Correlation of serum vitamin D level, bone mineral density and disease activity in Axial spondyloarthritis

Jyoti Ranjan Parida, Amit Kumar, Chandan Das, Srikant Kumar Dhar and Jatindra Nath Mohanty

Abstract
Chronic inflammation is always linked with accelerated loss of bone mineral density and new bone formation in axial spondyloarthritis (AxSpA). Vitamin D is an endogenous modulators of the immune system which generally slow down the inflammatory process by reducing the activity of T cell along with its proliferation. Here in this study we focused on the relationship between these elements in axial spondyloarthritis. A total of 40 cases were registered during the study period. In this observational study, we included cases of Spondyloarthritides (Sp) who were all having axial spondyloarthritis (SpAx). Along with all clinical profiling of these patients we also included the different history of the patients like duration of disease, addiction (drugs and smoking), steroid medication. We analysed here the Bone Mineral Density (BMD) along with the investigations like HLA B27, BATH indices and Vitamin D levels. A total of 27 cases (67.5%) was found decreased bone mass. There was a significant positive correlation of T-score with vitamin D levels (p=0.57, p=0.0001), which indicates that low vitamin D in serum is associated with osteoporosis (low T score). The BATH indices (BASDAI & BASMI) exhibited no correlation with serum vitamin D levels. In conclusion, BMD was low in majority of patients with AxSpA. In our study we found that factors that are related with low BMD in male patients of AxSpA may be multifactorial but it seems that vitamin D major role in osteoporosis.

Keywords: Axial spondyloarthritis, vitamin D, osteoporosis, BMD

Introduction
In axial spondyloarthritis (AxSpA), chronic inflammation is related with loss of bone mineral density and new bone formation [1]. Despite the fact that there have been developments in understanding the role of inflammation on bone loss, subsequent abnormal bone remodeling in AxSpA remains inadequately comprehended. Vitamin D is not only significant for calcium homeostasis and bone strength, but also has immunomodulatory effects. Many immune cells can alter 25-hydroxyvitamin D [25(OH)D] to its active metabolite, 1,25-dihydroxyvitamin D [1,25(OH)2D], which has been shown to inhibit T-helper 17 (Th17) and Th1 cell activity, and promote regulatory T-cells and Th2 cells [2]. Axial spondyloarthritis is related with reduced serum 25(OH)D levels when compared with healthy controls [3]. On the other hand, it is not clear from previous studies whether 25(OH)D levels are associated with increased disease activity and functional impairment. This is in part due to inherent difficulties in studying serum levels, as ultraviolet B (UVB) generation of 25(OH)D follows seasonal variation [4].

Given the potential for vitamin D to impact both bone metabolism and the immune system, it is hypothesized that vitamin D may influence AxSpA disease activity. This study aims to assess the association of vitamin D deficiency with increased disease activity and functional impairment in axial spondyloarthritis (AxSpA).

Material and Methods
A total of 40 cases were registered during the study period. The study included cases of spondyloarthritides (Sp) who were all having axial spondyloarthritides (SpAx). Maximum numbers of cases were taken in the age group 25 – 30 years (13 cases, 32.5%). The clinical data were collected during routine out-patient assessments. Patient characteristics (age, sex, smoking status recorded as ever or never smoking and body mass index) were recorded at the time of assessment. In addition, disease variables were recorded including symptom duration,
duration since diagnosis, human leukocyte antigen B27 (HLA-B27) status if available, and extra-articular disease features. Current use of non-steroidal anti-inflammatory drugs, tumor necrosis factor inhibitors, and any vitamin D supplementation were also recorded. Disease activity and functional status were assessed using the bath Ankylosing spondylitis disease activity index (BASDAI), BASMI (Bath AS Metrology Index).

Statistical analysis
The statistical analysis used SPSS® (Statistical Package for the Social Sciences, version 21) software. The descriptive statistics of categorical variables are presented as frequencies and continuous variables as mean and standard deviation. This result was also observed during correlation analysis, as seen using the scatter plots of t-scores with indices. Vitamin D deficient patients were compared with non-deficient patients using Student’s t-test for Gaussian, Mann-Whitney U for non-Gaussian, and chi-squared test for categorical variables.

