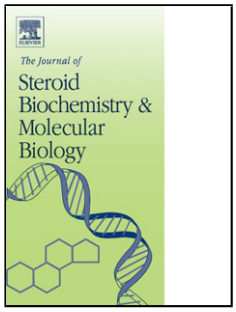

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Vitamin D supplementation guidelines

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Highlights of "Vitamin D supplementation guidelines- which to choose and why?"

- Vitamin D supplementation is crucial for both classic and pleiotropic effects.
- 25(OH)D concentrations of 30-50 ng/mL (75-125 nmol/L) are beneficial for overall health.
- Regional or nationwide vitamin D guidelines are more applicable for general population.
- Disease-specific vitamin D guidelines are applicable globally.
- Vitamin D therapeutic guidelines are applicable globally.

Abstract:

Research carried out during the past two-decades extended the understanding of actions of vitamin D, from regulating calcium and phosphate absorption and bone metabolism to many pleiotropic actions in organs and tissues in the body. Most observational and ecological studies report association of higher serum 25-hydroxyvitamin D [25(OH)D] concentrations with improved outcomes for several chronic, communicable and non-communicable diseases. Consequently, numerous agencies and scientific organizations have developed recommendations for vitamin D supplementation and guidance on

optimal serum 25(OH)D concentrations. The bone-centric guidelines recommend a target 25(OH)D concentration of 20 ng/mL (50 nmol/L), and age-dependent daily vitamin D doses of 400-800 IU. The guidelines focused on pleiotropic effects of vitamin D recommend a target 25(OH)D concentration of 30 ng/mL (75 nmol/L), and age-, body weight-, disease-status, and ethnicity dependent vitamin D doses ranging between 400-2,000 IU/day. The wise and balanced choice of the recommendations to follow depends on one's individual health outcome concerns, age, body weight, latitude of residence, dietary and cultural habits, making the regional or nationwide guidelines more applicable in clinical practice. While natural sources of vitamin D can raise 25(OH)D concentrations, relative to dietary preferences and latitude of residence, in the context of general population, these sources are regarded ineffective to maintain the year-round 25(OH)D concentrations in the range of 30-50 ng/mL (75-125 nmol/L). Vitamin D self-administration related adverse effects, such as hypercalcemia and hypercalciuria are rare, and usually result from taking extremely high doses of vitamin D for a prolonged time.

Key words: vitamin D, 25(OH)D, pleiotropic, extra-skeletal effects, vitamin D, global, recommendations

1. Introduction

Over the past ten years, more than 30,000 manuscripts have been published worldwide, demonstrating a variety of health benefits of vitamin D (1). Meanwhile, a relatively smaller number of publications reported insufficient evidence of extra-skeletal biological effects of vitamin D in humans (2). For example, Autier et al. (3) and Bolland et al.(4) published review articles suggesting that hypovitaminosis D is an epiphenomenon that coincides with poor health outcomes (3), and that the correction of vitamin D deficiency has no beneficial effects (3). They also claim that conducting randomized controlled trials (RCTs) searching for vitamin D-dependent health outcomes is futile (4), but their meta-analyses were far from satisfactory because of the bias of selection of studies.

In contrast, other reviews, original studies, and meta-analyses strongly pointed towards vitamin D as having significant beneficial effects and an important micronutrient component in the prevention of diseases (5-10). In fact, is it not surprising, when general practitioners (GPs) review scientific papers showing effects of vitamin D on reducing the risks of cardiovascular disease, stroke, heart failure,

cancer, diabetes, autoimmune diseases, infections, secondary to having year-around, higher 25-hydroxy vitamin D [25(OH)D] serum concentrations, they may be confused as to what to believe and are thus, skeptical.

A similar level of skepticism should be maintained when strong statements negating pleiotropic benefits of vitamin D using small-scaled, poorly designed and conducted short-term RCTs, and meta-analyses with an inherent selection bias in favor of conclusions (4,5,11). In spite of the confusion created in the scientific and clinical literature, the consumption of vitamin D supplements has continued to increase (12). In certain populations, such supplementation have led to a modest increase of serum 25(OH)D concentrations (13).

The concerns about adverse effects of vitamin D, in particular, increased risk for hypercalcemia, nephrocalcinosis, and kidney stones have kept some away from taking supplements. Furthermore, the negative experience gained through historical trends from other vitamins (e.g., vitamin A, C and E) and potential vitamin D "toxicity," may have increased their reluctance.

Despite criticisms, vitamin D is one of the most cost-effective micronutrient supplements, that leads to improving overall human health (5-10,14). During the past decade, a significant progress has been made in reference to understanding of the biology and pathophysiology of vitamin D and its metabolic pathways (5-10,14-16). These cumulative evidence have changed the views of scientists working in this field and those clinicians prescribing vitamin D. This has changed the paradigm from the "bone-centric" approaches to pleiotropic conceptions and approaches (15-16).

While the number of publications and data related to vitamin D has been increasing markedly, the gap of knowledge on the 25(OH)D concentration expected to capture all possible pleiotropic effects (or even a single benefit) as well as the vitamin D doses needed to achieve this is widening. Further, lack of consensus of contradictory claims and recommendations provided by various published guidelines (15-19) make decisions difficult or problematic, at least in some clinical conditions. Finally, the term "sufficiency" has led to confusion and endless debates between scientists and clinicians focused on "skeletal benefits" (17, 19) and those examining extra-skeletal vitamin D actions (5-10,15,16). Despite controversies, it seems important to look at the big picture and the pleiotropic actions with a balanced approach that would help overall human health of millions of people.

