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REVIEWS

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The effect of vitamin D deficiency and vitamin D supplementation on the risk of cardiovascular diseases

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A – Study Design, **B** – Data Collection, **C** – Statistical Analysis, **D** – Data Interpretation, **E** – Manuscript Preparation, **F** – Literature Search, **G** – Funds Collection

Summary Studies revealed an association between vitamin D deficiency and the frequency of cardiovascular diseases and their risk factors. This review is aimed at summarizing evidence for the association of vitamin D deficiency and vitamin D supplementation with the risk of cardiovascular diseases. The data was collected by surfing the Pubmed, Cochrane Central Registry and EMBASE databases for appropriate and related studies. Search terms included: "Vitamin D", "cardiovascular diseases", "CVD", "calcitriol" and "1,25-dihydroxy vitamin D". The abstracts of the discovered articles were reviewed, and the full texts of the articles that met the criteria were then evaluated to be used for the study. The large number of clinical trials, cross-sectional, prospective and systematic review studies are evidence that vitamin D deficiency is associated with most cardiovascular disease (CVD) risk factors and with the pathogenesis of CVD. However, with regard to the clinical trial studies evaluated in this work, vitamin D supplementation did not decrease the occurrence of cardiovascular events.

Key words: vitamin D deficiency, cardiovascular diseases, risk.

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Background

Vitamin D is a fat-soluble vitamin and exists in different forms. Cholecalciferol or vitamin D_3 is produced from 7-dehydrocholesterol in human skin at ultraviolet (UV) wavelengths. Vitamin D is required to be activated in the body by the hydroxylation process [1]. It first converts to 25-hydroxyvitamin D by 25-hydroxylase in the liver, and then it converts to 1,25-dihydroxyvitamin D or calcitriol by 1-α-hydroxylase in the kidney, which is the active form of vitamin D and which is responsible for most of its activities [2].

Vitamin D deficiency is extremely prevalent, and more than half of the worldwide population has levels less than 30 ng/ml [3]. The highest vitamin D deficiency levels are usually found in areas like the Middle East and South Asia [3]. Risk factors for vitamin D deficiency include older age, female gender, having dark skin, low exposure to the sun, dietary consumption and low vitamin D fortified foods and air pollution [4].

Vitamin D deficiency has been associated with numerous health problems, including rickets, osteoporosis osteomalacia and osteopenia [5]. It was also related to rheumatoid arthritis, multiple sclerosis, cancers [6], schizophrenia [7], depression [8], obesity [9], cystic fibrosis [9] and diabetes [10]. Moreover, it is linked to cardiovascular diseases, such as congestive heart failure [11], myocardial infarction [12], peripheral vascular disease [13], impaired systolic and diastolic function [14] and hypertension [15].

Cardiovascular diseases (CVDs) are the main reason for death worldwide. According to the World Health Organization (WHO), around 17.9 million persons died (31% of universal deaths) due to CVDs in 2016, most of which (85%) were due to heart attack and stroke, and 75% of CVD deaths happened in low- and middle-income countries [16].

The Vitamin D Receptor (VDR) is an intracellular receptor which binds to calcitriol, the active form of vitamin D. The binding of vitamin D to VDR causes the heterodimerization of VDR with the retinoic acid X receptor, which leads to expression/repression of many other genes [17, 18]. VDR and 1-α-hydroxylase are found in cardiovascular tissues [19]. The activation of VDR in endothelial cells controls the elements in the vascular endothelial growth factor (VEGF) promoter. Moreover, impaired metabolism of vitamin D in the human vasculature leads to the progression of atherogenesis and speeding up of the calcification of arterial wall [20]. In studies on animals with a lack of VDR expression, an amplified ventricular mass and greater levels of matrix metalloproteases and atrial natriuretic peptides was shown, thus stimulating the development of a fibrotic extracellular matrix [19, 20].

Increased levels of vitamin D3 have been shown to reduce cytokine and expression of the adhesion molecule. It has been shown to control the maturation of macrophages and infiltration of them into the vasculature, as well as controlling the pro-inflammatory cytokines and expression of adhesion molecules, which are important in atherosclerosis progress [21]. According to the studies, a number of the vasculoprotective activities of vitamin D could be interceded by raising nitric oxide production, preventing the conversion of macrophages to foams cell or decreasing the expression of the adhesion molecules in endothelial cells [22, 23].