Result
A total of 40 cases were registered during the study period. The study included cases of Spondyloarthritis (Sp) who were all having axial spondyloarthritis (SpAx). Mean age of the study participants was 30.7 years with a standard deviation of 7.0 years (range 20 – 45 years). Maximum number of cases were in the age group 25–30 years (13 cases, 32.5%). Mean duration of disease among the study subjects was found to be 51.6 months with a standard deviation of 50.3 months. Median duration of disease was however found to be less (36 months). Duration of disease was further classified into groups with duration less than a year, one to five years and more than five years so as to understand the chronicity of SpAx (Table 1).

Table 1: Disease duration of study subjects (in months) (n=40)

<table>
<thead>
<tr>
<th>Disease duration</th>
<th>Numbers</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1 year</td>
<td>13</td>
<td>32.5</td>
</tr>
<tr>
<td>1 – 5 years</td>
<td>16</td>
<td>40.0</td>
</tr>
<tr>
<td>&gt;5 years</td>
<td>11</td>
<td>27.5</td>
</tr>
</tbody>
</table>

It was seen that majority of the study subjects (34 cases, 85%) were found to be HLA B27 positive. There was no association of HLA B27 with osteoporosis in these subjects (Chi-square 3.11, p=0.078).

It was seen that BASDAI score ranged from a minimum of 2.4 to a maximum of 7.2. Mean BASDAI score among the study subjects was 4.97 with a standard deviation of 1.85. Maximum number of study subjects (Mode) had a BASDAI score between 4 – 5 (20 cases, 50%) (Fig 1).

BASMI score was ranged from a minimum of 1.6 to a maximum of 9. Mean BASMI score among the study subjects was 4.73 with a standard deviation of 1.98. Maximum number of study (Mode) subjects had a BASMI score between 4 – 5 (10 cases, 25%).

Mean t-scores of right femur, left femur and lumbar vertebra were analysed. It was seen that lumbar spine had less mean t-scores (-1.2±1.8) as compared to that at right or left femur (0.17±1.4, 0.03±1.7 respectively) (Table 2).

Table 2: Bone mineral density levels at various sites among study subjects (n=40)

<table>
<thead>
<tr>
<th>Bone</th>
<th>Mean t-score</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lumbar</td>
<td>-1.203</td>
<td>1.852</td>
</tr>
<tr>
<td>Right femur</td>
<td>0.173</td>
<td>1.437</td>
</tr>
<tr>
<td>Left femur</td>
<td>0.033</td>
<td>1.679</td>
</tr>
</tbody>
</table>

There was no case found having a bone mass in the category of osteoporosis in the right or left femur. There were around 9 cases (22.5%) having osteopenia in the right femur and 20 cases (50%) having osteopenia in the left femur. Osteoporotic bone mass was noted in 35% of the study subject in lumbar area (14 study subjects) (Fig-2). Osteopenia was also seen in 30% of these cases and rest 35% were having normal bone mass in lumbar spine. Thus, probably lumbar spine bone loss is more prevalent than both femur bone loss among SpAx cases.
There was a significant difference in the t-scores among those who were having history of addiction to alcohol than those who were not (p=0.019, Mann Whitney U test). Other factors like smoking and steroid history were found not to have any significant association in this study most probably due to small sample size. There was a significant positive correlation of t-score (lowest value used to define osteoporosis) with vitamin D levels in the body of SpAx cases (Spearman rank correlation ρ = 0.57, p = 0.0001). This means that with increase in vitamin D levels there is an increase in t-score. Individual correlations revealed that the correlation was more positive with lumbar spine (ρ = 0.56, p = 0.000) than with right and left femur (Table 3). We have not found any correlation between serum Vitamin D levels and BATH indices (BASDAI & BASMI).

Table 3: Correlation of BMD levels (femur and lumbar spine) with Vitamin D levels (n=40)

<table>
<thead>
<tr>
<th>Sl</th>
<th>T-score</th>
<th>Rho</th>
<th>Sig (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Right femur</td>
<td>0.37</td>
<td>0.019</td>
</tr>
<tr>
<td>2.</td>
<td>Left femur</td>
<td>0.47</td>
<td>0.002</td>
</tr>
<tr>
<td>3.</td>
<td>Lumbar</td>
<td>0.56</td>
<td>0.000</td>
</tr>
<tr>
<td>4.</td>
<td>Overall</td>
<td>0.57</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

There was a linear correlation of t-scores with BASDAI ($R^2 = 0.0002$). This means that with increase in disease activity there is no change in t-score.
There was no correlation seen between t-scores and BASMI ($\rho = 0.09$, $p = 0.59$)

**BATH indices and Vitamin D levels**

There was no correlation seen between t-scores and BASMI ($\rho = 0.09$, $p = 0.59$) and BATH indices and Vitamin D levels.

