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Health Care

Management of Vitamin D Deficiency

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Abstract **Review Article**

Vitamin D is a steroid hormone classically involved in the calcium metabolism and bone homeostasis. Vitamin D is produced by skin exposed to ultraviolet B radiation or obtained from dietary sources, including supplements. Vitamin D Deficiency is the most common nutritional deficiency worldwide, characterized by serum 25-hydroxyvitamin D <20 nanograms/mL. Vitamin D insufficiency is regarded as a serum 25-hydroxyvitamin D level between 21-29 nanograms/mL. The causes for vitamin D deficiency include those with inadequate sun exposure, limited oral intake, or impaired intestinal absorption .The other causes of D deficiency might be inherited disorders that either reduce or prevent the metabolism of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D, these disorders are present with biochemical and skeletal abnormalities, but in a more severe form. Most patients are asymptomatic. Severe prolonged vitamin D deficiency causes growth retardation and rickets in children and osteomalacia, osteopenia, and osteoporosis in adults. Moreover, in the last decades, several extra skeletal effects which can be attributed to vitamin D have been shown. These beneficial effects will be here summarized, Both vitamin D deficiency and vitamin D insufficiency are corrected by giving vitamin D2 or vitamin D3 in treatment doses followed by lifelong maintenance doses; adequate, sensible sunlight exposure should be encouraged. This review outlines strategies to prevent, diagnose, and treat vitamin D deficiency in adults and children.

Keywords: CKD = chronic kidney disease; D2 = vitamin D2; D3 = vitamin D3; 1,25(OH)2D = 1,25-dihydroxyvitamin D; HPT = hyperparathyroidism; 25(OH)D = 25-hydroxyvitamin D; PTH = parathyroid hormone; UVB = ultraviolet B.

INTRODUCTION

Vitamin D is essential for bone development in children and skeletal health in adults. It regulates calcium and phosphate absorption and metabolism [1].

It is required to maintain normal blood levels of calcium and phosphate that are in turn needed for the normal mineralization of bone, muscle contraction, nerve conduction, and general cellular function in all cells of the body. Therefore it has important role in skeletal development, bone health maintenance, and neuromuscular functioning.

Vitamin D achieves this after its conversion to the active form 1,25-dihydroxyvitamin D [1,25-$(OH)_2D$], or calcitriol [2].

Vitamin D is obtained through the direct action of sunlight on the skin (90%) or through dietary nutrients (10%), in particular, dairy products, eggs and fish.

The discovery dates back to one hundred years ago, but vitamin D has become a hot topic in endocrinology research only in the last decades, and it has recently emerged as a burning issue due to the COVID-19 pandemic, because of the alleged correlation between hypovitaminosis D and high risk of chronic pulmonary diseases and mortality.

In the 19th century, vitamin D deficiency was identified as the cause of the rickets epidemic in children living in industrialized cities. This discovery led to the fortification of various foods, and the resolution of a major health problem associated with vitamin D deficiency. However, recent studies have shown that vitamin D deficiency and insufficiency are associated with other pathologic conditions in persons of all ages [3].

It is now clear that vitamin D displays a complex multistep metabolism and acts as a hormone on many extra-skeletal targets.

Recent studies have shown that vitamin D deficiency and insufficiency are associated with other pathologic conditions in persons of all ages.

Common manifestations of vitamin D deficiency are symmetric low back pain, proximal muscle weakness, muscle aches, and throbbing bone pain elicited with pressure over the sternum or tibia. Because the signs and symptoms of vitamin D deficiency are insidious or nonspecific, it often goes unrecognized and untreated.

The goal of treatment is to normalize vitamin D levels to relieve symptoms and decrease the risk of fractures, falls, and other adverse health outcomes.

EPIDEMIOLOGY

Vitamin D deficiency is the most common nutritional deficiency worldwide in both children and adults [4-11].

