Section: Miscellaneous

Original Research Article

STUDY OF RELATIONSHIP OF SERUM VITAMIN D LEVELS WITH DISEASE ACTIVITY IN AXIAL SPONDYLOARTHRITIS

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ABSTRACT

Background: Several studies have demonstrated an association between vitamin D deficiency and increased risk of autoimmune diseases. In patients with Ankylosing Spondylitis few authors have noted an inverse relationship between serum 25-hydroxyvitamin D [25(OH)D] and disease activity. But these results are not consistent across all studies and some authors report no significant association between them. **Aim and Objectives:** Aim: To evaluate the relationship between 25(OH)D deficiency and disease activity in patients with axial spondyloarthritis (axSpA). Objectives: 1) To review and extract data from medical records of patients with axSpA, focusing on 25(OH)D levels and disease activity (ASDAS-CRP score). 2) To analyse the relationship between 25(OH)D levels and disease activity indices, identifying trends or significant associations.

Materials and Methods: This is a cross-sectional retrospective study based on the electronic medical records of our hospital. Serum 25(OH)D level and ASDAS-CRP score of axSpA patients documented during their visit in clinic were retrieved and statistical analysis was done.

Results: A total of 49 subjects with axSpA were included. 25(OH)D deficiency was associated with high disease activity (ASDAS-CRP $\geq$ 2.1) when compared to those with normal 25(OH)D levels ($p = .026$). Mean ASDAS-CRP was higher amongst individuals with 25(OH)D deficiency ($M = 2.27 \pm 0.60$) compared to individuals with normal 25(OH)D levels ($M = 1.77 \pm 0.50$), [$t(47) = 3.0174$, $p = .004$]. A weak negative correlation was noted between 25(OH)D level and disease activity ($r_s = -0.3265$, $p = 0.02$).

Conclusions: This study demonstrates 25(OH)D deficiency is associated with high disease activity in axSpA patients but there was weak negative correlation. Further prospective and interventional studies are needed to evaluate a potential causal relationship, as vitamin D supplementation may be a cost-effective adjunctive intervention to mitigate disease activity in axSpA.

Key-words: Ankylosing spondylitis; axial spondyloarthritis; serum 25-hydroxyvitamin D; vitamin D deficiency; ASDAS.

INTRODUCTION

Axial Spondyloarthritis (axSpA) is a chronic inflammatory systemic autoimmune disorder. The disease is characterized by bone formation and a simultaneous bone resorption process secondary to the effects of inflammatory cytokines released by immune cells.[1] Ankylosing Spondylitis serves as the hallmark condition within the axSpA spectrum.[2] Vitamin D is essential for maintaining bone health and also exhibits immunomodulatory effects. Numerous immune cells are capable of converting 25-hydroxyvitamin D [25(OH)D] into its active form, 1,25-dihydroxyvitamin D [1,25(OH)2D], which can suppress the activity of T-helper 17 (Th17) and Th1 cells while enhancing the functions of regulatory T-cells and Th2 cells.[3] Hitherto, several studies have demonstrated an

association between vitamin D deficiency and increased risk of some autoimmune diseases such as type I diabetes mellitus, systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA).[4] Similarly, it has been reported that Vitamin D deficiency is more common in Ankylosing Spondylitis patients than healthy controls.[5] For evaluation of the activity of axial spondyloarthritis: BASDAI (Bath Ankylosing Spondylitis Disease Activity Index) and ASDAS (Ankylosing Spondylitis Disease Activity Score) are the two main indices that are used. BASDAI depends entirely on patient self-assessment, while ASDAS also includes a parameter of inflammation such as erythrocyte sedimentation rate or C-reactive protein (CRP). As per recommendations of ASAS/EULAR (Assessment in Spondyloarthritis International Society/European Alliance of Associations for Rheumatology) 2022, ASDAS, especially ASDAS-CRP is the preferred tool for assessment of the activity of axSpA.[6] The ASAS group has established cut-off values (1.3, 2.1, and 3.5) to classify patients into 4 distinct disease activity states: inactive disease (ID; < 1.3), low disease activity (LDA; 1.3 ≤ ASDAS-CRP < 2.1), high disease activity (HDA; (2.1 ≤ ASDAS-CRP ≤ 3.5) and very high disease activity (VHDA; > 3.5).[7]

