Vitamin D Deficiency As A Contributor To Atherosclerosis Development – A Review

Anastasia V. Poznyak [1*], Victoria A. Khotina [2], Alexandra A. Melnichenko [2], Victor Y Glanz [2], Vasily N. Sukhorukov [2], and Alexander N. Orekhov [2*]

Highlights:

- Identification of novel association: The review may highlight any newly discovered associations between cholecalciferol (vitamin D3) deficiency and specific cardiovascular diseases such as atherosclerosis, ischemic stroke, and myocardial infarction. These findings would contribute to expanding the understanding of the role of vitamin D in cardiovascular health.
- Role in inflammation and oxidative stress: The review may identify novel insights into the impact of cholecalciferol on inflammation and oxidative stress, particularly concerning vascular inflammation and atherosclerosis progression. Understanding the intricate mechanisms by which cholecalciferol influences these processes could lead to potential therapeutic interventions.
- Link to vascular calcification: The review may explore the emerging evidence on the role of cholecalciferol in vascular calcification, a process closely associated with cardiovascular morbidity and mortality. Highlighting any significant findings regarding the influence of cholecalciferol on vascular calcification will contribute to the understanding of its potential preventive or therapeutic effects.

Gaps in Current Knowledge:

- Insufficient clinical trials: The review may identify a lack of well-designed clinical trials assessing the effects of cholecalciferol supplementation on cardiovascular outcomes. These gaps in clinical evidence could emphasize the need for further research to establish a more robust cause-and-effect relationship and potential clinical recommendations.
- Limited understanding of mechanistic pathways: The review may highlight gaps in our understanding of the precise mechanistic pathways by which cholecalciferol influences atherosclerosis and related conditions. Identifying these gaps would emphasize the need for more in-depth studies exploring the specific cellular and molecular mechanisms involved.
- Lack of long-term studies: The review may reveal a scarcity of long-term studies investigating the sustained effects of cholecalciferol supplementation on cardiovascular health. Highlighting this gap in knowledge would underscore the importance of conducting studies with extended follow-up periods to evaluate the durability and long-term benefits or risks associated with cholecalciferol supplementation.
- By emphasizing these highlights and gaps, the review would contribute to the existing literature by summarizing the current state of knowledge, identifying potential research directions, and underscoring the need for further investigation in specific areas related to cholecalciferol and cardiovascular health.

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Abstract

Vitamin D, obtained from food or synthesized in the skin through sun exposure, plays a vital role in various physiological processes. This review focuses on cholecalciferol (vitamin D3), specifically its production from 7-dehydrocholesterol in the skin. The aim is to evaluate the impact of vitamin D on the development of atherosclerosis and other pathological conditions. Atherosclerosis, a chronic vascular inflammation caused by innate immunity, is of particular interest. Understanding the role of vitamin D in reducing inflammation and oxidative stress holds significant implications for effective treatment strategies. Deficiency of vitamin D has been observed in individuals with cardiovascular disease, ischemic stroke, and myocardial infarction. Hypovitaminosis D is also suspected to contribute to vascular calcification, a factor closely associated with cardiovascular morbidity and mortality. Investigating the multifaceted effects of vitamin D on various pathophysiological processes is thus crucial.

Keywords: Atherosclerosis; Vitamin D; Nutrition.

Significance | Vitamin D deficiency and cardiovascular diseases, explores role in inflammation, oxidative stress, and vascular calcification

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Introduction

Vitamin D is a fat-soluble molecule made from cholesterol. It is produced in the skin as a result of a sun exposure-dependent chemical reaction. It can also be obtained from food, albeit in smaller quantities. In case of vitamin D deficiency, it can be obtained from dietary supplements. Serious hypovitaminosis D may lead to development of rickets in children and osteomalacia in adults (Dominguez et al., 2021). Although, advanced stages of such condition are not widespread in developed countries. However, mild vitamin D deficiency can cause osteoporosis and increase the risk of fractures. Whereas calcium and phosphorus homeostasis and bone remodeling are considered the primary functions of vitamin D, it also functions as a hormone. Vitamin D exhibits immunomodulating properties, maintaining the cell ability to proliferate and differentiate (De Martinis et al., 2021). It is strongly connected to decreased risk of adiposity, DM, CVD, and metabolic syndrome, and also shows a protective activity against neurodegenerative diseases and ageing (Pérez et al., 2016).