2. Vitamin D: A classic perspective in brief

Vitamin D is a fat-soluble vitamin; the term "vitamin D" refers to both ergocalciferol (vitamin D_2) and cholecalciferol (vitamin D_3), which are formed from their respective pro-vitamins, ergosterol and 7-dehydrocholesterol (7-DHC). The predominant natural source of vitamin D_3 in humans is production in the skin where 7-DHC follows a two step-reaction involving ultraviolet-B (UV-B) irradiation to form previtamin D_3 followed by a subsequent thermal isomerization to vitamin D_3 (20). Both vitamin D_3 and vitamin D_2 may be obtained in a lesser extent from varied diet and in more significant amounts from fortified foods and supplements. Fish liver oil, fatty fish or egg yolks contain higher amounts of vitamin D_3 compared to other food products, however even varied diet cannot be considered as effective source to provide recommended daily doses. Vitamin D_2 may be synthetized in plants and mushrooms involving UV-B action on ergosterol (21). Cultivated mushrooms contain lower amounts of vitamin D_2 than wild-grown, but if they are exposed to UV-B the amount of vitamin D_2 increases (22). Dietary vitamin D is absorbed predominantly in the small intestine via chylomicrons which enter the lymphatic system that drains into the superior vena cava.

After entering bloodstream, from intestinal absorption or skin synthesis, vitamin D is converted into 25-hydroxyvitamin D [25(OH)D] in the liver and then to 1,25-dihydroxyvitamin D [$1,25(OH)_2D$] in the kidneys (23-26). 25(OH)D and $1,25(OH)_2D$ circulate in the blood mostly bound to vitamin D-binding protein (DBP). After a release from DBP to tissues, $1,25(OH)_2D$ triggers through intracellular vitamin D receptor (VDR) a numerous metabolic actions throughout the body (23-26).

In tissues, $1,25(OH)_2D$ dissociate from DBP, and binds to intracellular vitamin D receptors (VDR), which triggers several ubiquitous metabolic actions in tissues and organs. The main function of $1,25(OH)_2D$ is to maintain a tight calcium and phosphorus homeostasis in the circulation. This is also modulated by parathyroid hormone (PTH), and fibroblast growth factor (FGF-23) (23-27).

In humans, serum calcium concentration is maintained at a very narrow range of about 2.45–2.65 mmol/L. Consequently, when the blood ionized calcium concentration decreases below the normal range, a series of anti-hypocalcemic events will occur to restore calcium levels back to the physiologic range (27). The main target tissues of $1,25(OH)_2D$ actions are, the intestine, kidneys and bone. In the kidneys, $1,25(OH)_2D$ stimulates PTH-dependent tubular reabsorption of calcium. PTH itself increases the conversion of 25(OH)D to $1,25(OH)_2D$ in the proximal renal tubules (23-27).

In the skeletal tissues, $1,25(OH)_2D$ and PTH works in conjunction to control bone turnover. $1,25(OH)_2D$ interacts with the intra-cellular VDR in osteoblasts, increasing the genomic expression of several genes, especially receptor-activating nuclear factor ligand (RANKL). This ligand interacts with its receptor, RANK on monocytes lineage, inducing them to aggregate to form multinucleated osteoclasts (28-30). Mature osteoclasts, after binding on to bone surfaces, release collagenases and hydrochloric acid, leading to degradation of collagen and releasing calcium back into the micro-environment, and consequently release calcium and phosphorus into the bloodstream (28-30).

In the intestine, $1,25(OH)_2D$ enhances calcium and phosphorus absorption. The activity of 25(OH)D-1α-hydroxylase (CYP27B1), the enzyme responsible for the conversion of 25(OH)D to $1,25(OH)_2D$ is stimulated by PTH and inhibited by $1,25(OH)_2D$ (23-26). In addition, $1,25(OH)_2D$ suppresses the activity of PTH, inhibits proliferation of parathyroid cells and its secretions, and involved in cell differentiation and inhibition of cell proliferation. Because the seco-steroid, $1,25(OH)_2D$ is a potent hormone involved in regulating calcium metabolism, to prevent the unregulated $1,25(OH)_2D$ activity and to prevent hypercalcemia, $1,25(OH)_2D$ induces its own destruction by markedly increasing the expression of the 25(OH)D-24-hydroxylase (CYP24A1) (31). This multi-functional enzyme, catalyzes the conversion of both $1,25(OH)_2D$ and 25(OH)D into biologically inactive water-soluble metabolites excreted into the bile (31).

From a classic perspective, vitamin D deficiency disturbs bone metabolism that manifest as rickets in children, and osteomalacia in adults. Both diseases are caused by the impaired mineralization of bone due to an inadequate calcium-phosphate product due to PTH's action on the kidneys causing phosphaturia (6, 7, 9, 23, 25-27,32).

Vitamin D appeared to be critically important during the evolution of vertebrates, when amphibians moved out from the sea to land. In evolutionary terms, vitamin D is one of the oldest hormones, that is also produced by some of the earliest phytoplankton life forms (33,34). PTH is responsible for enhancing dietary calcium absorption, thereby maintaining circulating calcium concentrations within the physiological range. Calcium and phosphate are deposited into the collagen matrix as calcium hydroxyapatite that provides the strength to the bones and their structural integrity allowing vertebrates to ambulate in their environment (32-34).

3. Vitamin D: pleiotropic perspective in brief

It is now recognized that almost all tissues and cells in the human body have VDR and that many cells and tissues also show the 25(OH)D-1α-hydroxylase (CYP27B1) activity (29,35); i.e., the ability to generate $1,25(OH)_2D$ in extra-renal tissues (29, 35, 36). The extra-renal CYP27B1 expression is not influenced by calcium homeostatic inputs, but in contrast to renal enzyme, is regulated by specific factors, including inflammatory signaling molecules or the stage of cell development (37-41). Further, extra-renal tissues have also ability to catabolize $1,25(OH)_2D$ by expression of CYP24A1 (24), and this important control mechanism decreases $1,25(OH)_2D$ auto- or paracrine signals and potential input of locally produced hormone into circulation (42-44). The extra-renal $1,25(OH)_2D$ auto- or paracrine actions are numerous and diverse and are switched on/off depending on 25(OH)D availability, cell- or tissue specific regulatory factors as well as anabolic-catabolic feedbacks of CYP27B1 and CYP24A1. In addition to the well characterized calcium-phosphate metabolism and bone mineralization, this would explain in part, its pleotropic actions in a variety of tides and organs.

