Diabetic CVD – Focus on Vitamin D

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Abstract: Cardiovascular disease (CVD) is the leading cause of mortality and morbidity among diabetics. Vitamin D deficiency is very common all over the world. Over last few years, vitamin D has been considered as an important regulating factor for cardiovascular health. Metabolic syndrome and obesity are highly prevalent in vitamin D deficient people. In fact all components of metabolic syndrome are affected by vitamin D. Vitamin D regulates insulin secretion and its action. It has also some controlling effect on Renin-Angiotensin system, which influences cardiomyocytes positively. Vitamin D plays a role in vascular system too. This vitamin reduces vascular calcification and inflammatory processes. Given the important role of Vitamin D in cardiovascular health, this review focuses on the impacts of vitamin D on the various CVD risk factors.

Keywords: Albuminuria, Cardiovascular Disease, congestive heart failure, Diabetes, hypertension, inflammation, insulin resistance, Metabolic Syndrome, obesity, Vitamin D.

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of mortality and morbidity among diabetics. Diabetes has a strong association with cardiovascular diseases and is considered equivalent to coronary ischemic disease [1]. Several well-known cardiovascular risk factors are simultaneously present in diabetes patients. These include hypertension, hyperglycemia, hyperlipidemia, obesity, insulin resistance and coagulation disorders. A considerable number of clinical and epidemiologic researches have indicated that there may be an association between vitamin D deficiency and diabetes, metabolic syndrome, insulin resistance, and hypertension. Vitamin D deficiency is very common in the world. Different epidemiologic studies implied that 30-50% of adult populations are at risk for vitamin D deficiency [2]. The aim of this article is to review the role of vitamin D deficiency as a possible risk factor for cardiovascular diseases (CVD) in diabetic patients.

VITAMIN D METABOLISM

In human, sun exposure is the main source for vitamin D synthesis. Only a little amount of vitamin D is absorbed from food intake [3-5]. Ultra violet exposure triggers vitamin D synthesis in skin by converting 7- dehydrocholestrol to cholecalciferol (vitamin D3). Season, daytime length, geographical altitude and skin color are the principal factors predicting vitamin D synthesis by sun exposure. However even with strong and long-term sun exposure, the maximum serum vitamin D concentration will be 60 ng/ml. It defines that there is a protective regulatory mechanism which prevents unusual high vitamin D concentration after strong and long-term sun exposure [5-7]. Bound to carrier proteins, vitamin D3 is transmitted to the liver. In liver vitamin D transforms to 25-hydroxy vitamin D (25(OH) D) by Hepatic 25- hydroxylase enzyme. 25(OH) D is the best indicator of the body vitamin D status.

In kidneys 1-alpha-hydroxylase transforms 25(OH) D to 1, 25-dihydroxy Vitamin D3 (1,25(OH)2D3). This product is the active form of vitamin D. Presence of 1 "alpha" hydroxylase enzyme in many organs and tissues including skin, colon, brain, osteoclasts, cardiomyocytes, macrophages and endothelial cells signifies its wide spectrum role in body performance. Fig. (**1**) demonstrates metabolism pathway for vitamin D.

Furthermore the vitamin D receptor (VDR) exists in many tissues including endothelial cells, vascular smooth muscle cells and cardiomyocytes [8]. Detection of VDR in these tissues led scientists to the idea that vitamin D has important functions beyond its effect on calcium and phosphorus metabolism in many organs like cardiovascular system.

DEFINITION OF VITAMIN D DEFICIENCY

Definition of vitamin D deficiency is varied between different studies. However most studies considered 25(OH) D concentration < 10 ng/ml as vitamin D deficiency. This level of vitamin D is associated with calcium malabsorption, osteomalacia, rickets and myopathy.

