Vitamin D supplementation guidelines – which to choose and why?

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Abstract

During the past two-decades extended research carried out in spectrum of medical sciences revealed pleiotropic vitamin D actions that regulate calcium and phosphate absorption as well as metabolism of organs, tissues and cells in human body. The optimal serum 25-hydroxyvitamin D [25(OH)D] concentrations were associated with improved clinical outcomes for several chronic, communicable and non-communicable diseases. As a result, medical scientific organizations developed guidelines for vitamin D supplementation to obtain and maintain optimal serum 25(OH)D concentrations both in general populations and risk groups. However, available guidelines differ significantly depending on the perspective on human health. 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 pleiotropic-centric guidelines 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 400-4000 IU/day. The guidelines to follow must depend on one's individual health outcome concerns, age, body weight, latitude of residence, insolation, dietary and cultural habits. Therefore, the regional or nationwide pleiotropic-centric guidelines appear more applicable in clinical practice, including the prophylactic and treatment regime of autoimmune disorders. The natural sources (sun, diet) are regarded ineffective to maintain the year-round 25(OH)D concentrations in the range of 30-50 ng/mL (75-125 nmol/L) in the general population. In consequence, vitamin D deficiency is highly prevalent irrespective of age and the most effective method to obtain and maintain proper vitamin D status and possible health benefits related to vitamin D is the regular supplementation of vitamin D with use of recommended daily vitamin D doses.

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

Vitamin D status

Vitamin D is an important pro-hormone that can be synthesized by skin exposed to sunlight (UVB) or ingested with food. However, low outdoor activity, sun protection and low vitamin D content of staple foods reduce the efficiency of sun and diet as natural sources for vitamin D, its metabolism and related health effects. In consequence, evidence from various populations highlighted vitamin D deficiency as a public health problem with high prevalence (1-17). The prevalence of vitamin D

deficiency depends on diagnostic thresholds defining vitamin D status that is determined by total 25(OH)D serum levels (18) and the recommended levels of 25(OH)D are still an issue of debate (19-22). Currently, it is accepted that maintaining serum 25(OH)D at a level of 20 ng/ml (50 nmol/l) or above is beneficial at least for bone health and calcium homeostasis (23-24). Levels required for noncalcemic functions of vitamin D seem to be higher (30-50 ng/ml; 75-125 nmol/l) (25), but still are considered uncertain. Some authors, however, argue that even for proper bone mineralization a levels higher than 30 ng/ml (75 nmol/l) are necessary (26). Indisputably, low 25(OH)D levels (below 20 ng/ml) are common and were reported worldwide (1-7) and this is a drawback because epidemiological data underlined an association between vitamin D deficit and a higher risk for chronic conditions and multi-morbidity, including musculoskeletal disorders, cancer, autoimmune diseases, cardiovascular disease, diabetes and infectious diseases (1,3,27-30).

Vitamin D: A classic perspective

The term "vitamin D" refers to both ergocalciferol (vitamin D2) and cholecalciferol (vitamin D3), which are formed from their respective pro-vitamins, ergosterol and 7-dehydrocholesterol (7-DHC). Vitamin D is a fat-soluble vitamin. The dominant natural source of vitamin D3 in humans is production in the skin where 7-DHC follows a two step-reaction involving ultraviolet-B (UV-B) irradiation to form previtamin D3 and then a subsequent thermal isomerization to vitamin D3 (31). Both vitamin D3 and vitamin D2 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 D3 compared to other food products, however even varied diet cannot be considered as effective source to provide recommended daily doses. Vitamin D2 may be synthetized in plants and mushrooms involving UV-B action on ergosterol (32). Cultivated mushrooms contain lower amounts of vitamin D2 than wild-grown, but when exposed to UV-B, the amount of vitamin D2 increases (33). 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 next to 1,25-dihydroxyvitamin D [1,25(OH)2D] in the kidneys (34-37). 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 (34-37).

In tissues, 1,25(OH)2D dissociates 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) (34-38).

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 (38). 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 (34-38).

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 (39-40). 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 (39-40).

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 (34-37). 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) (34-37,41). 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 (34-37).

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 (34-37,42).

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 (43,44). 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 (42-44).

