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REVIEW ARTICLE

A Narrative Review- Role of Vitamin D in CVD

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ABSTRACT
Every year, cardiovascular disease claims the lives of millions of people worldwide and is the leading cause of illness and death. By interacting with vitamin D receptors (VDR), numerous physiological systems are significantly regulated by Vitamin D. Low plasma 25-hydroxyvitamin D [25(OH)D] levels have been associated with Cardiovascular Disease (CVD), per epidemiological research studies. Moreover, low levels of Vitamin D increase parathyroid hormone, which increases insulin resistance and is connected to diabetes, hypertension, inflammation, and an increased risk of CVD, although there is contradictory data about the link between vitamin D levels and CVD. In this study, we investigate the relationship between Vitamin D deficiencies and CVD and associated risk factors that were concluded by several large-scale clinical trials and meta-analyses. Low plasma 25-hydroxyvitamin D levels may be biomarkers for CVD in the future, however this is not yet known. The role of Vitamin D deficiency in increasing cardiovascular morbidity and mortality is still up for dispute. Consequently, in order to identify the evidence relating to them, extensive, highly powered randomized controlled trials and research are required.

Key words: Cardiovascular disease, Vitamin D, VDR, 25-hydroxyvitamin D.

1. INTRODUCTION

Cardiovascular diseases (CVDs) are a significant global health concern, contributing to a substantial burden of morbidity and mortality. Research suggests that genetic factors, along with nutritional status, play a crucial role in the development and progression of CVDs. The World Health Organisation (WHO) estimates that CVDs cause 17.9 million deaths globally each year, and by 2030 that figure is anticipated to rise to 23.6 million [1]. A complex interplay of political, social, behavioural, physical, biological, and genetic variables contributes to the multifactorial etiology of CVD [2]. Whereas, genetic variation is a significant risk factor for the CVD condition. Apolipoprotein E (Apo E), a protein present in both high- density lipoproteins (HDL) and triglyceride-rich lipoproteins (TRL), is one of several proteins and macromolecules whose genetic polymorphisms are linked to an increased risk and incidence of cardiovascular illnesses [3]. There are now more than 100 single nucleotide polymorphisms (SNPs) connected to CVD. The exact process by which SNPs affect CVD is still not well understood, though [4]. Heart disease can be avoided by modifying certain variables. These include quitting smoking, maintaining a nutritious diet, and engaging in frequent, appropriate physical activity [2].

One significant potential gene for CVD is the vitamin D receptor (VDR) gene, commonly referred to as the calcitriol receptor or NR1I1 [17]. Four contiguous restriction fragment length polymorphisms for CVD have recently been discovered to be linked to **BsmI (rs1544410), TaqI (rs731236), FokI (rs2228570), and ApaI (rs7975232)** [18,19], but there is need of further investigations to say that these genetic polymorphism are correlated with CVD.

The possible function that vitamin D [5] may have in reducing CVD has garnered significant interest. According to a number of epidemiological studies, those with low blood levels of Vitamin D are more likely to experience heart disease, stroke, and high blood pressure.

However, the 2011 Institute of Medicine report oncalcium and Vitamin D intake was revised based solely on skeletal health, and it concluded that there was insufficient evidence to establish a cause and effect relationship between Vitamin D and the prevention of CVD, diabetes, or other cardio metabolic outcomes[5]. Recently in 2024, a two-year

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study in which 25,871 US adults participated in a double-blind, placebo-controlled randomized trial comparing the effects of omega-3 fatty acids and/or supplemental vitamin D3 against placebo in the prevention of cancer and cardiovascular disease found that neither treatment improved physical performance in this generally healthy adult population [32].

