Research Article

INTERNATIONAL RESEARCH JOURNAL OF PHARMACY

www.irjponline.com

VITAMIN D DEFICIENCY AND ITS ASSOCIATED DISEASES

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It is to confirm that the submitted work is original and it is not submitted anywhere else for publication. There is no conflict of interest.

Doi: http://doi.org/10.56802/irjp.2025.v16.i09.pp10-32

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ABSTRACT

The sunshine vitamin, Vitamin D, has been associated with reduction of many health related critical diseases. As per recent studies, Vitamin D is regarded as a nutrient involved in bone metabolism and presence of vitamin D receptor in number of different tissues implies that vitamin D has various physiological roles apart from calcium and phosphorus metabolism. The present review will examine the current literature regarding vitamin D deficiency and its association with various types of diseases like diabetes, hypertension, lung disease, cardiovascular diseases, obesity, childhood asthma etc. Various databases like Pubmed, Google Scholar, Embase has been searched for Vitamin D associated diseases and details compiled with scientific evidence.

Keywords: Vitamin D, Diabetes, Hypertension, Cancer, Lung disease, Cardiovascular diseases, Obesity, Pregnancy.

INTRODUCTION

Vitamin D deficiency associated diseases is now a prevalent problem. Several studies indicate that vitamin D possess a range of anti-inflammatory properties and may be involved in processes apart from calcium and phosphate homeostasis[1]. The occurrence of vitamin D deficiency has been increasing in general population in recent times mainly due to sun avoidance, indoor lifestyle, use of sunscreen and decreased intake of Vitamin D rich food[2]. The present review will examine the current literature regarding role of vitamin D deficiency in various diseases.

Vitamin D metabolism and deficiency

Vitamin D is an essential element in human diet and is acquired from dietary supplements or synthesised in human skin following exposure to sunlight. Some vitamin D sources include dairy products, fish liver, fish oil, and eggs[3]. Vitamin D deficiency occurs mainly due to inadequate sun exposure, malabsorbtion or inadequate vitamin D in diet. Several studies revealed that serum 25-hydroxyvitamin D_3 level less than 25 nmol/l increases the risk of osteomalacia in adults and rickets in children which increases the risk of other diseases.

Calcium and phosphate homeostasis are mainly regulated by Vitamin D and parathyroid hormone in the human body. Vitamin D and its metabolites target receptors located in bone, intestine and kidney. Calcitriol increases osteoblastic bone formation, intestinal calcium absorbtion and osteoclastic recruitment leading to bone reabsorption[3]. Studies have revealed new sites of action that may force the re-examination of vitamin D and its role in human physiology. Vitamin D receptor (VDR) have also been found in organs like pancreas, gonads, liver, heart, brain, breast as well as hematopoietic and immune system that are not involved with bone metabolism [3].

Studies have revealed that calcitriol has an ability to encourage differentiation of normal cell types (such as osteoblasts, osteoclasts, lymphocyte and hematopoietic cells,) and may produce significant effects on other aspects of immune system[3]. Studies support the concept that vitamin D has the ability to affect immune function along with its potential use as a treatment modality in various diseases. Vitamin D analogues such as calcipotriene are commonly used in the treatment of psoriasis. Both in vitro and in vivo studies demonstrated immunomodulatory effect of vitamin D in the skin[4]. Research demonstrated vitamin D has an important role in the prevention of development of certain autoimmune diseases such as ulcerative colitis and crohn's disease[5].

VITAMIN D DEFICIENCY AND CHRONIC LUNG DISEASE

Vitamin D deficiency has been established in many of chronic lung disease patients. About 59% of patients with diffuse parenchymal lung disease were found to have decreased vitamin D levels[6]. Children with diagnosis of wheezy bronchitis have more than two and half times the incidence of rickets than the age matched control. Incidence of wheezy bronchitis is 10 times more in children having rickets[7].

