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Vitamin D in Health and Disease: A Literature Review

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Abstract

"Vitamin D" the ''sunshine'' vitamin is a hot topic that attracted ample attention over the past decades, specially that a considerable proportion of the worldwide population are deficient in this essential nutrient. By encouraging the absorption and metabolism of calcium and phosphate, vitamin D is an essential prohormone for maintaining the health of bones and muscles. A sizeable amount of the body's vitamin D requirements are synthesized by the human body using ultraviolet B (UVB) radiation from sunshine in addition to dietary sources such fatty fish, eggs, fortified milk, and cod liver oil. Vitamin D is available in two different forms: D2 and D3 (cholecalciferol). Vitamin D2 is a synthetic version that is frequently found in fortified foods and is sourced from plants, but vitamin D3 is synthesized by the skin after exposure to sunlight and may be obtained from animal sources. The main function of vitamin D is thought to be the body's absorption of calcium from the gut, which is essential for skeletal health (bone mineralization, remodeling, and maintenance). But hypovitaminosis D, also known as a vitamin D deficiency, can have an impact on the bones, muscles, brain, heart, and immune system, among other components of the body. As a result, the shortage causes serious illnesses like cancer, diabetes, autoimmune diseases, infections, rickets (in children), osteopenia, osteoporosis, hypertension, fractures and falls in adults, and neurological abnormalities. A complete understanding of vitamin D sources, serum vitamin D levels, and deficient symptoms, connected to various clinical diseases, requirement and maintenance in the body, length of sun exposure, and effective treatment dose, is an effective strategy for deficiency prevention. The importance of Vitamin D, the causes of its shortage, and the sources accessible will therefore be highlighted in the current review.

Keywords Vitamin D, synthesis, levels and functions, sources, deficiency

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List of abbreviations: 1,25-(OH)2D = 1,25-Dihydroxyvitamin D, CD4 = Cluster of differentiation 4, D2 and D3 = Cholecalciferol, PTH = Parathyroid hormone, Th2 = T helper 2, TLR = Toll-like receptors, UVB = Ultraviolet B, VDR = Vitamin D receptor

Introduction

Since vitamin D is a fat-soluble vitamin, it must undergo two metabolic processes to become an active hormone: 25-hydroxylation in the liver and 1-hydroxylation in the kidney. The vitamin D receptor (VDR) binds to the active form, 1,25-(OH)2D, which then modulates gene transcription and controls mineral ion balance [(1)]. Vitamin D is available in two different forms: D2 and D3 (cholecalciferol). Vitamin D2 is a synthetic version that is frequently found in fortified foods and is sourced from plants, but vitamin D3 is synthesized by the skin after exposure to sunlight and may be obtained from animal sources. Vitamin D is essential for maintaining calcium homeostasis in the body and is thought to play a major role in the absorption of calcium from the intestine (bone mineralization, remodeling, and maintenance). Calcium absorption cannot be enhanced enough in vitamin D insufficiency to meet the body's calcium requirements [(2)]. As a result, the

parathyroid glands produce more parathyroid hormone (PTH), which is crucial for maintaining the body's immune system and bone growth while also mobilizing calcium from bone to maintain normal serum calcium levels. It has become increasingly evident over time that vitamin D plays an important role in cell proliferation and differentiation in addition to its role in bones [3]. In almost every tissue, vitamin D acts as a universal regulator of gene expression and signal transmission. By binding to the VDR in epithelial cells, vitamin D helps to maintain the differentiated, quiescent phenotype and supports pathways that protect cells from endogenous and external stresses [4] as shown in figure 1.

