Vitamin D–Practical Considerations and Clinical Guidance

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Abstract

Empirical evidence establishes the connection between exposure and clinical outcomes. Clinical studies show that chronic diseases and infections can be prevented by proactively correcting vitamin D deficiency in individuals who are vitamin D deficient, and in the community. In RCTs, with proper daily or once-a-week vitamin D supplementation in the intervention group, the serum 25(OH)D concentration must be meaningfully increased to the above pre-planned level to ensure the validity of the clinical study. Clinical outcomes correlate well with the serum 25(OH)D concentrations but not necessarily with the administered doses. It is a common error by researchers and healthcare workers to assume that the amount taken automatically produces the stipulated serum levels.

Keywords: morbidity ; mortality ; 25(OH)D

1. Vitamin D is a Threshold Nutrient

Vitamin D is also a threshold nutrient; thus, its beneficial effects can be demonstrated only in those deficient in vitamin D [1]. Unlike pharmaceutical agents, in those who are vitamin D sufficient, no matter how high the doses provided, no additional benefits are demonstrable [2] [with a few exceptions (disorders)]. Adequately powered RCTs, conducted in vitamin D-deficient subjects for sufficient duration, using proper doses of vitamin D (daily or once a week) almost always provided positive results [3][4][5][6][7]. Those investigated for vitamin D deficiency-related primary clinical outcome(s) (i.e., testing a hypothesis—with pre-determined serum 25(OH)D concentrations and health benefits) reported substantial benefits following the correction of vitamin D deficiency [8][9][10]. This is fully applicable to routine clinical practice.

Well-designed, statistically powered, properly conducted clinical studies invariably reported significant risk reductions, including for SARS-CoV-2 infection and complications [11][12][13]. Maintaining serum 25(OH)D concentrations above 50 ng/mL boost and maintain a robust immune system that lessens the risks from SARS-CoV-2 infection and its complications. This alters “cause-and-effect,” leading to better clinical outcomes (Koch’s postulates). This data provides strong evidence for a causal relationship between vitamin D and its physiological effects, as demonstrated in many studies, including UK BioBank data [14][15][16].

2. Adverse Effects of Vitamin D are Rare

Toxicity from vitamin D manifests exceptionally rarely. It could happen after consuming very high amounts (e.g., daily intake above 40,000 IU/day by a non-obese 70 kg person) for prolonged periods. It has been demonstrated that daily oral vitamin D doses of up to 15,000 IU are safe (up to 25,000 in obese persons) [17] and devoid of adverse effects [18]. Reported data, however, suggest that daily doses greater than 20,000 IU may overcome feedback control of calcium absorption, which could lead to excess circulatory calcium levels.

While adverse effects are rare, a few reported cases of vitamin D toxicity were due to mistaken doses or accidental use. Because of the built-in feedback control mechanisms within the skin, excessive exposure to UVB from sunlight does not cause vitamin D overproduction or toxicity. These rescue vitamin D catabolic pathways will divert the vitamin D metabolism to inert compounds such as 24(OH)D, 24,25$(OH)_2$D, and other inactive metabolites [19].

Nevertheless, protecting the eyes and face from sun exposure is recommended to avoid harm. Besides, excessive exposure to sunlight could increase skin damage risk and skin cancer [20][21]. However, the latter predominantly occurs in those with genetic vulnerability, like White Australians with freckled skin patterns. It is noteworthy that persons with morbid obesity, gastrointestinal absorption issues (e.g., following gastric bypass surgery), or those who are vitamin D resistant need much higher daily doses.

3. A Small number of People Require High Doses to Alleviate Intractable Symptoms

Data supports that a petite proportion of the population (i.e., less than 0.01%) requires very high doses of vitamin D to achieve and maintain high serum 25(OH)D concentrations, leading to a significant response rate. In these specific conditions, the circulatory 25(OH)D concentrations need to maintain above 80 ng/mL, up to 130 ng/mL. Such rare diseases include drug-resistant migraine or cluster headaches, multiple sclerosis, psoriasis, asthma, etc. [18][22][23][24]. During infectious pandemics and endemics, serum 25(OH)D concentrations also needed to be kept higher (between 50 and 80 ng/mL), somewhat higher than the generally recommended concentrations [25][26]. Such high doses were reported to alleviate intractable symptoms significantly and alleviate some of them.

