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# VITAMIN D DEFICIENCY: ITS ROLE AND IMPACT ON CARDIOVASCULAR DISEASE.

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**Abstract:**

*Vitamin D deficiency seems to be the front runner to cause various cardio-vascular diseases, a number of studies have shown that vitamin D insufficiency is prevalent among many populations among all age groups; this growing menace is of epidemic proportions across all ethnicities. Besides vitamin D established role in calcium homeostasis, its deficiency is emerging as a new risk factor for coronary artery disease. In India the socio-religious and cultural practices do not facilitate adequate sun exposure, thereby negating potential benefits of plentiful sunshine. Vitamin D deficiency is highly prevalent in urban and rural areas, and across all socioeconomic and geographic strata.*

*Vitamin D deficiency seems to predispose to recurrent adverse cardiovascular events, as it is associated with post-infarction complications and cardiac remodeling in patients with acute myocardial infraction. Coronary artery disease due to vitamin D deficiency have been constantly proven, many intervention trials are going on to show difference in terms of risk reduction with supplementation of vitamin D.*

*Vitamin D deficiency not only increases risk for a myocardial infarction by as much as 50% but also was associated with more than one 100 % increased risk of mortality from the heart attack. Further research in this direction is warranted and it is likely to open up new avenues for reducing the risk of cardiovascular disease.*

**Key Words:** *Vitamin D, myocardial infarction, coronary artery disease, cardiovascular disease.*

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## INTRODUCTION:

Cardiovascular disease remains one of the leading eradicators of the human race; it contributes to being one of the biggest health care expenditure around the globe. Cardiovascular disease is known to occur among individuals predicted to be at low or intermediate short-term risk. This has created a great interest in identifying innovative ways or factors that may help improve the risk prediction and bring about new treatments to prevent cardiovascular disease. [1]

Recent evidence suggests vitamin D may play a role in several chronic conditions, including cancer, autoimmune and kidney diseases, and cardiovascular disease [2]. The acceptance of Vitamin D deficiency is finally being recognized, it is of epidemic proportions for all age groups in most countries. Moreover there are a billion people worldwide who are vitamin D deficient.