Prevalence rates of severe vitamin D deficiency, defined as 25(OH) D <12 ng/ml or<30 nmol/L, of 5.9% (US) [10], 7.4% (Canada) [11], and 13% (Europe) [12] have been reported. Estimates of the prevalence of 25(OH)D levels < 20 ng/ml or <50 nmol/L have been reported as 24% (US), 37% (Canada), and 40% (Europe) [10-12]. This may vary by age, with lower levels in childhood and the elderly, and also ethnicity in different regions, for example, European.

Caucasians show lower rates of vitamin D deficiency compared with nonwhite individuals [12, 13].

Worldwide, many countries report very high prevalence of low vitamin D status. 25(OH) D levels < 12 ng/ml or <30 nmol/ in >20% of the population are common in India, Tunisia, Pakistan, and Afghanistan. For example, it has been estimated that 490 million individuals are vitamin D deficient in India [12, 13].

Specific categories of patients have a very high prevalence of vitamin D deficiency. Often, they are characterized by an insufficiency or failure of organs involved in vitamin D metabolism. Patients with chronic renal failure and on hemodialysis, renal transplant recipients affected with liver disease or after liver transplantation may have a prevalence of vitamin D deficiency ranging from 85 to 99% [14-16].

Similarly, critically ill patients have a very high prevalence of vitamin D deficiency, and low vitamin D levels are clearly associated with greater illness severity, morbidity, and mortality in both adult and pediatric intensive care unit (ICU) patients, as well as medical and surgical ICUs [17]. However, as in most other populations, the most important question remains unanswered: whether low vitamin D is an innocent bystander, simply reflecting greater disease severity, or represents an independent and modifiable risk factor amenable to rapid normalization through loading dose supplementation [18, 19].

The question is meaningful, since in this subgroup of patients, many factors contribute to low levels: hemodilution, reduced production and conversion by the liver, reduced synthesis of vitamin D-binding protein, higher consumption during the acute phase of disease and systemic inflammation, and increased tissue demand and enhanced catabolism of metabolites. More data are emerging from basic science about the immediate and late effects of vitamin D supplementation on endocrine, autocrine, and paracrine and genomic targets [20].

Fortification of foods with vitamin D and use of vitamin supplements have greatly reduced the incidence of clinically significant vitamin D deficiency in developed countries. Despite this, vitamin D deficiency still occurs with the consumption of unfortified foods, especially in the setting of limited sunlight exposure. It has been estimated worldwide that 40% of children and adults are vitamin D deficient and 60% are deficient or insufficient [4].

It is now recognized that vitamin D deficiency increases the risk of many chronic diseases, including cancer, autoimmune diseases, type 2 diabetes, heart disease and hypertension, neurocognitive dysfunction, and infectious diseases (including upper respiratory tract infections and tuberculosis), as well as osteoarthritis [4, 5, 21].

A strong association of vitamin D deficiency with an increased risk of prostate, colon, breast, ovarian, and pancreatic cancers, among many others, has been reported [22, 23].

Vitamin D deficiency has been linked with increased risk of hypertension and heart disease [24, 25]. One study looking at the vitamin D status in Framingham Offspring Study participants without prior cardiovascular disease (CVD) demonstrated a 50% increased risk of developing a myocardial infarction if the patient was vitamin D-deficient. It has also been suggested that patients with CVD who are vitamin D-deficient have a greater mortality risk [26]. In addition, it has been shown that adults with a serum level of 25-hydroxyvitamin D of >29 nanograms/mL have an 80% reduced risk of developing peripheral vascular disease [27].

It has also been observed that vitamin D deficiency is linked to preeclampsia, low birth weight

and preterm birth, and an increased risk of having a cesarean section [28-33]. Vitamin D3 supplementation during the third trimester enhanced postnatal linear growth [34, 31]. A meta-analysis revealed on the basis of available evidence that there was an association with vitamin D status and several outcomes in children including birth weight and dental caries [35].

Vitamin D deficiency has also been linked to an increased incidence of schizophrenia, Parkinson disease, cognitive dysfunction, Alzheimer disease, dementia, depression, and chronic obstructive lung disease [36-38]. High intake of vitamin D has been shown to decrease the incidence of acute respiratory infections, asthma, and wheezing illness.