Examples include intractable migraine headaches, asthma, psoriasis, specific autoimmune reactions, tissue/organ graft rejection, and vitamin D-resistant syndromes. These persons must be treated by specialists in this field, under their close medical supervision, to maximize benefits and minimize adverse effects. As per common sense and medical ethics, healthcare workers must strike a safe, right dose for a given condition to obtain maximum benefits while avoiding adverse effects.

4. Diagnosing Vitamin D-Related Toxicity

Hypervitaminosis D-induced toxicity should not be diagnosed solely based on elevated 25(OH)D levels. Instead, it should be recognized as a clinical syndrome in the presence of hypercalcemia, suppressed PTH, and hypercalciuria in conjunction with markedly elevated serum 25(OH)D levels (>150 ng/mL). The rare occurrence of vitamin D-related symptomatic adverse effects, such as hypercalcemia and hypercalciuria, could result from individuals taking extremely high doses of vitamin D (especially activated vitamin D analogs) for a prolonged time or taking substantial amounts inadvertently. The clinical signs and symptoms of vitamin D toxicity include hypercalcemia (e.g., nausea, dehydration, irritation (dryness) of the eyes, confusion, constipation, and electrocardiographic abnormalities), irritability, and hypercalciuria (generally reflected as polyuria and kidney stones).

Asymptomatic elevation of 25(OH)D without hypercalcemia needs to be investigated for the etiology of increased vitamin D levels. Unlike hypercalcemia (i.e., higher ionized calcium in the blood), increased vitamin D [25(OH)D] levels are not a medical emergency. If the issue is too much intake, it is essential to stop taking vitamin D supplements, including multivitamins and calcium supplements. Lower doses of vitamin D supplements can be restarted once the 25(OH)D level reaches a low normal range with modification of the amount and diet. Most patients with vitamin D toxicity have serum concentrations greater than 150 ng/mL (majority over 200 ng/mL).

Data indicate that regimens of vitamin D supplementation with 10,000 IU/day or 50,000 IU bimonthly (even weekly) are not associated with any laboratory or clinical variables of toxicity (manifested as serum calcium, bone alkaline phosphatase, and 24-h urine calcium), confirming the safety of such regimens [27]. Eleven patients with symptomatic hypercalcemia caused by hypervitaminosis D had taken supplement doses greater than 50,000 IU/day for a longer time, or 600,000 IU (injectable form) too frequently for various ailments, including back pains, osteoarthritis, or osteoporosis, for several months. Such toxicity is easily avoidable [28][29]. In rare occasions, macrophage-driven, autonomous production of $1,25(OH)_2D$ may occur in granulomatous tissues. A lack of feedback control of the 1α-hydroxylase enzyme in granulomas, such as sarcoidosis and tuberculosis, could cause hypercalcemic syndrome [30][31].

5. Personal Vitamin D Response and Targeted Serum 25(OH)D Concentrations

Standardized technology used in clinical practice assesses vitamin D status by measuring serum 25(OH)D—the predominant circulatory and storage form [32]. Unless in renal failure or unusual circumstances, there is no rationale for measuring $1,25(OH)_2D$ (calcitriol) concentrations in blood. Average serum concentrations of 25(OH)D and $1,25(OH)_2D$ are essential for optimal musculoskeletal and soft tissue health. However, the circulating physiologic calcitriol concentrations are unrelated to most extra-skeletal tissue functions and, thus, do not affect the biological functions of peripheral target cells, such as immune cells. Consequently, what matters for extra-skeletal body systems is having adequate concentrations of vitamin D or 25(OH)D in the circulation, enabling them to diffuse into peripheral target cells, which is crucial for their physiological functions [2][7].