Presently, deficiency of 25-hydroxy vitamin D is regarded as a pandemic. The most severe degree of 25-hydroxy vitamin D deficiency is observed in developing countries, where it occurs in 50-66% of adult people and shocking 90-99% of children. In the US this deficiency is found in approximately 37% of adult people and 46% of dark-skinned children (Amrein et al., 2020). A study performed in 2016 in Nordic and European people demonstrated a huge diversity between the countries, whereas Finnish research showed only 6.6% of people with the deficiency, Norwegian

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researches showed that 76% of people had this condition. This diversity can be explained by the differences in age of the researched cohorts (Voortman et al., 2015). Nordic studies included only adults and thus showed lower numbers, possibly owing to the higher level of fortification of foods or intake of supplements than in other countries such as the Netherlands, the UK, and Germany. Therefore, this information is important in terms of maintaining public health (Das et al., 2019).

Atherosclerosis (AS) is a chronic disease associated with hardening of vascular walls. AS progresses when fats internalize the tunica intima, forming fatty streaks (FS) that consequently progress into AS plaques which can cause arterial stenosis. Such condition can result in development of chronic ischemia (Linton et al., 2019). Plaque rupture may lead to thrombosis which can block the blood circulation and induce necrotic processes. Clinical manifestations of these processes are ischemic stroke (IS), IHD and PAD. Hereby, AS can result in development of cardiovascular disease, which is the leading cause of death worldwide. AS is considered a pandemic as well, and is more common in developing countries. CIMT values are increased in approximately 30% of the world population aged 30 to 79 years, and AS plaques were found in 21% of people. These two conditions are the results of AS processes in the vascular walls (Zito et al., 2020, Anastasia et al. 2023a, Anastasia et al. 2023b).

The inclusion criteria for selecting the studies for this review are as follows:

- Studies that investigate the relationship between vitamin D deficiency and cardiovascular diseases such as atherosclerosis, ischemic stroke, and myocardial infarction.
- Studies that examine the impact of vitamin D on inflammation and oxidative stress, particularly in the context of vascular inflammation and atherosclerosis progression.
- Studies that explore the role of vitamin D in vascular calcification, a closely related process to cardiovascular morbidity and mortality.
- Studies that investigate the effects of vitamin D on lipid profile, including total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C).
- Studies that examine the immunomodulatory properties of vitamin D, specifically its effects on immune cells such as macrophages, monocytes, and lymphocytes involved in atherosclerosis development.
- Studies that investigate the impact of vitamin D on endothelial cell function, including its effects on blood vessel tone regulation, nitric oxide synthesis, and oxidative stress.

By focusing on studies that meet these inclusion criteria, this review aims to provide a comprehensive evaluation of the role of vitamin D in multiple pathophysiological processes associated with atherosclerosis and other related conditions.

Vitamin D overview

Vitamin D is a family of substances made from 7-dehydrocholesterol (7-DHS). Although, in this review, vitamin D term refers only to its D_3 form (cholecalciferol), produced by skin phototransformation of 7-DHS. D_3 is an inert vitamin, but it can be transformed to a form that binds to the nuclear vitamin D receptor. Through the dermal tissues, vitamin D enters the bloodstream. In the bloodstream it has got a half-life of approximately 24 hours because of substrate-dependent transformation into the 25-hydroxy vitamin D in the liver (Göring, 2018). 25-hydroxy vitamin D is the dominant form of vitamin D in the bloodstream. It has a half-life of approximately 21 days and is necessary to define status of vitamin D, since its levels represent metabolism, nutrition and catabolism. Its low levels are a characteristic of osteomalacia and rickets induced by hypovitaminosis D. 25-hydroxy vitamin D is transformed into 1,25-dihydroxyvitamin D (calcitriol) by the 1-alpha-hydroxylase enzyme (Ramasamy, 2020). Calcitriol is a hormonally-active metabolite of vitamin D that exhibits high affinity for the nuclear vitamin D receptor and has a half-life of 4-6 hours (Institute of Medicine (US) Committee to Review Dietary Reference Intakes for Vitamin D and Calcium et al., 2011).

1-alpha-hydroxylase enzyme was first detected in renal PTECs, but later it proved to be produced in all parts of the nephron, such as collecting ducts (CDs) and distal convoluted tubules (DCTs). The majority of calcitriol in bloodstream, which mediates endocrine activities, is attributable to 1-alpha-hydroxylase in the kidneys (Fleet, 2017). It is produced ubiquitously, in such organs as brain (cerebral cortex and cerebellum), breast, testicles, prostate gland, lymph nodes, colon, skin, pancreas, placenta, adrenal medulla, and especially in ECs and VSMCs. Autocrine and paracrine (non-classical) activities of D_3 are mediated by its synthesis outside of the kidneys. The extent to which 1-alpha-hydroxylase affects the concentrations of vitamin D in blood remains unknown. Although, patients without functioning kidneys who received inactive vitamin D therapy demonstrated detectable levels of calcitriol in serum, which implies that the activity of 1-alpha-hydroxylase outside of the kidneys is considerable (Keung and Perwad, 2018).

