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Review Article

Vitamin D Deficiency and Manifestation of the Disease: Revisiting the Significance

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Abstract
It has been reported that vitamin D deficiency is associated with various health problems ranging from bacterial & viral infections to psychotic disorders. In this review we have summarized the role of vitamin D deficiency in the occurrence of bacterial diseases, viral infection, its role in depression and asthma as well as conditions associated with schizophrenia and other psychotic disorders. It has been shown that vitamin D can regulates nearly 5% of the human genome further strengthens its role in the overall well-being. More research is needed in order to understand the physiology and effect of supplementation of vitamin D on the outcome of disease.

Keywords:- *Vitamin D, Psychotic Disease, Bacterial Disease, Viral Disease.*

Introduction

The role of vitamin D in regulation of calcium homeostasis and its effect on the bone health is an established fact. But recent studies have shown the presence of Vitamin D Receptors (VDR) even on the cells that are not involved in calcium homeostasis. These findings have opened a series of research involving VDR receptors and their presence on variety of cells [(1)]. Later the microarray analysis has revealed that Vitamin D has the capability to regulate 5% of the human genome and generates responses in more than 36 cell types, plethora of research emerged after that [(1,2)]. Even though dietary supplements such as cod liver oil, eggs, milk, fishes are rich source of Vitamin D, the major source of Vitamin D in humans still remains its synthesis in skin by Ultra Violet B radiation. 7-dihydroxycholesterol is converted to Vitamin D by Ultra Violet B radiations from sunlight. The major reason which attributed to the Vitamin D deficiency in over one million people is our predominantly indoor lifestyle [(3)]. Vitamin D, either through dietary intake or synthesized in presence of sunlight, is first converted into 25-hydroxy-vitamin D in the liver by the action of Cytochrome P450 enzyme. 25-hydroxy vitamin is then taken up

by kidney where it is further converted into its bioactive form 1,25-dihydroxyvitamin by the action of 25-hydroxyvitamin D-1-α-hydroxylase (CYP27B1) [4]. Synthesis of 1,25-dihydroxyvitamin takes place not only in kidney but also in various other tissues such as brain, breast, prostrate, smooth muscle and variety of immune cells [5,6]. Role of Vitamin D in various diseases and physiological condition is a matter of research around the globe. The present review describes role of Vitamin D in psychotic conditions, respiratory illness as well as bacterial and viral infections.

Vitamin D and Multiple Sclerosis

Multiple Sclerosis is a disease of Central Nervous System which is often characterized by inflammatory lesions, loss of myelin sheath and affects approximately 2.5 million people around the globe[7]. Risk factors associated with disease progression are low vitamin D concentration, smoking, viral infections (Herpes, Epstein Barr Virus and retrovirus) and gut microbiota [8-11]. A recent study has also shown correlation between Epstein B virus and Vitamin D[9]. Multiple observational studies have shown the correlation between low level of Vitamin D and increased chances of multiple sclerosis. In a large study with a sample size of n= 1,87,563 patients intake of vitamin D decreased the risk of multiple sclerosis risk [12]. A case control study also reported that higher concentration of calcifediol (25 hydroxycholecalciferol) is assosciated with low multiple sclerosis risk [12]. It has also been observed that people with genetically lowered calcifediol (mutation in genes which are involved in Vitamin D metabolism) levels have increased susceptibility to multiple sclerosis [13]. One of the studies inferred the role of CYP27B1, which is involved in Vitamin D activation, in multiple sclerosis[14]. Studies employing molecular biology techniques to understand multiple sclerosis have found that its loci have a diverse amount of Vitamin D receptor binding sites. A double blind placebo controlled study enrolling 229 multiple sclerosis patients that are interferon-β-treated and having a low concentration of calcifediol i.e. ≤150nmol/L have shown interesting results. Administration of 14000 IU/day of choleocalciferol showed a reduction of 32% in the acive lesions in the secondary endpoint [15].

