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VITAMIN D DEFICIENCY IN NON-SKELETAL DISEASES: MORE THAN JUST A COEXISTENCE??

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ABSTRACT

Vitamin D deficiency (VDD) has emerged as a global epidemic in recent time across the world. Emerging evidences indicated a close link of VDD with non-skeletal diseases including diabetes, hypertension, chronic kidney disease, polycystic ovarian syndrome, cardiovascular disease and malignancies. The immunological role of vitamin D is the current focus of researchers and clinicians in addition to its traditional role of bone mineral homeostasis. The protective role of $1,25(OH)_2D_3$ has been demonstrated in the prevention of various autoimmune diseases like hashimoto's thyroiditis, rheumatoid arthritis and multiple sclerosis in numerous studies. The manifestation of vitamin D deficiency remains assymptomatic in most of the cases or bound to skeletal diseases, so its importance in the pathogenesis of metabolic disorders remain ignored till today. Rampant increase of metabolic diseases is of growing concern in India, so VDD should be considered in this context due to its close association with them. The contribution of vitamin D deficiency in the underlying mechanism of sixteen non-skeletal diseases and the prospect of routine vitamin D supplementation in the delay or prevention of these diseases have been elaborately discussed in this review.

KEYWORDS: VDD, DM, HTN, CKD, autoimmune diseases.

INTRODUCTION

Vitamin D deficiency (VDD) is considered to be a global health problem. Extra osseous effects of vitamin D is of growing interest across the world in recent time due to its profound effect on immune pathology. VDD has emerged as a key player in various non skeletal diseases apart from its traditional role in bone mineral homeostatis. A more extensive role of vitamin D such as cell differentiation, immunomodulation and anti-proliferation has been recognized in various extra-skeletal tissues. Genetic, environmental and epidemiological evidences link vitamin D with metabolic diseases including diabetes, hypertension, cardiovascular diseases and autoimmune disorders. Both human and animal model experiments emphasize on the hypothesis that the unrecognized epidemic of VDD is a contributing factor of various chronic debilitating diseases throughout the world. Inspite of its numerous biological functions and reported associations with various diseases it still remains the most common underestimated medical condition globally.

It has been estimated that more than one third of the world population have vitamin D deficiency or insufficiency.[1] VDD is reported in China, Pakistan, Middle East, Africa, Kuwait,[2] Italy [3], Norway [4], Oslo [5], Japan.[6] and the Netherlands [7] India is no exception, varying degree of (50- 90%) VDD is reported in Indians.[8] It has been demonstrated a striking 83.2% of VDD among the Bengalees of Kolkata by our earlier study.[9] This increased prevalence of VDD may be attributed to the increased tendency to avoid sun exposure, indoor life style and low intake of vitamin D fortified food. Vitamin D receptor (VDR) polymorphism also contributes a vital role to the varying degree of vitamin D deficiency. More over growing air pollution prevents ultra-violet rays to adequately synthesize vitamin D on the skin and cause vitamin D deficiency. Malnutritionised mothers with repeated pregnancies cause aggravation of vitamin D deficiency in mother and subsequently in the fetus in India. It is an international challenge to deal with vitamin D deficiency. The present study is directed to look at the interaction of VDD associated with several chronic diseases in Kolkata, West Bengal as well as to investigate the protective role of vitamin D in the pathophysiology of these diseases. To the best of our knowledge this is the first comprehensive review on the association of VDD with chronic metabolic diseases in Eastern India.

Metabolism of 25 (OH) vitamin D and its non-calcemic functions

It is a well known fact that secosterol or vitamin D3 which is synthesized on the skin and vitamin D2 coming from diet undergoes first hydroxylation in the liver to form 25(OH) vitamin D. This undergoes subsequent

hydroxylation in the kidney to create the active form of vitamin D which is 1,25(OH)2 D which in turn binds to the nuclear receptors present in various tissues like bone, kidney and intestine to regulate calcium metabolism. Presence of VDRs are reported in brain, skin, gonads, pancreas, stomach, activated T and B lymphocytes indicate the non-calcemic biological effects of vitamin D. 1,25(OH)D3 produced in these tissues regulate cell growth and decrease proliferative activity in an autocrine fashion. Once it is accomplished it induces vitamin D-24 hydroxylase which immediately inactivate intracellularly synthesized calcitriol and its active metabolites ultimately causing vitamin D deficiency.

