A Review on Vitamin D Deficiency and Related Disorders: What is the Right Serum Vitamin D Level?

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ABSTRACT

To maintain a healthy skeleton, vitamin D is crucial for phosphate as well as calcium uptake. It is of great significance for maintaining the various adaptive and innate immune response components. To reduce the development of various immune-related disorders, such as diabetes, hypertension, cardiovascular diseases, rheumatoid arthritis, and coronavirus disease 2019 (COVID-19), numerous studies evaluating the optimal threshold levels for serum 25-hydroxyvitamin D [25(OH)D]. It is documented in various evidence to increase the serum 25(OH)D intake from the current mindset of 30–50 ng/mL to attain the best overall vitamin D benefits. These values are in line with the various results of research showing that increased vitamin D intake is linked to a decreased risk of cancer and cardiovascular diseases. Therefore, it becomes vital to understand the “right” vitamin D levels to avoid deficiency along with its related disorders. In contrast to 30 ng/mL, this review emphasizes the significance of increasing vitamin D levels to 50 ng/mL to obtain several physiological benefits. An individual needs at least 60000 IU for 12 weeks to maintain serum vitamin D levels above 30 ng/mL. The article will interest physicians who desire to profit fully from vitamin D’s influence on clinical practice.

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INTRODUCTION

A crucial fat-soluble vitamin, vitamin D, is vital for maintaining calcium homeostasis. Its functions are multifold and help in sustaining bone health. The dietary source for vitamin D includes milk, red meat, egg yolk, and oily fish. It exists in two bioequivalent inert forms—ergocalciferol and cholecalciferol (D3). They are further converted to 25(OH)D (in the liver), a significant form of vitamin D that circulates. To maintain the physiological effects on the skeleton and extraskelatal tissues, adequate serum 25(OH)D levels are required. The total serum 25(OH)D level gives the best estimate of vitamin D supply in the body. Serum 25(OH)D levels are reported to be best between 30 and 80 ng/mL. Nevertheless, there may be disagreements regarding the definitions of insufficiency (30 ng/mL) and deficiency (20 ng/mL), with >30 ng/mL being seen as sufficient and 40–60 ng/mL being the ideal range or physiological range offering physiological benefits. Table 1 indicates the diagnostic cutoff level for serum 25(OH)D. The lack of vitamin D can raise the chance of developing rickets, osteoporosis, and other conditions like diabetes, cancer, tuberculosis, and heart problems.

Globally, vitamin D insufficiency is most pronounced in countries lacking food fortification programs. Also, in India, the problem is widespread, with high occurrence in young adults, pregnant and lactating women, and women above 50 years. The deficiency is widely spread over the Indian subcontinent, with a prevalence rate of 50–94%. Effects on the bones and musculoskeletal system are the most frequent consequences of vitamin D insufficiency. A recent study, however, indicates that vitamin D might also have an impact on other elements of health, such as asthma and respiratory infections. Nutritional rickets has become a source of concern for pediatricians worldwide. It is caused due to inadequate calcium intake in children. Also, dark-skin people with limited ultraviolet B exposure have a high chance of developing rickets. Adults with severe vitamin D deficiency may develop osteomalacia. Adults’ vitamin D levels should be closely monitored due to their significant impact on morbidities and high out-of-pocket expenditures. Babies born to pregnant women who are vitamin D deficient are more prone to have hypocalcemia and congenital bone disease.

Martineau et al. suggested that vitamin D insufficiency can potentially negatively impact respiratory outcomes. An estimated 1.7 million deaths are caused per year due to tuberculosis. Globally, 300 million people experience difficulties such as asthma, with over 2,50,000 causality. Therefore, reducing the prevalence of disease can significantly reduce overall global mortality. Vitamin D is assumed to aid in the prevention of Mycobacterium tuberculosis infection. A study demonstrated that a drop in vitamin D supplementation could increase the incidence of hypertension by 16%. This is because it is often conjectured that its deficiency raises blood pressure by stimulating the renin-angiotensin system. Vitamin D acts as a protective agent by accelerating apoptosis and preventing angiogenesis. Thus, vitamin D deficiency can be correlated with lung, breast, or colon cancer. Looking at the huge range of consequences, it becomes important to take measures to reduce the burden of its deficiency.