Therefore, for most people, vitamin D is primarily obtained by cutaneous production from sun exposure. However, many variables influence the amount of UVB from sunlight that reaches the skin and its effectiveness. These include time of day, season, latitude, altitude, clothing, sunscreen use, pigmentation, and age.

Even if regularly exposed to sunlight, elderly people produce 75% less cutaneous D_3 than young adults [4]. Further barriers to cutaneous vitamin D production are ongoing public health campaigns promoting sunscreen use, as advocated by the American Academy of Dermatology.

Causes of Vitamin D Deficiency

There are several causes of vitamin D deficiency, including decreased intake or absorption, reduced sun exposure, increased hepatic catabolism, decreased endogenous synthesis.

Groups at high risk of Having Vitamin D Deficiency

Older persons confined indoors may have low serum 25(OH)D concentrations. Cutaneous production of vitamin D declines with age and in the northern latitudes. In addition, dietary vitamin D intake is often low in older individual.

The major source of vitamin D for most humans is exposure to sunlight. Avoiding sun exposure, including heavy sunscreen use (sun protection factor [SPF] 8 might reduce vitamin D production by 92.5%, and SPF 30 might reduce vitamin D production by about 95%), season, latitude, and time of day strongly influence cutaneous vitamin D production [40, 41]. In addition, increased skin pigmentation is considered a risk factor due to the sun-screening action of melanin reducing the production of vitamin D in the skin. Aging is also considered a risk factor because the ability of the skin to produce vitamin D decreases with age (a 70-year-old has a 70% reduction in vitamin D production compared with a young adult) [42].

Vitamin D insufficiency appears to be common among several other populations including those who are:

- Taking medications that accelerate the metabolism of vitamin D (such as phenytoin)
- Hospitalized on a general medical service
- Institutionalized
- And those who have:
- Obesity
- Osteoporosis

There is evidence that this vitamin D deficiency contributes to declining bone mass and increases the incidence of hip fractures. Several groups have found that modest increases in vitamin D intakes (between 10 and 20 µg/day) reduce the rate of bone loss and the fracture rate.

Malabsorption, including inflammatory bowel disease and celiac disease. Patients with intestinal malabsorption syndromes, including celiac disease, cystic fibrosis, Crohn disease, Whipple disease, or short bowel syndrome, as well as those who have undergone gastric bypass surgery, are either unable to absorb vitamin D or they absorb it poorly [43].

- Patients with chronic kidney disease are unable to produce sufficient 1,25-dihydroxyvitamin D to regulate calcium metabolism
- Rarely, a vitamin D deficiency-like syndrome can occur as a result of several inherited disorders that either reduce or prevent the metabolism of vitamin D to 25-hydroxyvitamin D or 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D [44]. These include pseudo vitamin D-deficiency rickets, vitamin D-resistant rickets, X-linked hypophosphatemic rickets, and autosomal-dominant hypophosphatemia rickets. In addition, a benign or malignant tumor may produce an excessive amount of fibroblast growth factor 23 (FGF-23), causing severe hypophosphatemia, low levels of serum 1,25-dihydroxyvitamin D, and consequently oncogenic osteomalacia (also known as tumor-induced osteomalacia) [4, 44].

Infants

Infants constitute a population at risk for vitamin D deficiency because of relatively large vitamin D needs brought about by their high rate of skeletal growth. At birth, infants have acquired *in utero* the vitamin D stores that must carry them through the first months of life.

Breast-fed infants are particularly at risk because of the low concentrations of vitamin D in human milk [46]. This problem is further compounded in some infants fed human milk by a restriction in exposure to ultraviolet (UV) light for seasonal, latitudinal, cultural, or social reasons.

Infant formulas are supplemented with vitamin D at levels ranging from 40 international units (IUs) or 1 mg /418.4 kJ to 100 IU or 2.5 mg /418.4 kJ, that provide approximately between 6 mg and 15 mg of vitamin D, respectively. These amounts of dietary vitamin D are sufficient to prevent rickets.

