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Original Article

Internal Medicine Section

Vitamin D Levels and Associations in Indian Patients with Primary Sjögren's Syndrome

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ABSTRACT

Introduction: Vitamin D is a steroid hormone belonging to the class of secosteroids with myriad immune functions and has been implicated in aetiopathogenesis of various autoimmune diseases. Although, there have been various studies showing the association of vitamin D in rheumatoid arthritis and lupus in different populations, there have been limited studies on vitamin D and primary Sjögren's Syndrome (pSS). There are no studies on association of vitamin D and pSS from any tropical country including Indian subcontinent.

Aim: The purpose of the study was to look for any association between 25-hydroxyvitamin D (25(OH)D) levels and disease manifestations in Indian patients with pSS.

Materials and Methods: This is a retrospective cross-sectional study done at a tertiary teaching hospital in southern India in 235 patients with pSS. Patients satisfying the American European Consensus Group (AECG) or American College of Rheumatology (ACR) 2012 for pSS between 2008 and 2015 were included if baseline 25(OH)D levels using electrochemiluminescence were available in hospital's laboratory record, 25(OH)D <20 ng/ml,20-30 ng/ml and >30 ng/ml was defined as deficiency, insufficiency and normal, respectively. Clinical laboratory data and disease activity scoring by EULAR Sjögren's syndrome disease activity index (ESSDAI) were retrieved retrospectively. Latitude corresponding to residence of each patient and the season of performing the assay were recorded. Chi-square statistics was done to find associations between categorized 25(OH)D and outcomes and was reported as odds ratio(95% confidence interval).

Results: Mean 25(OH)D for 235 patients with pSS was 19.98(12.55)ng/ml. A vitamin D deficiency, insufficiency and sufficiency was seen in 141(60%), 60(25.5%) and 34.0(14.5%), respectively. No association was noted between latitude or season of performing assay and the levels. pSS with 25(OH)D ≤30ng/ml had more than two fold risk of higher grading on lip biopsy as well as Rheumatoid Factor (RF) positivity. However, low 25(OH)D seemed to be associated with lower ESSDAI and less pulmonary involvement.

Conclusion: Prevalence of 25(OH)D deficiency in Indian patients with pSS was comparable to that of general Indian population. Low 25(OH)D level ≤30ng/ml was associated with higher odds for RF positivity and positive grading on lip biopsy. Surprisingly, low 25(OH)D was associated with lower ESSDAI score.

Keywords: Autoimmune diseases, Cystic fibrosis, Rheumatoid arthritis

INTRODUCTION

Vitamin D is a steroid hormone, and belongs to the class of secosteroids. Apart from its well understood role in calcium metabolism and bone health, vitamin D has been shown to modulate both the innate and adaptive immune system [1]. Its role in response to infection as well as autoimmune processes has been a major focus of research in the recent years. Vitamin D levels widely vary with age, gender, dietary habits, skin pigmentation, geographical latitude and sun exposure [2]. A high prevalence of vitamin D deficiency in general populations have been observed [2,3]. Reports also suggest an association of vitamin D deficiency with chronic illness, autoimmune diseases and malignancies [3-5].

A number of reasons could contribute to the low levels of vitamin D in patients suffering from rheumatological illness. These include decreased exposure to sunlight and use of photoprotective agents. Low vitamin D level has been implicated as a possible environmental trigger for rheumatic diseases [6]. Cohort studies have demonstrated that populations with higher vitamin D levels have lower incidence of Rheumatoid Arthritis (RA) [7,8]. In many, but not all cross-sectional studies an association between deficiency and disease activity has been noted in diseases such as RA and systemic lupus erythematosus [9-13]. However, failure to adjust for various confounding factors in cross-sectional studies makes the assumptions of those data less robust. Moreover, cross-sectional data cannot imply causation and an alternate view states that vitamin D may not be the cause but the result of chronic inflammation [14].

Immunological effects of vitamin D are mediated via Vitamin D Receptor (VDR) that is expressed on immune cells. VDR dysfunction leads to loss of tolerogenic dendritic cells and T regulatory cells resulting in development of pathogenic Th1 and Th17 cells [1,15,16]. Similarly, B cell function is also modulated by vitamin D [17,18]. Due to these myriad of immune functions, vitamin D is believed to have a role in aetiopathogenesis of autoimmune diseases. Association of vitamin D receptor polymorphisms has been found in many autoimmune diseases but not in pSS [19].

