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Causes, Consequences and Ways of Correcting Vitamin D Deficiency

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ABSTRACT

Vitamin D deficiency is common worldwide and more prevalent than most people know. It is estimated that globally more than 1.8 billion people have vitamin D deficiency and another 2.7 billion have vitamin D insufficiency, which makes this disorder one of the most common nutritional deficiencies in the world. It has not only turned into a pandemic but also become an emergency. The positive effects of vitamin D on musculoskeletal issues, such as rickets and osteomalacia, have been known for some time. However, over the past two decades, more than 40,000 scientific publications have reported extra-skeletal benefits of multiple body systems by having physiologic vitamin D [25(OH) D] concentrations (i.e., greater than 30 ng/mLor 75 nmol/L). The pathway of synthesis of this hormone and the global prevalence, common causes, and consequences of the epidemic of hypovitaminosis D are discussed.

INTRODUCTION

The increasing incidence and high prevalence of vitamin D deficiency necessitate understanding the underlying causes and taking affirmative public health actions. The latter includes generating and implementing effective public health guidelines, advising on safe sun exposure and age- and disease-specific adequate daily oral supplementation, and targeting vitamin D food fortification. Governments and employers can help ensure that individuals have the opportunity to acquire vitamin D through sunlight exposure during peak hours of sunlight each day.

Estimates indicate medical disorders associated with vitamin D deficiency add more than $290 billion annually to the cost of healthcare worldwide. Meanwhile, vitamin D deficiency can be treated in world populations for less than $0.2 billion. Despite this, many countries and scientific societies are not embracing this important preventative public health issue. Considering the cost–benefit ratio, intervention on a global scale would provide a large positive outcome for a small investment in disease prevention.

Status of global vitamin D deficiency

Vitamin D deficiency is present in significant numbers in most communities and affects all age groups. Despite the presence of abundant sunlight, the incidence of vitamin D deficiency is astonishingly high even among those who live close to the equator, such as in India, Bangladesh, Sri Lanka, and the Far Eastern, Middle Eastern, and Persian Gulf nations [1-4].

Darker skin color is common among the inhabitants of those regions as an evolutionary engendered phenomenon that protects from sunburn, skin damage, and cancer, but it also restricts the generation of pre-vitamin D in the skin. The most common cause of

hypovitaminosis D is sun avoidance behaviors secondary to harsh climatic conditions, the frequent use of umbrellas and skin cover, and cultural habits associated with clothing that covers a great amount of skin [5,6]. Hypovitaminosis D can be cost-effectively prevented and treated through the combination of adherence to specific public health guidelines and vitamin D supplementation regimens.

WHY IS VITAMIN D IMPORTANT FOR HUMANS?

Vitamin D deficiency and insufficiency affect all segments of the population worldwide. Because of the relatively shorter half-life in the circulation and the lack of sunlight, deficiency is most prevalent during the winter and in those living in high and low latitudes or in constantly polluted environments, the elderly, and people with dark skin [7]. Despite the availability of sunshine, vitamin D deficiency is common in Asia, Northern Africa, the Sub-Saharan region, Latin America, the Caribbean, and Southern Asia [8,9].

During evolution, when our ancestors started to migrate northward from central Africa, they were exposed to environments with less available sunlight. This created an atmosphere of reduced fertility, increased susceptibility to infections, and premature death. To overcome this vicious cycle, an evolution-mediated mutation of the melanin gene occurred to produce less skin pigmentation. This allowed the generation of adequate quantities of vitamin D while preventing damage to skin cells from ultraviolet A and B (UVA and UVB) rays.

Those with the mutation, having lighter skin color, had a major survival advantage in less sunny terrains. Having lighter skin color allowed individuals to generate higher quantities of vitamin D [10], creating a natural balance between protecting dermal cells from UVA and UVB damage and avoiding vitamin D toxicity, and also maximizing vitamin D production in the skin.