Likewise, vitamin D receptor is produced in multiple human organs and tissues, which elucidates the multi-system effects that occur in vitamin D deficiency, a condition that leads to significant bone and mineral aberrations, such as attenuated intestinal Ca^{2+} and Pi absorption, elevated levels of parathyroid hormone, and

decreased bone density, the parameters observed in calcitriol receptor knockout mice. This is consistent with the available data, since the calcitriol concentrations are strongly controlled by parathyroid hormone, Ca^{2+} in serum, phosphorus, and FGF23. Ca^{2+} obtained from food is able to regulate the 1-alpha-hydroxylase by regulating concentrations of Ca^{2+} in serum (Christodoulou et al., 2013). Ca^{2+} and Pi both modulate this enzyme indirectly by controlling expression of parathyroid hormone at the PTG. Decreased levels of Ca^{2+} and Pi can drive the 1-alpha-hydroxylase enzyme to synthesize active calcitriol (de Brito Galvao et al., 2013).

Fibroblast growth factor-23 is a hormone that is secreted in bones. It inhibits the 1-alpha-hydroxylase enzyme directly inside the kidneys. Its activity depends on the production of a specific receptor in the kidneys, consisting of FGFR1 and the alpha-Klotho protein. Increased concentrations of FGF23 can inhibit the function of 1-alpha-hydroxylase and decrease the synthesis of calcitriol. In humans, alpha-Klotho protein is expressed outside the kidneys in multiple tissues, such as arteries, epithelium, endocrine tissues, ovaries, uterus and neural tissues (Ewendt et al., 2021). FGF23 is likely to be able to control the calcitriol production outside the kidneys in tissues that produce the alpha-Klotho protein. Increased calcitriol levels can decrease function of 1-alpha-hydroxylase by suppressing the expression of parathyroid hormone, thus making a negative feedback loop to avert the progression of vitamin D toxicity. Furthermore, the 24-hydroxylase up-regulated by increased levels of calcitriol can promote the catabolic pathway, leading to a decrease in calcitriol levels (Courbebaisse and Lanske, 2018).

Irving and colleagues performed a randomized controlled trial and demonstrated that in diabetic individuals, vitamin D supplements reduced absorption of LDL-C by monocytes, which is the initial stage of AS pathogenesis (Irving et al., 2015). It has been reported that in murine model macrophage and monocyte deficiency caused by vitamin D can induce absorption of cholesterol by AS plaque macrophages and enhance the monocyte transfer of cholesterol into the vascular walls. Likewise, in individuals with type 2 diabetes, vitamin D deficiency appeared to be related to elevated M2-monocyte phenotype expression, which releases molecules that promote adhesion to ECs. Based on this information, the researches confirmed that in diabetic individuals without complications associated with the condition and with an average baseline vitamin D concentration < 25 ng/mL, four-month administration of D_3 supplements at a dosage of 4000 IU per day decreased TC inside monocytes (Surdu et al., 2021). Although, this did not decrease the TGs, total cholesterol, low-density-Lp or HDL-C. This evidence supports the idea that vitamin D supplements might suppress the development of AS. With regard to these conclusions, further RCTs are required to confirm these connections in general population. Currently the relationship between hypovitaminosis D and inflammation of blood vessels has not been fully established (Morvaridzadeh et al., 2021).

