Vitamin D and Its Metabolites in Health and Diseases

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Abstract - CONSIDERABLE attention has been paid in recent times to understand the possible role of Vitamin D deficiency in the development of several chronic diseases. The prevalence of Vitamin D deficiency among Indian population is around 85%, and it is the only nutrition related deficiency which has not been paid much alteration by health care providers even though a series of health related disorders may be caused by such deficiency. Although sunlight is the main source of Vitamin D biosynthesis through skin, even in a tropical country like India, the deficiency is still the highest. Many food supplements from dietary sources are not adequately enriched by Vitamin D and its derivatives. Researchers in health care have identified several diseases associated with various organs due to Vitamin D deficiency. This review article presents the recent research findings on Vitamin D during the last 20 years highlighting the importance of Vitamin D and its metabolites in diseases related to liver, kidney, cardiac, immune, infections, bone, skeletal, endocrine and cognitive disorders.

Key Words: Vitamin D, CVD, CKD, CLD, DM.

I. INTRODUCTION

Vitamin D(VitD) is the name given to a group of fat-soluble prohormones and they are critical for diverting calcium and phosphorus to make strong bones and teeth. The first source for VitD is to exposure of skin to sunlight.VitD deficiency could cause a weakening of the bones leading to rickets in children and osteomalacia in adults.Two major forms of VitDfound in humans are $VitD_2$ orergocalciferol and $VitD_3$ or cholecalciferol. $VitD_2$ is made naturally by plants and $VitD_3$ is synthesised when skin is exposed to ultraviolet radiation present in sunlight. Both forms are converted to 25-hydroxyvitamin D(25OH VitD) in the liver and transported to the kidneys, where it is further modified to 1,25-dihydroxyVitD or calcitriol, the active form of VitD in the body.

Most people get at least some of the VitD they need through sunlight exposure. Dietary sources for VitD include fatty fish, fish liver oil and eggs. However, most dietary VitD comes from foods fortified with VitD, such as milk, juices and breakfast cereals. VitD can also be obtained through dietary supplements.Although the average dietary intakes of VitD in the United States are below guideline levels, data from the National Health and Nutrition Examination Survey revealed that more than 80 percent of Americans had adequate VitD levels in their blood. Even though most people are unlikely to have high VitD intake, it is important that excessive intake of any nutrient, including VitD, can cause toxiceffects. Too much VitD can be harmful as it may increase calcium levels leading to calcinosis. The safe upper intake level of VitD for adults and children older than 8 years of age is 100 µg per day (4000 IU per day). Toxicity from too much VitD is more likely to occur from high intakes of dietary supplements than from high intakes of foods that contain VitD. Excessive sun exposure does not cause VitD toxicity. However, the Institute of Medicine states that people should not try to increase VitD production by increasing their exposure to sunlight as it will increase the risk of skin cancer.

II. VITAMIN DIN GENERAL HEALTH

VitD3 is a prohormone produced in skin through ultraviolet irradiation of 7-dehydrocholesterol. It is biologically inert and must be metabolized to 25-hydroxyVitD3 in the liver and then to 1-α,25-dihydroxyVitD3 in the kidney before it shows its biological function. The hormonal form of VitD3, ie, 1-α,25-dihydroxyVitD3, acts through a nuclear receptor to carry out its many functions, including calcium and phosphorus absorption, phosphate absorption in the intestine, calcium mobilization in bone and calcium reabsorption in the kidney. It also has several noncalcemic functions in the body. It provides information on new selective analogs of 1-α,25-dihydroyVitD3 for therapy [1].

VitD and its metabolites have pleomorphic roles in both nervous system health and disease. Animal models have been paramount in contributing to our knowledge and understanding of the consequences of VitD deficiency on brain development and its implications for adult psychiatric and neurological diseases. The conflation of in vitro, animal model data provides compelling evidence that VitD has a crucial role in proliferation, differentiation, neurotrophism, neuroprotection neurotransmission and neuroplasticity. VitD exerts its biological function not only by influencing cellular processes directly, but also by

influencing gene expression through VitD response elements[2].

VitD functions by stimulating intestinal calcium and phosphorus absorption, bone calcium mobilization and increasing renal reabsorption of calcium in the distal tubule. These functions on bone and kidney, but not intestine, require the Parathyroid Hormone(PTH). As a result of these functions, serum calcium and phosphorus concentrations are elevated to supersaturating levels required for the mineralization of bone to prevent rickets, osteomalacia and hypocalcemic tetany. Recent experiments demonstrate that maintaining serum calcium and phosphorus levels in VitD-deficient rats in the normal range results in normal bone growth and mineralization. However, increased calcification results because bone resorption by osteoclasts is a VitD-dependent process. Thus, bone resorption, modeling and remodeling must be considered VitD-dependent processes[3].

