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Research Article

Assessment and evaluation of vitamin D levels in patients of moderate persistent asthma: a prospective study in rural hilly area

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ABSTRACT

Background: The discovery of non-classical actions of vitamin D has opened new applications. Among these is its anti-inflammatory role in inflammatory diseases like asthma. Low levels of vitamin D have been associated with asthma severity and recurrent exacerbations. Emerging evidence suggests that vitamin D deficiency (VDD) is also associated with increased airway hyper-responsiveness, decreased pulmonary function and decreased response to standard anti-asthma therapy.
Methods: In this prospective study, vitamin D levels were assessed in 50 consecutive consenting subjects of moderate persistent asthma diagnosed as per GINA guidelines. Levels were assessed in relation to exacerbations, seasonal variation in spring, rainy and winter season and lung function.
Results: 62% subjects were having deficient levels of 25 (OH) Vitamin D (<20 ng/ml). None of study participant had sufficient levels of vitamin D. There was lack of seasonal effect due to variation in sun exposure in different seasons on levels of vitamin D. This study found no correlation (r=0.078) between levels of vitamin D and number of exacerbations in patients of asthma on regular treatment. In subjects groups having less and more than 3 exacerbations in nine months, difference of vitamin D levels and lung function was also statistically not significant.
Conclusions: Findings of this study were consistent with HUNT study that concluded non association of low serum 25 (OH) D levels with airway obstruction. However, considerable variation in different study results with regard to seasonal, lung function and exacerbational variation underline the need for a meta-analysis in this field.

Keywords: Vitamin D in asthma, Seasonal variation of vitamin D, Lung function and vitamin D

INTRODUCTION

Vitamin D is a lipid soluble vitamin that acts as a hormone playing a pivotal role in Ca^{2+} homeostasis. It acts through nuclear receptors called vitamin D receptors (VDR). The principal provitamin found in humans is 7-dehydrocholesterol, synthesized in skin. UV exposure of skin converts it to cholecalciferol (vitamin D_3). Further, D_3 gets converted by 25-hydroxylation in the liver to 25-OH D_3.

Finally 1-α-hydroxylation takes place in the kidney (rate limiting step) and 1α, 25-$(OH)_2$ D_3 or calcitriol is formed. Calcitriol stimulates intestinal calcium and phosphate absorption and with its interplay with parathyroid hormone (PTH) maintains normal plasma Ca^{2+} concentrations from bone mobilization through bone growth, bone resorption and remodeling. It also raises plasma Ca^{2+} levels by decreasing its renal excretion and by increasing proximal tubular reabsorption.

VDRs are distributed widely throughout the body and believed to be involved in the regulation of cell growth, differentiation and apoptosis as well as modulation of the immune system by influencing cytokine production and other functions.[1]

Vitamin D by conventional wisdom should not be deficient in equatorial regions and in a tropical country like India because of the fact that India is located between 8.4° and 37.6° north latitude with majority of population living in regions experiencing ample sunlight throughout the year.

Some of the causes contributing to vitamin D deficiency (VDD) in India are decreased time outdoors as in the case of school children, house wives and office goers, dietary lack of consumption of vitamin D rich or fortified foods, diminished intake of dairy products especially in urban area on concerns of fat intake, increasing use of sunscreens to prevent sun tan, skin cancers or premature wrinkling and fear of ageing by exposure to sunlight.

The concern for vitamin D estimation has increased tremendously in India due to increase in reporting of the published data in the last 8 years regarding prevalence of VDD in the Indian subcontinent. As per the report of International Osteoporosis Foundation, in North India, 96% of neonates, 91% of healthy school girls, 78% of healthy hospital staff, and 84% of pregnant women were found to have hypo-vitaminosis D.[2]

Darker skin produces a significantly lesser amount of vitamin D when compared with the individuals with fairer skin, such as Caucasians.[3,4] Thus, for Indian skin tone, minimum "direct sun exposure" required daily is more than 45 min to bare face, arms and legs to sun's UV rays.[5] The most reliable marker of vitamin D status is the serum concentration of 25(OH) D. Vitamin D deficiency is defined as 25(OH) D <20 ng/mL, insufficiency as 20–29 ng/mL and sufficiency as ≥30 ng/mL.[5]

The discovery of non-classical actions of calcitriol has expanded and opened new vistas for its applications. Among these, its anti-inflammatory activity has drawn attention of researchers to investigate its role in regulating the progression of inflammatory diseases.

The expression of many inflammation-related genes is regulated by calcitriol through VDR in a large variety of cells including immune cells such as, but not limited to, macrophages, dendritic cells, T helper cells, and B cells.

