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Review Article

Maintaining Optimum Health Requires Longer-Term Stable Vitamin D Concentrations

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ABSTRACT

Humans are constantly invaded by environmental microbes. The body is protected from pathogen attacks by the immune defense system. In 99.8% of the time, our innate immune system is capable of getting rid of these organisms without before these can cause harm. Those who are with weaker immune systems constantly get infections and having chronic diseases. Among many factors contributing to maintaining a robust immune system, vitamin D has the highest impact. It has a major protective effect against acute respiratory infections and subduing both communicable and non-communicable diseases. A healthy person with stronger immunity may not manifest clinical signs and symptoms of COVID-19-silent, asymptomatic carriers of the virus and can be infectious. Whereas not all PCR positive persons are infectious. A rapid response occurs through the innate system that is followed by the adaptive response that lasts a longer period. Vitamin D kick starts both systems. However, the protective immune and other functions are damped in the presence of hypovitaminosis and also when the levels are fluctuating. Thus, the importance of maintaining serum 25(OH)D at a steady level above 30 ng/mL. When maintaining such, among all nutrients vitamin D has the widest benefits to multiple body systems. Thus, this sunshine vitamin (a steroid hormone) has been modulated through evolution to emerge as a key survival mechanism in humans. Nevertheless, vitamin D is not a panacea.

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Introduction

While, vitamin D is essential for physiological maintenance of calcium, its deficiency that are associated with a number of disorders has become a global pandemic [1]. This is attributable to the skin cancer scare raised by the dermatology community three decades ago. Consequently, many falsely believe that safe exposures to sunlight is unhealthy and can cause skin cancer [2]. In fact, the prevalence of melanoma, the most dangerous skin cancer is less in those who routinely exposed to sunrays [3]. Hypovitaminosis D affects people in all countries, irrespective of the economic status, gender and age. However, those with a darker skin

generate less vitamin D following exposure to sunlight. Therefore, such persons live in temperate climate have a significant prevalence of vitamin D deficiency, especially during the winter period.

Sun avoidance behaviour, clothing that excessively cover skin, and the regular use of sunscreens and lotions markedly reduces the ultraviolet B (UVB) rays reaching the skin and generating less amounts of vitamin D [1]. In addition, medications that increase the catabolism of vitamin D, such as anti-epileptic and anti-retroviral agents reduce the bioavailable vitamin D concentration [4]. The use of clothing that covers whole body or due to cultural or religious habits, and deliberately avoiding sun

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exposure, habitually using high sun protection factor containing sunscreens, increase the risks of developing hypovitaminosis. More than 80% of the required vitamin D is supposed to be generated by skin exposure to UVB rays in sunlight. Previtamin D₃ is generated from ergosterol in the dermal tissue after exposure to UVB photons [5].

Vitamin D is Essential for Calcium Homeostasis

Vitamin D facilitates dietary calcium and phosphorus absorption from the intestines, skeletal balance, and reabsorption from the kidney. The combination of these physiological actions maintains stable serum ionized calcium and overall homeostasis [4, 6]. Vitamin D is a fat-soluble vitamin; so its intestinal absorption is increased with availability of dietary fat. Encouraging the public to get adequate sunlight exposure and efforts to fortify foods with vitamin D (and other essential nutrients), especially dairy products, have reduced the incidence of vitamin D deficiency in recent years in the United States and Europe. However, the incidence is gradually increasing again, especially in infants, children, the elderly, during pregnancy, and in certain ethnic groups worldwide.

Vitamin D suppresses the release of parathyroid hormone (the release of which is dependent on magnesium sufficiency), a hormone that causes bone resorption [7]. Having normal serum 25(OH)D concentration keeps the parathyroid hormone under physiologic control and thus improved calcium homeostasis; prevents excessive bone resorption and future fractures. However, to achieve the mentioned physiological functions, it is necessary to have a longer-term stable blood and tissue concentrations of vitamin D [4].

Physiological Serum 25(OH)D Concentration

Recent data from epidemiological, cross-sectional and longitudinal studies support the need for maintaining physiological serum concentrations of 25(OH)D greater than 30 ng/mL (the minimum serum concentration) over a long period [8, 9]. The data also indicate that to achieve and maintain the physiological benefits, serum 25(OH)D concentrations should be maintained between 30 and 60 ng/mL (75 and 150 nmol/L) throughout life. This is particularly important during the pandemic of COVID-19 [10, 11]. Most people in industrialized countries, especially those located in northern and southern latitudes, do not get enough sun exposure to generate adequate levels of vitamin D from the skin. Thus, through the year, more than half of the world's population is subjected to vitamin D deficiency status. Since most diets have very little vitamin D, most adults need a daily maintenance dose of between 1,000 and 2,000 IU to avoid hypovitaminosis D [12].