The literature shows that multivitamins are generally beneficial to treat CVD, but it is still unknown how vitamin D [2] functions and how it relates to CVD. This is a crucial subject for further research, especially considering the high incidence of CVD. In the skin, 7- dehydrocholesterol is converted to Vitamin D when exposed to ultraviolet B (UVB) rays from the sun. The most reliable indication of Vitamin D levels in the body is the circulation of 25- 25(OH) D. Vitamin D is essential for many body systems, including as the cardiovascular and immunological systems, as well as conditions like rickets in children and osteomalacia in adults [2]. There is conflicting evidence about vitamin D's [7] protective effects against cardiovascular risk, despite generally consistent studies on its benefits for other medical problems. Evidence suggesting vitamin D is crucial for lowering the risk of a number of chronic diseases, including cardiovascular disease, was discovered throughan analysis of hundreds of research [7]. Therefore, the purpose of this narrative review is to summarize the evidences for association Vitamin D deficiency with CVD and risk factors, including Coronary Artery Disease (CAD), Inflammation, Hypertension and Insulin resistance.

2. CARDIOVASCULAR DISEASE

The heart and blood arteries make up the cardiovascular system (CVS). The CVS can develop a wide range of issues, such as endocarditis, rheumatic heart disease, irregularities in the conduction system, and more. The terms CVD and heart disease has four entities:

i. **CAD:** Often called Coronary Heart Disease (CHD), this condition is brought on by a reduction in myocardial perfusion, which can lead to heart failure, myocardial infarction (MI), and/or angina. It is responsible for between one-third and half of CVD cases.

ii. **Cerebrovascular disease (CVD):** Including transient ischemic attack (TIA) and stroke.

iii. **Peripheral artery disease (PAD):** Particularly arterial disease involving the limbs thatmight cause claudication.

iv. **Aortic atherosclerosis:** Including thoracic and abdominal aneurysms [16].

2.1 Modifiable risk factors that contributed to CVD deaths in 2021 include: [20]

1. High plasma glucose while fasting (2.3 million fatalities)
2. Air pollution (4.8 million fatalities)
3. High Body Mass Index (BMI)(2.0 million fatalities)
4. Tobacco use (3.0 million fatalities)
5. Insufficient exercise (397 000 deaths)
6. Blood pressure increase (10.8 million fatalities)

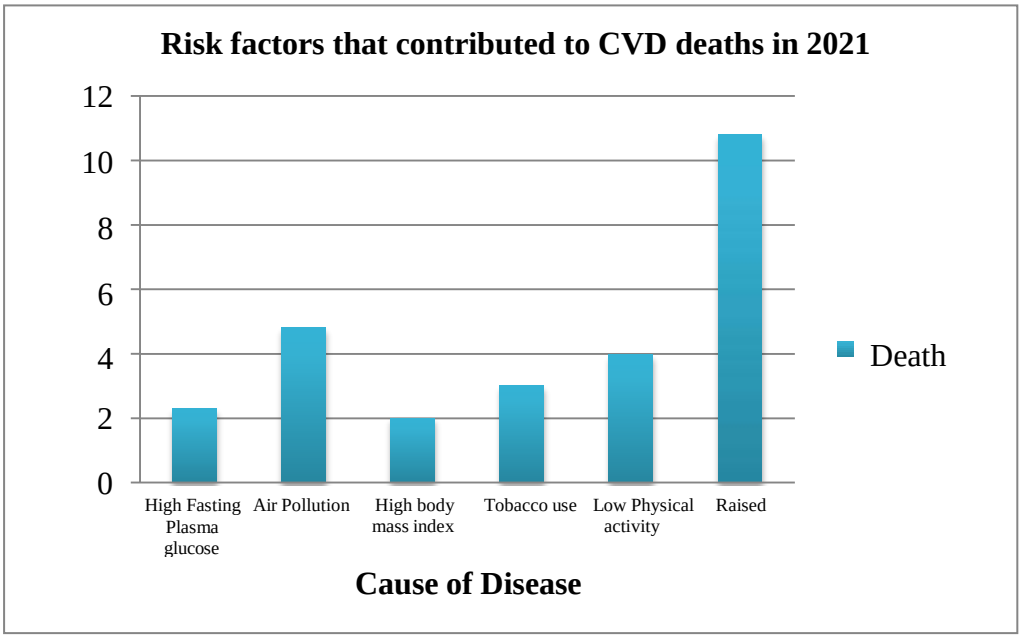

Figure 1: Risk factors that contributed to CVD deaths in 2021[20]

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The Global Burden of Disease Study estimates that in 2021, high blood pressure was the primarymodifiable risk factor for mortality worldwide, accounting for 10.8 million CVD deaths as shown in figure 1 [20].

