Correlation between Various Factors Influencing the Bone Health in Young Patients with Active Ankylosing Spondylitis

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ABSTRACT

Introduction: Ankylosing spondylitis (AS) is a chronic inflammatory disease that primarily affects the axial skeleton. The objective of the study was to elucidate the relation between bone mineral density (BMD), bone turnover markers (BTMs), and vitamin D in a cross-sectional cohort of Ankylosing Spondylitis (AS) patients with active disease.

Material and Methods: This cross-section study was conducted from Oct 2016 – Jul 2019 enrolling 60 adult Indian males with active AS (satisfying the ESSG and New York criteria), with a minimum disease duration of 05yrs, along with equal number of age and sex matched controls at a tertiary care hospital. BTMs {serum N-terminal peptide of type I collagen (sNTX), osteocalcin (OC), serum C-telopeptides of type I collagen (sCTX)}, vitamin D levels and BMD {by DEXA at lumbar spine (LS)/ femoral neck (FN)} were assessed for all the patients and controls. Statistics analytical tests and Pearson's and Spearman's correlation coefficients were used as appropriate to analyze the relationship between 2 continuous variables like BMD, BTM, vitamin D, and clinical measures of disease activity and physical function.

Results: The mean age (±SD) for cases was 38.4 ±9.6 years and that for controls was 39.8 ±11.40 years. There was a definite decrease in Vit D levels in the cases group when compared to controls (p=0.007). The markers of disease inflammation (OS) and the markers of bone resorption (CTx and NTx) were significantly raised in cases of AS as compared to controls. BMD was significantly lower in active AS cases compared to the controls.

Conclusion: Bone loss definitely occurs in AS and many factors independently influence this. Many factors like increased bone turnover, lack of exercise, inflammation, and low vitamin D levels are important in the pathophysiology of AS-related osteoporosis.

Keywords: Ankylosing Spondylitis, Bone Mineral Density, Bone Turnover Markers, Osteocalcin, Vit D

INTRODUCTION

Ankylosing spondylitis is characterized by new bone formation, which leads to the formation of syndesmophytes and ankylosis of the spine and sacroiliac joints.[1]

Osteoporosis is also a well-recognized complication of AS and is already observed in early stages of the disease. Early vertebral bone loss can be accompanied by severe complications. Previous studies have shown that, in contrast to non-vertebral fractures, the risk of clinical vertebral fractures is increased in AS patients and that vertebral fractures are frequently present in AS.[2,3]

Knowledge about the pathophysiology of AS related osteoporosis is limited. Various studies have shown involvement of inflammatory processes in the complex pathophysiological mechanism of AS-related osteoporosis.[4,5] Furthermore, various other factors such as drug intake and decreased mobility in relation to pain and stiffness may contribute to the development of osteoporosis in AS patients.[6] In addition, recent studies in AS have suggested that alterations in vitamin D (Vit-D) metabolism are associated with inflammatory activity and bone mineral density (BMD).[7,8] Non-invasive assessment of biochemical bone turnover markers (BTM) and quantitative ultrasound may provide more information about the pathophysiology of osteoporosis.[9,10] So far, conflicting data have been published about the relation between BTM, BMD, and disease activity in AS.[11,12] The objective of the study was to elucidate the relation between BMD, bone turnover markers (BTM), and vitamin D in a cross-sectional cohort of AS patients with active disease.

MATERIAL AND METHODS

Patients were included from the Rheumatology/ Medical OPD and inpatients of a tertiary care hospital. An equal number of controls were enrolled. Controls comprised of asymptomatic individuals, either relatives of the patients or healthy volunteers. The controls were matched in age and sex. The study was conducted from Oct 2016 – Jul 2019. 60 adult Indian males with active AS (satisfying the ESSG and New York criteria), with a minimum disease duration of 05yrs, were included in this study. Females, overlap syndromes, patients aged < 21 (i.e onset < 16 years, juvenile AS) and above 60 years (age related loss of BMD very significant) were excluded from the study. Sample size was calculated using the parameters such as normal BMD in lumbar spine being 0.965 g/cm^2, to detect a difference of 5% in BMD in both groups with an alpha value of 0.05, power of 80%, standard deviation (homodiastetic) of patients and controls being 0.10 (estimated). Sample size thus required was 58 in each group. BTMs {serum N-terminal peptide of type I

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collagen (sNTX), osteocalcin (OC), serum C-telopeptides of type I collagen (sCTX)}, vitamin D levels and BMD {by DEXA at lumbar spine (LS)/ femoral neck (FN)} were assessed for all the patients and controls. The study was approved by the institutional ethical committee.