## VITAMIN D: FORMS, METABOLISM AND FUNCTIONS:

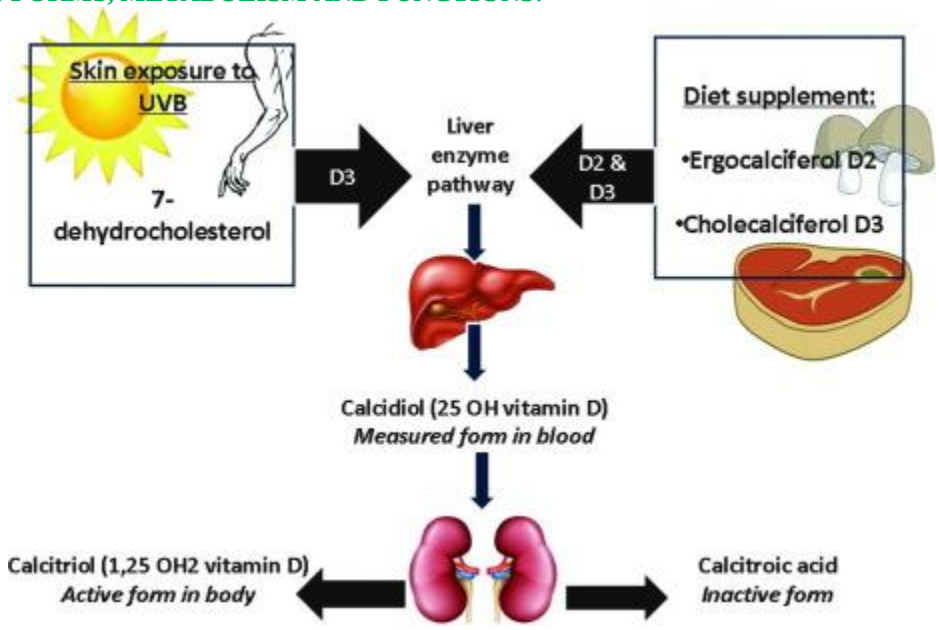


**Figure 1: Pictorial Different forms of Vitamin D.**

There are two forms of Vitamin D: D2 (ergocalciferol) and D3 (cholecalciferol). The sunshine vitamin D3, is formed during exposure to sunlight (7-dehydrocholesterol) in the skin absorbs UV B radiation and is converted to pre vitamin D3, which in turn isomerizes into vitamin D3, thru ultraviolet irradiation in the human epidermis [3], or is found in oily fish or in supplements. Vitamin D2 ergosterol is a product found in plants.

The liver and kidney converts the vitamin to calcidiol and calcitriol, respectively, specific tissues are targeted and acted upon via vitamin D receptors. Calcitriol, which is the active form of vitamin D binds to receptors in the intestines, bones, and kidneys, this helps in increasing the calcium absorption from the intestines, and promotes calcium deposition in the bones, it also decrease parathyroid hormone concentrations.[4]

Vitamin D receptors are also found in other tissues, like, the brain cardiac muscle cells, colon, smooth vascular muscle composing the majority of the wall of blood vessels., endothelial cells that line the interior surface of blood vessels and lymphatic vessels, cell in the pancreas that makes insulin, prostate, muscles which is connected to the skeleton, breast, phagocytic cell found in stationary form in the tissues, and skin, in the influencing effects of statins, and their expression , Hot or warm seasons when vitamin D can be produced in the skin, satisfy's most people's vitamin D requirement.

## POTENTIAL MECHANISMS AND RELATIONSHIP OF VITAMIN D:

There are several mechanisms that can be assumed to explain the link between Vitamin D deficiency and cardiovascular disease. It's know that 1, 25 (OH) D participates in the regulation of renin-angiotensin axis by suppressing renin gene expression this has been indicated in many experimental studies.

Express receptors for vitamin D of Vascular smooth

muscle cells and endothelial cells have the ability to convert circulating 25(OH) D to 1, 25 (OH) D.

Vascular effects of vitamin D are wide-ranging and include modulation of smooth muscle cell proliferation, inflammation, and thrombosis. . Vitamin D deficiency may also influence cardiac and vascular remodeling; hypertension could magnify the adverse effects of vitamin D deficiency on the cardio vascular system.

Vitamin D is photosynthesized in the skin and is also acquired by dietary intake. Two hydroxylation steps in the liver and the kidney are required for vitamin D activation, to form1,25-dihydroxyvitamin D.