Vitamin D's Action on Lipid Profile

In both interventional and observational trials, hypovitaminosis D is associated with adverse lipid concentrations in serum, while normal concentration of D_3 is associated with normal lipid levels. Recent research investigated a Polish group of people and showed a negative correlation between vitamin D values and TC, TGs, and low-density-Lp cholesterol (Figure 1). Another research evaluated the concentrations of 25-hydroxy vitamin D and different lipid fractions and demonstrated a marked connection between hypovitaminosis D and adverse lipid values. Furthermore, recent meta-analysis indicated that lipid levels are associated with D_3 values and D_3 supplements (Mousa et al., 2020). One analysis of 8 RCTs assessing how D_3 supplements affect lipid values showed that these supplements can reduce levels of triglycerides and are associated with an elevation in high-density-Lp cholesterol and low-density-Lp cholesterol. It is important to interpret these findings with caution due to the limited amount of research analyzed and the significant variability in results and interventions, such as the dosage of vitamin D administered (Dibaba, 2019). Another analysis assessed the combined impact of D_3 supplements on levels of triglycerides, total cholesterol, low-density-Lp cholesterol and high-density-Lp cholesterol in thirty-nine randomized controlled trials. The results showed a negative correlation between the supplements and triglycerides, total cholesterol, and low-density-Lp cholesterol. Conversely, these supplements elevated concentrations of high-density-Lp cholesterol (Wang et al., 2012). Consistently, a meta-analysis of 7 randomized controlled trials of vitamin D and Ca^{2+} supplement administration in individuals with excess weight and adiposity demonstrated that less than eight weeks of therapy decreased triglycerides, total cholesterol, and low-density-Lp cholesterol considerably, while elevating high-density-Lp cholesterol. Decreased values of vitamin D were observed in polycystic ovarian syndrome, particularly in individuals with adiposity or WHR of over 0.85. Moreover, hypovitaminosis D can be a risk factor for the progression of metabolic and endocrine diseases (Harahap et al., 2022). A meta-analysis of eleven randomized controlled trials involving 483 individuals with polycystic ovarian syndrome assessed the impact of D_3 supplement administration vs placebo. The results indicated that D_3 supplements decreased IR and total cholesterol compared to the control group, although, it did not ameliorate concentrations of high-density-Lp cholesterol and triglycerides in individuals with polycystic ovarian syndrome. Administering vitamin D supplements to children in order to maintain normal levels of 25-hydroxy vitamin D in serum has

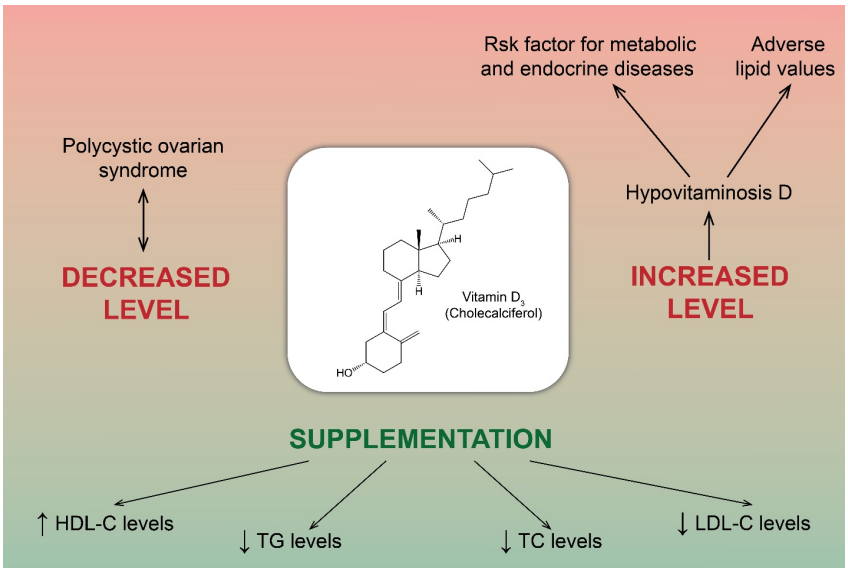

Figure 1. Influence of Vitamin D on Lipid Profile. Vitamin D has been found to have an impact on human lipid profile, specifically on cholesterol levels. Vitamin D deficiency is associated with higher levels of TC, LDL-C, and TG, while also being linked to lower levels of HDL-C. Moreover, decreased levels of vitamin D were observed in patients with polycystic ovarian syndrome.

