Overview

Vitamin D is a secosteroid which is converted into its active form via $1\alpha$-hydroxylase enzyme. Though kidney is the classical site for $1\alpha$-hydroxylase activity, it is also expressed in other tissues such as endothelial and vascular smooth muscle cells. Besides, vitamin D receptor (VDR) is present in more than 30 different tissues including pancreas, myocardium, lymphocytes, etc. The widespread distribution of VDR signifies important role of vitamin D in humans. While vitamin D is critical for calcium homeostasis, current studies also highlight role of vitamin D deficiency (VDD) in diseases other than the metabolic bone disorders. Studies from our center and other parts of India have drawn attention towards wide prevalence of VDD in Asian Indians when currently proposed cut-off are used to define vitamin D sufficiency. Although, VDD in Asian Indians has several potential implications, there has been no systematic efforts to date directed towards finding the importance of widespread VDD in our country. In the present article we would focus on the

Prevalence & potential significance of vitamin D deficiency in Asian Indians

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Studies from our center and other parts of India have drawn attention towards wide prevalence of vitamin D deficiency (VDD) in our country. VDD has been reported in all age groups including toddlers, school children, pregnant women and their neonates and adult males and females residing in rural and urban India. We reviewed implications of VDD in our population based on the preliminary data available from Indian studies on skeletal health. Besides, a brief review is made on the importance of VDD in various other disorders prevalent in equivalent proportions among Indians such as type 2 diabetes mellitus (DM), cardiovascular diseases (CVD), immune competence including relation to tuberculosis, malignancy and osteoarthritis. Data from the West have also associated VDD with increased prevalence of type 2DM, CVD, autoimmune disorders, tuberculosis, prostate, breast and colon malignancy and osteoarthritis. Such association has not been studied to date in our country. Overall results of various studies conducted to date in urban and rural Indians indicate that widely prevalent VDD is functionally relevant to skeletal health including osteomalacia and rickets. However, there is a need to explore its association with osteoporosis related fractures and various other non skeletal disorders linked with VDD.

Key words Osteomalacia - skeletal health - type 2 diabetes mellitus - vitamin D deficiency
implications of VDD in our population based on the preliminary data available from Indian studies on skeletal health. Besides we would briefly review the world literature related to VDD and several disorders which are prevalent in equivalent proportions among Indians such as type 2 diabetes mellitus (DM), cardiovascular diseases (CVD), immune competence including relation to tuberculosis, malignancy and osteoarthritis.

Prevalence of hypovitaminosis D in India

In the western view, VDD was considered to be rare in India. Such belief was based on studies measuring serum calcium and alkaline phosphatase in our population. However, till the year 2000, there was no systematic study which directly assessed body vitamin D status of Asian Indians residing in India. In 2000, we first measured serum 25(OH)D using sensitive and specific assay in apparently healthy subjects in Delhi and showed that significant hypovitaminosis D was present in up to 90 per cent of them. Subsequently, series of studies from different parts of our country have pointed towards widespread VDD in Asian Indians of all age groups including toddlers, school children, pregnant women and their neonates and adult males and females residing in rural or urban areas. Skin complexion, poor sun exposure, vegetarian food habits and lack of vitamin D food fortification programme in the country explain the high prevalence of VDD in India despite its sunny climate.

Vitamin D deficiency and skeletal health in Indians

Vitamin D deficiency rickets and osteomalacia are widely prevalent in our country. On an average 25-30 cases of clinically overt patients with vitamin D deficiency related osteomalacia in adolescent and adult age group are managed in our indoor endocrine services every year. Most of them have undetectable serum 25(OH) D levels with serum parathyroid hormone (PTH) values more than four folds above upper limit of normal. In such a scenario, anticonvulsant and antituberculous therapy, fluoride excess, prolonged steroid therapy and bisphosphonates easily precipitate clinically overt rickets and osteomalacia in our population. Almost one third of our patients with osteomalacia have history of anticonvulsant, anti-tuberculous therapy or steroid use in the immediate preceding years. Such therapies precipitate osteomalacia because of induction of vitamin D synthetic pathway towards inactive products. Because of these reasons it has been our standard practice to prescribe calcium and vitamin D supplementation in all the patients on steroid, anti-tuberculous or anticonvulsant therapy, at least in double the recommended daily allowance.

