Achieving Optimum Clinical Outcomes with Vitamin D

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Contributor: Sunil J. Wimalawansa

Musculoskeletal benefits of vitamin D include calcium homeostasis, bone mineralization, etc., through its hormonal actions. This requires serum 25(OH)D less than 20 ng/mL. In contrast, many other tissues require above 30 or 40 ng/mL steady-state concentrations. To reduce infections, autoimmune diseases, cancer, and all-cause mortality require a minimum level of 50 ng/mL. Vitamin D is an economical and widely available (generic) nutrient obtained over the counter without a prescription. At the recommended doses, vitamin D does not cause any adverse effects. Disease prevention and minimizing complications and premature deaths can be achieved by maintaining serum 25(OH)D concentrations between 50 and 80 ng/mL. This costs less than 0.01% of the cost of one day of hospitalization.

Keywords: 25(OH)D ; 1,25(OH)2D ; immune system ; SARS-CoV-2 ; Human health ; Disease prevention ; Micronutrients ; Cost-effectve therapies

1. Introduction

Most people know the musculoskeletal benefits of vitamin D. This includes calcium homeostasis—intestinal absorption and phosphate and mineral conservation, skeletal calcification, and its effects on the muscular system [1][2]. The bone formation, resorption, and mineralization involved the hormonal form of calcitriol with parathyroid hormone (PTH) [3]: the latter is a crucial hormone influencing renal tubular calcium and phosphate handling [4].

In renal tubular, parathyroid, fat, and musculoskeletal cells, an in-built active system transports steroidal molecules, especially vitamin D and 25(OH)D—megalin-cubilin endocytotic system [5]. Because of this energy-dependent system, these cells can internalize such molecules against a concentration gradient [5]. Consequently, even when the serum 25(OH)D and vitamin D concentrations are between 12 and 20 ng/mL, renal tubular cells continue to extract these molecules from the circulation. This is why, despite such low levels (i.e., by definition, vitamin D deficiency), kidneys can generate the hormonal calcitriol and maintain most of the above-mentioned musculoskeletal functions of vitamin D, such as preventing rickets in children and osteomalacia in adults.

Most steroid hormones enter cells via diffusion and endocytosis via the membrane-based, megalin-cubilin system, as in the kidney and parathyroid gland, muscle, and fat cells [5]. In addition, this mechanism of active cellular entry is essential for generating the hormonal form of calcitriol in renal tubules and parathyroid glands—for vitamin D's endocrine functions [3][5]. However, unlike the cells mentioned above, other peripheral target cells, like immune cells, do not have an active vitamin D megalin-cubilin transportation system [6]. Thus, in addition to some endocytosis, these cells mainly depend on a concentration-dependent gradient for diffusions of vitamin D and 25(OH)D (mostly bound to VDBP) into them [7].

2. Extra-Skeletal Benefits of Vitamin D

The biological activity of calcitriol in most extra-musculoskeletal tissues is activated following the generation of calcitriol within peripheral target cells—not via the circulatory hormonal form. In addition to genomic functions in these cells, it acts as a local cytokine and signaling molecule. The genomic functions include controlling the proliferation and maturity of cells, preventing cancer cell growth, brain development, respiratory and reproductive functions, and mitochondrial energy generation [8][9][10][11]. Vitamin D maintains a robust immune system, which helps to overcome infections, including COVID-19 [12][13][14], and prevents autoimmunity [15][16]. Calcitriol's primary life-saving extra-skeletal role is keeping a person healthy [17][18].

Extra Musculoskeletal Benefits of Vitamin D—Dissemination of Information

Large emerging data sets support multiple physiological vitamin D functions occurring via calcitriol. These data suggest vitamin D should considered for preventative and adjunct therapy for many disorders, including sepsis and COVID-19 infection [19][20][21][22]. With a handful of exceptions [23], vitamin D is almost never included in clinical protocols or

guidelines. No leading health authorities or governments advised their fellow citizens to keep them healthy by providing proper advice on micronutrients, especially vitamin D [11]. What they have provided is grossly outdated [24][25][26][27][28].