As already discussed, different limits have been defined for deficiency. This is because different aspects, such as genetics, age, calcium intake, obesity, and ethnicity, are taken into consideration. Though 30 ng/mL is the standard set for vitamin D sufficiency, changing world scenario suggests that 30 ng/mL might not be sufficient, and a switch should be made to a minimum of 50 ng/mL to maintain an optimum 25(OH)D levels. Studies show that 25(OH)D levels 30–50 ng/mL are linked with a reduced risk of nonskeletal diseases. It is suggested that in order to achieve parathyroid hormone suppression, 25(OH)D levels larger than 30 ng/mL are required. Despite extensive literature available on global vitamin D deficiency, physicians are not comfortable recommending larger doses of serum 25(OH)D levels. This can be due to the scarcity of reports on vitamin D toxicity and the fear associated with it. To obtain ideal 25(OH)D levels (40–60 ng/mL) with high-dose vitamin D supplementation, most adults (particularly the elderly, obese, and those with dark skin) will need substantially higher dosages (Table 2). A study suggested that patients receiving 25(OH)D levels greater than 30 ng/mL did not develop hypercalcemia. Thus, it becomes important
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Highlighting in this article, immunological-related disorders are also levels. The effect of vitamin D on the immune regimen to maintain the optimum serum

The table 2: Vitamin dose required for patients at risk for vitamin D deficiency. Adapted from — Holick et al.

<table>
<thead>
<tr>
<th>Individuals requiring high-dose vitamin D supplementation</th>
<th>Vitamin D dose</th>
<th>Maintenance therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obese adults</td>
<td>6000–10000 IU/day</td>
<td>3000–6000 IU/day</td>
</tr>
<tr>
<td>Individuals receiving anticonvulsant medications</td>
<td>6000–10000 IU/day</td>
<td>3000–6000 IU/day</td>
</tr>
<tr>
<td>Elderly (50–70 years or 70+ years)</td>
<td>1500–2000 IU/day</td>
<td>–</td>
</tr>
<tr>
<td>Lactating women</td>
<td>1400–1500 IU/day</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>4000–6000 IU/day</td>
<td>–</td>
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</table>

Vitamin D status | Serum level (in ng/mL) |
Severe deficiency | <10 |
Deficiency | <20 |
Insufficiency | 21–29 |

Serum 25(OH)D level from 30 to 50 ng/mL. Thus, a positive association can be

Optimal Serum 25(OH)D Levels in Various Chronic Health Conditions

Numerous immune-related disorders can be treated and prevented with the help of vitamin D. This section will elaborate on its role in various chronic health conditions such as bone health, infections, diabetes, hypertension, etc. A study proposed serum 25(OH)D levels between 36 and 48 ng/mL are advantageous in cancer prevention.11