Descriptive statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean ± SD (Min-Max) and results on categorical measurements are presented in Number (%). Significance is assessed at 5% level of significance. Student T test (two tailed, independent) has been used to find the significance of study parameters on continuous scale between the 2 groups. Chi-square has been used to find significance of parameters on categorical scale between two groups. Pearson's and Spearman's correlation coefficients were used as appropriate to analyze the relationship between 2 continuous variables like BMD, BTM, vitamin D, and clinical measures of disease activity and physical function. p values≤0.05 were considered statistically significant. The Statistical softwares SPSS 17.0 and PEPI were used for the analysis of the data and Microsoft Excel have been used to generate graphs, tables etc.

RESULTS

The mean age (±SD) for cases was 38.4 ±9.6 years and that for controls was 39.8 ±11.40 years. The youngest patient was 21yrs of age while the eldest was 60 yrs old. The mean duration of disease in our patients was 4.8+yrs. Almost 2/3rd of patients (38/60, 63.3%) had disease duration in the 3-5 yrs group. Only 2 patients had disease duration of more than 8 yrs (3.33%). Of the 60 patients of AS 24(40%) had peripheral arthritis whereas the remaining 36(60%) had only axial skeleton involvement. Most of these patients were subjected to medications in the form of DMARDs, NSAIDs, etc. They amounted to 48 out of the 60 cases (80%). The remaining 12(20%) were only on exercise and did not require regular medicines. Out of the medication seeking group 18 received a combination of SZA and HCQ, 24 received either MTX with HCQ or MTX alone, and the remaining received various forms of NSAIDs. The mean duration from disease onset to DMARD initiation was 2.5±0.4yrs. The mean values of BASMI, BASDAI and BASFI for the patients were 7.0, 6.8 and 6.5

The mean value of Vit D in patients with AS was 24.54±13.6ng/ml while it was 34.96±26.01ng/ml in the

Parameter	Patient (60)		Control (60)		P value
	Mean	SD	Mean	SD	
Vit D	24.54	13.6	34.96	26.01	0.007

Table-1: Comparison of Vit D values in cases and control

Parameter	Patient (60)		Control (60)		P value
	Mean	SD	Mean	SD	
Osteocalcin	13.25	4.32	7.06	5.05	0.000

Table-2: Comparison of Osteocalcin values in cases and control

Parameter	Patient (60)		Control (60)		P value
	Mean	SD	Mean	SD	
CTX	0.492	0.27	0.25	0.13	0.000

Table-3: Comparison of CTX values in cases and control

Parameter	Patient (60)		Control (60)		P value
	Mean	SD	Mean	SD	
NTX	24.95	9.3	12.4	6.07	0.000

Table-4: Comparison of NTX values in cases and control

Parameter	Patient (60)		Control (60)		P value
	Mean	SD	Mean	SD	
Age	38.4	9.6	39.8	11.4	0.47
Dexa LS	1.029	0.132	1.151	0.098	0.000
Dexa FN	0.9159	0.109	1.043	0.113	0.000
Vit D	24.54	13.6	34.96	26.01	0.007
Osteocalcin	13.25	4.32	7.06	5.05	0.000
CTX	0.492	0.27	0.25	0.13	0.000
NTX	24.95	9.3	12.4	6.07	0.000

Table-5: Comparison of variables among the cases and control group

Parameter	Correlation coefficient	P value
osteocalcin	-0.299	0.022
CTX	-0.259	0.048
NTX	0.237	0.070

Table-6: BMD dxa ls and BTM

Parameter	Correlation coefficient	P value
osteocalcin	-.075	.573
CTX	-.121	.363
NTX	0.466	3.98

Table-7: BMD dxa fn and BTM

		Vit D	CTX
Vit D	Pearson Correlation	1	-.260*
	Sig. (2-tailed)		.047
	Sum of Squares and Cross-products	10785.080	-55.758
	Covariance	185.950	-.961
	N	59	59
CTX	Pearson Correlation	-.260*	1
	Sig. (2-tailed)	.047	
	Sum of Squares and Cross-products	-55.758	4.280
	Covariance	-.961	.074
	N	59	59

Table-8: Correlation between Vit D and CTX

controls. There was a definite decrease in Vit D levels in the case group when compared to controls (p=0.007) (table-1).
Patients with AS had a mean value of osteocalcin of 13.25±4.32 ng/dL, while the control group had a value of 7.06 ±5.05 ng/dL. The inflammatory activity of AS was attributable to the rise in osteocalcin levels while it was significantly (p=0.000) low in the controls (table-2).
The bone resorption marker, Ctx, was 0.492± 0.27ng/ml in patients of AS and it was 0.25±0.13ng/ml in the controls. Corroborating with the fact that bone resorption markers are increased in AS, Ctx values were significantly raised in cases as compared to controls (p=0.000) (table-3).
The bone resorption marker, Ntx, was 24.95± 9.3ng/ml in patients of AS and it was 12.4±6.07ng/ml in the controls. Corroborating with the fact that bone resorption markers are increased in AS, Ntx values were significantly raised in cases as compared to controls (p=0.000) (table-4).

