Chapter

Vitamin D and Its Relationship with the Pathways Related to Thrombosis and Various Diseases

Syed Mohd, Swati Sharma, Aastha Mishra and Mohammad Zahid Ashraf

Abstract

Vitamin D known for its vital role in diverse biological function such as calcium and phosphorus homeostasis, also exert an anticoagulant effect emphasizing its essential role in the thrombosis pathogenesis. Thrombosis is the formation and propagation of a blood clot or thrombus either in the arterial or the venous system resulting in several severe complications. Various studies have also reported the association of vitamin D deficiency with the increased incidences of thromboembolism. This may be in part due to its anticoagulant effects through upregulation of thrombomodulin, an anticoagulant glycoprotein, and downregulation of Tissue Factor, a critical coagulation factor. The protective effects of vitamin D and its receptor in endothelial cells may further explain some of the reported beneficial effects of vitamin D in the prevention or treatment of cardiovascular diseases. Additionally, the immunomodulatory role of vitamin D has been observed through its ability to alter the secretion of inflammatory cytokines that can induce a procoagulant milieu by multiple pathways. Therefore, it becomes pertinent to discuss the close link between vitamin D and human health and to improve our knowledge of the molecular pathways regulated or influenced by vitamin D and its associated metabolites.

Keywords: vitamin D, vitamin D receptor, thrombosis, coagulation, immune response

1. Introduction

Vitamin D is a lipophilic, steroid hormone, obtained from various food sources as well as majorly synthesized by the body in the skin through exposure to ultraviolet irradiation [1, 2]. In nature, vitamin D exists in two forms, vitamin D2, and vitamin D3. 25-hydroxyvitamin D (25(OH)D) is the major circulatory form and 1,25-dihydroxyvitamin D (1,25(OH)2D) is the active form of vitamin D that exerts its activity by binding to and activating the nuclear vitamin D receptor (VDR), which is a ligand-inducible transcription factor [3]. Upon activation, VDR forms a heterodimer with the retinoid-X receptor (RXR) that interacts with particular DNA sequences in the promoter region of target genes called vitamin response elements (VDREs) [4]. Vitamin D exerts a diverse biological function such as cell

proliferation, calcium and phosphorus homeostasis, and cell differentiation. Most of these actions are carried out by regulating the expression of target genes through VDR activation [3].

Vitamin D deficiency is a widespread condition, reportedly occurring in 30 to 60% of the general population worldwide [5–7]. Vitamin D is commonly known for its vital role in calcium homeostasis and bone mineralization. It is also crucial in the prevention of rickets during early age and osteomalacia during adult age [8, 9]. Increasing evidence from clinical reports, cross-sectional studies, and cell culture studies further indicate that vitamin D may exert an anticoagulant effect emphasizing an essential role of vitamin D metabolites in the pathogenesis of thrombosis [10–12]. VDR is expressed throughout the body including various immune cells such as macrophages, dendritic cells, and lymphocytes [13–17]. They are also expressed in the vascular endothelial cells [18], which are relevant to hemostasis.

Thrombosis is the formation of a blood clot within the intact vascular system. It can occur in both arterial and venous systems [19]. Rudolf Virchow, a German scientist, and physician proposed the three main factors that may predispose an individual to the development of thrombosis: stasis, endothelial dysfunction, and hypercoagulability. Apart from these three factors, the innate inflammatory system also has an intrinsic link with coagulation, whereby activation of the inflammatory system promotes thrombosis and vice versa [20, 21]. Interventional studies have shown vitamin D treatment enhances endothelial functions and reduces the production of pro-inflammatory cytokines [22–24]. Apart from this, the anti-thrombotic effect of vitamin D on the pro-thrombotic and anti-thrombotic components of the coagulation system has also been well defined [25–27]. In this chapter, we are defining the effect of vitamin D deficiency in the three most important parameters viz. coagulation, endothelial activation, and immune responses affecting the occurrence of thrombosis. This chapter will also discuss the clinical impact of Vitamin D in various diseases including COVID-19.