In several animal and human studies, vitamin D has been linked to asthma. Wittke et al 2004[8] demonstrated that mice selectively bred without vitamin D receptors (VDR) fail to develop airway inflammation. These same mice also lacked the expected airway hyper-responsiveness despite elevated immunoglobin E and T helper 2 cytokine production. However treatment with 1,25 dihydroxyvitamin D_3 showed no effect on asthma severity in the wild type mouse population[8]. During pregnancy adequate vitamin D intake has been linked to decreased incidence of wheezing during childhood. Higher intake of Vitamin D during pregnancy is found to be linked with decreased risk of asthma or recurrent wheezing at 3 years of age [9]. Gaudet et al, 2022[10] demonstrated that vitamin D modulates the abnormal immune responses in chronic respiratory diseases. Many studies have proved that low level of vitamin D is associated with increased risk of asthma and other respiratory diseases [11,12]. Studies shows high prevalence of Chronic obstructive pulmonary disease, cystic fibrosis and respiratory infections occurs in vitamin D deficient subjects[13,14].

VITAMIN D DEFICIENCY AND HYPERTENSION

Hypertension or high blood pressure is one of the most chronic and deadliest disorders in the world. There are many risk factors for hypertension which include age, race, tobacco comsumption, high salt intake etc. As vitamin D receptor (VDR) is widely distributed in vascular endothelial cells, vascular smooth muscle cells and cardiomyocytes, the role of vitamin D and VDR in hypertension is greatly studied[15] Pathologically hypertension is strongest risk factor for cardiovascular disease[16] Low Vitamin D is one of the risk factors of hypertension[17]. One study demonstrated that systolic blood pressure, diastolic blood pressure and mean arterial pressure has increased among individuals having lack of vitamin D and proposed that vitamin D deficiency is associated with rennin angiotensin aldosterone system (RAAS) upregulation[18]. Study demonstrated that individuals with normal level of vitamin D had lower blood pressure and lower risk of developing hypertension[19]. Clinical and

epidemiological studies demonstrated an association between vitamin D deficiency, inadequate sunlight exposure and hypertension[20, 21]

An Italian study conducted by Carrara et al in 2016[22] reviewed the role of vitamin D supplementation on regulating the blood pressure in the body. They found that vitamin D levels increased throughout the study and blood pressures were greatly regulated. Here they concluded that vitamin D may help to reduce the risk of hypertension. Liang et al in 2018[23] demostrated an association of vitamin A and Vitamin D with hypertension in children. They found that serum 25(OH) D and 25(OH)D were significantly associated with blood pressure level. Ringrose et al in 2011[24] found an association of Vitamin D deficiency and hypertension in pregnant women. Here they concluded that women with low circulating vitamin D levels are more likely to develop hypertension.

VITAMIN D DEFICIENCY AND CANCER

Vitamin D is known mainly for its association with fractures and bone disease[25,26]. Studies demonstrated that Vitamin D is associated with several types of cancer. The high prevalence of vitamin D deficiency is associated with several thousand premature deaths from ovarian[27], breast[28], prostrate[29] and colon cancer[30]. Majority of studies found a protective relationship between sufficient vitamin D status and lower risk of cancer.

Death rates for colon cancer tend to be higher in areas with low winter sunlight and low in sunny areas. According to few studies, with Vitamin D below 30 ng/ml has approximately twice the risk of colon cancer as those with higher levels[31,32]. Several studies reported individuals with 25 (OH) D levels below 30 ng/ml had higher incidence of colonic adenomas[33,34]. Several epidemiological studies reported higher risk of colon cancer in individuals having low levels of vitamin D[35,36].

A number of studies have indicated that $1,25(OH)_2 D_3$ and its analogues may inhibit breast cancer cell growth by regulating cell cycle progression. Cell cycle gets arrested in G_0/G_1 estrogen receptor-positive MCF 7 breast cancer cells when treated with $1,25(OH)_2 D_3$ [37]. These effects are accompanied by alternation in expression of cell cycle regulators like cyclin dependent kinase (CDK) inhibitors and dephosphorylation of retinoblastoma protein [38] Death rates due to breast cancer are higher in areas with low levels of sunlight in winter and lower in sunny area[39]. Women regularly exposed to sunlight have sufficient amount of vitamin D and had significantly lower incidence of breast cancer[28]. Women having vitamin D deficiency had

5 times higher risk of breast cancer than those with highest level of vitamin D levels[40] Low vitamin D levels are associated with faster progression of metastatic breast cancer[41]. Shaukat et al 2017[42] reported the association of vitamin D deficiency and breast cancer. In their study on 94 female patients they found that 85.7% of breast cancer patients have vitamin D deficiency.

