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ROLE OF VITAMIN D IN CARDIOMETABOLIC DISORDERS - A REVIEW BASED ON PATHOPHYSIOLOGY AND CLINICAL EVIDENCES

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Keywords:

Cardiometabolic disorders, Vitamin D supplementation, Clinical trials, Observational studies, Interventional studies

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ABSTRACT: Background: Cardiometabolic syndromes are the co-occurrence of metabolic abnormalities such as obesity, insulin resistance, atherogenic dyslipidemia, and hypertension. Cardiometabolic disorders includes type2 diabetes mellitus, metabolic syndrome, and cardiovascular diseases. The prevalence of cardiometabolic disorders are growing in epidemic proportions all over the world; hence cardiometabolic disorders are a major health problem in developing as well as in developed countries. It has been observed in the previously reported clinical studies that deficiency of vitamin D is a highly prevalent risk factor in the patients with cardiometabolic disorders and it has been suggested that deficiency of vitamin D has a crucial role in the pathogenesis of cardiometabolic disorders. **Aim:** To reveal the role of vitamin D deficiency in cardiometabolic disorders and the opportunity of vitamin D supplementation as vital therapy in cardiometabolic disorders. **Methods:** We performed a systematic review based on available literature of vitamin D deficiency in cardiometabolic disorders using PubMed, Google Scholar, Science Direct, and Willey online library databases up to November 2020. **Conclusion:** Vitamin D deficiency has a significant role in the pathogenesis of cardiometabolic disorders. Therefore, vitamin D supplementation may help in mitigating cardiometabolic disorders. However, there is a need to generate large controlled clinical trials with an appropriate sample size.

INTRODUCTION: Cardiometabolic syndromes are a constellation of metabolic dysfunction, which is characterized by insulin resistance and impaired glucose tolerance, atherogenic dyslipidemia, hypertension, and intra-abdominal adiposity [1]. Cardiometabolic syndromes are now recognized as a disease entity by the American Society of Endocrinology, National Cholesterol Education Program (NCEP), and World Health Organization [1, 2].

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Cardiometabolic disorders including cardiovascular disease, type-2 diabetes mellitus, and metabolic syndrome are major causes of morbidity and mortality worldwide [3, 4, 5]. Approximately 25% of the world's adults are suffering from cardio-metabolic disorders [1]. Cardiovascular diseases are the leading cause of mortality in diabetes [6].

The previously reported studies have been identified vitamin D deficiency as a dominant risk factor for cardiometabolic disorders [7] which suggests that deficiency of vitamin D has a crucial role in the pathogenesis of cardiometabolic disorders and treatment of vitamin D supplement may be useful as a potential therapy in the cardiometabolic disorders with vitamin D deficiency. Both vitamin D deficiency and

cardiometabolic disorders are growing in pandemic [3]. Numerous studies reported abnormal levels of vitamin D with cardio-metabolic disorders or possible pathological association of vitamin D in cardiometabolic disorders [3]. This review is aimed to generate evidences regarding the role of vitamin D in cardio-metabolic disorders.

Vitamin D: Vitamin D is a lipophilic secosteroid pro-hormone that is responsible for intestinal absorption of calcium and phosphorus [8]. An extra skeletal benefit of Vitamin D is on research worldwide. It plays a major role in calcium homeostasis and bone metabolism [8]. Thus, vitamin D has a crucial role in the regulation of human physiology.

Methods: We searched the PubMed, Google Scholar, Science direct, and Willey online library databases for all research and review papers based on vitamin D and cardiometabolic disorders up to November 2020. Search terms included vitamin D, cardiometabolic disorders, metabolic syndrome, diabetes mellitus, cardiovascular diseases, trials of vitamin D supplementation on cardiometabolic disorders.

