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Review Article

Biology of Vitamin D

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ABSTRACT

Vitamin D is both a vitamin and a hormone. It has pleotropic actions that extend beyond calcium and phosphate homeostasis, regulation of parathyroid hormone, and the prevention of osteomalacia, rickets, falls, and fractures. Over 80% of the vitamin D requirement is expected to be generated in the skin following exposure to ultraviolet B in sunlight; globally most people are under-exposed to sunlight and ingest too little vitamin D. Although overexposure to sunlight does not cause hypervitaminosis D, it can cause damage to skin cells. However, both extremes of vitamin D concentrations can be harmful. Vitamin D is essential for life, including for reproduction, fetal growth, immunity, and proper functioning of body systems. Evidence supports wider beneficial effects of vitamin D but achieving such benefits requires maintaining serum 25 dihydroxyvitamin D [25(OH)D] concentrations greater than 30 ng/mL. This article reviews biological pathways that are critical for the generation of 25(OH)D in the liver and 1,25-dihydroxyvitamin D in the kidney, and key abnormalities of vitamin D metabolism that increase the risk of common diseases and disorders, including obesity, insulin resistance, type 2 diabetes, pregnancy complications, autoimmune disorders, certain cancers, impairment of DNA repair, systemic inflammation, and oxidative stress that potentiates metabolic illnesses, such as cardiovascular disorders. Treatment of vitamin D deficiency on average costs less than 0.1% (varies between 0.2% and 0.06%) of the cost of investigations and treatment of worsening comorbidities and complications associated with hypovitaminosis D. For example, the cost of vitamin D supplementation to maintain serum 25(OH) D is $12/year versus an average of $6,000 to 18,000/year per affected person to manage complications. Despite the high benefits relative to cost, millions of people continue to have vitamin D deficiency. The individual and the population health can be markedly improved by maintaining serum 25(OH)D concentrations of greater than 30 ng/mL (75 nmol/L), which would improve the quality of life and reduce all-cause mortality. However, for prevention of certain diseases, such as autoimmune disorders and cancer, and to reduce all-cause mortality, serum 25(OH)D concentrations should be maintained between 40 and 60 ng/mL.

Keywords: 25(OH)D; 1,25$(OH)_2$D; Aging; Human diseases; Epidemiology; Morbidity and mortality; Prevention; Parathyroid hormone; Osteoporosis; Ultraviolet

INTRODUCTION

Most of the vitamin D requirement in humans can be and is supposed to be generated following exposure to sunlight. The prevalence of vitamin D deficiency increases in countries farthest from the equator. However, despite the presence of abundant sunlight, the incidence of vitamin D deficiency is high even among those who live within 1,000 km of the equator, such as the populations of India, Sri Lanka, and Far Eastern, Middle Eastern, and Persian Gulf countries [1-4]. This is attributable to the combination of individuals having darker skin color, climatic conditions, cultural habits, and sun-avoidance behaviors [5,6]. Hypovitaminosis D is a disease that can be cost-effectively prevented and treated through the combination of adherence to specific public health guidelines and vitamin D supplementation regimens.

Vitamin D is a micronutrient that is metabolized into a multifunctional secosteroid hormone that is essential for human health, reproduction, and sustenance of life. Because dietary intake of vitamin D is low, humans are dependent on vitamin D synthesized in the skin. However, the rate of synthesis in the skin is affected by a variety of factors, including the density of melanin pigment; the use of sunscreen and ultraviolet (UV)-blocking creams and ointments, and clothing; and time of the day, month of the year, and duration of sun exposure [7-11]. Moreover, the dermal synthesis of vitamin D decreases in aging populations because of

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aging or scarred skin. Meanwhile, sunlight provides vitamin D that is essential for humans and has additional multi-system benefits, many of which are less understood [12].

