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Pandemic of vitamin D deficiency and its effect on human health

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Introduction

Vitamin-D is a group of fat- soluble seco-steroids responsible for increasing intestinal absorption of calcium, iron, magnesium, phosphate and zinc. In addition to known effects on calcium homeostasis, vitamin D has a variety of functions including immuno-modulatory and anti-inflammatory effects. Vitamin D is not strictly a vitamin, since it can be synthesized in the skin, and under most conditions that is the major source of the vitamin. Only when sunlight exposure is inadequate is a dietary source required. Its main function is in the regulation of calcium absorption and homeostasis; most of its actions are mediated by way of nuclear receptors that regulate gene expression. It also has a role in regulating cell proliferation and differentiation.7-Dehydrocholesterol (an intermediate in the synthesis of cholesterol that accumulates in the skin) undergoes a non-enzymatic reaction on exposure to ultraviolet light, yielding pre-vitamin D. This undergoes a further reaction over a period of hours to form cholecalciferol, which is absorbed into the bloodstream. In temperate climates, the plasma concentration of vitamin D is highest at the end of summer and lowest at the end of winter.(1)

The active form of vitamin D, 1, 25-dihydroxycholecalciferol, has several effects on the intestines, kidneys, and bones that increase absorption of calcium and phosphate into the extracellular fluid and contribute to feedback regulation of these substances. Vitamin D receptors are present in most cells in the body and are located mainly in the nuclei of target cells. Similar to receptors for steroids and thyroid hormone, the vitD receptor has hormone binding and DNA binding domains. The vit.D receptor forms a complex with another intracellular receptor, the retinoid X receptor, and this complex binds to DNA and activates transcription in most instances. In some cases, however, vit.D suppresses transcription. Although the vit.D receptor binds several forms of cholecalciferol, its affinity for 1,25 dihydroxycholecalciferol is roughly 1000 times that for 25hydroxy-cholecalciferol, which explains their relative biological potencies.(2)

Epidemiology of vitamin D inadequacy

Vitamin D has already become a largely unrecognized global epidemic rather pandemic, yet it is the most under-diagnosed & under-treated nutritional deficiency. Several studies showed that 40 to 100% of U.S. and European elderly men and women still living in the community (not nursing homes) are deficient in vitamin D. Vitamin D inadequacy can be seen in young adults as well as healthy children. For example, 48% of white preadolescent girls in a study in Maine and 52% of Hispanic and black adolescents in a study in Boston are vitamin D deficient. In Europe, where very few foods are fortified with vitamin D, children and adults would appear to be at especially high risk.(3) A study of middle aged British adults showed that 60% are vitamin D insufficient, and the number rose to 90% during winter and spring.

A study conducted in India by Metropolis Healthcare on Vitamin D/B12/B9 in Indian population, has shown that 81.28% of all samples tested were deficient in Vitamin D, 21.02% of all sample tested were deficient in Vitamin B12 and 15.06% of all sample tested were deficient in Vitamin B9.

In recent days, multiple works related to Vitamin D and its effect on almost all vital systems of body has been done and several works pertaining to it has been going on. These studies have drawn significant attention of clinician and have made drastic changes in the management. Based on several Randomized controlled trials and cross-sectional studies, various beneficial effect of Vitamin D has been seen as mentioned below system wise in a nutshell:

Immunity: As early as in the 19th century (1849), the British Scientist C.J.B. Williams described the use of cod liver oil (a rich source of vitamin D) for treating tuberculosis (TB). Skin exposure to sunlight was an effective therapy for treating Mycobacterium infections of the skin. In 1903, Finsen received the Nobel Prize for demonstrating that Lupus vulgaris, the epidermal form of TB, could be cured using light from an electric arc lamp. In early 1900s, growing awareness of benefits of sun exposure pertaining treatment of infectious diseases led to the development of sanatoriums in "sun-rich areas". These sanatoriums enabled regimented sun exposure, diet and exercise. These sanatoriums primarily hosted TB patients.(4) Recent studies have linked vitamin D deficiency with increased risk of developing TB, otitis media, upper respiratory tract infections and influenza.