Besides it is not unusual to find biochemical osteomalacia in our apparently healthy population on routine screening. Wide prevalence of clinically overt osteomalacia/rickets and associated pseudofractures could be due to VDD related low peak bone mass in Asian Indians. The beneficial effect of 25(OH) D supplementation in improving skeletal health would start from in utero and infancy and continue through childhood, adolescence and adulthood.

Newborns and vitamin D deficiency

Pregnant women in India have been shown to have up to 84 per cent prevalence of VDD which correlated significantly with serum 25(OH) D status of their newborns. Mothers with suboptimal vitamin D status have offsprings with reduced intrauterine and postnatal skeletal development. Brooke et al. first reported reduced incidence of low birth weight babies in vitamin D supplemented Asian mothers. Vitamin D and calcium supplementation of the pregnant mothers is associated with increased skeletal growth and bone mass in the offsprings. Marwa et al. from Rohtak, reported higher body weight, crown heel length, head circumference and mid arm circumference in mothers who received two doses of 60,000 IU of vitamin D3 during third trimester pregnancy compared to those who did not receive vitamin D3. Besides Apgar score at birth was higher in newborns of mothers with adequate calcium and vitamin D intake than in newborns whose mothers had inadequate intake. Mannion et al. have shown that each additional microgram of vitamin D, was associated with an 11 g increase in birth weight. Morley et al. showed that gestation length was 0.7 wk shorter and knee-heel length was 4.3 mm smaller in infants of mothers with 25(OH) D <11.2 ng/ml at 28-32 wk when compared to babies whose mothers had higher concentrations. Thus, VDD manifests with compromised length from birth itself without any potential for catch up growth in view of the fact that VDD continues to afflict even toddlers and school children in India. Finally, as discussed below it would manifest in compromised adult height.

School children and vitamin D deficiency

Marwaha et al. showed lower forearm bone density and mean serum 25(OH) D levels in school children from low socio-economic region as compared to...
children from high socio-economic region. Recently, Shatrugna et al\textsuperscript{21} from National Institute of Nutrition, Hyderabad, studied the effect of micronutrient supplementation in schoolchildren of 6 to 16 yr of age. After 14 months of supplementation, the increments in height, weight, whole body bone mineral content, and bone mineral density (BMD) at neck of the femur were significantly greater in the supplemented than in the placebo group. The above studies confirm that the suboptimal calcium and vitamin D status are important contributory factors in determining height and bone health in school children in India.

**Adults and vitamin D deficiency**

VDD in Asian Indians has been shown to be associated with higher serum PTH and lower serum calcium. Such effects would promote bone resorption and precipitate osteomalacia and osteoporosis in predisposed individuals. While it is common to see lower T and Z scores in BMD reports from our country, there is paucity of population based systematic data related to prevalence of osteoporosis in adult Indian population. Rarer are the adequately designed studies assessing association between serum 25(OH) D and BMD in Indian population. Shatrugna et al\textsuperscript{22} studied prevalence of osteoporosis in 289 middle aged women from Hyderabad. The prevalence of osteoporosis at the femoral neck was around 29 per cent. The T scores in the BMD of Indian women studied at all the skeletal sites were much lower than the values reported from the developed countries. BMD showed a decline after the age of 35 yr at lumbar spine and femoral neck. On multiple regression analysis, calcium intake of women appeared as an important determinant of BMD. However, 25 (OH) D status was not assessed in the study\textsuperscript{22}.

Several investigators from west have reported significantly lower hip BMD in subjects with low serum 25(OH)D concentrations\textsuperscript{23-26}. Besides, vitamin D supplementation led to beneficial effect on hip BMD\textsuperscript{27,28}. There have been only two studies which have directly assessed relationship between body vitamin D status and BMD in apparently healthy Asian Indians. Arya et al\textsuperscript{9} observed a positive correlation between serum 25(OH) D concentrations and hip BMD in a cohort of 92 healthy subjects from Lucknow. Recently we also observed a significant relation between serum 25(OH) D concentrations and hip BMD but not with lumbar spine or forearm BMD in an urban Delhi cohort\textsuperscript{29}. Differential effects of VDD on BMD at various sites possibly involve factors other than hypovitaminosis D.