It is known that the local production of $1,25(OH)_2D$ followed by its binding to VDR is responsible for upregulation of approximately 2,000 genes that are involved in many metabolic pathways (29,33). Plausibly, these are responsible for many of the non-calcemic benefits ascribed to vitamin D (5-10, 28, 29, 45,46). It was evidenced that $1,25(OH)_2D$ not only modulates cellular growth and differentiation, but also enhances the immune system (e.g., production of beta-defensin and cathelicidin, and modulation of production of anti-inflammatory cytokines: IL-4, IL-5) (7, 9, 45-52). In addition, it also increases the lymphocytic activity and stimulates insulin production (7, 9, 45,46). These findings help explaining many of the vitamin D actions and its association with the reduction of the risk of several diseases.

Vitamin D has shown a strong immunomodulatory capacity; high VDR levels have been reported in macrophages, dendritic cells, T lymphocytes, and B lymphocytes supports the conception of its fundamental role in combating bacteria, and preventing both autoimmune diseases and chronic inflammatory states (47-50). In a study of adults living in the eastern United States, 25(OH)D concentrations ≥ 38 ng/mL (≥95 nmol/L), compared to lower values, were associated with 2.7 times lower incidence of acute viral respiratory tract infections ($p=0.015$) and 4.9 times lower percentage of days ill (49). The authors postulated that, in the general population, an increase of 25(OH)D concentration to values above 38 ng/ml (95 nmol/L) would significantly reduce the incidence of upper-respiratory tract viral infections in adults (49). Another study from Sweden also revealed that vitamin D supplementation had a protective effect against respiratory tract infections (50, 51), leading to a decrease in the number of antibiotic-prescriptions (51).

Another target for vitamin D is the cardiovascular system since vitamin D-related components are abundant in the cardiovascular system; in the blood vessels and in the heart. This is exemplified by the seasonal and latitude-associated prevalence of CVDs and vitamin D deficiency (53). Data from a sub-study of the Cardiovascular Risk in Young Finns Study, a multicenter study of atherosclerosis precursors of Finnish children and adolescents, provided additional supporting evidence (54). A randomly selected cohort of 2,148 individuals with stored serum samples taken at the age of 3-18 years in 1980 and in 2007 (follow-up), and with ultrasound studies of carotid intima-media thickness (IMT; a marker of structural atherosclerosis), correlated with several cardiovascular risk factors and predicts future cardiovascular events in their adulthood (54). This study revealed that participants who had 25(OH)D concentrations in the lowest quartile (<40 nmol/L) during the childhood, had significantly increased odds of having high-risk IMT later in life, as shown in the analyses adjusted for age, sex and either childhood risk factors (odds ratio, 1.70 [95 % CI, 1.15–2.31], p = 0.0007) and adult risk factors, including 25(OH)D concentrations (odds ratio 1.80 [1.30–2.48], P = 0.0004) (54). These results have important clinical implications; as estimated by increased IMT in adulthood, vitamin D deficiency (<20 ng/mL; <50 nmol/L) during childhood is an important risk factor in adult for CVD.

Further, women with 25(OH)D concentrations ≥ 40 ng/mL (≥ 100 nmol/L) had a 67% lower risk of any invasive cancer (excluding skin cancer) compared to those with serum 24(OH)D levels less than < 20 ng/mL (50 nmol/L) (HR = 0.33, 95% CI = 0.12-0.90) (55). In a RCT, postmenopausal women in central United States a significant correlation of the provenience of cancer with serum 25(OH)D was reported. In this study, 25(OH)D was an independent predictor of cancer risk, and both improved calcium (supplementation of 1,400-1,500 mg calcium/day) and vitamin D (supplementation of calcium plus vitamin D in dose 1,100 IU/day) resulted in significant reduction of all-cancer risk (56).

Moreover, vitamin D status is an important factor in the reduction of risk of other cancers such as breast cancer, colorectal cancer and colorectal adenomas (57). The optimal 25(OH)D concentration for preventing and surviving cance seems to be between 30 and 40 ng/mL (75-100 nmol/L) (58). Moreover, individuals with higher 25(OH)D concentration at the time of a cancer diagnosis have better cancer-specific and overall survival rates (57,58).

Alzheimer's disease, dementia, cognitive decline and other forms of neurodegenerative disorders also benefited from having physiological blood 25(OH)D concentration. As shown in the InCHIANTI study, elderly people who revealed very severe vitamin D deficiency ,with 25(OH)D concentrations below 10

ng/mL (< 25 nmol/L) had an accelerated risk of cognitive decline over a 6-year period (RR=1.6, 95% CI: 1.2 to 2.0), compared to their counterparts with 25(OH)D levels more than 30 ng/mL (≥75 nmol/L) (59).

Similar findings were shown by Slinin et al.; the OR = 1.6 (95% CI: 1.1 to 2.2) for global cognitive decline was calculated basing on clinical data of men with 25(OH)D concentrations below 10 ng/mL (<25 nmol/L) compared to those with 25(OH)D concentrations ≥30 ng/mL (≥75 nmol/L) (60). In another study, very low 25(OH)D concentrations (< 10 ng/mL; <25 nmol/L) in elderly women at baseline predicted the onset of non-Alzheimer's dementia over 7-year period (61) and a higher vitamin D dietary intake was associated with a lower risk of developing Alzheimer's disease (62). Furthermore, a casual effect of vitamin D deficiency on multiple sclerosis (MS) susceptibility was recently evidenced using mendelian randomization (MR) analyses based on data of almost 7,500 patients suffering from this disease (63).

It was also suggested that low 25(OH)D concentrations are related to significantly increased risk of mortality (64-67). The large analysis of 73 cohorts with 849,412 study participants pointed that those participants with 25(OH)D <10 ng/mL (<25 nmol/L) compared to those with ≥30 ng/mL (≥75 nmol/L) had the relative risk of mortality of 1.50 (95% CI: 1.21-1.87) (68).

