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Review Article

Vitamin D associated inflammation and atherosclerosis

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Abstract

Vitamin D is known to play a crucial role in mineral homeostasis and bone metabolism. Recent discoveries showed that the vitamin also regulate the inflammatory mediators. A number of studies have reported on the association of low vitamin D levels with increased level of inflammatory parameters; which predisposes to atherosclerosis and development of cardiovascular diseases (CVD). Since inflammation is implicated in the pathogenesis of CVD, measurement of inflammatory marker levels has been proposed as a method to improve the prediction of these events. In this review, the mechanism of inflammation and role of vitamin D in combating inflammation are discussed

Keywords: *cardiovascular disease, endothelial function, inflammation, high sensitivity C-reactive protein (hsCRP), vitamin D*

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INTRODUCTION

Introduction to vitamin D

Traditionally vitamin D aids in bone development, growth and maintenance throughout life [1,2]. Vitamin D deficiency or insufficiency is common among the general population; many do not realize the importance of vitamin D. Apart from its classical actions in mineral homeostasis and bone metabolism, recent research shows wider biological actions of vitamin D which is likely due to presence of vitamin D receptor in a variety of target cells and tissues. The presence of vitamin D receptor (VDR) is not only confined to the classical vitamin D organs (intestine, bone, kidney and parathyroid) but also discovered in other organs such as the heart, vasculature, skin, muscle, pancreas, reproductive organs, hematopoietic and immune systems [3,4]. Their biological action in these organs include induction of cell differentiation, inhibition of cell growth, immunomodulation, neuroprotective effects, reduction in inflammation and control of other hormonal system [5,6].

Physiology of vitamin D

There are two major types of vitamin D classified as vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol) which both differs in their side chain. Vitamin D from either source is also called as sunshine vitamin D as both are synthesized under the influence of sunlight. Vitamin D2 is

produced from the irradiation of plant sterols (ergosterol). Exposure of sun light (UV rays with wavelength between 280 and 320nm) to human epidermis stimulates the non-enzymatic photolytic conversion of 7-dehydrocholesterol (cholesterol precursor) to previtamin D which will later undergo thermal isomerisation to produce vitamin D3 [6,7]. Vitamin D3 was found to be more effective in raising and maintaining serum 25- hydroxyvitamin D levels compared to vitamin D2 [8].

Vitamin D can be obtained from fortified foods or supplements and is absorbed in the small intestine [9]. Both types of vitamin D are biologically inert, which upon oral administration needs to be biologically activated via two hydroxylation processes—first in the liver (25-hydroxyvitamin D [25(OH) D]), and later in kidneys—to produce 1, 25 dihydroxyvitamin D3 (calcitriol) [6,7] (Figure 1).Calcitriol circulates throughout the body to exert its multiple biological effect by binding to vitamin D receptors, which are predominately present on numerous types of cells such as myocytes, cardiomyocytes, pancreatic beta-cells, vascular endothelial cells, neurons, immune cells, osteoblasts, circulating monocytes, transformed B-cells, activated T-cells , neurons, ovarian cells and pituitary cells [9,10].