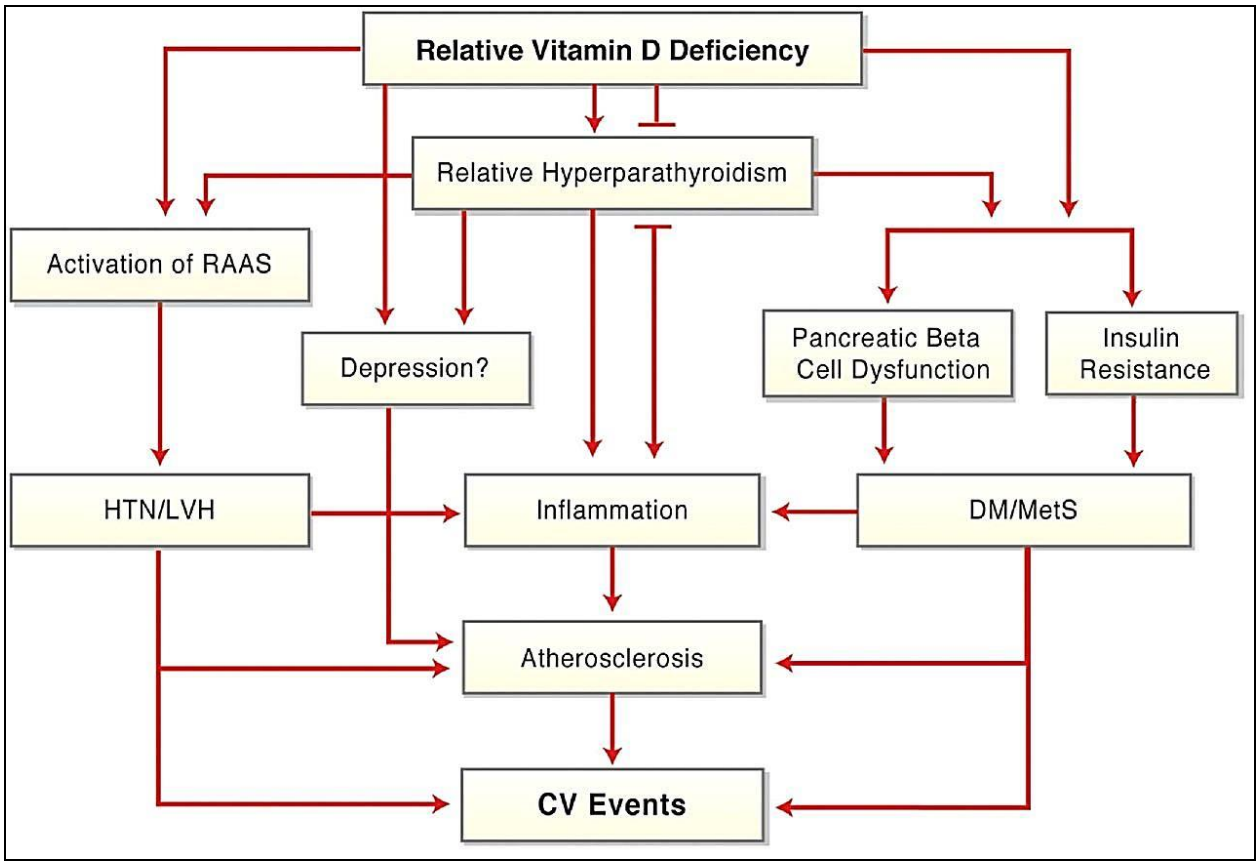


**Figure 2: Potential Mechanisms for cardiovascular disease.**

## POTENTIAL RISKS DUE TO VITAMIN D DEFICIENCY:

Vitamin D deficiency directly promotes the development of hypertension, which provides another potential mechanism hypertension, and cardiovascular risk.

Calcification is a common feature of atherosclerosis, and nearly all angiographic significant lesions are calcified. Calcification of coronary arteries has been associated with increased risk of MI and poorer survival.

Atherosclerotic calcification is a process regulated in ways similar to skeletal osteogenesis. A significant association exists between osteoporosis and vascular calcification, suggesting that osteoregulatory mechanisms related to bone development may affect calcification in the vasculature. Levels of 1, 25-dihydroxyvitamin D have been shown to be inversely associated with vascular calcification, suggesting that vitamin D may affect MI risk through its effects on vascular calcification. Other mechanisms could account for or contribute to the association between 25 (OH) D and MI risk [4].

Vitamin D deficiency, possibly combined with low calcium intake, has been associated with impaired fasting glucose and possibly risk of type 2 diabetes mellitus, risk factors for CVD.

Some studies suggest that there is an inverse relationship between vitamin D levels and the number of incidence of heart attack, if the Vitamin D

cell levels are low , there is a higher rate of incidence of heart attack.

## VITAMIN D DEFICIENCY ERADICATION:

Low serum vitamin D levels have been demonstrated in several studies in populations across the Indian subcontinent. The percentage of low serum vitamin D are between 80% to 95 % in most populations be it in the urban or the rural sectors across India [5].

