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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 vitamin D requirement is expected to generate in t he skin, following exposure to ultraviolet B sunlight; globally, majority of people are however, under-exposed to sunlight. Nevertheless, over exposure to sunlight, does not cause hypervitaminosis D but 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, and immunity, and proper functioning of body systems. Evidence supports wider beneficial effects of vitamin D but to achieve such, maintaining serum 25 dihydroxyvitamin D [$25(OH)_2D$] concentrations of more than 30 ng/mL is necessary. This article reviews biological pathways that are critical for generation of 25(OH)D in the liver and 1,25-dihydroxyvitamin D in the kidney, and key abnormalities of vitamin D metabolism that lead to common diseases, such as 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% of the cost of investigations and treatment of worsening comorbidities and complications associated with hypovitaminosis D (cost vary between 0.2% and 0.06%). For example, vitamin D treatment cost of $12/year versus, average cost for managing complications, of $6,000 to 20,000/year per affected person. 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). This would also improves the quality of life and reduces all-cause mortality. However, for prevention of certain other diseases and to reduce all-cause mortality, serum 25(OH)D concentrations need to be maintained between 40 and 60 ng/mL.

Keywords: 25(OH)D; $1,25(OH)_2D$; 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 furthest 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 a darker skin color, climatic conditions, cultural habits, and sun-avoidance behaviors [5,6]. Hypovitaminosis 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 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; the dermal synthesis of vitamin D decreases in aging populations that is attributable to aging or scarred skin; time of sun-exposure of the day; month of the year; and duration of sun exposure [7-11]. Meanwhile, sunlight provides vitamin D that is essential for humans and has additional multi-system benefits, many of are still less understood [12].

Although most cells have vitamin D receptors, 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 functions in humans, including modulation of the neuromuscular, 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, as well as dietary sources of vitamin D_2 and D_3 that are absorb from the intestine; these are 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) enzyme to 25(OH)D (calcidiol), the major circulating and storage form of vitamin D [18-20].

Vitamin D is a fat-soluble vitamin that is naturally present in small quantities in few foods, and available as a dietary supplement. Evolutionary terms, it is supposed to be produced endogenously in the skin following exposure to sunlight ultraviolet rays. Vitamin D obtained from sun exposure, food, and supplements is biologically inert and thus, must undergo two steps of activation-hydroxylation in the body. The first 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 (also in target tissues) and forms the physiologically active 1,25-dihydroxyvitamin D ($1,25(OH)_2D$), 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 contains the catabolic enzyme 24-hydroxylase, which direct catabolism of previtamin D to inactive metabolites [23]. This feed-back process is regulated by several factors, including dose 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 $1,25(OH)_2D$.

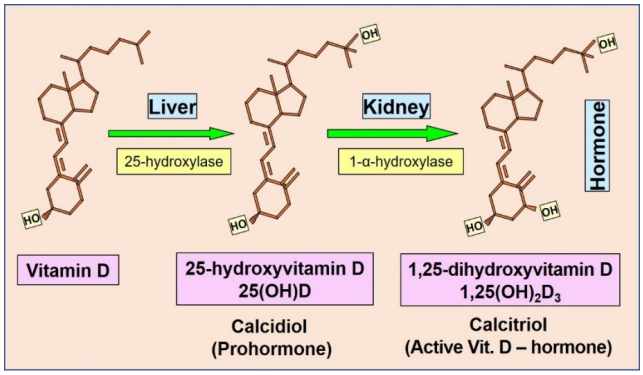

Figure 1: Essential activation steps of vitamin D to 25(OH)D and $1,25(OH)_2D$.

The activation of vitamin D to 25(OH)D in the liver and then to $1,25(OH)_2D$ in the kidneys and target tissues.

25(OH)D is 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]. A meta-analysis of randomized controlled clinical trials (RCTs) reported that compared with vitamin D_2, vitamin D_3 supplements increase and maintain serum 25(OH)D concentrations for a significantly longer period (p=0.001) (see section 2.4) [28]. Nevertheless, the 1,25-dihydroxy metabolites of these two 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/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 third decade and then plateaus. Although the potential peak bone mass and aspects of skeletal development in part determines by genetics, vitamin D, dietary calcium, physical activity (mechanical stresses), and hormonal status also 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, 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

In the liver, hydroxylated vitamin 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 $1,25(OH)_2D$ by the 1α-hydroxylase (CYP27B1) enzyme; the most biologically active form of vitamin D [18-20]. The VDBP-bound hormone, calcitriol is then delivered throughout the body [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 VDR, a ubiquitously expressed nuclear receptor in human cells, it elicits 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 extrarenal cells in target tissues also convert 25(OH)D to $1,25(OH)_2D$ [37]. However, as described later, the controls for this conversion are different and difficulty 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 tissues; this hormonal form interacts with the intracellular VDR leading to gene activation/suppression and activation of second messenger systems. The latter is activated after homodimerization 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]. At this stage, several other proteins also interact with this complex, acting as corepressors or coactivators, thus increasing or decreasing chromatin condensation. Consequently, these complexes either enhance or suppress target gene transcription [38,39].