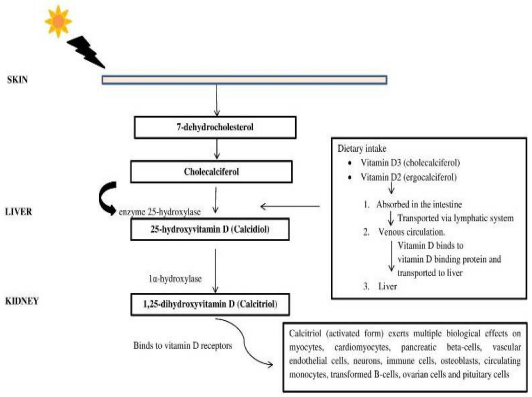

Figure 1: Production and distribution of vitamin D in human body

Though 1, 25$(OH)_2$D or calcitriol is the biologically active form of vitamin D; it is not the ideal marker for vitamin D status determination. Serum 25(OH)D serves as a good indicator to determine vitamin D levels, as it reflects the amount of vitamin D storage [11,12], while serum concentrations of 1, 25$(OH)_2$D are controlled mainly by parathyroid hormone which depends on the calcium needs in human [13]. The levels of calcitriol also do not significantly indicate the precise amount of vitamin D as calcitriol does not typically decrease until vitamin D deficiency condition appears [9]. In addition, serum 25(OH)D has longer circulating half-life of 15 days contrary to serum 1, 25$(OH)_2$D that has shorter half-life of 15 hours [12]. Many studies defined vitamin D deficiency as having circulating serum 25(OH)D less than 50 nmol/L (20ng/ml) [9,14,15]. Vitamin D insufficiency is defined as circulating serum 25(OH)D levels below 75 nmol/L (30 ng/mL) while vitamin D sufficient levels ranged between 75 and 150 nmol/L (30 and 60 ng/mL) [9,16,17].

Inflammation and atherosclerosis

Atherosclerosis, a major contributor to CVD [18], is a process that comprises a complex interplay between different factors and cell types, including cells of the immune system (e.g: monocytes/macrophages, T-cells and B-cells) and cells of the vessel wall (eg: endothelial cells and vascular smooth muscle cells).

Atherosclerosis is characterized by alterations in the normal functions of the endothelium, promoting an inflammatory response that results in plaque vulnerability and rupture. Chronic inflammatory events are initiated by lipid peroxidation [oxidized low-density–lipoprotein cholesterol (LDL-C)], endothelial injury and/or infection, which can be worsened by hypertension, diabetes, and smoking [19]. In atherosclerosis, endothelial cells over-express adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1), which then increases recruitment of leucocytes such as monocytes and T-cells to the site of endothelial injury. Leucocytes release monocyte chemo-attractant protein-1 (MCP-1) that magnifies the recruitment of additional monocytes. The monocytes become macrophages, which in turn release additional cytokines and migrate through endothelium into the intimal layer of the vessel wall. These macrophages later differentiate into foam cells that become the main core of atherosclerotic lesion [19].

Many mediators of inflammation influence the development of atherosclerotic plaque. Cytokines such as interleukin IL-1, IL-4, IL-6, interferon (IFN-γ) and tumor necrosis factor (TNF-γ) and MCP-1 are secreted by activated inflammatory cells. Two types of cytokines are produced, which are divided into pro-inflammatory (IL-1, IL-4, IL-6, IL-18, IFN-γ and TNF-α) and anti-inflammatory cytokines [IL-10 and transforming growth factor-β (TGF β)]. Anti-inflammatory cytokines may either inhibit pro-inflammatory cytokine synthesis or control pro-inflammatory cytokine-mediated cellular activities [20-22].

When the balance between the pro- and anti-inflammatory cytokines is disrupted, the net effect of inflammatory response is determined. Endothelial cells are vulnerable to the exposure of pro-inflammatory cytokines which leads to transient and reversible endothelial dysfunction [23,24]

Several serum inflammatory markers have been proposed to be used as markers to assess for risk of atherosclerotic lesions. The most widely used in current clinical practice include high sensitivity C-reactive protein (hs-CRP), IL-6, fibrinogen and serum amyloid A (SAA). Pro-inflammatory IL-6 causes the liver to increase hs-CRP and SAA. It also increases fibrinogen and plasminogen activator inhibitor type 1 and exhibit pro-coagulant responses.

Role of vitamin D in atherosclerosis

Vitamin D and Inflammation

Vitamin D has anti-inflammatory properties. Vitamin D has been reported to increase production of anti-inflammatory cytokine IL-10 and decrease the pro-inflammatory cytokines IL-6, IL-12, IFN-γ, and TNF-α production [25-27]. In experimental hypercholesterolemic swine model, it has been shown that vitamin D-deficient group have significantly higher expression of pro-inflammatory cytokines including TNF-α, IL-6, MCP-1 and decreased anti-inflammatory adiponectin in epicardial adipose tissue compared to vitamin D-sufficient swine model [28].