In addition, recommendations from medical and scientific societies are confusing, contradictory [29][30], and out-of-date [31][32]. Despite this negative publicity, public awareness of vitamin D and its beneficial effects on the immune system has improved since the COVID-19 pandemic. This is primarily due to relentless positive work by individuals and small groups of scientists, although the negative publicity by big pharma. In contrast, clinical guidelines from the Front-Line COVID-19 Critical Care Alliance [23] and affirmative Substack articles provided reliable data to the public [33].

3. Mechanisms and Clinical Relevance

Sufficient calcitriol synthesis within immune cells prevents chronic diseases, autoimmunity, inflammation, and infections [34][35]. These physiological actions manifest by several mechanisms, including suppressing inflammatory cytokines and increasing anti-inflammatory cytokines and anti-oxidative compounds [21][36]. Chronic diseases are associated with chronic inflammation, which maintains and gradually worsens the disease process [34]. In addition, calcitriol enhances the production and release of antimicrobial peptides, cathelicidin, and beta-defensin via its autocrine and paracrine actions. These antimicrobial peptides stimulate white blood cells, macrophages, and natural killer cells and direct the circulating viruses to macrophages to destroy them [37].

3.1. Mechanisms of Action of Calcitriol

Vitamin D signaling plays a crucial role in intrinsic defense against intracellular microorganisms via generating antimicrobial proteins like cathelicidin [35]. In addition, calcitriol stabilizes tight junctions of epithelial cells of the respiratory tract and cardiovascular system, protecting them from fluid leakage and viral dissemination into soft tissues [38][39]. **Figure 1** illustrates the generation of calcitriol and its broader actions. Notably, it demonstrates the critical difference between the actions of the hormonal form vs. the non-hormonal form of calcitriol (the bottom half).

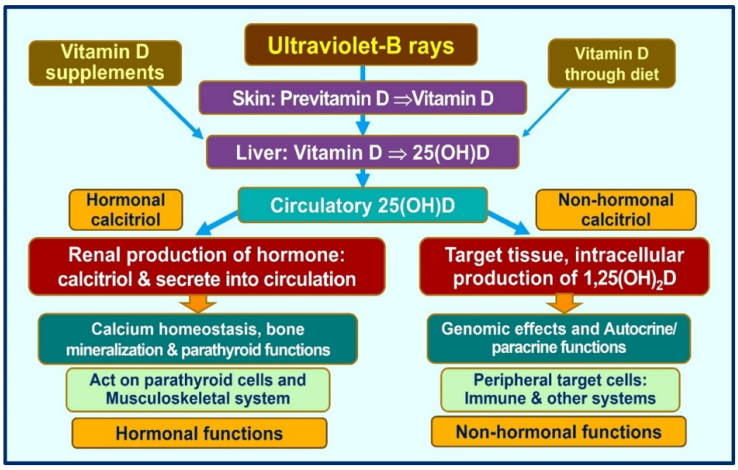

Figure 1. Vitamin D is expected to be generated predominantly following exposure to ultraviolet-B (UCB) rays. The amounts of vitamin D obtained via diet are small supplements. Therefore, those not exposed to sufficient UVB exposure depend on vitamin D supplements for their health. The figure illustrated the main differences between the circulatory hormonal form of calcitriol (generated in renal tubular cells) vs. the intracellularly generated calcitriol in peripheral target cells (as in immune cells).

3.2. Importance of Circulatory Vitamin D and 25(OH)D for Target Cell Generation of Calcitriol

The past few decades have focused on cholecalciferol (D_3) in preventing musculoskeletal disorders [40]. However, in the past 15 years, several fundamental advances were made in researchers in understanding the biology and physiology of calcifediol and calcitriol. These delineate how and when to use them properly as therapies. Yet, as described above, the doses recommended are grossly inadequate, and no attempts were made to update them. Emerging evidence has provided more value in recent years, highlighting the importance of different vitamin D compounds in human biology and clinical immunology [5]. While the musculoskeletal system functions maintained with smaller doses, of between 800 and 1,000 IU/day, higher amounts, like 5,000 to 10,000 IU per day or 50,000 IU once a week are necessary for a non-obese 70 kg adult, to maintain serum 25(OH)D concentrations above 50 ng/mL—that needed to overcome infections [6][13] and overcome cancers [41][42].