Dyslipidemia and vascular calcification are important predictors of Cardio Vascular Disease (CVD). VitD may have an influence on these two CVD risk markers. The vast majority of intervention studies did not show an effect of VitD on serum cholesterol levels. There is however evidence for a triglyceride-lowering effect of VitD which primarily comes from studies with chronic kidney disease patients, a group with elevated triglyceride levels. The previously presumed influence of statins on the actions of circulating and cellular VitD remains obscure. Epidemiological studies on VitD and vascular calcification are inconsistent at present, but are probably biased by confounding. Prospective cohort studies consistently indicate an enhanced multivariable-adjusted CVD mortality risk when circulating VitD levels are below 25 nmol/L. Adequately designed randomised controlled trials investigating the dose-response effect of VitD on different CVD outcome parameters are now warranted[4].

Worldwide reports have highlighted a variety of VitD insufficiency and deficiency diseases. Despite many publications and scientific meetings reporting advances in VitD science, a disturbing realization is growing that the newer scientific and clinical knowledge is not being translated into better human health. Over the past several decades, the biological sphere of influence of $VitD_3$, as defined by the tissue distribution of the Vitamin D Receptors (VDRs), has broadened at least 9-fold from the target organs required for calcium homeostasis (intestine, bone, kidney and parathyroid)[5].The role of VitD in skeletal health is well established, but more recent findings have also linked VitD deficiency to a range of non-skeletal conditions such as CVD, cancer, stroke and metabolic disorders including diabetes. Cognitive impairment and dementia must now be added to this list. VDRs are widespread in brain tissue and the biologically active form of [1,25(OH)(2)D3] has shown neuroprotective effects including the clearance of amyloid plaques, a hallmark of Alzheimer's Disease. Two large prospective studies recently indicated that low VitD concentrations may increase the risk of cognitive decline. Large, well designed randomized controlled trials are now needed to determine whether VitD supplementation is effective at preventing or treating Alzheimer's disease and dementia[6].VitD deficiency has potential adverse effects on neurocognitive health and subcortical function. However, no studies have examined the association between VitD status, dementia and cranial MRI indicators of CVD.VitD insufficiency and deficiency was associated with all-cause dementia, Alzheimer disease, stroke (with and without dementia symptoms) and MRI indicators of CVD. These findings suggest a potential vasculoprotective role of VitD[7].

Numerous epidemiologic studies suggest that exposure to sunlight, which enhances the production of VitD3 in the skin, is important in preventing many chronic diseases. Because very few foods naturally contain VitD, sunlight supplies most of our VitD requirement. VitD is the metabolite that should be measured in the blood to determine VitD status. Greater awareness of the insidious consequences of VitD deficiency is needed. Annual measurement of serum VitD is a reasonable approach to monitoring for VitD deficiency. The recommended adequate intakes for VitD are inadequate and in the absence of exposure to sunlight, a minimum of 1000 IU VitD/day is required to maintain a healthy concentration of VitD in the blood[8].Although chronic excessive exposure to sunlight increases the risk of nonmelanoma skin cancer, the avoidance of all direct sun exposure increases the risk of VitD deficiency, which can have serious consequences. Monitoring VitD concentrations yearly should help reveal VitD deficiencies.

Sensible sun exposure (usually 5-10 min of exposure of the arms and legs or the hands, arms and face, 2 or 3 times per week) and increased dietary and supplemental VitD intakes are reasonable approaches to guarantee VitD sufficiency[9].Calcium is necessary for insulin secretion, suggesting VitD may contribute to maintaining insulin secretion. VitD, formed in skin in bright sunshine, is scarce in foodstuffs. Data linking hypovitaminosis D to hyperglycemia, T2DM and metabolic disorders increasing cardiovascular risk has accumulated over ≈40 years. If on-going/ planned RCTconfirms causality, maintenance of adequate VitD status at the population level by food-fortification or supplementation would be cost-effective measures likely to reduce the burden and costs of diabetes to individuals and health services. Additionally, VitD(2/3) supplementation is cheap but whether some non-

hypercalcemia-inducing analogue may prove safer has not yet been addressed at the population level[10].