While a personal vitamin D response index may provide better guidance for optimizing vitamin D supplementation for individuals than broader population-based recommendations [33][34], it is associated with unnecessary and unjustifiable costs, which prevents its use. Such an index could be helpful only if performed inexpensively, like finger-stick blood sugar

measurement [35]. Even if an index and testing provide theoretical benefits of a targeted increase of serum 25(OH)D concentration, such results may be difficult to sustain. While an exciting hypothesis, currently, it is not a useful practical utility.

Circulating 25(OH)D sufficient for target tissue cell activation of calcitriol (and indirectly, VDR) allows beneficial modulatory effects on cellular functions, especially mitochondrial activity, enzymatic reactions, and hormone synthesis and secretion. Examples of the latter include insulin PTH, renin–angiotensin–aldosterone, and FGF23–Klotho system. In conjunction with well-designed, adequately supplemented clinical studies, data from metabolomics and transcriptomics would provide better information on longer-term extra-skeletal benefits. In addition, adequate vitamin D supplementation allows personalized and targeted measures to reduce skeletal and soft tissue health risks cost-effectively [36][33].

6. Vitamin D Deficiency Increases Vulnerability to SARS-CoV-2 Infections

Evidence strongly supports that low vitamin D status increases the rates of infections, complications, and mortality rates for intracellular bacterial diseases such as tuberculosis and viral respiratory illnesses in both children [37] and adults [38][39], including from SARS-CoV-2 infection [3][4][5][6][7]. In addition, pre-existing vitamin D deficiency increases the risks of SARS-CoV-2 infection [11][12][13], its complications [12][40][41], hospitalizations [14][15][16][42][43], and deaths [41][44][45][46][47]. In contrast, proper doses and frequency of vitamin D supplements in deficient persons significantly reduce risks for infections, complications, and deaths from SARS-CoV-2 [11][12][13][14][15][16][40][41][42][43][43][46][47].

Reported data validate Bradford Hill's criteria for causation of diseases [48]—Hypovitaminosis D increases the vulnerability to SARS-CoV-2, increasing complications and deaths. Vitamin D deficiency causing cancer [49][50][51], multiple scleroses [52][53], the risk of contracting SARS-CoV-2 infection [11][12][16][54][55][56], and the severity [57], and the vulnerability and complications for SARS-CoV2 [4][5][6][7][11][12][13]. Further, the crucial mechanism of action of intracellular calcitriol in immune cells supports the biological plausibility that low vitamin D increases the risks for infections, including SARS-CoV-2 [46][51][57][58][59][60][61]. In addition, data demonstrated that vitamin D significantly reduces complications and deaths from SARS-CoV-2 [11][12][13][14][15][16][40][41][42][43][46][47][59][61].

7. Issues with Published RCTs and Limitations of Data and Interpretation

Adequately powered, well-designed epidemiological studies and RCTs that used adequate doses of vitamin D supplementation to achieve a predefined target serum 25(OH)D concentration in subjects with hypovitaminosis D reported favorable outcomes. Such studies have demonstrated the importance of maintaining an optimum serum 25(OH)D concentration for normal physiologic functions and improved quality of life. While in some areas, definitive evidence is lacking, it is mainly due to published RCTs with major study design errors. The overall data support the protective effects of vitamin D in humans when 25(OH)D serum concentration is maintained above 50 ng/mL [2]. From the practical and community's point of view, the goal for sufficiency should be above 40 ng/mL to achieve a balance.

As described above, there is little evidence from RCTs regarding the optimum serum 25(OH)D levels for preventing various disease-related complications. This confusion derives from the non-standardized, poorly designed clinical studies using different serum 25(OH)D concentration targets or no targeted serum 25(OH)D concentrations and attempted to correlate clinical outcomes with administered dose than with what achieved (or effective) circulatory concentrations [62]. These confusions partly derived from failing to understand that vitamin D is a threshold nutrient [1][63][64], not a synthetic pharmaceutical agent. This major misunderstanding exists even in extensive and expensive, public-funded vitamin D RCTs and almost all pharma-designed vitamin D-related RCTs, as they have done for pharmaceutical agents [1][2].

