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Opinion Article

Time for New Recommendation of Upper Limit of Serum Vitamin D in Humans

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Abstract

There is a continued debate and exchange of knowledge with respect to serum 25- hydroxyvitamin D (25(OH)D) cut-off levels. Based on our current knowledge it is time to reconsider our recommendations of the optimal level of serum 25(OH)D in the clinical setting and not only focus on low levels but also recommend an upper serum limit of around 125 nmol/L (40–50 ng/mL) among healthy and diseased.

Keywords: Vitamin D

Issues and Opinions

There is a continued debate and exchange of knowledge with respect to serum 25-hydroxyvitamin D (25(OH) D) cut-off in the lower end and when to start supplementation. This debate includes the general population as well as in a long list of diseases. The discussion of a cut-off level insufficiency and deficiency of25 mmol/L (10 ng/mL) and 50 mmol/L (20 ng/mL), respectively, is one debate another is the optimal level of serum 25(OH)D and of most importance a missing debate of a recommended upper limit.

It is well known that vitamin D plays an essential role in the regulation of metabolism, calcium and phosphorus absorption. Essentially, the effect of vitamin D is in the hydroxylated form 1,25-dihydroxy vitamin D. However, the effects of vitamin D are not limited to mineral homeostasis and skeletal health maintenance. The presence of Vitamin D Receptors (VDR) in other tissue and organs suggest that vitamin D physiology extends well above and beyond bone homeostasis in cell and animal studies. There has been an association of serum 25(OH)D deficiency to several diseases among others osteoporosis, cancers, autoimmune disorders, infectious diseases, cardiovascular disease, Type 2 Diabetes (T2D) and neurological disorders such as sclerosis [1]. Knowledge from the literature is that low levels are problematic and strong associations are published indicating higher morbidity and mortality among individuals with the low levels of serum 25(OH)D<50 mmol/L (20 ng/mL). On the other hand, clinical randomized studies do not so far support the beneficial effect of vitamin D supplementation other than in osteoporosis, falls and fractures.

A vitamin D dose range of 20–25 µg (800–1000 IU) per day has been effective in several studies whereas lower doses have generally been ineffective. Further hereto several doses above this range have increased the risk of falls and therefor the recommendation is that older adults with serum 25(OH)D levels < 40 nmol/L likely have fewer falls if supplemented with 20–25 µg (800–1000 IU) per day of vitamin D [2]. A recent RCT showed maximum decrease in falls at 12-month serum 25(OH)D level of 80–95 nmol/L (32–38ng/mL) and of extreme importance is that the faller rates increase when the serum 25(OH)D level exceed 40–45 ng/mL (100–112.5 nmol/L) [3].

We have learned from clinical randomized studies (RCT) with high-dose vitamin D supplementation that for mental health benefit is seen when normalizing. But no benefit is seen of higher high levels of monthly doses of vitamin D compared with the standard monthly dose of 600 µg (24,000 IU) [4]. Monthly high-dose vitamin D supplementation does not prevent Cardio-Vascular Disease (CVD) [5] and a combined study evaluating supplementation with vitamin Ddid not show a lower incidence of cardiovascular events or invasive cancer than placebo [6]. Long-term vitamin Dsupplementation, which increased mean 25-hydroxyvitamin D3 concentration >100 nmol/L for 18 months, had no effect on systolic or diastolic BP in predominantly white, healthy adults without severe vitamin D deficiency [7].In a long-time the authors of a RCT showed no significant lung function improvements in a study of high-dose vitamin D versus placebo [8]. It is often claimed that vitamin D might protect colo-rectal cancer but among patients with metastatic colo-rectal cancer, addition of high-dose vitamin D_3 vs standard-dose of vitamin D_3 to standard chemotherapy was inconclusive indicating the need of further and larger multicenter randomized clinical trials [9]. Related hereto, patients with digestive tract cancer, vitamin D supplementation, compared with placebo, did not result in significant improvement in relapse-free survival at 5 years [10]. Looking at neurology, the latest published meta-analysis of vitamin D supplementation in sclerosis were including all the RCT's and highlighted the very low-quality of these and the missing evidence of effect as data suggests no benefit of vitamin D for patient-important outcomes among people with

multiple sclerosis (MS). Several studies inMS is initiated and will likely provide further evidence that can be included in a future updates [11]. A meta-analysis of 19 RCT's of vitamin D supplementation in T2D patients shows that supplementation seem to improve HbA1c, insulin resistance, and insulin in short-term intervention, suggesting that vitamin D can be considered as a therapeutic agent along with the other treatments for T2D if patients are supplemented at low serum levels [12]. In patients with pre-diabetes and hypovitaminosis D, high dose vitamin D improves insulin sensitivity and decreases risk of progression toward diabetes [13]. In thyroid disease no significant changes were observed in the serum levels of T3 and T4 hormones to vitamin D supplementation and therefore further well controlled, large, longitudinal studies are needed [14]. In all these executed studies the included patients mostly improve serum 25(OH)D from low to normal levels and in few cases to high levels and as presented the risk of fall increases.

Several epidemiologic studies support a serum 25(OH)D upper limit of 100–125 nmol/L (40–50 ng/mL) when evaluating all-cause mortality [15,16], CVD [17] and cancer [18]. The J-shaped curve indicate significant higher risk than benefits at levels higher than 100–125 nmol/L (40–50 ng/mL) and the above mentioned high-dose RCT's does not report on benefits.

In the literature the excess and toxicity levels of serum 25(OH)D are as high as 250 nmol/L (100 ng/mL) and 325 nmol/L (150 ng/mL), respectively. Based on the literature we have no evidence in support of a normal level up to 250 nmol/L (100 ng/mL).

I think it is time to reconsider our recommendations of the optimal level of serum 25(OH)D in the clinical setting and not only focus onlow levels but also recommend an upper serum limit of around 125 nmol/L (40–50 ng/mL) among healthy and diseased (Table 1).

Table 1. Diagnostic clinical cut-offs of levels of serum 25(OH)D

Serum 25(OH) Level (nmol/L)	Serum 25(OH) Level (ng/mL)	Laboratory Diagnosis
<25	<10	Insufficiency
<50	25	Deficiency
50–125	25–50	Normal
>125	>50	Excess
>325	>150	Intoxication

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