Vitamin D and Schizophrenia

Schizophrenia affects both males and females and develops during adolescent or early adulthood. It hampers the ability of the patient to function and behave normally in the society because of delusions, hallucinations, anhedonia, alogia, avolition that person faces during course of the psychotic disease [16]. Epidemiological studies suggest that people born in spring or winter are more prone to schizophrenia and with the increasing latitude there is an increase in the schizophrenia prevalence [17]. It has also been observed that dark skinned people living in colder areas are at greater risk of developing schizophrenia [18]. In one of the studies it was seen that patients suffering from schizophrenia had lower Vitamin D levels as compared to healthy controls [19]. In some studies Vitamin D levels have been shown to be inversely related to anhedonia, alogia, avolition and depression [20]. In one of the prospective cohort studies researchers found that vitamin D supplementation in males during first year of their birth significantly reduces the risk of developing schizophrenia in the later stages [21]. Although a study involving 45,604 control and 34,241 schizophrenic patients have found no correlation between Vitamin D and Schizophrenia while studying serum associated SNP's.

Vitamin D and Autism Spectrum Disorder (ASD)

Autism spectrum disorders are a group of neurodevelopmental disorders that hampers normal brain development. In a recently concluded study it was found that 1 out of 68

children are suffering from ASD(22). Abnormalities in communication as well as repetitive behavioral tendencies, dampened social skills, learning and cognitive defects are the diagnostic markers of ASD. There have been studies that have linked the change in the immune response found in ASD to the behavioral change in the patient. Change in the cytokine profile with the increased level of inflammatory cytokine is seen in ASD cases [23]. It has been proposed that this dampening immune response could be due to the autoimmune response generated early on the brain of the fetus by maternal antibodies [24]. Studies have correlated low levels of Vitamin D with autism disorders in children as compared to the levels found in their siblings or parents [25]. Children diagnosed with ASD had low level of Vitamin D concentration during their birth [26]. Also low level of maternal Vitamin D affects the cognitive abilities of the child(27). In one of the studies it was found that children which were administered pharmacologically recommended doses of vitamin D had improvement in the symptoms of the disease[28]. On the other hand it was found administration of vitamin D during pregnancy as well as during early childhood years significantly decreases the chances of ASD in siblings [29]. Genetic predispositions also affect the outcome of the disease. VDR BsmI and homozygous variant genotype of paternal VDR Taq1 and child's GC AA genotype/A-allele are found to be linked to ASD. Child's CYP2R1 AA genotype had low predisposition for ASD.

Vitamin D and Depression

Various studies have observed the effect of incidence of light on the mood pattern. Study involving 29 patients in which 16 had seasonal affective disorder (SAD) and 13 served as control. One hour of light therapy significantly lowered the depression symptomps in the SAD group (30). It has been found that people having Vitamin D deficiency had higher incidence if depression as compared to the one having low or normal concentration of Vitamin D [31]. In a study by Hoogendijk et al. which conducted a cohort study among 1200 people of the age 65 and above. They found that concentration of Vitamin D was 14% lower in people suffering from minor and major depression [31]. The exact mechanism of vitamin D association with depression is largely unknown but there are reports that have examined the presence of vitamin D receptors in hypothalamus which might play a role in the neuroendocrine functioning and development [32].

Vitamin D and Asthma

First association between Vitamin D and Asthma was observed when it was examined that both of them have same risk factors such as obesity[33], urban residence [34] and being from African-American [35] community. In one of the studies it was found that aVDR-knockout mice had increased collagen deposition in the airway passage [36]. It was also found that maternal diet enriched with Vitamin D, Vitamin E and antioxidants lowers the risk of childhood asthma& children who are born to mothers deficient in Vitamin D are prone to develop asthma. Also it was found that Single Nucleotide Polymorphism present in Vitamin D hydroxylase gene are correlated with early prognosis of asthma in children [37].

Vitamin D and Tuberculosis

Mycobacterium tuberculosis remains the hardest bacterial infection to treat. Owing to its cell wall diversity and thickness, it has been able to resist the antibiotic penetrance. With the emergence of drug resistant strains the fight against this deadly pathogen has become more dreadful [38]. Role of vitamin D in the treatment of tuberculosis was first highlighted by Williams CBJ wherein he observed marked improvement in the patient suffering from tuberculosis who was administered cod liver oil [39]. Until the discovery of anti-mycobacterial

chemotherapy patients were treated with sunlight exposure or administration of Vitamin D rich diet [40]. It has been observed that majority of people suffering from tuberculosis have vitamin D deficiency [41]. 1,25 dihyroxy Vitamin D combats Mycobacterium tuberculosis via the production of antimicrobial peptide cathelicidin which has a direct effect on the survival of M. tuberculosis [42]. Vitamin D has been shown to enhance the autophagy of Mtb infected monocytes as well as it induces the phago-lysososme fusion [43]. Also Vitamin D presence is essential for the IFN-γ mediated antimicrobial activity of macrophages.