Most cells have vitamin D receptors and many target tissue cells have the CYP enzyme that is capable of intracellular generation of 1,25-dihydroxyvitamin D [1,25$(OH)_2$D]. Moreover, several key genes that encode proteins and peptides are modulated in part by vitamin D and thus, affect musculoskeletal functions, mitochondrial respiration, cell growth, proliferation, differentiation, and apoptosis [13]. Vitamin D has many other functions in humans, including modulation of the neuromuscular actions, cell growth, inflammation, and immune functions [14,15].

LITERATURE REVIEW

Generation of vitamin D

Solar ultraviolet B (UVB) photons (approximately 290 to 310 nm) [12] are absorbed by 7-dehydrocholesterol in the epidermis of the skin and isomerized into previtamin D_3 [16], which is further isomerized to form vitamin D_3 [17]. Vitamin D binding protein (VDBP) has high affinity to previtamin D_3 and for dietary sources of vitamin D_2 and D_3 that are absorb from the intestine; VDBP-bound vitamin D is transported *via* the circulation to the liver, where converted to 25(OH)D. In the liver, vitamin D is hydroxylated by the 25-hydroxylase (Cytochrome P450 enzymes; CYP2R1 and CYP27A1) enzymes to 25(OH)D (calcidiol), the major circulating and storage form of vitamin D [18-20].

Vitamin D is fat-soluble and naturally present in small quantities in few foods and is available as a dietary supplement. In evolutionary terms, it is supposed to be produced endogenously in the skin following exposure to ultraviolet rays of sunlight. Vitamin D obtained from sun exposure, food, and supplements is biologically inert and thus must undergo two steps of activation-hydroxylation in the body. As described, the first hydroxylation occurs in the liver, converting vitamin D to 25-hydroxyvitamin D [25(OH)D], also known as calcidiol. The second hydroxylation occurs in the kidney (and also in target tissues) *via* CYP27B1 and forms the physiologically active 1,25$(OH)_2$D, also known as calcitriol [21].

The physiologic way of producing vitamin D_3 is synthesis of previtamin D from 7-dehydrocholesterol in response to UVB-in the skin [22]. However, any excess precursors produced in the skin are destroyed by UVB rays, preventing an accumulation of excess vitamin D in skin cells. Skin also contains the catabolic enzyme 24-hydroxylase, which catabolizes excess previtamin D to its 24-hydroxylated form, which is an inactive metabolites [23]. This feed-back process is regulated by several factors, including dose (exposure) of UVB, serum parathyroid hormone (PTH), and ionized calcium concentrations [24,25]. These inherent protective mechanisms prevent excessive retention of vitamin D in the skin [26]. Thus, sun exposure does not cause hypervitaminosis D or hypercalcemia. Figure 1 illustrates the basic activation steps of vitamin D to 25(OH)D and further hydroxylation to 1,25$(OH)_2$D.

Illustrates the activation of vitamin D to 25(OH)D in the liver and then to 1,25$(OH)_2$D in the kidneys and target tissues.

25(OH)D, a secosteroid generated from its precursors; ergocalciferol (vitamin D_2) and cholecalciferol (vitamin D_3). The half-life of 25$(OH)D_2$ is 10 to 12 days and that of 25(OH) D_3 is 20 to 24 days [27]; this is a clinically important biological

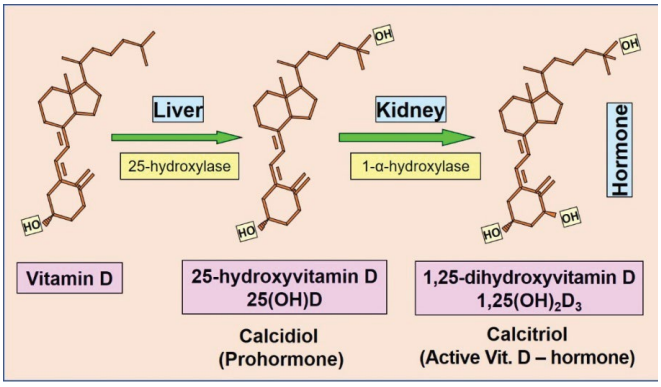

Figure 1: Essential activation steps of vitamin D to 25(OH)D and 1,25$(OH)_2$D.

