 ng/ml, but there is a positive association in women between BMD and serum 25(OH)D levels up to 36 ng/ml throughout adulthood. From the data he presented, it is the conclusion of Dr. Lips that there is no clinical evidence for an effect of vitamin D outside of the musculoskeletal system [16].

Following these four presentations, each member of a panel of four additional vitamin D scientists was invited to present his or her point of view. Dr. Lamberg-Allardt expressed support for minimum serum 25(OH)D levels of 20–25 ng/ml and concern regarding the lack of evidence for higher levels, such as >60 ng/ml. She raised questions about the variability in the measurement of 25(OH)D concentrations as well as the added complication of seasonal variation in selecting an appropriate desired level. Also she emphasized that it was important to understand the vitamin D status of the fetus and mother during pregnancy and how this could affect the health of the newborn [17]. Dr. Pettifor's view is that the biggest problem is the large number of people whose 25(OH)D levels are below 20 ng/ml and that we must address this major issue about which we all are confident before and separately from addressing issues based on associations.

Dr. Dawson-Hughes emphasized the importance of targeting 25(OH)D levels in the elderly in order to decrease fall and fracture incidence; she suggested a minimum of 30 ng/ml to achieve this objective. She also expressed interest in the idea of addressing the seasonal variation, but noted that trying to do so in a recommendation could render it too complex to be effective. There is also the complication that these seasonal variations are reversed in the Northern and Southern hemispheres. Dr. Ebeling was supportive of the target of 30 ng/ml proposed by Dr. Dawson-Hughes to prevent fractures; he also expressed concern about higher levels leading to soft tissue calcification in some individuals [18].

Dr. Gallagher, who recommends serum levels of 25(OH)D averaging 25 ng/ml throughout the year (20–30 ng/ml are typical levels in the winter and summer, respectively, in his mid-western geographical area of the US) augmented his belief in the need for more evidence from random controlled trials with the observation that these are not as available as they might be since vitamin D is not a product of a large pharmaceutical company. He also noted that the largest such placebo controlled study using vitamin D 400 IU/day + calcium (1000 mg/day) showed a significant increase in kidney stones [19].

From the above discussion as well as comments from the audience, it is apparent that there are several unresolved questions, clear answers to which would make reaching consensus (and perhaps even broad agreement) on a single recommendation much easier. Among these are:

1. How closely can we predict the attained serum 25(OH)D levels as a function of dosage regime? What factors, such as age, body weight, endogenous production (season and geographic locale), ethnic background, diet, and underlying health conditions, will affect the relationship between vitamin D dose and serum concentration of 25(OH)D ?
2. How should the variation in measured serum 25OHD concentrations be taken into account when settling upon a recommendation?
3. How should we deal with the situation that epidemiological studies appear to be showing different effective serum 25OHD concentrations for different diseases?

These open questions, although important and requiring answers eventually, do not need to prevent us from reaching consensus on the following important points:

1. The large number of people of any age in the world who are frankly vitamin D deficient or insufficient (serum levels below 20 ng/ml) is at risk for a several poor health outcomes. We should make an unambiguous statement about the need to address this issue through vitamin D supplementation. We should agree upon a 25(OH)D serum concentration that
   a. is achieved through supplementation rather than diet fortification;
   b. is achieved through the use of vitamin D rather than vitamin D_2;
   c. is approximately ~20–25 ng/ml (~50–62.5 nmol/l).
2. A panel of vitamin D investigators should use all currently available evidence to determine as closely as possible what dose of vitamin D is likely to achieve serum concentrations of 25(OH)D of ~20–25 ng/ml.
3. The vitamin D dose agreed upon in point 2 should be that considered for supplementation in vitamin D deficient/insufficient populations throughout the world. Vitamin D scientists should immediately lend their support to the implementation of this supplementation.
4. While some experts consider the available RCTs and associational studies to be an insufficient basis for public policy formulation at this time, the aggregate evidence should, nevertheless, be made known to physicians and patients for their personal use. Certain risk groups, most notably pregnant women and the elderly, should be given additional specific information regarding the probable benefits of increasing their vitamin D intake and serum 25(OH)D concentrations well beyond that recommended for other groups. For example, in order to reduce falls and fractures, a serum concentration of 25(OH)D of at least 25 ng/ml might be the recommended target in the elderly.
5. Vitamin D scientists should turn their attention to examining the evidence for and ultimately demonstrating a cause and effect relationship between vitamin D status and disease for specific conditions. For example, emerging data of cellular mechanisms of the role of vitamin D in the cardiovascular system suggests that it should be the focus of attention and resources in order to establish the nutritional role of vitamin D and good health.

Consensus on these points leads to clear actions that cannot fail to increase the health and well-being of people throughout the world based on what we know now while clarifying the research directions that require continued energetic pursuit; see also Ref. [20].

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