Biology of Vitamin D and Metabolism: Vitamin D is available in two isoforms ergocalciferol (Vitamin D2) and cholecalciferol (Vitamin D3) [9]. Vitamin D2 is dominantly present in invertebrates and plants, whereas Vitamin D3 is dominantly present in humans. Vitamin D3 can be endogenously synthesized in the skin as well as can be obtained from vitamin D rich foods such as eggs, meat, fish *etc.* 7-dehydrocholesterol (a precursor for cholesterol synthesis) present in the cutaneous region of human, in the presence of sunlight (UV-B) it converts into cholecalciferol [9]. Vitamin D3 when circulates in the blood bound to vitamin D binding proteins and from the liver it is converted into calcidiol, 25-hydroxyvitamin D {25(OH)D} [9]. Under the effect of parathormone, 25(OH)D is converted into calcitriol {1,25(OH)2D} by the kidney in the presence of 1-α-hydroxylase enzyme [Summarized in **Fig. 1**] [7]. Calcitriol is known to have active form of vitamin D [7]. Calcitriol has a short half-life than calcidiol and have higher affinity towards vitamin D receptor (VDR) [9]. VDR is activated by 1, 25(OH)2D through genomic/non-genomic pathways are present in most of cell types which includes adipocytes, pancreatic β-cells, endothelial cells, cardiomyocytes, innate and adaptive immune cells [9]. Presence of VDR in these cells suggests a possible pleiotropic role of vitamin D. In the genomic pathway, VDR is a type 2 nuclear receptor, which is bind with calcitriol and then VDR interacts with retinoid-X receptor and then forms a heterodimer that binds to response elements in the gene regions directly controlled by calcitriol [9].

Activated VDR–retinoid X receptor–DNA modulates gene expression in several non-calcaemic tissues and regulates gene transcription of proteins which is related to traditional genomic functions of vitamin D, such as stimulating intestinal calcium and phosphate absorption for skeletal and mineral ion homeostasis [9]. In the non-genomic pathway, calcitriol binds to VDR associated with caveolae of the plasma membrane (with a planar-shaped ligand) to activate signal transduction pathways that generate rapid responses, like insulin secretion through stimulating exocytosis or regulation of chloride or calcium channels [9].

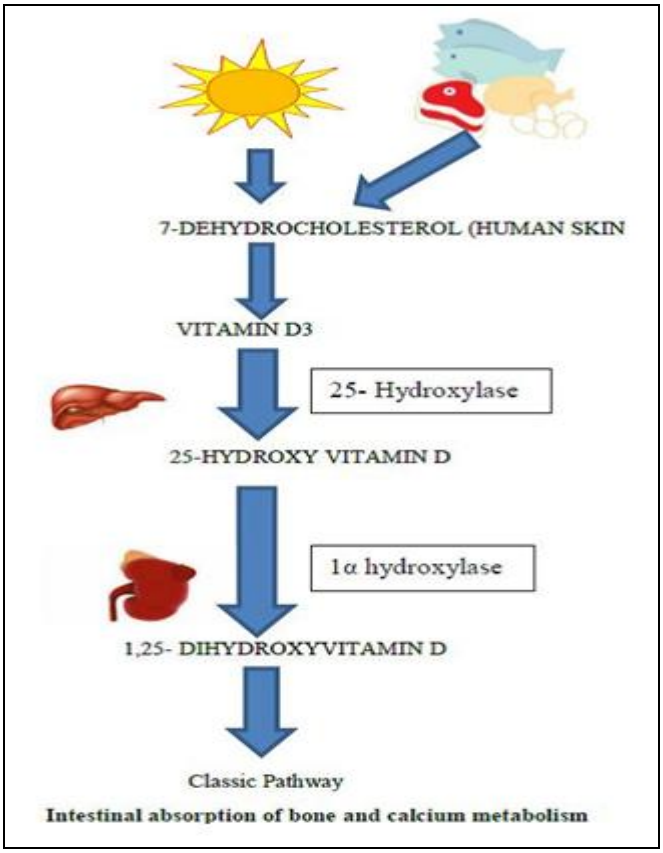

FIG. 1: BIOSYNTHESIS OF VITAMIN D

Vitamin D Deficiency and Cardiometabolic Disorders: Vitamin D status is assessed based on the circulating 25(OH)D concentration [10]. Based on circulating 25(OH)D, the North American Institute of Medicine (IOM) classified vitamin D deficiency 11 as shown in **Table 1**. According to Institute of Medicine, vitamin D deficiency is defined as a concentration of 25-hydroxyvitamin D below 12 ng/ml (or 30 nmol/l), 25-hydroxyvitamin D levels higher than 50 ng/ml is considered as vitamin D intoxication, levels of 25-hydroxyvitamin D between 12 and 19.9 ng/ml indicate a condition of vitamin D insufficiency, whereas levels between 20 and 50 ng/ml (50-125 nmol/l) are considered as satisfactory vitamin D level [11].

Despite this recommendation by IOM, Vitamin D deficiency is prevalent worldwide [9]. Vitamin D deficiency <10ng/ml is very much prevalent in South Asia and Middle East [7]. Vitamin D deficiency is very much prevalent in different parts of India among all age groups despite its sunny climate [7]. Vitamin D deficiency among Indians may be due to skin complexion among Indians, poor sun exposure, lack of vitamin D fortification foods [7]. The causes for vitamin D deficiency are given in **Table 2**.