Bone Health and Vitamin D

Vitamin D consumption and calcium absorption are positively correlated. According to a study by Gallagher et al., serum 25(OH)D levels increase from 20 to 66 ng/mL, leading to a 6% increase in calcium absorption.12 Vitamin D is significant for keeping bones healthy, and its deficiency may lead to bone demineralization with an increased risk of fractures. This is because, with decreased calcium absorption, it is released from the bones leading to osteomalacia and osteoporosis.13 It has been observed that 40–50 ng/mL serum 25(OH)D level improved muscle strength, reduced muscle fatigue, and increased bodily function in postmenopausal women. Peak 25(OH)D levels of 50 ng/mL are linked to optimal neuromuscular function. Various studies have pointed out the reduced occurrence of fracture when supplemented with vitamin D.14 Trivedi et al. observed a decreased first fracture rate in comparison to the placebo group when administered with 100000 IU D3. Four monthly supplements of 1,000,000 oral vitamin D helped in preventing fractures in both genders (<65 years). Additionally, there was a 22 and 33% decrease in the overall fracture incidence and fractures in significant osteoporotic locations, respectively.14 Hillstroms et al. investigated how postmenopausal women’s structure and function were affected by elevated vitamin D and calcium levels.15 A total of 26 postmenopausal women (with serum levels between 20 and 30 ng/mL) were enrolled in the study. They received serum concentrations between 40 and 50 ng/mL and serum calcium concentrations greater than 9.2 mg/dL. Results, including muscle strength and fatigue, postural balance, and the amount of time needed to complete functional tasks, were investigated. The results showed that vastus lateralis increased as serum levels rose, and the time needed to climb stairs decreased. Thus, the preliminary results indicated that enhancing vitamin D levels may augment muscle structure and functional task performance. Therefore, a clinical trial with a bigger sample size and control group is necessary. Another such study by Lolason et al. discovered that postmenopausal women with serum levels >30 ng/mL had improved physical performance, greater handgrip strength, and knee extension strength in comparison to the group with serum levels lesser than 30 ng/mL.16 Thus, a positive association can be found between bone health and serum levels.

Defense against Infections

As mentioned, vitamin D may enhance the overall immune response because of its ability to improve the functions of macrophages and dendritic cells.17 Deficiency can lead to respiratory and viral infections. With the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic spreading at an alarming rate, it becomes vital to understand the relationship between the virus and vitamin D. Supporting the immune system is one of vitamin D’s many crucial roles. It aids in lowering coagulation problems in COVID-19 patients and can lower the inflammation spread by reducing cytokine production.18,19 Cytokine release syndrome responsible for multiple organ failures in COVID-19 patients can be attenuated by vitamin D.20,21 Numerous studies have established the beneficial relationship between vitamin D supplementation and patients with severe COVID infections. The ideal vitamin D level is 125 nmol/L or 50 ng/mL 25(OH)D, which could prevent fatalities and lessen the effects on patients with comorbid conditions.22–24

Various studies also depicted that people having high vitamin D levels are unlikely to experience fatal outcomes of COVID-19. Thus, a lower threshold of 50 ng/mL of vitamin D could be recommended to reduce the impact in comorbid patients.24 A similar study pointed out that patients provided with 55 ng/mL of vitamin D displayed the least infections.25 Therefore, the data strongly suggest that the COVID-19 mortality risk is inversely correlated with vitamin D status and that at 50 ng/mL across latitudes, different races, ethnicities, sexes, and ages, a death rate close to zero may theoretically be obtained. Hence, the insinuations are huge and can provide a cheap alternative for preventing COVID-19 infection.25 This result was long established by Zhang et al., which demonstrated that serum levels higher than 30 ng/mL were sufficient to inhibit interleukin 6 and tumor necrosis factor a production by lipopolysaccharide and cytokine production in human monocytes.26 Directors of an Iranian hospital observed that patients with vitamin D levels above 40 ng/mL were released from the facility before 4 days had passed without hypercoagulation or cytokine storm.27 Lakkhiredy et al. demonstrated the use of pulse D therapy helps to lower the COVID-19 inflammatory cytokines. Vitamin D levels were found to be increased from 16 ± 6 ng/mL to 89 ± 32 ng/mL, and a highly significant decrease (p < 0.01) in assessed inflammatory markers was observed without any side effects. Thus, this method can be used safely to enhance the current COVID-19 treatment protocols.28 Hence, increasing the vitamin D supplementation to 50 ng/mL will not only help in strengthening the immune system but can also help in increasing the success of vaccination.