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, including 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 mediation [42-44] but on swift increases in intracellular calcium [45] (see section 3.6).

In addition to its well-known musculoskeletal benefits, 25(OH)D adequacy decreases the severity of extra-skeletal diseases /disorders, including insulin resistance, severity of type 2 diabetes mellitus (T2D), prediabetes, metabolic syndrome, inflammation, and autoimmunity. In addition to its endocrine effects, vitamin D 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 of the vitamin D status [47]; serum concentrations of less than 30 ng/mL (75 nmol/L) (some consider <20 ng/mL; which is adequate for skeletal physiology but not in other tissues) are defined as vitamin D deficiency (Grant, 2011 #55873). 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 [40,49,50].

Recent *in vitro* data suggest another internal control mechanism for maximizing the utility of vitamin D in skeletal muscle cells: feedback actions of calcitriol modify the VDBP-dependent internalization and intracellular release of 25(OH)D [51,52]. It is likely that this mechanism contributes to the longer half-life of 25(OH)D_3 than of 25(OH)D_2 [48]. Nevertheless, the 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 the 25(OH)D_3 is almost double that of the D_2 metabolite.

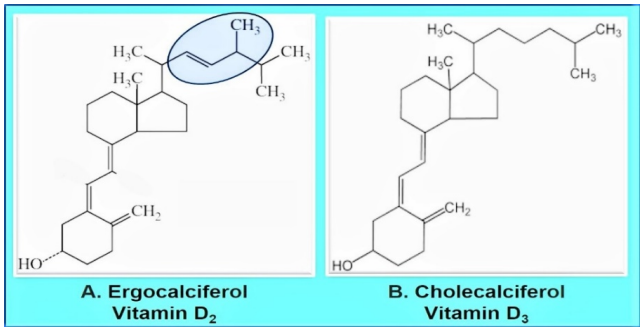

Figure 2: Molecular structures of vitamin D_2 and D_3.

The structure 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

The gradual process of changing skin color in humans has evolved over thousands of years to maximize survival and protect humans from diseases [53]. When people started to migrate north from Africa, the insufficient sunlight (UVB exposure) became a major reproductive and survival disadvantage. Consequently, those who developed lighter skin color through mutagenesis of melanin generating genes, had an overwhelming survival advantage in less sunny climates; the beginning of the white race (Caucasians). In evolutionary terms, geographic location and lighter degrees of skin pigmentation have permissible to generate optimal quantities of vitamin D in individuals; 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. Whereas, as humans moved away from the equator, paler skin facilitated increased synthesis of vitamin D in the skin. Unfortunately, paler skin also increases the risk of sunburn and skin cancer (especially those with skin-freckles), and high UV exposure enhanced cell division and an increase need for DNA repair. This increases the demand for folate, while enhanced melanogenesis reduces the need for folate in those with darker skin [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, biology, and physiology of this key secosteroid hormone generation and its physiological actions will help clinicians determine the best way to guide patients to obtain improved or optimal clinical outcomes. In target tissues, intracellular 1,25$(OH)_2$D acts as a paracrine and autocrine signaling: a cell produces and secretes a hormone or messenger that has its effects within that cell. However, 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 bone turnover.

Vitamin D deficiency leads to increased secretion of PTH (i.e., secondary hyperparathyroidism), higher bone turnover, and the consequent loss of bone mineral content [58,59]. In addition, suboptimal 1,25$(OH)_2$D levels decrease intestinal calcium absorption and increase urinary calcium loss [60]; overall causing a negative calcium balance.

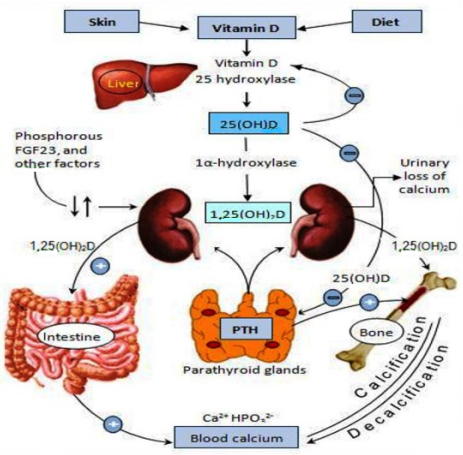

Figure 3: The interactions and pathways for generating vitamin D, 25(OH)D, and 1,25$(OH)_2$D.

The common path of activation of skin-derived and oral/dietary vitamin D to its active hormonal form, 1,25$(OH)_2$D. Although 25-hydroxylase activity is exclusive to the liver, conversion of 25(OH)D to 1,25$(OH)_2$D 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 renal handling 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 of authors, and the lack of properly designed RCTs with specific vitamin D-related primary outcomes.