In this context we studied genetic variation related to VDR polymorphism. Among the three VDR single nucleotide polymorphisms studied (TagI, FokI and BsmI), subjects with TagI-TT genotype had a significantly higher BMD at the forearm than did subjects with Tt and tt genotypes\textsuperscript{29}. The finding of correlation of VDR gene polymorphism with forearm BMD among Indians is interesting and indicates that even in a severely hypovitaminotic D population, variations in BMD at forearm could be explained by genetic factors.

Overall results of various studies conducted to date in urban and rural India indicate that widely prevalent VDD is functionally relevant in view of associated increase in serum PTH and low BMD. However, there has been no systematic study which has assessed the association between osteoporosis related non-trivial fracture rates and serum 25(OH) D status among Indians. If such study is being planned it would also be important to take into consideration variables such as poor musculoskeletal strength and propensity to fall. Both these factors have also been reported to contribute to fractures in hypovitaminosis D state\textsuperscript{30,31}.

**Vitamin D deficiency and type 2 diabetes mellitus**

Currently the prevalence of type 2 DM is high in urban as well as rural India\textsuperscript{12,33} and by 2030, Asians Indian would bear the maximum burden of the disease in the world\textsuperscript{34}. Glycaemic control tends to worsen in winter months and is believed to be because of concomitant fall in 25(OH) D in this season\textsuperscript{5,36}. Pittas\textsuperscript{37} has systematically reviewed world literature related to (i) association between VDD and prevalence/incidence of type 2 DM in different population, and (ii) randomized trials assessing role of vitamin D supplementation on glucose metabolism.

The cross-sectional study involving largest cohort of non diabetic Americans (n = 6288) reported an inverse relationship between serum 25(OH) D concentration and fasting or post glucose load values\textsuperscript{37,38}. A meta-analysis carried out after combining data from all studies revealed an odds ratio of 0.54 (95% CI, 0.23-1.27) for the highest versus lowest 25(OH)D concentration (25–38 vs. 10-23 ng/ml, respectively)\textsuperscript{37}. In nine of 13 case-control studies reviewed by the authors, patients with type 2 diabetes showed a lower mean 25(OH)D concentrations than the non diabetic controls\textsuperscript{37}. Association between vitamin D intake and incidence of type 2 DM was examined in Women’s Health Study\textsuperscript{37,39}. Subjects with daily vitamin D intake...
>511 IU had lower risk of incidence of DM when compared to a cohort with daily vitamin D intake of <159 IU per day (2.7% vs. 5.6%). Pittas et al. also examined association between combined vitamin D and calcium intake and incidence of type 2 DM among 83,806 women in Nurses’ Health Study. After adjusting for age, BMI, and non dietary covariates, a significant inverse association was observed between vitamin D intake and calcium intake on one hand and risk of type 2 DM on the other.

There is a paucity of interventional trials assessing effect of vitamin D supplementation on glycaemic control over long term period. Pittas et al. studied 92 diabetic subjects and reported decrease in fasting plasma glucose after 3 yr in group receiving daily supplementation of 700 IU of vitamin D and 500 mg of calcium citrate. The potential mechanisms of beneficial effect of vitamin D in type 2 DM include (i) improved β-cell function via direct effect of vitamin D or by increase in the intracellular ionized calcium which therefore would result in enhanced insulin release, (ii) increased insulin sensitivity related to expression of insulin receptor or via calcium dependent pathways in target cells leading to increase in the glucose utilization, and (iii) inhibition of β-cells apoptosis due to VDR transcription factor mediated inhibition of cytotoxic cytogene gene expression. While there is a possibility that widespread prevalence of type 2 DM observed in Asian Indians could be partially related to VDD, there are no data available among Indian subjects on VDD and its effect on beta cell function or insulin sensitivity.

Vitamin D deficiency in cardiovascular diseases

Rheumatic heart disease and associated heart failure are common in India. The estimated prevalence of coronary heart disease is also high (8-10%) in urban India. The high prevalence of CVD in renal failure is linked with lower levels of vitamin D metabolites. There is increasing evidence that VDD might be an important determinant in the pathogenesis of CVD, hypertension and congestive heart failure.