Vitamin D Deficiency and its contribution in the underlying pathology of chronic diseases

A close association between the vitamin D deficiency with various chronic diseases has been revealed from numerous meta-analysis and experimental observations. Some of the most important diseases appear to be predisposed by VDD are discussed here.

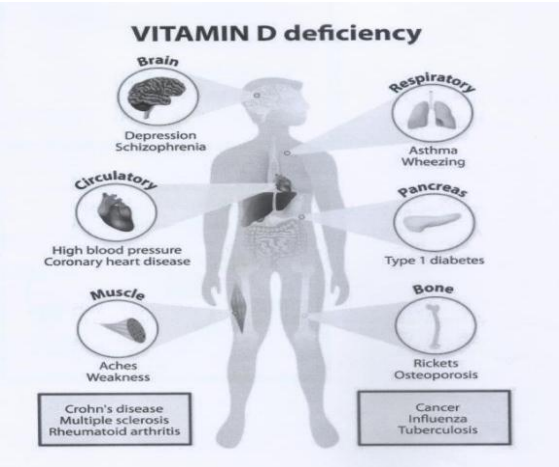

Fig 1: Vitamin D deficiency in Chronic Diseases
(Ref: http://www.shutterstock.com/pic-302169479)

1. Vitamin D Deficiency in chronic liver diseases (CLD)

Multifactorial causes are thought to be responsible for vitamin D deficiency in chronic liver diseases.[10] Decreased production of vitamin D carrier proteins and albumin are noticed in CLD patients as a result of hepatic injury and inhibits hepatic hydroxylation of vitamin D.. Vitamin D levels were observed to be positively correlated with the albumin level during active phase of chronic liver diseases.[11, 12] It is observed that vitamin D level <10 ng/ml might be a predictor of CLD and inversely associates with the degree of severity of CLD.[13]

2. Vitamin D Deficiency with Hypertension

Vitamin D regulates blood pressure via RAAS (Renin Angiotensin Activtion Seystem) activation. Calcitriol is recognized as a negative regulator of RAAS.[14] and this suppression of renin activity by vitamin D may be explained through increased intracellular calcium level .[15] Studies showed a negative correlation of serum vitamin D with blood pressure[16] though some researchers found very weak evidence to support the role of vitamin D on blood pressure in hypertensive patients. The pathway of RAAS activation was demonstrated in genetically engineered VDR knockout mice by Li et,al. Hypovitaminosis D promotes increased production of renin by juxtaglomerular cells which subsequently augments angiotensisn II ultimately responsible for hypertension.[14]

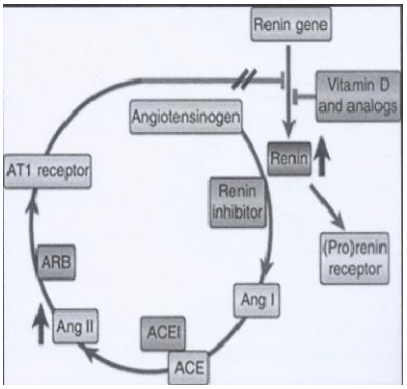

Fig 2: Mechanism of vitamin D deficiency causing Hypertension

3. Vitamin D Deficiency with Type 2 Diabetes Mellitus (T2DM)

Vitamin D regulates glucose homeostasis. The potential influence of vitamin D on type II diabetes can be explained by the presence of specific vitamin D receptors (VDR) on pancreatic β-cells and skeletal muscle. Calcitriol binds to the vitamin D receptors in β cell and in turn influences secretion of insulin and β cell growth.[17,18] Intracellular calcium levels play a crucial role in the β cell regulation via vitamin D. Numerous experiments revealed that vitamin D deficiency causes insulin resistance and β cell dysfunction in human subjects through modulation of systematic inflammation.[9]