III. VITAMIN D AND DIABETES MELLITUS

VitD deficiency appears to be related to the development of T2DM and the Metabolic Syndrome (MS). VitD may affect glucose homeostasis and is found to be inversely related to glycosylated hemoglobin levels (HbA1c) in Gestational Diabetes Mellitus(GDM)[11].VitD levels appears to be lower in T2DM patients than in the control group and is being related to glycemic control. These findings may have therapeutic implications as cautious VitD supplementation may improve glycemic control in T2DM[12].The presence ofVDRs and VitD-binding proteins (DBP) in pancreatic tissue and the relationship between certain allelic variations in the VDR and DBP genes with glucose tolerance and insulin secretion have further supported this hypothesis. The mechanism of action of VitD in T2DM is thought to be mediated not only through regulation of plasma calcium levels, which regulate insulin synthesis and secretion, but also through a direct action on pancreatic beta-cell function[13].

The majority of RCTs in healthy or prediabetic individuals have, however, failed to demonstrate relevant VitD effects on Insulin Resistance (IR) or diabetes incidence. In patients with T2DM, a few RCTs reported some moderate effects of VitD on glycemic control and IR. While these findings warrant further in-depth studies, the current evidence is insufficient to recommend VitD supplementation for the prevention or treatment of T2DM[14].The active metabolite of VitD regulates transcription of multiple gene products with antiproliferative, prodifferentiative, and immunomodulatory effects. Although VitD deficiency is frequently unrecognized clinically, laboratory measurement is easy to perform and treatment of VitD deficiency is relatively well tolerated and inexpensive. The high prevalence of VitD deficiency and plausible molecular mechanisms linking this to diabetes and CVD risk suggest treatment of VitD deficiency to prevent and/or treat diabetes is a promising field to explore[15].Well-designed trials that focus on intermediate biomarkers of diabetes risk in response to increased VitD intake are still needed. It will be important to include in the design of these studies selection of IR study subjects who have a low (< 50 nmol/L) initial serum VitD status and administration of sufficient VitD to adequately increase their status to > 75 nmol/L[16].

An association between VitD insufficiency and incident T2DM has been reported in longitudinal observational studies, but the association is not consistent. Results from small underpowered trials and post-hoc analyses of data from larger trials designed for bone-specific outcomes show no effect of VitD supplementation on glycemia in healthy adults but VitD may retard the progression to diabetes in adults with glucose intolerance. Because VitD is an excellent marker of general health status, the positive results reported in some observational studies might reflect unmeasured and unaccounted confounding. Therefore, the hypothesis that VitD may modify diabetes risk needs to be confirmed in trials specifically designed for that purpose[17].While in all T2DM groups circulating levels of VitD increased after supplementation, in T2DM patients on insulin in combination with other drugs benefitted the most in improving CVD risk. Metformin improves VitD levels but did not seem to confer other added cardiometabolic benefits[18].Accumulating evidence links VitD deficiency with abnormal glucose metabolism, and epidemiological studies have shown that women who develop GDM are more likely to be VitD deficient. There are many emerging evidence that associates VitD deficiency with the risk of developing GDM indicating a need for intervention trials to test the possible beneficial effect of VitD supplementation in pregnant women with low VitD status to reduce the risk of developing GDM[19].

T2DM and VitD deficiency are both common in Saudi Arabian population. New roles of VitD have emerged recently especially in the prevention of CVD, cancer and IR[20].VitD deficiency was associated with GDM. Given that VitD is hydroxylated by CYP27B1 to the bioactive 1,25(OH)2D form, and CYP24A1 catabolizes both VitD and 1,25(OH)2D to the inactive metabolites, respectively, indicating that the elevated activity of CYP24A1 in the placenta may play a key role in the development of VitD deficiency in GDM[21].VitD concentration was significantly lower in diabetic patients than the healthy individuals. Although the mean concentration of VitD in males in both groups was equal but in the women with diabetes was lower than the healthy women[22].Calcium is a recognized as second messenger implicated in insulin secretion. VitD plays a role in calcium metabolism. It is well documented that measurement of circulating 25 (OH)VitD_3 is a marker of total VitD status and25(OH) VitD_3 as well as calcium and magnesium level weres significantly low among T2DM cases in comparison to healthy controls. There was significant negative correlation between VitD status and insulin levels and insulin resistance.A significant negative correlation between VitD status and insulin levels suggest that the supplementation of VitD has the potential to increase insulin sensitivity and lower the risk of developing T2DM[23].