difference. A meta-analysis of randomized controlled clinical trials (RCTs) reported that vitamin D_3 supplements, when administered intermittently, increase and maintain serum 25(OH) D concentrations for a significantly longer period (p=0.001) than do vitamin D_2 supplements [28]. Nevertheless, the 1,25-dihydroxy metabolites of these two vitamin D forms compete for the vitamin D receptor (VDR) in an equipotent manner [28,29]. Because D_3 has a longer half-life in circulation, it is considered the preferred form for supplementation [30,31]. However, D_2 which is plant or yeast-based is a good option for strict vegetarians (vegans).

Peak bone mass generally occurs during adolescence, but bone mass accrual slows toward the end of the third decade and then plateaus. Although the potential peak bone mass and aspects of skeletal development are in part determined by genetics, vitamin D, calcium, physical activity (mechanical stresses), and hormonal status influence the peak bone mass achieved and the rate of accrual of skeletal mineral content [32,33]. For those who do not live near the equator and are not regularly exposed to UVB rays, the cutaneous production of vitamin D or intake from vitamin D-rich or enriched foods occurs intermittently, especially during winter months. Thus, supplemental doses of vitamin D and sensible sun exposure are needed to prevent deficiency in many populations.

Transportation of vitamin D

Vitamin D generated in the skin binds to vitamin D binding protein (VDBP) and is transported to the liver, where it is hydroxylated to generate 25(OH)D. 25(OH)D, binds to VDBP and is transported throughout the body *via* the circulation. Upon reaching the proximal tubules of kidney and in extra-renal target tissues (see section 3.4), 25$(OH)D_2$ and 25$(OH)D_3$ are further hydroxylated to generate 1,25$(OH)_2$D by the 1α-hydroxylase (CYP27B1) enzyme, the most biologically active and the hormonal form of vitamin D [18-20]. The VDBP-bound hormone calcitriol is then delivered throughout the body for its endocrine function, including to bone, intestine, and kidney, where it contributes to key physiological actions [34,35].

Following high-affinity binding of free calcitriol to the vitamin D receptors (VDRs), a ubiquitously expressed nuclear receptor in human cells, leads to physiologic actions. VDR acts as a ligand-modulated transcription factor, which belongs to a family of receptors that include steroid, thyroid, and retinoic acid receptors [36]. In addition to renal tubular cells, many extra-renal target tissues cells also convert 25(OH)D to 1,25$(OH)_2$D [37]. However, as described later, the controls for this conversion are different and the amounts generated intracellularly are difficult to quantitate.

Modulation of genes through the "VDR calcitriol complex"

The active hormone calcitriol reaches target cells through the circulation or is synthesized intra-cellularly in target tissue cells. The hormonal receptor interactions activate homodimerizations to form VDR:VDR or heterodimerization with the retinoic X receptors to form VDR:RXR complexes that are capable of binding to nuclear DNA [38]. Interactions of calcitriol with intracellular VDR leads to modulation of genes (activation or suppression), and activation of second messenger systems. At this stage, several other proteins interact with this complex as corepressors or coactivators, increasing or decreasing chromatin condensation. As a result, these complexes either enhance or suppress target gene transcription [38,39].

Mechanistically, excess vitamin A can change the ratio of RXR to retinoic acid receptor (RAR) (RXR/RAR) heterodimers. This may reduce the availability of RXR for heterodimerization with VDR and thus, dampen vitamin D signalling. This phenomenon could lead to the development of rickets even when vitamin D is replete. In part, this may be responsible for the higher fracture risks observed in older women with high serum vitamin A concentrations. Because of the differences in microcellular environments between different cells and epigenetic DNA modifications, the same activator can cause tissue-specific, different responses through the nuclear receptors. This process activates numerous genes, such as osteocalcin, bone sialoprotein, osteopontin, CYP24A1 and CYP27B1, TRPV6, PTH, PTH-related peptide, and the calcium-binding protein calbindin [40,41]. The rapid nongenomic effects of vitamin D do not depend on VDR-mediated activation [42-44] but respond to swift changes in intracellular calcium [45].