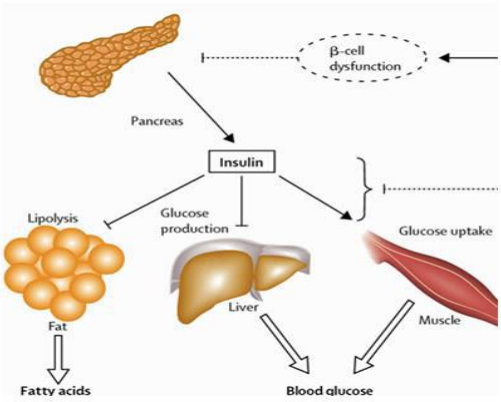

Fig 3: Mechanism of VDD causing T2DM
Ref: trialx.com/cure-talk/2011/01/11risk-of-cvd-in-diabetes-mellitus-patients/)"

4. Vitamin D Deficiency with hypothyroidism

Subclinical hypothyroidism is defined as the early stage of hypothyroidism when serum TSH increases but thyroid hormones remain normal. Vitamin D stimulates iodide uptake by the thyrocytes and stimulate the growth by attenuating TSH directly. The effect of T3, T4, and TSH on renal metabolism of vitamin D has been proved by mouse model studies.[19] Thus when VDD occurs,

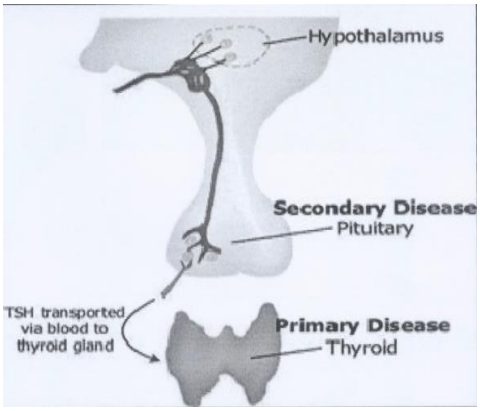

Fig. 4: Mechanism of VDD causing Hypothyroidism

(Ref : www.wndocrinesurgeon.co.uk/index.php/what-is-hypothyroidism-myxoedema)"

TSH levels rises as it does not get enough vitamin D to metabolize, or when TSH level rises vitamin D gets metabolized in large amount causing VDD. Which one is preceded by the other is not yet understood but the negative relationship between serum vitamin D and TSH was observed in hypothyroid patients.[20]

5. Vitamin D Deficiency with chronic kidney disease (CKD)

Vitamin D has emerged as one of the vital components of CKD.[21] as 1, 25(OH) 2 vitamin D, an active metabolite of vitamin D is synthesized by kidney. Studies indicated the autocrine role of vitamin D in the renal, immune and cardiovascular outcome in end stage renal disease patients (ESRD) undergoing dialysis.[22] The explanation behind is that with the deterioration of kidney function level of calcitriol declines leading to hypocalcaemia and compensatory elevation of PTH. ESRD patients suffer from reduced cardiac iontrophy, increased heart weight, increased myocardial antigen and increased vascular smooth muscle proliferation due to depletion of vitamin D. On the other hand vitamin D encompasses the regulation of the angiotensin system (RAS).[21,23] Sequential activation of angiotensin II is induced by RAS pathway which seems to have a deleterious effect on blood pressure and ultimately leads to parenchymal damage in the patients with CKD (21). This kind of evidential proofs strengthened the association of vitamin D with CKD.

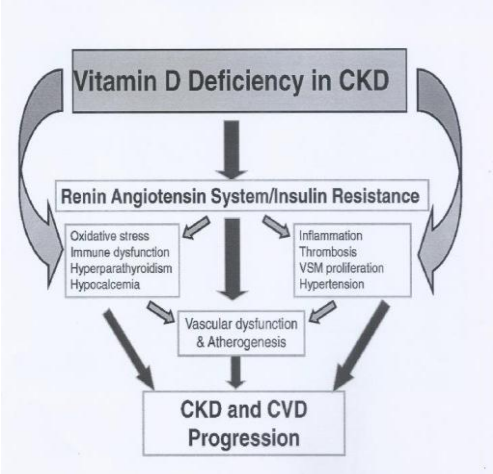

Fig 5: Mechanism of VDD causing CKD

(Ref: Zhang Z, Yuan W, Sun L, Szeto FL, Wong KE, Li X, Kong J, Li YC. 1,25-Dihydroxyvitamin D3 targeting of NF-kappa B suppresses high glucose-induced MCP-1 expression in mesangial cells. Kidney Int 2007; 72(2):193–201)