There was an observed effect of VitD supplementation on glycemic control in replete, T1DM patients. Further studies are needed to determine if these findings are applicable[24].Whether glycemic control contributes to a

decreased number of fractures or favorably impacts bone density in patients with T2DMhas not been well established. VitD deficiency appears to be related to glycemic control in patients with T2DM. In the group of patients with poorly controlled T2DM, 25(OH)D3 levels were not significantly lower in comparison with the optimal control group. No statistically significant linear relationship between HbA1c and 25(OH)D3 levels was established. The frequency of osteoporosis and osteopenia was not significantly different between groups. The group with optimal glycemic control had an increased number of Osteo Porotic Fractures (OPF) events[25].Glycemic control prevents microvascular complications in patients with T1DM such as retinopathy, nephropathy and neuropathy that influences quality of life. Some studies show the immunomodulatory effect of VitD in synthesis and secretion of insulin and supplement causes the improvement of HbA1C in all groups of glycemic control. This supplement transfer patients towards better glycemic control for the entire group[26].

African Americans have a higher prevalence of DM and associated complications. Replacement with VitD was associated with significant improvement in HbA1c to previously unmatched levels of glycemic control. Given the current pandemic of VitD deficiency and the plethora of potential benefits, it is important to maintain adequate VitD reserves in DM patients with a special emphasis on minority populations[27].After adjusting for Body Mass Index (BMI) z-score, lipids, or blood pressure, the relationship of VitD with Pulse Wave Velocity (PWV) was not significant.VitD levels were inversely associated with PWV in adolescents with T1DM, but not independently of BMI, lipids, or blood pressure. Further research is indicated to determine if VitD supplementation would be beneficial to lower CVD risk in adolescents with T1DM with VitD insufficiency or deficiency[28].was no significant relation between HbA1c and VitD level prior the study. After intervention, VitDlevel in interventional group was found to be significantly higher compared to that of control group. HbA1c in male interventional group was significantly less than that of control group.Weekly VitD supplementation had beneficial effect on glycemic parameters in male T2DM[29].

Circulating VitD levels, preeclampsia, GDM, Small for Gestational Age (SGA), low birth weight, preterm birth weight, cesarean section and Mantel-Haenszel fixed-effects models were used owing to expected scarcity of outcomes. Effects were reported as relative risks and their 95% confidence intervals (CIs). Incidence ofpreeclampsia, GDM, SGA, low birth weight, preterm birth, and cesarean section were not influenced by VitD supplementation. Across RCTs, the doses and types of VitD supplements, gestational age at first administration, and outcomes were heterogeneous.VitD supplementation during pregnancy was associated with increased circulating VitD levels, birth weight, and was not associated with other maternal and neonatal outcomes. Larger, better-designed RCTs evaluating clinically relevant outcomes are necessary to reach a definitive conclusion[30].

IV. VITAMIN D AND OTHER DISEASES

Recent research has implicated VitD deficiency with a number of chronic conditions, including autoimmune conditions such as multiple sclerosis, lupus, and psoriasis, and chronic conditions such as osteoporosis, osteoarthritis, MS, fibromyalgia and chronic fatigue syndrome. It has been assumed that low levels of VitD accurately indicate its storage and VDRs-mediated control of calcium metabolism and innate immunity. A strong positive association between these autoimmune conditions and levels of 1,25-D3>110 pmol/L. However, there was little association with VitD deficiency or the other inflammatory markers, meaning that the results challenge the assumption that serum levels of VitD are a sensitive measure of the autoimmune disease state. Rather, these findings support the use of 1,25-D_3 as a clinical marker in autoimmune conditions. High levels of 1,25-D_3 may result when dysregulation of the VDR by bacterial ligands prevents the receptor from expressing enzymes necessary to keep 1,25-D in a normal range[31].The use of VitD supplements to prevent and treat a wide range of illnesses has increased substantially over the last decade. Epidemiologic evidence links VitD deficiency to autoimmune disease, cancer, CVD, depression, dementia, infectious diseases and musculoskeletal decline. VitD supplementation should not be offered routinely to other patient populations. Although results from some prospective clinical trials are promising, most have not been robustly designed and executed. The decision by young, otherwise healthy adults to take VitD in doses of 2000 IU/day or lower is unlikely to cause harm. For patients who are not at risk for developing VitD deficiency, sensible sun exposure is an inexpensive and enjoyable way to maintain VitD stores[32].

VitD deficiency has been associated with numerous health outcomes, including risk of rickets in children or osteomalacia in adults, increased risk of fractures, falls, cancer, autoimmune disease, infectious disease, DM, hypertension, heart disease and multiple sclerosis[33].few prospective clinical studies have been conducted to examine the effect of VitD supplementation on cardiovascular outcomes. The mechanism for how VitD may improve CVD outcomes remains obscure; however, potential hypotheses include the downregulation of the renin-angiotensin-aldosterone system, direct effects on the

heart and vasculature or improvement of glycemic control[34].