Vitamin D is also capable of preventing inflammation by down regulating nuclear factor NF-κB activity. NF-κB is a transcription factor that plays an essential role in the immune system. Many pro-inflammatory cytokines and chemokines, such as IL-1, IL-6, IL-8, IL-12 and TNF- α, are targets of NF-κB activity [29]. NF-κB activity is inhibited by the inhibitor of κB (IκB) [29]. Previous research work reported that vitamin D is able to reduce NF-κB by up-regulating the levels of IκB expression [30,31]. Vitamin D receptor is suggested to be directly involved in the suppression of NF-κB activation by direct involvement in the regulation of IκB expression [32,33]. Besides, vitamin D also induces superoxide dismutase activity, which has been suggested to inactivate NF-κB pathways and therefore may play an important role in the prevention of inflammation [27].

In vitro studies showed that vitamin D represses endoplasmic reticulum (ER) stress in macrophages from diabetic patients and thus prevents foam cell formation, indicating that vitamin D displays anti-atherogenic properties through an ER stress-dependent mechanism. It demonstrated that vitamin D acts as a natural monocyte/ macrophage ER stress reliever that stimulates an anti-inflammatory monocyte/ macrophage phenotype and therefore lessens inflammation and vascular complications in diabetes [34-36].

Pre-treatment of human microvessel endothelial cells (HMEC) with vitamin D inhibits enteric Gram-negative bacterial lipopolysaccharide (LPS) activation. Activation of vascular endothelium by LPS results in production of various pro-inflammatory molecules including NF-κB, IL-6 and IL-8 [37]. The outcomes from the study showed that vitamin D and its analogues may exert immune regulatory functions on endothelium. Since microbial antigen-induced endothelial cell activation is involved in sepsis and atherosclerosis, vitamin D therapy might be used as an alternative treatment for sepsis and atherosclerosis.

Vitamin D and endothelial function

Vitamin D may exert protective effects against endothelial dysfunction, which is the precursor to the development of atherosclerosis [38]. Under the presence of vitamin D receptor in endothelial cells, vitamin D is produced locally since the cells express 1-alpha-hydroxylase that allows them to convert 25(OH)D to $1,25(OH)_2D$ and therefore aids in slowing down the progression of endothelial dysfunction and subsequent atherosclerosis development [39].

Endothelial dysfunction is mainly characterized by the reduction in NO production which can be due to reduced expression of the NO synthesizing enzyme, endothelial NO synthase (eNOS). Vitamin D directly enhance transcriptional activity regulator of eNOS; vitamin D insufficiency is associated with endothelial dysfunction and hypertension [40]. In human umbilical endothelial cells culture (HUVEC), vitamin D in a dose-dependent manner stimulates the production of NO through eNOS activation [41]. Moreover, vitamin D has a direct effect on phosphatidylinositol 3 kinase in endothelial cells [42,43]. Phosphatidylinositol 3 kinase is involved in the activation of eNOS which in turn catalyses the production of NO from L-arginine [44]

One of the causative agents that lead to endothelial damage is the presence of oxidative stress. Increased production of reactive oxygen species (ROS) [45] with diminished antioxidant

defence mechanism is a significant contributor to endothelial damage. Vitamin D has been reported as an agent that enhances antioxidant defence and therefore reduced the damage caused by oxidative stress. Studies showed that vitamin D reduced lipid peroxidation [46-48] and maintain a steady level of glutathione (GSH), a potent intracellular antioxidant [49]. Vitamin D also protected injury to endothelial cells by suppressing the formation of oxidative stress by counteracting superoxide anion generation [50-52]. In vivo and in vitro experiments showed that 22-oxacalcitriol (vitamin D analogue) improved endothelial dysfunction in DM rats by suppressing ROS generation through p22phox expression, which might contribute to improved eNOS uncoupling [53]. Vitamin D analogs are able to suppress renin production, while vitamin D deficiency stimulates renin expression [54]. Increase in renin production increases production of angiotensin II. Angiotensin II is a potent activator of NAD(P)H oxidase in the CVS system, and augments production of reactive oxygen species (ROS) [55]. Vitamin D decreases renin expression by blocking the activity of cyclic AMP response element in the renin gene promoter and therefore normalizes the expression of angiotensin II receptor type 1 and preventing ROS overproduction [56,57]