3. EPIDEMIOLOGY

A number of factors have been linked to the prevalence of Vitamin D deficiency, including older women, higher latitudes, winter, less exposure to sunlight, skin pigmentation, diet, and a low intake of foods fortified with Vitamin D. The lowest levels of Vitamin D are typically found in regions like the Middle East and South Asia [31]. An estimated 30 to 50% of the general population is thought to be deficient in Vitamin D. Moreover, Vitamin D insufficiency is still widespread in regions with lots of sunshine [33]. In a major Middle Eastern research, 82.5% of the 60,979 patients from 136 nations with year-round sunshine were found to be Vitamin D insufficient [38]. Between 1988 and 1994, a sample of 18,158 people in the United States showed a rising incidence of Vitamin D insufficiency, and between 2000 and 2004, a sample of 20,289 people showed a 5-to 9 nmol/l drop in Vitamin D levels [39]. In 2018 Rishikesh (Uttarakhand), of the 100 participants, 21 (21%) had inadequate vitamin D, 69 (69%) had insufficient, and 10 (10%) had sufficient. Eighteen (85.71%) of the twenty-one defective subjects were Hindus, two (9.52%) were Muslims, one (4.76%) was Sikh, and there was no deficiency among the Christian patients. An inadequate Vitamin D level was observed in 1 (4.76%) of the lower, four (19.04%) and sixteen (76.19%) participants belonged to the highest socioeconomic strata, respectively [40]. WHO report depicted that global progress against CVD is flatlining. More than half a billion people around the world continue to be affected by CVD, which accounted for 20.5 million deaths in 2021 [20]. Another study by Tandon in 2016 in India demonstrated that the overall share of cardiovascular illnesses was 28·1% (95% UI 26·5–29·1) of all fatalities and 14·1% (12·9–15·3) of all Disability- adjusted life years (DALYs), as opposed to 15·2% (13·7–16·2) and 6·9% (6·3–7·4) in 1990 [41].
Furthermore, we concluded by the epidemiological studies that there is high rate of vitamin d deficiency.