Cellular studies revealed that Vit D modulates the activity of various defense and immune cells including monocytes, macrophages, lymphocytes, or epithelial cells. It is seen that with Low vit. D level, activity of macrophages is markedly reduced and with supplementation enhanced activity of macrophage seen.

Mycobacterial activation of toll-like receptor-2 (TLR-2) leads to an increased expression of VDR and CYP27B that results in an increased conversion of 25-$(OH)D_3$ to 1,25-$(OH)_2D_3$ and subsequent expression of the antimicrobial peptide cathelicidin via VDR.[3]

B lymphocytes: It has been shown that 1,25-$(OH)_2$ D_3 plays a role in β-cell homeostasis by the inhibition of proliferation and induction of apoptosis of activated β-cell. 1,25-$(OH)_2$ D_3 inhibits the differentiation of B-lymphocytes to plasma cells and memory β-cell. These mechanisms may contribute to the pathogenesis of B-lymphocyte related diseases like systemic lupus erythematosus (SLE). Patients with SLE have significant lower serum concentration of both 25-$(OH)D_3$ and 1,25-$(OH)_2D_3$.

T lymphocytes: A well-established function of Vit D within the adaptive immune system is its ability to modulate T lymphocyte proliferation and function. The biologically active 1, 25-$(OH)_2D_3$ inhibits proliferation of T_H lymphocytes and shifts the expression of cytokines from a T_H1 based response towards a T_H2 based profile. Although 1,25-$(OH)_2D_3$ might be able to involve direct effects on T lymphocytes through the support of differentiation of regulatory T cells, current data indicate that 1,25-$(OH)_2D_3$ exerts its influence on the adaptive immune response by modulating the functions of dendritic cells (DCs). Regulatory T cells seem to be activated by Vit D with skewing of the Th1/Th2 balance towards Th2. Of note, there is evidence for and against the role of Vit D in Th2 biased diseases.[5]

Dendritic cells: The response of DCs to 1,25-$(OH)_2D_3$ is restricted to myeloic DC, that express a different set of TLRs and cytokines than plasmacytoic DCs, which showed no tolerogenic response to 1,25-$(OH)_2D_3$. 1,25-$(OH)_2D_3$ inhibits the maturation of DCs and enhances the expression of cytokines like IL-10, thereby 1,25-$(OH)_2D_3$ induces tolerance through the suppression of T_H1 lymphocyte development and the induction of regulatory T cells.

Epithelial cells: Airway epithelial cell express enzymes of the Vit D metabolism and are capable to convert the precursor 25-$(OH)D_3$ into the active 1,25-$(OH)_2D_3$ from.[12] They are an important source of 1, 25-$(OH)_2D_3$ that induces the expression of cathelicidin or CD14 by cells of the innate immune system. 1,25-$(OH)_2D_3$ converted by airway epithelial cells is able to modulate the inflammatory profile after a viral infection by blocking the poly(I:C) induced chemokine and cytokine production while maintaining the antiviral activity . As epithelial cells are primary targets of respiratory pathogens and cathelicidin has antibacterial and antiviral activity, a seasonal decrease of Vit D-dependent epithelial host defense could contribute to increased numbers of lower respiratory tract infection (RTI) during winter.