Objectives

Studies revealed an association between vitamin D deficiency and the frequency of cardiovascular diseases and their risk factors. This review is aimed at summarizing the evidence for the association of vitamin D deficiency and vitamin D supplementation with the risk of cardiovascular diseases.

Material and methods

The data was collected by surfing the Pubmed, Cochrane Central Registry and EMBASE databases for appropriate and re-

lated studies. Articles published between the years 2000–2019 were explored, and 40 articles were selected. Search terms included: "Vitamin D", "cardiovascular diseases", "CVD", "calcitriol", and "1,25-dihydroxy vitamin D". 62 articles were found. The abstracts of the discovered articles were reviewed, and the full texts of the 43 articles that met the criteria were then evaluated to be used for the study.

Literature review

In a large cohort by Vacek et al., the association between vitamin D deficiency and supplementation and cardiovascular health was assessed. Serum vitamin D level was measured for 5.8 years, and vitamin D levels < 30 ng/ml were considered as deficient. 7,665 (70.3%) from 10,899 patients showed vitamin D deficiency. Vitamin D deficiency was related to cardiovascular diseases, such as coronary artery disease, hypertension and cardiomyopathy (all $p < 0.05$). They concluded that the lack of vitamin D was related to the risk of a cardiovascular event and reduced survival. Moreover, vitamin D supplementation was meaningfully related to better survival, especially in individuals with a recognized deficiency [24].

In a cohort study by Wang et al., the relation between vitamin D deficiency and cardiovascular disease risk was evaluated for 1,739 individuals without previous cardiovascular disease. 28% of the participants had vitamin D levels of less than 15 ng/ml, and 9% had vitamin D levels of less than 10 ng/ml. During 5.4 years of follow-up, 120 individuals showed their first cardiovascular issues. In comparison to participants with 25-OH D more than 15 ng/ml, those with vitamin D levels of less than 10 ng/ml had a multivariable-adjusted hazard ratio of 1.62 for the occurrence of cardiovascular problems. There was an increase in the risk of cardiovascular events across categories of 25-OH D, with multivariable-adjusted hazard ratios of 1.53 for vitamin D amounts of 10 to < 15 ng/ml and 1.80 for amounts less than10 ng/ml. Therefore, they found that vitamin D deficiency is related to the occurrence of cardiovascular diseases [25].

Faridi et al., in 2017, performed a cross-sectional study on 4,591 participants. In multivariable-adjusted models, participants with lower 25(OH)D had an increased odds ratio of elevated CAD biomarkers, such as Hemosystein (OR = 2.53), hs-CRP (1.62), cystatin-C (2.02), creatinine (2.06), GGT (1.39), uric acid (1.60) and HbA_{1c} (2.47). They concluded that low 25(OH)D is related to raised levels of many cardiovascular risk biomarkers [26].

Sivritepe et al. evaluated 108 diabetic cases with vitamin D insufficiency (≥ 10–30 ng/ml) and 100 cases with vitamin D deficiency (< 10 ng/ml). They found a close correlation with the Framingham cardiovascular risk score in patients with type 2 diabetes with very low levels of serum vitamin D. Cardiovascular risk, as measured by the Framingham's scale, rises with declining vitamin D levels [27].

In a study by Aljack et al. in 2019, 205 patients with type 2 diabetes were evaluated for vitamin D deficiency and the risk of cardiovascular diseases. According to their results, patients with vitamin D deficiency had a higher risk of cardiovascular disorders [16].

In a cross-sectional study by Alkhatatbeh et al., 104 patients who underwent cardiac catheterization which did not show any cardiac origin for their chest pain were evaluated. High-density lipoprotein cholesterol (HDL-C) was significantly higher in patients with sufficient vitamin D in comparison to patients with deficient vitamin D ($p < 0.01$). 25-hydroxyvitamin D was directly correlated with HDL-C ($p < 0.01$) and adversely correlated with HbA_{1c} ($p = 0.02$). They concluded that low serum vitamin D could decrease HDL-C and raise HbA_{1c} and may increase the risk of cardiovascular events in non-cardiac chest pain subjects [28].

Schierbeck et al. evaluated 2,016 healthy, newly postmenopausal females. The follow-up time was 16 years. Vitamin D serum levels of < 50 nmol/l were defined as a deficiency. In comparison to vitamin D-replete females, females with vitamin D deficiency showed more cardiovascular risk factors. Female with low vitamin D levels showed higher BMI and triglycerides and lower HDL levels than the vitamin D-replete group. A primary endpoint was experienced by 118 (15%) individuals with vitamin D deficiency and by 125 (10%) of vitamin D-replete individuals. The hazard ratio was 1.49 in the vitamin D deficient group, and the adjusted hazard ratio was 1.32. They concluded that healthy postmenopausal females with vitamin D deficiency have an increased risk of cardiovascular events [29].