Those who are obese, taking medications that increase catabolic activity of vitamin D (e.g., anti-epileptic and retroviral agents), or have significant fat malabsorption require severalfold higher doses than those mentioned above. Even with such amounts, unless a loading dose is administered [43][44], a vitamin D-deficient person takes several months to increase their serum 25(OH)D to therapeutic levels of over 50 ng/mL [6]. Using the mentioned doses of vitamin D, even in a vitamin D-sufficient person to reach and maintain a serum 25(OH)D concentration of above 40 ng/mL (as guidelines for community-dwelling persons) would take a few weeks to raise serum 25(OH)D concentration above 50 ng/mL [13]. Therefore, such doses could be insufficient and ineffective to achieve the desired target serum 25(OH)D concentration in emergencies. Consequently, even moderately high daily doses without administering an upfront (one-time) loading dose are unlikely to significantly benefit a person in overcoming critical disorders like infections, sepsis, and cancer.

4. Doses of Vitamin D Needed to Overcome Disorders

Serum 25(OH)D concentrations are reduced in chronic diseases like metabolic disorders, obesity, cancer, infections, and all-cause mortality [45][46][47][48][49]. Less frequent administration—intervals of less than once a month—(i.e., intermittent bolus dosing) and even repeat administration of higher doses, like 300,000 once in six months, do not generate the intended clinical outcomes and thus should be avoided. This is because the half-life of vitamin D is about one day, and 25(OH)D is between two to three weeks, depending on the vitamin D status. No matter the dose, the serum 25(OH)D concentration would not remain high enough for more than three months [50][51][52]. In addition, infrequent administrations lead to unphysiological fluctuation of serum and tissue levels of vitamin D metabolites and could stimulate catabolic enzymes, like 24-hydroxylase (see below).

4.1. Clinical Study Outcomes Using Higher Doses of Vitamin D

Meta-analyses of RCTs concerning vitamin D supplementation reported a significant reduction in the incidence and severity of respiratory tract infections. Daily vitamin D supplements provide better clinical outcomes than with infrequent administration. In contrast, when vitamin D is administered at longer intervals than once a month, benefits are less, and the outcomes are not satisfactory [53][54].

Using higher doses of vitamin D consistently has been reported to have better clinical outcomes than the government-recommended doses of 800 IU/day, which has no tangible effect on any disease other than muscular skeletal disorders [26][55]. For example, adequate supplementation with vitamin D reduces cancer [49][56], regress prostate cancer [57], lowers blood pressure (especially in African Americans) [58], and reduces insulin resistance [59][60], including in obese children [61], and prevent multiple sclerosis [62][63].

However, those studies that used pediatric doses of vitamin D in adults based on outdated recommendations (i.e., using 280 IU/day or less than 1,000 IU/day) [64][65], as with the Women's Health Initiative study of cancer prevention and infrequent administration of 100,000 IU vitamin D_3 quarterly [66], failed to prevent cancer and other disorders. Based on vitamin D biology and physiology, this is not surprising. Most clinical studies reported an inverse association between vitamin D status and mortality [48][67], and the relation is curvilinear [31].

4.2. Entry of D and 25(OH)D into Peripheral Target Cells

In peripheral target cells as immune cells, genomic action follows binding to vitamin D/calcitonin receptors, and non-genomic functions, like intracrine/autocrine and paracrine signaling/functions of calcitriol, are driven by calcitriol synthesized within these cells. In these peripheral target cells, calcitriol is synthesized by 1a-hydroxylase enzyme, transcribed by the CYP27B1 gene. This hydroxylation of 1a-position, however, is dependent on the ability to diffuse enough vitamin D and 25(OH)D from the circulation [6][13]. This mainly occurs via the diffusion of these two molecules across the cell membranes, which is crucial for all immune cell activities. This is the prime reason why, in contrast to musculoskeletal tissues, peripheral target cells (tissues) need higher circulatory 25(OH)D concentrations.