Studies of calcitriol in these immune cells have shown both direct and indirect immune-modulatory activities affecting innate and adaptive immune responses. Moreover, calcitriol can also exert its anti-inflammation effects through regulating the biosynthesis of pro-inflammatory molecules in the prostaglandin pathway or through nuclear factor kappalight-chain-enhancer of activated B cells (NFκB) by affecting cytokine production and inflammatory responses.

These actions of calcitriol may explain the associations between vitamin D levels and inflammatory diseases such as rheumatoid arthritis, inflammatory bowel disease, psoriasis, multiple sclerosis and asthma.[6]

Vitamin D levels, lung function and airway remodelling

Asthma is one of the most prevalent chronic diseases worldwide, globally affecting more than 200 million people.[7] 25(OH) D levels below 30 ng/ml are common in adult asthma and most pronounced in patients with severe and/or uncontrolled asthma, supporting the hypothesis that improving suboptimal vitamin D status might be effective in prevention and treatment of asthma.[8]

In fact, those with a vitamin D deficiency turn out to be 25 percent more likely than other asthmatics to have had at least one flare-up in the recent past.[9] VDD and asthma share several common risk factors including high latitude, winter season, industrialization, poor diet, obesity. Vitamin D has been demonstrated to possess potent immunomodulatory effects, including effects on T cells and B cells as well as increasing production of antimicrobial peptides (e.g. cathelicidin).

This immunomodulation may lead to asthma specific clinical benefits in terms of decreased bacterial/viral infections, altered airway smooth muscle-remodeling and -function as well as modulation of response to standard anti-asthma therapy.[10]

Low levels of vitamin D have been associated with asthma severity and loss of control, together with recurrent exacerbations. Remodeling is an early event in asthma described as a consequence of production of mediators and growth factors by inflammatory and resident bronchial cells. Consequently, lung function is altered, with a decrease in forced expiratory volume in one second and exacerbated airway hyper-responsiveness. Subepithelial fibrosis and airway smooth muscle cell hypertrophy are typical features of structural changes in the airways.

Emerging evidence suggests that VDD is associated with increased airway hyper-responsiveness, decreased pulmonary function, worse asthma control, and possibly decreased response to standard anti-asthma therapy. [11]It is with such intention whether above observations are consistent with rural cases of moderate persistent asthma (a less researched subtype), current study was planned to measure and evaluate vitamin D levels.

METHODS

This prospective study was conducted in the Department of Pharmacology and Pulmonary Medicine, Dr. RPGMC Kangra at Tanda, Himachal Pradesh, India after getting protocol approval of Institutional ethics committee. The place of study was a rural hilly area in middle and lower hills of Himalayas thus bringing out the observations in an entirely different setup. Informed consent was taken from all participating subjects. Consecutive patients (new and old) of either sex and of any age diagnosed by physician as having moderate persistent asthma as per

Global Initiative for Asthma (GINA) 2004 updated guidelines were included in the study (Table 1).

Table 1: GINA 2004 updated guidelines of moderate persistent asthma.

Symptom along with time
Symptom during daytime - Daily and attacks affect activity
Symptom during night >1 time a week
PEF or FEV1 60%-80%
PEF variability >30%
Note: The presence of one of the features of severity is sufficient to place a patient in this category.

Instead of currently prevailing GINA 2016 guidelines, 2004 guidelines were chosen due to ease of clinical diagnosis and categorisation. Patients not willing to participate were the exclusion criteria.

63 consecutive consenting patients having moderate persistent asthma diagnosed as per stated criteria were enrolled for the study. (Figure 1) Due to various reasons including financial constraints, erroneous sampling, refusal for repeat testing and follow ups by consenting subjects, 25(OH) Vitamin D levels could be assessed correctly three times in 25-35 subjects for each of three test seasons (spring, rainy and winter) three months apart. Randomization was done by serially doing the test in every second reporting eligible patient thus saving on test costs.

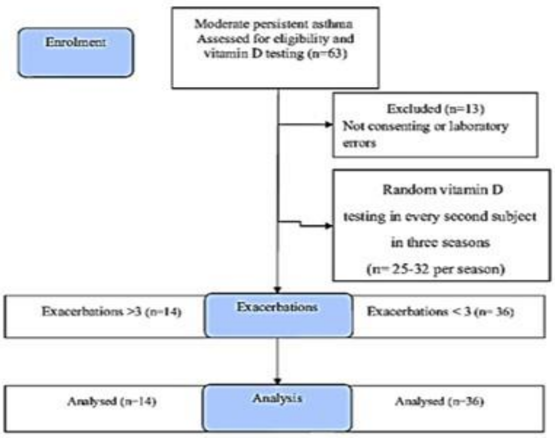

Figure 1: CONSORT flow diagram.