TABLE 1: VITAMIN D STATUS {25(OH)D}[11]

Vitamin D status	ng/ml	nmol/l
Vitamin D deficiency	<12	<30
Vitamin D insufficiency	12-19.9	30-49.9
Vitamin D sufficiency	20-50	50-125
Vitamin D intoxication	>50	>125

TABLE 2: CAUSES OF VITAMIN D DEFICIENCY [52]

1	Low Exposure to UV Light
2	Dark Pigmentation Of Skin
3	Older Age
4	Being Institunalised
5	Decreased Dietary Intake Of Vitamin D
6	Living In Northern Latitutdes
7	Malabsorption Syndromes
8	Pharmaceutical Drugs That Increase Metabolism of Calcitriol (Ex.: Phenytoin, Phenobarbital, Corticosteroids)
9	Chronic Kidney Diseases
10	Liver Dysfunction
11	Obesity

Experimental studies suggested that there is a link between the abnormal levels of Vitamin D and cardiometabolic disorders [3]. Vitamin D deficiency is highly prevalent in most parts of the world [3]. Most of the adult population and older population are at major risk for Vitamin D deficiency [3]. Nowadays, it has been identified that vitamin D supplementation reduces the risk of cardio-metabolic disorders, which can raise the possibility of the use of vitamin D supplementation in patients with cardio-metabolic disorders.

Possible Pathophysiological Mechanisms between Vitamin D and Cardiometabolic Disorders: Most human tissues and cells which include cardiomyocytes, endothelial and arterial smooth muscle cells, express VDR and 1α hydroxylase, which supports the hypothesis for pathophysiological mechanism between Vitamin D and Cardiometabolic disorders [12, 13] **Fig. 2**. Expression of insulin and insulin-related genes in pancreatic cells are regulated by VDR, 1α hydroxylase activity was also found in pancreatic cells, which suggests the autocrine control of insulin secretion by 1, 25 dihydroxy vitamin D [14]. In Addition to this VDR mediate the modulation of calbindin expression and also indirect control over intracellular calcium flux, which in turn causes insulin secretion, which is exerted by 1,25 dihydroxy vitamin D [15].

Calcitriol inhibits foam cell formation and inhibits macrophage cholesterol uptake in diabetic patients [6]. The molecular effects of vitamin D on Renin Angiotensin Aldosterone System (RAAS) have been cleared and its results suggests that liganded VDR suppress renin expression by binding to the transcription factor which is known as cAMP-response-element binding protein (CREB) [16]. This suggests that vitamin D regulates RAAS system which is responsible for regulation of blood pressure. 1, 25 dihydroxyvitamin D stimulates suppressor of cytokine signaling (SOCS1) factor which modulates Toll-like receptor (TLR) signaling, which in turn inhibits phosphorylation of p38Mitogen-Activated Protein Kinase(MAPK) pathway and activation of nuclear factor-κβ (NF-κβ) signaling in macrophages which causes decreases in gene expression and protein release of proinflammatory mediators [17]. This suggests that decreasing the pro-inflammatory cytokines causes decreases in insulin resistance, atherosclerosis event by vitamin D. The main mechanism which is postulated for vitamin D mediated reduction in serum triglycerides is that vitamin D enhances intestinal calcium absorption by increasing serum

calcium which may lead to a reduction in serum triglycerides by reducing hepatic triglyceride formation and secretion [18]. Another possible mechanism of action for reducing triglycerides is that vitamin D shows an oppressive effect on Parathyroid hormone (PTH) concentration [18]. Elevation of PTH concentration causes a reduction in the plasma post heparin lipolytic activity; therefore low serum PTH level may reduce serum triglycerides by increased peripheral removal [18]. Low vitamin D causes a rise in PTH levels due to this, it also promotes intracellular calcium flux in adipocytes which in turn promotes lipogenesis and weight gain [19]. Furthermore, Calcitriolregulates runx2 in the vessel wall for osteoblast differentiation, an action that may encourage vascular calcification [20]. The most widely accepted explanation for the role of vitamin D in obesity is that vitamin D is sequestered in adipose tissue of obese individuals, which results in less bioavailable [25] (OH)D in the circulation [21]. Clinical studies also proved that low vitamin D level was observed in obese people with increased visceral adipose tissue [22].