6. Vitamin D with neuropathy

Recent studies highlighted a role of vitamin D on the nervous system and in particular central nervous system (CNS). The potential influence of vitamin D has been deciphered in the cerebral development, neuro transmission, neuro protection, and neuro immunomodulation due to the recognition of VDR on human brain tissues. The synthesis of Ca related cytoplasmic proteins like calbindin or parvalbumin.[24] and intraneuronal calcium homeostatis stimulates neuro-protective role of vitamin D.[25] Hypovitaminosis D is associated with psychiatric and neurological disorders like dementia, perkinson diseases, cerebral ischemia. Vitamin D increases the synthesis of neuro tropic agents like (NGFs) or nerve growth factors, glial cell line derived neurotrophic factors (GDNF). In addition to that it plays a pivotal role in the regulation of numerous neurotransmitters like acetyl choline, dopamine, serotonin and gamma amino butyric acid in rat brain.[26,25,27]

7. Vitamin D Deficiency with cardiovascular disease (CVD)

Systematic reviews and meta-analysis reports demonstrated the relationship between serum vitamin D level with cardio-metabolic disorders like diabetes, cardiovascular disease and metabolic syndrome. The interaction of vitamin D deficiency with diabetes, obesity, hyperlipedimia and hypertension, the primary complaint of cardiovascular disease has been discussed in multiple studies.VDD has already been linked with blood pressure[28] and augments rennin synthesis, insulin production and decreases myocardial contractility.[14,29,30] Intracellular calcium metabolism of the cardiomyocyte is impaired due to vitamin D deficiency and results in hypocalcaemia. This leads to PTH elevation and

promotes atherosclerosis and cardiovascular risk.[31] Fig.6.

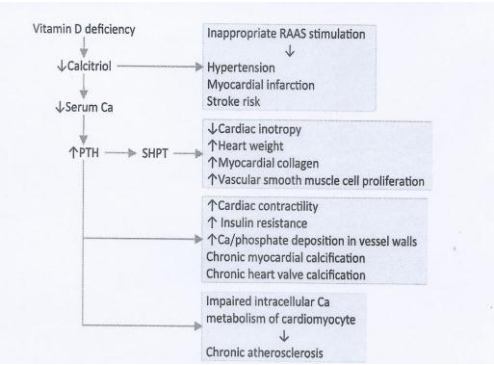

Fig 6: The role of vitamin D deficiency in Cardio-vascular disease

(Ref: Lakemond R. The influence of vitamin D on cardiovascular diseases. Australian Medical Student Journal 2015;[31-34]

8. Vitamin D Deficiency with chronic lung disease

An inverse relationship between vitamin D deficiency and chronic lung diseases have been established in many cross sectional studies. Increased risk of respiratory infection from influenza and mycobacterium tuberculosis[32,33,34] are observed in vitamin D deficient patients. Other chronic lung related diseases which are related with VDD include cystic fibrosis, tuberculosis.[35] interstitial lung disease (ILD) and chronic Obstructive lung diseases (COPD).[36-40] though the precise mechanism of VDD predisposing poor lung function is not clearly explained. It is hypothesized that the presence of α-1-hydroxylase activity in many extra renal tissues like epithelial lining of the lung and other immune cells of the lung contributes a lot in the hydroxylation of 25(OH)vitaminD to 1,25(OH)2vitamin D and which in turn increases antimicrobial peptide production, regulates inflammatory response and controls airway remodeling.