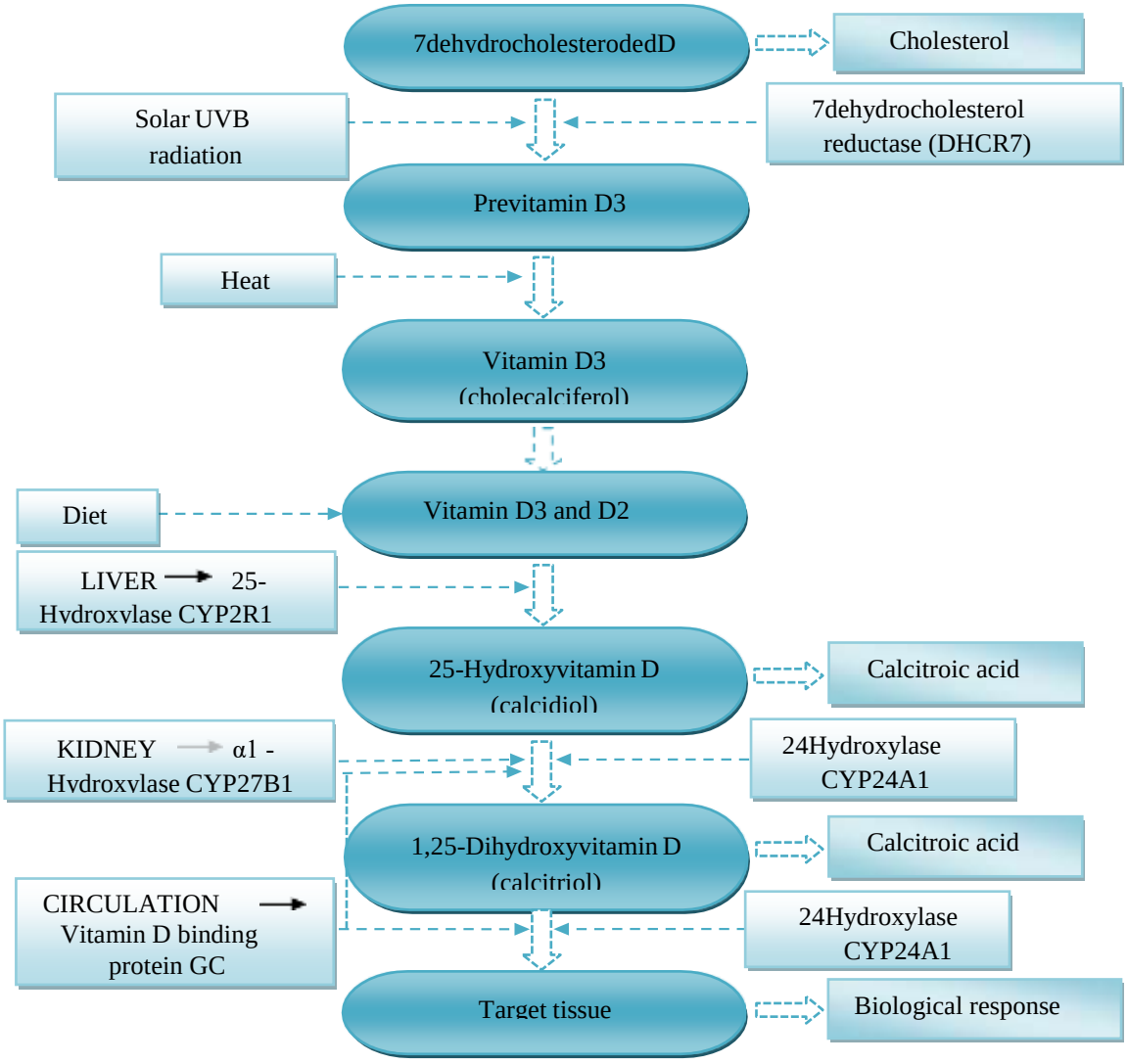

Figure 2: Vitamin D physiology and genes involved in metabolic pathway of Vitamin D [10,11]

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4. VITAMIN D PHYSIOLOGY AND METABOLISM [10,11]

Season and latitude-dependent UVB radiation-mediated skin biosynthesis is the primary sourceof Vitamin D. Eating foods high in Vitamin D, including fatty fish, fortified foods, and supplements, can help improve Vitamin D status, or serum concentrations of 25(OH)D. Moreover, mutations in genes encoding proteins involved in the synthesis, transport, and catabolism of Vitamin D metabolites affect serum 25(OH)D, as illustrated in figure 2 [10].

Genes involved in the metabolic pathway of 7-dehydrocholesterol reductase, which converts 7- dehydrocholesterol into cholesterol, is encoded by the DHCR7 gene. The substrate for the cutaneous production of vitamin D3 is 7-dehydrocholesterol. A hepatic NADPH-dependentenzyme encoded by CYP2R1 hydroxylates Vitamin D3 (and D2) to 25(OH)D. The NADPH-dependent mitochondrial enzyme encoded by CYP27B1 is mostly expressed in the kidneys and hydroxylates 25(OH)D to produce 1,25-dihydroxyvitamin D (1,25(OH)2D), the active form of Vitamin D. Group-specific complement, a Vitamin D binding protein that carries Vitamin D and its metabolites throughout the body, is encoded by the gene GC. The Vitamin D receptor, encoded by VDR, mediates the physiologic effects of 1,25(OH)2D, the active form. The enzyme that turns 1,25(OH)2D and 25(OH)D into water-soluble calcitroic acid is encoded by the CYP24A1 gene [11].