Hosseinpanah et al. performed a nested case-control study on 251 individuals without prior cardiovascular disease and who developed a cardiovascular disease during the 5.7 years of follow-up. After adjustment for potential confounders, the odds ratio of serum vitamin D less than 10 ng/ml for having cardiovascular disease outcomes was 2.90 in comparison to serum vitamin D ≥ 15 ng/ml ($p < 0.001$). They indicated that the serum concentration of 25-OH-D has an independent association with cardiovascular outcomes in Tehranian adults [30].

In a cross-sectional study by Kim et al., the occurrence of hypovitaminosis D in patients with cardiovascular diseases was evaluated using data from the National Health and Nutrition Examination Survey from 2001 to 2004. Hypovitaminosis D was considered as vitamin D levels less than 30 ng/ml. Of the 8,351 patients, the frequency of hypovitaminosis D was 74%. Hypovitaminosis D is more prevalent in patients with coronary heart disease (77%; odds ratio: 1.48, 95% CI = 1.14 to 1.91). According to their results, hypovitaminosis D was extremely prevalent in US adults with cardiovascular diseases [31].

Nargesi et al. assessed the influence of vitamin D deficiency on the risk of coronary heart disease in patients with hypertension. In that cohort, they followed 1,586 individuals with hypertension for 8 years and 5 months. Individuals in the lowest quartile of 25-Hydroxy-Vitamin-D showed the highest number of coronary artery events. A significant linear trend was detected in hazard ratios of the occurrence of coronary artery disease events in 25-Hydroxy-Vitamin-D quartiles, which is also significant after adjustments for conventional CAD risk factors. They demonstrated that that serum vitamin D is independently associated with future hard CAD incidences [32].

Wasson et al. studied 244 randomly selected participants in the Canadian Nova Scotia Health Survey 1995 whose plasma vitamin D was tested and had a previous history of cardiovascular disease, such as ischemic heart disease (IHD). 114 IHD events happened during the 10 years of follow-up. Levels of vitamin D < 30 ng/ml were associated with a hazard ratio of 1.33 ($p = 0.172$) for IHD events in comparison to vitamin D levels ≥ 30 ng/ml. For vitamin D levels of < 15 ng/ml, the hazard ratio was 2.30 ($p = 0.035$) for IHD events in comparison to ≥ 30 ng/ml. They showed that in patients with previous cardiovascular diseases, noticeable vitamin D deficiency was related to an increase in the risk of IHD events [33].

Martins et al. studied the relation of serum levels of 25-hydroxyvitamin D and cardiovascular disease risk factors in US adults. There were 7,186 male and 7,902 female adults over 20 years of age with accessible data in the Third National Health and Nutrition Examination Survey. Female, elderly (≥ 60 years), racial/ethnic minorities and individuals with obesity, hypertension and diabetes had lower levels of 25 (OH). The adjusted frequency of hypertension (OR: 1.30), obesity (OR: 2.29), diabetes (OR: 1.98) and high serum triglyceride (OR: 1.47) was significantly more in the first quartile than in the fourth quartile of serum vitamin D amounts ($p < 0.001$). They found that serum 25 (OH)D amounts are related to significant cardiovascular disease risk factors in US adults [34].

Siadat et al. showed that after adjustment with cardiovascular risk factors, the odds ratio of being affected by CAD in patients with low vitamin D levels (< 30 ng/ml) was 5.8. They mentioned that 25(OH)D deficiency is associated with the incidence of CAD independent of cardiovascular risk factors [35].

In a systematic review by Mirhosseini et al., the effect of vitamin D supplementation and serum 25(OH)D levels on cardiovascular disease risk factors were assessed. The meta-analysis showed a significant decrease in systolic blood pressure, diastolic blood pressure, serum PTH, hs-CRP, total cholesterol, LDL, triglycerides, as well as a significant increase in HDL with vitamin D supplementation. These outcomes stayed significant in sensitivity analyses for blood pressure, serum PTH, serum hs-CRP and lipid profile. They suggested that vitamin D supplementation may protect against CVD by improving CVD risk factors [36].

A study by Veloudi et al. evaluated 57 RCTs and concluded that vitamin D supplementation was not effective in improving cardiovascular health in different patient populations [37].