In addition to its well-known musculoskeletal benefits, 25(OH) D adequacy decreases risks and the severity of many extra-skeletal diseases and disorders, including insulin resistance, severity of type 2 diabetes mellitus (T2D), prediabetes, metabolic syndrome, inflammation, and autoimmunity. In addition to its endocrine effects, calcitriol also exerts autocrine and paracrine effects at target tissues and may modulate effects through epigenetic processes [46].

Circulatory 25(OH)D and cellular internalization

Serum 25(OH)D is the most sensitive biomarker for establishing vitamin D status [47]; serum concentrations of more than 30 ng/mL (75 nmol/L) are defined as vitamin D adequacy. However, some consider adequate serum concentration as above 20 ng/mL. The latter is adequate for skeletal physiology but not for other tissues VDBP containing 25(OH)D is internalized by renal tubular and muscle cells through a megalin/cubilin-dependent plasma membrane transport mechanism [30,40,48]. In muscle cells, the internalized VDBP binds to actin, which contains high-affinity binding sites for 25(OH)D. When the VDBP undergoes proteolytic degradation in target tissue cells, 25(OH)D is released intracellularly [30], where it can be activated to calcitriol by intracellular CYP27B1 [40,49,50].The feedback actions of calcitriol modify VDBP-dependent internalization and intracellular release of 25(OH) D, another mechanism for maximizing the utilization of vitamin D in skeletal muscle cells [51,52]. The vitamin D-DBP as well as vitamin D-albumin complexes are filtered through the glomeruli and re-uptake by megalin in the proximal tubule. Consequently, in kidney diseases that are characterized by tubular damage, vitamin D-DBP complexes are lost *via* urine. Thus, measurement of these can be used as a non-specific marker for renal tubular diseases. The

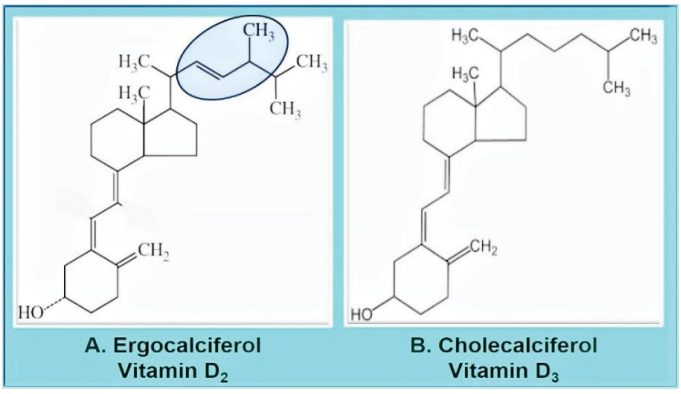

Figure 2: Molecular structures of vitamin D_2 and D_3.

structure of D_2 differs from D_3 only by having a c22-23 double bond and a methyl group at c24 (Figure 2), but the half-life of 25(OH)D_3 is almost double that of the D_2 metabolite. It is likely that a combination of mechanisms contributes to the longer half-life of 25(OH)D_3 than of 25(OH)D_2 [48].

Illustrates that the structures of D_2 differs from D_3 by having a double bond between c22-23 and a methyl group in c24 of the basic vitamin D molecule.