People who are at a higher risk for the development of hypovitaminosis D, having comorbidities, metabolic disorders such as diabetes, obesity, autoimmune diseases, those who are frequently getting infections, and during pregnancy, likely to require between 4,000 and 6,000 IU/day to maintain the optimal physiological effects [1, 13]. This is particularly important for prevention of COVID-19 and its complications [10]. Doses as great as 10,000 IU/day have been reported to be safe [14]. Different modes of safe regimens and adequate replenishment of vitamin D had been presented previously [15, 16].

Activated Vitamin D has no Place in Vitamin D Supplementation:

Except in those with liver or kidney failure, there is no scientific reason to prescribe any form of activated vitamin D. Activated forms of vitamin D, such as derivatives of one-alpha or 25-hydroxylase activated forms, are not only expensive but also can have major adverse effects. Therefore, they should never be prescribed as vitamin D supplementation. However, activated forms of vitamin D generate rapid actions.

Taking cod liver oil (and some fish oils) is not a good option for vitamin D supplementation because these oils contain too much vitamin A. Excessive vitamin A intake over a period can cause liver damage and skeletal fractures. Individuals with some conditions, especially diseases affecting the intestinal tract (such as celiac disease, Crohn's disease and ulcerative colitis), and gastric bypass surgery or cystic fibrosis, have significant problems with intestinal absorption of vitamin D and thus are unable to maintain serum 25(OH)D levels, thus requiring higher supplemental doses. Such patients might require higher doses such as, in excess of 10,000 IU/ daily oral vitamin D supplementation.

Vitamin D and Respiratory Infections

The lack of exposure to ultraviolet B rays from the sunlight is the drive for the pandemic of hypovitaminosis D and the wintertime respiratory infections. The worldwide rapid spread of COVID-19 during the first half of the year 2020 mostly affected the countries subjected to less sunlight. It coincided with the flu season, especially those countries located in northern and southern latitudes. However, this is reverse in the middle east, where hypovitaminosis D is predominant during the summertime, when people avoid the sun. In either case, the lack of adequate exposure to summer-like sunlight causes vitamin D deficiency, reduced immune functions, and increase the risks of acquiring respiratory viral infections.

In addition to vitamin D, for the optimum functioning of the immune system requires mental and physical support and micronutrients, including zinc, selenium, omega-3, vitamin K2, resveratrol, quercetin, and magnesium. The combination would stimulate not only the innate immune system but also increase the expression of vitamin D receptors in immune cells, thus, increase the biological and physiological actions of calcitriol [17]. Those countries with population serum 25(OH)D concentrations are lowest were the most severely affected with COVID-19 [18, 19]. Having prolonged low vitamin D concentration, weakens the immunity, thereby increasing the risk of contracting COVID-19, associated complications and deaths [20, 21]. At present there is no specific antiviral, or safe, effective, and affordable vaccine against COVID-19; it is unlikely such would materialize during the year 2020. Therefore, the only medical intervention that could prevent COVID-19 and reduce complications and deaths is vitamin D. Calcitriol is a multifunctional agent, its broader functions are illustrated below (Figure 1).