Vitamin D also is seen to inhibit endothelial-dependent contractions and lowers BP [58]. Vitamin D might inhibit the synthesis of endothelium-derived contracting factors via several mechanisms. It prevents the influx of the calcium into endothelial cells which results in the inactivation of calcium-dependent phospholipase A2. Activation of phospholipase A2 converts membrane phospholipids into arachidonic acid, which ultimately produces endothelial-derived contracting factors. Vitamin D decreases the release of these arachidonic metabolites by preventing the calcium increase. A recent study showed that vitamin D reduced the expression of cyclooxygenase-2 (COX-2), which is responsible for the synthesis of prostaglandins [59]. COX-2 is normally not presence in intact blood vessels; however, it is expressed in atherosclerotic lesions endothelium and vascular smooth muscle (VSMC) in response to inflammatory stimuli. Vitamin D represses the protein and mRNA expression of COX-2, thereby suppressing the production of several pro-inflammatory cytokines. It also up regulates the expression of 15-hydroxyprostaglandin dehydrogenase, the enzyme that inactivates prostaglandin and down regulates the expression of prostaglandin receptors [59]. Vitamin D3 has also been shown to increase the production of prostacyclin in VSMC through the COX pathway [56].

Vitamin D and studies in humans

Many cross sectional and interventional studies conducted in human population showed the association between vitamin D level and cardiovascular risk. Low vitamin D is commonly reported in older [61-63] and obese [64] populations, and among patients with CVD diseases [65,66] (Table I). Emerging evidence show that low vitamin D status is linked with elevated inflammatory parameters, impaired vascular endothelial function and augmented oxidative stress.

Vitamin D deficiency is associated with increased inflammatory markers and therefore supplementation of vitamin D may be useful in preventing the vascular inflammatory process, hence CVD. Several randomised controlled trials have been conducted to examine the effects of vitamin D on inflammatory profile and endothelial function (Table 2). It was reported that treatment with vitamin D analogue (0, 1 or 2 µg of paricalcitol for one month duration) reduced hsCRP levels in chronic kidney disease patients who were vitamin D deficient (<75 nmol/L). High dose treated patients experience a greater reduction in hsCRP levels, however no changes were noted in FMD and BP [67].

In congestive heart failure (CHF) patients with low vitamin D levels, supplementation with 50 mg of cholecalciferol vitamin D3 for 9 months showed improvement in the cytokine profile by increasing IL-10 level and suppressing the production of pro-inflammatory cytokine, TNF-α [68].Similarly, in infants with CHF and low vitamin D levels, 3 months treatment with oral drops of vitamin D3 demonstrated an increased in IL-10 and decreased parathyroid hormone, IL-6, and TNF-α levels which was associated with significant improvements in their cardiovascular profile (improvement in HF score, left-ventricular (LV) end-diastolic diameter, LV end-systolic diameter, LV ejection fraction %, and myocardial performance index) as the increasing concentrations of pro-inflammatory cytokines contributes to the pathogenesis of CHF [69].

In a randomized study performed in healthy overweight subjects with inadequate levels of vitamin D [<30 nmol/L], 12 months treatment with vitamin D (which vitamin D) (83 µg/daily) showed decreased levels of TNF-α and triglycerides [70].

Treatment with vitamin D was also seen to alter the hsCRP levels in obese patients who had serum vitamin D level repleted (≥80 nmol/L) with the treatment, while no improvement of hsCRP was observed in those with 25(OH)D ≤ 80nmol