In addition to diffusion, a smaller proportion of VDBP-bound D and 25(OH)D enters these cells via endocytosis [68]. Since the affinity of vitamin D to VDBP is less than 25(OH)D, given the same concentration in the blood, more D is likely to enter immune cells. However, since the half-life of vitamin D is only one day, the total entry of D is still less than 25(OH)D. **Figure 2** illustrates the mode of vitamin D and 25(OH)D access in peripheral target cells, like immune cells [13]. This entry of vitamin D and 25(OH)D from the circulation into immune cells allows the generation of calcitriol intracellularly [31], which is crucial for both genomic, autocrine, and paracrine functions of immune cells and other peripheral target cells [14][69][70][71].

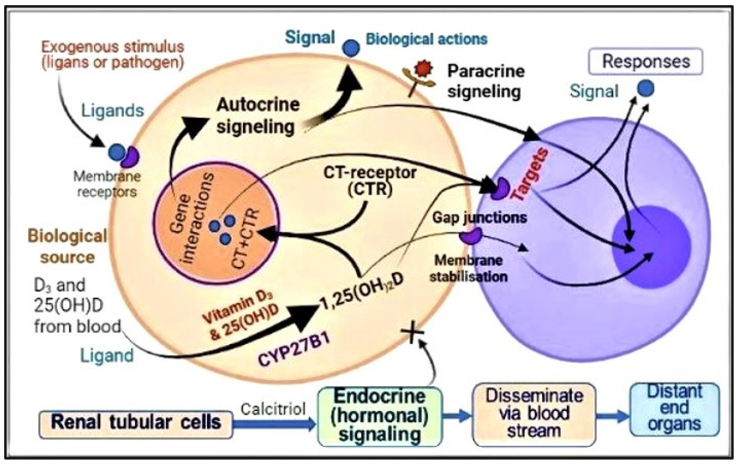

Figure 2. Pathways and mechanisms of actions of calcitriol activating immune cell functions: Activation of D and 25(OH)D into calcitriol [1,25$(OH)_2$D] intracellularly leads to genomic actions, autocrine (activation of functions within the same cells) and paracrine (indicating cell to effector cells) signaling.

When vitamin D is taken daily, the circulatory vitamin D concentrations are more stable and likely higher than 25(OH)D concentrations than when the same dose is taken once in two weeks or monthly [31]. Therefore, more vitamin D is likely to diffuse into peripheral target cells because of the higher concentration gradient of D with daily doses than 25(OH)D. When this is the case, the measurement of serum 25(OH)D alone, as done in routine clinical practice today, may not provide the correct information about vitamin D adequacy or guide the replacement requirements for physiological functions, including maintaining a robust immune system. The opposite happens when the same dose of vitamin is consumed infrequently; a higher concentration of 25(OH)D is present in the circulation than in vitamin D.

4.3. Vitamin D, Epithelial Barriers, and Gap Junction Stability

D_3 enhances epithelial and endothelial stability, independent of canonical pathways through calcitriol/CTR-derived genomic outcome [72]. Disruption of endothelial stability and an enhancement of vascular leak is prevented by D_3 supplementation. These rapid membrane-related actions of vitamin D, 25(OH)D, and 1,25$(OH)_2$D, are at a similar potency.

The deficiency of D_3 and its metabolites impairs endothelial barriers, leading to vascular fluid leakage into soft tissues [72]. Similarly, weakening gap junctions and epithelial barriers lead to viral infiltration and propagation of infections, as seen in sepsis and viral infections like SARS-CoV-2 [73]. These non-transcriptional (non-genomic) mechanisms are essential in controlling inflammation and preventing endothelial and epithelial cell destabilization.