Inadequate dietary intake of vitamin D and increased concern about the risk of skin cancer from sun exposure have both adults and children participating in fewer outdoor activities.

Children and adults exposed to natural or artificial ultraviolet B radiation can satisfy their vitamin D requirement. The skin has a huge capacity to produce vitamin D.

Exposure of a healthy adult to one minimal erythemal dose of sunlight is equivalent to taking between 10 000 IU and 20 000 IU of vitamin D, Because melanin is such an effective sunscreen, Population's closer to the Equator with darker skin pigmentation require 2 to 10 times the exposure than that of a fair skinned person to satisfy their body's vitamin D requirement. Although aging markedly diminishes the capacity of the skin to produce vitamin D3, elders exposed to sunlight can still raise their blood levels of 25(OH) D into a satisfactory range.

As per literature 90 % to 95 %of our vitamin D requirement has to come from exposure to sunlight. Many experts believe that in the absence of sun exposure, a minimum of 1000 IU - 2000 IU of vitamin D/day is required to fulfill an adult's vitamin D need. 400 IU of vitamin D/day are required by children and if the intake is 1000 IU/d there may be additional health benefits for them. If all people irrespective of age received sensible exposure to sunlight during the hot and sultry seasons, they are able to store vitamin D in their body fat and call upon it during the winter when the sunny days are fewer [6].