Table 1: Relationship between vitamin D and inflammatory marker

Study populations	Vitamin D levels (nmol/L)	Summary of findings	References
Healthy Irish adults (n=957; male n=481, female n=476) Mean age: 70.5 (65.9-74.9) years old	Serum 25(OH)D Deficiency status: < 25 Sufficiency status: > 75	• Significant reduction of IL-6, CRP, ratios of IL-6 to IL-10 and ratios of CRP to IL-10 in vitamin D deficient group	Laird et al., 2014 [61]
Men (n=47) Postmenopausal women (n=28) Age: 50-79 years old	Serum 25(OH)D Deficiency status: < 50 Insufficiency status: 50-72.5 Sufficiency status: > 72.5	• Plasma IL-6 was higher in deficient than sufficient group • Expression of NFκB was greater in endothelial cells of deficient group • Vascular expressions of VDR and 1α-hydroxylase were lower in deficient group	Jablonski et al., 2011 [62]
Normal population cohort (n=253) Age: 51-77 years old	Serum 25(OH)D Deficiency status: < 50 Sufficiency status: 60-160	• Low level of vitamin D is inversely correlated with ADMA, hs-CRP and BMI	Ngo et al., 2010 [63]
Obese Caucasian children (n=66; male n= 41, female n=25) Children with normal BMI (n=39; male n=19, female n=20) Age: 7-14 years old	Serum 25(OH)D Deficiency status: < 50 Insufficiency status: ≥ 50	• Mean vitamin D levels were lower in obese children • MDA, MPO, 3-nitrotyrosine, IL-6, sVCAM-1 were elevated in obese children with vitamin D insufficiency.	Codoner-Franch et al., 2012 [64]
Patients underwent angiography (n=2015; male n=1383, female n= 632) - Patients with CAD - Patient without CAD	Serum 25(OH)D CAD patients: 43.5±23.5 control: 46±29.3 Serum 1,25$(OH)_2$D CAD: 86±33.25 controls: 88.3±31.75	• Serum vitamin D levels were similar in CAD patients and controls • Neopterin and hs-CRP levels were higher in CAD patients than controls • Vitamin D levels were inversely correlate with serum neopterin levels	Murr et al., 2012 [65]
Heart failure patients (n=548) - Deficient group, n=182 - Insufficient group, n=183 - Sufficient, n=183 Median age: 74 (68-80) years old	Serum 25(OH)D First tertile/deficient, n=182: < 29.6 Second tertile/insufficient, n=183: 29.6–43.9 Third tertile/sufficient, n=183: > 43.9	• Low level of vitamin D is associated with high levels of PRA and CRP in heart failure patients	Liu et al., 2011 [66]

1,25$(OH)_2$D; 1,25-dihydroxyvitamin D; 25(OH)D, 25-hydroxyvitamin D; ADMA, asymmetric dimethylarginase; BMI, body mass index; hs-CRP; high sensitivity C-reactive protein; IL-6, interleukin-6; IL-10, interleukin-10; MDA, melondialdehyde; MPO, myeloperoxidase; NFκB, nuclear factor κB; PRA, plasma renin activity; VCAM-1, vascular cell adhesion molecule-1; VDR, vitamin D receptor

[71]. In another study, weight-loss intervention together with 2000 IU/day oral vitamin D3 for six months significantly reduced IL-6 level in patients with obesity and vitamin D deficiency (<80nmol/L) [72].

A study by Arson and colleagues [73] shows that supplementation with vitamin D_3 (4000 IU for 5 days) reduces IL-6 and hsCRP levels in patients with acute myocardial infarction which had low vitamin D levels (<50nmol/L). In type-2 diabetic patients with low level of vitamin D, reduction in TNF α was also observed with vitamin D_3 treatment (400 IU/daily for 14 weeks) [74].

Positive changes in anti-inflammatory phenotypes (lower IL-10 and higher IL-17 levels) and markers of subclinical atherosclerosis (FMD and EPC) were achieved following vitamin D_3 treatments (50000 IU weekly for 8 weeks followed by maintenance dose of 1500 to 2000 IU daily for 6 months) in vitamin D deficient young pre-menopausal women [75].

However not all the studies reported changes in inflammation markers with vitamin D supplementation. In type-2 diabetic patients, 24 weeks treatment with cholecalciferol 2,000 IU + calcium 200 mg daily) failed to improve hsCRP level [76]. As suggested by the researcher of the study, the dose given might not able to improve hsCRP level. Additional high dose vitamin D with longer term of interventions in severe vitamin D-deficient populations should be carried out as proposed by the researcher of the study.

Another intervention study which was performed in type-2 diabetic patients demonstrated that treatment with oral 5000 IU vitamin D3 supplement (for twelve weeks) did not show any changes in hsCRP levels, oxidative stress markers, circulating levels of EPCs and vascular function [77]. The study conducted above included vitamin D deficient and non-deficient populations and it appears that the effect of vitamin D more pronounced in vitamin D deficient patients compared to non-deficient.