This also resulted in random repeat testing of subjects which helped to arrive at a mean level for each subject in a nine month study period covering stated major seasons. Such random repeat testing was also done to even out changes in levels due to variations in laboratory and assess variation with time (if any). Patients were allowed to continue the treatment for moderate persistent asthma as advised by the treating physician. A note was made of number of acute exacerbations experienced by patients during study period of six months to find any relation between degree of deficiency of vitamin D levels and number of exacerbations suffered by patients. Lung functions were assessed by spirometry.

RESULTS

Mean age of 50 participants in the study was 41.2±15.5 years. There were 16 males and 34 females in the study. Mean BP in participants was 120mm systolic and 80mm diastolic. Mean 25(OH) Vitamin D levels found among the participants was 18.9±6.7 ng/ml (Table 2). This was well below sufficiency level of 30 ng/ml (Table 2).

Table 2: Status of vitamin D level in moderate persistent asthma patients.

Vit D ng/ml	N	Status	Percentage
< 20	31	Deficient	62%
20-29	19	Insufficient	38%
> 30	0	Sufficient	0%

62% subjects were having deficient levels of 25(OH) Vitamin D. None of study participant had sufficient levels of vitamin D. Only 2 participants in the study had mean 25(OH) Vitamin D levels below 10 ng/ml. An average of 1.8 (~2) asthma exacerbations were experienced by each participant over a period of nine months despite taking treatment. FVC (Forced vital capacity) in the group was 83%, FEV1 (Forced expiratory volume in one second) 71%, FEV1/FVC ratio 88%, PEFR (Peak expiratory flow rate) 70% and MEFR/FEF2575 (Mid expiratory flow rate) 44% respectively of the predicted values.

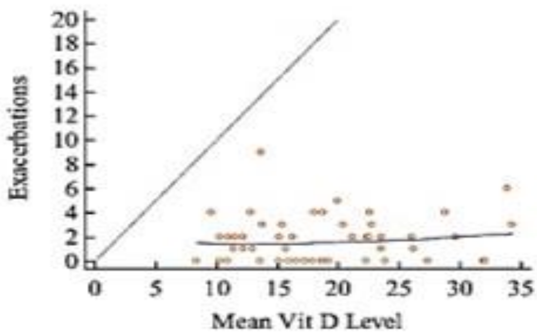

Figure 2: Correlational analysis of asthma exacerbation and mean vitamin D levels.

Analysis of vitamin D level in each season for all study participants (n=50) showed mean level of 18.93±6.09 ng/ml (n=26) in spring season, 19.9±8.91 ng/ml (n=32) in rainy season and 18.89±8.37 ng/ml (n=25) in winter season. The comparison of values was statistically not significant. (p value 0.84) thereby showing lack of seasonal effect due to variation in sun exposure in different seasons on levels of vitamin D. It also showed lack of variation in vitamin D levels with time (over a period of nine months) if left untreated. Data analysis (Figure 2) revealed no correlation (r = 0.078) between levels of vitamin D and number of exacerbations in patients of asthma (p value 0.58).

Table 3: Status of vitamin D level in relation to exacerbation in moderate persistent asthma.

Study participants	25(OH) VIT D (Mean± SD) ng/ml	Vitamin D comparison	Exacerbation comparison
Less than 3 exacerbation (n=36)	18.4 ± 6.4	p value 0.4	p value 0.73
More than 3 exacerbation (n=14)	20.4 ± 7.6		

Table 4: Lung function status in relation to exacerbation in moderate persistent asthma

Exacerbation	FVC % predicted (Mean±SD)	FEV1 % predicted (Mean±SD)	FEV1/FVC % predicted (Mean±SD)	PEFR % predicted (Mean± D)	FEF2575 % predicted (Mean ± SD)
Less than 3 (n= 36)	86 ± 18.9	74 ± 24.1	89 ± 19.3	59 ± 26.7	46 ± 26.6
More than 3 (n=14)	78 ± 11.5	66 ± 17.7	86 ± 17.5	50 ± 22.1	40 ± 18.3
p value	0.16	0.22	0.73	0.27	0.41

It was hypothesized that patients having asthma of moderate grade can have at least one episode of acute exacerbation in one season which lasts approximately three months in India. For the same reason, study was done for nine months to cover three seasons (spring, rainy and winter) with one vitamin D test done in each season in which stable patients were expected to have exacerbations. Assuming one exacerbation for each aggravating season, results were further analyzed for levels of vitamin D for participants having less and more than 3 exacerbations.