2. Vitamin D in coagulation

Vitamin D deficiency is defined based on the plasma levels of 25(OH)D. Individuals with plasma levels under 20 ng/mL are considered vitamin D deficient. Vitamin D deficiency is highly prevalent worldwide with approximately 30–50% incidences [28–30]. Several reports have established the significant association of vitamin D deficiency with the increased risk of various cardiovascular diseases (CVDs) and mortality [31–33]. Various studies have also reported the association of vitamin D deficiency with the increased incidences of thromboembolism [34–36]. As suggested by the studies, the underlying molecular mechanism for the antithrombotic potential of vitamin D includes up-regulation of thrombomodulin and downregulation of tissue factor (TF) [25, 36, 37]. Additionally, vitamin D upregulates and increases the level of anti-inflammatory cytokines like IL-10 [24, 38]. The expression profile of more than 200 genes involved in the regulation of cellular proliferation, differentiation, apoptosis, and angiogenesis is directly or indirectly regulated by vitamin D [39]. The experimental shreds of evidence obtained from cell culture studies depicted that biologically active form of vitamin D_3 i.e., 1,25(OH)2D, and its synthetic analogs exerted the anticoagulant effects [40]. Koyama et al. have demonstrated in their experiments on human peripheral monocytes that 1,25(OH)2D exerted the anticoagulant effects by upregulating the expression of thrombomodulin, an anticoagulant glycoprotein, and downregulating the expression of TF, a critical coagulation factor [13]. 1,25 (OH)2D directly suppresses renin gene expression via a vitamin D-response (VDR) element that is

present in the renin gene [41]. Different studies on mouse embryonic fibroblasts from VDR Knockout (VDRKO) mice asserted an increase in pro-fibrotic factors including nuclear factor kappa B, interleukin (IL)- 6, and TNF-α suggesting that 1,25 (OH)2D may have antifibrotic effect and hence modulates multiple signaling pathways, like the transforming growth factor-β/Smad signaling [42]. Experiments with VDRKO mice showed enhanced ADP-induced platelet aggregation, down-regulation of thrombomodulin and anti-thrombin, and upregulation of TF at mRNA level [43]. The VDR system has a physiological role in the maintenance of anti-thrombotic homeostasis as exacerbated multiorgan thrombus formation has been observed in VDRKO mice after lipopolysaccharide injection [43]. Recently, it has been documented that human platelets and megakaryocyte lineage also express VDR [44]. Hyppönen et al. documented that serum 25(OH)D level inversely associated with tPA antigen, fibrinogen, and D-dimer, suggesting a possible role for vitamin D3 status in determining thrombolytic profile [45]. It is well studied that inflammation can cause coagulation with high sensitivity C-reactive protein (hs-CRP) [46, 47]. A study comprising of 206 individuals reported significant inverse associations between 25(OH)D and PAI-1 and tPA antigen levels and between 1,25(OH)2D and tPA and hs-CRP levels [48].

However, because of the small number of clinical trials and heterogeneity, more studies need to be conducted to further define the haemostatic abnormalities seen in individuals with vitamin D3-deficiency, and to precisely define the potential benefits of vitamin D3 supplementation as a preventive measure for various CVDs.