Adolescents

Another period of rapid growth of the skeleton occurs at puberty and increases the need not for the vitamin D itself, but for the active form 1,25-$(OH)_2$D. This need results from the increased conversion of 25-OH-D to 1,25-$(OH)_2$D in adolescents. Furthermore, unlike infants, adolescents are usually outdoors and therefore usually are exposed to UV light sufficient for synthesizing vitamin D for their needs. Excess production of vitamin D in the summer and early fall months is stored mainly in the adipose tissue and is available to sustain high growth rates in the winter months that follow [47]. Insufficient vitamin D stores during these periods of increased growth can lead to vitamin D insufficiency [23].

Pregnancy and lactation

Even in pregnancy, the changes in vitamin D metabolism which occur, namely an increase in the maternal plasma levels of 1,25-$(OH)_2$D [49] due to a putative placental synthesis of the hormone (do not seem to impinge greatly on the maternal vitamin D requirements. The concern that modest vitamin D supplementation might be deleterious to the fetus is not justified. Furthermore, because transfer of vitamin D from mother to fetus is important for establishing the newborn's growth rate, the goal of ensuring adequate vitamin D status with conventional prenatal vitamin D supplements probably should not be discouraged.

In lactating women there appears to be no direct role for vitamin D because increased calcium needs are regulated by PTH-related peptide [50, 51] and recent studies have failed to show any change in vitamin D metabolites during lactation.

Furthermore, there is little evidence that increasing calcium or vitamin D supplements to lactating mothers results in an increased transfer of calcium or vitamin D in milk [52]. Thus, the current thinking, based on a clearer understanding of the role of vitamin D in lactation, is that there is little purpose in recommending additional vitamin D for lactating women. The goal for mothers who breast-feed their infants seems to be merely to ensure good nutrition and sunshine exposure in order to ensure normal vitamin D status during the perinatal period

Vitamin D metabolism

Vitamin D is obtained through the direct action of sunlight on the skin (90%) or through dietary nutrients (10%), in particular, dairy products, eggs and fish.

The liver converts vitamin D to 25OHD. The kidney converts 25OHD to 1,25(OH)2D and 24,25(OH)2D. Once formed, 1,25-dihydroxyvitamin D travels to the small intestine and interacts with its nuclear receptor (vitamin D receptor [VDR]) to enhance the efficiency of the intestine to absorb dietary calcium. In a vitamin D-deficient state only about 10% to 15% of dietary calcium is absorbed, whereas vitamin D sufficiency improves intestinal calcium absorption in the range of 30% to 40%. At times, when there is a great increased requirement for calcium (including in teenagers during their growth spurt, pregnancy, and lactation), efficiency increases to as much as 60% to 80%.

1,25-dihydroxyvitamin D also increases phosphate absorption mainly in the jejunum. In a vitamin D-deficient state approximately 60% of dietary phosphate is absorbed, and in a vitamin D-sufficient state this is improved by about 20% to 80% [45].

1,25-dihydroxyvitamin D interacts with its VDR in osteoblasts, this results in an increase in the expression and production of the major non collagenous protein in the bone, osteocalcin.

Skeletal action of vitamin D

- Children: vitamin D deficiency is the most common cause of rickets Vitamin D deficiency prevents efficient absorption of dietary calcium and phosphorus. The poor absorption of calcium causes a decrease in serum ionized calcium, resulting in secondary hyperparathyroidism. Parathyroid hormone (PTH) decreases phosphorus reabsorption in the kidneys, causing loss of phosphorus into the urine. Therefore, the serum calcium is usually normal in a vitamin D-deficient infant or child. However, the serum phosphorus level is low or low-normal, and therefore there is an inadequate calcium-phosphorus product, causing a defect in the mineralization of the collagen matrix.
- Adults: vitamin D deficiency results in an increase in PTH levels, which in turn increases osteoclastic activity, resulting in the removal of the matrix and mineral from the skeleton. As a result, vitamin D deficiency in adults reduces bone mineral content, leading to osteopenia and osteoporosis. In addition, the secondary hyperparathyroidism results in phosphorus loss in the kidneys, resulting in a normal serum calcium with a low-normal serum phosphorus level. This causes a low calcium-phosphorus product in the blood, which results in the inability of the collagen matrix to be mineralized, leading to osteomalacia. Therefore, for adults, vitamin D deficiency is associated with a normal serum calcium, low-normal or normal serum phosphorus, elevated PTH, and a normal or elevated alkaline phosphatase. The blood level of 25-hydroxyvitamin D is <30 nanograms/mL and

the 1,25-dihydroxyvitamin D level is usually normal or elevated.