Many authors have studied the association of Vitamin D levels with disease activity in Ankylosing Spondylitis patients. ZHAO et al. found that increasing BASDAI, spinal pain visual analog scale, and C-reactive protein were each significantly associated with 25(OH)D deficiency.[8] Durmus et al. in a cross - sectional study found no significant difference in 25(OH)D3 levels between the Ankylosing Spondylitis patients and controls. However, pain, ESR, CRP and BASDAI scores were higher in the low 25(OH)D3 level subgroups and also inversely correlated to the 25(OH)D3 levels.[9] Hmamouchi et al. also noted a negative correlation between 25(OH)D level and BASDAI.[10] Lange et al. also reported serum levels of 1,25 vitamin D3 were negatively correlated with BASDAI.[11] But Mermerci et al. did not find a statistically significant negative correlation between 25(OH)D3 levels and disease activity in Ankylosing Spondylitis patients.[12] Arends et al. also noted no significant correlation between 25(OH)D levels and ESR, CRP, BASDAI and ASDAS.[13] Thus, conflicting results have been obtained from previously done studies and further studies need to be done to conclusively establish relationship between Vitamin D levels and disease activity in axSpA.[14,15]

Aim and objectives

Aim: To evaluate the relationship between 25(OH)D deficiency and disease activity in patients with axial spondyloarthritis (axSpA) by analysing previously collected clinical and laboratory data.

Objectives

1. To review and extract data from medical records of patients with axSpA, focusing on 25(OH)D levels and disease activity (ASDAS-CRP score).
2. To analyse the relationship between 25(OH)D levels and disease activity indices, identifying trends or significant associations.

MATERIALS AND METHODS

This is a cross-sectional retrospective study based on the electronic medical records of our hospital. All known or newly diagnosed Axial spondyloarthritis patients visiting Rheumatology Clinic at our hospital during the period from 1st March 2024 – 31st October 2024 were included in our study. All patients either had sacroiliitis on MRI and at least one SpA feature or HLA-B27 positive and had at least two Spondyloarthritis feature as defined by ASAS Classification Criteria for Axial Spondyloarthritis.[16] Vitamin D deficiency in our laboratory was defined as Serum 25(OH)D level below 10 ng/ml (Normal range: 10-50 ng/ml). Demographic details, Serum 25(OH)D levels, and ASDAS-CRP scores documented during their visit in clinic were retrieved from their records and statistical analysis was done. Fisher exact test and unpaired two tailed t-test were the statistical tests applied. Spearman's correlation coefficient, rs was calculated to demonstrate correlation between variables. Multivariate linear regression analysis was done to examine the relationship between Vitamin D level and age of patient with disease activity. Coefficient of regression (β) was calculated for both.

RESULTS

A total of 49 subjects were included in the study. The descriptive analysis of the gender distribution of the subjects are shown in Figure - 1.

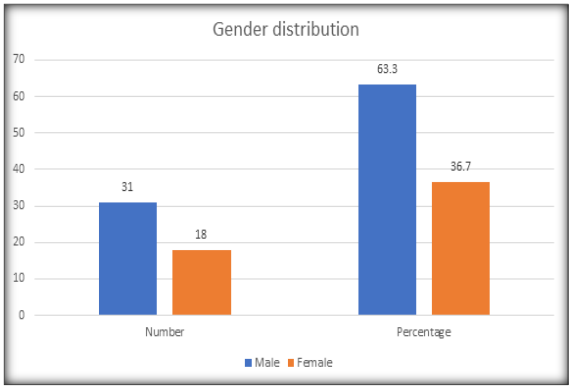

Figure 1: Gender distribution of all subjects

There were 31 males and 18 female subjects which constituted 63.3% and 36.7% of the cohort respectively. Mean age of subjects was 42.67 ± 13.66 years and disease duration since their diagnosis was 10.36 ± 8.02 years.