Skin is the organ generating vitamin D_3

In humans, skin thickness and the color have changed gradually, over thousands of years to maximize survival and protect humans from diseases [53]. When people started to migrate northward, from Africa, insufficient sunlight (thus, less UVB exposure) and less generation of vitamin D in the skin, negatively affected fertility and reproduction and the survival. During the process of migration northward, those who developed lighter skin color through mutagenesis of melanin-generating genes, had an overwhelming survival advantage in the less sunny climates (the beginning of the Caucasians. In evolutionary terms, in northern latitudes, having a lighter skin pigmentation created a favorable condition for generating optimal quantities of vitamin D, facilitating a balance between protecting dermal cells from UV damage, maximizing vitamin D production, and avoiding vitamin D toxicity [54-56].

In our equatorial ancestors, dark skin evolved to protect against sunburn and skin cancer. But, as humans moved away from the equator, paler skin facilitated increased synthesis of vitamin D in the skin, but it increased the risk of sunburn and skin cancer. Especially in those with skin-freckles, high UV exposure enhances the cell division and DNA damage, and leads to increased need for DNA repair. Folates is an essential component for DNA repair, so those with paler skin have an increased need for folate in those with darker skin. The latter group has enhanced melanogenesis but fewer dermal cell divisions, thus, a reduced the need for folate [54,55].

Biological activities of vitamin D

Key functions of vitamin D include the facilitation of calcium and phosphate absorption *via* the intestine and the regulation of bone metabolism. Together with PTH, vitamin D plays a key role in tightly maintaining serum ionized calcium concentrations [56]; this is exemplified by the negative correlation of serum 25(OH)D with PTH concentrations [25,57].

An understanding of the biochemistry and biology of this key steroid hormone and its generation and physiological actions, will help clinicians determine the best way to guide patients to obtain

improved clinical outcomes. In target tissues, $1,25(OH)_2D$ is mostly generated intracellularly and acts as an autocrine signal: a cell produces and secretes a hormone or messenger that has its effects within that cell. In paracrine signaling, hormones and chemical messengers are secreted by a cell or a group of cells leading to local effects around the secretory cells. Figure 3 illustrates the cycle of generation of vitamin D in the skin, together with need-based activation of 25(OH)D and calcitriol in target tissues and the control of serum ionized calcium concentrations through intestinal calcium absorption and increased bone turnover.

Vitamin D deficiency leads to increased secretion of PTH (i.e., secondary hyperparathyroidism), higher bone turnover, and the consequent loss of calcium and bone mineral content [58,59]. Moreover, suboptimal $1,25(OH)_2D$ concentrations decrease intestinal calcium absorption and increase urinary calcium loss [60]; causing an overall negative calcium balance.

Skin- and oral/dietary-derived vitamin D is activated to its hormonal form, $1,25(OH)_2D$ through a common path. Although 25-hydroxylase (CYP27B1) activity is exclusive to the liver, conversion of 25(OH)D to $1,25(OH)_2D$ *via* the 1α-hydroxylase enzyme occurs predominantly in renal tubules but also in target tissue cells. Also illustrated is the control of serum ionized calcium levels through intestinal absorption and bone turnover, together with the PTH-mediated increased renal tubular absorption of calcium.

⊕ Activated or upregulated; ⊖ Suppressed or downregulated.

Better vitamin D repletion is associated with reductions in the incidence and severity of several non-musculoskeletal disorders [61], including diabetes mellitus (T1D and T2D), insulin resistance, and metabolic syndrome [62-65], depression, infectious diseases, autoimmune diseases, cardiovascular diseases (CVDs), neurocognitive dysfunction, and specific cancers [66-82]. Prospective epidemiological studies conducted with stable, long-term 25(OH)D concentrations demonstrated reduced risks of these conditions with higher baseline vitamin D status. However, many such findings have not been substantiated through RCTs [15]. This is in part due to design failures of RCTs, inherent bias, and the lack of properly designed RCTs with vitamin D-related primary outcomes.