Incidence of ovarian cancer is also lower in sunny areas[43]. The incidence of prostate cancer is also lower in sunny areas and those with a history of exposure to high levels of sunlight[44,45]. In a study of 19000 men, those having vitamin D deficiency below 16 ng/ml had 70% higher incidence rate of prostate cancer than those with levels above 16 ng/ml[46]. In younger men with vitamin D level below 16 ng/ml the risk is 3.5 times higher than those with levels above 16 ng/ml[47]. Schwartz 2005[48] found that mortality rates from prostrate cancer are significantly higher in African Americans than Caucasian Ameericans and are inversely related to the availability of ultraviolet radiation. In this study he found that prostrate cancer has an association with low Vitamin D deficiency. Fig 1 demonstrate Vitamin D status in the studied population and Fig 2 (a to e) demonstrates Vitamin D status in various Cancers in the studied population.

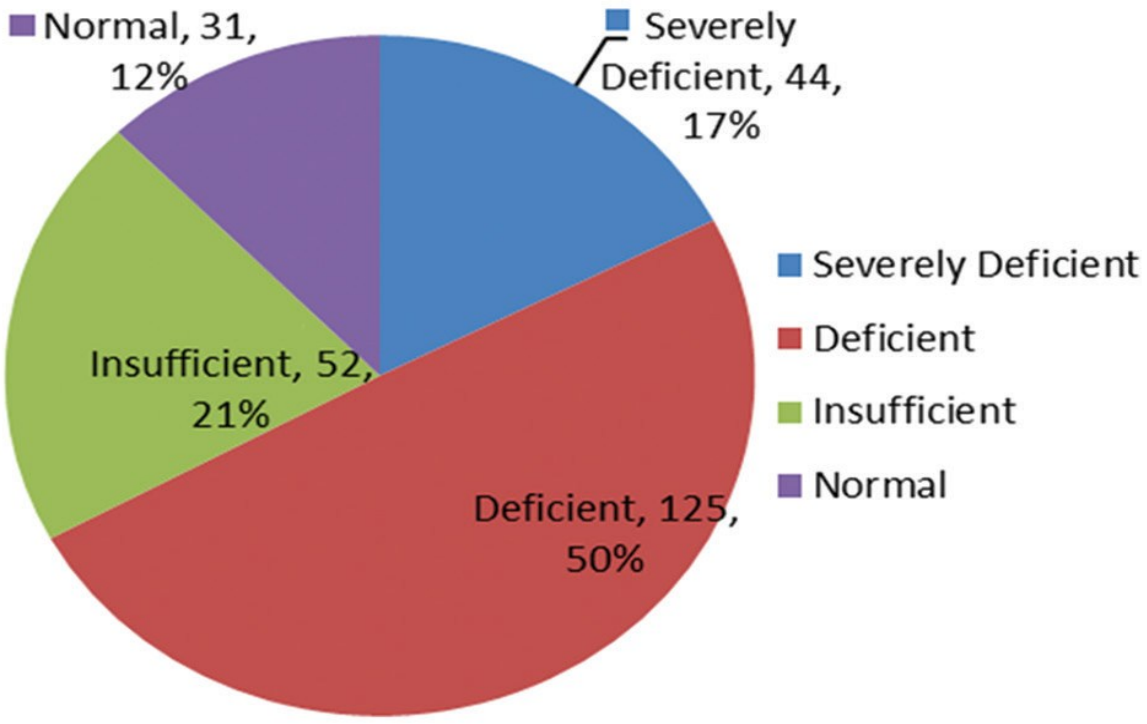

Fig 1: Pie chart depicting the vitamin D status in a study population cohort (n=252). Normal vitamin D level> 30ng/ml, insufficient vitamin D level 20-30 ng/ml, deficient vitamin D level 10-20ng/ml, severely deficient vitamin D level < 10ng/ml[49]