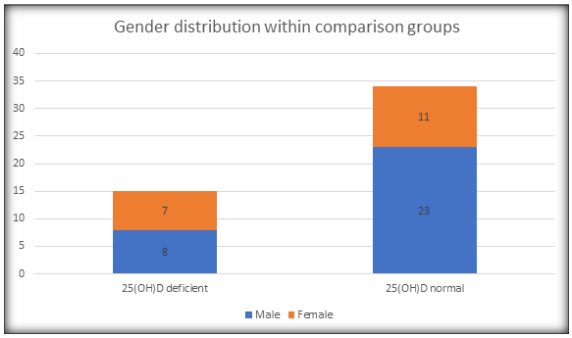

Figure 2: Gender distribution within comparison groups

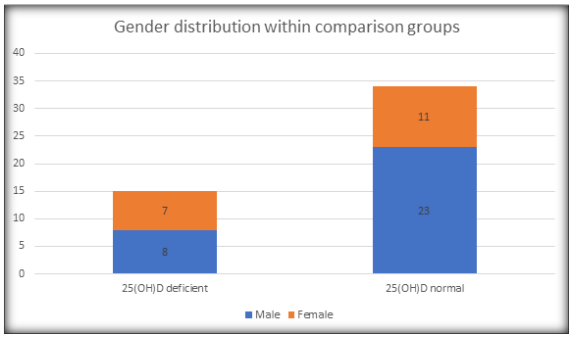

Figure 2: Gender distribution within comparison groups

Group with Vitamin D Deficiency: 15 subjects (8 males, 7 females), mean age = 36.73 ± 13.14 years. Group with Normal Vitamin D Levels: 34 subjects (23 males, 11 females), mean age = 45.29 ± 13.23 years. Statistically significant difference in age between the two groups [t (47) = 2.0909, p = .042], but no significant difference in gender distribution (p = .35).

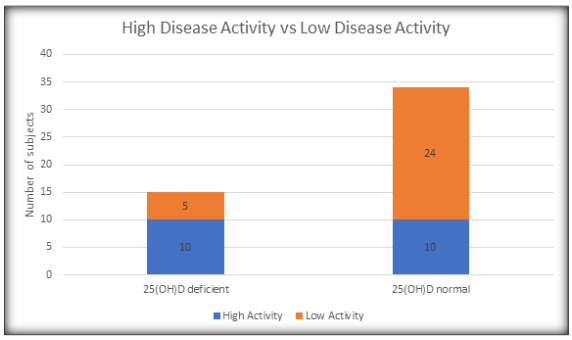

Figure 3: Disease Activity of subjects in comparison groups

In the Vitamin D deficiency group, ten subjects had high disease activity (ASDAS-CRP ≥ 2.1), and five subjects had low or inactive disease (ASDAS-CRP < 2.1). In the normal vitamin D group, ten subjects had high disease activity, and 24 subjects had low or inactive disease. Overall, 20 subjects in the entire cohort had high disease activity. Subjects with 25(OH)D deficiency had significantly higher disease activity compared to those with normal 25(OH)D levels (p = .026). Mean ASDAS-CRP score was higher in the deficiency group (2.27 ± 0.60) compared to the normal 25(OH)D group (1.77 ± 0.50) (p = .004). When compared to individuals with normal 25(OH)D levels, subjects with 25(OH)D deficiency were associated with high disease activity (p = .026). Also, mean ASDAS-CRP was higher in 25(OH)D deficient group (Mean = 2.27 ± 0.60) compared to group with normal 25(OH)D levels (Mean = 1.77 ± 0.50), [t (47) = 3.0174, p = .004]. However, only a weak negative correlation was noted between 25(OH)D levels and ASDAS-CRP score (Spearman's correlation coefficient, rs = -0.3265, p (2-tailed) = 0.02). Multivariate linear regression analysis was carried out for ASDAS-CRP score with 25(OH)D level and age of subjects as independent variable; the regression equation was noted to be:

ASDAS-CRP score = -0.01765 [25(OH) D level] + 0.00248 [Age] + 2.1141

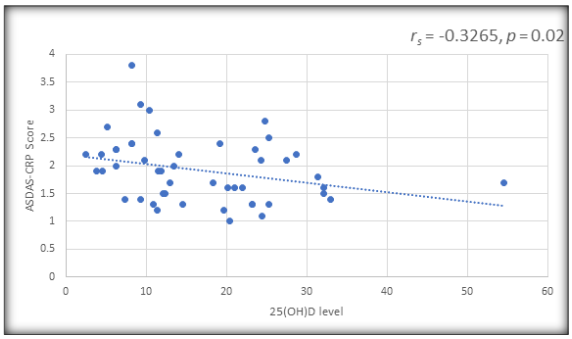

Figure 4: Scatter plot of ASDAS-CRP Score with 25(OH)D level

Mean 25(OH)D levels were compared between subjects with high disease activity (n=20, Mean = 13.87 ± 8.73 ng/ml) and those with either low disease activity or inactive disease (n=29, Mean = 18.72 ± 10.89 ng/ml). No statistically significant difference was noted in Mean 25(OH)D levels between the two groups [t (47) = 1.6542, p = .104].