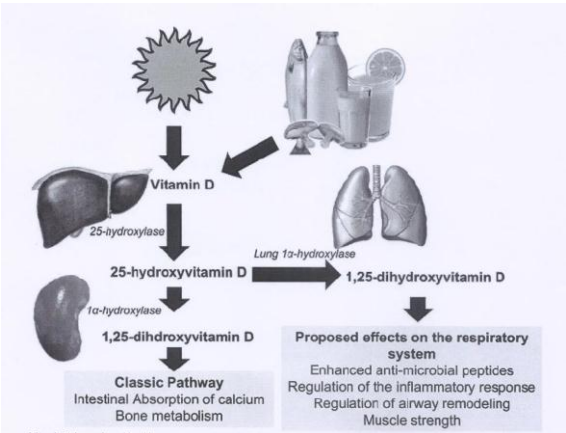

Fig 7: Proposed effect of VDD in CLD

(Ref: Finklea J D, Grossmann R E, Tangpricha V. Vitamin D and Chronic Lung Disease: A Review of Molecular Mechanisms and Clinical Studies. American Society for Nutrition. Adv. Nutr. 2011; 2: 244–253,)

a. ILD (interstitial lung diseases)

It is characterized by the damage of lung, parenchyma,. Recent association of VDD has been illustrated with the severity of ILD (37). According to their study 1,25(OH)2D3 inhibits TGF β-1 stimulation of profibrotic phenotypes in lung fibroblast and epithelial cells.. Ramirez et al explained VDD in interstitial lung disease patients through murine model.

b. **COPD (Chronic obstruction of pulmonary diseases)**

It has been predicted that COPD will be one of the leading major causes of death worldwide. COPD associates with significant and progressively irreversible airflow obstruction. Association of COPD and VDD is a subject of large discussion today. Smoking and low UVB exposure on skin might aggravate vitamin D deficiency in COPD patients.[41,42]

9. Vitamin D Deficiency with obesity

Studies detailed the prevalence of vitamin D deficiency in obese patients and high body mass index (BMI) is associated with low serum vitamin D level.[43] Obese subjects are generally reluctant to participate in physical activity, thus limiting their exposure to sunlight and resulting in lower 25(OH)D concentrations. Additionally, inflammatory cytokines upregulated in adiposity are known to inversely affect 25(OH)D bioavailability and increase its metabolic clearance.[44] Finally, poor dietary habits leading to obesity often provide a poor source of oral vitamin D intake. The inverse relationship between obesity and vitamin D deficiency might be explained due to sequestration of vitamin D in adipose tissue leading to reduced bio availability of vitamin D in systemic circulation.

10. Vitamin D Deficiency with anaemia

Association of anaemia with hypovitaminosis D has been reported in various parts of the world including India.[45] Vitamin D is thought to play a role in erythropoiesis as vitamin D receptors are hugely expressed in on bone marrow. Vitamin D deficiency causes an upsurge of cytokines causing an increase of inflammatory milieu that can lead to anaemia of chronic disorder.[46] It has been demonstrated in many studies that production of hepcidin – the key regulator of iron homeostasis is supressed by vitamin D due to inhibition of HAMP gene expression by vitamin D in human.[47] Renal anaemia, a characteristic feature of most CKD patients is caused by elevated serum hepcidin which seems to be positively correlated with haemoglobin concentration and negatively correlated with vitamin D deficiency.[48]

11. Vitamin D Deficiency with auto immune disorders

Vitamin D exerts immunomodulation via vitamin D receptors (VDR) which have been discovered on antigen presenting cells, activated T & B lymphocytes. Regulatory T cells and NK cells are induced by vitamin D whereas Th1 cell response is inhibited by it. So, vitamin D is claimed to be an immune suppressor.

Various prevalence studies argued that vitamin D deficiency is one of the most important features of Hashimoto's thyroiditis. The presence of high prevalence of thyroid autoimmune disorders and vitamin D deficiency in West Bengal, Eastern Indian population, provide us an excellent opportunity to elucidate an association between the two variables.[49] This immunomodulatory property of vitamin D hormone might explain the reported association of VDD with T1DM, rheumatoid arthritis, autoimmune thyroid disorders and cancer.