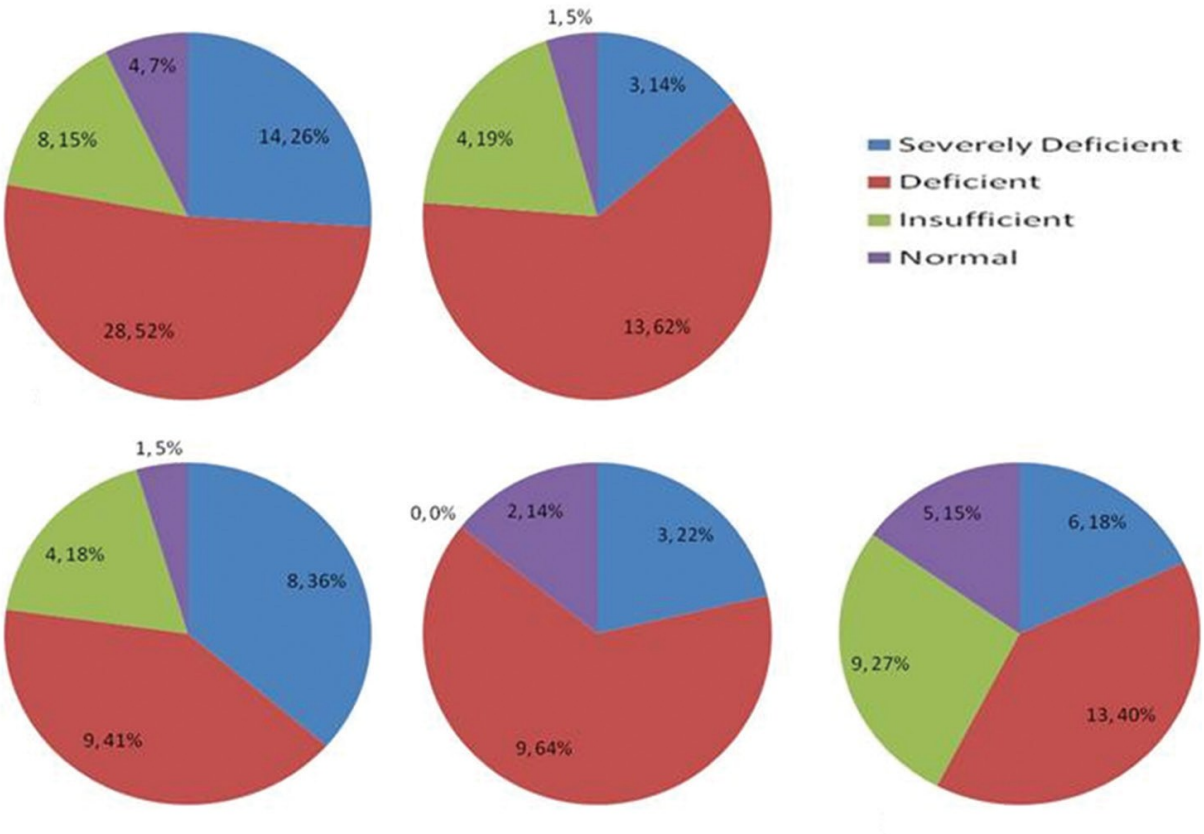

Fig 2: (a-e): Pie chart showing vitamin D status across a) breast (n=54), b) ovarian (n=21), c) colorectal (n=22), d) upper gastrointestinal tract (n=14), e) gall bladder cancer (n=33), respectively. Normal vitamin D level >30ng/ml, insufficient vitamin D level 20-30 ng/ml, deficient vitamin D level 10-20 ng/ml; severely deficient vitamin D level < 10ng/ml[49]

VITAMIN D DEFICIENCY AND OBESITY

Several evidences have been found which relates vitamin D deficiency and obesity. Wortsman et al 2000[50] found that obesity is associated with vitamin D insufficiency and secondary hyperparathyroidism. They observed that obese subjects had significantly lower basal 25-hydroxyvitamin D concentrations and higher parathyroid hormone concentrations. Song and Sergeev, 2012[51] suggested that role of calcium and vitamin D in obesity. They found that low calcium intake and low vitamin D level have been linked with an increased risk of obesity in epidemiological studies. Matrix metalloproteinases (MMPs) are proteolytic enzymes that are