5. Novel Information Related to Clinical Aspects of Vitamin D

5.1. Amounts of Daily Vitamin D Doses Needed to Maintain Clinically Effective Serum 25(OH)D Concentrations Cover 99.5% of Disorders

Different dosing schedules have varied effects on serum vitamin D and 25(OH)D concentrations—daily doses (but not infrequent doses) maintain a stable circulating concentration [74]. In contrast, ingesting vitamin D longer than monthly intervals results in significant circulatory 25(OH)D concentration fluctuations, which is not physiological and may not benefit [53][75][76]. Schedules recommended below for vitamin D supplementation as prophylactic and longer-term RCTs in hypovitaminosis D will significantly increase (at least double) the serum D and 25(OH)D concentrations, thus profoundly affecting intended beneficial clinical outcomes. A simplified formula is illustrated below for calculating the vitamin D dose for an individual based on BMI (body weight and fat mass) for different body weight groups [6][13].

Not obese (average wt.: BMI, <29): 70-90 IU/kg BW

Moderately obese (BMI, 30-39): 100-130 IU/kg BW

Morbid obesity (BMI, over 40): 140-180 IU/kg BW

5.2. What has Changed Over the Years Related to Vitamin D?

A century ago, it was observed that exposure to sun rays *(vitamin D)* reversed rickets in children, and it was effective against tuberculosis. Since then, much scientific evidence has demonstrated that vitamin D is central to disease prevention, complications, and deaths [77]. Previously, it was believed that exposure to sufficient UVB rays generated

about 3,000 IU/day. However, recent data confirmed a person with a lighter skin color could generate up to 10,000 IU of vitamin D_3 within one hour following exposure of a third of the upper body to sunlight [78][79][80].

Maintaining a steady state of D and 25(OH)D in circulation is helpful for physiological functions. In contrast, marked fluctuating serum 25(OHD concentrations from intermittent administration of high doses of vitamin D is unphysiological. Such could over-express the catabolic enzyme, 24-hydroxylase enzyme (via CYP24A1). Based on the circulatory half-life, the frequency of administration of vitamin D must not exceed once a month, preferably not more than two-week intervals [76]. This would avoid significant fluctuations in serum 25(OH)D concentration [53][75].

Most of the positive respiratory tract infections-related RCTs are conducted in children [42][43][57][58][59], using daily doses of vitamin D [46][47][81]. Meta-analysis of RCTs on vitamin D in respiratory tract infections reported that vitamin D is more effective as a treatment when administered in daily doses than intermittently [82]. Chronic diseases are most common among older people partly due to longer-term vitamin D deficiency [83] and are associated with an increased rate of deaths [67][77]. They also have multiple co-morbidities associated with hypovitaminosis D and low circulating ACE-2 receptors, increasing the vulnerability to infections and other pathological ailments (**Figure 3**).

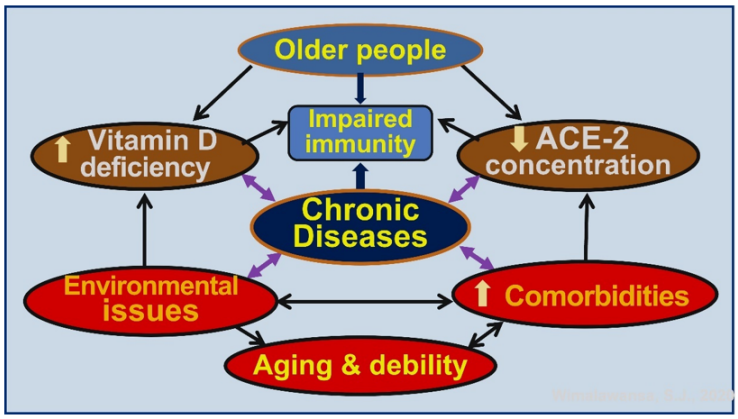

Figure 3. Schematic representation of how chronic diseases increase morbidity and mortality in older people. These are exacerbated by hypovitaminosis D, low angiotensin converting enzyme-2 (ACE-2) concentrations, environmental issues/pollution, and co-morbidities.