3. Vitamin D in endothelium homeostasis

The pathogenesis of cardiovascular diseases is governed by endothelium homeostasis. The vascular endothelium is of mesodermal origin and is located at the confluence between blood and the underlying vascular tissues. It not only works as a barrier function but also exerts several vasoprotective roles, and is considered as the main regulator of blood vessel homeostasis. Due to its inherent capability to perceive humoral and hemodynamic stimuli [49], the endothelium is instrumental in local regulation of vascular tone and structure, regulation of migration and growth of VSMCs, and controlling the adhesion and extravasation of leukocytes [50, 51]. Destabilization and activation of the endothelium take place as a result of injury, hemodynamic alteration, response to inflammatory cytokines, as well as genetic disorders [52, 53]. Endothelial dysfunction is found in various conditions that adversely affect the cardiovascular system, including hypertension, diabetes mellitus, atherosclerosis, chronic renal failure, and Deep venous thrombosis (DVT) [54]. Endothelial cells (ECs) in a quiescent form exhibit an anti-coagulant, vaso-dilatory, and anti-adhesive property [55]. However, when activated they express pro-coagulant, vasoconstricting, and pro-adhesive properties [56]. Hemostasis is facilitated by an equilibrium of anticoagulant and procoagulant factors [56]. On one side of the hemostatic equilibrium, the ECs express anticoagulant factors such as thrombomodulin TM, tissue factor pathway inhibitor (TFPI), and tissue-type plasminogen activator (t-PA). On the other side, they express thrombin receptors, TF, plasminogen activator, and von Willebrand factor (vWF) [56].

The VDR has been identified in endothelium cells, and hydroxylation of 25(OH) D to 1,25(OH)2D also takes place in the endothelium [18, 57]. The expression of VDR and 1-alfa hydroxylase in the endothelium was found to be decreased with 25(OH)D deficiency [58]. In the vascular system, it has been recognized that vitamin D controls the proliferation of endothelial cells and vascular smooth muscle cells [59, 60]. Vitamin D up-regulates the production of nitric oxide (NO) in ECs [31],

by increasing eNOS expression [61], which helps in reducing arterial stiffness [62]. Various randomized control trials (RCTs) have demonstrated an improvement in endothelial dysfunction in healthy individuals [23, 63, 64], as well as in patients [65, 66] and improvement of arterial stiffness with improved flow-mediated dilation (FMD) after vitamin D supplementation [67]. A study by Davide Carrara et al. showed restoration of normal vitamin D levels after prolonged supplementation with a high dose of cholecalciferol (50,000 IU/week orally for 8 weeks) is associated with inhibition of peripheral renin-angiotensin system and with an improvement of FMD in essential hypertensive patients with hypovitaminosis [68]. The 25(OH)D presumed to be an inactive sterol is also found to be a potent mediator of endothelial stability in a non-genomic manner at physiologically relevant levels [69].

1,25(OH)2D3 supplementation reduces oxidation stress, NF-kappa B activation, Intercellular Adhesion Molecule 1 (ICAM-1), and Monocyte chemoattractant protein-1 levels in the endothelium cells [70]. Vitamin D also downregulates platelet-activating factor (PAF) induced ICAM-1 expression in the ECs [71]. Another study observed a greater level of p65 subunit of NF-kB, and IL-6 in vitamin D deficient groups as compared to the vitamin D sufficient group [72]. Vitamin D has also been shown to inhibit activation of proinflammatory TF, NF-kB, and its downstream target, IL-6 [73], which is a pro-inflammatory cytokine in cultured vascular ECs [74] In addition, Vitamin D has been demonstrated to reverse Angiotensin II (Ang II) induced oxidative stress, a key mediator of endothelial dysfunction [75]. Ang II not only induces the production of ROS but also activates TF NF-kB, which further upregulates several cytokines such as TNF-alfa, IL-6, and adhesion molecules ICAM-1, Vascular cell adhesion molecule 1 (VCAM-1), and E-selectin prompting vascular injury [76]. In vivo, VDR knockdown leads to an increase in leukocytes-endothelial interaction associated with endothelial cell activation markers VCAM-1 and ICAM-1 in endothelial cells [77].

Given the recognized significance of endothelial function in the homeostasis of the cardiovascular system, the protective effects of VDR in endothelial cells may explain by some of the reported beneficial effects of vitamin D attributed to the prevention or curing of cardiovascular disease [78, 79]. Vitamin D therapy has been observed to be associated with improvement in endothelial function in ischemic heart disease (IHD) patients with vitamin D deficiency or insufficiency [80]. Further, *in vitro* supplementation of vitamin D improved endothelial progenitor cell ability in the formation of colonies in type 2 diabetes mellitus patients [81]. Cuenca *et al.* demonstrated that paricalcitol, a vitamin D substitute attenuates the endothelium damage induced by the chronic kidney disease in the thoracic aorta and directly mediates stability of endothelium in vitro by enhancing cell–cell interactions resembling a protective mechanism [82].