Broader benefits of vitamin D

Vitamin D is essential for reproduction, healthy life, proper functioning of the human body systems, and survival. Two well-known benefits of vitamin D are calcium metabolism and physiologic functions of the musculoskeletal system. Vitamin D is essential for bone and mineral metabolism, particularly for calcification of collagenous osteoid tissues in bone; deficiency states can lead to rickets in children and osteomalacia on adults.

Nevertheless, vitamin D has pleiotropic actions that extend beyond the well-understood calcium and phosphate homeostasis, regulation of parathyroid hormone, mineralization of bone, and the prevention of osteomalacia, rickets, falls, and fractures [9,11]. In fact, recent scientific and medical evidence support wider beneficial effects of vitamin D in humans. For example, activated vitamin D is a neuroactive hormone that is essential for normal brain development and functioning [12] (Figure 1). Illustrates some of the multiple direct and indirect benefits from having vitamin D sufficiency.

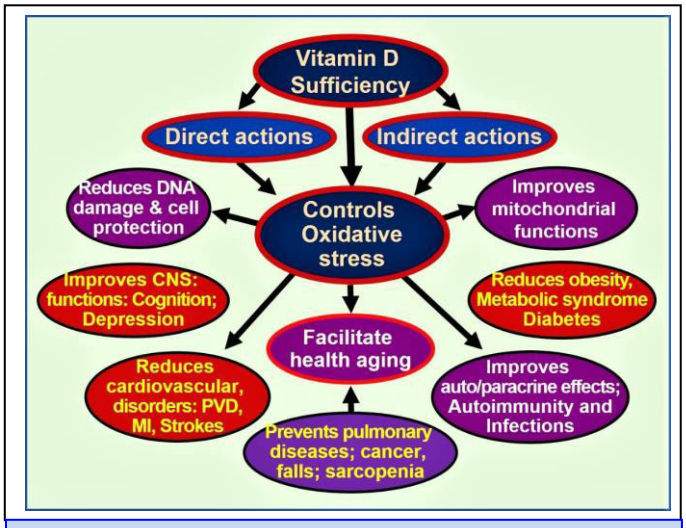

Figure 1: Vitamin D has a verity of physiological functions benefitting many body tissues. It also highlights its potent effects of subduing oxidative stress and inflammation, and facilitating healthy aging.

During the past 15years, a range of additional benefits of vitamin D has been discovered, including coordination of the neuromuscular system (e.g., reflexes), cell growth, modulation of inflammation and immune functions, and prevention of autoimmune diseases and cancer [9,13] (Figure 1). In addition, vitamin D is essential for successful reproduction (fertility), and the growth of foet uses and infants [14]. It facilitates the human body to overcome invading pathogens and strengthens immunity; it also promotes proper functioning of all body systems.

Some of the recently discovered additional biological effects of vitamin D include regulation of the circadian clock and certain metabolic functions; however, these are mediated by vitamin D metabolites other than 1,25(OH)2D and interaction with its classic receptor. These less-known vitamin D metabolites

include but are not limited to 20(OH)D, 20,23(OH)2D, and possibly their interactions with the retinoid orphan receptor and the aryl hydrocarbon receptor [15]. More research in needed in these areas to fully understand the implications of these findings.

Common causes of vitamin D deficiency

Hypovitaminosis is common among infants, children, women (especially those of child-bearing age), and the elderly. Other vulnerable groups include anyone with gastrointestinal disorders that interfere with fat absorption (e.g., celiac disease, Crohn's disease, or after gastric bypass surgery); those taking medications that increase the catabolism of vitamin D (such as anti-epileptic drugs, glucocorticoids, and retroviral drugs) [16-18]; and those who are overweight or obese (sequestration of vitamin D in fatty tissues) [19,20] or have a sedentary lifestyle and staying indoors [21,22].

Those who receive insufficient sun exposure have darker skin or damaged or scarred skin, and exclusively breastfed infants and children who receive no vitamin D supplementation are at a higher risk of developing vitamin deficiency and associated complications. Effects from these factors may be exaggerated based on where a person lives (latitude), lifestyle choices (sun avoidance), and associated comorbidities [23,24].