It is now clear that VitD has important roles in addition to its classic effects on calcium and bone homeostasis. As VDRs are expressed on immune cells (B cells, T cells and antigen presenting cells) and these immunologic cells are all are capable of synthesizing the active VitD metabolite, VitD has the capability of acting in an autocrine manner in a local immunologic milieu. VitD can modulate the innate and adaptive immune responses. Deficiency in VitD is associated with increased autoimmunity as well as an increased susceptibility to infection. As immune cells in autoimmune diseases are responsive to the ameliorative effects of VitD, the beneficial effects of supplementing VitD deficient individuals with autoimmune disease may extend beyond the effects on bone and calcium homeostasis[35].VitD deficiency is a global health problem, its role as an immune modulator has been recently emphasized. The evidence is increasingly pointing towards VitD significant role in reducing the incidence of autoimmune diseases. However, at this time the research on its role in autoimmune and thyroid disease is not conclusive. VitD deficiency was designated at levels lower than 20ng/mL. Thyroid hormones (TSH, T3 and T4) and calcium levels were evaluated in all participants.Serum VitD was significantly lower in hypothyroid patients than in controls. Its level was insignificantly decreased in females than male patients. Moreover, serum calcium levels recorded a significant decrease in hypothyroid patients when compared to controls.Patients with hypothyroidism suffered from hypovitaminosis with hypocalcaemia that is significantly associated with the degree and severity of the hypothyroidism recommending its supplementation and screening for VitDand calcium levels for all hypothyroid patients[36].

Epidemiological data support a potential relationship between VitD deficiency and an increased risk of developing multiple sclerosis (MS). In vitro studies have expanded the potential role of VitD and VDRs beyond calcium modulation, regulation, maintenance of bone mineralization along with immune modulation.Further prospective studies are needed to identify VitD levels during the various phases of MS, including relapses, remissions and progression and to determine whether correcting VitD during any or all of these phases may affect the incidence or even the course of the disease[37].More rigorously designed clinical trials are needed for further evaluation of the relationship between VitD status and the immune response to infection as well as for delineation of necessary changes in clinical practice and medical care of patients with VitD deficiency in infectious disease settings[38].VitD is mainly derived from endogenous ultraviolet-B induced VitD synthesis in the skin and the current high prevalence of VitD deficiency can, therefore, largely be attributed to lifestyle related low sunlight exposure. Regulation of bone and mineral metabolism is a classic VitD effect, but the identification of the VDRs in almost all human cells suggests a role for VitD in extra-skeletal diseases. Experimental studies demonstrated several antihypertensive and vascular protective effects of VitD, such as suppression of the renin angiotensin aldosterone system, beneficial modulation of classic cardiovascular risk factors and anti-atherosclerotic properties including improvements of endothelial function. Whereas some RCTs suggest that VitD supplementation might modestly reduce blood pressure, this has not been consistently observed in all studies. It is, therefore, premature to recommend VitD supplementation for the prevention and treatment of arterial hypertension and stroke. Nevertheless, the fact that patients with arterial hypertension and cerebrovascular disease are at a relatively high risk of VitD deficiency and associated musculoskeletal diseases can serve as a rationale for the evaluation, prevention and treatment of VitD deficiency in these patients[39].

VitD is now known to be of physiological importance outside of bone health and calcium homeostasis and there is mounting evidence that it plays a beneficial role in the prevention and/or treatment of a wide range of diseases. VitD appears capable of inhibiting pulmonary inflammatory responses while enhancing innate defence mechanisms against respiratory pathogens. Population-based studies showing an association between circulating VitD levels and lung function provide strong justification for randomized controlled clinical trials of VitD supplementation in patients with respiratory diseases to assess both efficacy and optimal dosage[40].Insufficient VitD nutritional status has been associated with a host of other diseases, most notably cancer. There is evidence that supplementation with VitD reduces the overall incidence of cancer, although current evidence is insufficient to prove a causative effect. Sunscreen use blocks the ability of the skin to photosynthesize VitD, although the effect this has on the VitD status of the general population is unclear[41].In adults, VitD supplementation reduces the risk of fractures and falls. The evidence for other purported beneficial effects of VitD is primarily based on observational studies[42].