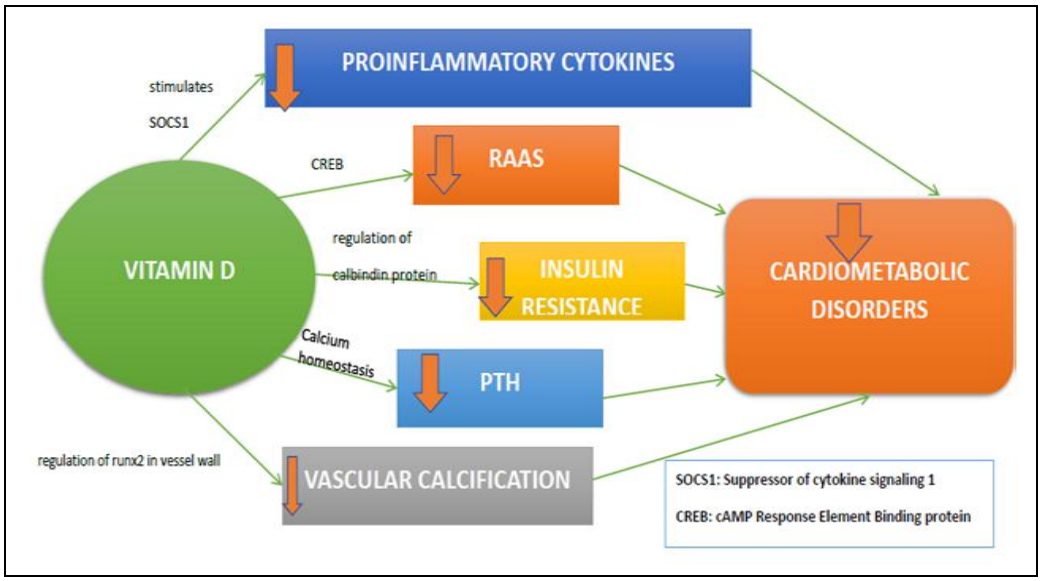

FIG. 2: POSSIBLE MECHANISM OF ACTION OF VITAMIN D IN CARDIOMETABOLIC DISORDERS [10]. SOCS1, SUPPRESSOR OF CYTOKINE SIGNALING 1; CREB, CAMP RESPONSE ELEMENT-BINDING PROTEIN; RAAS, RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM; PTH, PARATHYROID HORMONE.

Clinical Evidences for the Role of Vitamin D as Emerging Adjunct Therapy in Cardiometabolic Disorders:

Observational Studies: There are numerous observational studies that show the relationship between vitamin D and cardiometabolic disorders. It is reported in cohort study, 454 men who reported nonfatal acute MI or fatal CHD had significantly lower levels of vitamin D23.In another cross-sectional study, serum 25(OH)D concentrations were measured at a single outpatient visit of more than 400 diabetic patients but without renal or hepatic disease, and it was found that patients with vitamin D levels below 20 ng/mL had a higher prevalence of cardiovascular disease [7]. Lupton JR reported data of US adults (n=20,360) of their lipid profile with 25(OH)D deficient serum was <20 ng/ml which was linked to lower HDL (-5.1%) and higher total cholesterol (+9.4%), directly measured LDL (+13.5%), VLDL(+19%) And TG (+26.4%) when compared with a control group of vitamin D (≥30 ng/ml) [24]. Patel *et al.*, recruited 120 healthy premenopausal women (20-45 years) from Gujarat, India, and found that serum [25] (OH)D had a positive correlation with HDL (r=0.250, P=0.006) [25]. Chaudhuri *et al.*, found that deficiency of 25-hydroxyvitamin D was significantly associated with dyslipidemia (P=0.0001) in the Indian population [18]. A study from Womack Army Medical Center, North Carolina observed in 3,053 cases that vitamin D was significantly positively correlated with HDL and negatively correlated with total cholesterol and LDL [26]. Cheng *et al* found from the data of 4,095 third-generation study participants of Framingham Heart Study, who had at least one parent in the offspring cohort that in a multivariable –adjusted regression models, 25(OH)D was inversely linked to waist