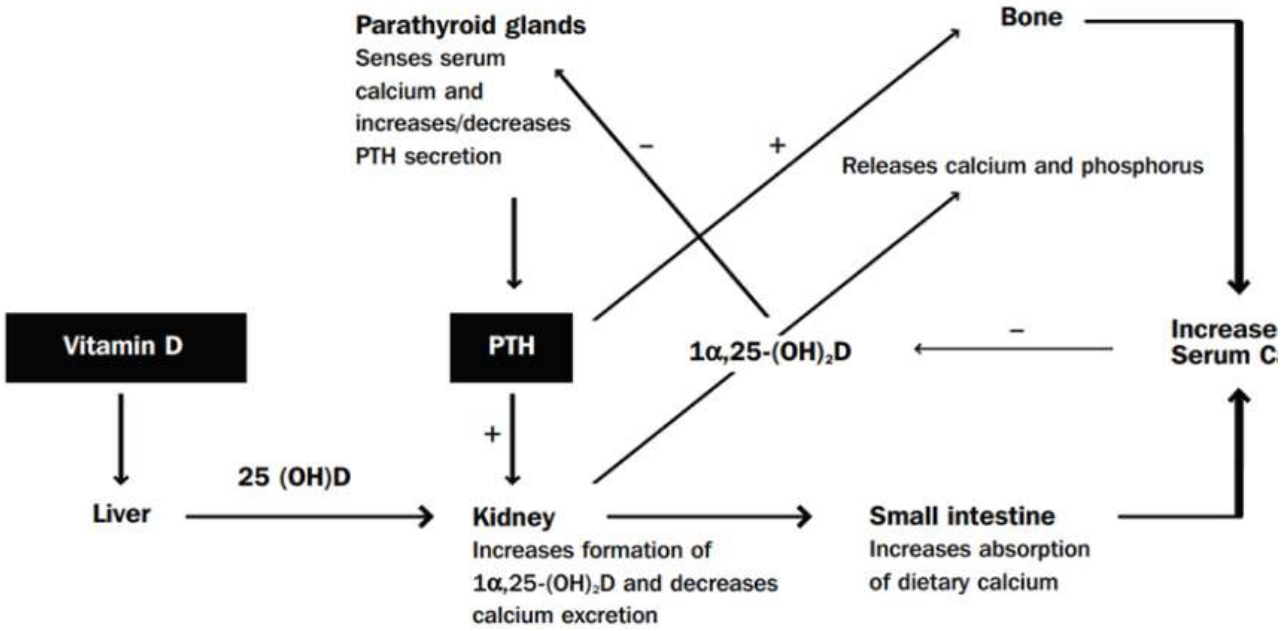

Figure 1. Physiological role of PTH in the maintenance of serum calcium level. Key target organs for PTH – bone, kidney and intestine and their feedback interactions with calcium are shown [5]

Synthesis Of Vitamin D

The body gets vitamin D from synthesis in two different ways. Dietary consumption of animal origin can provide a limited amount of active vitamin D in the form of calcitriol; foods with high quantities include egg yolks and some blue fish, as demonstrated in table 1.

Small levels of ergocalciferol, another type of pre-vitamin D, are present in meals of a vegetable origin. The other way the body gets vitamin D is by being exposed to sunlight. The epidermis' 7-dehydrocholesterol is photo-isomerized by ultraviolet B (UVB) radiation into precholecalciferol, which is subsequently quickly transformed into cholecalciferol or vitamin D3 via a heat-mediated process [6]. Both molecules are hydroxylated in the liver to calcifediol (25(OH)D), which is then hydroxylated in the kidneys by the enzyme 25(OH)D-1-hydroxylase to calcitriol, the active metabolite that binds to its cell receptor to carry out a variety of distinct tasks. In addition to transforming growth factor beta, other elements that regulate this process include calcium and phosphorus levels, PTH as shown in figure 2.

Table 1. Food rich in vitamin D [6]

Food	IU per Serving
Cod liver oil (5 mL)	1360
Salmon (100 g)	360
Mackerel (100 g)	345
Sardines in oil (100 g)	500
Tuna in oil (100 g)	238
Fortified milk (250 mL)	115-124
Fortified orange juice (250 mL)	100
Fortified yoghurt (1.5 L)	80
Margarine (5 mL)	60
Cereals (fortified) (250 mL)	40
Eggs (1)	25
Cheese (28 g)	6-12