VitD deficiency may well be an important factor in autoimmune rheumatic disease, including initial disease development and worsening the disease once present. This is testable and there is a pressing need for therapeutic studies[43].Individuals with higher serum VitD concentrations showed a reduced risk of Parkinson's disease. The relative risk between the highest and lowest quartiles was 0.33 (95% CI 0.14–0.80) after adjustment for

sex, age, marital status, education, alcohol consumption, leisure-time physical activity, smoking, body mass index and month of blood draw[44].

V. VITAMIN D AND CARDIO VASCULAR DISEASES

CVD is a major cause of morbidity and mortality worldwide. Recently VitD deficiency has been identified as a potential risk factor for many diseases not traditionally associated with VitD, such as cancer and CVD. VDR are expressed in a variety of tissues, including cardiomyocytes, vascular smooth muscle cells and endothelial cells and VitD has been shown to affect inflammation and cell proliferation and differentiation. While much evidence supports a potential antiatherosclerotic effect of VitD, prospective, placebo-controlled randomized as well as mechanistic studies are needed to confirm this association. Since VitD deficiency is easy to screen for and treat, the confirmation of such an association could have important implications for both, patient care and health policy[45].LowVitD levels have been associated with the CVD risk factors of hypertension, obesity, DM, MS, as well as CVD events including stroke and congestive heart failure. Studies suggest VitD deficiency may be a contributor to the development of CVD potentially through associations with diabetes or hypertension. Further larger observational studies and randomized clinical trials are, however, needed to determine whether VitD supplementation could have any potential benefit in reducing future CVD events and mortality risk[46].

The mechanism of how VitD may improve CVD outcomes remains obscure; however, potential hypotheses include the downregulation of the renin-angiotensin-aldosterone system, direct effects on the heart and vasculature or improvement of glycemic control[47].CVD which includes coronary artery disease and stroke, is the leading cause of mortality in the nation. Excess CVD morbidity and premature mortality in the African American community is one of the most striking examples of racial/ ethnic disparities in health outcomes. African Americans also suffer from increased rates of hypovitaminosis D, which has emerged as an independent risk factor for all-cause and cardiovascular mortality. The potential role of hypovitaminosis D as a contributor to racial and ethnic disparities in CVD, the epidemiology of VitD and CVD in African Americans and the emerging biological roles of VitD in key CVD signaling pathways that may contribute to the epidemiological findings may provide the foundation for future therapeutic strategies for reducing health disparities[48].

There is strong experimental evidence that VitD status may influence cardiovascular structure and function. The number of clinical studies has steadily grown in recent years, with the largest number comprising observational studies showing associations between low VitD status, the presence of various cardiovascular risk factors and adverse cardiovascular outcomes. Despite substantial clinical evidence linking VitD deficiency with increased cardiovascular risk, it remains to be established whether this represents a causal association. Further studies are needed with prospective, randomized controlled trials before VitD supplementation could be routinely recommended for the primary or secondary prevention of CVD[49].Considerable attention has been paid recently to the possible role of VitD deficiency in the development of several chronic diseases. In particular, VitD deficiency is associated with an increase in conditions such as obesity, IR, hypertension, diabetes and an increased risk of death from these pathologies. There is also a significant correlation with mortality for major cardiovascular events such as heart failure, myocardial infarction, sudden cardiac death, stroke, atrial fibrillation and peripheral vascular disease. The pathophysiological mechanisms of these correlations are yet to be determined, but hyperactivity of the renin-angiotensin-aldosterone system seems to play a leading role. The role of therapy with VitD supplements in improving cardiovascular outcome in patients with low levels of VitD remains to be determined[50].

VitD status was inversely associated with mortality, but this was not explained by an association with CVD. Rather, the association seemed to be caused by an inverse association with death caused by digestive disease, endocrine, metabolic and nutritional diseases and respiratory disease. Further studies, e.g. RCTs or Mendelian randomisation studies, are needed to clarify whether low VitD status is a causal and reversible factor to prevent disease and mortality[51].An association between VitD deficiency and CVD factors has been shown in general population studies. VitD deficiency has been noted in systemic lupus erythematosus (SLE) and CVD is a major cause of morbidity and mortality in SLE. Whether low baseline VitD levels predict future CVD in patients participating in an international inception cohort.Patients in the higher quartiles of VitD were less likely to have hypertension and hyperlipidemia and were more likely to have lower C-reactive protein levels and lower Systemic Lupus Erythematosus Disease Activity Index 2000 scores at baseline when compared with the first quartile. VitD levels were not independently associated with CVD event incidence; however, hazard ratios for CVD event incidence decreased with successively higher quartiles.Lower baseline VitDlevels are associated with higher risk for CV risk factors and more active SLE at baseline. There may be a trend towards a lower likelihood of CVD events in those with higher baseline VitD levels[52].Emerging data suggest a pleiotropic role of this agent in a variety of functions in humans. Epidemiological studies indicate an

inverse association between VitD deficiency and the prevalence of CVD, as well as individual cardiometabolic risk factors, such as hypertension, diabetes, dyslipidemia and the MS. Moreover, VitD deficiency has been implicated in the atherosclerotic process[53].