Recently, Zittermann et al. reviewed various studies reporting association between CVD and VDD in context of increased prevalence of coronary artery disease (CAD), vascular calcification and essential hypertension. Besides, intervention trials assessing role of vitamin D supplementation in CVD were also reviewed. Study by Watson et al. reported inverse correlation of serum 1,25(OH)2D3 and presence of coronary artery calcification in subjects with hypercholesterolemia who are at high risk for CAD (Framingham cohort) and also in asymptomatic individuals from Southway with moderate risk of CAD when followed up for four years. Circumstantial evidences also indicated an increase in the risk of CAD with increasing geographic latitude and associated fall in serum 25(OH)D. On the contrary, there was a decline in mortality from CAD for males in the New Mexico with higher altitudes. On an average, an increase of 1000 meter in the altitude of residence was associated with a 28 per cent decrease in mortality rates associated with CAD. In addition, several studies also demonstrated increase in the coronary events and associated mortality (up to 40%) in winter season when compared to other seasons. We reported seasonal variation of serum 25(OH) D levels with almost undetectable 25(OH) D levels in winter in Indians despite its sunny climate. Zitterman et al also suggested high prevalence of CAD in urban population when compared to the rural population could be due to VDD secondary to environmental pollution linked block in UV rays. Agarwal et al also reported environmental pollution and haze related fall in serum 25(OH) D in urban Delhi.

The incidence of hypertension also followed an inverse relation with serum 25(OH) D and increased intake of vitamin D was associated with 9.3 per cent decrease in systolic blood pressure. Interventions had also shown up to 40 per cent fall in C-reactive protein (CRP) and interleukin-6 (inflammatory markers of CAD) at the end of one year in patients with CAD put on three monthly injections of 1250 µg cholecalciferol. Similar fall in CRP levels were also observed during short term intervention with daily 12.0 µg vitamin D in patients admitted for short duration in an intensive care unit. Besides, McGonigle et al. found significant improvement in left ventricular function with 1 α vitamin D3.

The possible reasons for the harmful effect of VDD on CAD, HT and congestive heart failure (CHF) reported in various studies could be due to the combination of the following (i) inhibition of VDR mediated Gla matrix protein expression which would result in activation of vascular calcification, (ii) increased PTH levels and associated myocardial, valvular and vascular calcification, (iii) activation of pro-inflammatory cytokines, (iv) suppression of an anti-inflammatory cytokine IL-10, and (v) stimulation of renin angiotensin system.
to be affected with CAD in our country. Interestingly, CHD also manifests almost a decade earlier in India when compared to western countries. Though there have been a few case reports showing improvement in ejection fraction following calcium and vitamin D supplementation in Indian patients with CHF and hypocalcaemia, there is no systematic study assessing association of VDD with postpartum cardiomyopathy, CHF and CHD.

**Vitamin D deficiency and immune system**

Vitamin D deficiency and autoimmunity: Most of the autoimmune disorders are observed in immunogenetically predisposed individuals when exposed to adverse environmental agents such as viruses and altered nutritional factors. The classical example is increase in the incidence of autoimmune thyroiditis following iodine supplementation in iodine deficient population. Recently, VDD has been implicated as a triggering factor in autoimmune disorders such as type 1 diabetes mellitus (T1DM), inflammatory bowel disease (IBD) and multiple sclerosis (MS). VDR is expressed in peripheral blood monocytes, macrophages, dendritic cells, leukocytes and activated CD4+ and CD8+ T cells and as a result VDD can have widespread effects on immune effectors response. 1,25(OH)2 D3, mediating its action through VDR has been reported to inhibit proliferation of Th1-helper cells and secretion of cytokines such IL-2 and interferon gamma (INF-γ). Vitamin D enhances IL-4 response due to its stimulatory effect on Th2 cells. Therefore, vitamin D modulates T cell differentiation towards Th2 phenotype and inhibits Th1 development and could result in predisposition to various autoimmune disorders.