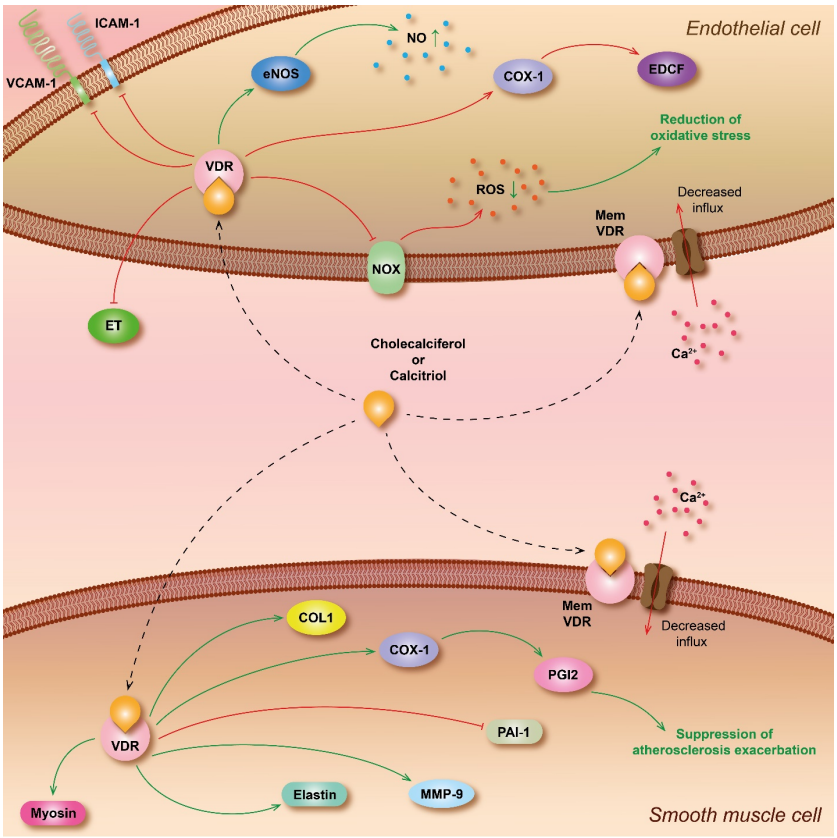

Figure 2. Effects of vitamin D on vascular cells. Vitamin D have a complex role in the regulation of blood vessel tone, protection against oxidative stress, modulation of vascular smooth muscle cell function, and suppression of factors contributing to atherosclerosis development. When the VDR is activated, it regulates blood vessel tone through various pathways. One of the effects is the promotion of NO synthesis via the activation of eNOS. Another effect is the reduction of COX-1 expression, a primary source of EDCFs. The activation of the VDR also leads to a decrease in calcium influx into cells, protection against oxidative stress by inhibiting the production of ROS by NOX. Moreover, vitamin D reduces monocyte migration due to inhibition of ICAM-1 and VCAM-1 expression. Also, vitamin D can suppress the activity of ET thus promoting anti-proliferative function. In turn, activation of VDR promotes the synthesis of myosin, elastin, COL1, and MMP-9 in vascular smooth muscle cells. Furthermore, vitamin D promotes the synthesis of PGI2 through the activation of COX-1 pathway in vascular smooth muscle cells, which helps suppress the progression of atherosclerosis. Additionally, vitamin D appear to inhibit PAI-1. Abbreviations: COL1 – type I collagen; COX-1 – cyclooxygenase 1; EDCF – endothelium-derived contracting factor; eNOS – endothelial nitric oxide synthase; ET – endothelin; ICAM-1 – inter-cellular adhesion molecule 1; MMP-9 – matrix metalloproteinase-9; NO – nitric oxide; NOX – nicotinamide adenine dinucleotide phosphate oxidase; PAI-1 – plasminogen activator inhibitor-1; PGI2 – prostaglandin I2; VCAM-1 – vascular cell adhesion molecule 1; VDR – vitamin D (calcitriol) receptor.

been linked to a reduced risk of T1DM and improved management of the disorder (Miao et al., 2020).

Furthermore, vitamin D has been found to have anti-inflammatory effects, which can indirectly impact lipid profile. Increased levels of vitamin D can, in turn, lead to hypovitaminosis D, which is associated with adverse lipid levels in serum and may serve as a risk factor for the progression of metabolic and endocrine diseases. Overall, maintaining adequate levels of vitamin D through sunlight exposure, diet, or supplementation may have a positive impact on human lipid profile, helping to maintain healthy cholesterol levels and reduce the risk of cardiovascular diseases. Abbreviations: HDL-C – high density lipoprotein cholesterol; LDL-C – low density lipoprotein cholesterol; TC – total cholesterol; TG – triglycerides.

Inflammation and Atherosclerosis

Atherosclerosis development is closely related to vascular chronic inflammation induced by cells responsible for the innate immune response, including macrophages and monocytes. Development of AS encompasses inflammation and infiltration of tunica intima by macrophages and monocytes (Anastasia et al. 2023a, Anastasia et al. 2024a, Anastasia et al. 2024b, Anastasia et al. 2024c). Whereas macrophages constitute the majority of cells in the AS plaque, adaptive immune cells such as T-lymphocytes and B-lymphocytes also take part. Apart from traditional lipid-reducing treatment, regulation of the immune responses in AS also might give positive results (Milutinović et al., 2020). In some cases, vitamin D functions as an antiinflammatory mediator, suggesting that it could lead to a decrease in progression of AS. Vitamin D is believed to elevate antiinflammatory type 2 cytokines, such as interleukin-4, interleukin-5, interleukin-10; and decrease pro-inflammatory type 1 cytokines, such as interleukin-12, interleukin-6, interleukin-8, interferon γ, and tumor necrosis factor alpha. Rheumatoid arthritis (IR) is a disorder that involves elevated inflammation related to preAS, endothelial dysfunction, and elevated risk of cardiovascular disease. In individuals with RI, concentrations of vitamin D tend to be reduced and are associated with the disorder (Calton et al., 2015). Hypovitaminosis D is more commonly found in children than adults, and studies have shown that hypovitaminosis D correlates with inflammation and oxidative stress (OS) in children. They have been found connected via the surrogate molecules, including interleukin-6, adiponectin, and cathepsin. In addition, a connection has been observed between hypovitaminosis D and frequency and extent of viral RTIs. Vitamin D exerts an anti-viral function that depends on the inhibition of excessive expression of pro-inflammatory cytokines and regulation of NK cells activity and TLR expression (Filgueiras et al., 2020).