4. Inflammation and thrombosis

Thrombosis and inflammation are the two intrinsically interlinked processes. Inflammation can induce a procoagulant milieu by multiple pathways such as by causing an imbalance between procoagulant and anticoagulant characteristics of the endothelium that can lead to local stimulation of coagulation cascade. TNF-α, a pro-inflammatory cytokine that is a potent inducer of the immune defense mechanism and the first to be released at the site of infection promotes a pro-coagulant state by eliciting the production of TF on the endothelium [83] and suppressing the synthesis of the anticoagulant protein C [84], thereby stimulating fibrin formation. Inflammatory stimuli change the cellular program of the endothelium by expressing adhesion molecules such as p-selectin and E-selectin facilitating a transition toward a more procoagulant phenotype [85].

Other cells of the circulation are also customized by inflammatory molecules toward a pro-thrombotic state such as neutrophils and monocytes expression of TF [86, 87], which is upregulated upon inflammation. The role of sterile inflammation has also been demonstrated in the thrombosis by a direct association between nucleotide-binding domain, leucine-rich-containing family, pyrin domain containing 3 (NLRP3) inflammasome complex, and hypoxia-inducible factor-1 alpha in hypoxia-induced thrombosis associated with an increase in the relative expression of caspase-1, interleukin-1beta and IL-18 transcripts in the individuals with venous thrombosis [20]. In recent years, the role of vitamin D as a regulator of both innate and adaptive immune responses has become very clear [88]. Local synthesis of 1,25-(OH)2D at the site of inflammation can modulate the immune response in a paracrine manner [89]. 1,25(OH)2D binds to the nuclear VDR which has been found to be expressed in various cells of the immune system such as macrophages, activated T-cells, B-cells, Dendritic cells, and monocytes [90, 91].

The immunomodulatory role of vitamin D has been observed through its ability to alter the secretion of inflammatory cytokines [92, 93]. Additionally, multiple studies are suggesting an inverse association between vitamin D level and inflammatory cytokines such as TNF-α, IL-6, and CRP [16–20], which are correctable by vitamin D supplementation [94–96]. Furthermore, lower vitamin D levels have also been associated with an increase in the levels of cellular adhesion molecules such as VCAM and ICAM [97].

Moreover, an increased incidence of auto-immune disorders in higher latitudes has been reported, which could be attributed to low UV-radiation that reduces the ability to synthesize vitamin D [98, 99]. Elderly peoples usually tend to have Hypovitaminosis D [26], which has been associated with an increased risk for chronic diseases where inflammation plays an integral component [100, 101]. A study by EM Akbas *et al*. revealed an inverse association between Vitamin D levels and inflammation through Neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) which are novel and inexpensive markers of inflammation. They found a significantly higher NLR and PLR in patients with lower 25(OH)D status [102].

Further, several cross-sectional studies have associated vitamin D levels and inflammation. Amer and Qayyam Studied 15,167 men and women aged 18 years and older [103]. They observed a negative association between vitamin D and inflammatory markers such as CRP and IL-6 in the vitamin D deficient groups (<25 nmol/L). This association was not observed in groups with insufficient and sufficient vitamin D status [104]. Bellia et al. examined the association of vitamin D and inflammatory markers in 137 morbidly obese individuals including both men and women. They also observed a significant inverse association between serum 25(OH)D levels and inflammatory markers like CRP, IL-6, and TNF-α [105]. A clinical trial by SS Bidar et al. observed a significant decrease in the systemic inflammatory markers including hsCRP, serum amyloid A, TNF-α, and IL-6 with the increase in circulating vitamin D after a daily intake of vitamin D fortified yogurt drink in the subjects with type 2 diabetes (T2D) [96]. However, in another clinical trial, Jorde et al. [106] observed no significant effects on hsCRP levels in the subjects randomly assigned to the therapy for 1 year with vitamin D3 40,000 IU per week, 20,000 IU per week, or placebo.