Epidemiological studies support association between VDD and seasonal pattern in the onset of T1DM, IBD and MS. Population based studies had shown that vitamin D supplementation during early years of life was associated with decreased frequency of T1DM. Rickets during first year of life was associated with increased risk of T1DM. Further, presence of islet auto-antibodies in offspring was inversely related to maternal vitamin D intake during pregnancy. The higher prevalence of IBD was also reported form the geographical regions of North America and Northern Europe with limited sunshine. Higher incidence of IBD was reported in Asians migrated to Europe.

T1DM was considered to be rare in India. However, studies have indicated that T1DM is the second most common autoimmune endocrine disease in India with an annual incidence of 10.5/100,000. Similarly, contrary to the previous belief about the rarity of IBD in India, Sood et al. showed that disease is widely prevalent in India when careful house-to-house surveys were carried out in Punjab. Interestingly, it has been suggested that environmental triggers play a major role in Indian patients with multiple sclerosis in view of absence of family history in majority of the patients, unlike in USA. VDD could be one such triggering factor in view of its linkage with MS. Though autoimmune disorders such as T1DM, MS and IBD are common in India, there have been no study to date assessing the role of VDD among Indians in any of the above disorders.

**Vitamin D deficiency and tuberculosis**

Tuberculosis is an important public health problem in India. Role of VDD in predisposition to tuberculosis has been speculated for a long time. Cod liver oil was first advocated for the treatment of tuberculosis in 1770 and was widely used till the 19th century. Patients with tuberculosis were also advised treatment at sanatorium where sunshine was available in plenty. Calciferol was used to treat tuberculosis in the late 1940s and treatment was rationalised based on its role in the calcification of tuberculosis lesions. With the advent of effective antituberculosis drugs in the mid 1950s, enthusiasm for treating tuberculosis with vitamin D subsided. However, it formed the basis of subsequent investigations linking VDD with pulmonary tuberculosis. Davies reported significantly lower levels of serum 25(OH)D in patients with untreated tuberculosis in comparison to healthy controls. In a similar study, Grange et al. showed that patients with higher 25(OH)D levels had less extensive radiographic disease. Douglas et al. reported a striking seasonal variation of tuberculosis incidence, with peak during the summer and nadir in the spring; unlike other respiratory diseases. Seasonal changes in vitamin D levels were suggested as the possible cause for the paradoxical reversed seasonality of tuberculosis.

**Vitamin D supplementation in tuberculosis**

Recently, Nursyam et al. carried out a placebo-controlled randomized trial of vitamin D supplementation (0.25 mg/day for initial 6 wk) in 67 patients with pulmonary tuberculosis. All the subjects in the vitamin D supplemented group and only 76.7 per cent in the placebo group had sputum conversion. In another randomized control trial, addition of vitamin D to standard antitubercular therapy resulted in higher rate of clinical and radiological improvement.
Vitamin D, immune shifts and tuberculosis: Incubation of macrophages with physiological concentration of 1, 25(OH)₂D (10⁻⁹M) led to inhibition of intracellular growth of *Mycobacterium tuberculosis*<sup>85</sup>. In *in vitro* studies 1,25-dihydroxycholecalciferol had significant immunomodulatory effects leading to a shift in cytokine profile of T-helper (Th1 to Th2) and reduced antigen presentation<sup>86</sup>. With the currently available knowledge it is difficult to explain beneficial effect of vitamin D supplementation on the basis of shift in the immune mechanism because vitamin D supplementation would enhance Th2 cytokine response rather than beneficial Th1 response. Recently Liu <i>et al</i><sup>97</sup> have shown that vitamin D supplementation results in increased expression of antimicrobial peptide ‘cathelicidin’ in the macrophage culture, which could result in killing of the intracellular *M. tuberculosis*. This is a potential mechanism which could logically explain role of vitamin D in enhancing innate immunity in patients with tuberculosis. However, studies related to the shift in immune responses in vitamin D deficient state have only been conducted in experimental and *in vitro* conditions. There is a paucity of comprehensive and systematic studies on the impact of vitamin D therapy in human subjects with tuberculosis in terms of immunity.