Vitamin D and Cardiometabolic Disorders

Type 1 diabetes prevention is another potential benefit of vitamin D. Furthermore, children with increased vitamin D ingestion have a reduced
chance of developing type 1 diabetes. A meta-analysis demonstrated that circulating 25(OH)D levels were negatively and significantly correlated with the risk of type 2 diabetes. Every 10 nmol/L increase in vitamin D levels was related to a 4% decreased incidence of type 2 diabetes, according to linear trend analysis \( p < 0.0001 \). According to a study, individuals with higher vitamin D (greater than 25 ng/mL) have a 43% lower chance of acquiring type 2 diabetes than individuals with less than 14 ng/mL. Vitamin D also reduces insulin resistance.\(^{29}\) Interest in vitamin D's involvement in cardiovascular health has grown significantly in recent years. The observational evidence suggests that the optimal range of serum 25(OH)D levels (20–50 ng/mL) may influence a reduction in cardiovascular disease events at both low (<50 nmol/L) and high (>50 ng/mL) levels of 25(OH)D.\(^{30}\)

According to a cohort study, individuals receiving <50 mmol/L vitamin D had increased chances of high blood pressure and hypertension after 6 years.\(^{31}\) Around >1 billion people have hypertension, and the number is expected to reach 29% by 2025.\(^{32}\) Studies have suggested it might be connected with low vitamin D levels.\(^{33}\) According to a meta-analysis, a negative correlation exists between 25(OH)D levels and incident hypertension, decreasing by 7% for every 25 nmol/L increase in 25(OH)D levels. As 25(OH)D declined, the risk of hypertension rose significantly below 75 nmol/L but remained substantial over the range of 75–130 nmol/L. Different studies suggest diverse opinions on vitamin D in hypertension. Therefore, additional randomized controlled trials (RCTs) are necessary to determine the optimum dose and dosing interval to validate its actual impact on hypertension.\(^{34,35}\)

Additionally, it has been demonstrated that a deficiency of vitamin D increases the risk of dyslipidemia.\(^{36,37}\) Dyslipidemia can be linked to increased plasma cholesterol or a low level of high-density lipoprotein cholesterol (HDL-C). This is further linked with a high chance of developing atherosclerosis. According to the study by Wang et al., this association is more prominently visible in males than females.\(^{38}\) A meta-analysis by Dibaba highlighted the beneficial effects of vitamin D on serum total cholesterol, triglycerides, and low-density lipoprotein-cholesterol. However, HDL-C showed no discernible impact. It is also evidenced that hypercholesterolemia patients with vitamin D insufficiency may benefit from increased vitamin D levels.\(^{39}\)