Effects on vascular cells

Activation of calcitriol receptor in endothelial cells are able to regulate blood vessel tone via multiple pathways (Figure 2). Vitamin D modulates the expression of vasoconstrictive metabolites of ARA, promotes synthesis of nitric oxide via activation of NOS, and reduces expression of COX-1, primary origin of EDCFs. Calcitriol receptor activation can decrease influx of Ca^{2+} into the endothelial cells, thus keenly regulating vessel tone. In vitro vitamin D proved to protect against oxidative stress in endothelial cells by inhibiting the reduced nicotinamide adenine dinucleotide phosphate oxidase, resulting in a decrease in production of superoxide and blockade of the external caspase cascade (Hiemstra et al., 2019). It is noteworthy that in vitro vitamin D is able to suppress ICAM-1 and VCAM-1 in endothelial cells, factors that take part in monocyte migration and consequent formation of foam cells (Sen et al., 2022).

Vascular smooth muscle cells constitute the tunica media of vessels. They greatly influence the development of AS via morphological alterations and their ability to proliferate and migrate to the tunica intima and to secrete proinflammatory factors. In vitro vitamin D appears to modulate calcium influx into the cells and to promote anti-proliferative function of vascular smooth muscle cells by suppressing EGF and endothelin (ET) (Durham et al., 2018). Administration of calcitriol at high dosage proved to stimulate migration of vascular smooth muscle cells, and physiological doses of 25-hydroxy vitamin D and calcitriol appeared to suppress proliferation and migration of cells. Activation of vitamin D receptors enhanced formation of elastic fibers and stabilized the vascular smooth muscle cell layer by promoting synthesis of myosin, elastin, type I collagen, and MMP-9. In vitro calcitriol promotes synthesis of prostaglandin I2 through the COX pathway in vascular smooth muscle cells, thus suppressing exacerbation of AS. Activated vitamin D analogues appear to inhibit PAI-1, which has pro-thrombotic and pro-atherogenic properties in HCASMC (Tukaj, 2008).

Vascular calcification (VC) is observed in healthy ageing together with AS (VC of the tunica intima). It develops faster in chronic kidney disease (VC of tunica intima and tunica media), where it correlated with CVD and death. In many researches, hypovitaminosis D is linked to elevated VC and progression of CAC. Vitamin D is able to trigger synthesis of VKDPs and it exhibits synergistic activity. Since hypovitaminosis K correlated with VC, their interplay is considered crucial. Experimental trials indicate that the role of vitamin D receptor activators in the modulation of VC possibly depends on the analogue (Dube et al., 2021). In animals, calcitriol in effective doses elevated VC of the aorta. Although, this effect has not been detected in animals receiving paricalcitol, a synthetic analogue of calcitriol. One study showed that both paricalcitol and calcitriol exerted protective

function against VC, when administered in doses high enough to improve secondary hyperparathyroidism (Becker et al., 2011).

Activated vitamin D sterols therapy in vivo led to a decrease in D_3 levels in plasma due to powerful induction of the vitamin D catabolic pathway. These discoveries correspond with the observations that CYP24A1 gene polymorphisms, which can reduce levels of 25-hydroxy vitamin D, correlate with high CAC (Płomiński et al., 2022). Hereby, provision of vitamin D repletion can facilitate paracrine and autocrine calcitriol production in CV tissues, thus triggering activation of VC inhibitory pathways that depend on calcitriol receptor. Systemic therapy with calcitriol and its analogues can induce expression of 24-hydroxylase, thus suppressing autoregulation. This may lead to hypovitaminosis D in the tissues (Lehmann, 2009; Wu-Wong, 2009).