Non-skeletal action of vitamin D

Most tissues and cells in the body have a vitamin D receptor. Furthermore, many of these tissues and cells also have a 25-hydroxyvitamin D-1-hydroxylase capable of converting 25 hydroxyvitamin D to 1,25-dihydroxyvitamin D [53, 45].

Vitamin D is a major factor in immune modulation. Activated T and B lymphocytes have a vitamin D receptor, and their immunologic activities are regulated by 1,25-dihydroxyvitamin D [4]. Macrophages make 1,25-dihydroxyvitamin D for the purpose of inducing the production of cathelicidin, a protein that kills infectious agents, including *Mycobacterium tuberculosis* [54]. In addition, 1,25-dihydroxyvitamin D manufactured in monocytes or macrophages is most likely released to act locally on activated T and B lymphocytes, which regulate cytokine and immunoglobulin synthesis, respectively. These immunologic actions are thought to play a role in reducing the risk for autoimmune diseases and infectious diseases [55, 45, 56].

Mortality

Vitamin D deficiency has been strongly associated with various health outcomes, including all-cause mortality (57). A 2014 Cochrane meta-analysis showed a relevant and significant lower all-cause mortality of ~7% and cancer mortality of ~13% in patients who received vitamin D3 [58]. However, despite a cohort of >10,000 participants, it was still too underpowered to confirm a causal relationship [59].

Lung

The effect of vitamin D on the lungs has a strong rationale, demonstrated by basic science, due to its immunomodulant, anti-inflammatory, and anti-infective role that has been highlighted in patients with community-acquired infections, acute respiratory failure, as well as in lung transplantation recipients (this is a very specific model for severe infective and inflammatory lung disease) [15].

Vitamin D supplementation reveals direct anti-inflammatory properties in the lungs. This is due to local inhibition of nuclear factor-κB and mitogen-activated protein kinase activity, reducing the secretion of inflammatory cytokines and chemokines involved in the lung inflammatory process and extravascular leaking, such as interleukin (IL)-1β, IL-6, and IL-8. This, in turn, also influences the number of inflammatory cells infiltrating the interstitial space [60]. Moreover, $1,25(OH)_2D$ is also implicated in the reduction of oxidative stress by inhibiting anti-protease activity and acting on the nuclear factor erythroid-related factor 2, a transcriptional regulator of most antioxidant genes. Moreover, vitamin D acts with well-known anti-infectious properties by increasing proliferation of monocytes to macrophages (acting as a fine tuner of the innate and adaptive immunity).

Finally, $1,25(OH)_2D$ inhibits the expression of several metalloproteinases in airway smooth-muscle cells and alveolar macrophages, thus being involved in the tissue remodeling pathway by regulating the process of bronchial airway muscle activation and extracellular matrix deposition by fibroblasts. All these complex pathways, partially modified by vitamin D, warrant supplementation in patients with respiratory disease. Significant benefits have already been shown in adults and children with asthma, and for the prevention of respiratory tract infections, particularly in severe vitamin D deficiency.

Sepsis

Sepsis, a complication of severe infection, is characterized by signs of systemic inflammation expressed with failure of organs often remote from the site of the initial infection. Septic patients have high mortality and lower circulating levels of vitamin D. The interest in vitamin D for infection has risen after the recognition of the expression of the vitamin D receptor, ubiquitous in cells of the innate and adaptive immune system. Vitamin D is an important link between Toll-like receptor activation and antibacterial responses. The in vivo supplementation of a high dose of cholecalciferol (400.000 IU as a single bolus) in the early stage of sepsis and septic shock has been shown able to safely and rapidly increase the level of vitamin D, as well as the circulating level of cathelicidin, a vitamin D-dependent endogenous anti-microbial and endotoxin-binding peptide largely found in human neutrophils [61]. These findings were corroborated by the significant reduction of IL-1β and IL-6, which play important roles in the early inflammatory response.

