Challenging the present definition of “normal” vitamin D levels obtained by a single blood test. Can we develop a formula to predict vitamin D levels in the 4 seasons from a single season’s measure?

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ABSTRACT

Publications on the health effects of vitamin D (25(OH) D) had almost triplicate in the last 10 years, not only for its known “calcemic effects” (calcium, phosphor, PTH), but for the more recent findings on its “non-calcemic effects” (all-cause and cardiovascular mortality, and relation with certain types of cancer). Part of these publications deal with the definition of what is a “normal” circulating level of 25(OH) D that may distinguish between health and disease. The literature also deals with seasonal variations of vitamin D, showing levels that rise in summer and fall in winter and with DBP phenotypes and geographical location that affect seasonality of 25(OH) D measurements. Despite the knowledge of the existence of these phenomena many studies on vitamin D fail to acknowledge the time of the year the blood sample was extracted. Thus, when we compare results from different studies without defining the season that the samples were drawn, we compare incomparable figures. Furthermore, it is quite absurd to define “normal levels” as a static measure (over or under a certain value) using a single blood test when the value measured is known to change with seasons.

Knowing that people have different vitamin D levels in different seasons of the year, we should ask ourselves which of these measurements should be used to define a “real” or “normal” level? Is it the lower one? Is there a “mean measure” that should be used for this matter? If yes, how do we obtain it? Do we have to make 4 seasonal measurements in each patient? Alternatively, might there be a possibility of developing a formula to help us obtain the mean from a single season’s measure or one season’s prediction from another season’s measurement? And knowing that DBP phenotypes and geographical location affect seasonality of 25(OH) D measurements; shouldn’t we include this in the equation?

In this article I will discuss the hypothetical existence of an Individual Mean Annual vitamin D level that I will call the “IMAD level” and a recovery formula “RF” that may be used to calculate this mean having one single measure (in any of the 4 seasons) and to predict any season’s value from another season’s measurement. IMAD levels should be obtained in the two main DBP phenotypes, taking into account the geographical location of the test.

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Introduction

Publications on the health effects of vitamin D had almost triplicate in the last 10 years. In the past, vitamin D was mostly related to bone metabolism because it regulates calcium and phosphorus levels, inhibits parathyroid hormone secretion, and when deficient leads to rickets in children and osteomalacia in adults. Later, it was also related to muscle strength and stability, and its deficiency showed to be related to muscle weakness and falls in the elderly. These “calcemic” effects of vitamin D have been known for about a century. During the past two–three decades “non-calcemic” effects of vitamin D have been observed [1]. A possible association between low serum 25-hydroxyvitamin D (25(OH) D) levels, mortality (all-cause and cardiovascular), and certain types of cancer has been found in recent research.

In order to distinguish between health and disease one should define a “normal” circulating level of 25(OH) D. In the past, this was addressed by simply gathering a diverse population of subjects who were asymptomatic for disease, measuring circulating 25(OH) D, and plotting the data using a Gaussian distribution. Today, assessing “normal” circulating 25(OH) D levels based on a Gaussian distribution of its values is considered a grossly inaccurate method of identifying the normal range for vitamin D [2]. Levels
of 25(OH) D vary between countries and these variations are due not only to latitude but also to time, total ozone, clouds, pollution, aerosols, surface reflectivity and altitude, skin pigmentation and exposure of the skin (affected by dress codes) [2–5]. But the most important determinants of circulating 25(OH) D are sun exposure and dietary intake and, since there is heritability in vitamin D levels, genetic determinants may also play a role. This was confirmed in a study by Wang et al., in which a genotype score was constructed. Individuals in the top quartile of genotype scores had 2 to 2.5-fold elevated odds for vitamin D insufficiency [6]. Other genome-wide association study by Ahn et al. [7] reported that a SNP in the gene coding for the group specific complement (vitamin D-binding protein, DBP) is associated with serum levels. So, although sun exposure increases vitamin D levels consistently, the genotype of the individual influences the blood levels reached [8]. Vitamin D concentrations are highest in subjects with genotype GC 1/1, intermediate in GC 1/2 and lowest in GC 2/2 [9]. Seasonal variations of vitamin D have been widely described in the literature [10–13], with levels rising in summer and falling in winter. This seasonality may be different for a DBP 1-1 subject vs. a DBP 2-2 subjects. But despite the knowledge of the existence of seasonal variations, most studies on vitamin D fail to acknowledge the time of the year the blood sample was extracted, and when comparing results from different studies without defining when the samples were drawn, we compare incomparable figures. For example, if one uses samples taken on winter for a causation study, may wrongly arrive to the conclusion that low levels of vitamin D have a causative effect on the studied event. If a second study is performed using summer samples, they will show an opposite relation, since measurements in vitamin D levels consistently, the genotype of the individual influences the blood levels reached [8]. Vitamin D concentrations are highest in subjects with genotype GC 1/1, intermediate in GC 1/2 and lowest in GC 2/2 [9]. Seasonal variations of vitamin D have been widely described in the literature [10–13], with levels rising in summer and falling in winter. This seasonality may be different for a DBP 1-1 subject vs. a DBP 2-2 subjects. But despite the knowledge of the existence of seasonal variations, most studies on vitamin D fail to acknowledge the time of the year the blood sample was extracted, and when comparing results from different studies without defining when the samples were drawn, we compare incomparable figures. For example, if one uses samples taken on winter for a causation study, may wrongly arrive to the conclusion that low levels of vitamin D have a causative effect on the studied event. If a second study is performed using summer samples, they will show an opposite relation, since measurements in vitamin D levels will be higher.