The available evidence of extra-skeletal vitamin D actions and related health benefits is growing (5,7,9,45-69). Indisputably, 25(OH)D availability for endocrine, autocrine and paracrine pathways appeared crucial to lower the risks of cancers, autoimmune diseases (e.g., multiple sclerosis, type 1 diabetes, etc.), asthma and recurrent wheezing, CVD and stroke, systemic lupus erythematosus, atopic dermatitis, neurocognitive dysfunction including Alzheimer’s disease, autism, infectious diseases including influenza and tuberculosis, pregnancy complications, type 2 diabetes, falls, osteoporosis and fractures, rickets, osteomalacia and others (5,7,9,45-69), as well as the all-cause mortality (5,64-68).

Science needs to be balanced, so results from a review of 290 cohorts and 172 RCT (3), which included vitamin D and/or its metabolites and showed no major health benefits, should be kept in mind. On the other hand, in addition to the selection bias, most of the studies included to abovementioned review were not specifically designed with vitamin D-related hard end points. Moreover, conclusions of this paper are very difficult to apply on an individual basis, where the need for vitamin D supplementation may be obvious.

4. Vitamin D: minimum, maximum, optimum

There have been controversy about what exact 25(OH)D concentrations define vitamin D deficiency and sufficiency. The aim of vitamin D supplementation is to achieve and maintain the optimal 25(OH)D concentrations with no adverse effects. 25(OH)D is the substrate for 25(OH)D-1α-hydroxylase (CYP27B1) in both renal and extra-renal tissues for the synthesis of $1,25(OH)_2D$. It was reported that only 50% of maximal 25(OH)D-1α-hydroxylase activity (K_m) is achieved when 25(OH)D concentration close to 40 ng/mL (100 nmol/L), which in turn depends on having adequate amounts of vitamin D (26).

Additional evidence emerged on minimal 25(OH)D concentrations required for triggering a number of extra-skeletal effects. Majority of these studies revealed optimal 25(OH)D concentrations ranging between 30 and 50 ng/mL (75-125 nmol/L), being close to K_m of 1α-hydroxylase (26). 25(OH)D-1α-hydroxylase kinetics and the results of numerous meta-analyzes, RCTs, and observational studies provide convincing data that a target 25(OH)D concentration likely to meet requirements of human tissues containing vitamin D receptor (VDR) is approximately 40 ng/mL (100 nmol/L) (5, 7, 9, 28, 32,45,48,53,58,59). However, the tissue dependent differences of a minimal effective concentration may vary (69-71). The latter suggestion led to the concept that a different 25(OH)D critical concentration is required by 1α-hydroxylase to synthetize 1,25(OH)2D in endocrine actions compared to autocrine/paracrine pathways (26,69-71).

If 25(OH)D availability falls below cell- or tissue-specific critical concentrations, the cell or tissue enters into vitamin D deficiency state with its local metabolic consequences (24, 54-56), while the serum 25(OH)D could be still within the 'so-called' normal range. When cells or tissue are exposed to a physiologically sub-optimal or pathological levels of 25(OH)D concentration (i.e., below that requires to ensure an effective 1α-hydroxylase activity) it is likely to have a tissue-specific, deleterious consequences (26,69-71).

A diverse minimum effective 25(OH)D concentration associated with the lowest risk for bone disorders and for non-skeletal diseases was proposed by Spedding et al. (70). As demonstrated by Australian investigators, a minimum effective serum 25(OH)D concentrations appeared lower for skeletal disease, e.g., rickets (10 ng/mL; 25 nmol/L) or osteoporotic fractures (20 ng/mL; 50 nmol/L), comparison to prevent premature mortality (30 ng/mL; 75 nmol/L) or non-skeletal diseases including depression (30 ng/mL; 75 nmol/L), diabetes and cardiovascular disease (32 ng/mL; 80 nmol/L), falls and respiratory tract infections (38 ng/mL; 95 nmol/L), and cancer (40 ng/mL; 100 nmol/L) (70).

5. Vitamin D guidelines: need to choose wisely

5.1. Recommendations for general population

Up to late 2000's, (1990s-2000s), before the US Institutes of Medicine (IOM) publication in 2010, the recommended vitamin D daily allowance (RDA) up to the age of 50 years was 200 IU/day (5 μg/day) (19, 28, 32-34). This recommendation was based on the belief that 200 IU/day was sufficient to prevent rickets (72). However, this assumption disregards all other physiological beneficial effects of vitamin D. Even recently, the vast majority of multivitamin preparations in Europe and in many other countries, contain only 5 μg (200 IU) of cholecalciferol labeled as "100% of RDA". In 2010, the IOM recognized 200 IU/day as inadequate, and recommended 400 IU/d (10 μg) for infants, 600 IU/d (15 μg) for children, adolescents and adults, and 800 IU/d (20 μg) for adults aged over 70 years to maintain a desirable 25(OH)D concentration (19). As with the IOM recommendation, the minimal 25(OH)D concentration of 20 ng/mL (50 nmol/L) is considered to be physiologically adequate, but this has been contested by many (16,73-75).

However, the majority of studies that included 25(OH)D concentrations to analyze relations between health and the risk of diseases pointed on higher 25(OH)D concentrations, i.e., in the range of 30-50 ng/mL (75-125 nmol/L) or 40-60 ng/mL (100-150 nmol/L), not on 20 ng/mL (50 nmol/L) as the necessary minimal concentration for human well-being (5,7,9,16,45,46,49,51,55,57,58,70,73-78). Even for proper bone mineralization, the IOM recommended concentration of at least 20 ng/mL (50 nmol/L) is controversial, and a 25(OH)D concentration >30 ng/mL (75 nmol/L) is a better fit to prevent subclinical osteomalacia (75).