Vitamin D: pleiotropic perspective

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 (39,45); i.e., the ability to generate 1,25(OH)2D in extra-renal tissues (39, 45, 46). 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 (47-51). Further, extra-renal tissues have also ability to catabolize 1,25(OH)2D by expression of CYP24A1 (34), and this important control mechanism decreases 1,25(OH)2D auto- or paracrine signals and potential input of locally produced hormone into circulation (52-54). 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 (39,43). Plausibly, these are responsible for many of the non-calcemic benefits ascribed to vitamin D (38, 39, 55,56). 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) (55-62). In addition, it also increases the lymphocytic activity and stimulates insulin production (55,56). 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 (57-60). 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 (59). 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 (59). Another study from Sweden also revealed that vitamin D supplementation had a protective effect against respiratory tract infections (60, 61), leading to a decrease in the number of antibiotic-prescriptions (61).

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 (63). 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 (64). 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 (64). 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) (64). 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) (65). 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 (66).

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 (67). The optimal 25(OH)D concentration for preventing and surviving cance seems to be between 30 and 40 ng/mL (75-100 nmol/L) (68). Moreover, individuals with higher 25(OH)D concentration at the time of a cancer diagnosis have better cancer-specific and overall survival rates (67,68).

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) (69).

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) (70). 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 (71) and a higher vitamin D dietary intake was associated with a lower risk of developing Alzheimer's disease (72). 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 (73).

It was also suggested that low 25(OH)D concentrations are related to significantly increased risk of mortality (74-77). 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) (78).

The available evidence of extra-skeletal vitamin D actions and related health benefits is growing (55-79). 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 (55-79), as well as the all-cause mortality (74-78).

Science needs to be balanced, so results from a review of 290 cohorts and 172 RCT by Autier P, Boniol M, Pizot C, Mullie P in their paper titled: "Vitamin D status and ill health: a systematic review." Published in The Lancet Diabetes & Endocrinology in 2014 [2(1):76-89], 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.

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 (Km) 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 (35-37).

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 Km of 1α-hydroxylase (36). 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) (38, 42,55,58,63,68,69). However, the tissue dependent differences of a minimal effective concentration may vary (79-81). 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 (36,79-81).

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 (34, 64-66), 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 (36,79-81).

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. (80). 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) (80).

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) (38, 42-44). This recommendation was based on the belief that 200 IU/day was sufficient to prevent rickets (82). 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. 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 (83-85).

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 (55,56,59,61,65,67,68,80,83-88). 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 (85).

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). 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). For obese people (BMI >30 kg/m2) a daily vitamin D dose was set as "three times" greater than the recommended dose for subjects with normal body weight.

In 2013, the Central European recommendations were published highlighting a problem of vitamin D deficiency in that region (86). Contrary to IOM guidelines, the Endocrine Society, American Academy of Developmental Disability (87), and Central European recommendations (86) were developed acknowledging the evidence on both skeletal and the pleiotropic vitamin D effects, thus are relevant to clinical practice. The European Vitamin D Association (EVIDAS) 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) (86). 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 (88). Of note, vitamin D deficiency is one of the highest in this sun-rich part of the world (88).

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 (89). 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 (55, 63,68,83,86-88).

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. Further, the IOM guidelines were established based on evidence that only focused on calcium-phosphate metabolism and bone health requirements. 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 in their 25(OH)D reporting, is a major mistake, which is not only misleading but also harmful to some patients.

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 (89).

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) (90), European Menopause and Andropause Society (EMAS) (91), Kidney Disease: Improving Global Outcomes Clinical Practice (KDIGO) (92), or American Geriatrics Society (93), American Academy of Developmental Medicine and Dentistry (AADMD) (87,94), 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" (90). 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 D3 and sensible exposure to solar UVB radiation" (87).

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." (93). 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 (95).

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 (95).

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) (86). 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 (96).

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) (95).

Stay on safe side

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. 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.

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) (86,88,95). 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 1.

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

Table 1: The guidelines for age-dependent tolerable upper limits that pose no adverse events.

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

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.

The major causes of the global vitamin D deficiency pandemic are, (I) a lack of appreciation that sensible sun exposure is a safe and inexpensive way of obtaining vitamin D naturally; (II) very few foods naturally contain vitamin D and therefore a healthy, balanced diet will not provide an adequate amount; (III) 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. 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.

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