Ruwanpathirana et al. studied the effectiveness of oral vitamin D in the prevention of cardiovascular diseases in migrants in Australia. Adult migrants who had vitamin D deficiency were included in the study. Vitamin D oral supplementation for 10 years could potentially prevent 31 non-fatal and 11 fatal cardiovascular events in a migrant population of 10,000 [38].

In a meta-analysis by Barbarawi et al. on randomized clinical trials that measured the association of vitamin D supplementation with decreased CVD events, 21 randomized clinical trials were assessed. Vitamin D supplementation was not related to decreased cardiovascular events, nor the secondary endpoints of myocardial infarction, stroke and CVD mortality. According to the results, vitamin D supplementation was not correlated with decreased cardiovascular events [39].

In a clinical trial study by Scragg et al., the effectiveness of monthly high-dose vitamin D Supplementation on CVD was evaluated. Participants received oral vitamin D with a first dose of 200,000 IU, followed every month after by a doses of 100,000 IU/mon or placebo for an average of 3.3 years. Of 5,108 participants, 1,270 participants (24.9%) had vitamin D deficiency. The primary outcome of CVD occurred in 11.8% of individuals in the vitamin D group and 11.5% of individuals in the placebo group, with an adjusted hazard ratio of 1.02. Monthly high-dose vitamin D supplementation does not prevent CVD. This study does not recommend the use of vitamin D supplementation for reducing CAD events [40].

Zittermann et al. performed a randomized controlled trial on 161 patients with heart failure who received a daily vitamin D supplement for 3 years. Lipid parameters and vascular calcification markers did not differ significantly between groups. Therefore, vitamin D had no positive effect on the lipid profile and no effect on the calcification inhibitors (fetuin-A) in heart failure patients [41].

In the Manson et al. nationwide, randomized, placebo-controlled trial study, vitamin D_3 (2,000 IU per day) and omega-3 fatty acids (1 g per day) were administered for the prevention of cardiovascular disease. During 5.3 years of follow-up, cardiovascular events occurred in 396 patients in the vitamin D group and 409 patients in the placebo group, with a hazard ratio of 0.97. Therefore, supplementation with vitamin D did not decrease the occurrence of cardiovascular events when compared to a placebo [42].

Angellotti et al. evaluated the effect of vitamin D supplementation on cardiovascular risk in patients with type 2 diabetes. A double-blind, randomized, placebo-controlled clinical trial was performed for 127 cases with stable diabetes. They received vitamin D_3 (4,000 IU/day) or placebo for 1 year. No significant alteration was observed in the lipid profile, C-reactive protein and cardiovascular risk. However, vitamin D improved triglyceride levels in patients who did not use cholesterol medication [43] (Table 1).

Table 1. Studies that evaluated the effect of vitamin D deficiency and vitamin D supplementation and the risk of cardiovascular diseases

Study	Measurement	Outcome of the study
Vacek et al. (2012) [24]	Vitamin D deficiency and supplementation and cardiovascular health assessed in a cohort study on 10,899 patients.	The lack of vitamin D was related to the risk of a cardiovascular event and reduced survival. Vitamin D supplementation was related to better survival.
Wang et al. (2008) [25]	In a cohort study, the relation between vitamin D deficiency and cardiovascular disease risk was evaluated on 1,739 individuals without previous cardiovascular disease.	Vitamin D deficiency was related to the occurrence of cardiovascular disease.
Faridi et al. (2017) [26]	A cross-sectional study on 4,591 participants.	Low 25(OH)D is related to raised levels of many cardiovascular risk biomarkers.
Sivritepe et al. (2019) [27]	They evaluated 108 diabetic cases with vitamin D insufficiency and 100 cases with vitamin D deficiency.	Cardiovascular risk rises with declining vitamin D levels.
Aljack et al. (2019) [16]	205 patients with type 2 diabetes were evaluated for vitamin D deficiency and the risk of cardiovascular diseases.	Patients with vitamin D deficiency had a higher risk of cardiovascular disorders.
Alkhatatbeh et al. (2019) [28]	In a cross-sectional study, 104 patients who underwent cardiac catheterization which did not show any cardiac origin for their chest pain was evaluated.	Low serum vitamin D could decrease HDL-C and raise HbA_{1c} and may increase the risk of cardiovascular events in non-cardiac chest pain subjects.
Schierbeck et al. (2016) [29]	Vitamin D deficiency in postmenopausal, healthy women predicts increased cardiovascular events.	Healthy postmenopausal female with vitamin D deficiency have increased risk of cardiovascular events.
Hosseinpanah et al. (2011) [30]	Case-control study on 251 individuals without prior cardiovascular disease who developed cardiovascular disease during 5.7 years of follow-up.	The serum concentration of 25(OH)D has an independent association with cardiovascular outcomes in Tehranian adults.
Kim et al. (2008) [31]	In a cross-sectional study, the occurrence of hypovitaminosis D in patients with cardiovascular diseases was evaluated using data from the National Health and Nutrition Examination Survey.	Hypovitaminosis D was extremely prevalent in US adults with cardiovascular diseases.