The Endocrine Society in the USA made recommendations to treat and prevent vitamin D deficiency; it recommended achieving serum 25(OH)D concentrations more than 30 ng/mL (>75 nmol/L), with the preferred range of 40-60 ng/mL (100-150 nmol/L) (16). It was also recommended infants up to 1 year, 400-1,000 IU/day (10-25 μg), for children over 1 year 600-1,000 IU/day (15-25 μg) and for all adults 1,500-2,000 IU/day (37,5-50 μg) (16). For obese people (BMI >30 kg/m^2) a daily vitamin D dose was set as "three times" greater than the recommended dose for subjects with normal body weight (16).

In 2013, the Central European recommendations were published highlighting a problem of vitamin D deficiency in that region (76). Contrary to IOM guidelines (19), the Endocrine Society (16), American Academy of Developmental Disability (77), and Central European recommendations (76) were

developed acknowledging the evidence on both skeletal and the pleiotropic vitamin D effects, thus are relevant to clinical practice. The European guidelines recommended the use of vitamin D supplements to obtain and maintain the optimal target 25(OH)D concentration in a range of 30-50 ng/mL (75-125 nmol/L) (76). In addition, the clinical practice guidelines for vitamin D in the United Arab Emirates (UAE) and the Gulf population, encompass the pleiotropic actions of vitamin D (78). Of note, vitamin D deficiency is one of the highest in this sun-rich part of the world (78).

It should be highlighted that, in terms of everyday practice, the selection of adequate recommendation from a variety of available vitamin D supplementation guidelines depends on several factors, including clinical and environmental (15,79). Moreover, the differences related to latitude of residence, sunlight exposure, skin pigmentation, dietary practices, clothing and cultural habits, health care system, and many other population-specific factors, needs to be considered in making uniform guidelines (45, 53,58,73,76-78).

Therefore, for the general population, otherwise considered as healthy, the selection of a guideline for vitamin D supplementation should be specific for age group, body weight, ethnicity (skin type), and latitude of residence. The IOM guidelines were commissioned by the United States and Canadian Governments for public health purposes and not to use as clinical practice guidance, for the population living in North America (19). Further, the IOM guidelines were established based on evidence that only focused on calcium-phosphate metabolism and bone health requirements (19). Consequently, these IOM bone-centric guidelines should be considered, to some extent, as suitable for bone health, and most likely, the IOM recommendations utility is limited to population living in North America. Further, the IOM recommendations cannot be used as a guidance for treating patients.

Considering the above statements, the age-, body weight- and latitude-dependent recommendations seem as *sine qua non* or at least a more rational tool counteracting vitamin D deficiency at the national or regional level. It is of concern that certain diagnostic laboratories have adapted IOM cut-off points (19) in their 25(OH)D reporting, is a major mistake, which is not only misleading but also harmful to some patients.

Table 1 provides an overview on vitamin D guidelines released to medical community since 2010.

AADMD, American Academy of Developmental Medicine and Dentistry; EMAS, European Menopause Andropause Society; ESCEO, European Society for Clinical and Economic Aspects of Osteoporosis and

Osteoarthritis; ESPGHAN, European Society for Paediatric Gastroenterology Hepatology and Nutrition; EVIDAS, European Vitamin D Association; SBEM, Sociedade Brasileira de Endocrinologia e Metabologia (Brazilian Society of Endocrinology and Metabology)

5.2. Recommendations for patients suffering from a disease

For an individual patient suffering from a disease, a wise choice of vitamin D recommendations should rely on the specificity of a particular disease that coincides with or is a result of vitamin D deficiency. The recently published "Global Consensus Recommendations on Prevention and Management of Nutritional Rickets" is a good example and fair postulate, because these guidelines were established only for this single specific disease, and based on the available evidence for nutritional rickets risk factors, course and therapy of the disease, its prevalence and incidence (86).

Other examples of vitamin D supplementation guidelines that are disease-specific come from several professional scientific societies such as the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) (83), European Menopause and Andropause Society (EMAS) (81), Kidney Disease: Improving Global Outcomes Clinical Practice (KDIGO) (87), or American Geriatrics Society (84), American Academy of Developmental Medicine and Dentistry (AADMD) (77,88), etc. These disease-specific vitamin D recommendations were developed mainly as an addendum to therapy of the diseases or joined prevention strategy for these diseases and their clinical complications.

For example, "…in fragile elderly subjects who are at elevated risk for falls and fracture, the ESCEO recommends a minimal serum 25(OH)D concentration of 75 nmol/L (30 ng/mL), for the greatest impact on fracture" (83). Similarly, "The Vitamin D Task Force of the American Academy of Developmental Medicine and Dentistry (AADMD) recommends that 25(OH)D concentrations (for optimal health of people with neurodevelopmental disorders and intellectual disabilities) to be in the range of 30-50 ng/mL (75-125 nmol/L), which can be achieved using between 800 and 4,000 IU/day vitamin D_3 and sensible exposure to solar UVB radiation" (77).

Moreover, the guidelines established by the American Geriatrics Society Workgroup on Vitamin D Supplementation for Older Adults stated, "… a serum 25- hydroxyvitamin D concentration of 30 ng/mL (75 nmol/L) should be a minimum goal to achieve in older adults, particularly in frail adults, who are at higher risk of falls, injuries, and fractures." (84). In general, the majority of disease-specific recommendations state consistently that the minimum serum 25(OH)D concentration should be 30

ng/mL, and upper limit, up to 50 or 60 ng/mL (75-125 up to 150 nmol/L); obtaining and maintaining such values require a regular vitamin D supplementation with doses of 3,000-5,000 IU/day (89).

5.3. Recommendations for treatment of vitamin D deficiency

For patients with a laboratory confirmed vitamin D deficiency, i.e., 25(OH)D concentration lower than 20 ng/mL (50 nmol/L), a vitamin D treatment should be implemented. In vitamin D deficient patients an age- and body weight-dependent therapeutic dosage should be administered according to available regional or national treatment recommendations with a treatment duration of 1 to 3 months. The first follow-up of 25(OH)D concentration should not be earlier than 8-12 weeks after the beginning of treatment (16,76,78,90,91).