Catabolism of vitamin D

Although extrarenal target tissue cells generate $1,25(OH)_2D$, the concentrations achieved are unclear because it remains within the target tissue cells. Nevertheless, such extra-renal production of hormone provides biologically and physiologically important autocrine and paracrine functions. The amounts of $1,25(OH)_2D$ generated in renal tubules and target cells can vary from person to person and day to day. In addition, the catabolic activity of 24-hydroxylase in target tissues plays a part in regulating intracellular concentrations of vitamin D metabolites, and thus, the availability of active, free hormone (Figure 4).

Although calcitriol in the circulation is modulated by PTH and the serum ionized calcium concentration [25], the intracellular content is regulated largely through serum 25(OH)D (substrate) availability and, calcidiol and calcitriol catabolism through hydroxylation at C-24 and C-23 by a specific 24-hydroxylase (CYP24A1). Unlike in renal tubular cells, extrarenal tissues' (target tissue cells and macrophage) conversion of 25(OH)D to $1,25\text{-}(OH)_2D$ is sensitive to

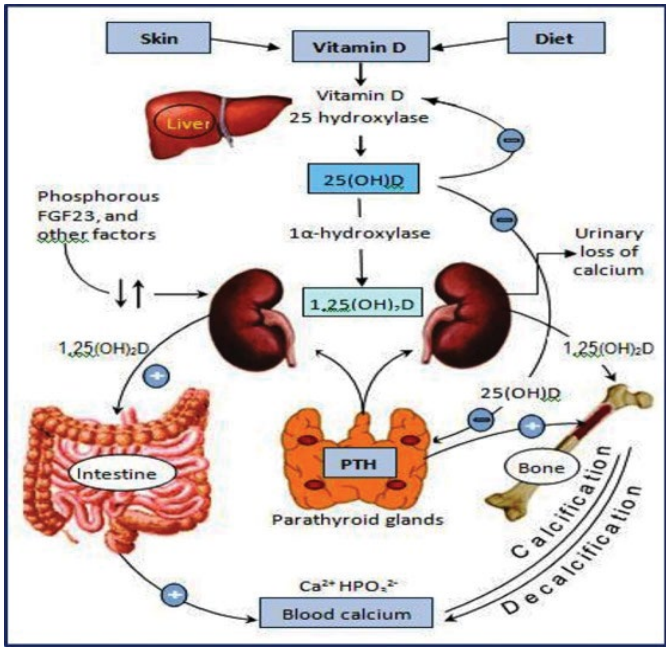

Figure 3: The interactions and pathways for generating vitamin D, 25(OH)D, and $1,25(OH)_2D$.

medications, such as glucocorticoids. The renal 25(OH)D-1 alpha-hydroxylase (CYP27B1) is not sensitive to hydroxychloroquine, ketoconazole or glucocorticoids [83]. Thus, when hypercalcemia is caused by extra-renal over production of calcitriol, as occurs with granulomatous diseases such as sarcoidosis, it can be controlled at least temporarily with these medications.

Catabolic pathways of vitamin D: The 24-hydroxylase (CYP24A1) enzyme generates biologically inactive, 24-hydroxylated products that are excreted as calcitroic acids through the biliary tract; whereas, the 23-hydroxylase pathway produces are excreted as 1,25-26,23 lactone. The importance of biologically active calcitriol concentrations has been demonstrated in a study with CYP24A1 knockout mice, in which the animals developed impaired bone mineralization and hypercalcemia and had perinatal death rates of approximately 50% [84,85]. However, these characteristics do not exist in CYP24A1/VDR double knockout mice, suggesting that increased calcitriol levels, but not the absence of 24- or 23-hydroxylated vitamin D metabolites, are responsible for this abnormal phenotype.

A protective biofeedback mechanism is also present in the liver; when excess 25(OH)D is formed, it is catabolized to 24(OH)D or $24,25(OH)_2D$, both of which are biologically inert [86]. Similarly, in the renal tubular cells and target cells, if and when excess $1,25(OH)_2D$ is generated, it is catabolized into $1,24,25(OH)_3D$, another biologically inactive vitamin D metabolite. Depending on the target tissue, calcitriol and its products can be metabolized into additional inactive metabolites, but this happens in smaller quantities and current methodologies preclude quantitating them (Figure 4).