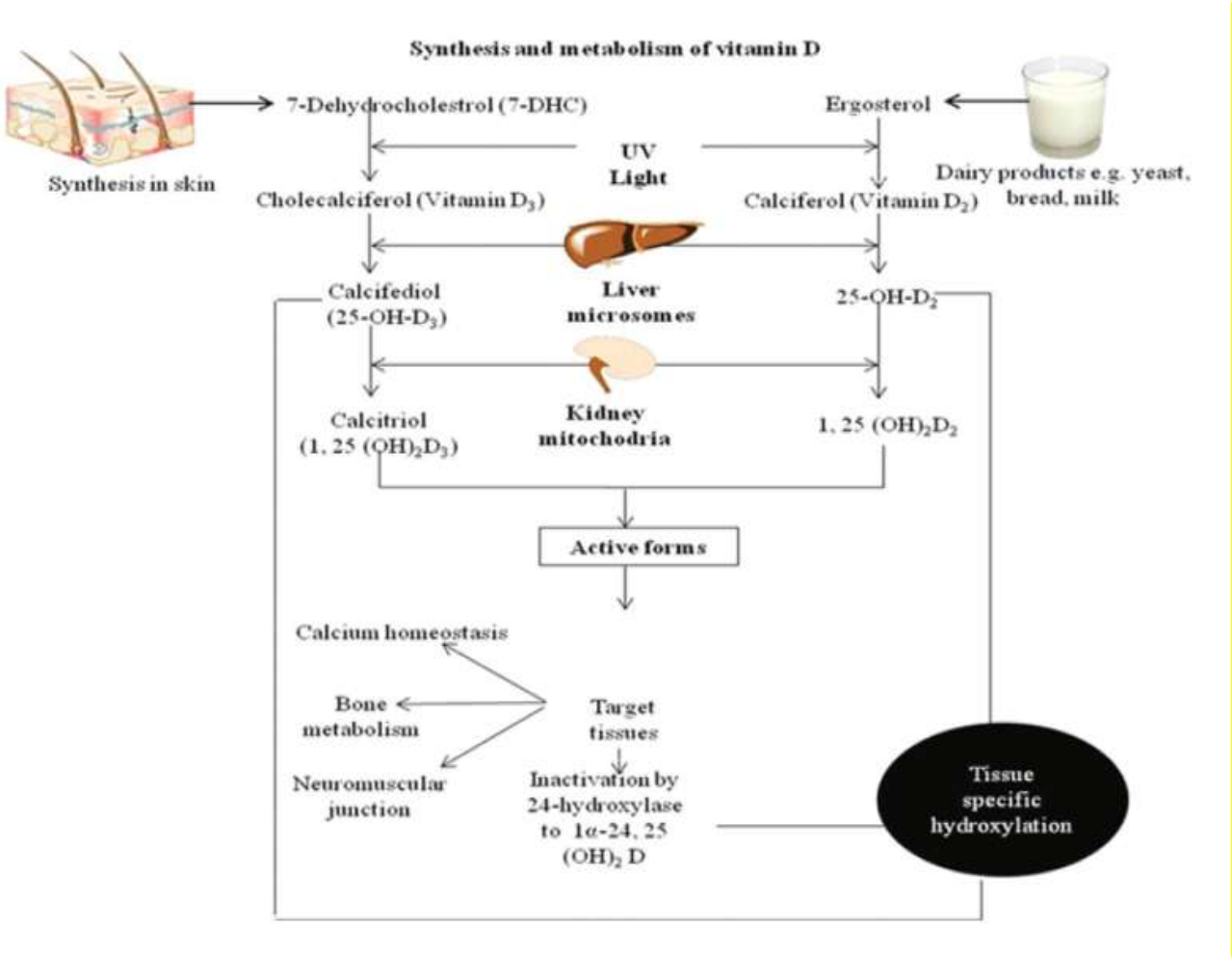

Figure 2. Synthesis and metabolism of vitamin [7]

Vitamin D sources

Only 3 sources are known to contain vitamin D: direct sunlight, dietary sources (animal and natural sources), and over-the-counter vitamin D supplements [8-10] according to figure 3.

Sunlight

Sunlight is one of the best sources of vitamin D, and it is sometimes referred to as "the sunshine vitamin" because it causes the production of vitamin D in the skin cells. When the skin is exposed to UVB rays from the sun, a specific form of cholesterol that is already present in our body changes into vitamin D. Sunlight exposure was necessary for the creation of vitamin D in order to prevent vitamin D insufficiency and skin problems. The generation of vitamin D in the skin is influenced by a variety of factors, including skin pigmentation, topical sunscreen use, age, latitude, sun zenith angle, duration of sunlight exposure, length of clothing, head covering according to religious culture, and season of the year [11,12].

Diet sources

Diet sources of vitamin D was already summarized in table 1

Vitamin D market supplements

Those who cannot obtain enough vitamin D from their food or from exposure to sunlight may decide to take vitamin D supplements. There are two primary types of vitamin D: D2, which comes from plants, and D3, which comes from animals. The market offers supplements that provide vitamin D. In typically, multivitamins contain 400, 800, and 1000 IU of Vitamin D, but these days, a variety of supplements that contain only Vitamin D are offered in different IU, including 400, 1000, 2000, 4000, 5000, and 50000 IU of Vitamin D3 [13].