Meanwhile, it is important to be aware of coexisting disease(s) prior to the beginning of treatment. The dosing should be as follows (the ranges depend on body weight): for neonates (i.e. younger than one month) 1000 IU/day (25 μg/day); for infants older than 1 month and toddlers 2000-3000 IU/day (50–75 μg/day); for children and adolescents aged 1 to 18 years 3000-5000 IU/day (75–125 μg/day); for adults and the elderly 7000–10,000 IU/day (175–250 μg/day) or 50,000 IU/week (1250 μg/week) (76). Further, for patients with intestinal malabsorption, vitamin D should be administered in larger oral doses up to 50,000 IUs/2-3 times a week or intramuscular doses of vitamin D if available. An alternative is to be exposed to sunlight or simulated sunlight either from a light device with tanning bed that emits UVB radiation or from a tanning bed that emits UVB radiation (92).

Patients with a severe liver dysfunction or chronic renal disease are the only groups that require the use of activated vitamin D metabolites. For chronic liver disease it is recommended to use calcifediol, if available, and for chronic kidney disease – alfacalcidiol or 1,25-dihydroxyvitamin D3 (calcitriol) are regarded optimal. Patients with chronic kidney disease should also receive an adequate amount of vitamin D to maintain blood levels of 25(OH)D of at least 30 ng/mL (75 nmol/L). Granulomatosis diseases (e.g., sarcoidosis) and some lymphomas require careful watching because patients suffering from these diseases can become hypercalcemic when 25(OH)D concentrations are above 30 ng/mL (75 nmol/L). These patients should maintain the blood level of between 20-30 ng/mL to prevent osteomalacia as well as hypercalcemia. Patients with primary hyperparathyroidism and who are hypercalcemic should be treated for their vitamin D deficiency since there is no concern for them worsening there hypercalcemia. Some patients who have tertiary hyperparathyroidism due to chronic vitamin D deficiency or chronic

renal failure can often benefit with reduction in their serum PTH and calcium by treatment with vitamin D to achieve 25(OH)D concentration of at least 30 ng/mL (75 nmol/L) (93).

6. Less is sometimes more beneficial

An increasing number of over-the-counter vitamin D supplements available in pharmacies and through the Internet accompanied by media campaigns and product advertisements raised worries in medical community about vitamin D safety. In fact, because of the advertising tactics/errors, some consumers may believe miracles that the intake of more vitamin D equals more health benefits. While the latter is not necessarily true, such behavior can lead to overdosing. If used inappropriately, the long term self-administration of vitamin D may lead to hypercalcemia and hypercalciuria (94). Thus, the medical community and public health policy makers should be alerted and take proactive actions to minimize such hazards due to ignorance and marketing tactics. Educating consumers and addressing important issues such as efficacious dosage are recommended (94).

A simple and effective tool to help prevent uncontrolled overuse of vitamin D for healthy population is a guideline for an upper tolerable intake values (upper limit; UL) (16,19,76,78,95). Surprisingly, the upper limit values reported so far are generally agreeable for a given age irrespective of source of reference, unlike the disputable recommended vitamin D doses to treat and prevent vitamin D deficiency and the definition of 25(OH)D concentrations reflecting vitamin D sufficiency. The global, regional or nationwide guidelines emphasize that daily vitamin D doses that pose no risk are illustrated in the Table 2.

Further, the dose of 10,000 IU/d was also found as the no-observed-adverse-effect level (NOAEL) elucidating vitamin D safety limits (16,19).

7. Vitamin D: the ominous J / U shape curve for health outcomes:

There have been a number of studies that evaluated association between serum 25(OH)D concentration and the chronic illnesses or mortality (96). Some of the studies plotted serum 25(OH)D concentrations versus a chronic illness mortality demonstrated, that vitamin D deficiency was associated with an increased risk and that the risk gradually decreased with increasing 25(OH)D concentrations that reached a nadir plateau being usually between 30-40 ng/mL (75-100 nmol/L) (5,70,96).

However, a few reports indicated that there appears to be a slight increase in risk for a chronic illness or mortality with 25(OH)D concentrations beyond 50 ng/mL (125 nmol/L) (97-98). This has raised the question whether there is a potential negative health impact, if such concentrations (e.g., sustained serum 25(OH)D concentration above 50 ng/mL) were attained with vitamin D supplementation. The IOM suggested that there could be an increase in risk for mortality if 25(OH)D concentrations increased above 30 ng/mL (75 nmol/L) (17,19).

In contrast, the Maasai warriors who live in outdoor most of the time, have an average of 25(OH)D concentrations of approximately 50 ng/mL (125 nmol/L), and appear to be in good health (99).

For the vast majority of people, their diet does not provide an adequate amounts of vitamin D on a daily basis. Thus, without being exposed to an adequate amount of sunlight daily, it is unlikely to achieve 25(OH)D concentrations of 30 ng/mL (125 nmol/L) unless a rare mutations related to 24-hydroxylase (CYP24A1) is present (23-25,100,101).

Consistent with other studies, a meta-analysis by Garland et al. reported that vitamin D deficiency was associated with a higher risk for mortality and that the risk for mortality gradually declined to a nadir plateau at 25(OH)D concentrations near 36 ng/mL (90 nmol/L) and it was sustained up to at least 70 ng/mL (175 nmol/L) with no evidence of a U or J-shaped curve (5). Similar results were shown in a recent study investigating U- or J-shaped relations between 25(OH)D concentrations and health outcomes (102), with few health conditions for which higher 25(OH)D concentrations might be associated with adverse outcomes - allergic reactions (102). There is also limited evidence that 25(OH)D concentrations >40 ng/mL (>100 nmol/L) for those undergoing cardiac surgery are associated with higher risk of adverse outcomes (103). There have been some recent reports of J-shaped 25(OH)D concentration-CVD mortality rate (98). However, to reach 25(OH)D concentrations >40 ng/mL (>100 nmol/L) generally takes vitamin D supplementation, and most observational studies such as that one did not inquire about supplementation. As discussed by Grant et al., if supplementation was initiated shortly before enrollment in the cohort study, perhaps due to a physician's recommendation due to a vitamin D-deficient condition such as osteomalacia or osteoporosis, some of those with the highest 25(OH)D concentrations are classified in the incorrect 25(OH)D quantile (102).