As vitamin D is known to regulate immune mechanisms, it is likely that deficiency could possibly modify the disease pathogenesis in pSS. The first study on the association of vitamin D with pSS included 35 patients and was from Denmark [20]. The Danish study reported mildly lower 25(OH)D levels in cases. They subsequently found negative association of 25(OH)D with clinical and inflammatory markers [21]. Another small study from Hungary reported similar levels between cases and controls [22]. Recently, there have been two large studies which included 107 and 176 patients from Turkey [23] and Europe [24], respectively. The latter reported lower levels in pSS whereas, the former study found no difference between cases and controls. Further, the European study found low 25(OH)D levels to be associated with neuropathy and lymphoma [24]. There are no studies on association of 25(OH)D and pSS from any tropical country including Indian subcontinent. To understand potential associations between clinical manifestations, disease activity and 25(OH)D levels in Indian patients with pSS, we retrospectively analysed the titres

of antibodies, histopathological scoring and disease activity in patients.

MATERIALS AND METHODS

This is a retrospective cross-sectional study done at a tertiary teaching hospital in south India. Electronic medical records were screened for patients with diagnosis of pSS between 2008 and 2015. The study was approved by the Institutional review board.

Inclusion criteria were as follows: pSS satisfying the American European Consensus Group (AECG) or American College of Rheumatology (ACR) 2012 criteria and patients with available baseline 25(OH)D levels. We excluded patients with any other co-existing connective tissue disease, chronic hepatitis B, C, chronic HIV infection and sarcoidosis. Clinical and relevant laboratory data were retrieved retrospectively from medical records. Commercial ELISA kit (Euroimmun, Lubeck, Germany) was used for detection of anti-Ro (or anti-SSA) and anti-La (or anti-SS-B) antibodies and a value of > 20 Ru/ml was considered to be positive. Rheumatoid factor was done by nephelometry and values greater than 20 IU/ml were considered positive. Baseline disease activity scoring was done by ESSDAI. Clinical ESSDAI was done where biological domain scoring was not possible. Mild, moderate and severe disease activity were defined as ESSDAI scores of <5, 5-13 and ≥14, respectively [25].

Vitamin D estimation

Plasma 25(OH)D3 levels were estimated using electrochemi-luminescence from 2008-2012; in subsequent years, total 25(OH)D was measured using the same technique by Roche e411 kit till 2015. The cut-offs for both techniques were the same. A 25(OH)D <20 ng/ml, 20-30 ng/ml and >30 ng/ml was defined as deficiency, insufficiency and normal, respectively. As the ICC between two methods was high (0.84), the data has been analysed together. As 25(OH)D levels are known to differ with latitude and season, latitude corresponding to address of each patient and season of performing the assay were recorded.

STATISTICAL ANALYSIS

Categorical data were expressed as percentage and continuous data as mean along with standard deviation. Patients were divided into two groups: low 25(OH)D and sufficient 25(OH)D defined by 25(OH)D ≤30 ng/ml and >30 ng/ml, respectively. Association between categorized 25(OH)D (≤30 ng/ml and >30 ng/ml) and outcomes (focus score, serologies, organ involvement and ESSDAI score) were analysed using Chi-square statistics and the odds ratio (95%CI) were reported with woolf approximation. A p-value<0.05 was considered as significant. All statistical procedures were carried out using STATA/IC 13.1 (StataCorp LP, Texas, USA).

RESULTS

A total of 302 patients with pSS fulfilled either of the criteria in the time period between 2008 and 2015, 25(OH)D levels were available for 235 patients. Out of the 235 patients, 228 were female, with a male to female ratio of 1:32.57. Mean age of the group was 43(10.96) years. Mean ESSDAI of the patients was 5.71(7.45). The most common extra glandular feature was articular followed by renal. Serological, histopathologic features and disease activity features of the patients are given in [Table/Fig-1].