Respiratory System

Tuberculosis: A number of candidate polymer-phisms of Vit D receptor (VDR) and Vit D binding protein (DBP) have been identified that modulate the development of tuberculosis. The genotype tt (detected by Taq I digestion) is associated with decreased risk of tuberculosis. As described by Lewis et al., larger studies are required to determine whether VDR polymorphisms play a role in genetic susceptibility to tuberculosis worldwide. In a recent meta-analysis, low serum levels of 25-$(OH)D_3$ were associated with a higher risk of active tuberculosis. The pooled effect size was 0.68 with 95% CI 0.43 - 0.93. The authors concluded that the low Vit D levels increase the risk of active tuberculosis.[6] There are several randomized, double blind, placebo-controlled trials of Vit D treatment in tuberculosis. In one study, 67 tuberculosis patients were randomized to receive Vit D (0.25 mg/day) or placebo during the 6 initial week of Tb treatment. A statistical significant difference in sputum conversion (i.e., the change of detectable to no detectable Mycobacteria in the sputum) was discovered in favor of the Vit D group (100% vs. 76.7%; p = 0.002). Another trial was conducted in 192 healthy adult tuberculosis contacts in London, United Kingdom. Participants were randomized to receive a single oral dose of 2.5 mg Vit D or placebo and followed up at 6 weeks. Vit D supplementation significantly enhanced the ability of participants' whole blood to restrict BCG-lux luminescence after 24 hours in vitro as compared with placebo, but did not affect antigen-stimulated IFN-gamma secretion after 96 hours. As the innate immune responses are mobilized more rapidly than acquired immune responses, the authors interpreted the 24- and 96-hour results as indicators of innate and acquired responses, respectively. They concluded that vitamin D supplementation may primarily enhance innate responses to mycobacterial infection. Wejse et al. included 365 tuberculosis patients starting anti-tuberculotic treatment in Guinea Bissau. 281 patients completed the 12 months follow-up. The intervention was 100,000 IU cholecalciferol or placebo at inclusion and again at 5 and 8 months after start of treatment. Reduction in TB score and sputum smear conversion rates did not differ among Vit D and placebo treated patients.

Respiratory tract infections (RTI): RTI are more common in the winter period than during summertime. Because the food intake of Vit D is insufficient, sunlight exposure is the primary determinant of Vit D status in humans, and seasonal differences in Vit D level in human are well documented.[9] During the winter months, there is insufficient UV-B exposure to produce sufficient amounts of Vit D. Wintertime Vit D insufficiency may explain seasonal variation in influenza and other, mostly viral, RTIs. Ginde et al. performed a secondary analysis of the Third National Health and Nutrition Examination Survey,

hypothesizing an association between 25-$(OH)D_3$ level and self-reported upper respiratory tract infections (URTI) in 18883 subjects . After adjusting for season, body mass index, smoking history, asthma, and COPD, lower 25-$(OH)D_3$ levels were independently associated with recent URTI. In patients with respiratory tract diseases (asthma and COPD) the association between 25-$(OH)D_3$ level and URTI seemed to be even stronger (OR, 5.67 and 2.26, respectively). Avenell and colleagues used data from the RECORD trial (VitD in secondary prevention of osteoporotic fractures; n = 5292). In a "per protocol" analysis, a trend towards a benefit of Vit D vs. placebo was detected, though not statistically significant. Despite the large number of patients in these studies, restrictions arise from the retrospective data analysis. A prospective cohort study included 800 young Finnish men serving on a military base.[7] Their serum 25-$(OH)D_3$ was measured in the beginning of a 6 month observational period. Subjects with low 25-$(OH)D_3$ levels had significantly more days of absence from duty due to respiratory infection than did control subjects ($p = 0.004$). In a case control study a total of 150 children (80 cases, 70 controls) was enrolled. Low serum 25-$(OH)D_3$ ($\leq$ 22.5 nmol/l) was associated with a significantly higher odds ratio for having severe acute lower respiratory tract infections ($p < 0.001$). There is growing evidence for a protective role of Vit D in the development of RTI but high qualities randomized clinical trials within a sufficiently high number of patients and for a sufficient period of time are missing. In a recently published trial, the supplementation of 1500 E Vit D per day resulted in deceases incidence of influenza A by 64%.

Asthma: A connection between Vit D status and asthma has been considered since many years. Vit D deficiency has been blamed as one cause of increased asthma prevalence in the last decades. VDR variants were found to be associated with asthma in patient cohorts. A recent clinical investigation showed that high Vit D levels are associated with better lung function, less airway hyper responsiveness and improved glucocorticoid response. A population-based study suggested that lower Vit D levels are associated with increased requirements for inhaled corticosteroids in children. Vitamin D insufficiency is common in children with mild-to-moderate persistent asthma and is associated with higher odds of severe exacerbation. Epidemiologic studies have also shown that maternal Vit D intake during pregnancy protects from wheezing in childhood. In contrast, also data exist that children whose mothers had high Vit D levels in pregnancy had an increased risk of eczema and asthma, suggesting that the time point of Vit D supplementation seems to determine the susceptibility to atopic disease. On the experimental level in a murine asthma model, the VDR is necessary for the development of an allergic airway inflammation. Interestingly, application of Vit D is potentially capable to overcome the poor glucocorticoid responsiveness in severe asthmatics by upregulation of IL-10 production from CD4+ T cells.[8]