A recent study reported that in diabetic nephropathy patients, hsCRP level remained unchanged in patients who receive alfacalcidol 0.25 mcg for six months; however significant increase was seen in the control group, suggesting that vitamin D might suppresses inflammatory progression in diabetic nephropathy patients [78]. Both studies conducted above included vitamin D deficient and non-deficient populations and it appears that the effect of vitamin D more pronounced in vitamin D deficient patients compared to non-deficient.

In patients with coronary artery disease, no changes were seen in pro-inflammatory cytokines (IL-12, IFNγ, hsCRP and IL-6), BP and endothelial function with 50,000 IU of oral vitamin D2weekly for 12 weeks [79]. However, several reports stated that vitamin D3 is more effective in raising vitamin D levels compared to vitamin D2 which might influence the study outcome [80,81]. No changes were also seen in hsCRP, endothelial function and arterial stiffness in vitamin D deficient patients with peripheral arterial disease following a single oral high-dose cholecalciferol supplementation (100 000 IU) with the parameters investigated evaluated at baseline and after one month of cholecalciferol intake. Although this was study conducted in vitamin D deficient population, shorter period of vitamin D intervention may influence the negative study outcomes. A longer treatment may be needed for vitamin D to produce significant improvement on hsCRP, endothelial function and arterial stiffness in peripheral arterial disease patients [82].

A study conducted among vitamin D deficient obese population prescribed with 7000 IU of vitamin D daily for 26 weeks) did not cause significant changes to inflammatory markers (hsCRP and IL-6), body fat, insulin level and BP [83]. Another study also shared similar outcome, where there was no significant reduction in hsCRP or any other cytokines in overweight subjects following one year intervention with 40,000 IU vitamin D3 per week, 20,000 IU vitamin D per week, or placebo [84]. Both studies involved healthy subjects where they might not be exposes to any risk factors that increase the inflammation levels in their body. It is possible that the effect of vitamin D is more obvious when the immune system is induced such as in patients with inflammatory or autoimmune diseases.

CONCLUSION

Studies suggest that the effects of vitamin D is more beneficial in reducing inflammation levels and improving cardiovascular risk markers in those with vitamin D deficiency compared to those with sufficient vitamin D levels.

Table 2: Effects of vitamin D intervention on inflammatory related markers

Study populations	Study duration	Intervention groups	Summary of findings	References
CKD patients with vitamin D levels < 75 nmol/L (n=22) Age: 67-73 years old	1 month	Randomized double blind pilot trial 3 groups: - placebo, n=7 - paricalcitol 40 IU/d, n=7 - paricalcitol 80 IU/d, n=8	• hs-CRP levels increased in placebo, while decreased in treatment group in dose dependent manner • No changes in FMD and BP in both groups	Alborzi et al., 2008 [67]
CHF patients (n=93) vitamin D levels < 82 nmol/ L	9 months	2 groups: - vitamin D (cholecalciferol 2000 IU/d + calcium 500 mg/d), n=61 - placebo + calcium 500 mg/d, n=62	• Serum vitamin D, PTH, TNF-α and IL-10 increased in treatment group than placebo	Schleithoff et al., 2006 [68]
Infants with CHF (n=80) vitamin D levels < 82 nmol/ L	12 weeks	Double-blind, placebo-controlled intervention study 2 groups: - vitamin D (cholecalciferol 1000 IU/d), n=42 - placebo, n=38	• Serum vitamin D and IL-10 increased in treatment group than placebo • PTH, IL-6, and TNF-α levels decreased in treatment group than placebo	Shedeed, 2012 [69]
Healthy overweight subjects with mean vitamin D levels of 30 nmol/L (n=165)	12 months	Randomized, double-blind, placebo-controlled design 2 groups: - vitamin D (cholecalciferol 3332 IU/d) + weight loss, n=82 - placebo + weight loss, n=83	• No changes in weight loss, BP and hs-CRP levels • TNF-α levels decreased in treatment group	Zitterman et al., 2009 [70]
Postmenopausal obese women with vitamin D levels of 25 - 80 nmol/L (n=188) Age: 50–75 years old	12 months	Randomized, double-blind, placebo-controlled design 2 groups: - vitamin D (cholecalciferol 2000 IU/d) + weight loss, n=94 - placebo + weight loss, n=94	• No changes in hs-CRP levels, insulin and weight lost between two groups. • However, compared with women who achieved 25(OH)D <80 nmol/L, women randomly assigned to vitamin D who became replete (≥80nmol/L) experienced greater improvements in weight, insulin and CRP levels .	Mason et al., 2014 [71]
Postmenopausal obese women with BMI >25 kg/m^2 and vitamin D levels of 50 - 80 nmol/L (n=218)	12 months	2 groups: - vitamin D (cholecalciferol 2000 IU/d) + weight-loss intervention - placebo + weight-loss intervention	• No changes in IL-8, IL-10, TNF-α, adiponectin and leptin • IL-16 decreased in subjects with weight loss of 5% of baseline weight compared to subjects with no weight loss and placebo	Duggan et al., 2015 [72]
Acute myocardial infarction patients (n=41) Mean age: 59.7±13.4 – 61.6±12.7 years old) Initial vitamin D levels = 46.25± 17.75 nmol/L	5 days	Prospective, randomized, open-label, single center trial 2 groups: - vitamin D (cholecalciferol 4000 IU/d), n=19 - control, n=22	• IL-6 and IL-8 levels decreased in treatment group, while increased in control group • TNF-α levels mildly decreased in both groups • CRP levels increased in both groups • VCAM-1 levels increased in control group, while decreased in treatment group • E-selectin levels decreased in both groups • ICAM-1 and VEGF levels increased in both groups	Arnson et al., 2013 [73]