It is important to note that physiological 25(OH)D concentrations (i.e., between 30 and 50 ng/mL) are associated with several pleiotropic health benefits and all-cause mortality risk reduction. Nevertheless,

obtaining and maintaining higher 25(OH)D concentrations than that above recommended is not advisable; more is not always better. Self- administration of vitamin D, particularly parenteral doses, is not a *panacea* for treating diseases nor for reducing the risk of death, and caution is advised for use of vitamin D doses in amounts higher than that recommended for the general population. The exception is a laboratory confirmed vitamin D deficiency, which should be treated with short-term therapeutic doses under a supervision of a physician.

8. Can higher doses of vitamin D be toxic?

Vitamin D toxicity remains a concern for physicians and government public health agencies. Although there is no recent scientific data, this is an important reason why governments resist foods fortified with vitamin D; such as milk and dairy products D. Before the 1950s, there was widespread fortification of vitamin D because it was considered to be one of the miracle nutrients regarded useful for treating chronic illnesses, from tuberculosis to rheumatoid arthritis (104).

Indeed, besides milk being fortified with vitamin D, also custard in England, beer in the United States, shaving cream and soap in Germany, etc. were fortified with this fat-soluble vitamin (104,105). However, in the early 1950s several cases of infants with facial abnormalities, supra-valvular aortic stenosis, mental retardation and hypercalcemia were reported in Great Britain (106). This was followed by additional reports of hypercalcemia in some infants in Great Britain (107-109). The Royal College of Physicians and the British Pediatric Association were charged with finding the cause. After scrutiny of the literature and surveys of dietary intakes, they concluded that the possible causes were unregulated over fortification of milk with vitamin D as well as excessive intakes of vitamin D from various foods fortified with vitamin D (107-109).

Although the Royal College of Physicians failed to provide strong evidence, they predominantly based their conclusion on literature on pregnant rodents receiving high doses of vitamin D who delivered pups with dysmorphic features, aortic stenosis and hypercalcemia. The British Pediatric Association documented hypercalcemia but only in isolated cases of infants who had approximate intakes of 1,500-1,725 IU of vitamin D, daily (107-109); however, they may have been given additional replacements that were not sought out or documented. Moreover, at this time there was no reliable assay for measurement of vitamin D or reliable estimates for dietary intake of vitamin D; so these intakes were rough estimations. It is likely that some of these infants (isolated incidences) had a Williams-Beuren

syndrome, which was associated with elfin facies, aortic stenosis, mental retardation and hypercalcemia due to a hypersensitivity to vitamin D (110-112). As a consequence, the government introduced policies to strictly regulate vitamin D food fortification and vitamin D supplements to the general public. Consequently, in some countries today, children and adults may only receive vitamin D supplementation when prescribed by healthcare workers (86,110,113).

It is generally accepted that a serum 25(OH)D concentration of up to 100 ng/mL (250 nmol/L) is safe for children and adults, with the exception of those who have a hypersensitivity to vitamin D. The latter includes, children and adults with idiopathic infantile hypercalcemia (100,101), Williams-Beuren syndrome (111,112), granulomatous disorders and some lymphomas (105,110). The Endocrine Society guidelines concluded that vitamin D toxicity is not only extremely rare, but 25(OH)D concentration of at least 150 ng/mL (375 nmol/L) is required before there would be evidence of vitamin D toxicity (16,105,110).

The first manifestation of excess vitamin D activity is increased excretion of urinary calcium due to a decrease calcium absorption of from renal tubules secondary to low levels of PTH. In the presence of lesser renal excretion, when the kidneys can no longer deal with the amount of calcium entering into the circulation from diet and bone mobilization, the serum calcium begins to rise. The decrease in PTH also causes a decrease in phosphate excretion by the kidneys.

The elevated 25(OH)D concentrations directly interacts with the VDR in the bowel further increasing intestinal calcium and phosphate absorption. This results in an increase in both serum calcium and serum phosphate resulting in a super-saturating calcium phosphate product, which is likely to be deposited in soft tissues including the kidneys, resulting nephrocalcinosis and in atherosclerotic vascular calcification (tertiary hyperparathyroidism) (20,105,110). The hypercalcemia also leads to vasoconstriction which causes hypertension. The hypercalcemia causes several other nonspecific symptoms including constipation, depression, confusion, polyuria and polydipsia, and cardiac arrhythmias (110).

There are numerous studies demonstrating that vitamin D is probably one of the least toxic fat-soluble vitamins. Dudenkov et al. (114) evaluated more than 20,000, serum 25(OH)D measurements performed at Mayo Clinic from 2002 to 2011 to assess the potential vitamin D toxicity (as determined by presence of hypercalcemia). Whereas, they observed a 20-fold increase in the number of individuals with a serum

25(OH)D > 50 ng/mL (>75 nmol/L) these concentrations were associated with a normal serum calcium concentration (114). They found only one person having hypercalcemia with the blood 25(OH)D concentration of 364 ng/mL (910 nmol/L) (114).

Pietras et al. (115) reported that healthy adults in a clinical setting receiving 50,000 IUs of vitamin D_2 once every 2-weeks (equivalent to approximately 3,300 IUs daily) for up to 6-years, maintained 25(OH)D concentrations in the desired range of 40-60 ng/mL (100-150 nmol/L), without any evidence of vitamin D toxicity. Consistent with the observation, Ekwaru et al. (89) reported that Canadian adults, who ingested up to 20,000 IUs of vitamin D_3 daily, had a significant increase of 25(OH)D concentrations, up to 60 ng/mL (150 nmol/L) but without any evidence of toxicity. Consistent with the Endocrine Society guidelines, they also confirmed that obese adults required 2.5 times more vitamin D supplementation to maintain the 25(OH)D concentrations in the same range as a normal weighted person (89).