Chronic Obstructive Pulmonary Diseases (COPD): The connection between VitD status and COPD has attracted attention in the recent years. This is based on data from observational studies that determined levels of Vit D in COPD patients. Black and colleagues examined data from the NHANES III data set (cross-sectional survey of 14091 adults in the US). After adjustment for potential confounders, a strong relationship between serum levels of Vit D and lung function (FEV_1 and FVC) was found. Although a significant correlation with airway obstruction could not be found, the observed dose-response relationship may suggest a causal link.[18] A number of studies have reported on 25-$(OH)D_3$ levels in COPD patients. Forli et al. found VitD deficiency (in this study defined as below 20ng/ml) in more than 50% of a cohort waiting for lung transplantation. In an outpatient study on patients with COPD in Denmark, 68% of the participants had osteoporosis or osteopenia. A recent study showed that Vit D deficiency is highly prevalent in COPD and correlates with variants in the Vit D binding gene. There are several factors that could account for Vit D deficiency in COPD patients: Poor diet, a reduced capacity of aging skin for Vit D synthesis, reduced outdoor activity and therefore sun exposure, an increased catabolism by gluco-corticoids, impaired activation because of renal dysfunction, and a lower storage capacity in muscles or fat due to wasting.[9] Many steps of the Vit D pathway (intake, synthesis, storage, metabolism) can potentially be disturbed in COPD patients.

A single nucleotide polymorphism (SNP) of the DBP was shown to be associated with a decreased risk of COPD by a mechanism that is unclear. Similar SNPs in the gene coding for DBP may influence the level of circulating 25-$(OH)D_3$ and 1,25-$(OH)_2D_3$. Therefore it has been hypothesized that their protective role might be mediated by the bioavailability of 1,25-$(OH)_2D_3$.

Cancer: A number of studies suggest that low levels of Vit D are associated with an up to 50% increased risk of colon, prostate, or breast cancer. As an example, a recent nested case-control study showed that pre-diagnostic levels of Vit D are inversely correlated with the risk of colon cancer. For lung cancer, the picture is not clear at the present time. While TaqI polymorphism of the VDR gene appears to be a risk factor for lung cancer, low levels of Vit D were only a cancer risk factor in subgroups, i.e., in women and young individuals.[10] In patients with diagnosed lung cancer, there was no main effect of Vit D level on overall survival. In preclinical animal models using carcinogen (NNK)-induced lung carcinogenesis, application of 1,25-$(OH)_2D_3$ resulted in decreased cancer growth .

Cardiovascular system: Cardiovascular diseases (CVDs), including heart failure and coronary artery disease are a major cause of morbidity and mortality

worldwide. There is accumulating epidemiological evidence from observational studies suggesting that CVDs are associated with vitamin D deficiency. Increased risk of hypertension was associated with living at higher latitudes. 25(OH)D level <21 ng/mL was associated with increased risk of hypertension, diabetes, obesity and high triglyceride levels—all associated with increased cardiovascular mortality. Various studies have reported reduced 25(OH)D concentrations in patients with previous and prevalent cardiovascular or cerebro vascular diseases.

Hypertension: Millions of people are affected by hypertension worldwide. Growing evidence in recent years suggests that vitamin D has an important association with blood pressure. Animal experiments implicate 1,25-dihydroxyvitamin D in inhibiting renin expression in the juxta glomerular apparatus and blocks proliferation of vascular smooth muscle cells (VSMC), which could influence systemic blood pressure.[9] Studies showed that Afro-Americans have a significantly higher prevalence of diastolic hypertension and have lower 25-hydroxyvitamin D levels compared with white Americans.