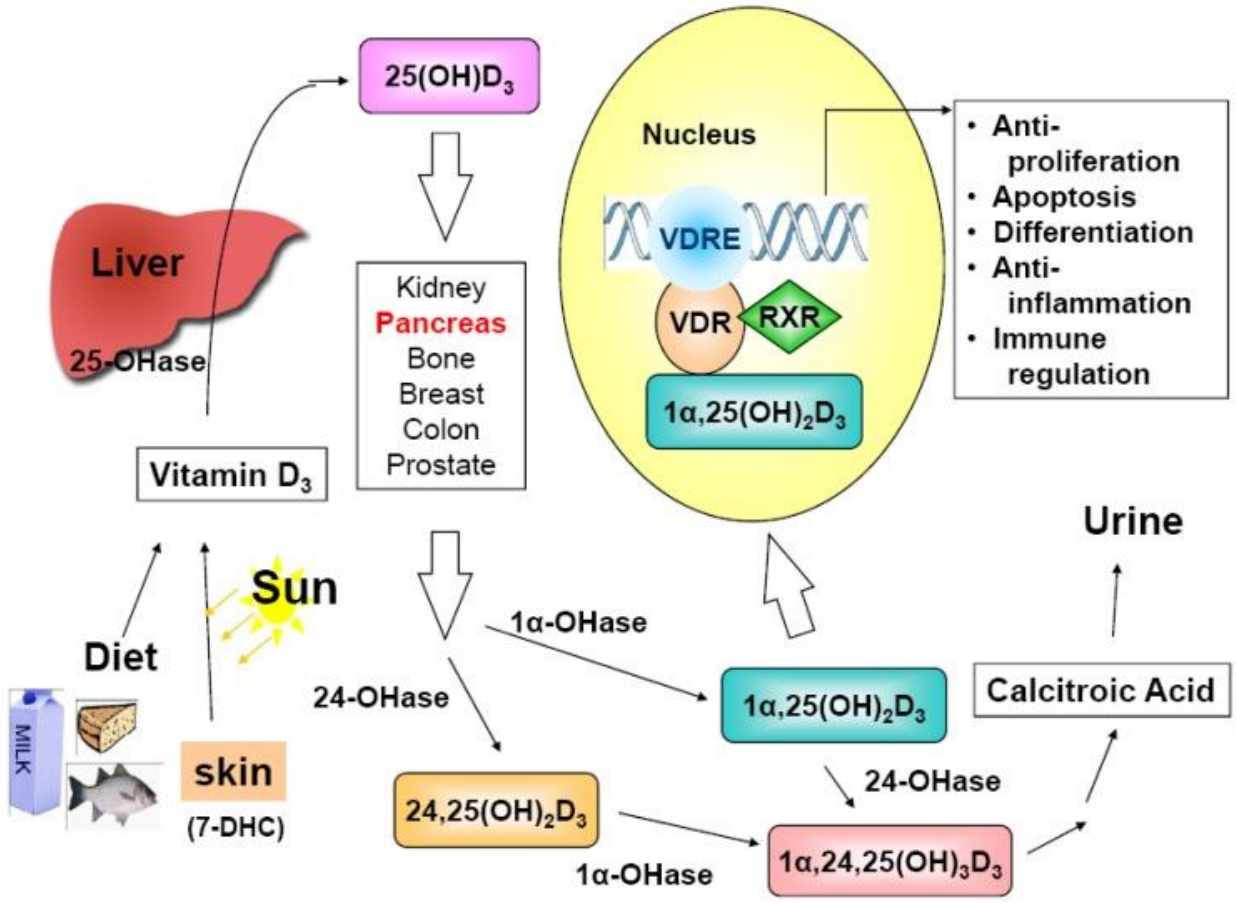


**Figure 3: Vitamin D Sources, metabolism, mechanism of action and biological activities. .**

Thus, there is a need to re-examine the message that any exposure to sunlight requires some type of sunscreen or sun protection. Sensible and limited exposure to sunlight, typically no more than 5-15 minutes a day on arms and legs (depending on time of day, season, skin sensitivity, latitude) between 10 a.m. and 3 p.m. Taking a multi vitamin containing 400 IU of vitamin D will satisfy approximately 20 percent of an adult's requirement. Thus, there is a need for additional supplementation and/or foods that contain vitamin D to satisfy the 1000 to 2000 IU and 400 to 1000 IU of vitamin D that adults and children respectively require to raise their blood levels of 25 (OH)D above 30 ng/ml, which falls in between the level of 20 ng/ml to 50 ng/mL is considered adequate level of Vitamin D for healthy population.

This type of induced marketing strategies made by Pharmaceutical companies have made good on effecting the psyche of the population to such an extent that people have stopped harnessing the easiest way to keeping good health .

When people increase their intake of dark meat, cold-water fish, they have fewer heart attacks and strokes and fewer deaths from these causes. The omega 3 fats in fish are also high in vitamin D [7].

Fat cells are biologically active, they produce hormones and molecules that affect metabolism and promote inflammation. Vitamin D counteracts this inflammation. When such inflammatory cells stick to the walls of blood vessels and are activated, they cause blood vessel damage that leads to plaque formation (arteriosclerosis).

Vitamin D present in the smooth vascular muscle reduces the stickiness of the blood vessel-lining cells and calms white blood cells that might otherwise become inflamed. Thus, preventing plaque formation.

Normalizing vitamin D alone will not prevent development of the metabolic syndrome, but improving your diet will help reduce your weight, blood pressure, diabetes and cholesterol.

Evidence suggests that low levels of vitamin D may adversely affect the cardiovascular system. Vitamin D receptors have a broad tissue distribution that includes vascular smooth muscle, endothelium, and cardiomyocytes. 1, 25 dihydroxyvitamin D (1, 25 OH D) activated directly suppresses renin gene expression, regulates the growth and proliferation of vascular smooth muscle cells and cardiomyocytes, and inhibits cytokine release from lymphocytes.
It unfortunately has put many people at risk for vitamin D deficiency and many of the serious chronic diseases that have been associated with inadequate sun exposure and vitamin D deficiency.

## VITAMIN D DEFICIENCY AND CARDIOVASCULAR DISEASE STUDIES:

Some studies referred to are like the Framingham Offspring Study, which is a landmark epidemiological study, which longitudinally followed up individuals (n = 1739) for a mean length of 5.4 years. There was no prior history of cardiovascular disease in this cohort, and pre specified baseline 25 hydroxy vitamin D (25 OH vitamin D) levels were used to stratify deficiency (<10ng/ml, < 15 ng/ml and > 15 ng/ml) [8]. The composite of cardiovascular events were classified as myocardial infarction, cardiac insufficiency, angina, stroke, transient ischemic attack, peripheral claudication or heart failure.