VI. VITAMIN D AND KIDNEY DISEASES

Chronic kidney disease (CKD) is an emerging public health problem and one of the most powerful predictors of premature CVD. Emerging evidence suggests that the progression of CKD and many of the CVD complications may be linked to hypovitaminosis D. Patients with CKD have an exceptionally high rate of severe VitD deficiency that is further exacerbated by the reduced ability to convert 25-(OH)VitD into the active form, 1,25 dihydroxy-VitD. As new evidence has improved our understanding of classical, as well as the nonclassical, functions for VitD, it has become apparent that the autocrine role of VitD is an important modulator of several systems including the immune, renal and cardiovascular systems. Because of the high rates of hypovitaminosis D and progression of CKD to end-stage renal disease in minority populations, these findings are highly relevant to the national efforts to reduce health disparities. Healthcare providers are called to join the intensified efforts of public health officials to disseminate and implement updated guidelines and recommendations to halt the growing epidemic of VitD deficiency, particularly in high-risk populations[54].VitD has garnered much research and debate about supplementation in recent years, not only as it pertains to patients with kidney disease but also to those in the general population[55].

The reduction in functional renal mass and the retained phosphorus act to reduce renal 1-α-hydroxylase activity and thus the renal production of calcitriol. Further compensation to maintain normal serum calcium and phosphorus homeostasis includes increased production and release of PTH and potentially other phosphaturic factors, such as fibroblast growth factor-23 (FGF23) and increase of this contributes to maintain normal serum phosphate independent of PTH but may worsen calcitriol deficiency by also inhibiting renal 1-α-hydroxylase activity. The decrease in calcitriol also results in promoting further hyperparathyroidism and parathyroid gland hyperplasia, because calcitriol normally inhibits the production of prepro-PTH and parathyroid cell proliferation[56].

Activated VitD, a hormone produced by the proximal convoluted tubule of the kidney, appears to have beneficial effects beyond suppressing PTH. However, activated VitD also can cause hypercalcemia and hyperphosphatemia in CKD. Newer agents such as VDR activators (eg, paricalcitol) suppress PTH with reduced risk of hypercalcemia and hyperphosphatemia. Recent evidence from animal and preliminary human studies supports an association between VDR activators and reduced risk of CVD deaths, irrespective of PTH levels. New pathways of VitD regulation also have been discovered, involving FGF23 and klotho. Although considerable work has been performed to advance our understanding of the effects of VitD in health and CKD, more investigations and randomized trials need to be performed to elucidate the mechanistic underpinnings of these effects[57].VitD deficiency is highly prevalent among patients with CKD. The benefits and harms of VitD supplementation (ergocalciferol or cholecalciferol) were assessed in patients with nondialysis-dependent CKD, dialysis-dependent CKD, and renal transplant recipients.Available evidence from low-to-moderate quality observational studies and fewer RCTs suggests that VitD supplementation improves biochemical endpoints. However, whether such improvements translate into clinically significant outcomes is yet to be determined[58].

In CKD patients, VitD deficiency is common and progression of CKD is associated with low active VitD levels. Moreover, in animal models of CKD, treatment with VitD analogues alone or in combination with Renin-Angiotensin-Aldosterone System (RAAS) blockade reduces proteinuria, glomerulosclerosis and tubulointerstitial fibrosis. Potential underlying mechanisms include suppression of the RAAS, modulation of immune cell function and direct protective effects on renal cells such as podocytes. Whether VitD analogues could further optimize existing therapies in human renal disease is currently under investigation[59].Individuals have an inactive life style and have reduced exposure to sunshine and UV light, thus limiting the actinic synthesis of VitD. The nephrology community seems to have overlooked the importance of VitD for overall health and well-being in patients with CKD. Recently however, several authors have called attention to the role of plasma 25(OH)D3 levels in mineral metabolism dysregulation in patients with CKD and those on dialysis. VitD not only contributes to skeletal health but also plays a major role in the health of a wide variety of other organ systems. It seems that supplementation is the most effective way of preventing VitD deficiency[60].