**Vitamin D deficiency and malignancy**

Schwartz <i>et al</i><sup>98</sup> first provided evidence of relationship between VDD and cancer by reporting higher mortality in patients with prostate cancer with increasing latitudes. Giovannucci <i>et al</i><sup>99</sup> reported 17 per cent reduction in cancer incidence and 29 per cent reduction in total mortality for 10 ng/ml increase in predicted 25(OH) D concentrations. The maximum beneficial effect was observed for gastrointestinal cancer. Skinner <i>et al</i><sup>100</sup> reported 41 per cent lower risk of pancreatic cancer among subjects consuming >600 IU vitamin D daily in comparison to those with <150 IU per day. Similar inverse relation with vitamin D nutritional status was also reported for colorectal adenomas, endometrial and breast carcinoma. Besides, Hartman <i>et al</i><sup>101</sup> reported 18 per cent lower recurrence of adenomatous polyps in ‘Polyp Prevention Trial’ among subjects on vitamin D supplementation. Various mechanisms implicated in anticancer effects of vitamin D involve cell cycle regulation, induction of apoptosis, cell differentiation, disruption of growth factor mediated cell survival signals and inhibition of angiogenesis and cell adhesion<sup>102</sup>.

Average annual incidence rates of cancer in India range from 5.0 to 9.1 per 100,000/yr for prostate and 7.2 to 31.3 per 100,000/yr for female breast<sup>103</sup>. Hebert <i>et al</i><sup>103</sup> also reported that most of the prostate and breast carcinoma in India were diagnosed in the late stages in comparison to the USA where only 15 per cent cases were diagnosed in the advanced stage. Role of VDD deficiency in wide prevalence of advanced carcinoma of the breast and prostate in India is not known. Interestingly, vitamin D and its analogues inhibit the invasiveness and angiogenesis of several cell types in *in vitro* studies<sup>104,105</sup>. There is a need to perform studies relating VDD and advanced stage of malignancy observed in India.

**Vitamin D deficiency and osteoarthritis**

Osteoarthritis of the knee and hip are common in India. Community surveys carried out in adult population in rural Pune and rural and urban subjects in Chandigarh revealed up to 29 and 33 per cent prevalence of osteoarthritis of the knee joint in these regions, respectively<sup>106,107</sup>. VDD had also been associated with poor BMD in subjects with osteoarthritis of the knee and hip joint<sup>108,109</sup>. Several investigators have assessed the possible relation between presence and progression of osteoarthritis of the knee joint and VDD<sup>108-110</sup>. Bischoff-Ferrari <i>et al</i><sup>111</sup> studied prevalence of knee osteoarthritis in elderly subjects with mean age of 75 yr and reported comparable prevalence of osteoarthritis in vitamin D sufficient and deficient subjects (43.6 versus 50.4%).

Felson <i>et al</i><sup>112</sup> carried out a follow up study of 715 subjects with osteoarthritis recruited in Framingham and 277 adults with established osteoarthritis of knee joint recruited in the ‘Boston osteoarthritis of knee study’. Progression of the osteoarthritis was assessed by sensitive measures such as radiographs and MRI of the knee joint over a period of 9 yr. On an average, one fifth of subjects showed worsening of the osteoarthritis as revealed by narrowing of the joint space and loss of the cartilage on MRI. Besides, there was no significant association between baseline 25(OH) D levels and radiographic worsening. Thus, contrary to the popular belief the results of the recent studies involving sufficient number of subjects and statistical power did not reveal association between VDD and osteoarthritis. However, in most of the above studies mean serum 25(OH) D values at baseline were > 20 ng/ml; almost double the mean value observed in Asian Indians<sup>4</sup>. In view of high prevalence of osteoarthritis and potential
benefit in Indians, there is a need to perform studies assessing prevalence and worsening of osteoarthritis with severe hypovitaminosis D in our country.

Conclusion

Overall results of various studies conducted to date in urban and rural India indicate that widely prevalent VDD is functionally relevant to skeletal health including osteomalacia and rickets. There is a need to explore its association with osteoporosis related fractures and various other non skeletal disorders linked with VDD. Considering the wide prevalence of VDD in rural areas of India, that too in the southern Indian States with almost perennial sunshine, it is unlikely that sunshine exposure alone as a healthy lifestyle measure would result in vitamin D sufficiency in us. This is predominantly due to skin pigmentation. In such a scenario active intervention is required in the form of a National policy for vitamin D food fortification programme in our country.

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