Regulation of immune cells

Atherogenesis encompasses innate and adaptive immunity. Low-density-Lp particles transport vitamin D, that is then absorbed by different cells, including monocytes, that comprise functional 1-alpha-hydroxylase. Monocyte are able to migrate through the vascular wall and convert into foam cells. Local production of calcitriol may reduce monocyte adhesion modify macrophage gene expression, promote efflux of cholesterol, suppress formation of foam cells, reduce absorption of oxLDL and acLDL, and affect atherogenesis by modulating endothelial cells and vascular smooth muscle cells (such as VEGF production, MMPs, type I collagen) (Abe et al., 2022). In vitro, activation of vitamin D receptor leads to suppression of IFNγ and induction of interleukin-10 secretion. Moreover, vitamin D receptors suppress secretion of interleukin-1 beta and interleukin-6, which averts activation of macrophages and destabilization of AS plaques. In vitro, up-regulation of interleukin-4 by vitamin D receptor activation enhances atheroprotective function of T helper 2 cells, which produce anti-atherogenic cytokines, including interleukin-5, interleukin-10, interleukin-13. It appears that the vasoprotective effect of vitamin D receptor activators may be attributed to these alterations (Di Liberto et al., 2019).

Indirect effects of vitamin D on atheroma formation

Calcitriol receptor activators exert an indirect atheroprotective function, modulating other important mechanisms throughout the body. Vitamin D can modulate the renin-angiotensin-aldosterone system, which is crucial for regulation of BP. Both ALD and ANG II can influence the AS pathogenesis, which is facilitated by hypovitaminosis D that triggers activation of the renin-angiotensin-aldosterone system (Santoro et al., 2015). On the contrary, calcitriol receptor activators are able to block the NF-κB pathway, thus inhibiting expression of renin and AGT genes. Vitamin D also appears to modulate activity of beta cells and sensitivity to insulin. Hypovitaminosis D seems to correlate with dyslipidaemia, which can enhance atherogenesis. Although, a comprehensive examination of this topic is outside the purview of this article (Szymczak-Pajor et al., 2020).

Clinical Studies on Atherosclerosis and Vitamin D Deficiency and Vitamin D Supplementation

New evidence has emerged recently regarding the assessment of the impact of hypovitaminosis D and D_3 supplements on the occurrence of MI and IS. An observational study which included about 340 people demonstrated that individuals with decreased vitamin D values correlated with incidence of CAD, which was diagnosed by CCTA, whereas the median vitamin D levels in these individuals were below those considered to be a deficiency, 20 ng/mL (Legarth et al., 2019). Another research assessed hypovitaminosis D in 637 individuals using coronary catheterization. The results indicated a connection between high concentrations of vitamin D and reduced amount of AS lesions. One retrospective research assessed concentrations of vitamin D in ACS individuals and showed a direct correlation between decreased vitamin D values and incidence of acute coronary syndrome, as well as a negative correlation between decreased D_3 values and concentrations of hs-cTnT (Gondim et al., 2016). Prospective research was conducted in a group of people with unstable angina (UA), STEMI and NSTEMI. The results demonstrated a marked correlation between reduced D_3 values and the acute coronary syndrome, compared to the control group. And conversely, the D_3 values of the control patients without ACS were considerably higher (Silva et al., 2015). 72% of individuals with the acute coronary syndrome showed D_3 insufficiency, whereas 89% of that group had D_3 concentrations < 30 ng/mL. 27.5% of the control patients had D_3 insufficiency and 41.6% – D_3 deficiency. Another research, that included Polish individuals with AMI without complications, showed that all subjects with AMI (n = 59) had D_3 values < 30 ng/mL, and approximately 90% of those subjects had D_3 deficiency with values < 20 ng/mL. There is also information on the connection between vitamin D deficiency and incidence of IS (Dziedzic et al., 2022). Brondum-Jacobsen and colleagues performed an analysis of the Copenhagen City Heart Study which included more than ten thousand subjects (Brøndum-Jacobsen et al., 2015). The results demonstrated a connection between reduced 25-hydroxy vitamin D concentrations and a higher risk of IS. This analysis displayed that the median D_3 levels in individuals in the 50th to 100th percentile were 62 nmol/L, whereas the individuals in the 25th percentile had concentrations of 19 nmol/L. It appears that individuals in the 25th percentile had a marked HR for stroke of 1,45 (1,16-1,80; 95% CI), an elevation of 45%. One research assessed the vitamin D profiles of individuals with IS (n = 168) and demonstrated that the

median D_3 values of this group were considerably lower than in the control group. In the IS group, D_3 deficiency was found in 43% of patients (Nnakenyi et al., 2022; Bilinski et al., 2021). In the control group, D_3 concentrations less than 20 ng/mL were found in 6% of patients. Another Polish research assessed vitamin D profiles and incidence of death in 240 subjects with IS. The results indicated that in the IS group, normal concentrations of vitamin D (> 30 ng/mL) were found in 1,3%. Within 45 months of observation, the subjects with severe vitamin D deficiency (< 10 ng/mL) showed increased death rate: 4,81% versus 1,89% in subjects without severe vitamin D deficiency. Hereby, serious hypovitaminosis D is a major risk factor for mortality in individuals with IS (Wajda et al., 2019).