Table 2: Effects of vitamin D intervention on inflammatory related markers **(continued)**

Type II diabetic patients with vitamin D levels of 21.81 ± 4.99 nmol/L (n=51, male=21; female=30)	14 weeks	Randomized double blind placebo-controlled trial 2 groups: - vitamin D (cholecalciferol 400 IU/d), n=26 - placebo, n=25	• Serum TNF-α and leptin were decreased in treatment group compared to placebo. • No changes in body fat mass and HbA1c	Ghavamzadeh et al., 2014 [74]
Premenopausal women with vitamin D deficiency (n=31, mean age: 33.1 ± 5.7 years old) Control subjects (n=27, mean age: 34.1 ± 7.6 years old)	6 months	Cross sectional study Vitamin D deficient group received cholecalciferol treatment (50000 IU/week for 8 weeks) and maintenance dose (1500 – 2 00 IU/day)	• Serum vitamin D level was increased after cholecalciferol treatment • No changes in BMI, BP, cIMT and IFN-γ after cholecalciferol treatment • FMD, ratio of EPC, IL-10 and 1L-13 levels increased after cholecalciferol treatment • 1L-17 level decreased after cholecalciferol treatment	Gurses et al., 2014 [75]
Type II diabetic patients with vitamin D levels <50 nmol/L (n=62) Mean age: 54.5±7.4 – 56.7±7.9 years old	24 weeks	Prospective, randomized, double blinded placebo-controlled trial 2 groups: - vitamin D (cholecalciferol 2000 IU/d + calcium 200 mg/d), n=32 -placebo (calcium 200 mg/d), n=30	• Vitamin D levels were higher in the treatment group than placebo • No changes in HbA1c, HOMA-IR, hs-CRP, cSBP and arterial stiffness (baPWV and AIx)	Ryu et al., 2014 [76]
Type II diabetic patients with vitamin D levels < 75 nmol/L (n=100)	12 weeks	Double-blind, placebo-controlled trial 2 groups: - Vitamin D (cholecalciferol 5000 IU/d), n=50 - Placebo, n=50	• Serum vitamin D levels increased in treatment group • No changes in FMD, EPC, PWV, BP, lipid profile, HbA1c, hs-CRP and oxidative stress markers (8-isoprostanes and SOD)	Yiu et al., 2013 [77]
Type II DN patients (n=60) - vitamin D deficient group (< 50 nmol/L) - vitamin D non-deficient group (> 50 nmol/L)	6 months	2 groups: - vitamin D (alfacalcidol 10 IU), n=28 - control, n=30	• No changes of microvascular endothelial function in DN patients • Central BP and arterial stiffness were improved in alfacalcidol treatment group • No changes of hsCRP level in alfacalcidol treatment group, however it was increased in control group	Munisamy et al., 2015 [78]
CAD patients with vitamin D levels < 50 nmol/L, (n=90)	12 weeks	Randomized, double-blind, placebo-controlled trial 2 groups: - vitamin D (ergocalciferol 50 000 IU/week), n=45 - placebo, n=45	• Serum vitamin D increased from baseline in treatment group • No changes in endothelial function (RH-PAT), ICAM-1, VCAM-2, IL-6, IL-12, IFN-γ, BP, e-selectin, hs-CRP, chemokine CXCL-10	Sokol et al., 2012 [79]
PAD patients with vitamin D levels < 75 nmol/L (n=62) Mean age: 74.8±14.6 years old	1 month	Double-blind, placebo-controlled, interventional pilot study 2 groups: - vitamin D group (single treatment of cholecalciferol 100000 IU), n=31 - placebo, n=31	• Serum vitamin D levels increased in treatment than placebo group • No changes in markers for thrombin generation (TAT and F1+2), fibrinolysis (D-dimer and PAI-1), platelet activation (sCD40L) and hs-CRP	Stricker at al., 2012 [82]