responsible for remodeling the extracellular matrix and regulating leukocyte migration through the extracellular matrix. This migration is an important step in inflammatory and infectious pathophysiology. MMPs are produced by many cell types, including granulocytes, lymphocytes, activated macrophages and astrocytes,. There is growing evidence that MMPs play an important role in the pathogenesis of obesity. Bouloumiéet al.[52] provided the first evidence that human adipose tissue releases MMP-2. Overweight/obese women had significantly higher plasma activity of MMP2 than controls[53]. One study found that polymorphisms in the *VDR* gene have been associated with obesity traits in some but not all, studies. Thus, results are inconclusive. Other genes aside from *VDR* have also been investigated in relation to obesity-related traits. However, again, findings suggests that the *DBP/GC* gene could be an important protein-linking obesity and vitamin D status. Some studies suggest that vitamin D, due to its fat-soluble characteristic, is retained by the adipose tissue and has the capacity to metabolize 25(OH)-D locally, that can be altered in obesity. Additionally, vitamin D is capable of regulating the gene expression related to adipogenesis process, inflammation, oxidative stress, and metabolism in mature adipocytes[54] According to a study 63% morbidly obese individuals had metabolic syndrome and vitamin D deficiency occurred in 50.7% of them[55]. It proves that vitamin D deficiency is closely related to morbidly obese individuals alongwith the metabolic syndrome, compared to normal weight individuals. In another study on Canadian normal weight, overweight and obese children and adolescents, it was found that vitamin D deficiency was in 27% of overweight and obese youth while it was only 12% in normal weight youth. This study confirmed that obesity was associated with 25 (OH)D concentration in Canadian youth and it was independently associated with vitamin D supplementation and daily milk comsumption[56].

VITAMIN D DEFICIENCY AND ATHEROSCLEROSIS AND CARDIOVASCULAR DISEASES (CVD)

Atherosclerosis, the principal factor of cardiovascular diseases (CVDs), is a process that involves a complex interplay among different factors and cell types, including cells of the immune system (T cells, B cells, natural killer cells, monocytes/macrophages, dendritic cells) and cells of the vessel wall (endothelial cells [ECs], vascular smooth muscle cells [VSMCs]). The atherogenic process evolves in different stages, starting from inflammatory endothelial activation/dysfunction and resulting in plaque vulnerability and rupture.[57] The endothelium is the key vessel wall component in the initiation of the atherogenic process[58]

Studies revealed that ECs express VDRs and they have the ability to synthesize calcitriol [1a,25$(OH)_2D_3$] because of the expression of 1a-hydroxylase.[59] The coexistence of these crucial elements of vitamin D metabolism proves the hypothesis of an autocrine/intracrine mechanism of vitamin D action as a modulator of endothelial functions.[60]

Atherosclerosis is the build up of cholesterol rich lipids on the arterial wall accompanied with inflammatory responses[61]. Vitamin D deficiency is related with increased risk of atherosclerosis. A positive inverse correlation is seen between atherosclerotic plaque formation and level of circulating vitamin D. In Oh et al's study in 2009 [62] they found that vitamin D protects against foam cell formation and inhibits macrophage cholesterol uptake in patients with type 2 diabetes mellitus. When macrophages isolated from diabetic patients were cultured in media with or without adding vitamin D and was loaded with modified low density lipoprotein cholesterol, 1-25 $(OH)_2$ D_3 inhibited the foam cell formation by reducing uptake of acetylated low density lipoprotein(LDL) or oxidised LDL (OxLDL) cholesterol in diabetic patient only. The modified LDL induced foam cell formation in VDR deleted macrophage from diabetic patients. Vitamin D prevented Ox LDL derived cholesterol uptake as well as downregulated the C Jun N terminal kinase activation, reduced PPAR expression and CD 36 expression. Another study an African Americans where evaluated they found that 25(OH) D had a positive association with aorta and carotid artery calcified atherosclerotic plaque formation in African American[63].

Recent research highlighted the importance of vitamin D deficiency in several CVD conditions. Vitamin D deficiency has been positively correlated with poor cardiac contractility[64], increased myocardial collagen content and cardiac tissue maturation[65]. VDRs have a broad tissue distribution that include vascular smooth muscle, endothelium and cardiomyocytes[66]. Occurrence of CVD related mortality has a strong association with environmental factors like geographic latitude, altitude, season and place of residence[67]. All these factors have a strong relationship with UVB exposure and therefore the serum vitamin D level[68]. Therefore it can be said that vitamin D has a critical role in maintaining cardiovascular health. Studies revealed that excessive renin–angiotensin–aldosterone system (RAAS) activation leads to cardiac hypertrophy and hypertension, and these abnormalities have been found in expertimental models of Vitamin D deficiency. Similar findings have been obtained in nongenetic experimental models of vitamin D deficiency. In a study where low vitamin D was induced by dietary deprivation, blood pressure, heart contractility, and vascular contractility were tested in vitamin D-free diet mice and vitamin D-included diet mice. This study suggests that, in the