A 25(OH) D level of 10-30ng/ml is described as vitamin D insufficiency or inadequacy. This level of Vitamin D is also associated with negative impacts on body health. Although the optimal serum concentration for 25(OH) D is higher than 30-32ng/ml, this cut point varies in different societies. Variation in vitamin D degradation due to different 24-hydroxylase capacities can rationally explain this diversity [9]. If we consider serum level more than 30-32ng/ml as the optimal concentration for vitamin D, vitamin

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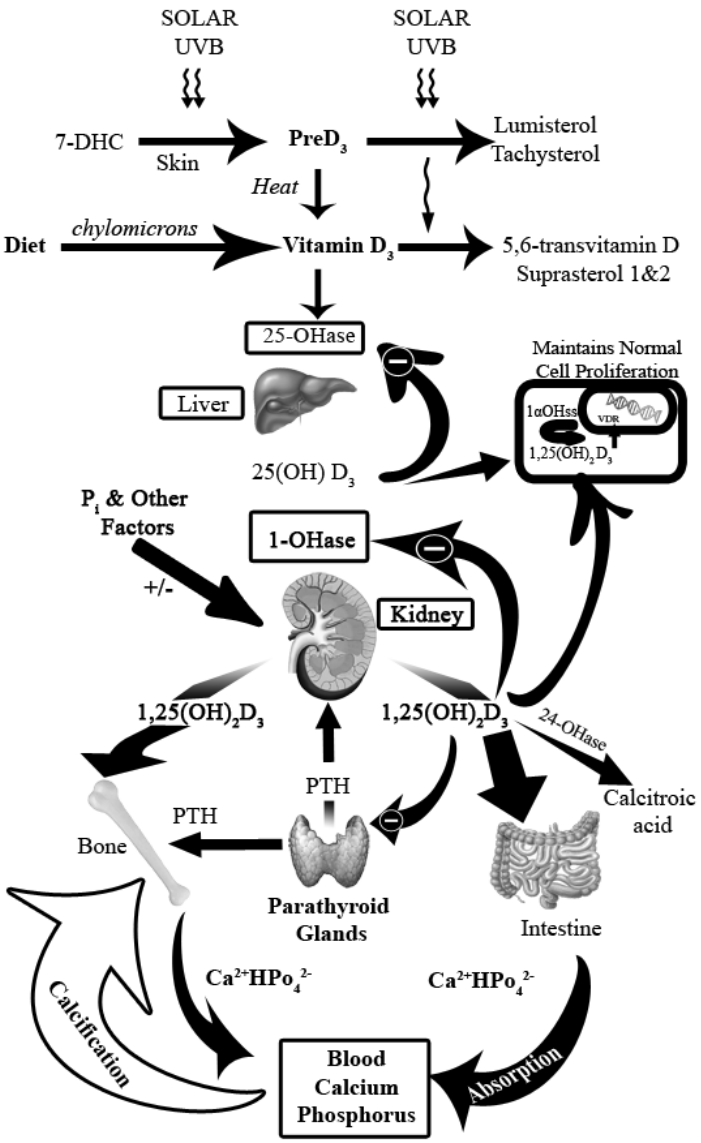

Fig. (1). vitamin D metabolism in the human body. DHC, 7- Dehydrocholestrol; UVB, Ultraviolet B radiation(290-315 nm); 25(OH)ase, 25- hydroxylase; 1-OHase, 1-alpha-hydroxylase, 25(OH)D3, 25-hydroxy vitamin D3; 1,25(OH)2D3, 1, 25-dihydroxy Vitamin D3.

D deficiency will be very common in the world. In some cohort studies, 52-77% of population has vitamin D deficiency. Even if someone decreases the vitamin D deficiency cut point to< 20ng/ml, still 18-38% of world population will lay in the deficiency range [10].

EFFECTS OF VITAMIN D DEFICIENCY ON THE CVD RISK FACTORS

Effects of Vitamin D on Vascular System

Vascular calcification is assumed to be a cardiovascular mortality predictor. Several human studies have shown reverse association between vitamin D level and existence of vascular calcification and its severity [11, 12]. Furthermore some studies found a significant correlation between vascular calcification and osteoporosis which both conditions are explained by vitamin D deficiency [13].

The effect of vitamin D on the different parts of vessels is varied. Vascular smooth muscle and endothelial cells have VDR and are able to transform 25(OH)D to 1,25(OH)2D3 [14]. One of the important effects of vitamin D on the vascular system is its impact on inflammatory factors. Inflammation has been considered as a crucial pathology for atherosclerosis induction. T cells and macrophages release cytokines including IL1, IL4, IL6 and IFNɣ and TNFα. These cytokines stimulate smooth muscle cell proliferation and increase synthesis of acute phase proteins such as CRP which have important effect on initiation and outcome of cardiovascular diseases [15]. Vitamin D has immuno-suppressive effects. It decreases lymphocyte proliferation and cytokine production. Vitamin D seems to down regulate NF (nuclear factor)-Kβ activity and increase IL10 [16]. These changes lead to a cytokine profile, which is less inflammatory.