Table 2: Effects of vitamin D intervention on inflammatory related markers **(continued)**

Healthy adults with BMI > 30 kg/m^2 and vitamin D levels < 50 nmol/L, (n=43) Age: 18-50 years old	26 weeks	Randomized, double-blind design study 2 groups: - vitamin D (cholecalciferol 7000 IU/d), n=22 - placebo, n=21	• Serum vitamin D levels increased in treatment group • No changes in hs-CRP, IL-6, MCP-1, HOMA-IR and BP	Wamberg et al., 2013 [83]
Overweight subjects with BMI between 28-47 kg/m^2 (n=307) Age: 21-70 years old	1 year	3 groups: - group DD (cholecalciferol 40000 IU/week), n=104 - group DP (cholecalciferol 20000 IU/week), n=98 - placebo, n=105	• No differences in hs-CRP, IL-2, IL-4, IL-5, IL-10, IL-12, IL-13, IL-17, ICAM-1, IFN-γ, MCP-1 between three study groups.	Jorde et al., 2010 [84]

AIx, radial augmentation index; baPWV, brachial-ankle pulse wave velocity; BMI, body mass index; CAD, coronary artery disease; CHF, chronic heart failure; CKD, chronic kidney disease; SBP, central blood pressure; cIMT , carotid intima media thickness; DN, diabetic nephropathy; EPC, endothelial progenitor cells; F1+2, prothrombin fragment 1+2; FMD, flow-mediated diameter; HbA1c, glycated haemoglobin; HOMA-IR, homeostasis model of assessment –insulin resistance; hs-CRP, high sensitivity C-reactive protein; ICAM-1, intercellular cell adhesion molecule-1; IFN-γ, interferon- γ; IL-interleukin; MCP-1, monocyte chemoattractant protein -1; PAD, peripheral arterial disease; PAI-1, plasminogen activator inhibitor-1; PTH. Parathyroid hormone; RH-PAT, reactive hyperemia peripheral arterial tonometry; SOD, superoxide dismutase; TAT, thrombin antithrombine complex; TNF-α, tumor necrosis factor-α; VEGF, vascular endothelial growth factor; VCAM-1, vascular cell adhesion molecules-1

It also appears that longer period of vitamin D interventions may be needed in patients with diseases such as DN, CKD or those with clinical manifestation of vasculopathy since these diseases have manifested for a long duration and may require substantial amount of time to observe any improvement or reversal in the existing pathology. Furthermore, prescription of active vitamin D analogues such as calcitriol, doxecalciferol and alfacalcidol should be considered instead of nutritional vitamin D (cholecalciferol or ergocalciferol) to patients with diminished kidney or liver functions as nutritional vitamin D has to undergo activation in the body, which included by the above-mentioned organs.

DECLARATIONS

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Conflict of interest

No conflict of interest is associated with this work.

Contribution of authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors.

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