### Table 3: Different studies highlighting dosage regimens to comprehend the role of vitamin D in overall health

<table>
<thead>
<tr>
<th>Author and year</th>
<th>Study design</th>
<th>Results</th>
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<tbody>
<tr>
<td>Rastogi et al., 2022(^{47})</td>
<td>Patients received either 60000 IU of cholecalciferol daily for 7 days or a placebo (control group). 40 SARS-CoV-2 positive patients, with 16 and 24 individuals in the intervention and control groups, respectively.</td>
<td>A total of 10 patients achieved vitamin D levels greater than 50 ng/mL by day 7 and another two by day 14. 20.8% of participants (control arm) and 62.5% of participants (intervention group) both developed SARS-CoV-2 RNA negative status ( p &lt; 0.018 ).</td>
</tr>
<tr>
<td>Sandhu et al., 2015(^{45})</td>
<td>A 12-week, open-label research on vitamin D and type 2 diabetes insufficiency involved 50 participants. 60000 IU of vitamin D per week (for 12 weeks) was administered orally.</td>
<td>HbA1c reduced significantly ( p &lt; 0.05 ), and FBG levels significantly decreased. A highly significant increase in vitamin D levels ( p &lt; 0.001 ) and a considerable ( p &lt; 0.05 ) rise in calcium levels were both noted.</td>
</tr>
<tr>
<td>Salehpour et al., 2011(^{50})</td>
<td>A double-blind, randomized, placebo-controlled study in two groups. ( n = 77 ) participants. Cholecalciferol (1000 IU/day), 25 gm/day, was given to group I ( n = 42 ) women. Group II (placebo, ( n = 43 ) women) (1000 IU/day)</td>
<td>Group I: Increased level of serum 25(OH)D than group II Vitamin D treatment reduced the level of serum iPTH. When compared to the placebo group, group I’s body mass significantly decreased ( p &lt; 0.001 ). 25(OH)D levels and body fat mass were found to have an inverse relationship.</td>
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<tr>
<td>Harris et al., 2011(^{46})</td>
<td>A double-blinded, randomized clinical trial comprised two groups: one that received vitamin D and the other that received a placebo. (16 weeks, ( n = 57 ) women) The placebo group received an identical placebo containing silica, while the vitamin D group received oral vitamin D3.</td>
<td>In the placebo and vitamin groups, the serum concentrations rose significantly. Only the group receiving vitamin D indicated a reduction in FMD ( (1.8 \pm 1.3%) ).</td>
</tr>
<tr>
<td>Chaudhary et al., 2016(^{48})</td>
<td>102 patients were randomly assigned to groups I and II (intervention and control groups, respectively). For 8 weeks, group I received cholecalciferol at 60000 IU/week and calcium at 500 mg/day; group II received calcium at 500 mg/day.</td>
<td>100 AITD patients’ results were analyzed. Patients with the lowest 25(OH)D quartile were found to have the highest TPO-Ab titters. At the end of 3 months, group I showed a significant decrease in TPO-Ab.</td>
</tr>
<tr>
<td>Bhatt et al., 2020(^{51})</td>
<td>121 females with vitamin D deficiency and prediabetes were randomly assigned to the intervention ( n = 61 ) and placebo ( n = 60 ) groups</td>
<td>A significant difference between the intervention group and the placebo group in terms of FBG, 2 h blood glucose HbA1c. Following intervention, the intervention group’s subscapular and suprailiac skinfolds were considerably lower than those of the control group.</td>
</tr>
</tbody>
</table>

DM, diabetes mellitus; FBG, fasting blood glucose; HbA1c, hemoglobin A1c; BMI, body mass index; iPTH, intact parathyroid hormone; FMD, flow-mediated dilation; AITD, autoimmune thyroid disease; TPO-Ab, thyroid peroxidase antibody
dosage. The maintenance dose is essential to preserve the benefits of vitamin D.

Guideline Recommendations on Dosing and Duration of Vitamin D Supplements

Endocrine Society recommends people should have blood levels of at least 30 ng/mL 25(OH)D levels to maintain the appropriate bone condition and strength. Therefore, to prevent vitamin D deficiency, the Endocrine Society suggests 1500–2000 IU/day for all adults to maintain overall health. In the case of obese individuals, the level should be 2–3 times more than the prescribed values. However, the Institute of Medicine (IOM) advised 600 IU/day (15 gm/day), which supports 97.5% of the population, using a more restricted approach. The IOM used average group serum 25(OH)D levels as 600 IU/day (physiological range 40–60 ng/mL); however, it cannot suffice for people living in colder areas or individuals with darker skin living in temperate latitudes. In contrast to IOM, the Endocrine Society suggests 4000 IU/day and 10000 IU/day for children and adults, respectively.40 To maintain sufficient blood levels, 50000 IU must be taken every week for 8 weeks.41

The American Academy of Pediatrics suggests 400 IU/day for children and supplementation of a minimum of 700–800 IU/day for grown-ups to avoid severe health conditions such as osteomalacia or increased incidence of fracture. Treatment for vitamin D deficiency involves taking 50000 IU/week for 8 weeks and at least 800–1000 IU/day as a maintenance dose from food and supplements.42

Clinical Evidence: How Much Vitamin D Supplementation Is Enough?