Vitamin D decreases production of tissue matrix metalloproteinase (MMPs). MMPs are a group of connective tissue enzymes secreted from activated macrophages during inflammatory processes. MMPs cause the collagens within the atherogenic plaque to break and this cause plaque rupture and thrombosis. In some studies there have been negative correlation between serum MMPs and CRP levels, and the vitamin D concentration [17]. Vitamin D seems to decrease the MMPs activity and reduce vessel- wall calcification.

Vitamin D also decreases vascular smooth muscle cells replication. It reduces vascular mitogenic response to stimulatory factors like thrombin and platelet-derived growth factor (PDGF). In diabetics, vitamin D even prevents negative effects of advanced-glycosylation-end (AGE) products on endothelial cells [18]. Vitamin D shows some anticoagulation action by increasing thrombomodulin production [19]. Genetic studies have shown that vitamin D regulates genes involved in the cell cycle in the vessels. It inhibits cellular proliferation, increases fibrinolysis, induces vascular relaxation and endothelial regeneration [20].

In addition, vitamin D deficiency causes secondary hyperparathyroidism. Excess parathyroid hormone (PTH) has pro-inflammatory actions and stimulates cytokine release from smooth muscle cells. The result is vascular wall calcification. Vitamin D increases endothelial progenitor cells release from the bone marrow. These cells have cardio protective actions [18].

Effects of Vitamin D on Cardiomyocytes

VDR is expressed on cardiomyocytes. Preliminary studies have revealed that low level of vitamin D increases cardiac contractility which in long term will result in cardiac hypertrophy.

Myotrophin has been connected to cardiac hypertrophy. It regulates normal cardiomyocyte development and seems to induce compensatory mechanism for congestive heart failure (CHF). Active vitamin D increases myotrophin production which consequently cause normal cardiomyocyte development and heart failure prevention [21].

The concentration of the N terminal proatrial natriuretic peptide (NT-proANP), which is a CHF predictor, has negative correlation with the serum vitamin D level [22]. C-MYC is a proto-oncogene that stimulates cellular growth. A few studies demonstrated that 1,25(OH)2D3 reduces the C-MYC level [21].

In chronic kidney patients, low serum vitamin D levels and simultaneous secondary hyperparathyroidism reduce cardiac inothropy and increase the heart weight and collagen content [23]. Vitamin D deficiency also influences the distribution of both V1 and V3 myosin chains with predominant V1 isotype. This change in myosin isotypes alters myocyte contractility, indicating the role of vitamin D deficiency in CHF pathogenesis [24].

Effects of Vitamin D on Renin-angiotensin System and Blood Pressure

Owing to its regulatory effects on the peripheral vascular system, heart, brain, kidney and adrenals, angiotensin II has an important contribution on vascular resistance and extracellular fluid homeostasis. Renin secretion is basically stimulated by volume reduction, salt depletion, sympathetic nervous system activation and low renovascular perfusion. Preliminary animal studies have demonstrated that VDR null mice show increase in their renin level without previously mentioned stimulatory factors. Elevated renin, consequently causes thirst sensation and through angiotensin II effects on brain's thirst center and kidney sodium re-absorption, increase water consumption. Since Angiotensin II has important role in inducing hypertension and ventricular hypertrophy, VDR null mice have increased risk for these disorders [25]. On the other hand, vitamin D deficiency results in renin increment independent of ionized sodium level. Active form of vitamin D disrupts cAMP signaling pathway, which contributes in renin biosynthesis, and decreases renin gene expression.

Activated T cells increase oxidative stress followed by accelerated angiotensin II secretion [26]. Vitamin D as an anti inflammatory factor can eventually reduce angiotensin II concentration [26, 27]. A study on patients with chronic kidney disease reported that treatment with intravenous calcitriol can cause left ventricle hypertrophy regression, plasma rennin activity reduction and angiotensin II level decline [28]. Vitamin D is a negative regulator of rennin biosynthesis. Active form of vitamin D3 directly and independently reduces rennin synthesis. This effect has beneficial impacts on blood pressure control and cardiovascular health.