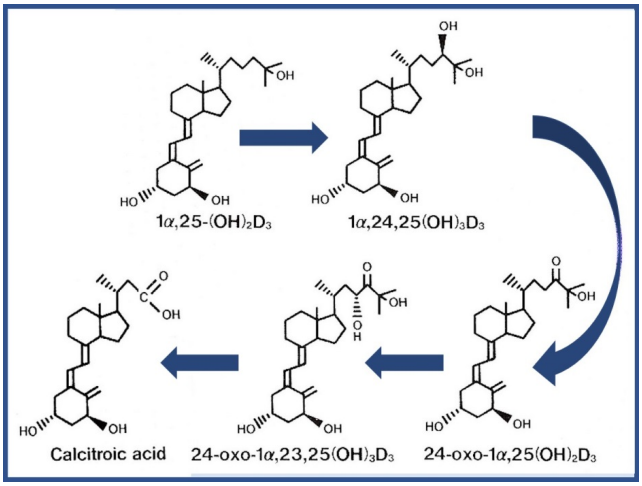

Figure 4: Catabolism of vitamin D.

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, these extra-renal production of vitamin-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 its intracellular concentrations and thus, the availability (Figure 4). Although the 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).

Catabolic pathways of vitamin D: The resulting biologically inactive 24-hydroxylated products are excreted as calcitroic acid through the biliary tract [23-hydroxylase pathway produces 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% [83,84]. 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, in which, 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 [85]. Similarly, in the renal tubular cells and in target cells, $1,25(OH)_2D$ generated in excess 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 happen in smaller quantities (Figure 4).

The paths of catabolism and 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) [85]. 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 children and osteomalacia in adults, as well as proximal myopathy [86]. In these systems, vitamin D influences the physiologic activities, such as maintaining calcium and phosphorus homeostasis, subduing autoimmunity and infections, controlling cell growth, innate and adaptive immunity, mitochondrial respiration, and metabolic activities [87-90]. Both type 1 and type 2 diabetes can lead to renal failure and resultant lowering of the generation of $1,25(OH)_2D$. Hypovitaminosis D, however, does not cause renal impairment, but the latter 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, etc.

What causes 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 a healthy adult. In addition, stored vitamin D quantity decreases with advancing age, especially during winter months, in those who live in locations far from the equator. Having gastrointestinal diseases, such as celiac and Crohn's disease, and cystic fibrosis reduces the capacity of the intestine to absorb vitamin D. Similarly, gastrointestinal surgeries, particularly bypass procedures, lead to low vitamin D status.

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 leads to reduced efficacy of vitamin D (i.e., reduced levels of activating enzymes). Thus, people with chronic liver or kidney diseases are at 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 of generation of active vitamin D (or biologically inactive form of the vitamin or enhanced catabolism), abnormalities of vitamin D-binding protein and/or VDR abnormalities. Any of these abnormalities/

syndromes can present with low vitamin D activity, but these disorders are rare; however, all need to be considered when assessing the vitamin D status/adequacy of an individual person.

Discussion and Conclusion

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, 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 many 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 [91,92]. 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, for persons with certain disorders, such as obesity, metabolic disorders, autoimmunity and cancer, may require higher levels; between 40 and 60 ng/mL. To achieve the mention levels, adequate exposure to UVB rays and/or vitamin D_3 supplements between 2,000 and 6,000 IU per day is required. It has been demonstrated that daily intake of 10,000 IU is safe [93]. Elderly, the obese, those who are taking medications that activate hepatic cytochrome P450 enzymes that enhance catabolism of vitamin, and during pregnancy and lactation, 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., >30 ng/mL) leads to a reduced incidence of many extra-musculoskeletal disorders, including diabetes [94-96], osteoporosis [97,98], multiple sclerosis [99], rheumatoid arthritis [100], and certain types of cancer [101-103].

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, and facilitates its intended positive or negative modulatory effects. These include enzymatic reactions, secretion of hormones, such as insulin and PTH, and the renin–angiotensin–aldosterone and FGF23–Klotho systems [104]. Meanwhile, data from metabolomics and transcriptomics promise the generation of improved longer-term extra-skeletal outcomes.

Vitamin D metabolism and actions are influenced by many medications, environmental pollutants, and physical activities/lifestyles, which also modulate the balance between energy intake and expenditure [105]. Cumulative evidence supports biological associations of vitamin D adequacy with disease risk reduction and improved physical and mental well-being [106]. In this regard, CYP27B1-mediated "target tissue" production of 1,25(OH)D was neglected till recently but is critically important. So, as the paracrine and autocrine functions of calcitriol is essential for full biological spectrum of activities of vitamin D.

While the number of diseases and disorders related to vitamin D deficiency is vast, the cost of investigating and managing the complications associated with disorders are extremely high. Maintaining serum 25(OH)D concentrations between 30 and 60 ng/mL would significantly reduce the severity of these diseases and prevent complications. This approach is highly cost-effective. The positive impact on benefits in humans and the economy of following public health approaches would exceed the benefits derived from, the combined targeting of infectious and parasitic diseases.

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