circumference and serum insulin (P<0.005) [27]. McGill *et al.,* reported that in a cross-sectional study of 250 overweight and obese adults of different ethnicities were modest inverse associations of vitamin D3 with bodyweight (r = 0.16, P=0.0009), BMI (r = -0.18, P=0.005), waist circumference (r = -0.14, P=0.03) and Hb A1c (r = -0, 16, P = 0.01)28. Multivariate regression was found out separately for BMI and waist circumference, which showed a decrease of 0.74 nmol/l (P=0.002) in vitamin D3 per 1 kg/m^2 increase in BMI and a decrease of 0.29 nmol/L (P=0.01) per 1 cm increase in waist circumference [28]. Marwaha RK *et al.* from North Iran reported that serum 25(OH)D was negatively correlated with BMI (r = -0.128, P=0.05) [29]. In another study, Faraji *et al.* reported that level of vitamin D had a significant correlation with waist circumference (WC) and waist-hip ratio (WHR) (P<0.02 for WC, P<0.007) respectively [30].

Rocha LM *et al.* reported in a cross-sectional study of 106 adults which includes both genders found that the patients with vitamin D deficient level group has higher triglycerides, VLDL, fasting blood glucose, insulin, glycated haemoglobin, BMI, waist circumference and HOMA –IR than those of the patients with vitamin D sufficiency level group (P<0.05) [31]. Sorkin *et al.,* reported that in a cross-sectional study of 239 overweight and obese, sedentary postmenopausal women without diabetes, 25 (OH) D was inversely correlated with fasting blood glucose, 2h-insulin, HOMA-IR, visceral abdominal fat, PTH, percentage fat, and triglycerides [32]. Pacifico *et al.,* reported that low serum 25(OH)D were seen to be inversely correlated with total adiposity, metabolic syndrome, and hypertension in a cohort of Caucasian children and adolescents [33].

Mitri *et al.,* reported that in 1959 US adults, the participants which in the highest tertile of 25(OH)D had lower prevalence of metabolic syndrome (OR 0.62;95%CI 0.45-0.84) than the participants which are in the lowest tertile of 25(OH)D [34]. Higher plasma 25(OH)D level is associated with greater insulin sensitivity and lower insulin secretion [34]. Ju et al. reported that in meta-analysis study, which includes 18 relevant studies (16 cross-sectional, 1 case-control study, 1 nested case-control) revealed that vitamin D levels are associated with risk of metabolic syndrome in cross-sectional studies but not in longitudinal studies [35]. The pooled odds ratio of metabolic syndrome per 25 nmol/L increments in the serum 25 (OH)D concentration was 0.87 (95% CI 0.83-0.92. i2 = 85%) which was based on 16 cross-sectional studies [35]. Parker *et al.* reported an inmeta-analysis study which revealed that the highest levels of serum 25 (OH) D were associated with a 43% reduction in cardiometabolic disorders [OR 0.57, 95%(CI 0.48-0.68)] 3 whereas on the contrary, in the study from Turkey [36], metabolic disorders are not correlated with the presence of vitamin D deficiency.

Observational studies for the role of vitamin D in hypertension are very limited in the literature review. Forman *et al,* reported that the effect of vitamin D supplementation for 6 months which included African Americans showed that each 1 ng/mL increase in 25(OH)D caused a significant 0.2 mm Hg drop in systolic blood pressure (SBP) but no effect on diastolic blood pressure (DBP) [37]. Mirhosseini *et al.,* showed that in a community-based open-label study in Canada where participants were provided vitamin D3 supplements and were encouraged to achieve >40 ng/mL 25(OH)D, those who were hypertensive at baseline (SBP-155mm Hg, DBP- 95 mm Hg) reduced their SBP by 14-18 mm Hg and DBP by 12 mm Hg whereas prehypertensive participants did not have a significant reduction in blood pressure [38]. A meta-analysis study reported the effect of vitamin D supplementation on CVD risk factors of 81 participants, which found to have significant beneficial effects on blood pressure, lipid profile, parathyroid hormone and serum high-sensitivity C-reactive protein (hs-CRP) [39].

So, we can conclude from observational studies that there is the role of vitamin D could play an important role in preventing cardiometabolic disorders.