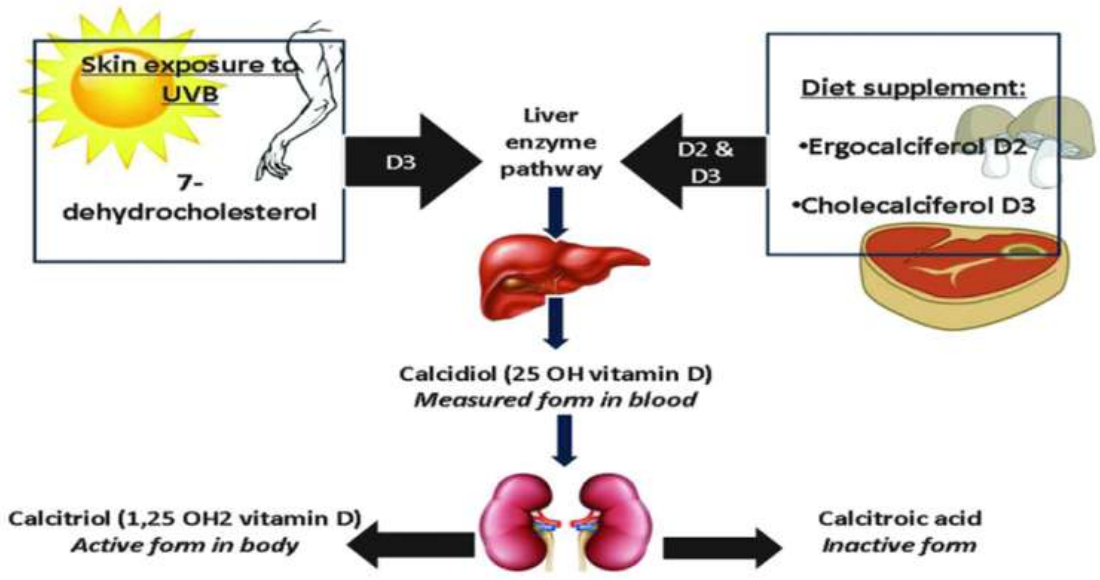

Figure 3. Sources of vitamin D [14]

Vitamin D - Levels and functions

Up until recently, many cut-off points for vitamin D's normal threshold were employed [15]. Most studies define 25(OH)D insufficiency as a level of 50 nmol/L, whereas others consider 37.5 nmol/L as the minimum threshold of sufficiency [16-18]. However, more research indicates that the ideal 25-(OH)D level

is at least 75 nmol/L and is required to cover all physiological functions of vitamin D [19-23]. Adults need to be exposed to sunlight in order for UVB rays to naturally trigger the creation of vitamin D in the skin. Vitamin D levels must be maintained in adults. The roles that vitamin D plays metabolism of bone minerals, regulation of cancer development and metastasis suppresses angiogenesis, induces apoptosis, stimulates differentiation, reduces proliferation, and aids in DNA repair, blood sugar control, reduces peripheral insulin resistance, controls pancreatic insulin secretion, regulate lipid synthesis, blood pressure control via influencing the renin-angiotensin-aldosterone system, inhibits the kidneys' ability to express renin, stimulates the cardiovascular system's nitric oxide production, influence of immunomodulation on keratinocytes. controls early proliferative and differentiation stages, controls the hair follicles' development cycle, controls the immune system's innate and adaptive mechanisms, supports differentiation of T helper2 (Th)2 and T regulators, contributes to the proliferation and activation of dendritic cells, controls the activation of CD4 lymphocytes, inhibits the growth of Th 1-9-17 cells, and plays a part in the activation of selective Toll-like receptors (TLR 1/2) [24] (Figure 4).