5. Clinical impact of vitamin D in various diseases

There is a close link between vitamin D and human health, vitamin D deficiency is widely associated with several diseased conditions by physicians and patients.

The various diseases affected by vitamin D deficiency can be categorized as cardiovascular disease (hypertension, thrombosis), various cancers, autoimmune diseases like multiple sclerosis, rheumatoid arthritis, and metabolic syndromes like osteomalacia, diabetes, and muscle weakness (**Figure 1**).

Osteomalacia is a classical human manifestation associated with vitamin D deficiency. It is a clinical condition in which bone mineralization is hampered due to low concentrations of phosphorus and calcium in the extracellular fluid [107]. Vitamin D plays a crucial role in maintaining an adequate level of serum phosphorus and calcium. In the absence of vitamin D or its deficiency, only 10 to 15% of dietary calcium and 60% of phosphorus are absorbed in the human body [108–110]. With the advent of technologies, molecular biology has permitted a more detailed characterization of the effects of vitamin D deficiency, via working on the animals lacking the VDR and studying their phenotype. Subtle abnormalities in the immune and cardiovascular system have been defined in the global VDRKO mouse, but their relevance to human disease is still obscure [111]. Greater awareness of the high prevalence of vitamin D inadequacy and its associated abnormalities is required among researchers, clinicians, and patients. There has been a large number of trials concerning the effects of vitamin D on the management and prevention in the last two decades. The most studied diseases in this aspect have been discussed below:

5.1 Osteoporosis

The association between osteoporosis and vitamin D deficiency is well established especially in the elderly. Vitamin D deficiency has been linked with the significant suppression in intestinal Calcium absorption and the impairment of its balance, which causes low bone mineral content and density. Decreased bone mineral density (BMD) raises the risk of bone fractures, which contributes significantly to the hospitalization, morbidity, and mortality of elderlies [112, 113]. Several studies have demonstrated the efficacy of vitamin D as a preventive measure for fractures. Clinical trials recommending the use of 700 to 800 IU/d oral vitamin D with or without Ca supplementation reported a significant 26% decrease in the risk of sustaining a hip fracture and a significant 23% decrease in the risk of sustaining any non-vertebral fracture vs. placebo or Calcium alone [114].

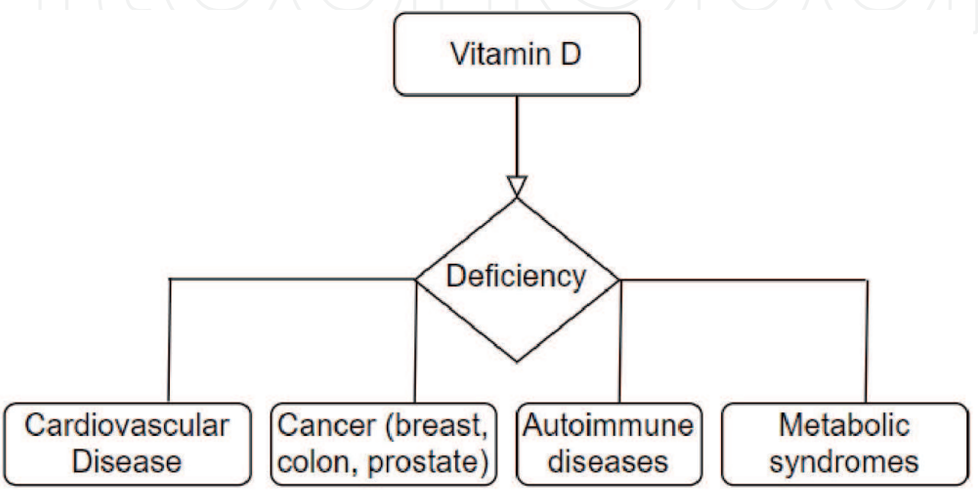

Figure 1.
Reported Association of Vitamin D deficiency with various human disease.