Table 1. Studies that evaluated the effect of vitamin D deficiency and vitamin D supplementation and the risk of cardiovascular diseases

Study	Measurement	Outcome of the study
Nargesi et al. (2016) [32]	The influence of vitamin D deficiency on the risk of coronary heart disease in patients with hypertension.	They demonstrated that that serum 25(OH)D level is independently associated with future hard CAD incidence.
Wasson et al. (2011) [33]	244 randomly selected participants in the Canadian Nova Scotia Health Survey who had a previous history of cardiovascular disease.	In patients with previous cardiovascular disease, noticeable vitamin D deficiency is related to an increase in the risk of IHD events.
Martins et al. (2007) [34]	The relation of serum levels of 25-hydroxyvitamin D and cardiovascular disease risk factors in US adults.	Serum 25(OH)D amounts are related to significant cardiovascular disease risk factors in US adults.
Siadat et al. (2012) [35]	Association of vitamin D deficiency and coronary artery disease with cardiovascular risk factors.	25(OH)D deficiency is associated with the incidence of CAD independent of cardiovascular risk factors.
Mirhosseini et al. (2018) [36]	In a systematic review, the effect of vitamin D supplementation and serum 25(OH)D levels on cardiovascular disease risk factors was assessed.	They suggested that vitamin D supplementation may protect against CVD by improving CVD risk factors.
Veloudi et al. (2017) [37]	Effectiveness of vitamin D supplementation for cardiovascular health outcomes by evaluating 57 RCTs.	Vitamin D supplementation was not effective in improving cardiovascular health in different patient populations.
Ruwanpathirana et al. (2015) [38]	Study on the effectiveness of oral vitamin D in the prevention of cardiovascular diseases in migrants in Australia.	Vitamin D oral supplementation for 10 years could potentially prevent 31 non-fatal and 11 fatal cardiovascular events in a migrant population of 10,000.
Barbarawi et al. (2019) [39]	A meta-analysis on 21 randomized clinical trials that measured the association of vitamin D supplementation with decreased CVD events.	Vitamin D supplementation was not correlated with decreased cardiovascular events.
Scragg et al. (2017) [40]	A clinical trial study on the effectiveness of high-dose vitamin D supplementation on CVD was evaluated.	This result does not recommend the use of vitamin D supplementation for reducing CAD events.
Zittermann et al. (2019) [41]	A randomized, controlled trial on 161 patients with heart failure who received daily vitamin D supplement for 3 years.	Vitamin D had no positive effect on the lipid profile and no affect the calcification inhibitors in heart failure patients.
Manson et al. (2019) [42]	Randomized, placebo-controlled trial study where vitamin D_3 and omega-3 fatty acids were administered for the prevention of cardiovascular disease.	Supplementation with vitamin D did not decrease the occurrence of cardiovascular events when compared to a placebo
Angellotti et al. (2018) [43]	Evaluated the vitamin D supplementation effect on cardiovascular risk in patients with type 2 diabetes.	No significant alteration was observed in lipid profile, C-reactive protein and cardiovascular risk.

Conclusions

Studies have shown a relationship between vitamin D deficiency and the frequency of cardiovascular diseases and their risk factors. In this study, we summarized the evidence for the association of vitamin D deficiency and vitamin D supplementation with the risk of cardiovascular diseases. Vitamin D deficiency is an extremely widespread situation. A large number of clinical trials, cross-sectional, prospective and systematic review studies are evidence that vitamin D deficiency is associated with most CVD risk factors and with the pathogenesis of CVD. However, with regard to the clinical trial studies evaluated in this work, vitamin D supplementation did not decrease the occurrence of cardiovascular events.

Abbreviations. CVD – cardiovascular diseases; UV – ultraviolet; VDR – vitamin D receptor; VEGF – vascular endothelial growth factor; IHD – ischemic heart disease.

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