Irrespective of the number of participants enrolled in recent RCTs, as in the case of the US taxpayer-funded VITAL study [65][66], because of its poor study design led to disarray because of poor study design [67]. Before studies commenced, we formally informed these fatal errors to relevant senior officials of NIH—the agency that funded this study but that opted not to rectify those errors. Adequately powered studies with an appropriate format and suitable study duration recruited 25(OH)D deficient participants. The target serum 25(OH)D concentrations achieved and maintained during the RCT allow proper testing of specific vitamin D-related hypotheses [2]. While such studies are not so frequent, they have ubiquitously demonstrated the protective effects of vitamin D [68].

Future vitamin D-related clinical studies must target predefined serum 25(OH)D concentrations for statistical correlations and use vitamin D supplementation as the only (or at least as the key) intervention to address vitamin D-related risk reductions as the primary hard endpoint specifically. Despite the accumulating data, awareness lags behind the beneficial

effects and the optimal serum 25(OH)D concentrations concerning humans in non-musculoskeletal diseases [21][69]. Disagreements abound regarding optimal serum 25(OH)D concentrations, recommended oral supplementation doses, properly designed and adequately powered randomized clinical studies (RCTs), and outcome data.

Some authors of RCTs and meta-analyses repeatedly call for additional RCTs despite having plenty of well-designed published RCTs with firm conclusions about the advantages of vitamin D in specific disorders in vitamin D-deficient persons. Their only rationale is political reasons and to obtain new funding to justify their academic careers and increase publications. Consequently, it is fruitless to repeat such mindless jargon that 'more RCTs are necessary to make conclusions.' Such should not be included in RCTs, systematic reviewers, or meta-analyses. If the studies are insufficient, authors should not have done such analyses for publications. They should do better by designing and carrying out RCTs before engaging in unproductive and duplicate meta-analyses.

8. New Vitamin D Recommendations

Individual countries and scientific societies need to re-assess vitamin D guidelines to raise the recommended dietary allowance (RDA) of vitamin D, including higher amounts for food fortification guidelines and new targets to achieve better health for the public, as described above. Studies reported from Western Europe suggest that the use of such approaches may reduce the economic burden of common medical disorders, such as type 2 diabetes (T2D), cardiovascular diseases (CVDs), and cancer [70].

Steady-state serum 25(OH)D concentrations depend on vitamin D intake, body weight (BW), and total fat mass. While body mass index (BMI) (validated only for White Caucasians) is not a good indicator of body fat estimation in ethnic groups like Asians. However, it is still a helpful indicator encompassing fat and muscle mass and is readily available. Therefore, for calculating vitamin D dose for individuals, one can use either the BMI or the body weight, as illustrated below [71]. These simplified calculations are based on the detailed tables published in Nutrients in 2022 [71]. The following summarizes vitamin D dose calculation for an individual, applicable across all body weight groups.

1. **Not obese (average wt.: BMI, <29): 70-90 IU/kg BW**
2. **Moderately obese (BMI, 30-39): 100-130 IU/kg BW**
3. **Morbid obesity (BMI, over 40): 40-180 IU/kg BW**

All current vitamin D guidelines are based on decades-old concepts (some are false) and research; they are outdated. Based on recent data, raising the minimum and maximum serum 25(OH)D concentrations to 50 and 80 ng/mL, increasing the safe upper limit of intake to 15,000 IU/day, and the average daily intake of vitamin D based on 5000 IU for a non-obese 70 kg adult (70–90 IU/kg body weight) is logical. Such will significantly reduce disease and hospital burdens, healthcare costs, loss of productivity and absenteeism.