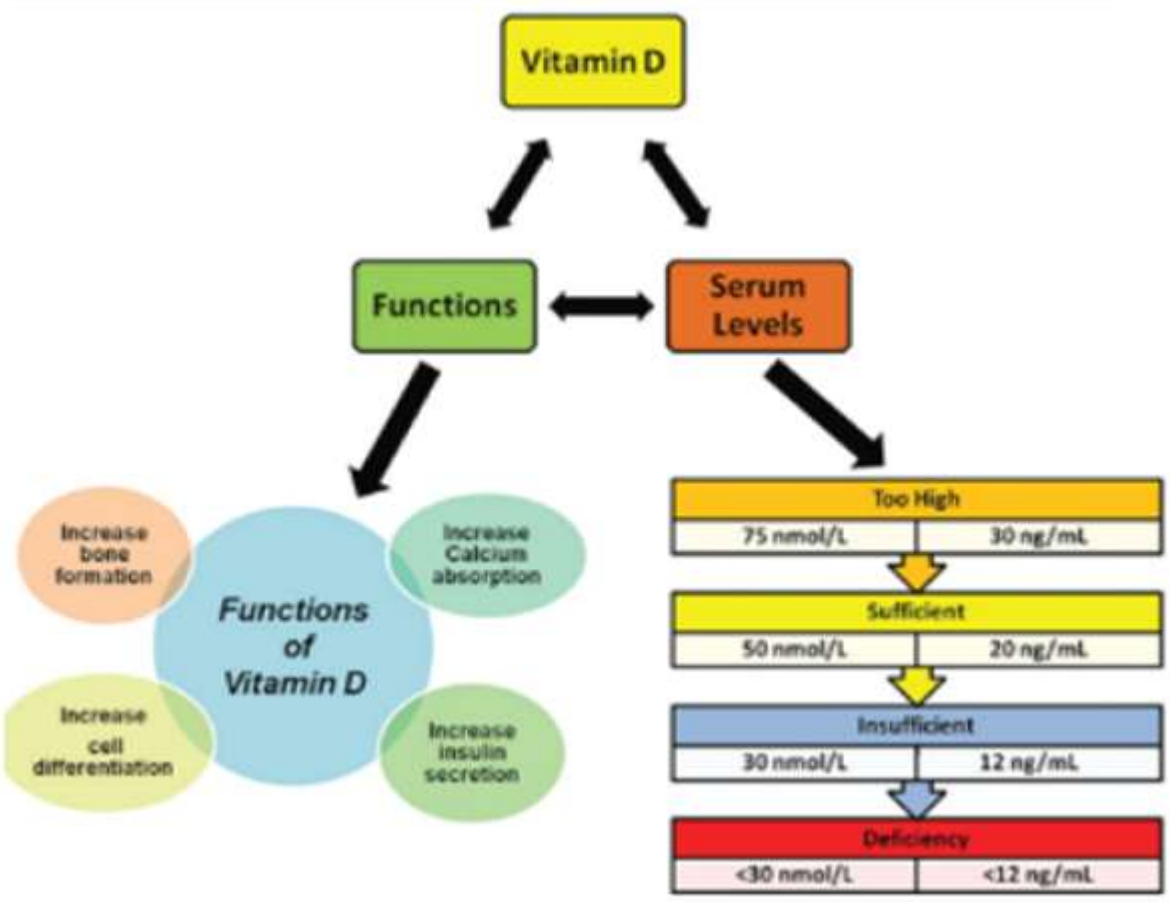

Figure 4. Various levels and functions of vitamin D [24]

Deficiency of vitamin D and its symptoms

A level of less than the recommended minimum of 20 ng/mL is considered to be vitamin D insufficiency, which can affect some persons more than others. Obesity, smoking, a high skin phototype, insufficient sun exposure, age, and insufficient sun exposure are risk factors for vulnerability [25]. The body's capacity to hydroxylate vitamin D in the liver and kidney also declines as we age. The skin produces less of the precursor 7-dehydrocholesterol in the epidermis, intestinal absorption of vitamin D declines due to a decrease in the number of VDR in enterocytes, and intestinal absorption of vitamin D declines as well. Patients with specific clinical disorders are more likely to have low vitamin D levels [26]; these include celiac disease, hyperparathyroidism, hyperthyroidism, chronic renal disease, liver failure, and inflammatory bowel disease. Long-term use of specific medications, such as corticosteroids, anticonvulsants, antiretrovirals, rifampicin, hormonal therapies for breast and prostate cancer, is another risk factor. Low 25(OH)D levels can also result from pregnancy (Figure 5). Overall, this causes osteoporosis, musculoskeletal pain, weakness, decreased mineral density, and a higher risk of fractures and falls [27]. Recent studies have indicated that this deficit is associated to a number of health problems, including Type-2 diabetes, sleep difficulties, cancer, fractures, cardiovascular illnesses, muscle weakness, sore joints, and asthma, with symptoms ranging from mild to severe [28].