Various studies have predicted the Vitamin D supplementation as an adjunct therapy to anti-tuberculosis chemotherapy prevalent today although with varying degree of efficacy. It has been shown that Vitamin D supplementation enhances the culture conversion rate [44,45]. A study published in 2006 observed a significant increase in the culture conversion rate upon vitamin D administration at a concentration of 0.25mg/day [46]. Study by Kota et al have shown that with the supplementation of vitamin at a concentration of 60,000 IU/Units per week and 1g/day of Calcium Carbonate along with Anti tuberculosis treatment (ATT) decreases the time required for the culture conversion. In one study patients that were supplemented with 4 doses of 2.5 mg of Vitamin D were sputum AFB negative approximately one week before the placebo group, but the difference was not significant [47]. In a clinical trial comprising of 259 tuberculosis patients who were administered 6,00,000 IU Vitamin D3 had significant weight gain, decreased pulmonary zones and significantly smaller cavities [48]. Another study involving TB close contacts, supplementation of 2.5 mg Vitamin D enhanced immunity against M. tuberculosis [49].

There is also a correlation between season and TB incidence rate. In United Kingdom TB incidence rate is higher in spring season in which serum Vitamin D concentration is low& this relationship has also been observed in countries such as India, South Africa and even in the entire European subcontinent [49]. Therefore supplementation of Vitamin D along with ATT has various benefits and it can be an adjunct to current therapy.

Vitamin D and Viral Infections

Recently reports have emerged where cathelicidin was found to be inhibiting vaccinia virus, retrovirus, Herpes simplex Virus type 1 and adenovirus at some minimum concentration [50]. There have been various studies that have shown the correlation between administration of vitamin D supplementation and their effect on respiratory tract infection. In 1994 one of the studies from India reported that there was a significant reduction in respiratory tracts infections in children who were administered vitamin D for a period of six weeks[51]. Although in a study done in UK, 1740 elderly people suffering from respiratory infections were supplemented with 800 IU/day for a period of 2 years but there was no significant decrease in the respiratory tract infections [52]. In a US based study also there was no significant difference in the infection incidence rate when patients were administered vitamin D [53].

There are studies where low Vitamin D concentration has been observed in HIV patients. In a study 47.6% of AIDS patients had low level of Vitamin D. In another study 25 female patients suffering from AIDS had low vitamin D concentration as compared to their healthy counterparts. A study done in Norway also correlated low Vitamin D concentration and prevalence of HIV. Although there are many studies that have suggested a correlation but the exact nature and mechanism is poorly understood [50]. Further research is required to understand this.

There are few studies which have correlated Hepatitis B infection and supplementation of Vitamin D. Polymorphism in codon 35 of

Vitamin D receptor gene (Silent mutation from T to C) was found to be associated with less incidence of persistent hepatitis infection [54]. This same VDR polymorphism was also involved in the resistance against dengue virus [55]. In one of the studies, immunocompetent patients having low Vitamin D concentration showed a poor response to Anti Viral Therapy (AVT) against hepatitis C viral (HCV) infection [56].

Conclusion

Recent evidences have shown the role of Vitamin D in maintaining the overall health of the individual and reducing the risk of chronic diseases. The identification of VDR in number of cells other than involved in calcium homeostasis provides evidence for non-skeletal health benefits. Deficiency in Vitamin D increases the risk of neurological damage including multiple sclerosis, schizophernia and autism. Vitamin D deficiency affects a person's mental health and makes one prone to condition like depression. Adequate Vitamin D levels in the body decreases the chances of asthma. Vitamin D rich diet if given to the mother during pregnancy decreases the chance of asthma in the child. Studies have shown that Vitamin D if given together as adjunct therapy along with the regular treatment regimen in case of tuberculosis improves the clearance of bacteria and better management of the disease. Vitamin D decreases the respiratory tract infection in children too. A lot of studies have shown adequate Vitamin D levels helps in better disease management in various viral infections including AIDS(HIV) and Hepatitis B. Humans have always been synthesizing vitamin D in sunlight but recent change in life style including reduced exposure to sunlight has made major population of the world deficient in Vitamin D, thus to compensate the Vitamin D requirement of the body, we have to make adjustments in lifestyle along with incorporation of Vitamin D rich diet in order to improve the overall health of human kind.

Conflicting Interest (If present, give more details): Nil

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