5. VITAMIN D AND CVD RISK FACTORS

Lack of Vitamin D has been connected to a number of cardiovascular risk factors. Vitamin D deficiency can cause an increase in the synthesis of renin and angiotensin II, which in turn can cause an increase in reactive oxygen species and the G protein RhoA. This can inhibit the pathways required for the intracellular glucose transporter, leading to the development of insulin resistance and metabolic syndrome [33]. Furthermore, the direct impact of Vitamin D on the calcification and proliferation of smooth muscle may be a contributing factor to its effects on cardiovascular health [8]. The relevance of Vitamin D to CVD was discovered in a comparative study including 200 adult patients with CVD and healthy people as the control group [13].

Using data from National Health and Nutrition Examination Survey (NHANES) 2001–2004, Kim and colleagues have discovered a significant frequency of hypovitaminosis D in people with cardiovascular disorders, including CHD and heart failure, after adjusting for age, race, and gender [14]. Moreover, insufficient Vitamin D was linked to CVD and a few CVD risk factors, such as obesity, hypertriglyceridemia, and diabetes mellitus (DM), according to an analysis of NHANES 2011–2012 [12]. Another comparison investigation with 638 CVD patients and 504 control participants revealed a strong correlation between the pathophysiology of CVD and serum 25(OH)D levels and VDR SNPs [9]. Additionally, a prospective cohort research conducted from January 2017 to December 2018 revealed that patients in the age range of 18 to 45 had the greatest levels of vitamin D deficiency, while those in the age group of 50 to 60 years had the lowest levels which cause CVD risk factors [15].

A portion of the data that is currently being collected about the potential correlation between Vitamin D and CVD risk factors is compiled here. A summary of the potential processes that underlie the connections between Vitamin D insufficiency and a number of CVD risk factors is shown in Figure 3.

5.1 Vitamin D and Coronary Artery Disease

Numerous researches have examined the connection between Vitamin D deficiency and CADs [33, 34, 35]. The first evidence of Vitamin D deficiency in individuals with acute myocardial infarction (AMI) or stable angina came from a study which is published in 1978 [26]. In 1990, a case–control study confirmed that AMI patients had lower vitamin D levels than controls and interestingly, the relative risk of AMI reduced throughout rising quartiles of vitamin D [27]. The Health Professionals Follow-up Study, which involved 18,225 participants, published similar results. Participants in this trial who had normal Vitamin D levels at the 10-year follow-up had around half the risk of MI [28]. During nine years of follow-up, a large prospective study (n = 10,170) indicated that low Vitamin D levels were related with an elevated risk of ischemic heart disease [IHD], MI, and early mortality [29]. Furthermore, low Vitamin D levels were linked to a higher risk of IHD and early death in a meta-analysis of 18 trials [29].

5.2 Vitamin D and Inflammation

Inflammation may be reduced by Vitamin D. T-cell proliferation is inhibited by VDR signaling, as is the production of pro-inflammatory cytokines. The growth of lymphocytes and their ability to produce lymphokines and antibodies is inhibited by 1,25(OH)2D [5]. A meta-analysis of studies, starting in 2009 does not find that vitamin D has a positive impact on vascular reactivity [30]. TNF-α concentrations were suppressed in one research [42], whereas 25(OH)D levels were inversely correlated with CRP and interleukin 6 (IL6) in two cohorts [36, 37]. Two trials examined the effects of Vitamin D therapy on CRP in specific demographics, with varying degrees of success [43, 44]. The first study found that Vitamin D supplementation had no effect on fibrinogen or C-reactive protein in older people [43]. In the latter, administering a Vitamin D analogue to those with renal illness resulted in a 50% decrease in CRP [44].It is necessary to clarify contradicting information about Vitamin D and inflammation.