Vitamin D blunts cardiomyocyte hypertrophy, improves insulin sensitivity, reduces free fatty acid concentration and has regulatory effects on natriuretic peptide receptor [29]. All of these actions contribute to blood pressure control. However several meta-analyses failed to prove a long term association between serum vitamin D level and blood pressure control [30]. Also using vitamin D supplementation for treatment or prevention of hypertension has been the subject of debate. On the other hand, several studies have revealed that vitamin D deficiency results in hypertension [31-33]. One study proved that 25(OH)D levels less than 15ng/ml will result in future hypertension [34]. Powerful randomized clinical trials should be designed to detect effects of vitamin D on blood pressure control.

Effects of Vitamin D on Insulin Resistance

Insulin resistance is an independent risk factor for CVD. It induces and accelerates dyslipidemia. Insulin resistance reduces the lipoprotein lipase level and causes increased free fatty acid production. Free fatty acids produce VLDL in liver, increase triglyceride production, increase HDL catabolism and ultimately decrease HDL, and reduce apoprotein A production [35]. Association of insulin resistance and hypertension double fold the risk of cardiovascular disease. Insulin resistance impairs vasodilatation and alters blood flow due to inability of insulin to increase the production of nitric oxide by endothelial cells. In patients with insulin resistance, insulin activates sympathetic nervous system and increases salt and water reabsorption, which both contribute to hypertension [36, 37]. It also plays an important role in clot formation due to increasing fibrinogen, factor VII and

plasminogen activator inhibitor -1(PAI-1) concentration. There is a proven and close relationship between elevated PAI-1 and CVD [38, 39]. Finally, insulin resistance results in central obesity, which is a crucial cardiovascular risk factor.

There are strong evidences that an optimal amount of vitamin D concentration is necessary for efficient insulin function [40-44]. Vitamin D regulates calcium pool which is essential for insulin action. Vitamin D is able to stimulate insulin receptor independently and modulate cytokines actions which both are essential for improving insulin function in peripheral tissues [3, 45].

Systemic inflammation can increase insulin resistance [42]. On the contrary, vitamin D is an anti inflammatory and immune modulator, which improves inflammation. Vitamin D deficiency induces hyperparathyroidism and elevated PTH decrease insulin sensitivity [46]. "Calcium paradox" phenomenon is the probable mechanism by which PTH increases insulin resistance. An optimal amount of intra-cellular calcium (140-370 nM) is necessary for insulin action in peripheral tissue. Higher amounts of intracellular calcium may diminish insulin response in peripheral tissues [47]. Moreover, vitamin D deficiency can indirectly increase insulin resistance by obesity induction.

Studies that evaluated independent role of vitamin D supplement on improving insulin resistance have shown conflicting results. Most studies which were done on chronic renal failure (CRF) patients, demonstrated that with vitamin D supplement, insulin resistance decreases independent of serum PTH and calcium levels [42].

Effect of Vitamin D Deficiency on Blood Sugar in Diabetes

Apart from vitamin D effects on insulin sensitivity, there are evidences that vitamin D also influences insulin secretion. Pancreatic islets have VDRs. Vitamin D increases insulin response to glucose stimulation. This effect can be due to changes in intracellular calcium or may be an independent phenomenon. Vitamin D deficiency and consequential changes in intracellular and extracellular calcium balance lead to impaired synthesis and secretion of insulin by pancreatic cells. Hyperparathyroidism on the other hand increases intracellular calcium which prevents calcium to induce glucose stimulated insulin secretion, again due to the "calcium paradox" phenomenon.

Several cross-sectional studies have shown correlation between diabetes risk factors including insulin secretion impairment and increased insulin resistance, and vitamin D deficiency [48-51]. Prospective studies have shown that the vitamin D level is a predictor of future glycemic status in type 2 diabetes [52, 53]. The results of 5-year follow-up of patients in this study showed that each 25 nmol/l increase in 25(OH) D from baseline is associated with at least 0.05mmo/l decrease in fasting blood sugar and 0.25 mmol/l decrease in postprandial glucose.

Studies on vitamin D effects on blood sugar control in diabetics and non diabetics did not show similar results. However, most of these studies have limitations for example they were not randomized clinical trials (RCT), the studies period were short or their sample sizes were small. Yet most RCTs have shown an improved glucose tolerance test, better insulin function and increase insulin secretion in the vitamin D treated groups [54-56]. Some studies on the other hand revealed no effect of vitamin D on glycemic indexes [57, 58]. This diversity in results may be due to differences in prescribed vitamin D doses, treatment duration and subjects' race among various studies and it certainly demands conducting powerful RCT studies.