36 participants in study comprising 12 males and 24 females had less than 3 exacerbations. (Figure 3) Mean age was 40.6±15.4 years. Mean vitamin D levels in these were 18.4±6.4 ng/ml.Average asthma exacerbation in these was 0.8 (~1) in nine months. Remaining 14 participants comprising 4 males and 10 females had mean age of 42.4±16.1 years with 3 or more exacerbations in nine month observation period. Mean vitamin D levels in these were 20.4±7.6 ng/ml.

Table 5: Lung function status in relation to vitamin D level in moderate persistent asthma

	FVC % predicted (Mean ± SD)	FEV1 % predicted (Mean ± SD)	FEV1/FVC % predicted (Mean ± SD)	PEFR % predicted (Mean ± SD)	FEF2575 % predicted (Mean ± SD)
Vitamin D less than 20 (n=23)	84 ± 18.5	72 ± 22.9	87 ± 19.0	59 ± 24.9	47 ± 26.9
Vitamin D 20-39 ng (n=17)	82 ± 15.7	71 ± 22.7	88 ± 18.1	53 ± 25.7	39 ± 19.9
p value	0.69	0.92	0.86	0.49	0.32

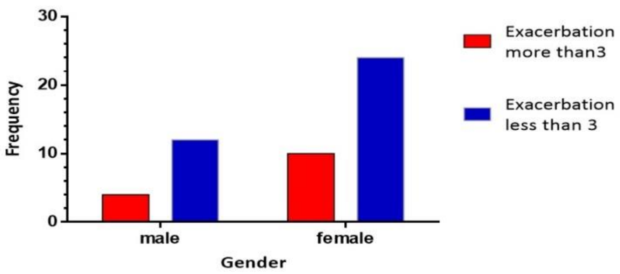

Figure 3: Asthma exacerbation and gender distribution in the participants.

Average exacerbation in these was 4.2 (~4) in nine months despite taking treatment. The statistical comparison of mean 25(OH) vitamin D levels between two groups was not significant.(p value 0.40) Similarly, statistical comparison of exacerbations between these two groups was also statistically not significant (p value 0.73) thereby showing lack of difference (Table 3). The difference in lung function between two groups in relation to exacerbation (Table 4) and in relation to vitamin D levels (Table 5) was also statistically not significant (Table 5).

DISCUSSION

Mean vitamin D levels in this study were in agreement to other studies in which these were found deficient.[12] However, in a similar study, the mean vitamin D levels in asthma patients (25.6 ng/ml) were the same as controls (26.2 ng/ml).[8] One more study reported levels of vitamin D to be lower among asthmatic compared to non-asthmatic.[13]Since controls were not taken in this study design, the deficiency of vitamin D among asthmatics could not be established with certainty.

There can be valid reasons for vitamin D deficiency in India. As in the rest of the world, in India too, slow cooking is widely practiced leading to thermal instability of vitamin D. Vitamin D is degraded at temperatures above 200 °C as in shallow and deep frying of foods. Its thermal stability is inversely related to temperature and time. Most cooking fats and oils have smoke points above 180 °C. When foods are fried, vitamin D in the food comes out into the cooking medium and is thermally degraded. Short-time pressure cooking is definitely advisable to retain at least some of the thermally more stable essential nutrients in cooked food, including vitamin D.[5]

Exacerbations of asthma found in this study in relation with vitamin D levels were in disagreement with a similar study which reported increase in exacerbations in moderate asthmatics with vitamin D deficiency over a four year period.[14] One more study in children and adolescents reported lack of correlation of vitamin D with asthma severity similar to current study findings.[15]

Vit D levels and lung function tests by spirometry in this study were in discordance with other study that found decreased vitamin D levels with lower lung function. (FEV1) ($p = 0.006$).[8] Another study from korea also found significant relationship between vitamin D deficiency and airflow limitation.[16] However findings of this study were consistent with HUNT study that concluded that low serum 25(OH)D level was not associated with airway obstruction in most asthma adults.[17]

The current study showed lack of seasonal variation in vitamin D levels which were consistent with a study from Iran.[18] However many other studies reported seasonal variation with an increase in value in the summer season.[19-21] The same finding could not be replicated in this study as current study was done in hilly area which has constant low temperatures. This makes patients to wear clothes which cover most body parts thus reducing skin exposure to sunlight and affecting vitamin D synthesis.

CONCLUSION

Findings of this study were consistent with HUNT study that concluded non association of low serum 25 (OH) D levels with airway obstruction. However, considerable variation in different study results with regard to seasonal, lung function and exacerbational variation underline the need for a meta-analysis in this field.

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