5.3 Vitamin D and Hypertension

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There is an increasing amount of data points to a connection between Vitamin D and blood pressure. In 2013 a randomized prospective trial of 101 participants study showed, in CHF patients, dietary Vitamin D3 supplementation (2.000 IU/d) raised Vitamin D levels and successfully decreased plasma renin activity (PRA) and plasma renin concentration (PRC) in comparison to control [46]. Another Randomized Control Trial (RCT) in 2014 showed that supplementing with Vitamin D did not significantly affect blood pressure or any of the cardiovascular risk variables, although it did cause a notable rise in triglycerides [47]. Similar results showed in an another study in 2018 that supplementing with Vitamin D3 decreased parathyroid hormone (PTH) but had no effect on cardiac conduction, blood pressure, or the RAAS [48]. In 2017 a randomized double blinded and placebo controlled- study of 339 postmenopausal women revealed that depending on age and BMI, Vitamin D insufficiency and Taq-I polymorphism are linked to stage 2 hypertension in postmenopausal women [22]. Another double blind RCT's of 534 participants in 2017 revealed that neither the primary end point nor any of the minor end points showed any discernible differences. After six months, there was no evidence of a correlation between changes in 24-hour systolic blood pressure and changes in 25(OH)D [45]. Although a recent double blinded RCT's in 2021 revealed that in postmenopausal hypertensive women, supplementing with calcium alone or calcium and Vitamin D is linked to a considerable reduction in diurnal blood pressure and inflammatory biomarkers [49].

5.4 Vitamin D and Insulin Resistance

Reduced insulin sensitivity, insulin turnover, and poor glucose tolerance are all linked to Vitamin D insufficiency. In addition, independent of other nutritional parameters, Vitamin D repletion enhances glucose clearance in animals lacking in the vitamin [5]. Studies on humans also corroborate the link between Vitamin D and insulin sensitivity. The genetic relationships between four polymorphisms in the VDR—TaqI, BsmI, ApaI, and FokI variants—and insulin-resistant illnesses were examined in a recent meta-analysis involving 9232 persons in 2017. It was discovered that in Asians and populations residing in middle-latitude regions, there is a correlation between the VDR ApaI variant and disorders associated to insulin resistance. Dark-pigmented Caucasians have higher prevalence of the BsmI and TaqI alleles. In addition, no correlation was found between the VDR FokI variation and disorders linked to insulin resistance in people with varying skin pigmentation and latitudes [23]. In 2019 a meta analysis RCT's results that high-dose calcium (≥1000 mg/day) and Vitamin D (≥2000 mg/day) supplements have been shown to have advantageous effects over an extended period of time (>12 weeks) [50]. Furthermore a recent RCT's revealed that insulin resistance does not decrease with Vitamin D intake [51]. Thus, the findings to date are contradictory, and more compelling evidence is required.