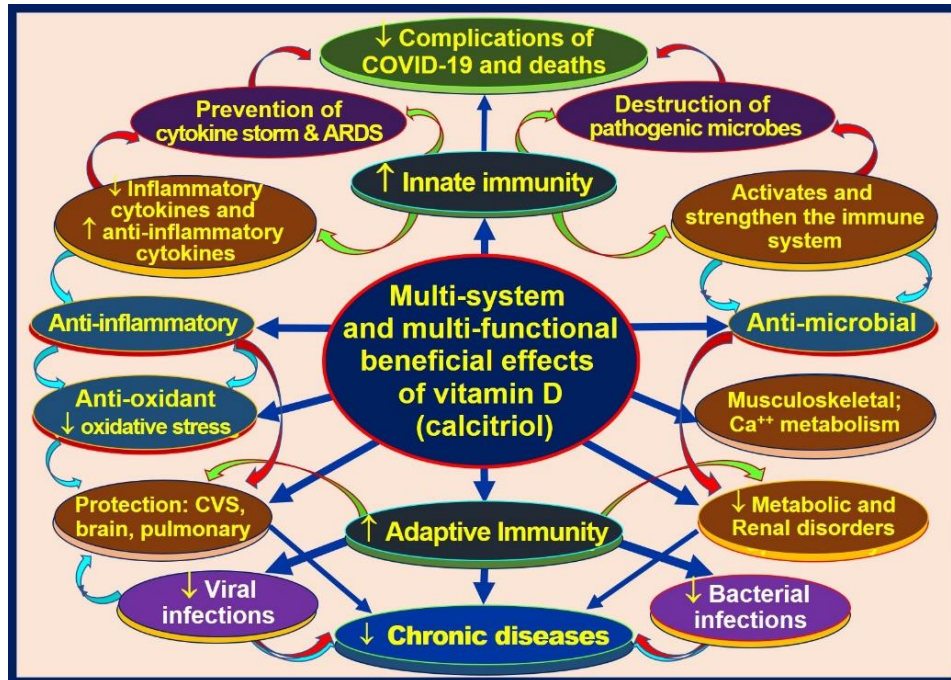


Figure 1: The key control functions of the innate and adaptive immune systems by calcitriol [1,25(OH)2D]. It illustrates major immunological functions of vitamin D, anti-inflammatory, anti-microbial, and anti-oxidant, collectively lead to control viral growth (depicted in blue ovals). These mechanisms modulate all immune cells, thereby reduce the multiplication and destruction of COVID-19 and other pathogenic microbes, tighten gap junctions, thus preventing pathogen infiltration, increase the expression of ACE-2, and reduce the concentration of angiotensin-II, thereby diminish the risk of cytokine storm, acute respiratory distress syndrome (ARDS), and death (depicted in red ovals). Brown oval.

Patients with Renal Failure

Compared with those with normal renal function, patients with chronic kidney disease (CKD), both have lower serum 25(OH)D and 1,25(OH)2D concentrations. Patients with CKD not only need one- α activated forms of vitamin D but also normal vitamin D to reduce mortality [22]. They need supplementation of both vitamin D and 1 α -, partially or fully activated vitamin D supplements. In those with CKD, vitamin D supplements also reduce proteinuria but may not prevent gradual deterioration of renal functions [23]. Higher levels of serum 25(OH)D were associated with a lower risk of all-cause mortality in patients with CKD, but no conclusive evidence exists regarding serum levels of greater than 35 ng/mL.

Low concentration of serum 25(OH)D, increase the serum parathyroid hormone, enhancing secondary hyperparathyroidism and bone turnover [24]. When patients with CKD are treated with both vitamin D and its one- α activated form, such as alfacalcidol (rocaltol, paricalcitol, doxercalciferol, etc.), mortality is significantly reduced [22, 25]. Such synthetic vitamin D analogs are also indicated in hypophosphatemia and hypoparathyroidism [26]. Next section examined pregnancy as one example to illustrate the importance of vitamin D sufficiency.

Vitamin D in Pregnancy

Maintaining appropriate physiological serum 25(OH)D levels during pregnancy would reduce the incidences and severity of several pregnancy-associated issues, including preeclampsia, cesarean deliveries, premature deliveries, hypertension during pregnancy, as well as premature delivery, small-for-gestation neonates, infant mortality,

and minimize several common illnesses during early childhood [8, 27, 28]. Having 25(OH)D concentrations above 40 ng/mL before and during pregnancy would substantially reduce these maternal and fetal complications [8, 27]. In addition, maintaining serum 25(OH)D concentrations is essential in the post-pregnancy period and during lactation. Moreover, maternal and neonatal vitamin D deficiency increase the risk of autism spectrum disorders and enhance the severity of neurodevelopmental disorders [29].

Vitamin D adequacy can be assessed only through the measurement of serum 25(OH)D. Recent data from epidemiological, cross-sectional, and longitudinal studies support that having physiological serum concentrations of 25(OH)D (i.e., >30 ng/mL) leads to a reduced incidence of many extra-musculoskeletal disorders, including diabetes, osteoporosis, multiple sclerosis, rheumatoid arthritis and certain types of cancer [30-39].

Conclusion

Maintenance of adequate serum 25(OH)D concentrations is necessary to generate its active hormone, 1, 25(OH)2D (calcitriol). In addition to renal tubular cells, activation of 25(OH)D is also occur in target tissue cells, which is essential for autocrine and paracrine actions of vitamin D. The latter is especially important for maintaining the functions of the immune system, which is essential to overcome COVID-19 [40, 41]. Vitamin D is an integral part of biology and physiology of human systems and to facilitate its beneficial, modulatory effects [17]. These include enzymatic reactions, mitochondrial function, subduing inflammation and oxidative stress, immune protection, secretion of hormones, such as insulin and PTH, and modulating the renin-

angiotensin-aldosterone and FGF23-Klotho hormone systems [42]. In addition, metabolomics and transcriptomics advances will enable generation of improved longer-term extra-skeletal outcomes with targeted vitamin D therapy.

Vitamin D metabolism and actions are influenced by many medications, environmental pollutants, and physical activities/lifestyles, ratio of body muscle mass to fat mass; collectively, these modulate the balance between energy intake and expenditure [43]. Thus, chronic insufficiency of vitamin D tend to increase body fat mass leading to obesity, further reducing the serum 25(OH)D concentration. Cumulative evidence supports biological associations of vitamin D adequacy with a significant risk reduction of a variety of illnesses and improved physical and mental well-being and reduce all-cause mortality [44-46]. In this regard, CYP27B1-mediated target tissue production of 1,25(OH)D was neglected till recently but physiologically, it is critically important. The latter function is essential for the defense against invading pathogens, subduing autoimmunity, and paracrine and autocrine functions of calcitriol that are essential for full biological activity of vitamin D and for optimum health [47, 48].

Conflicts of Interest

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