Casual exposure to sunlight is insufficient for even those who have lighter skin color. Just as with physical activities, it has been estimated that the average person needs at least 30 minutes of sunlight exposure of the skin surface of about one-third of the body on a regular basis. For those with darker skin, the time needed to generate adequate amounts of vitamin D is much higher.

Safe sun exposure

Safe sun exposure is the best option for obtaining vitamin D. The lack of sufficient sun exposure is the number one cause of vitamin D deficiency. Although our ancestors seem to have spent a length of time in the sun with bare bodies, current humans do not; most people work indoors. Three decades ago, the dermatology community created a public scare about sun exposure and skin cancer; consequently, people started to avoid sun exposure altogether.

Overexposure to the sun causes damage to dermal cell DNA and the skin and consequently could increase the incidence of a few nonlethal cancer types and premature atrophy of the skin. However, the incidence of the dangerous cancers, such as melanoma, is proportionately reduced with increased sun exposure. In fact, the most common site of melanoma is the sole (plantar aspect) of the foot and back of the body, which receive little sun exposure [25,26].

Exposure to UVB and the resultant production of vitamin D has a profound effect on vitamin D, which has a profound effect on controlling cell proliferation [27,28], thus reducing cancer risks [29,30]. Excessive exposure to sunlight does not cause hypervitaminosis D because of the inherently built-in safety mechanisms in the skin; instead of making previtamin D, the human body begins to generate inactive vitamin D metabolites, and any excess previtamin D is catabolized.

Contrary to popular belief, higher quantities of vitamin Dare generated when skin is exposed to sunlight between 10 AM and 3 PM, when the sun's rays are at a reasonably shallow angle (zenith angle) that allow better penetration of the skin. Depending on the darkness of the skin, daily exposure of one-third of the body's skin surface to sunlight (between 20 and 50 minutes) is needed to generate the body's daily requirement of vitamin D. The availability of such sunlight during early morning, evening, and even during the midday in winter months is insignificant. Other factors leading to hypovitaminosis D include the availability of UV rays, such as location (latitude), and the effects of environmental pollution (e.g., smog, clouds, and smoke).

Presentation of hypovitaminosis D and response to treatment

Persons with vitamin D deficiency usually present with vague symptomatology or signs and symptoms related to another disease. The former includes ambiguous ill health, pain, weakness, lethargy, or difficulty in performing day-to-day activities [31,32]. Individuals can present to a healthcare worker with nonspecific complaints and a variety of signs and symptoms [33]. These include but are not limited to aches and pains, proximal muscle weakness (shoulder-girdle myopathy), low back pain, muscle pain and weakness, chronic fatigue, mental cloudiness, impairment of memory, excessive sleepiness during the day and sleep apnoea, or even manifestation of an autoimmune disease [34].

The signs and symptoms of vitamin D deficiency will lessen or disappear within a matter of days after adequate vitamin D

replacement, especially when a loading dose is used [35]. Because sustainable positive changes of habit are difficult, those with vitamin D deficiency are likely to need lifelong supplementation, especially the elderly and those with comorbidities, such as obesity, short bowel syndromes, metabolic disorders, cardiovascular diseases, autoimmune disorders, cancer, and diabetes [9,36].

HOW MUCH SUPPLEMENT IS NEEDED?

In the absence of adequate exposure to sunlight, most healthy people need vitamin D supplements of between 1,000 and 2,000 IU/day [6,35,37]. Vulnerable groups of people, such as the elderly, those who are overweight or obese, and those who are taking medication that increases the catabolism of vitamin D, likely require higher doses of supplements [38,39]. For example, when pregnant women maintain their serum 25(OH)D concentration greater than 40 ng/mL, common maternal complications associated with pregnancy, such as preeclampsia, the rate of caesarean sections, and foetal complications are significantly reduced [14,40,41].