9. Discussion

The current paradigms related to vitamin D are primarily based on retrospective analyses, case reports, and epidemiological studies—cohort, cross-sectional, observational, prospective, and ecological studies) [72][73][74]. However, virtually all clinical research studies overwhelmingly support the positive effects of vitamin D outside the musculoskeletal body systems [75][76][77][78][79]. Despite using small amounts of vitamin D supplements in these studies, they reported positive results primarily due to the low serum 25(OH)D levels needed to achieve these endpoints (e.g., between 15 and 20 ng/mL).

During the past decade, significant advances were made in understanding the physiology and biological actions of vitamin D. Synthesis of these allowed demonstrations of mechanisms of action and how vitamin D reduces risks and improves general health and well-being. Together, these data have facilitated the understanding of new mechanisms and pathways of vitamin D (calcitriol) actions and means of effective interventions to prevent and treat human diseases.

The proper functioning of the vitamin D endocrine, paracrine, and autocrine systems is essential for many physiological activities and for maintaining good health. Based on the need for vitamin D intakes and circulatory concentration to reduce risks for most disorders, evidence suggests that serum 25(OH)D concentrations of more than 40 ng/mL. Below this, it would increase hazards of illnesses and disorders and all-cause mortality, even among otherwise healthy individuals [80].

Examples of the reduction of the incidence and the severity of disorders include diabetes [81][82][83], MS [84], rheumatoid arthritis [85], osteoporosis [86][87], autoimmune diseases [88], and certain types of cancer [89][90][91][92], and reducing all-cause mortality [80]. Based on the need for the circulatory 25(OH)D concentrations, the dosages of vitamin D intake needed for a non-obese 70 kg person is between 4,000 and 7,000 IU/day, 20,000 IU once or twice a week, or 50,000 IU

once or once in 10 days [93]. This requires maintaining serum 25(OH)D concentrations above 50 ng/mL (125 nmol/L). Such doses would allow approximately 97.5% of people to keep serum 25(OH)D concentrations above 40 ng/mL [74][94][95]. However, intermittent doses at intervals longer than once a month are unphysiological and thus ineffective [96][97]. Studies have shown that daily vitamin D supplements are more beneficial than supplementation administered less frequently [98][99][100][101][102].

Strategies to maintain sufficient circulating vitamin D concentrations include fortifying food, advocating safe sun exposure, and supplementing vitamin D. Diets provide little vitamin D; thus, one cannot depend on food to provide adequate vitamin D for most people. Clinical practice recommendations should be geared toward healthcare professionals and the public, guiding patient education and informing the public regarding appropriate actions to avoid the most prevalent micronutrient deficiency in humans.

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. Besides, it minimizes infection-related complications, including COVID-19-related hospitalizations and deaths. Vitamin D is the most cost-effective way to reduce chronic illnesses, infections, and healthcare costs. It should be a part of public health and routine clinical care.

Despite this, most countries do not have policies or guidance on sun exposure, vitamin D intake, or cost-effective public health interventions for micronutrients. Those countries with guidance are grossly outdated, like the USA, UK, and Australia. It is time to update guidelines based on research published within the last decade. In addition to updating their micronutrient guidelines/policies, all countries should consider embracing cost-effective measures to prevent diseases, significantly reducing healthcare costs.

10. Conclusions

Vitamin D deficiency leads to a weaker immune system with dysfunctional responses and higher rates and severity of infections, including SARS-CoV-2. Viruses and bacteria) harm humans when the immune system is weak. Maintaining circulatory 25(OH)D concentrations between 50 and 85 ng/mL will minimize most chronic diseases and infections. A strong immune system with micronutrients, especially vitamin D, prevents developing complications or dying from infections (at least from the current viruses). Continuing experimenting with gain-of-function research (by Big Pharma/Bioweapon labs) may change this horizon. Nevertheless, these agents invade and harm people only when the immune system is fragile. A robust immune system will overcome even bio-weapon-grade viral epidemics—the most cost-effective way to minimize harm to the population.

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