Organ Transplantation Recipients

Several studies have highlighted that lower 25(OH) D levels are associated with prolonged hospitalization and mortality, also in the postsurgical setting. Given its wide immunobiological effects, vitamin D has been frequently considered a potential modulating factor after solid organ (and stem cell) transplantation (mainly liver, kidney, and lung). The transplantation recipient population is particularly prone to infections, mainly in the early stage after transplantation, due to immunomodulation/chronic immunosuppressive therapy and to long-term bone dysfunction. The recipients of solid organ transplantation are, by definition, vitamin D insufficient for manifold reasons, including limited sunlight exposure, limited physical activity, reduced dietary intake of vitamin D in food, as well as liver and kidney dysfunction according to their main disease. As an example, in liver transplantation recipients (a group of patients with very low vitamin D levels), osteoporosis has a high prevalence, with a large decline in bone

mineral density in the first year after transplantation. Moreover, a negative association between low vitamin D levels and graft function, as well as a role of vitamin D in reducing the recurrence of hepatitis C virus infection, has been demonstrated. Several interventional trials on vitamin D supplementation in lung and kidney recipients are ongoing under the hypothesis that vitamin D supplementation may contribute to reducing the occurrence of rejection by it immunomodulating action.

Pregnancy

In 2019, two Cochrane analyses on vitamin D and pregnancy were published. They suggested that vitamin D supplementation may reduce gestational diabetes, low birth weight, and preeclampsia, but a higher than currently recommended dose appeared to have no additional benefit except for possible further reduction of gestational diabetes [63, 64]. However, several studies in recent years have highlighted that women are at high risk for vitamin D deficiency, and this is associated with adverse pregnancy outcomes, including preeclampsia and gestational diabetes [65-67, 69]. It has been demonstrated that vitamin D supplementation is able to reduce adverse pregnancy outcomes when a higher level is achieved, with an increasing efficacy when the target level is raised from 20 to 40 ng/mL or 50 ng/mL. Interestingly, the maximum change is achieved 6–8 weeks after initiating the treatment, likely exerting the genomic actions of vitamin D [70-72]. Three major adverse pregnancy outcomes appear to improve with vitamin D supplementation: a 60% reduction in preeclampsia, a 50% reduction in gestational diabetes, and a 40% reduction in preterm delivery [73].

Taking into account the recent literature, vitamin D deficiency is associated with worse outcomes during pregnancy, and at least 400–600 IU of daily vitamin D supplementation is reasonable for women with a vitamin D level <40 ng/mL, with higher required doses in more severe deficiency.

Cancer

The risk of common cancers has been shown to be reduced in the presence of normal 25-hydroxyvitamin D levels. This is thought to be due to the production of 1,25-dihydroxyvitamin D in the breast, colon, prostate, and other tissues.

Vitamin D supplementation as a strategy for preventing cancer was considered, as results from several observational studies suggested an association between vitamin D deficiency and risk for several types of cancer [74]. Ecologic studies revealed a decreased cancer mortality in areas with greater sun exposure [75]. Over the decades, vitamin D and its anticancer action was investigated for various malignancies resulting in mixed findings [76]. Hence, the cancer-protective effect of vitamin D remained unclear. In 2014, two meta-analyses revealed no significant decrease in the incidence of cancer in association with vitamin D supplementation, but a significant reduction in the rate of death from cancer. However, as most of the data derive from observational studies, correlation does not imply causation.

