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Non-Skeletal Manifestations of Vitamin D Deficiency- A Review

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Abstract:

Objective: *There are lots of important non-skeletal systemic consequence of vitamin D deficiency which was often was underestimated. The purpose of this review is to discus the non-skeletal systemic manifestations of vitamin D deficiency.*

Data Sources: *We searched Medline, Pub med, Google Scholar & individual searches.*

Keyword: *Vitamin D, VDR, autoimmune disease, cancer, MTB.*

Introduction:

It was presumed that the risk of hypovitaminosis D is low in the tropical region like Bangladesh because of adequate sunlight, but later different studies found poor vitamin D status especially in Bangladeshi women regardless of their age, lifestyle and clothing [1]. It could be due to other causes of vitamin D deficiency apart from inadequate sun exposure like dietary deficiency, malabsorption, accelerated loss, liver disease, renal failure etc. Over the past few years there has been a renascent of interest in vitamin D outside of it's well known role in bone diseases. Vitamin D deficiency is now considered to be an important factor for the maintenance of not only bone health but also other conditions. Vitamin D plays an important role in the immune system in particular on the T-cell mediated immunity. A little ignorance about one's vitamin D status can put a person to the risk of cardiovascular diseases, autoimmune diseases, different types of cancers, neurological and psychiatric problems and many more. So in this review we wanted to highlight the non-skeletal manifestations of vitamin D deficiency.

Functions of vitamin D:

Vitamin D is a group of sterols produced by the action of ultraviolet light on certain provitamins in the skin. Although the best known function of vitamin D is to regulate calcium homeostasis, it also has important effects on the differentiation of immune cells and modulation of immune response, cell proliferation, apoptosis, regulation of blood pressure, development of brain and it's function, regulation of insulin secretion [2] etc.

Mechanism of action of vitamin D :

Vitamin $D_3(1,25(OH)_2D_3)$, the biologically active form of vitamin D is best regarded as a steroid hormone. Like other steroid hormone it acts by binding to a high affinity receptor. Vitamin D receptors are found in significant concentration in the 'T' lymphocytes and macrophages in the brain, heart, skin, gonads, breast, prostate etc. Vitamin D also acts as a natural inhibitor of signal transduction by hedgehog(Hh). Hedgehog signaling pathway is involved in the morphogenesis [3] , biology of cancer stem cells (CSC) and in the acquisition of epithelial cells to mesenchymal transition (EMT). Liao X et al in his study investigated 80 cases of primary epithelial ovarian tumour and found significantly elevated expression of Sonic hedgehog messenger RNA in ovarian cancers compared with normal tissues and benign ovarian tumors and such differential expression was specific to histological types ($P < 0.05$).[4] Hh signaling pathway is involved in a variety of human cancers including skin, brain, gastrointestinal, lung, breast, prostate cancers, etc.[5-8] Isohata N et al in his study of hedgehog and EMT signaling pathway in normal and malignant cells on 42 esophageal squamous cell carcinoma (ESCC) tissues and their matched noncancerous tissues provided by the Central Hospital at the National Cancer Center compared the expression profiles of Hh and EMT signaling molecules of these cells with those of cancers.[7] They found activated Hh signal in most primary ESCCs and Hh signal inhibition effectively suppressed cell invasion and growth of Hh signal-activated ESCC cell lines in their study.

Systemic manifestations of vitamin D deficiency:

Immune system:

Vitamin D plays a significant role as selective immunosuppressant which can be proved by their ability to either prevent or markedly suppress animal models of the autoimmune diseases [9]. There are many studies where $1,25(OH)_2D_3$ was found to be associated with autoimmune

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encephalomyelitis, rheumatoid arthritis(RA), Systemic Lupus Erythematosuss(SLE), type-1 & type-2 DM,Inflammatory bowel disease(IBD), multiple sclerosis etc.[9-11,13-15]. A study in 143 apparently healthy Bangladeshi adults demonstrated the association between VDR gene polymorphism, type-1 diabetes, insulin secretion and the insulin resistant syndrome [11]. It was also seen in a study where dietary vitamin D supplementation was associated with reduced risk of type-1 DM [12]. In a study of vitamin D3 metabolism in rheumatic diseases researchers found it of interest to study the serum levels of the major metabolites of vitamin D3 in patients with SLE (n = 21), rheumatoid arthritis (RA) (n = 29) and osteoarthritis (n = 12).[13] In patients with SLE the levels of 25-OH D3 were below those of the controls (p = 0.0008) and OA (p = 0.0168). Research is continuing to detect role, prevalence and clinical consequences of vitamin D deficiency in other autoimmune conditions like SLE [13-15]. Vitamin D may also have a protective role against multiple sclerosis (MS), it has been seen that higher maternal milk and vitamin D intake during pregnancy may associated with a lower risk of developing MS in off springs[16]. Studies have indicated that the dysregulation of VDR may lead to exaggerated inflammatory responses, raising the possibility that defects in vitamin D and VDR signaling transduction may linked to bacterial infection and chronic inflammation [17]. Numerous studies link vitamin D and influenza [18]. It was observed in study that sub clinical vitamin D deficiency is associated with acute lower respiratory infection in children less than 5 years of age[19]. Vitamin D metabolites leads to activation of macrophages and restrict the intracellular growth of *Mycobacterium tuberculosis* thus decreases the risk of tuberculosis infection[20]. In a retrospective audit of 375 African immigrants moderate to severe 25(OH)D deficiency was reported in 31 (78%) of 40 patients with TB/ past TB, 27 (33%) of 81 with LTBI, and 2 (6%) of 34 with no MTB infection. Thus the study showed that vitamin D deficiency is associated with tuberculosis and latent TB infection [21].A case control study by Ehlayel MS et al in Qatar showed a significant difference between asthmatic subjects and controls with respect to serum level of vitamin D ($p < 0.001$). [22] Large number of vitamin D deficiency was found among children with asthma, allergic rhinitis, atopic dermatitis, acute urticaria and food allergy. In addition, vitamin D deficiency was associated with IgE atopy markers in asthmatic children more than controls in the study[22].