Multivariate adjustment for conventional risk factors was made, those with vitamin D levels of less than or equal to 15ng/ml had a hazard ratio of 1.62 (95% CI 1.11 to 2.36; p = 0.01) for incident cardiovascular events compared with those with vitamin D levels of greater than 15 ng/ml .

This increased risk was even more evident in those with hypertension, hazard ratio: 2.13 (95% CI 1.30 to3.48). Furthermore, A graded cardiovascular risk increase was noticed across the categories with a hazard ratio of 1.53 (95% CI 1.00 to 2.36) for levels of vitamin D of 10 to 15 ng/ml and 1.80 (95\% CI 1.05 to 3.08) for levels of vitamin D of less than 10 ng/ml.

For comparison with traditional risk factors, a recent meta-analysis demonstrated that for every 1 SD increase in triglycerides and non-high density lipoprotein cholesterol (HDL C), the hazard ratio for coronary heart disease was 1.37 (95\% CI 1.31 to 1.42) and 1.56 (95\% CI 1.47 to 1.66), respectively [9].

While these studies provide compelling evidence for a strong association of vitamin D deficiency with cardiovascular disease, the key issue remains as to whether correction of this deficiency can slow progression or even prevent cardiovascular events.

Another large noteworthy trial was the Ludwigshafen Risk and Cardiovascular Health (LURIC) study, which assessed a consecutive cohort of 3258 individuals scheduled for coronary angiography. Sudden cardiac death and death due to heart failure were independently and inversely associated with

25(OH) vitamin D, and stroke was related to both 25(OH) vitamin D and 1,25(OH)2 vitamin D levels [10].

The NHANES III study subgroup (n = 3408) analysis supported these findings as 25(OH) vitamin D was inversely associated with all-cause mortality over a mean period of 7.3 years [45]. Compared with individuals with 25(OH) vitamin D levels of 40 ng/ml or more, in those with 25(OH) vitamin D of less than 10 ng/ml, the adjusted risk was approximately 83\% higher [11].

This study was conducted nationwide in the United States, The Vitamin D and Omega-3 Trial (VITAL), which randomized 20,000 healthy older men and women to receive vitamin D3 (cholecalciferol) at a dose of 2000 IU per day and marine n 3 (also called omega-3) fatty acids at a dose of 1 g per day for the prevention of cancer and cardiovascular disease , Age group men 50+ years and women was 55 + years [12].

Primary end points were invasive cancer of any type and major cardiovascular events (a composite of myocardial infarction, stroke, or death from cardiovascular causes). Secondary end points included site-specific cancers, death from cancer, and additional cardiovascular events. The results of the comparison of vitamin D with placebo are as follows

A total of 25,871 participants underwent randomization. Supplementation with vitamin D was not associated with a lower risk of either of the primary end points (invasive cancer of any type and major cardiovascular events). During a follow-up of 5.3 years, A major cardiovascular event occurred in 805 participants (396 in the vitamin D group and 409 in the placebo group; hazard ratio, 0.97; 95% CI, 0.85 to 1.12; P = 0.69).
In the analyses of secondary end points, For the expanded composite end point of major cardiovascular events plus coronary revascularization, 0.96 (95% CI, 0.86 to 1.08); for myocardial infarction, 0.96 (95% CI, 0.78 to 1.19); for stroke, 0.95 (95\% CI, 0.76 to 1.20);and for death from cardiovascular causes, 1.11 (95% CI, 0.88 to 1.40). [12]