VII. VITAMIN D AND LIVER DISEASES

The disturbances in VitD metabolism in patients with Chronic Liver Disease (CLD) and biliary disease are associated with disturbances in calcium homeostasis and together they present clinically as hepatic osteodystrophy. The latter consists of osteomalacia, possibly sometimes complicated by secondary hyperparathyroidism, osteoporosis, and periosteal new bone formation[61].The

immune regulatory functions of VitD are demonstrated by induction of antimicrobial peptides, suppression of innate immune response, induction of Th2 cytokines and stimulation of T-regulatory T cells. VitD deficiency or insufficiency is overwhelmingly associated with viral hepatitis, cirrhosis and fatty liver diseases. Recent clinical trials have shown that VitD supplements significantly enhance the efficacy of interferon plus ribavirin therapy through sustained virological response. A recent study showed that VitD rather than 1,25-dihydroxyVitD could directly suppress hepatitis C virus assembly. Moreover, clinical evidence has shown that VitD deficiency is associated with alcoholic and Non-Alcoholic Fatty Liver Diseases (NAFLD)[62].There is an emerging interest to explore the relationship between VitD deficiency and prevalence and severity of Non-Alcoholic Fatty Liver Disease (NAFLD) and response to antiviral therapy in hepatitis C[63].

Concomitantly, NAFLD has become the most common form of CLD in western countries. NAFLD and VitD deficiency often coexist and epidemiologic evidence has shown that both of these conditions share several cardiometabolic risk factors[64].The insufficiency or deficiency of VitD is common in various kinds of CLD including viral hepatitis B and C. Serum VitDand VDRs are possibly interrelated with the incidence, treatment and prognosis of diseases. Though the evidence of VitD supplementation in viral hepatitis and associated liver diseases is still limited, there is great potential to apply this adjuvant therapy to improve the treatments.Although the exact role and mechanisms of VitD have not been fully elucidated in CLD, it is potentially beneficialfor the treatment of CLD. Further mechanistic studies are needed to validate its clinical application[65].Suboptimal VitD status is prevalent among individuals with gastrointestinal and liver disease and the etiology of this finding is multifactorial and disease dependent. Although replacement and supplementation guidelines have not been well defined and could be different in different diseases and disease states, practitioners should aim for a serum VitD level of at least 32 ng/mL when undertaking these tasks. The contribution of VitD status to the bone health of individuals with gastrointestinal and liver disease may be different between active and quiescent phases of the disease. Finally, the role of VitD in altering disease course through its actions on the immune system remains to be elucidated[66].

A significant correlation was observed between VitD levels and fractional calcium absorption, but no correlation was found between 1,25(OH)D3 levels and fractional calcium absorption. Calcium malabsorption was common in this series of patients and serum 1,25(OH)D levels were useful in predicting fractional calcium absorption. Treatment with oral 1,25(OH)D3 was accompanied by improved calcium absorption[67].Urinary excretion over days 0-3 of radioactivity from both vitamins D2 and D3 was significantly higher in the primary biliary cirrhosis group than in controls. VitD2-derived urinary radioactivity in primary biliary cirrhosis correlated strongly with serum bilirubin. The metabolism of labelled 1,25(OH)D3 studied in patients with alcoholic liver disease has found out impaired hepatic synthesis[68].Hypovitaminosis D is prevalent among individuals with gastrointestinal and liver disease. Although replacement and supplementation guidelines have not been well defined, practitioners should aim for a serum VitD level of at least 32 ng/mL. The contribution of VitD to the bone health of these individuals and its role in altering disease course through its actions on the immune system remain to be elucidated[69].Patients with CLD with cholestasis for at least a year are at risk from osteomalacia and that those likely to have this complication may be identified by serumVitDand/or fasting urine hydroxyproline/creatinine ratio measurements. The diagnosis can only be made with certainty by bone biopsy[70].

VIII. CONCLUSIONS

This review article has highlighted the research findings carried out during the last20 years on vitamin D and its metabolites deficiency in human health and diseases, its beneficial effect on a wide range of disease such as DM, cardiac, liver, Immune, degenerative, endocrine, psychiatric neurological, stroke, musculoskeletal, metabolic cognitive disorders, dementia, Alzheimer's, autoimmune, cancers and Parkinson's disorders. The contents of this review article will serve for future researchers to undertake more research in the disorders cited and to find ways and means to suggest corrective therapies for patients suspected of having such diseases linked to vitamin D deficiencies and to include Vitamin D and Vitamin D3 as routine assays in some selected disorders in which chronic deficiencies of these are confirmed.

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