Mean 25(OH)D for the group was 19.98(12.55)ng/ml. Vitamin D deficiency was seen in 141(60%), whereas 60(25.5%) and 34.0(14.5%) had vitamin D insufficiency and sufficiency, respectively. Place of origin of the patients varied from latitude of 8.73°N to 28.8° N. No relation was found between latitude and 25(OH)D levels. The distribution of 25(OH)D testing according to seasons was as follows: Summer- 47(20%); Rainy season - 96(40.9%); Autumn- 41(17.4%); and Winter- 51(21.7%). No association was noted between season of performing 25(OH)D assay and the levels.

Parameter	n=235
Positive minor salivary gland biopsy	190/216(87.96%)
ANA positivity	179/226(79.20%)
RF positivity	99/190(52.10%)
Anti-SSA positivity	175(74.5)
Anti-SSB positivity	99/229(43.2)
ESSDAI	
<5	136(57.9)
5-13	68(28.9)
>14	31(13.2)
Domains of ESSDAI	
Constitutional	20(8.5%)
Lymphadenopathy	15(6.5%)
Glandular	17(7.3%)
Articular	53(22.6%)
Cutaneous	29(12.3%)
Pulmonary	9(3.83%)
Renal	38(16.2%)
Muscular	5(2.1%)
Peripheral nervous system	13(5.6%)
Central nervous system	2(0.8%)
Haematological	24(10.2%)
Biological markers	111/225(49.33%)

[Table/Fig-1]: Baseline clinical, disease activity and immunological profile of pSS patients. Denominator is 235 unless specified.
*ANA-Antinuclear Antibody

In Chi-square analysis, the association of RF positivity, lip biopsy grading, ESSDAI score and pulmonary involvement reached statistical significance. Results are shown in [Table/Fig-2]. pSS patients with 25(OH)D ≤30ng/ml had more than two fold risk of higher grading on lip biopsy as well as RF positivity. However, low 25(OH)D seemed to be associated with lower ESSDAI and lesser pulmonary involvement.

DISCUSSION

In this study, we have investigated for any association between 25(OH)D levels and disease manifestations in 235 patients with pSS in a tropical country. In the present analysis, we observed 25(OH)D deficiency in 60% of our patient cohort. Since our hospital is a tertiary care centre and caters to patients from different parts of the country, which is ethnically, linguistically diverse and have varied cuisine and food habits, it was impossible for us to derive a matched control set for the analysis. Hence we relied on epidemiologic data on vitamin D from India. A recent review on vitamin D status in healthy Indian adults reported deficiency in 50-100% of population in different parts of the country [26]. The deficiency was observed more in women as compared to men, with most studies reporting a prevalence of 65% and above in women. In this context, the prevalence of deficiency in our patients with pSS is lesser or at the most comparable to that in the general population. In one of the earlier studies, prevalence of 25(OH)D deficiency was reported to be 50% in pSS patients and controls [24]. Vitamin D level is known to vary with latitude and seasons, especially in latitudes above and below 35°N and 35°S, respectively [27–29]. As in other tropical regions, the cutaneous production of vitamin D occurs throughout the year in India and does not significantly vary with latitude, which was also observed in our study [30].

The association of 25(OH)D deficiency with rheumatoid factor(RF) positivity and higher focus score on minor salivary gland biopsy in this study may be a reflection of the immunosuppressive role of vitamin D. Association of vitamin D deficiency with RF has been reported

Variables	25(OH)D			OR	CI	p-value
		≤30ng/ml	>30ng/ml			
Sex	Female	194	33			0.99
	Male	6	1			
Grading on lip biopsy	<3	19	7	2.68	1.01-7.06	0.047
	≥3	167	23			
ANA	0	42	5			0.34
	1	150	29			
RF	0	73	18	2.47	1.05-5.81	0.039
	1	90	9			
anti-SSA	0	53	7			0.48
	1	148	27			
anti-SSB	0	115	15			0.11
	1	80	19			
ESSDAI	<5	123	13	0.39	0.19-0.83	0.01
	≥5	78	21			
Constitutional	0	186	29			0.16
	1	15	5			
Lymphadenopathy	0	187	33			0.38
	1	14	1			
Glandular	0	186	32			0.74
	1	15	2			
Articular	0	153	29(85.29)			0.24
	1	48	5(14.71)			
Cutaneous	0	178	28(82.35)			0.31
	1	23	6(17.65)			
Pulmonary	0	196	30(88.24)	0.19	0.049-0.75	0.018
	1	5	4(11.76)			
Renal	0	172	25(73.53)			0.078
	1	29	9(26.47)			
Muscular	0	197	33(97.06)			0.72
	1	4	1(2.94)			
PNS	0	191	31(91.18)			0.36
	1	10	3(8.82)			
CNS	0	200	33(97.06)			0.15
	1	1	1(2.94)			
Haematological	0	182	29(85.29)			0.35
	1	19	5(14.71)			
Biological	0	98	16(48.48)			0.79
	1	94	17(51.52)			