A study analyzed nine RCTs, and it was observed that vitamin D at a high dose of 1000/day could lower the risk of cancer. Mixed-effect dose-response analysis revealed that a 10 nmol/L increase in 25(OH)D concentration could lower the risk of colorectal cancer by 6%.43 People having a body mass index (BMI) greater than 30 kg/m² require for at least 4–5 half-lives to attain the steady-state level. In some cases, ≥1 dose than the maintenance dose can be given at the beginning with a loading dose. In a study, patients received vitamin D (60000 IU) orally for 12 weeks, after which the glycemic status was compared to the starting points.45 It was observed that fasting blood glucose (FBG) levels (p < 0.001) and glycated hemoglobin reduced significantly (p < 0.05). Thus, vitamin D therapy can help in the improvement of glycemic control and subsequently help in delaying the advancement and problems associated with type 2 diabetes mellitus.46 Another such study found that African American people receiving 60000 IU of oral vitamin D each month (for 4 months) helped to improve vascular endothelial functioning.47 Table 3 helps in comprehending the role that vitamin D plays in overall health.

Rastogi et al. showed that a single high dose of 600000 IU did not exhibit any instances of hypercalcemia, indicating the safety of short-term high doses of vitamin D supplementation.48 In a study, a weak inverse relationship was found between thyroid peroxidase antibody (TPO-Ab) and 25(OH)D levels. As a result, vitamin D insufficiency is related to autoimmune thyroid disorders, and vitamin D supplementation may have a large influence since it can lower TPO-Ab titers.48

Therefore, daily supplementation of 4000–10000 IU is required for ideal vitamin D blood levels in the 40–60 ng/mL range. In addition, it can be safely used when combined with vitamin K2 (200 µg/mL).49 However, the medical community does not utilize vitamin D to its full potential, and regretfully, outdated warnings regarding the dangers of vitamin D overdoses are still frequently propagated.50

As highlighted, the health benefits of vitamin D can be experienced at 25(OH)D blood levels greater than 30 ng/mL.51 Therefore, a big initial dose of 600000 IU administered intramuscularly monthly, or an oral dose of 200000 IU monthly, or 50000 IU weekly for 8 weeks, should be the optimal regimen to maintain 25(OH)D blood levels in healthy persons.52 As recommended by the Endocrine Society, Khawaja et al. administered 50000 IU bimonthly to maintain 25(OH)D serum levels above 30 ng/mL.52 A study conducted in North India points out that a starting dose of 1200000–1800000 IU of vitamin D is needed to raise 25(OH)D above the deficiency level. However, the improved serum values started declining after 2 months, and hence maintenance dose of 60000 IU was required to achieve the optimum level. It was also observed that maintenance dose at a shorter interval was effective in maintaining the required levels.52 Healthcare practitioners can greatly profit from this finding by using the recommended dosage to treat and maintain the proper 25(OH)D blood concentration.

Conclusion

The maintenance of the metabolism of calcium, phosphate, and bone is greatly aided by vitamin D. According to historical evidence; our ancestors had vitamin D levels between 10 and 50 ng/mL.53 Serum 25(OH)D levels in native Maasai herdsmen and Hadza tribesmen ranged from 40 to 60 ng/mL. They are thought to have a minimal chance of developing certain cancers, cardiovascular conditions, and autoimmune illnesses. Therefore, a person needs 4000–6000 IU of vitamin D daily to keep their blood 25(OH)D levels at a constant 40–60 ng/mL range.54 It is evident that vitamin D is crucial for boosting the immune system. Researchers can further explore its effect on the immune system to fully utilize its potential. The bottom line is that one should take a loading dosage regimen of 60000 IU for 12 weeks followed by maintenance therapy of 60000 IU monthly or bimonthly to achieve serum vitamin D levels of 50 ng/mL rather than the traditional sufficiency level of 30 ng/mL to enjoy the physiological benefits of the vitamin.

Author Contribution

The author has contributed to the concept, design, review, and finalization of the manuscript.

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References

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