The paths of catabolism/inactivation of active vitamin D metabolites. Excess 25(OH)D and $1,25(OH)_2D$ are catabolized to inactive forms 24(OH)D, $24,25(OH)_2D$ (mainly in liver and in target tissues), and $1,24,25(OH)_3D$ (renal cells and target tissues) [86]. The threshold and modes of inactivation vary among tissues.

Broader effects of vitamin D: Hypovitaminosis D can have significant musculoskeletal consequences, such as rickets in

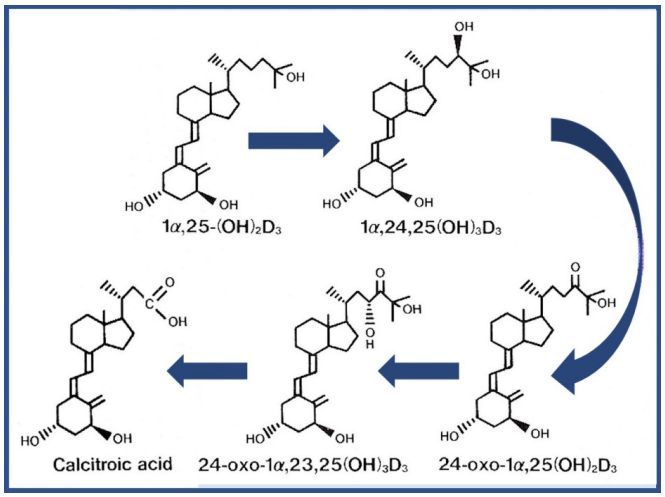

Figure 4: Catabolism of vitamin D.

children and osteomalacia in adults; many such patients present with the inability to raise arms above the head and difficulty in getting up from a chair (i.e., signs of proximal myopathy) [87]. Vitamin D influences many physiologic activities, including maintaining calcium and phosphorus homeostasis, subduing autoimmunity and infections, controlling cell growth, innate and adaptive immunity, mitochondrial respiration, and metabolic activities [88-91]. Although, diabetes can lead to renal failure and the resultant lowering of the generation of $1,25(OH)_2D$, hypovitaminosis D does not cause renal impairment. Renal failure causes deficiency of $1,25(OH)_2D$ and an array of other disorders. In addition, hypovitaminosis is known to worsen several metabolic disorders, including metabolic syndrome, insulin resistance, and diabetes.

Common causes of vitamin D deficiency: Those with dark skin, those who have less exposure to sunlight, and older persons, all have less capacity to generate vitamin D compared with a healthy adult. In addition, stored vitamin D quantity decreases with advancing age, especially during winter months, irrespective of living location. Having gastrointestinal diseases that cause fat malabsorption, such as celiac and Crohn's disease, short bowel syndrome including gastric bypass, and cystic fibrosis also reduces the capacity to absorb vitamin D.

To be biologically effective, vitamin D molecules requires activation. Because activation (*via* hydroxylation) occurs in the liver and kidney, failure of either of these organs (because of reduced levels of activating enzymes) leads to lesser amounts of vitamin D. Thus, people with chronic liver or kidney diseases are at a high risk of having low concentrations of 25(OH)D and/or $1,25(OH)_2D$.

Genetic causes of low vitamin D serum concentrations include lack or impairment of generation of active vitamin D (or formation of inappropriate amounts of biologically inactive forms or enhanced catabolism), abnormalities of vitamin D-binding protein and/or VDR abnormalities. Any of these abnormalities or syndromes can present with low vitamin D activity, but these disorders are rare; however, they need to be considered when assessing the vitamin D deficiency of an individual person.