[Table/Fig-2]: Association of vitamin D with serological, histopathological and disease activity in pSS. 25 (OH)D>30ng/ml was taken as reference for calculating odds ratio.
*OR- Odds Ratio
*CI- Confidence Interval
*PNS- Peripheral Nervous System

previously [20]. Infiltrates on salivary gland biopsy consists mainly of T cells and B cells. As severity of glandular inflammation increases, B cells predominate [31]. Vitamin D deficiency causes proliferation of pathogenic T cell subsets Th1 and Th17 [1,32]. Active metabolite of vitamin D acting via VDR was found to inhibit proliferation of active B cells [17,18]. Further, focus score of salivary gland histopathology has been recently found to correlate well with interferon gamma expression and 1,25(OH)2D3 has been shown to inhibit interferon-gamma production [33,34]. Taking all these evidences together, biologically it is possible that vitamin D deficiency could be inversely related with higher grade on lip biopsy. In addition to its effect on T and B cells, vitamin D also modulates antibody production [35] and this could explain why those with vitamin D deficiency had two and a half fold higher risk of being RF positive.

Paradoxically, this study found that those with vitamin D deficiency were more likely to have low ESSDAI(<5). One possible explanation could be that pSS patients with musculoskeletal symptoms and arthritis cluster with low vitamin D as reported in an earlier study [36]. These manifestations score low on ESSDAI. The cut-off of ESSDAI <5 was chosen as there were relatively less number of patients in moderate and higher ESDDAI groups. We could not find any association with neuropathy as described in literature, nor could we test for association with lymphoma as there was no patient with lymphoma in this group [24]. In summary of the clinical correlations, our study found an association between vitamin D deficiency and low ESSDAI score as well as lesser pulmonary system involvement.

It is difficult to comment on the association of low vitamin D with lesser pulmonary and renal involvement as the numbers were small and due to retrospective nature of the study. In literature, association with low vitamin D has been reported in connective tissue disease related interstitial lung disease, as well as in other respiratory conditions like asthma, chronic obstructive lung disease and cystic fibrosis [37–39]. Most common renal involvement in our group of patients was renal tubular acidosis. A previous case series on RTA observed that pSS patients with RTA had higher vitamin D levels [40]. The authors contemplated that damage to renal tubules in RTA could cause loss of 1-alpha-hydroxylase function. This could result in low 1,25-dihydroxyvitamin D levels but normal 25(OH) D3 levels akin to vitamin D dependent rickets type I.

LIMITATION

The study is not without limitations. We have excluded patients who were prescribed high dose vitamin D supplementation at time of testing. However, due to the retrospective nature of the study, it is not always possible to exclude vitamin D supplementation not mentioned in the patient charts. Though the study showed association of 25(OH)D levels with lip biopsy, it would be desirable to look for correlation between 25(OH)D levels and focus scoring. Most of the associations seen in this study need to be interpreted with caution in view of small numbers and retrospective nature of the study especially when the results are contradictory to the expected notion. Large longitudinal studies are required to understand causality.

CONCLUSION

In conclusion, this study on Indian pSS patients found the prevalence of vitamin D deficiency to be comparable to that of general Indian population. Low vitamin D was associated with higher odds for RF positivity and higher grading in minor salivary gland histopathology. Surprisingly, low vitamin D was associated with lower ESSDAI score and seemed to protect against pulmonary involvement in our patients.

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