subgroup of the vitamin D-free diet, systolic blood pressure and myocardial/vascular contractility were increased with respect to the subgroup fed with vitamin D. To exclude that these findings were related to hypocalcemia elicited by hypovitaminosis D, a group of rats was tested during a vitamin D3-deficient diet, allowing normal plasma ranges of calcium and phosphates. Under these experimental conditions, similar results were found with regard to blood pressure and heart/vasculature contractility[69]. A study carried out on a large population of newly diagnosed hypertensive patients detected an inverse and strong relationship between hypovitaminosis D and 1 h post-load glucose in normo-glycemic subjects. The population with hypovitaminosis D and glucose values >155 mg/dl at 1 h post-load glucose had worse metabolic and cardiovascular outcomes; thus, showing multiple subclinical organ damage[70] A meta-analysis suggests that vitamin D supplementation may decrease blood pressure in hypertensive patients characterized by vitamin D deficiency[71]..A wide range of mechanisms may play role in vitamin D dependent cardiovascular health maintenance that include suppression of renin–angiotensin–aldosterone system (RAAS)[72], inhibition of growth of vascular smooth muscle cell[73], the suppression of vascular calcification[74], the upregulation of anti inflammatory cytokines by suppressing pro-inflammtory cytokines[75] and prevention of secondary hyperparathyroidism[76] Wang et al[77] conducted a study on 1739 subjects without previous CVD history. About 37% of the subjects showed marked deficiency of vitamin D. Within a span of 5.4 years 120 subjects encountered the first cardiovascular event. Another study reported that 60000 IU of monthly oral vitamin D supplementation for 16 weeks improved the vascular endothelial function significantly in 45 African American adults[78] Endothelial dysfunction and RAAS modulation are the main causative factors for the development of arterial hypertension due to vitamin D deficiency in animal reversible models, where supplementation of vitamin D restored or improved the cardiovascular impairment[79]. Fig 3 demonstrates the metabolism and actions of vitamin D in cells and tissues that are implicated directly and indirectly in the atherogenic process.