This study concludes that Supplementation with vitamin D did not result in a lower incidence of cardiovascular events than placebo, participants who were given the omega-3 fatty acids supplementation has shown that 386 major cardiovascular disease events occurred among the 12,933 participants receiving omega-3 fatty acids, as compared with 419 such events among the 12,938 participants receiving placebo, an 8\% reduction that was not significant. Upon closer examination, this result was due almost entirely to a reduction in heart attacks without a reduction in strokes. Specifically, the omega-3 fatty acid intervention lowered the risk of heart attack by 28% and the risk of fatal heart attack by 50\% but had no benefit on stroke or cardiovascular deaths not related to heart disease. Additionally, omega-3 fatty acids reduced the rate of angioplasty procedures by 22%.

## DISCUSSION:

The possible beneficial effects of Vitamin D supplementation is the main focus of this view. It is well documented that vitamin D insufficiency/deficiency is a major public health problem observed in all age groups. In relation to physical activity, vitamin D deficiency is associated with a decrease in neuromuscular function including muscular strength, walking speed, and aerobic capacity [13].

Hypertension usually developed when the balance between vasodilation and vasoconstriction is shifted towards vasoconstriction. When there is an unstable balance, vitamin D deficiency triggers a shift toward vasoconstriction [14]. The unequivocal cross-sectional and prospective inverse relationship between vitamin D deficiency and elevated blood pressure (BP) suggests involvement of vitamin D metabolism in the pathogenesis of hypertension [15].

Arterial hypertension belongs to the most prevalent diseases and accounts for about 7.5 million deaths per year (about 13% of all deaths) worldwide. According to the WHO, hypertension is a major risk factor for the development of a variety of diseases, including cardiovascular diseases (CVD), kidney failure, and cognitive impairment etc. [16] .It is estimated that approximately 22% (about 1 billion individuals) of the adult population above 25 years of age worldwide suffer from arterial hypertension [16].

Obesity and overweight are among the most health-threatening disease [17], Obesity is associated with many chronic diseases such as cardiovascular disease, especially in people with abdominal obesity [16-18].diseases. this is also caused by deficit of Vitamin D .

Clinical studies have reported cross-sectional associations between lower vitamin D levels and plasma renin activity, blood pressure, coronary artery calcification, and prevalent cardiovascular disease.

Additionally, ecological studies have reported higher rates of coronary heart disease and hypertension with increasing distance from the equator, a phenomenon that has been attributed to the higher prevalence of vitamin D deficiency in regions with less exposure to sunlight. The possibility of a causal link between vitamin D deficiency and cardiovascular disease is supported by biological plausibility, the demonstration of a temporal association, and the finding of a dose response between 25-OH D deficiency and risk. These data raise the possibility that treatment of vitamin D deficiency, via supplementation or lifestyle measures, could reduce cardiovascular risk.

## CONCLUSION:

A commonly overlooked but major complicating factor in determining the effects of vitamin D on BP and cardiac diseases is that exposure to UV light also causes reductions in BP, independent of vitamin D photosynthesis. Significant hypotensive effects of erythemal and pre-erythemal doses of UV irradiation have been demonstrated in both normotensive and hypertensive subjects (19–21).

Vitamin D (ie, low 25[OH]D levels) has recently emerged as a novel risk factor that can predict increased risk for CVD events and mortality above and beyond traditional risk factor assessment. Vitamin D deficiency can be easily modified in a cost-effective manner via supplementation or sensible exposure to sunlight.

From observational studies, the risk of cardiovascular mortality is increased twofold in those deficient in 25(OH) vitamin D, [22] compared with those with 'adequate' levels, although the definition of adequate may need modification in the context of non-bone/metabolic conditions. Prospective, randomized, placebo-controlled trials in cardio metabolic syndromes are urgently required to establish whether vitamin D replacement lowers cardiovascular risk. However, despite the accumulating evidence of a consistent link between vitamin D and blood pressure, more studies are needed to ascertain the effectiveness of vitamin D supplementation as a treatment strategy.

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