DISCUSSION

Although adequate vitamin D is important for proper muscle functioning and skeletal development and maintenance, evidence suggests that vitamin D facilitates the prevention of several diseases, including diabetes mellitus, hypertension, autoimmune diseases, and certain common cancers. Consequently, in the presence of insufficient vitamin D, the body's systems are unlikely to work optimally. Epidemiological data reported a high prevalence of vitamin D inadequacy among children, the elderly, and those with osteoporosis. Low sunlight exposure, age-related decreases in cutaneous synthesis, and diets low in vitamin D, contribute to the high prevalence of vitamin D inadequacy worldwide [12].

The proper functioning of the biology of vitamin D-endocrine, paracrine, and autocrine systems is essential for most physiological activities. Normal serum concentrations of 25(OH)D and the intracellular concentration of $1,25(OH)_2D$ are essential for optimal musculoskeletal and soft tissue health. Vitamin D deficiency, as determined by serum 25(OH)D concentrations of less than 30 ng/mL, is associated with increased risks of illnesses and disorders and increased all-cause mortality even among apparently healthy individuals [92,93]. In addition, having lower serum 25(OH)D concentrations can cause dysfunctions in many systems, despite the presence of physiologic concentrations of calcitriol.

The minimum recommended steady-state, serum 25(OH)D concentration is 30 ng/mL (75 nmol/L). In general, the range between 30 and 60 ng/mL is considered as healthy (physiological); no known adverse effects related to vitamin D occur till the serum 25(OH)D concentration exceeds 125 ng/mL (375 nmol/L). However, persons with certain disorders, such as obesity, metabolic disorders, autoimmunity and cancer, may require higher levels (concentrations between 40 and 60 ng/mL). To achieve such concentrations, adequate exposure to UVB rays and/or vitamin D_3 supplements of between 2,000 and 6,000 IU per day are required. It has been demonstrated that daily intake of 10,000 IU is safe [94]. The elderly, the obese, those who are taking medications that activate hepatic cytochrome P450 enzymes that enhance catabolism of vitamin, and pregnant women and those who are lactating require higher intakes (i.e., vitamin D_3, 6,000 IU/day) of vitamin D.

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., more than 30 ng/mL) leads to a reduced incidence of many extra-musculoskeletal disorders, including diabetes [95-97], osteoporosis [98,99], multiple sclerosis [100], rheumatoid arthritis [101], and certain types of cancer [102-104].

Having adequate serum 25(OH)D concentrations allows vitamin D to generate its active hormone, $1,25(OH)_2D$ (calcitriol) in renal tubules and in target tissues with some feedback controls and facilitates its intended positive or negative modulatory effects. These include enzymatic reactions; synthesis and secretion of hormones, such as insulin and PTH; and modulating the renin–angiotensin–aldosterone and FGF23-Klotho systems [105]. Meanwhile, data from metabolomics and transcriptomics promise the generation of improved longer-term extra-skeletal clinically meaningful outcomes.

CONCLUSION

Vitamin D metabolism and actions are influenced by many medications, environmental pollutants, and physical activities and lifestyles; some of these also modulate the balance between energy intake and expenditure. Cumulative evidence supports biological associations of vitamin D adequacy with disease risk

reduction and improved physical and mental well-being. In this regard, few investigations were done on CYP27B1-mediated "target tissue" production of 1,25(OH)D until recently; thus, expansion of research into this area is important. In addition to the endocrine role of vitamin D, the paracrine and autocrine functions of calcitriol are essential for full biological activity of vitamin D but not yet fully understood.

Although many diseases and disorders are related to vitamin D deficiency, the costs of investigating and managing the complications associated with hypovitaminosis D-induced metabolic disorders are extremely high. Maintaining serum 25(OH)D concentrations between 30 and 60 ng/mL would significantly reduce the severity of and complications associated with several common diseases. Because of the favorable cost-benefit ratio, this approach is highly beneficial. The positive impact on benefits in humans and on the economy by following public health approaches would exceed the benefits derived from the combined targeting of infectious and parasitic diseases globally.

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