Vitamin D deficiency may be even associated with type 1 diabetes. There is a relationship between season or geographic latitude and prevalence of type 1 diabetes which implies an association between type one diabetes and vitamin D deficiency [59, 60]. The immune modifying effects of vitamin D which stops pathologic immune process is the possible mechanism by which vitamin D protects pancreatic beta cells from destruction [61-63].

Effects of Vitamin D on Obesity and Metabolic Syndrome

Obesity is associated with increased risk of coronary heart disease (CHD). A Meta analysis showed that for each 5-unit increase in body mass index (BMI), CHD risk accelerates by 29% [64]. Obesity seems to be an independent CHD risk factor. Usually several risk factors coexist in obese patients which simultaneously increase CHD risk. Insulin resistance, type2 diabetes, lipid disorder, hypertension, sympathetic system dysfunction and obstructive sleep apnea are related risk factors exist in obese people and each one increase the risk of CHD.

Considerable numbers of studies have illustrated a close relationship between vitamin D deficiency and metabolic syndrome. There seems to be a mutual relationship between them. In obese people less physical activity, less sun exposure and also deposition of vitamin D in body fat result in less bioavailable vitamin D [65]. Moreover vitamin D deficiency itself induces obesity [66, 67].

Oxidative stresses and systemic inflammation are present in obesity and metabolic syndrome. The immune modulator effects of vitamin D are the means by that vitamin D improves obesity and metabolic syndrome. Some studies showed that increased PTH level secondary to vitamin D deficiency, can predict obesity and metabolic syndrome [68-71].

Effects of Vitamin D on Albuminuria

Albuminuria is a known predictor of the cardiovascular disorders progression. Its mechanism is not well known. However impairment in vasodilatation and increased VWF "von willebrand" level which are associated with obstructive thrombosis may be factors that make diabetics patients with albuminuria, vulnerable to cardiovascular accidents. Animal and cell-culture studies have demonstrated that vitamin D suppresses renin transcription, angiotensin 2 production, podocyte loss, glumerulosclerosis and eventually albuminuria [72-75]. Human studies have also shown reverse association between serum vitamin D level and albuminuria [76-80]. Vitamin D improves albuminuria by several mechanisms:

1) Decreased renin transcription: the over activity of renin angiotensin system is an important factor in pathophysiology of kidney diseases and albuminuria progression. Vitamin D treatment reduces renin and angiotensin II level.
2) Vitamin D improves blood pressure and this reduces albuminuria.
3) The effect of vitamin D on pancreas results in correct beta cell function and reduces insulin resistance. Diabetes and insulin resistance are both well known risk factors for albuminuria.
4) Vitamin D exerts a direct effect on mesangial cell proliferation, differentiation and apoptosis [81, 82), which all reduce renal interstitial fibrosis. Vitamin D may also decrease the TGF-β concentration and prevent serious renal cellular injury.

Some researches proved that with vitamin D treatment alone or in combination with angiotensin converting enzyme inhibitors (ACEI) or Angiotensin receptor blockers, can reduce albuminuria in diabetic patients or in patients with chronic kidney diseases [83-85]. These studies demonstrated that active form of vitamin D induces vasodilatation by increasing both nitric oxide and cyclooxygenase synthesis. It also blocks oxytocin receptors that have a vasoconstrictor effect. The previously mentioned effects of vitamin D on blood pressure can also decrease albuminuria. Effects of vitamin D on modifying albuminuria have important clinical impact on cardiac health.

Hypothetical effects of vitamin D in cardiovascular system listed in Table **1**.

VITAMIN D AND CARDIOVASCULAR DISEASE

Early studies, available since 1978, showed that Coronary Heart Diseases (CHD) were more common in patients with low 25(OH)D level [86]. However, continuous studies over time, have shown conflicting results.

Cardiomyocytes have VDR, 1α-hydroxylase and 24-hydroxylase enzymes. These enzymes are required for 25(OH)D transformation to its active form or for its breakdown. In 2006 a study found that there are 170 vitamin D responsive genes in coronary artery smooth muscle cells. Low vitamin D level cause dysfunction of these genes, and thereby increased risk of coronary vascular disorder [20].