5.2 Muscle weakness

One of the prominent features of vitamin D deficiency is muscle weakness. Several clinical data of patients with nonspecific muscle weakness, muscle aches, and pains have shown vitamin D inadequacy [115, 116]. It has been reported that skeletal muscle tissue contains VDR and needs vitamin D to attain maximum function [117]. Recent studies have associated the increased vitamin D levels with improved muscle performance, and thereby reduced incidences of fall and fracture. A 5-month randomized controlled trial study has exhibited a 72% reduction in the risk of falls as compared with the placebo group in elderly people in a nursing home receiving 800 IU of vitamin D2 plus calcium daily [118].

5.3 Hypertension

Hypertension affects the population globally. Increasing evidence in recent times suggests that vitamin D has a crucial role in regulating blood pressure. Animal studies indicate that 1,25-dihydroxy vitamin D inhibits renin expression in the juxtaglomerular apparatus and blocks the proliferation of vascular smooth muscle cells, which affects systemic blood pressure [119]. People taking oral supplementation of vitamin D were found to have reduced blood pressure. The exposure of skin to UVB rays, a major source of vitamin D formation, has been associated with lower blood pressure [120–122].

5.4 Multiple sclerosis

Multiple sclerosis (MS) is an auto-immune disease characterized by the attack of self- immune system on the myelin sheath which works as a nerve insulator. The transmission of nerve signals gets affected leading to disrupted communication between the body and brain.. There have been several reports claiming the increased frequency of MS in temperate climates than in the tropics [123, 124]. Furthermore, studies also suggest that there is a strong negative correlation between the short annual, winter hours and frequency of occurrence of MS [125, 126]. Hence, these studies could hypothesized that vitamin D synthesized during sun exposure exerted a protective effect [127–129]. In addition, There are few studies that indicated low or insufficient levels of vitamin D in MS patients [130–132].

5.5 Rickets

The re-arrival of worldwide vitamin D deficiency has led to the re-emergence of rickets. Low levels of vitamin D in breastfeeding mothers can, often, lead to deficiencies in their children. The recommended levels of vitamin D supplements are 400 IU/d for infants to avoid diseases such as rickets [8].

5.6 Cancer

Garland and Garland for the first time reported that vitamin D deficiency could be associated with a higher risk of colon cancer mortality. Recent studies have reported an increased risk of several cancers with vitamin D deficiency, suggesting that vitamin D deficiency may account for premature mortality from colon, breast, ovarian, and prostate cancer [133–135]. Vitamin D is a potent hormone and regulates cell growth. VDRs are expressed by various cells and get activated by 1,25(OH)2 D, inducing differentiation into normally functioning cells, and inhibiting proliferation, angiogenesis, invasiveness, and metastatic potential.

Studies reveal that tumor models of lung, colon, kidney, breast, and prostate cancer, vitamin D showed activity against metastasis [136–141]. These studies have also shown the immunomodulatory effect of Vitamin D. It has been reported that when elicited by an inappropriate and overly exuberant immune response, vitamin D acts in a paracrine manner and decreases T cell responsiveness via inhibition of cellular proliferation and reduced lymphokine production. Thus, vitamin D shows a beneficial effect as an immunosuppressant.

5.7 Diabetes

Vitamin D deficiency is known to inhibit pancreatic secretion and turnover of insulin, causing impaired glucose tolerance. An association was found between a low level of vitamin D and a high incidence of type 1 diabetes [142].