Interventional Studies: There are clinical trials published in literature sources for the role of vitamin D supplementation in cardiometabolic disorders. Pittas *et al.* [40] suggested that the treatment of vitamin D may be effective in patients with cardiometabolic disorder having vitamin D deficiency. Salekzamani *et al.* [41] reported a significant decrease in TG level with vitamin D

supplementation dosage of 50,000 IU for 16 weeks in the Iranian population. Kuchay *et al.* [42] reported that the treatment of vitamin D derived (60,000 IU) for 1 year period significantly decreased the glycemic parameters (FBG, PPBG, HbA1c) in the Kashmiri population. Fatemeh *et al.* [43] reported that the supplementation of vitamin D (1000 mg capsule) for 1 month in healthy school children significantly improved the HDL level. Pfeifer *et al.* [44] showed the significant reduction of blood pressure by vitamin D supplementation in elder women. Ryu *et al.* [45], Ramly *et al.* [46], Wood *et al.* [47] reported that there was no significant effect of vitamin D supplement on cardiometabolic disorders. Clinical trials for the effect of vitamin D supplementation on cardiometabolic disorders showed controversial results [40, 41, 48, 49]. Clinical trials thus suggests that the role of vitamin D supplementation in cardiometabolic disorders is not evident.

Challenges for Vitamin D Supplement as Potent Adjuvant Therapy: Ultimately, clinical studies, including observational as well as interventional studies, revealed that vitamin D deficiency is a potent and high risk factor for cardiometabolic disorders and it has an important role in the pathogenesis of cardiometabolic disorders. However, there is no evidence from interventional studies which shows the beneficial effects of vitamin D on cardiometabolic disorders.

The possible reasons for the lack of conclusive results may be due to incorrect duration, dosage, route of administration, patient's characteristics, and inadequate outcome measures [46]. Clinical studies showed mixed results for the effect of vitamin D supplementation on cardiometabolic disorders. However, there are also some interventional studies that showed beneficial effects of vitamin D supplementation on cardiometabolic disorders. In most of the trials, serum 25(OH)D is not measured always, seasons in which vitamin D level were different in different trials, confounding variables are also not considered in the trials. Apart from this, vitamin D level as a deficiency is still debatable globally, and various studies used different threshold values as vitamin D deficiency. There is a need to make uniformity in considering the vitamin D level as a deficiency in a specific population according to their physiology and environmental factors. Previous studies showed the link between vitamin D and cardiometabolic disorders, but mostly vitamin D deficiency level they considered is less than 20 ng/ml. However, Vitamin D and type 2 diabetes (D2d) study of American Diabetes Association 2019 suggested that vitamin D level less than 12 ng/ml significantly increase the risk of type 2 diabetes, and treatment of vitamin D in such patient may reduce the risk of type 2 diabetes mellitus [50]. The vitamin D threshold level which is mentioned in this study is also supported by the Institute of Medicine, which is recommended in the guideline that vitamin D levels less than 12 ng/ml should be considered as vitamin D deficient [11]. Moreover, Nemerovski *et al.* [51] also reported that vitamin D level less than 15 ng/ml is generally associated with a higher risk of cardiovascular disease risks than the risks which is seen upto 20 ng/ml vitamin D deficient level.

Till now up to our knowledge, none of the studies is available, which used the threshold level less than 12 ng/ml of 25(OH)D concentration in the clinical study of vitamin D supplementation in patients with cardio-metabolic disorders. Furthermore, specific preferred formulation, duration, dosage regime of vitamin D supplementation is still not been clearly established. Cholecalciferol 40 is used in some studies, whereas some studies used Ergocalciferol [52].

Most reported studies were used the duration of vitamin D supplementation less than 1 year, while some other studies used the insufficient dose of vitamin D for the prevention of cardiometabolic outcomes. Norris *et al.* [53] observed that there was variation in the effect of vitamin D in humans as per the race/ethnicity group. So, it can also be concluded that variation in race/ethnicity can also affect vitamin D supplementation to achieve outcome measures. Most trials involve supplementation of vitamin D in patients which are not categorized in vitamin D deficient levels, but the fact is that vitamin D supplementation is most beneficial to patients who are in deficient level when provided in doses that are optimal to achieve repletion and for the duration that are enough for the development of outcome of interest [9]. In summary, all the studies showed a strong relationship between a low level of 25(OH)D and

cardiometabolic disorders, but there is a lack of uniformity in consideration of vitamin D deficiency, dose, dosage regime, and dosage form D and measurement of outcome parameters. Literature also proved that the role of vitamin D in cardiometabolic disorders is evident and future long-term systematic randomized controlled trials are needed to prove it.

CONCLUSION: Thus, vitamin D deficiency is a potent and highly prevalent risk factor for cardiometabolic disorders and vitamin D supplements may be useful as adjuvant therapy in cardiometabolic disorders.

However, there is a need of clinical studies which showing the significant beneficial effect of vitamin D and answering the controversial questions and challenges.

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ETHICAL CLEARANCE: Not Required

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