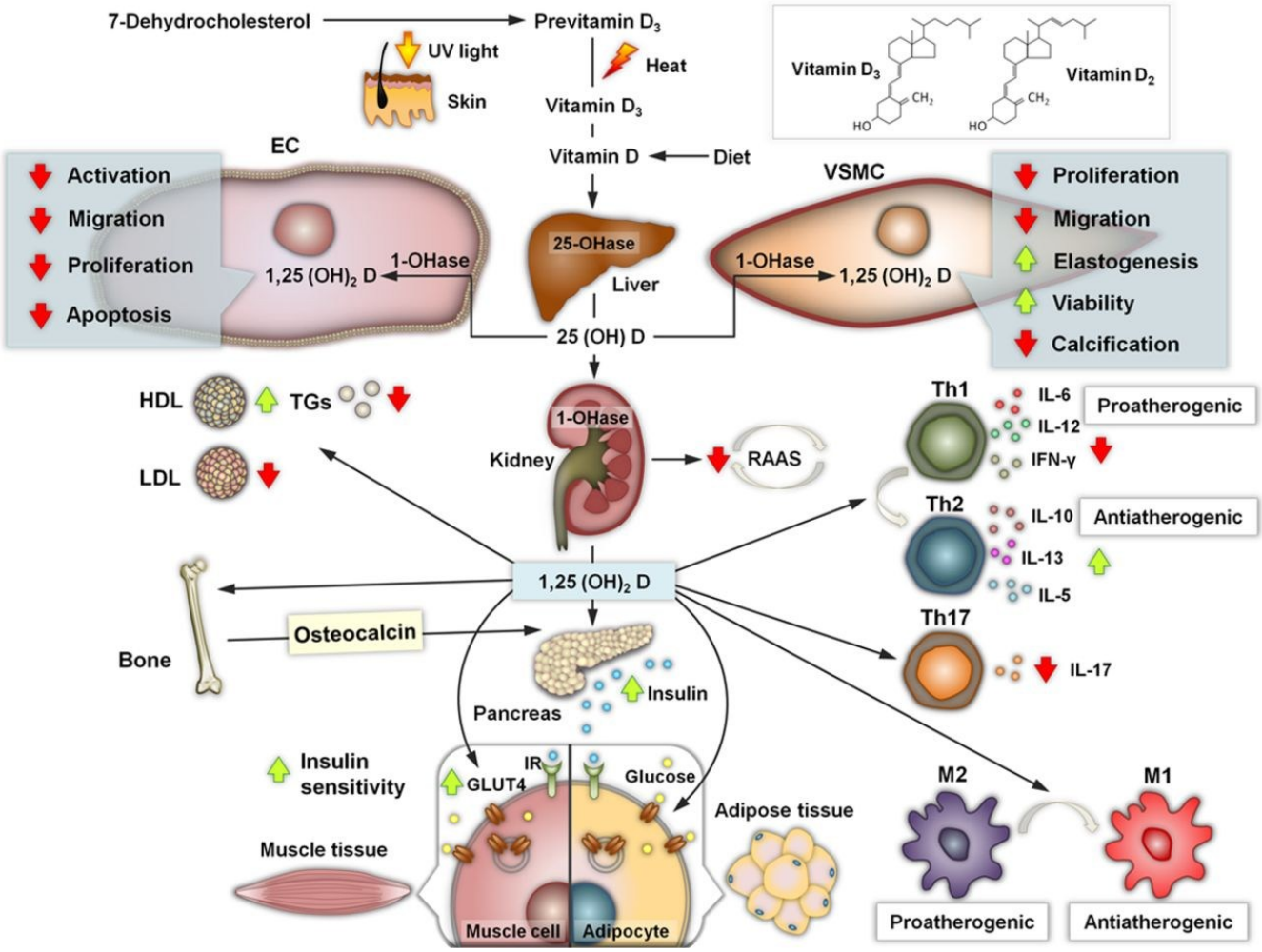

Fig 3: Schematic representation illustrating synoptically the metabolism and actions of vitamin D in cells and tissues that are implicated directly and indirectly in the atherogenic process. EC indicates endothelial cell; Glut-4, glucose transporter 4; HDL, high-density lipoprotein; IL, interleukin; IR, insulin receptor; LDL, low-density lipoprotein; M1, macrophage/monocyte 1; M2, macrophage/monocyte 2; RAAS, renin-angiotensin-aldosterone system; TGs, triglycerides; Th, T helper; and VSMC, vascular smooth muscle cell[58]

VITAMIN D DEFICIENCY AND DIABETES

Vitamin D receptors are present in both pancreatic beta-cells and immune cells. Vitamin D stimulates the activity of beta cell calcium-dependent endopeptidases which promotes conversion of proinsulin to insulin and thereby increases the insulin output. In peripheral insulin target tissues, vitamin D increases the insulin action via regulation of the calcium pool. Vitamin D also acts as a potent immunosuppressor. It tends to downregulate the transcription of various proinflammatory cytokine genes like Tumor Necrosis Factor-α, Inter-leukin-2 and Interlukin-12. It promotes production of anti-inflammatory cytokines, the induction of

regulatory T-lymphocytes and protects beta-cell from destruction. Vitamin D deficiency leads to type 1 diabetes in animal models and humans. Vitamin D deficiency impairs insulin secretion and leads to glucose intolerance. Several vitamin D related genes are associated with different pathogenetic traits of the disease. Vitamin D supplementation has shown to reduce the risk of developing type 1 Diabetes. Vitamin D has also been shown to reduce the risk of diabetes associated complications[80]. The relationship between sunlight exposure and the incidence of type 1 Diabetes mellitus has been reported[81]. A study showed that in North Europe where daylight hours are shorter than in other countries providing vitamin D supplements to infants decreased the risk for new-onset of type 1 DM[82]. As VDRs in pancreatic β-cells play an important role in the progression of type 2 DM[83], vitamin D deficiency is related to insulin resistance, insulin secretion, and β-cell dysfunction in the pancreas[84]. Vitamin D deficiency is related to less secretion of pancreatic insulin in the diabetic animal model[85]. Administration of vitamin D restores glucose-stimulated insulin secretion and promotes β-cell survival by modulating the generation and effects of cytokines[86]. The insulin deregulation and diabetes mellitus are co related. Many studies has repeatedly found a clear association between low vitamin D levels in patients with insulin resistance and a high risk of developing type 2 diabetes. With vitamin D supplementation prior to diagnosis or soon after, the body retains the ability to respond better to insulin which counters the hallmark of type 2 diabetes i.e insulin resistance. People with high BMI in young age suffers from diabetic complication in middle age. Insulin resistance increases the risk of other disease like cardiovascular disease[87], kidney disease[88]. Many evidences suggest that decrease in insulin secretion in both humans as well as animal models has a strong correlation with vitamin D deficiency[89]. It has been reported in several studies that lower level of vitamin D leads to the development of insulin resistance and thus NIDDM by deregulating the insulin sensitivity or beta cell function or both[90]. As per a study vitamin D supplementation in two elderly female subjects decreased the glycosylated haemoglobin level from 8.4% to 7.4% and 13.3% to 12.2% respectively[91]. This showed that vitamin D sufficiency improves glucose tolerance. In a study by He et al, 2018[92] insulin sensitivity and type 2 diabetes mellitus were improved in diabetic subjects when given a supplement dose >2000 IU/day.