6. Discussion

The current paradigms related to vitamin D are primarily based on retrospective analyses and epidemiological studies (cohort, cross-sectional, observational, prospective, and ecological studies) [5][31]. Many have used false concepts and assumptions of doses and serum 25(OH)D concentration needed to improve outcomes based on outdated information [31][84]. In contrast, recent reports overwhelmingly support the positive effects of vitamin D in extra-musculoskeletal disorders, including chronic diseases and infections.

During the past decade, many advances were made in understanding the physiology and biology of vitamin D and its receptor ecology. The knowledge of the physiology of D_3 and vitamin D–VDR has advanced the understanding of the biology, metabolism, and effects of gene polymorphisms on the vitamin D axis. Data pointed towards the need for a minimum serum 25(OH)D concentration of 50 ng/mL for extra-musculoskeletal target cell physiological activity. It will take time to incorporate such into vitamin guidelines and recommendations.

Evidence supports strong physiological associations of vitamin D with disease risk reduction and improved physical and mental functions. Together, these data have facilitated the understanding of new rationale to prevent and treat diseases cost-efficiently. Overall evidence suggests that vitamin D deficiency, as determined by maintaining serum 25(OH)D concentrations of more than 40 ng/mL, is associated with increased risks of many illnesses and disorders and higher all-cause mortality, even among otherwise healthy individuals. The proper functioning of the vitamin D endocrine, paracrine, and autocrine systems is essential for many physiological activities and maintaining good health.

Recent data from epidemiological, cross-sectional, and longitudinal studies support that having physiological serum concentrations of 25(OH)D, levels greater than 40 ng/mL, significantly reduces the incidence of extra-musculoskeletal disorders. The latter includes diabetes, MS, rheumatoid arthritis, osteoporosis, autoimmune diseases, and certain types of cancer [49], as well as reducing all-cause mortality.

The dosages of vitamin D prescribed for non-obese deficient persons of average weight of 70 kg should be between 4000 and 7000 IU/day, 20,000 IU twice a week, or 50,000 IU once a week or once in 10 days. Such doses would allow approximately 97.5% of people to maintain their serum 25(OH)D concentrations above 40 ng/mL [5][30]. However, intermittent doses at intervals longer than once a month are unphysiological and thus ineffective. Daily vitamin D supplements are more beneficial than supplementation administered less frequently.

Furthermore, some medications, environmental pollutants, and physical activities/ lifestyles influence vitamin D metabolism and actions, modulating the balance between energy intake and expenditure. However, using vitamin D analogs is inappropriate for alleviating hypovitaminosis D or treating osteoporosis. In the absence of adequate exposure to sunlight, average-weight non-obese individuals require daily vitamin D intake (food plus supplements) of between 5000 and 7000 IU to maintain serum 25(OH)D concentrations above 50 ng/mL (125 nmol/L). Longer-term maintenance of a steady state of the serum 25(OH)D concentration is necessary to have a meaningful impact on reducing disease incidences and all-cause mortality.

Clinical practice recommendations should be geared toward healthcare professionals and the public, patient education, and informing the public regarding appropriate actions for avoiding micronutrient deficiency. However, most countries neither have policies or guidance on sun exposure and vitamin D intake nor cost-effective public health interventions, especially for micronutrients. They should consider embracing cost-effective measures to prevent diseases, significantly reducing healthcare costs.

Maintaining serum 25(OH)D concentrations above 50 ng/mL improves overall health and reduces the severity of chronic diseases, infection and autoimmunity, and all-cause mortality. Furthermore, it minimizes infection-related complications, including COVID-19-related hospitalizations and deaths. Vitamin D sufficiency is the most cost-effective way to reduce illnesses, infections, and healthcare costs. It should be a part of routine public health and clinical care.

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