For those with no symptoms, it is reasonable to test their serum 25(OH)D concentrations to assess their vitamin status, which is the only way to confirm deficiency or adequacy. However, testing for serum 25(OH)D is costly, so unless there is an indication, routine testing is not recommended. If the concentration is low (i.e., vitamin D deficiency or insufficiency), an oral supplement is indicated [42,43]. This preferably is provided along with advice on safe sun exposure together with a loading dose of oral vitamin D if the serum 25(OH)D concentration is less than 20 ng/L[9,11]. Such a loading dose should be followed with a daily supplement to maintain physiological concentration in the blood greater than 30 ng/mL (75 nmol/L) [34]. Although the recommended safe upper limit of vitamin D is 5,000 IU per day, daily doses as high as 15,000 IU have been shown to be safe [44].

Up-frontloading doses of oral vitamin D

When the serum 25(OH)D concentrations are less than 20 ng/mL, it is advisable to give an up-front loading dose of oral vitamin D to bring the serum concentration to normal and replenish tissue stores [35,37,45]. The dose of the loading dose depends on the serum vitamin D concentration and the Body Mass Index (BMI). The lower the serum 25(OH)D concentration and the higher the BMI, the larger the up-front loading dose required. A table illustrating the loading doses needed based on serum 25(OH)D concentrations and BMI are previously published [34]. Total loading doses vary between 100,000 IU and 1million IU administered: for example, a regimen may be one 50,000 IU vitamin D_3 capsule administered two to three times a week for a few weeks until the required total dose is achieved [34].

It is important that after a course of high-dose (loading dose) oral vitamin D supplementation is completed, repeat testing for serum 25(OH)D levels is not essential in patients. It should be repeated in highly vulnerable persons with very low blood vitamin D levels, together with comorbidities, but only after 3 to 4 months of completion of the high dose vitamin D course. This is in part because of the longer half-life, large storage capability, and the time taken to establish equilibrium of the serum 25(OH)D concentration. If the blood level is still deficient, a second 6-to10-week course of higher-dose (e.g., 50,000IU/week) cholecalciferol(D_3) can be prescribed.

Purchasing vitamin D capsules

Most multivitamins now contain 1,000 IU per tablet. Taking doses less than that per day is no better than taking a placebo. Over-the-counter vitamin D gel capsules that contain 1,000, 2,000, 5,000, or 10,000 IU per capsule are available; the larger the quantity, the lower the price. In most countries, gel capsules containing higher doses of vitamin D, such as 50,000 IU, require prescriptions. Nevertheless, higher doses of vitamin D capsules are freely available for purchase on the Internet at a lower cost than can be found at local pharmacies.

Some of the vitamin D capsules (e.g., Biotech Pharmacal) and liquid forms (Micro D_3nano emulsion) sold via websites are high quality, but not all such products. Therefore, as with any other nutrient supplement, one should be vigilant of the quality, strength, and purity of the product, which also should have no toxic contaminants. Food and Drug Agency in U.S. recently warned about the poor-quality nutrient supplements sell in the market.

For up-frontloading doses and for once-a-week or once-in-two-week dosing, taking 50,000 IU capsules is the most convenient. Vitamin D is a fat-soluble compound, so the absorption of orally administered vitamin D is enhanced when the dose is taken immediately after a meal containing some fat to

stimulate the favorable gastrointestinal secretions needed for intestinal absorption.

Explanation of why recent, large vitamin D clinical trials failed

Thousands of well-controlled and well-conducted clinical studies supported an array of benefits for treatment of those with hypovitaminosis D [46-48]. However, a recently published handful of large sponsored randomized studies that investigated the health benefits of vitamin D failed to demonstrate clear benefits. These have added a cloud of uncertainty and controversy to the current knowledge. Most of these studies have major design faults, including the inclusion of subjects who are already vitamin D sufficient [49-51]. Many study subjects were taking over-the-counter vitamin D and other nutrient supplements; investigators allowed study subjects to continue these during the study period [52].