Studies that evaluated benefits of D_3 supplements in decreasing cardiovascular burden have not shown favorable results. A randomized controlled trial conducted in 2020 in individuals with a mean age of 75 demonstrated that D_3 supplement therapy at a dosage of 2000 IU per day for 36 months did not decrease the high BP, systolic or diastolic, which was initially elevated mainly because of the AS. The median concentrations of vitamin D in these individuals were about 22 ng/mL, and about 40% of individuals receiving supplement therapy were vitamin D insufficient (Pilz et al., 2022). These data indicate that D_3 supplement therapy for less than 36 months in elderly patients does not affect systolic or diastolic blood pressure. Increased BP can lead to development of AS. In animals, it was associated with decreased CD (carotid distensibility) and was considered a risk factor for AS. At the same time, one of the risk factors for AS is elevated blood pressure, which probably makes a positive feedback loop between said cardiovascular disorders (Dominguez et al., 2020). Likewise, a randomized controlled trial conducted in 2017 assessed effects of a D_3 supplement therapy at a dosage of 100,000 IU per month. The results did not show any positive impact on CVD, HT or angina, that follow AS. The study included mostly European individuals with an average age of 66, the follow-up observation continued for approximately 3,3 years. The median concentrations of vitamin D in these patients were 25 ng/mL, however, about 30% had levels less than 20 ng/mL (Scragg et al., 2017). The Randomized Evaluation of Calcium or Vitamin D study did not indicate any positive impact of D_3 supplement administration at low dosage of 400-800 IU in terms of two- to seven-year CV death and total death rates (Grant et al., 2005). In addition, the Women's Health Initiative study demonstrated a slight negative impact of D_3 supplement and calcium therapy on cases of vascularization, non-fatal MI, and CAD mortality (Prentice et al., 2021). Moreover, another research which included approximately 26 thousand randomized subjects evaluated the impact of D_3 supplement therapy at a dosage of 2000 IU per day combined with 1 g of omega-3 FAs. The results did not indicate any decrease in CVD, including MI, IS, and CV mortality, during a 5.3-year observation. In this research, 12,7% of the subjects showed concentrations of 25-hydroxy vitamin D lower than 20 ng/mL. This evidence implies that D_3 supplements are probably not essential in decreasing CVD burden in individuals with normal concentrations of 25-hydroxy vitamin D. Whereas reaching normal vitamin D concentrations is advised for individuals with hypovitaminosis D, additional randomized controlled trials are required to definitively assess the impact of D_3 supplements on decreasing the incidence of MI, IS, and cardiovascular disease burden in individuals with hypovitaminosis D (de la Guía-Galipienso et al., 2021).

Whereas hypovitaminosis D seems to be a crucial risk factor for CVD, further comprehensive research is necessary to investigate the advantageous clinical impact of D3 supplements in individuals with initial vitamin D deficiency (Mandarino et al., 2015).

Conclusion

Available data indicate that vitamin D may greatly contribute to the development of numerous disorders. Its impact on different biological pathways has been detected in a number of randomized controlled trials. However, further research is necessary to definitively establish the exact ways of influence. In the past years attention has been drawn to the role of vitamin D deficiency or supplementation in progression of cardiovascular disease and the corresponding complications. Insufficient levels of vitamin D have been found to correlate with presence of acute coronary syndrome. A number of studies have reported that hypovitaminosis D correlates with coronary artery calcification, which is strongly related to atherosclerosis, CV events and death. Deficient levels of vitamin D also proved to correlate with abnormal lipid values, while normal concentrations of D3 positively affect the lipid levels. Vitamin D was shown to decrease the risk of mortality in individuals with ischemic stroke, decrease the levels of inflammatory cytokines, ameliorate insulin sensibility, lower the levels of monocyte cholesterol. While emerging evidence implies that D3 supplementation might suppress pathogenesis of atherosclerosis and other disorders, additional extensive research is needed to develop therapeutic strategies.

Author contribution

A.V.P. wrote, drafted; V.N.S., A.A.M., V.I.G., V.A.K., A.N.O. wrote, reviewed and edited the paper. All authors have read and agreed to the published version of the manuscript.

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Competing financial interests

The authors have no conflict of interest.

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