Diabetes Mellitus: Type 1 diabetes (T1D) is caused by autoimmune destruction of pancreatic β cells, which eventually leads to insulin-dependent diabetes. Higher rates of incidence of T1D were observed at higher latitudes worldwide. Epidemiological association of vitamin D intake and reduced risk of T1D was also seen.[12] A meta-analysis of observational studies showed a 30% reduction in risk of T1D in children receiving vitamin D supplements.

Type 2 diabetes (T2D) is marked by insulin resistance (IR). In IR insulin is adequately or overproduced by pancreatic β-cells, but is ineffectively utilized by the target cells of adipose, hepatic and skeletal muscles tissues. As a response to hyperglycemia, β-cells further increase insulin production leading to hyperinsulinemia, which is often indicative of a pre-(T2D) stage. Hyperinsulinemia is associated with hypertension, obesity, dyslipidemia, and glucose intolerance.[13] These conditions are collectively known as "metabolic syndrome". A meta-analysis of observational studies showed inverse relation of 25(OH)D levels and calcium status with insulin resistance and hyperglycemia.

Multiple sclerosis: Multiple sclerosis (MS) is an autoimmune disease in which the body's immune system attacks myelin, a key substance that serves as a nerve insulator and helps in the transmission of nerve signals. It has been long recognized that MS is more common in temperate climates than the tropics,[14] and annual and winter hours of sunlight have been proved to have the strongest negative correlation with the prevalence of MS. One explanation is that the increase of vitamin D results from sunlight exerting a protective effect. Studies also found that individuals with MS tend to have insufficient vitamin D levels. However, only a few reports are available on the use of vitamin D in treating MS patients. One study (6 months) of the cytokine profile in MS patients with vitamin D (1000 IU/day) and calcium (800 mg/day) showed that 25-hydroxyvitamin D significantly increased from 42.5 ± 15 to 70 ± 20 nmol/l. Also vitamin D supplementation significantly increases serum transforming growth factor (TGF)-b1, which has been shown to be an important anti-inflammatory cytokine in animal models of MS [6]. The increased TGF-b1 suggests that vitamin D supplementation could potentially improve the symptoms of MS patients.

Musculo-Skeletal: Calcitonin, cortisol, high phosphate levels and 25-$(OH)D_3$ suppress the 25-hydroxyvitamin D-1α-hydroxylase activity. 1,25-$(OH)_2D_3$ itself works as its own negative feedback regulator by induction of the expression of a 24-hydydroxylase (CYP24A1). Further, $1,25(OH)_2D_3$ decreases the production and secretion of PTH. PTH synthesis and secretion is induced by decreased serum calcium levels, which are detected by the calcium sensing receptor of the parathyroid gland. PTH effects renal tubular reabsorption of calcium, renal production of 1, 25-$(OH)_2D_3$ and promotes osteoclastogenesis[15] Low Vitamin D level will lead to an increase in serum Parathyroid Hormone which will lead to increased tubular reclamation of calcium in kidneys & resorption from the skeleton at the cost of lowering bone density, which will lead to weakened and brittle bones that breaks easily and leads to Rickets, Osteoporosis, Osteomalacia and bone fracture.

Roles of Vit. D in pulmonary diseases: Vit. D has complex effects on pulmonary cell biology and immunity with impact on inflammation, host defense, wound healing, repair, and other processes. While the knowledge on direct mechanistic links between Vit. D and lung diseases is limited, a number of epidemiological and experimental are available that highlight the relevance of this connection.

Role of Vitamin D in COPD: The association of Vit.D deficiency and reduced lung function could depend on the calcemic effects of Vit D. The vital capacity and total lung capacity was found to decline with an increasing number of thoracic vertebral fractures as a direct consequence of Vit.D deficiency. Nuti et al. observed 3030 ambulatory COPD patients and found a strong association between COPD severity and fractures. Kyphosis related to osteoporosis caused limitation in rib mobility and inspiratory muscle function and correlated with a reduction in FEV_1 and FVC. The altered properties of the thoracic skeleton could result in failure of the respiratory muscles contributing to the pathophysiology of COPD.