DISCUSSIONS

Demographics

The study included 49 subjects (31 males and 18 females), with a gender distribution of 63.3% males and 36.7% females. Mean age of 42.67 ± 13.66 years with disease duration since diagnosis of 10.36 ± 8.02 years.

Previous Studies

First Author	Male	Female	Age (years)
Durmus [9]	84.8%	15.2%	36.8 ± 10.8
Hmamouchi [10]	100%	0%	40.0 ± 12.0
Lange [11]	65.5%	34.5%	38.4 (Standard Deviation not mentioned)
Mermerci [12]	75%	25%	39.9 ± 10.9
Arends [13]	93%	7%	41 ± 11.0
Ismail [17]	76.6%	23.4%	31.7 ± 9.1

Gender distribution in our study differed slightly from earlier studies, likely due to small sample size. Mean age of subjects in our study was slightly higher than previous studies due to longer disease duration.

Disease Activity

Subjects with 25(OH)D deficiency had significantly higher disease activity compared to those with normal 25(OH)D levels (p = .026). Mean ASDAS-CRP score was higher in the deficiency group (2.27 ± 0.60) compared to the normal 25(OH)D group (1.77 ± 0.50) (p = .004). ZHAO et al. found that increasing BASDAI, spinal pain visual analog scale, and C-reactive protein were each significantly associated with 25(OH)D deficiency.[8] This supports the findings in our study that vitamin D deficiency is associated with higher disease activity.

A weak negative correlation was found between 25(OH)D levels and ASDAS-CRP scores (rs = -0.3265, p = 0.02). Ismail M et al. in a case control study of 60 patients found significant inverse correlation between Vitamin D deficiency and disease activity; Vitamin D vs BASDAI (r = −0.57, p < 0.001), Vitamin D vs ASDAS (r =−0.37, p = 0.04).[17]

Previous studies	Coefficient of correlation Vitamin D vs. BASDAI
Durmus, 2012 [9]	-0.304
Hmamouchi, 2013 [10]	-0.32
Lange, 2005 [11]	-0.567

Mild inverse correlation between Vitamin D levels and disease activity was noted in all these studies just like ours. This suggests that vitamin D may modestly influence disease activity, but other factors, such as environmental factors, genetic predisposition, or medication use (e.g., TNF inhibitors), might play a more substantial role.

The multivariate linear regression equation for ASDAS-CRP score implied that for each 1 ng/ml increase in 25(OH)D level, the ASDAS-CRP score decreased by 0.01 (Coefficient of regression, β = -0.01765). The multivariate regression model in our study indicated that both age and Vitamin D had a small impact on disease activity, reiterating that other factors might contribute to disease activity more than vitamin D levels. This again implies a mild association between 25(OH)D levels and disease activity.

Mean 25(OH)D levels were compared between subjects with high disease activity (n = 20, mean = 13.87 ± 8.73 ng/ml) and those with low disease activity or inactive disease (n = 29, mean = 18.72 ± 10.89 ng/ml). No statistically significant difference was found between the two groups in terms of 25(OH)D levels (p = .104). Yagiz et al. (2015) observed no significant difference in Vitamin D levels among Ankylosing Spondylitis subjects in a subgroup with low versus high disease activity (p > .05).[18] This lack of a significant difference in vitamin D levels between patients with high disease activity and those with low or inactive disease (p = 0.104) is in keeping with our study findings. Absence of significant difference might be influenced by confounders such as – Age, BMI, physical activity, or dietary Vitamin D intake which were not adjusted. Small sample size in our study could have also limited the ability to detect subtle differences.

CONCLUSION

- Vitamin D deficiency is associated with higher disease activity in axSpA, but the correlation is weak in our study. This supports the hypothesis that while vitamin D deficiency may contribute to disease severity, but it is not the sole factor.
- Multifactorial Influence: The lack of a strong correlation in our study suggests that disease activity in axSpA may be influenced by a combination of factors, including genetic predisposition, inflammation, medication use, and lifestyle factors like physical activity or BMI.
- Future Research: Larger prospective studies and intervention trials (e.g., vitamin D supplementation) could help better define the role of vitamin D in managing disease activity in axSpA.

Conflict of Interest

The authors declare that they have no conflict of interest.

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