9. Conclusion

It is recognized that vitamin D deficiency is a global health problem. This global vitamin D deficiency pandemic is having adverse consequences on the health and welfare of children and adults as well as on the health care systems. It has been suggested that there could be a significant reduction in most healthcare costs related with diseases that have been associated with vitamin D deficiency and insufficiency (116-118).

The major causes of the global vitamin D deficiency pandemic are, (A) a lack of appreciation that sensible sun exposure is a safe and inexpensive way of obtaining vitamin D naturally; (B) very few foods naturally contain vitamin D and therefore a healthy, balanced diet will not provide an adequate amount; (C) the unfounded concerns by governments, health authorities and healthcare professionals that vitamin D is an extremely toxic fat-soluble vitamin and therefore needs to be highly regulated contributing to vitamin D deficiency, and the (D) limited support from RCTs that vitamin D has health benefits.

The likely reason for the failure of many vitamin D RCTs is that the trials data were derived primarily from pharmaceutical drug studies (i.e., secondary outcomes), rather than those appropriate for nutrient-specific studies. Trials for pharmaceutical drugs falsely assume that the only source of the

nutrient-agent is in the trial and that what they provided, there is a linear dose-response relation. Neither assumptions are correct for vitamin D. Future such studies should adhere to outlined the guidelines for clinical trials of nutrient effects by Heaney et al. and others (15,46,105).

As applied to vitamin D, the first step would be to obtain a reliable measurement of blood 25(OH)D concentration-health outcome relations of interest, measure serum 25(OH)D concentration prior to the enrollment and only enroll those with low concentrations, give sufficient vitamin D_3 to achieve 25(OH)D concentration, to where a reasonable benefit would occur, then measure achieved 25(OH)D concentration to assure levels are maintained (15).

A practical solution to conquer this health crisis is for the health authorities and legislative bodies to implement supplementation of foods with the appropriate and needed amounts, such as milk, bread and pasta with vitamin D; these values are likely to vary between countries and society's need (105). In addition, the admonitions to avoid sun exposure to reduce the risk of skin cancer and melanoma should be coupled with a recommendation to get vitamin D, either from a few minutes of sensible sun exposure during midday or from supplements.

In the absence of regular sun exposure, using appropriate doses of vitamin D supplements are the most efficient way to increase 25(OH)D concentrations. Furthermore, even with food fortification, intake of vitamin D is inadequate to obtain and maintain target 25(OH)D concentration of at least 30 ng/mL (75 nmol/L), and some of the modes used to generate fortified food do not reach those who need them (e.g., rice). The US Food and Drug Agency, recently approved an increase of the amount of vitamin D that may be added as an optional ingredient to milk, and approved the addition of vitamin D to beverages made from edible plants intended as milk alternatives, such as beverages made from soy, almond, and coconut, and edible plant-based yoghurt alternatives (119). These are correct steps in the right direction, which can be adapted by other countries.

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Table 1. Selected vitamin D supplementation guidelines published since 2010.

Organization	Countries	Target population	Age (years)	Conditions	25(OH)D (nmol/L)	Oral vitamin D (IU/d)	Reference
Institute of Medicine	USA, Canada	General population	<1 1-70	Bone health	>50	400 600	Ross, 2011(19)
			>70			800	
Endocrine Society	USA	General population	0-1	Risk of vitamin D deficiency		400	Holick, 2011 (2012) (16)
			1-18		>75	600-1000	
			>19			1500-2000	
DACH countries	Austria	General population	<1	Bone health	>50	400	DGE, 2012 (80)
	Germany		>1			800	
	Switzerland						
EMAS		Postmenopausal women		General health	>75	800-1000	Pérez-López, 2012 (81)
ESPGHAN		Infants,	<19	General health	>50	400	Braegger, 2013 (82)
		children, adolescents					
Vitamin D opinion leaders (EVIDAS)	Central Europe	General population	0-6 mos	General health	>75	400	Pludowski, 2013 (76)
			6-12 mos			400-600	
			1-18			600-1000	
			>18			800-2000	
		Women	16-45	Prevention of pregnancy and fetal development complications		1500-2000	
ESCEO		Elderly women		Bone health	>50	800-1000	Rizzoli, 2013 (83)
		Fragile elderly			>75		
American Geriatrics		Elderly		Falls, fractures	>75	1000+	Judge, 2014 (84)

Society							
SBEM		People with osteoporosis		Prevention of secondary hyperparathyroidism, fall prevention, bone mass & density	>75	1000-2000	Maeda, 2014 (85)
AADMD		People with neurodevelopmental disorders and intellectual disabilities		General health	>75	800-4000	Grant, 2015 (77)
Consensus of 11 organizations	Global	Infants	<1	Rickets prevention		400	Munns, 2016 (86)
			>1	Rickets, osteomalcia prevention		≥600	
				Rickets treatment		2000-6000, depending on age	
GULF	United Arab Emirates	General population	0-6 mos	General health	>75	400	Haq, 2016 (78).
			6-12 mos			400-600	
			1-18			600-1000	
			19-65			800-2000	
			>65			1000-2000	
		Women	16-45	Prevention of pregnancy and fetal development complications		1500-2000	

Table 2: The guidelines for age-dependent tolerable upper limits that pose no adverse events:

Age Group	**Tolerable upper limit**	**References**
Neonates (i.e. younger than one month)	Up to 1,000 IU/day (25 μg/day)	(16,19,76,78)
Infants and children aged 1 month to 10 years	Up to 2,000 IU/day (50 μg/day)	(16,19,76,78)
Children and adolescents aged 11 to 18 years	Up to 4,000 IU/d (100 μg/day)	(16,19,76,78)
Adults and the elderly	Up to 4,000 IU/day (100 μg/day) Up to 10,000 IU/day (250 μg/day)	(16,19,76,78) (16,76,78)