Since vitamin D interferes with many of cardiovascular risk factors (mentioned above), several studies have been done to investigate it.

Data from NHANESIII on 13000 cases, showed that lower levels of 25(OH)D is associated with 45% increase in the risk of cardiovascular disorders. By surprise this relationship was stronger in women than men [87]. Another prospective study which was conducted between 1978 and 1980 on Finish adults with mean follow-up time of 27.1 years showed that cardiovascular mortality has a negative, statistically significant, correlation with serum vitamin D level. In the highest quartile of blood vitamin D levels, CVD mortality is decreased by 24% [88]. The Framingham offspring study confirmed that the risk of first CVD events increase to 80%, if the serum level of 25(OH)D was in the lowest quartile <10 [34]. This risk decreased to 35% when the 25(OH)D level was between 10-15ng/ml and it

Table 1. Possible mechanisms of action of vitamin D in cardiovascular system.

Possible Mechanism	Key Evidence	References
Antiatherosclerosis, protection against vascular injury	Immunosuppressive effects, inhibition of lymphocyte proliferation and inflammatory cytokine production, down regulation of NF (nuclear factor)-Kβ activity and expression of the tissue matrix metalloproteinase (MMPs), stimulation of IL10 as an anti-inflammatory cytokine, reduces vascular smooth muscle cells replication, up regulates thrombomodulin expression, increases fibrinolysis and vascular relaxation	[15-18]
Prevention of cardiac hypertrophy	Increases myotrophin expression, inhibition of the N terminal proatrial natriuretic peptide and c-myc level, Vitamin D deficiency influences the distribution of both V1 and V3 myosin chains with predominant V1 isotype and reduces cardiac inothropy and increases the heart weight and collagen content	[19-21]
Regulation of renin-angiotensin system and blood pressure	(VDR) null mice have increased renin gene expression, Active form of vitamin D disrupts the cAMP signaling pathway that involved in rennin biosynthesis, regression of left ventricle hypertrophy and reduces plasma renin activity and the angiotensin II level, has regulatory effects on natriuretic peptide receptor	[22-27]
Reduction in Insulin resistance and improvement of insulin secretion	Vitamin D regulates calcium pool that is essential for insulin action; stimulate insulin receptor expression, improvement of insulin action in peripheral tissues, anti-inflammatory effects.Increases insulin response to glucose stimulation	[37-42, 45-48]
Effects of vitamin D on obesity and metabolic syndrome	D deficiency induces obesity through activation of Oxidative stresses and systemic inflammation and increase in PTH level	[63-68]
Reduction of albuminuria	Suppression of renin transcription, angiotensin 2 production, podocyte loss, glumerulosclerosis and albuminuria, improvement of blood pressure	[73-77]

Table 2. Human studies evaluating vitamin D supplementation and cardiovascular health.

References	Study Design	Results
Wang L *et al*., [106]	17 prospective studies and randomized trials that examined vitamin D supplementation, calcium supplementation, or both and subsequent cardiovascular events.	a slight but statistically nonsignificant reduction in CVD risk with vitamin D supplementation
Hsia J *et al*., [108]	Randomized clinical trial in 38282 postmenopousal women that compared vitamin D (200 IU) and calcium (500) mg daily supplementation with placebo over a 7- years use period	No decreased in coronary and cerebrovascular risk
Autier *et al*., [109]	18 randomized controlled trial including 57311 participants	no significant difference in cardiovascular events after daily vitamin D supplementation (300-2000) unit but showed that vitamin D decreases all cause mortality
Sun *et al*., [110]	2 large cohorts, consisting of 74272 women and 44592 men	higher intake of vitamin D is associated with a lower risk of cardiovascular events in men but not in women

reduced dramatically when 25(OH)D level was more than 20 ng /ml.

A study on 7161 individuals with 11.7 years follow-up showed that there was a 32% increase in all cause mortality when the serum vitamin D level was at its lowest quartile. However CVD mortality did not increase at this level [89]. It is concluded from other prospective studies that the lower the vitamin D level, the higher the CVD risk and the higher its mortality rate will be [90-92]. These observations lead to the idea that 25(OH)D levels < 25ng/ml is persistently associated with increased risk of CVD [93].