Cardiovascular system:

Vitamin D is related to cardiovascular events as vascular smooth muscle, endothelium and cardiomyocytes contain vitamin D receptors. A study on 1739 Framingham offspring showed a graded increase in cardiovascular risk across categories of 25-OH D, with multivariable-adjusted hazard ratios of 1.53 (95% CI 1.00 to 2.36) for levels 10 to <15 ng/mL and 1.80 (95% confidence interval 1.05 to 3.08) for levels <10ng/mL (P for linear trend=0.01).[23] There is another study showed that vitamin D insufficiency is associated with increased arterial stiffness and endothelial dysfunction in the conductance and resistance blood vessels in human which also explain higher risk of cardiovascular disease in vitamin D depleted individual.[24] In a study myocardial Infarction was found to be associated with vitamin D deficiency[25]. There is another study where sub- optimal level of vitamin D was found to activate Renin-Angiotensin-Aldosterone system and increase parathyroid hormone level. Activated Renin-Angiotensin-Aldosterone can predispose to hypertension and left ventricular hypertrophy and parathyroid hormone excess is associated with heart failure.[25,26] As it also alters mineral metabolism in congestive cardiac failure vitamin D is thought to be a contributing factor in the pathogenesis of congestive heart failure [27]. Recently in a study researchers found that 70.3% of study populations who are at significantly higher risk for a variety of cardiovascular disease are deficient in vitamin D [28]. Considering all these things vitamin D deficiency can be regarded as a risk factor for cardiovascular disease.

Malignancy :

"This is like the Holy Grail of cancer medicine; vitamin D produced a drop in cancer rates greater than that for quitting smoking or indeed any other counter measure in existence"

-Dennis Mangan, clinical laboratory scientist

The quote signifies the importance of the vitamin D deficiency in the development of cancer. Those who have vitamin D deficiency are believed to have risk of developing some types of cancers like breast, colon, prostate, and ovarian cancers. Many studies are there to propose vitamin D is a protective factor against colon cancer[29-31]. Vitamin D metabolites induce differentiation with or without inhibition of proliferation of a number of malignant and non-malignant cell types including prostate cancer cells [32-33]. It inhibits prostate cancer cell growth also by inducing apoptosis and cell cycle arrest [34]. In a randomized controlled trial conducted on 250 bladder cancer cases matched with 1:1 controls researchers found that lower 25(OH)D was associated with a statistically significantly increased risk of bladder cancer (versus e"50 nmol/L; <25 nmol/L: OR, 1.73; 95% CI, 1.03-2.91; 25 to <37.5 nmol/L: OR, 1.81; 95% CI, 1.05-3.14; 37.5 to <50 nmol/L: OR, 1.76; 95% CI, 1.02-3.02; P trend=0.04) [35]. Decreased serum concentration of $1,25(OH)_2D_3$ is associated with increased risk of bladder cancer compared to a man with higher concentrations .It might be due to

exposure of bladder mucosa to vitamin D metabolites. These metabolites could promote transitional cell differentiation and apoptosis and thus reduces epithelial proliferation and neoplasm.

Sometimes vitamin D_3 is misinterpreted as one of the factor of epidermal carcinogenesis. However recent studies indicate that the role of vitamin D and it's receptor in protecting against the development of epidermal tumour deserves a closure look. One such study found mice lacking the vitamin D receptor (VDR) were quite sensitive to epidermal tumour. Similarly they were more sensitive tumour formation following UVR. Two interacting pathways critical for epidermal and hair follicle function â catenin and Hedgehog result in epidermal tumours when they are activated abnormally. Vitamin D suppresses hedgehog signaling pathway, in addition it was observed that transcriptional activity of â catenin was increased in keratinocytes lacking VDR. These results lead to the hypothesis that VDR with it's ligand $1,25(OH)_2D_3$ function as tumour suppressant with respect to epidermal tumour formation [36].

Nervous system:

Vitamin D deficiency by increasing the risk of hypertension and arterial stiffness increases the risk of stroke. It was also proved in a study involving analysis of health records for nearly 8,000 blacks and whites and covered a period of 14 years [37]. It was observed in the study that deficient levels of vitamin D are associated with increased risk of fatal stroke in whites [37]. However it was not found in women [38]. Vitamin D deficiency has also been associated with cognitive impairments in older adults and there is increased risk of Alzheimer's disease [39] also. Epidemiological evidence shows an association between reduced sun exposure and depression [40]. Studies indicate vitamin D improves mental illness.

Conclusion:

This is true that many systemic diseases have been recognized which are associated with or caused by vitamin D deficiency, but further studies should be continued to detect other diseases which are still unknown to be caused by vitamin D deficiency.

Conflict of Interest: None

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