Defining “normal levels” as a static measure (over or under a certain value), using a single blood test seems absurd when the value measured is known to change with seasons. Despite these obvious facts, the consensus of scientific understanding appears to be that vitamin D deficiency is reached for serum 25(OH) D levels less than 20 ng/ml (50 nmol/L), insufficiency in the range from 20 to 32 ng/ml, and sufficiency in the range from 33 to 80 ng/ml, with normal in sunny countries 54–90 ng/ml [14] (in a single blood test, and disregarding seasonality or DBP type.

**Hypothesis**

Knowing that people have different vitamin D levels in different seasons of the year, we should ask ourselves which of these measurements should be used to define a “real” or “normal” level? Is it the lower one? [12] Is there a “mean measure” that should be used for this matter? If yes, how do we obtain it? Do we have to make 4 seasonal measurements in each patient? Alternatively, might there be a possibility of developing a formula to help us obtain the mean from a single season’s measure or one season’s prediction from another season’s measurement? And what about the DBP type? How will this influence year’s variability?

In this article I will discuss the hypothetical existence of an Individual Mean Annual vitamin D level that I will call the “IMAD level” and a recovery formula “RF” that may be used to obtain the mean by one single measure in any of the 4 seasons and the prediction of any season’s value from another season’s measurement.

**The IMAD level and the RF**

In the absence of data from the literature about intrapersonal variation, I will use hypothetical measurements obtained from the Sine curves published in the work of Bolland et al. [15], and data extrapolated from Tandeter et al. [11]. From figure #1 in Bolland’s article let’s assume that the intrapersonal variations in this hypothetical individual are: 60 nmol/L in mid-summer (MSu), 50 nmol/L in mid-autumn (MAu), 40 nmol/L in mid-winter (MWi), and 50 nmol/L in mid-spring (MSp). From the second study (presenting percentage of the total population with levels < 20 ng/ml), I will use the data as if it was of 25 OH D levels. In this case the numbers will be 82.4 nmol/L (100-17.6) in MSu, 54.3 nmol/L in MAu (100-45.7), 28.2 nmol/L in MWi (100-71.8), and 47.6 nmol/L in MSp (100-52.4).

The IMAD and RF obtained from both studies are presented in Table 1.

Assuming that 25(OH) D levels follow a fix seasonal curve in each individual and that an IMAD level and RF are confirmed in a prospective study, we will be able to calculate vitamin D levels in any season by a single measurement, following this formula presented in Table 2. IMAD levels should be obtained in the two main DBP phenotypes, taking into account the geographical location of the test.

**Discussion**

The hypothesis here presented might be a to-good-to-be-true situation, and individual measurements may behave not exactly like a Sine curve or like the other numbers presented. Differences might be found between men and women measures [12]. There may also be different curve-behaviors in patients with a tendency to normal vales and those with low 25(OH) D levels across the year. And, since normality may not be solely defined by vitamin D levels but also by PTH levels (due to an inverse relationship between circulating 25(OH) D and PTH and the presence of secondary hyperparathyroidism), we might also need to measure PTH in each patient and create another formula including PTH in vitamin D measurements.

The use of solar air-mass/solar altitude has shown also to be helpful in predicting the seasonal variation of 25(OH) D. Researchers from the US studied pooled data from 3.44 million samples of serum 25(OH) D, providing estimates of the seasonality of serum 25(OH) D levels which may be extrapolated to other studies [10].

### Table 1

<table>
<thead>
<tr>
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<th>IMAD levels and RF.</th>
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<tr>
<td></td>
<td>Bolland</td>
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<td></td>
<td>50 nmol/L</td>
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<tr>
<td></td>
<td>RF</td>
</tr>
<tr>
<td>MSp IMAD x 1</td>
<td>50</td>
</tr>
<tr>
<td>MSu IMAD x 1.2</td>
<td>60 (50 × 1.2)</td>
</tr>
<tr>
<td>MAu IMAD x 1</td>
<td>50</td>
</tr>
<tr>
<td>MWi IMAD x 0.8</td>
<td>40 (50 × 0.8)</td>
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### Table 2

Comparing different seasons/transformation formula.

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<thead>
<tr>
<th></th>
<th>Summer to winter</th>
<th>Winter to summer</th>
<th>Winter to autumn</th>
<th>Spring to summer</th>
<th>Spring to autumn</th>
<th>Spring to winter</th>
<th>Autumn to winter</th>
<th>Autumn to spring</th>
<th>Autumn to summer</th>
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<tbody>
<tr>
<td></td>
<td>MSp x 0.53</td>
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The problem is that the data available in the literature shows seasonal 25(OH) D variations based in population studies (interpersonal variations) but we do not have data on intra-personal variations (how do vitamin D levels change in isolated individuals along the 4 seasons of the year). Although studies like the one by Azizi et al. [16] did four consecutive seasonal measurements in their study population, the results were presented as means and not as individual measurements, making them unfit as data for our purposes. In order to achieve the information needed, we should perform a study in which individuals are tested four times during the year (mid-summer, mid-autumn, mid-winter and mid-spring) to see whether all the subjects tested have the same grade of variation across the seasons, or if curves can be created for different situations (gender, normal range, low range). Genotype analysis may also be performed in order to test whether DBP 1-1 subject and DBP 2-2 subjects show different curves.

In order to perform a prospective study that may answer the here presented questions one may confront an ethical dilemma: what to do if one of the seasonal measurements is low? Obviously, even when low vitamin D levels are very prevalent in asymptomatic people that may never be tested for vitamin D levels, every ethics committee will impose researchers to stop the study and start vitamin D supplementation as low levels are detected. Since we haven’t found yet the way to avoid the ethical limitations, the present hypothesis is presented as a theoretical framework about what is to be expected if the study is carried on.

Conflict of interest

No conflict of interest.

References