Several cross-sectional studies have also shown conflicting results for vitamin D deficiency effects on cardiovascular risk factors. However, majority of them agreed that cardio metabolic risks decreased with increase in 25(OH) D levels [94-99].

Considering the Vitamin D influences on insulin resistance, obesity and hyperglycemia, diabetic patients are more prone to cardiometabolic complications of vitamin D deficiency. Many cross-sectional studies in diabetic patients indicated that cardiovascular disorders are more prevalent with low vitamin D levels [88, 100-104]

According to a recent Meta analysis, high levels of vitamin D is linked with reduction in all the cardiometabolic diseases including 55% reduction in diabetes, 33% reduction in coronary vascular diseases and 51% reduction in metabolic syndrome [105].

EFFECTS OF VITAMIN D SUPPLEMENTATION ON CARDIOVASCULAR DISEASE

Considering the possible effects of vitamin D on cardiometabolic risk factors, the question is whether treatment with vitamin D supplements reduces cardio-vascular events? Information available from randomized clinical trials are (Table **2**): a recent systemic review demonstrated that moderate to high doses of vitamin D (about 1000 units daily) may diminish CVD risk insignificantly (pooled relative risk=0.95, 95% CI, 0.77 to 1.05) [106].

In a large clinical trial in the UK researchers prescribed daily vitamin D(83 units) or placebo to 2686 patients (about 100.000 units every 4 months) and followed them for 5 years. They found an insignificant decrease in cardiovascular events and CVD mortality [107].

The largest available RCT was the women health initiative (WHI) study, performed on 36282 postmenopausal women. It revealed no decrease in cardiovascular events after calcium and vitamin D supplementation [108]. The main problem of this study was inappropriately low dose of vitamin D (400units daily).A meta-analysis of 18 randomized trials revealed no significant difference in cardiovascular events after vitamin D supplementation [109]. However it showed that vitamin D decreases all cause mortality. All other conducted studies had also limitations like technical problems, small sample size, low power of the study, and short duration of follow-up. Sun *et al.,* prospectively examined the association between vitamin D intake and CVD in participants of two cohort studies, consisting of 74272 women and 44592 men [110]. They suggested that a higher intake of vitamin D is associated with a lower risk of cardiovascular events in men but not in women. Thus, available evidences are inconsistent, inconclusive and not sufficient to inform vitamin D requirement [111]. Large Placebo- controlled, population-based RCTs should be designed for confirming effects of vitamin D supplementation on cardiovascular risk and its mortality.

CONCLUSIONS

Despite the growing body of evidence that demonstrate a role of vitamin D in cardiovascular health, no clear data exist about the effects of supplementation of vitamin D on improvement in cardiovascular disease outcomes. Three randomized trials (NCT01169259, NCT00736632, and NCT01145703) are in progress for evaluating of the effects of vitamin D supplementation in cardiovascular disease and may demonstrate clear benefits of vitamin D.

Powerful placebo-controlled, population-based RCTs should be designed for detecting and confirming effects of vitamin D supplementation on cardiovascular risk and its mortality.

ABBREVIATIONS

1, 25(OH) 2D3	=	1, 25-dihydroxy Vitamin D3
25(OH) D	=	25-hydroxy vitamin D
ACEI	=	Angiotensin converting enzyme inhibitors
BMI	=	Body Mass Index
cAMP	=	Cyclic AMP
CHD	=	Coronary heart disease
CHF	=	Congestive heart failure
CRF	=	Chronic renal failure
CRP	=	C reactive protein
CVD	=	Cardiovascular diseases
HDL	=	High density lipoprotein
IFNɣ	=	Interferon gamma
IL1	=	Interleukin 1
IL4	=	Interleukin 4
IL6	=	Interleukin 6
MMPs	=	Matrix metalloproteinase
NT-proANP	=	N terminal proatrial natriuretic peptide
PAI-1	=	Plasminogen activator inhibitor -1
PDGF	=	Platelet-derived growth factor
PTH	=	Parathyroid Hormone
RCT	=	Randomized clinical trials
TNFα	=	Tumor necrosis factor alpha
VDR	=	Vitamin D receptor
VLDL	=	Very low density lipoprotein
VWF	=	Von willebrand factor
WHI	=	Women health initiative

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflicts of interest.

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