VITAMIN D IN PREGNANCY AND LACTATION

Some studies showed that vitamin D deficiency is a risk marker for reduced fertility[93] Low vitamin D levels during pregnancy and infancy may lead to adverse health outcomes such as

preclamsia, low birth weight, neonatal hypocalcemia, poor post natal growth, bone fragility and increased incidence of autoimmune diseases[94]

Several studies have reported an association between infant size and vitamin D status. In a study in 449 Iranian pregnant women, higher mean birth length was found at delivery in babies from mothers who received the recommended dietary allowance of calcium and vitamin D[95]. The importance of vitamin D for fetal and infant skeletal mineralization in utero that occurs due to vitamin D deficiency may lead to congenital rickets, craniotabes or osteopenia in new born infants[96,97]. Vitamin D deficiency during pregnancy may lead to asthma and type 1 diabetes in their children[98,99].

In the first 6-8 weeks of postnatal life the vitamin D of a neonate is dependent largely on vitamin D that is acquired from the mother through placental transfer[100]. In most infants vitamin D stores acquired from the mother are depleted by 8 weeks of age approximately[101]. After that vitamin D is derived from diet, sunlight and supplements. Generally formula fed babies receive adequate vitamin D because it is added to all formulas as per recommendation. While exclusively breast fed babies are at higher risk of vitamin D deficiency[102]. Human milk contains a very low concentration of vitamin D (20-60 IU/L) which represent 1.5-3% of the maternal level[103]. This concentration is not sufficient to maintain an optimal vitamin D level in the baby if exposure to sunlight is limited. Breast fed infants from vitamin D deficient mothers sometimes may suffer from life threatening conditions such as hypocalcemic seizures and dilated cardiomyopathy[104,105]. The vitamin D–deficient neonate is at risk to develop hypocalcemia, rickets, and possibly extraskeletal disorders (e.g., type 1 diabetes)[106]

CONCLUSION

Vitamin D deficiency is associated with many diseases. So adequate amount of vitamin D is needed. Vitamin D supplementation dosage is still an issue of controversy. In 2010, the Food and Nutrition Board of the Institute of Medicine, US recommended the dietary reference intake (DRI) allowance of vitamin D to be 400 IU/day (10 mcg/day) for infants and 600 IU/day (15 mcg/day) for children and adult male and female upto 70 years of age, whereas for above 70 years the intake level is 600 IU (15 mcg/day) (Institute of Medicine 2011)[107]. The DRI allowance of vitamin D and effective recommendation were based on the calcium metabolism by vitamin D and effective elimination/ or prevention of rickets. The vitamin D toxicity is a matter of concern, but the intoxication caused by ingestion of high dosage deliberately because

the vitamin D synthesis resulting from the exposure to sunlight, and those obtained through fortified foods do not sum up to make large amounts of vitamin D.

The major side effect resulting from vitamin D toxicity is increased calcium deposition in the body leading to hypercalcemia. Mild asymptomatic hypercalcemia has been reported after supplementation of 1400-4000 IUs of vitamin D leading to increase in serum vitamin D level between 197 and 255 nmol/l in children[108]. Severe hypercalcemia is caused by exposure to large oral vitamin D doses of upto 60000 IU in infants[109]. Wheareas in healthy adults in a clinical set up it was found that supplementation even upto 50000 IUs of vitamin D every alternate week for a period of 6 years helped in maintaining the 25 (OH)D concentration at a range of 100-150 nmol/l without promoting any vitamin D toxicity[110].

ACKNOWLEDMENT: Nil

CONFLICT OF INTEREST: There is no conflict of interest

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