The VITAL clinical study, one of the largest nutrient clinical studies, assessed health benefits of omega-3 fatty acid and vitamin D supplements [53] on cardiovascular events or cancer; the study had major design failures. These included the failure to measure baseline serum 25(OH)D concentrations; setting no predetermined concentration to be achieved or maintained; no loading doses were administered; participants were allowed to take over-the-counter nutrient supplements; and the doses given were half that of clinically effective doses. Thus, data from such studies reporting no clinical benefit seem meaningless [52,54].

Several other recent studies with fundamental study design failures have led to erroneous data sets and conclusions. One such is the Randomized Controlled Trial (RCT) published by Burt et al, who reported an unexpected loss of bone mass in subjects treated with moderate disease of vitamin D [55]. Among other study design errors, many participants at study entry had serum 25(OH)D concentrations greater than 30 ng/mL. From a skeletal point of view, one cannot demonstrate clear beneficial effects of vitamin D in those having serum 25(OH)D concentration more than 20 ng/mL [32].

Many of these studies are large, and sponsors paid millions of dollars to the researchers. Despite these and oversights, almost all of these clinical trials had significant study design flaws [31]. Thus, despite the great publicity, the validity of the results from these studies and their interpretations are questionable [52,56]. Nevertheless, all RCTs conducted in subjects with vitamin D deficiency with adequate doses and comparable control groups reported significant health benefits [57]. However, as in the case with recently published larger clinical studies, when vitamin D supplementation is provided to vitamin D-sufficient people, little or no benefit is demonstrable or expected.

HOW MUCH VITAMIN D DO HUMANS NEED?

Most scientists consider serum 25(OH)D levels between 20 and 30 ng/mL (50 to 75 nmol/L) as vitamin D insufficiency and levels less than 20 ng/mL (50 nmol/L) as deficiency [9,43,58,59]. To achieve benefits from vitamin D requires longer-term maintenance of serum 25(OH)D concentrations in blood of greater than30 ng/mL (75 nmol/L). UV-exposed mushrooms (D_2) and oily fish, such as salmon (D_3), have reasonable amounts of vitamin D. The average egg yolk contains between 35 and 70 IU of vitamin D. Because of the high concentration of phosphorus and lipids/cholesterol, routine consumption of egg yolks is not recommended to obtain vitamin D. Other food has little vitamin D.

Most people are not getting enough vitamin D through their diet and are inadequately exposed to sunlight. Therefore, to achieve and maintain the required serum 25(OH)D levels requires supplementation. Most require between 1,000 and 2,000 IU per day. However, those who are at higher risk and vulnerable to the development of hypovitaminosis D and complications require higher doses of vitamin D, such as between 4,000 and 6,000 IU per day, to obtain optimal physiological effects [60].

In many people, doses of vitamin D in excess of 6,000 IU/day are required to achieve serum 25(OH)D concentrations greater than 40 ng/mL (100 nmol/L), especially in individuals who were overweight or obese without any evidence of toxicity [44]. Serum 25(OH)D concentrations to 300 nmol/L were found to be safe. Hypovitaminosis not only reduces fertility but also causes increased risk of complications in women and foet uses during pregnancy [61].

The vulnerable groups include those with comorbidities, the elderly, those who are overweight or obese, those taking medications such as anti-epileptic drugs that enhance vitamin D catabolism or those who are pregnant or breastfeeding. Those with hypovitaminosis D will benefit from the administration of a

loading dose (i.e., high-dose, short-term vitamin D supplements) to rapidly correct their deficiency status, followed by a daily maintenance dose, as described previously [37,62].

CONCLUSIONS

Vitamin D deficiency increases vulnerability to several common diseases and disorders. These include obesity, insulin resistance, type 2 diabetes, pregnancy complications, autoimmune disorders, impairment of DNA that increases the risk for certain cancers, and systemic inflammation. Hypovitaminosis D also causes chronic low-grade inflammation and excessive oxidative stress that potentiates metabolic illnesses, such as metabolic syndrome and cardiovascular disorders, and thus increases the risk of premature death. The prevention and treatment of vitamin D deficiency are highly cost-effective. Both vitamin D deficiency and excess—the two extremes—can be harmful and should be avoided.

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