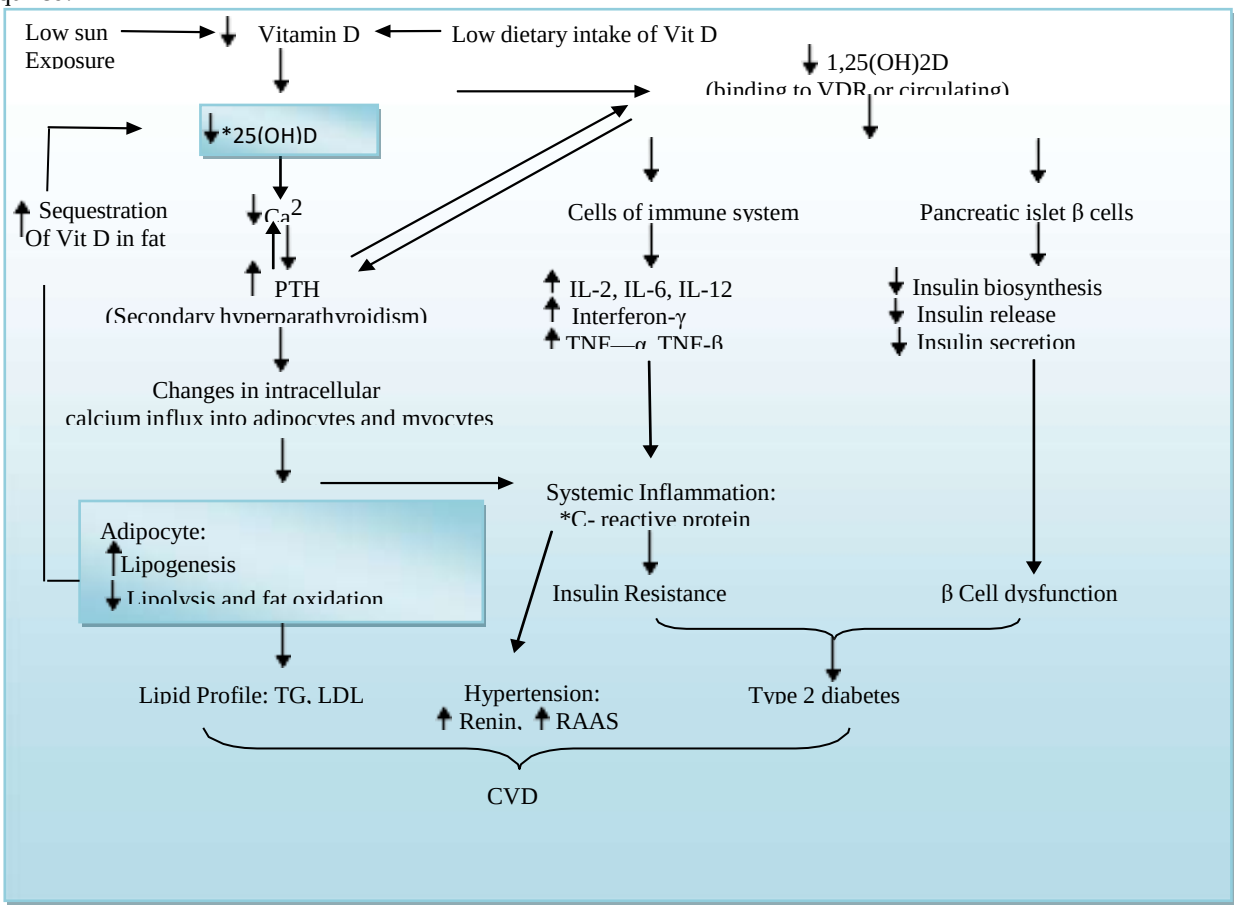

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Figure 3: Vitamin D and Cardiovascular risk factors [33,34]

6. PROTECTIVE ROLE OF VITAMIN D IN CVD

There are still unsolved concerns about Vitamin D's role in preventing CVD [52,53,54]. Data from ecological studies [55, 56], laboratory trials, and epidemiological research [57,58] indicate that Vitamin D can prevent CVD [6,21]. The possible preventative mechanisms of Vitamin D for specific illnesses are shown in the figure 4 [5, 25]. Every single cell in the circulatory system expresses the Vitamin D receptor. Many cell types, including vascular smooth muscle cells, cardiomyocytes, and endothelial cells, produce 1α-hydroxylase, which converts 25(OH)D into calcitriol, the natural ligand of the Vitamin D receptor. It has been shown that calcitriol has anti-inflammatory properties, decreases coagulation, regulates the renin-angiotensin system, and inhibits the proliferation of vascular smooth muscle cells [5,25].