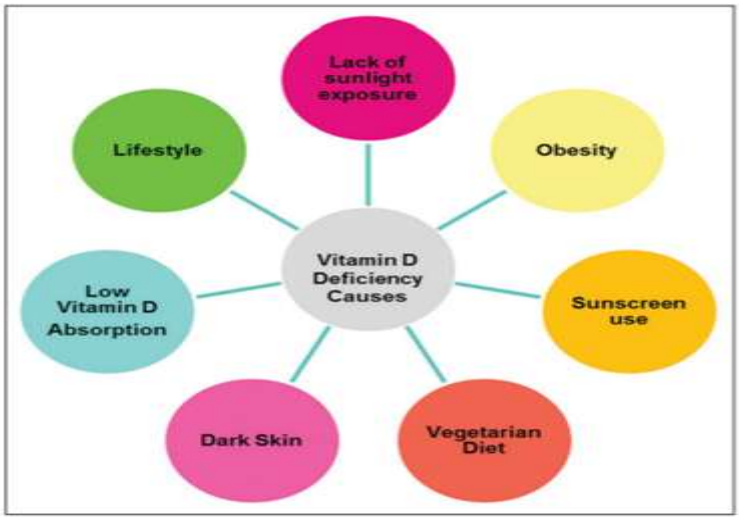

Figure 5. Causes of vitamin D deficiency in the body [28]

Risk factors associated with low vitamin D levels

Although there is not enough data to support either screening for or against vitamin D insufficiency, there are a number of factors that are linked to reduced vitamin D levels (Table 2). Lower 25(OH)D levels may be linked to inadequate dietary vitamin D intake [28]. A higher risk of low vitamin D levels is also linked to older age and little or no UVB exposure (e.g., due to winter season, high latitude, or sun avoidance) [29-33]. Depending on the threshold used to diagnose insufficiency, obesity is linked to reduced 25(OH)D levels [33] and those who are obese have a 1.3- to 2-fold higher chance of being vitamin D deficient [28,29-35]. This finding's

precise process is not fully understood. The prevalence of vitamin D deficiency is 2 to 10 times higher in non-hispanic black people than in non-Hispanic White people, depending on the serum threshold used to identify deficiency. This discrepancy is probably due to variations in skin pigmentation [28,30,35]. These prevalence estimates, however, are based on total 25(OH)D levels, and it is still debatable whether this represents the most accurate indicator of vitamin D status across various racial and ethnic groups. The risk variables mentioned above appear to account for only 20-30% of the range in 25(OH)D levels in individuals, which leaves a large percentage of the variability in 25(OH)D levels unexplained [32,36].

Table 2. Risk factors associated with low vitamin D levels [37]

isk Factors for hypovitaminosis D
xposure to sunlight (controversial)
moking
)besity
ligh skin phototype (IV or greater)
)lder age
ıstitutionalization
urrent treatment with corticosteroids, antiepileptics
lormone therapies for breast or prostate cancer
ımmunosuppressants
ıntiretrovirals History of osteoporosis
hronic kidney disease
iver failure
ıflammatory bowel disease
lyperparathyroidism
lypogonadism
eliac disease

Prevention of vitamin D deficiency

- The best strategies to avoid a vitamin D deficit are to consume foods high in this nutrient and to spend time outside each day. Here are some suggestions for doing so:
- Retaining a healthy body weight: Walking or cycling can give you exercise and solar exposure.
- Treating underlying medical conditions: People with health issues that interfere with nutrient absorption may discover that treating the underlying illness increases their levels of specific nutrients, such as vitamin D.
- Being proactive in maintaining good health: Those who have a family history of osteoporosis or vitamin D deficiency may want to consider discussing screening with their doctor [7].

Conclusion

Vitamin D deficiency is on the rise in the modern world as a result of people's ignorance of the benefits of sun exposure and vitamin D-rich foods. This shortage is widespread across all age groups, and a number of things make it worse and contribute to insufficiency. A sufficient supply of Vitamin D is mostly provided by exposure to sunlight. To ensure that UVB rays reach the skin and that Vitamin D

is produced, everyone should spend at least 15 minutes each day in the sun without wearing sunscreen. There are also other sources from plants and animals that have enough levels of vitamin D, such as fish, mushrooms, and dairy products. The greatest approaches to prevent a vitamin D shortage include maintaining a healthy body weight, managing medical issues, and being proactive about preventative health.

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