5.8 Tuberculosis

Tuberculosis (TB) is one of the global health problems causing 2 million deaths a year. It is estimated that approximately one-third of the global population carries latent TB infection, which poses potential health risks of reactivation in the future. Before the use of antibiotics to treat TB, high doses of vitamin D were widely used [143]. Cross-sectional studies indicated that patients with TB possess a decrease 25(OH)D levels in comparison with the control population.

5.9 Thrombosis

As discussed in previous sections, vitamin D can tackle thrombosis by influencing inflammatory pathways, coagulation factors, and endothelium homeostasis in a pleiotropic manner. **Figure 2** illustrates a possible mechanism through which vitamin D might impart its protective role against the occurrence of thrombosis. Several clinical trials have also highlighted the anti-thrombotic actions of vitamin D. A study by TM Beer *et al.* involving 250 cancer patients for high dose calcitriol supplementation, a total of 13 thrombotic events were observed of which 11 occur placebo-treated and only 2 occur in high dose calcitriol-treated cancer patients [35]. Vitamin D has been found to inhibits *in-vitro* anti beta2GPI antibodies (purified from patients with antiphospholipid syndrome (APS)) induced TF expression indicating the association of vitamin D deficiency and decreased inhibition of TF expression and increased coagulation in APS [34]. M Blondon *et al.* investigated the role of oral supplementation of vitamin D3 in the placebo-controlled RCT in 36,282 postmenopausal women. Subjects were randomized to receive 1000 mg of calcium carbonate and 400 IU of vitamin D3 per day for an average period of 7 years and observed a reduced risk of idiopathic VTE in women randomized to calcium and vitamin D [144]. A 60% lower rate of VTE was observed in 769 renal transplant recipients after combined therapy with calcitriol 0.5ug/day, angiotensin-converting enzyme inhibitor (ACEi), and angiotensin receptor blocker (ARB) [145]. Another prospective study which included a cohort comprising of 40,000 women followed for a mean period of 11 years concluded a 30% lower risk of VTE in women with a habit of more active sun exposure [146]. Moreover, another study determined a 50% increased risk of VTE in winter, during which vitamin D status has been established to be the lowest as compared to another season [147].

5.10 COVID-19

The COVID-19 pandemic has affected all of us globally. The lack of understanding of the mechanism of action of SARS-CoV2 virus has generated an overall