The significant role of vitamin D as selective immune suppressant is also demonstrated by their ability to either prevent or markedly suppress the autoimmune diseases in animal experiments.[50] Recently, greater intake of vitamin D was associated with a lower risk of rheumatoid arthritis (RA), as well as lower vitamin D was found to be associated with higher disease activity in RA.[51] Role of ultraviolet radiations (UVR) on three autoimmune diseases: multiple sclerosis, type 1diabetes and RA in relation to recent developments in photoimmunology has been analyzed by Powsoby et.al,. indicating its association with VDD[52] and autoimmune activity in the patients with these diseases can be attenuated by UVB and UVA irradiation.[53] Interestingly, polymorphisms in the vitamin D receptor (VDR) have been correlated with increased susceptibility of many auto immune diseases like RA, type I diabetes mellitus and Hashimoto thyroid disorders.[54] Vitamin D deficiency causes an upsurge in cytokine level leading to the production of autoantibodies which infiltrate the β-cells of Islet of Langerhans of pancreas or thyrocytes of thyroid gland and cause the apoptosis of insulin producing β-cells or thyorocytes ultimately results in Type 1 dm, auto immune thyroid disorders.

12. Vitamin D Deficiency with cancer

Majority of studies found a protective role of 1, 25(OH) on the low incidence of cancer. The exact mechanism by which cancer development is influenced by vitamin D status is still being delineated but the presence of vitamin D responsive elements on 200 human genes responsible for encoding proteins important in the regulation of cell differentiation linking the role of vitamin D in cancer. These activities are impaired if the vitamin D status is low as evidenced by the enhancements of cancer development and growth in vitamin D receptor knockout mice.[55] Increased association between cancer mortality and VDD has been described for cancers of lung, pancreas, uterus, kidney, ovary, rectum, stomach, prostate, oesophagus.[56, 57] Vitamin D and its metabolites reduce the incidence of many types of cancer by inhibition of tumor angiosis.[58]

13. Vitamin D Deficiency with gastrointestinal diseases

Growing research detailed the role of vitamin D deficiency in the pathogenesis of gastrointestinal disorders.[59] though the mechanism is not properly understood. Malabsorption mightone of the causes of VDD in celiac disease. After gastectromy and gastric by-pass surgeries steatorrhoea impairs the reabsorption of 25(OH)vitamin D undergoing enterohepatic circulation. Moreover calcium and vitamin D intake is decreased due to transient secondary lactate deficiency in celiac disease. Osteomalacia and vitamin D deficiency are two well documented complications of gastectomy. Presence of inflammatory cytokines such as iterleukin (IL6), tumor necrosis factor α and interleukin 1α in inflammatory bowel diseases inhibits differentiation of osteoblasts, increase osteoclastic bone resorption and sensitizes osteoblasts to apoptosis.[60]

14. Vitamin D Deficiency with prostatomegaly

Benign Prostrate Hyperplasia (BPH) is a cluster of symptoms affecting older men including obstructive symptoms such as decreased force of stream, hesitancy, straining, incomplete bladder emptying, and nocturia. BPH is due to the excessive growth of both stromal and epithelial cells of the prostate. Detailed studies have even shown an inverse correlation between the geographic distributions of prostate cancer and the exposure to UV radiation.1,25-dihydroxyvitamin D3 (1,25(OH)2D3) and analogues may have an impact on BPH.[61]

15. Vitamin D Deficiency with PCOS

Polycystic ovary syndrome (PCOS) is a common cause of ovarian dysfunction in women with anovulation characterized by hyperandrogenism, and hyperinsulinemia. Vitamin D deficiency can be an effective factor in development of PCOS. Low circulatory vitamin D level was observed in obese patients with PCOS and that vitamin D administration has a positive effect on clinical and biochemical symptoms. In addition, genetic PCOS related with vitamin D receptor variances have been described.[62] But whether vitamin D deficiency plays a role in PCOS pathogenesis or it is a result of PCOS still remains a debate. The symptoms of PCOS, including insulin resistance, ovulatory, menstrual irregularities, infertility, hyperandrogenism are exacerbated by vitamin D deficiency.