Diabetes

Several studies demonstrated a link between 25(OH)D levels and diabetes, and revealed a higher frequency of vitamin D deficiency in patients with type 1 diabetes mellitus (T1DM) compared with healthy individuals [79-82]. Investigating prenatal vitamin D exposure of the fetus, a lower gestational 25(OH)D level [83] or avoiding vitamin D-fortified food [84] was significantly associated with higher risk of developing T1DM. In infancy, vitamin D supplementation [84] or vitamin D-fortified margarine [85] was shown to reduce the risk of developing type 1 diabetes mellitus. The effect of vitamin D supplementation on T1DM onset seems to be dependent on life stage. Supplementation between 7 and 12 months of age resulted in an almost twofold lower risk of developing T1DM compared with earlier supplementation [86]. In adolescents, many studies revealed no association between 25(OH)D level and onset of T1DM [87-89]. However, there is a clear effect of vitamin D in young adults, as low 25(OH)D levels were significantly associated with developing T1DM [90]. However, according to the available literature, the cause-and-effect relationship is inconclusive. On the other hand, diabetes per se results in physiological changes too, such as increased renal elimination of vitamin D-binding protein compared with healthy individuals. Therefore, the value of hypovitaminosis D as a trigger for developing T1DM remains unclear. Vitamin D deficiency was also shown to have a negative impact on insulin resistance [92]. Hence, a higher risk of developing type 2 diabetes mellitus (T2DM) in individuals with low 25(OH)D levels was assumed. However, vitamin D supplementation did overall not result in a lower risk of developing T2DM [93, 94].

HOW TO PREVENT AND TREAT VITAMIN D DEFICIENCY

Many patients and physicians think that adequate vitamin D intake can be obtained via diet alone. This assumption is erroneous. With the exception of fatty fish, the vitamin D content of most foods, including fortified dairy products, is relatively low to nonexistent.

Vitamin D supplementation is safe [95] and inexpensive, but vitamin D deficiency often remains undiagnosed or is undertreated.

Both D_2 (ergocalciferol) and D_3 (cholecalciferol) are available as dietary supplements. The relative efficacy of D_2 vs D_3 in humans continues to be debated, although both appear to be effective for preventing or treating disease, provided that an

adequate total 25(OH)D blood level is obtained. The variable efficacy of D_2 vs D_3 may relate primarily to differences in serum half-life and is clinically relevant for dosing and monitoring frequency.

- For patients with serum 25(OH)D <12 ng/mL (30 nmol/L), not infrequently associated with hypocalcaemia and osteomalacia, one common approach is to treat with 50,000 international units (1250 micrograms) of vitamin D2 or D3 orally once per week for six to eight weeks, and then 800 international units (20 micrograms) of vitamin D3 daily thereafter. However, the efficacy of this practice compared with daily, weekly, or monthly dosing has not been rigorously established.
- For individuals with serum vitamin D levels of 12 to 20 ng/mL, initial supplementation with 800 to 1000 international units (20 to 25 micrograms) daily may be sufficient. A repeat serum 25(OH)D level should be obtained after approximately three months of therapy to assure obtaining the goal serum 25(OH)D level. If goal level is not achieved, higher doses may be necessary.
- For individuals with serum 25(OH)D levels of 20 to 30 ng/mL (50 to 75 nmol/L), 600 to 800 units (15 to 20 micrograms) of vitamin D3 daily may be sufficient to maintain levels in the target range.
- For patients with malabsorption, oral dosing and duration of treatment depend upon the vitamin D absorptive capacity of the individual patient. High doses of vitamin D of 10,000 to 50,000 international units (250 to 1250 micrograms) daily may be necessary to treat patients with gastrectomy or malabsorption. Patients who remain deficient or insufficient on such doses will need to be treated with hydroxylated vitamin D metabolites because they are more readily absorbed, or with sun or sunlamp exposure
- Multiple dosing regimens have been shown to treat vitamin D deficiency effectively [96-97]. Although large, intermittent (eg, monthly, yearly) doses of vitamin D3 increase serum 25(OH)D levels, we do not use them in patients with normal absorptive capacity. In one trial, a large, annual oral dose of 500,000 international units of vitamin D3 had the undesirable effect of increasing falls and fractures in older adults [98]. Additionally, monthly dosing with 60,000 international units [99] and 100,000 international units [100] has had the undesirable effect of increasing risk of falling in older adults and nursing home residents, respectively.

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