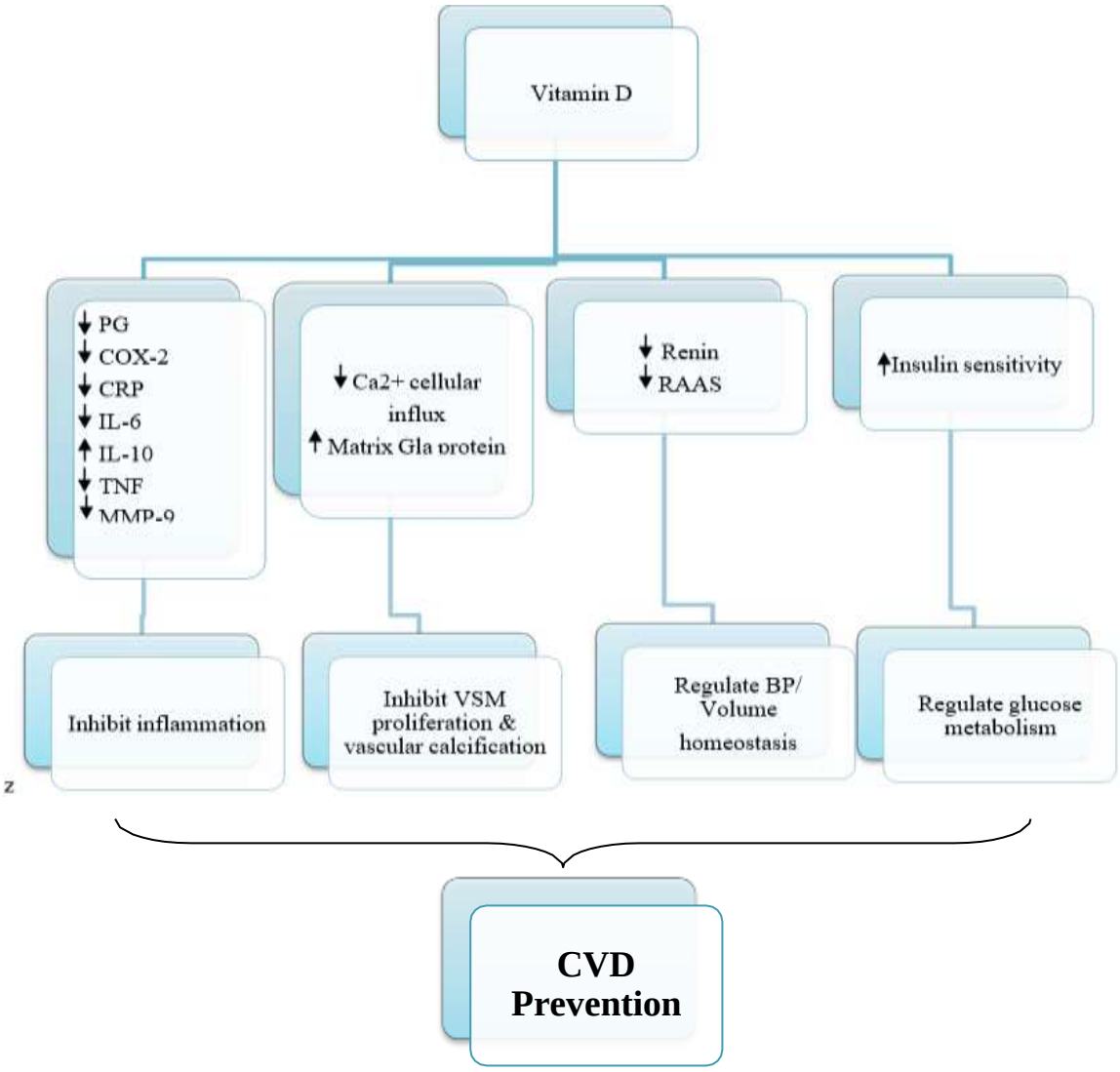

Figure 4: Mechanism by which Vitamin D may lower CVD Risk [5, 25]

7. CONCLUSION

A widespread condition with a high prevalence worldwide is Vitamin D insufficiency. Low vitamin D levels have been linked to a number of disorders, not just those affecting the bones and calcium metabolism. In fact, available data points to a direct correlation between cardiovascular disorders and hypovitaminosis D. Although there is biological justification for Vitamin D to have a part in preventing CVD, randomized trials must be finished before there is enough information to determine dietary needs. But the available evidence does not provide full support to consider Vitamin D alteration reliable to CVD risk factors in population. As per our study we conclude that, there is need of further investigations to find the correlation between Vitamin D levels with CVD which is a controversial topic. Also further investigations are required to find potential advantages of Vitamin D supplementation to reduce the CVD risk factors.

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