16. Vitamin D Deficiency with sleep disorders

Obstructive sleep apnea (OSA) is associated with recurrent, partial or complete upper airway closure during sleep. Increased incidence and severity of OSA is reported in winter according to a study.[63] The seasonal variation in OSA may be due to the coinciding winter nadir of vitamin

D3.Low circulating 25-hydroxyvitamin D [25(OH)D] concentrations are correlated with poor musculoskeletal function.[64,65] due to poor control of upper airway muscle tone which contributes majorly to the occurrence of OSA. Patients with low 25(OH)D concentrations might have an increased risk of OSA .Type 2 diabetes mellitus, metabolic syndrome and obesity, which are frequently

found in patients with OSA seem to have a close relationship with Vitamin D deficiency.[65]

Prevalence of metabolic diseases accompanied with VDD

Increased prevalence of Vitamin D deficiency is reported in extra-skeletal disorders in various parts of the world. This has intrigued a new research interest among the clinicians, researchers and geneticists to investigate the immunomodulatory role of vitamin D in a wide spectrum of various diseases. It has been hypothesized that Vitamin D deficiency predisposes to numerous metabolic diseases including diabetes, hypertension, CKD, CLD, cancer, polycystic ovarian syndrome etc. De Boer IH et al reported that degree of albuminuria is inversely related with serum vitamin D level in CKD.[66] Anti proteinuric effect of vitamin D via RAS- angiotensin II mediated mechanism has been reported [21]. Many experimental observations found a close link of VDD with neurological disorders. VDD is thought to be accompanied with anxiety, depression, Schizophrenia and epilepsy. The association of VDD with CKD.[21,30] CVD.[28] HTN.[16] lung diseases..[33,34] CLD.[10,11] anaemia.[46] Obesity.[43,44] PCOS.[62] OSA.[63] hypothyroid.[20,9] cancer.[55,56] diabetes.[9] autoimmune diseases.[51,52] neurological disorders.[67,68,69,70,71,72] has already been discussed in this paper ,although there are contrasting views regarding the association of these diseases with VDD like Goswami et. al did not find any correlation of vitamin D deficiency with Anti TPO in north Indian population.[73]

We previously published an inverse association of serum 25(OH) level with anti TPO in Hashimoto thyroiditis among the Bengali population of Kolkata.[49] A close association of VDD with diabetes, hypothyroidism and hypertension in west Bengal, India was revealed by our early study.[10] which was in accordance with multiple studies but some studies revealed no association of VDD with the disease.[73]

There are many studies on the immunologic role of vitamin D all over the world including India which yielded conflicting results. The reasons of these inconsistent findings might be either due to different ethnic origin or genetic drift to different techniques of genotyping assays might attribute to the conflicted results.

Vitamin D supplementation –A new addition to the modern therapeutic management of chronic diseases:

Beneficial roles of vitamin D supplementation in numerous non-skeletal diseases still remains under appreciated due to scarcity of adequate clinical trials to test the efficacy of vitamin D supplementation as a treatment part on these patients. Evidential proofs opened a new paradigm of treatment with vitamin D supplementation in VDD patients with CKD and education of premature morbidity and mortality in CKD patients.[74] Increasing number of studies are in favor of positive association of vitamin D and neurological disorders. Vitamin D supplementation might have protective role on the reduction of neurological disorders.[75] Some researchers claimed that vitamin D replacement could reduce the death rate due to cardio-vascular complains in ESRD (end stage renal disease) patients.[76,77] According to proposed mechanism that vitamin D supplementation downregulates the inflammatory cytokines and renin angiotensin aldosterone system (RAAS) [78] and ultimately reduces cardiovascular risk. The effect of vitamin D supplementation on lung function[79] is proved to be beneficial on the reduction rate of pneumonia and TB. Harari M (2011) reported the clinical improvement of RA by vitamin D therapy (80)**.** It was corroborated by Sharma R. who suggested a therapeutic role of 1,25(OH)vitamin D in RA disease. Vitamin D supplementation was found to be effective in CKD and DM patients.[74,81]

A meta analysis reviewed the role of serum vitamin D in PCOS patients (82). The post interventaional results of vitamin D supplementation and placebo supplementation showed fasting insulin levels were significantly higher among supplemented patients than placebo.[82,83]

CONCLUSION

This review will definitely create a mass awareness about the possible outcome of vitamin D deficiency among all sections of the society which remains totally asymptomatic and underestimated in most of the cases. This association will educate the common people not to ignore the vitamin D deficiency which might predispose to many diseases in future. The effect of vitamin D suuplementation on the clinical improvement of the diseases is not studied much in Eastern India but clinicians' recommendation of routine vitamin D supplementation as a part of therapeutic regime on the prevention of many diseases might be expected from this review.

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