Vit.D deficiency could result in altered host defense of the lung with subsequent growth of an abnormal flora that triggers inflammation. Acute exacerbations of COPD are an important cause of hospitalization and lead to a faster decline in FEV_1.

Exacerbations are triggered by viruses, bacteria, atypical strains, or a combination of these.[14] Potential bacterial pathogens are detected in about 50% of exacerbations. A therapeutic consequence would be the up-regulation of the innate immune defense system. Wang and colleagues demonstrated that genes coding for the antimicrobial peptide cathelicidin (LL-37/hCAP-18) are regulated by VDRE-containing promoters. In cultured monocytes, a local increase of the 1,25D3-VDR complexes stimulates the production of LL-37, resulting in an improved intracellular eradication of Mycobacterium tuberculosis. The data demonstrated that the activation of TLRs on human monocytes triggers a micro-bicidal pathway that is dependent on both the endogenous production and action of 1, 25-$(OH)_2D_3$ through the VDR.

The effect of Vit D on extracellular matrix homeostasis not only in bone tissue, but also within the lung may have a role in COPD development. Boyan et al. found Vit D to be an autocrine regulator of extracellular matrix turnover and growth factor release via matrix metalloproteinases. Matrix metalloproteinasis-9 (MMP-9) has been shown to be elevated in induced sputum of COPD patients and a causative role has been suggested in the development of COPD. Vit D also to attenuate TNF-alpha induced up-regulation of MMP-9 in keratinocytes. Vit D deficiency may lead to a reduced attenuation of MMP-9 activity resulting in enhanced degradation of lung parenchyma.

Vit.D has a number of activities in addition to its effect on calcium and bone homeostasis and influences process such as immune regulation, host defense, inflammation, or cell proliferation. Several hurdles must be overcome to validate the benefit of Vit.D-based therapies:

1. Basic mechanisms are not clear and the involved molecular pathways are likely difficult to identify because Vit.D impacts on a variety of biological processes in parallel.
2. Conclusive data from interventional studies are missing for many disease entities.
3. Since Vit.D has been used for many years, the pharmaceutical industry might hesitate in starting a development program. Nevertheless, the data available indicate that Vit.D could be beneficial for the prevention or therapy of important lung diseases.

Conclusion

Ironically, deficiency of Vitamin D, a naturally produced hormone activated in skin upon exposure to sunlight has become a big threat to human health. Widespread prevalence of vitamin D deficiency across the globe is undeniable. Not surprisingly, Farmers were seen to have adequate level of Vitamin D, while urban population was observed to have markedly reduced serum Vitamin D level. Factually, sun exposure is an untenable solution, for most individuals, towards attaining vitD sufficiency. VitD modulates a variety of processes and regulatory systems including host defense, inflammation, immunity, and repair. Epidemiological data indicate that low levels of serum VitD are associated with impaired pulmonary function, increased incidence of inflammatory, infectious or neoplastic diseases.

In fact, this review summarizes the knowledge on the classical and newly discovered functions of Vit.D, the molecular and cellular mechanism of action and the available data on the relationship between lung disease and Vit.D status. Although, there are some controversies regarding exact mechanism on how Vitamin D affects various body systems, most RCT, Case control studies as well as cross-sectional studies together with meta-analysis done are strongly showing its significant role on various body system.

Finally, to highlight few most alarming points of Vitamin D on health are mentioned below:

1. Maintains calcium & Bone homeostasis leading to preventive effect on cardiovascular, pulmonary and skeletal system.
2. Improves lung function.
3. Decreases airway hyper responsiveness.
4. Improved glucocorticoid response.
5. Improves host defense by Modulating T-Lymphocytes.
6. It decreases Matrix Metalloproteinase-9 (MMP-9).

Hence, the authors strongly commend early morning sun-exposure, in addition to VitD supplementation where required to prevent progression of several chronic disease which indeed will lead to decrease economical burden and improved health status of an individual & ultimately reflecting the whole nation development. We also believe, robust and clear-cut guidelines be provided in near future to further act in this sector as well like other diseases e.g. Tuberculosis, Hypertension, Diabetes, Asthma, COPD etc.

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