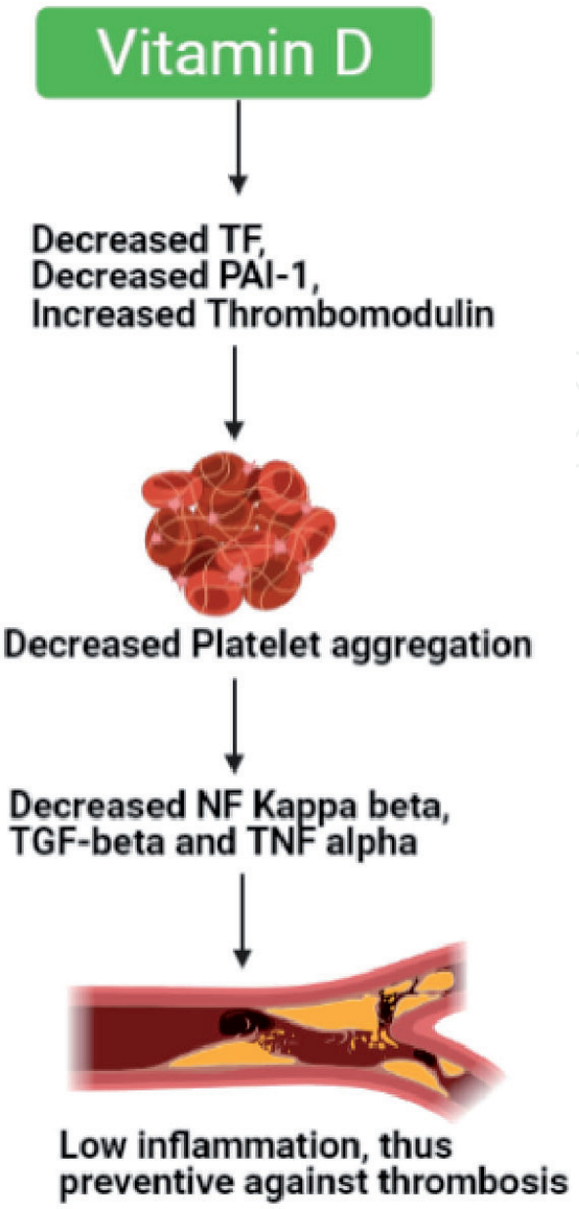

Figure 2.
Possible mechanism of the protective role of vitamin D in the occurrence of thrombosis.

interest in understanding the potential risk factors that may explain the mechanistic basis for disease propagation and control. The role of vitamin D has emerged in COVID-19 as well. The innate immune system forms the first line of defense against invading pathogens including viruses. 1,25(OH)2D enhances innate defense by inducing antimicrobial peptides like cathelicidin that result in the destruction and clearance of viral particles via several molecular mechanisms. It also helps in the recruitment of neutrophils, monocytes/macrophages, and dendritic cells for killing and clearance of viral particles, and initiation of the immune response. Further, the chronic activation of the innate immune system in COVID-19 infection results in a cytokine storm. It has been hypothesized that 1,25(OH)2D helps in curtailing this chronic innate immune response through various biological mechanisms such as downregulation of TLRs and direct inhibition of TNF/NFκB and IFNγ signaling pathways. 1,25(OH)2D, regulates adaptive immune response by limiting maturation of dendritic cells along with their ability to present antigen to T cells, thus limiting shifting of the T cell profile from proinflammatory Th1 and Th17 subsets to Th2 and Treg subsets. Thus, inhibits the pro-inflammatory processes. Although all these findings come from different studies with a variety of pathogens (virus/bacteria)

the relevance of these protective actions of vitamin D on SARS-CoV-2 can merit further investigation [148]. In a recent study of hospitalized COVID-19 patients, vitamin D deficiency was reported in 75% of the overall cohort and in 85% of those who required ICU admission [149]. Also, a European study analysis of SARS-CoV-2 severity based on vitamin D status suggested that countries with the highest rate of vitamin D deficiency are associated with the highest rates of COVID-19 infection and mortality [150]. Therefore, vitamin D supplements as a part of standard nutrition in COVID-19 may provide certain clinical benefits though more research related to this subject is solicited [151].

6. Conclusion

Inadequacy or deficiency of vitamin D is a global problem. Though recent studies have established vitamin D as a key regulatory molecule in various physiological processes and have proposed it as a promising predictive/therapeutic tool still the close association of vitamin D with human health, and its deficiency in the body is not widely recognized as a health concern by both common man and physicians. The relation between vitamin D deficiency and the associated risk of various chronic and acute diseases is still obscure and requires intensive research efforts. In recent years, various studies have explored several non-calcemic consequences of vitamin D. There are reports that corelates lower doses of vitamin D with thrombosis and various cardiovascular diseases. Still, there is an impelling need to enhance our knowledge of the molecular pathways regulated/influenced via vitamin D and their effect on various organ systems including the cardiovascular system. This would require conducting large-scale intervention clinical trials to firmly establish the association of vitamin D status to cardiovascular health. Additionally, it is important to state that although deficiency of vitamin D is common and widespread, it can be safely corrected with a variety of supplement types and regimens available and thus should be identified and addressed in the clinical practice of treating diseases associated with it.

Conflict of interest

The authors declare no conflict of interest.

Author details

Syed Mohd[1†], Swati Sharma[1†], Aastha Mishra[2] and Mohammad Zahid Ashraf[1*]

1 Department of Biotechnology, Jamia Millia Islamia, Delhi, India

2 CSIR-Institute of Genomics and Integrative Biology, Delhi, India

*Address all correspondence to: zashraf@jmi.ac.in

† These authors have contributed equally to this work.

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