**Disease duration and osteoporosis among study subjects**

Duration of disease was compared among cases having osteoporosis and those not having, and it was seen that there was no difference between these two groups ($p = 0.853$). Thus, disease duration might not be a factor in causing osteoporosis in these cases of SpA.

**Discussion**

Mean duration of disease among the study subjects was found to be 51.6 months. Contrary to the finding by Stephan et al. and Mitra et al. [5] that BMD loss was directly proportional to the disease duration of AS, our study did not show any such significant correlation. A possible explanation to this finding is that in most of the cases the disease duration was too short (only about 4-6 years) and requires long term follow up. Osteoporosis was found to be present in 14 cases (35% of the study subjects) and osteopenia was present in 13 subjects (32.5%). Thus, a total of 27 cases (67.5%) had decreased bone mass. This finding of decrease in BMD in patients of AS is consistent with the previous studies done by Mullaji et al. [6], Upadhay et al. [7], Ayla Layan et al. [8].

The most important gene associated with ankylosing spondylitis is HLAB27. It is present in more than 90% of patients [14] number association was found between osteoporosis and HLA B27 positively in this study (Chi-square 3.11, $p=0.078$). 85% of our study group are HLA B27 positive.

There was a significant difference in the t-scores among those who were having history of addiction to alcohol than those were not ($p=0.019$, Mann Whitney U test). Other factors like smoking were found not to have any significant association in this study which may be due to low sample size. Severity of lumbar vertebra getting affected by AxSpA was more as compared to femur, as revealed by the mean T-scores. Lumbar spine had less mean t-scores (-1.2±1.8) as compared to that at right or left femur (0.17±1.4, 0.03±1.7 respectively). This contrasts with the study done by Capacie et al, Singh et al. and Will et al. [6, 9, 10] where femoral measurements exhibited grater severity than lumbar. It is known that trabecular bone loss is more prominent than cortical bone loss in osteoporosis [11]. Therefore, it is expected that BMD might be lower in the lumbar region which is of trabecular bone when compared to the femoral area.

There was a significant positive correlation of T-score with vitamin D levels ($p=0.57$, $p=0.0001$), which indicates that low vitamin D in serum is associated with osteoporosis (low T score). Lumbar spine ($p=0.56$, $p=0.000$) was found to have better association with vitamin D levels than the T score of both femur (right and left) (Table 3). The mean vitamin D levels were found to be more in cases without osteoporosis which is consistent with lange et al, who found that as patients with osteoporosis had significantly lower vitamin D levels. Amento et al. reported...
that vitamin D is an endogenous modulator of the immune response, which may slow down the inflammatory process by suppressing active T cells and cell proliferation [12]. In this study the BATH indices (BASDAI & BASMI) exhibited no correlation with serum vitamin D levels (Fig 6-8) which is not consistent with Mermersl at al. [13], who showed negative correlation between serum vitamin D level and disease activity but did not reach a statistically significant level. Since these BATH indices measurements, vitamin D estimation and other parameters are done at a single point of time without any follow up, the results hence may differ from other studies. So it would be beneficial to monitor vitamin D level together with BMD and disease activity to further investigate the risk of osteoporosis.

Conclusion
Our study failed to find any correlation between serum Vitamin D level & disease activity of patients having AxSpA. Our study has two important limitations. The sample size was very low and it is a cross sectional study. This cross sectional study in AxSpA patients indicates that bone loss occurs in AxSpA and is multi-factorial in nature. There is a possible role for vitamin D supplements as prophylactic and therapeutic measure in the prevention of osteoporosis in AxSpA. But a longitudinal follow up study with more sample size will be require to explore the relationship between vitamin D deficiency and disease activity in these patients. Combining biochemical bone turn over markers and BMD measurements may be useful to identify AxSpA patients with osteoporosis. In daily clinical practice lumbar spine BMD, measured by DXA may be better way to estimate the bone loss in patients with AxSpA.

References