Analysis between patients and controls

With application of the T test for comparison of the various under mentioned parameters between cases and controls we found that there was a significant correlation of each of these in the disease group as compared to the controls (table-5).
Correlations between BMD, BTM, vitamin D, and clinical assessments of disease activity and physical function were calculated to obtain more knowledge about the pathophysiology of AS-related osteoporosis.

Bone turnover markers

There was a difference in the correlation between BTM and BMD at lumbar spine and femoral neck. BMD at lumbar spine had a significant correlation with osteocalcin (p= 0.022) and CTX (p=0.048), while it did not correlate with NTX (p=0.070).
BMD at the femoral neck did not have any significant correlation with any of the studied BTM (table-6,7).
Among the AS patients 64.44% had osteoporosis and 20% had osteopenia. Our assessment till now revealed that many factors relate with low BMD. They were different at LS and FN. In bivariable analysis these were low Vit D, bone turnover markers and lack of exercise**.** On multivariable regression analysis, only hypovitaminosis D was found to be associated with low BMD at FN. However, none of the factors were associated with low BMD at LS.
By applying the Pearson Correlation, we found that Vit D and sCTX had a modest negative correlation, meaning that hypovitaminosis D leads to higher bone turnover(p=0.047). However, VitD and both Osteocalcin and NTX had a poor correlation (table-8).

DISCUSSION

The objective of the study was to elucidate the relation between BMD, bone turnover markers (BTMs), and vitamin D in a cross-sectional cohort of AS patients with active disease. In addition, we have tried to study the various factors involved in the pathogenesis of osteoporosis in AS and their effects on each other. Femoral measurements exhibited greater severity of reduced BMD than lumbar spine values consistent with previous findings.[3,5] It is well known that trabecular bone loss is more prominent than cortical bone loss in osteoporosis.[13] Therefore, it is expected that BMD might be lower in the lumbar region which is rich of trabecular bone when compared to the femoral area. But we found lower BMD values for the femoral region. This discrepancy might be due to new bone formation in lumbar spine area such as syndesmophytes, inter-apophyseal joint and interpedicular ankylosis rather than differences in bone remodeling between these two sites.[4,6]
Serum Vitamin D levels had a significant negative correlation with disease activity (BASDAI other Bath indices) and bone turnover markers. AS patients with osteoporosis had significantly lower vitamin D levels compared to AS patients with normal BMD (p=0.0001). Our finding that 25OH-vitD level had an independent significant inverse influence on sCTX and Z-score (p=0.047) suggests that low vitamin D levels play a role in the development of AS-related osteoporosis. The importance of vitamin D

was also suggested in previous studies.[7] 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.[14,15]

Vit D supplementation may be useful in improving bone strength and needs further evaluation. Lange et al. found negative correlations between serum levels of vitamin D and markers of disease activity or inflammation in AS patients.[8] They also showed that AS patients with osteoporosis had significantly lower vitamin D levels compared to AS patients with normal BMD.

We found that bone turnover markers (sCTX and OC) and Z-scores are independently related to low BMD in the lumbar spine in patients with AS. Significant negative correlations were found between sCTX or OC and Z-scores and LS BMD T-score, and a higher sCTX or OC, Z-score was independently related to low BMD. These findings suggest that that sCTX and OC, Z-scores are valuable markers to detect bone loss in AS and that high bone turnover is associated with bone loss in AS. This finding is in agreement with the previous studies by S Arends and Spoonrenberg et al.[8,9] Ankylosing Spondylitis is characterized by both increased bone formation and increased bone resorption.[16] Since the anterior-posterior lumbar spine BMD measured by DXA can be overestimated by the presence of syndesmophytes, ligament calcifications, and fusion of facet joints, an accurate and easily accessible marker of bone loss is needed in patients with advanced AS. The role of these bone turnover markers hence becomes significant.

To summarize the finding in this study, BMD was low in patients with AS compared to controls. In bivariate analysis in our study, we found that factors that related with low BMD in male patients of AS were low Vit D, bone turnover markers and lack of exercise. Also, they were different for BMD of LS and FN. On further analysis using linear regression method between these three variables, we found that only in BMD FN were they significant.

CONCLUSION

In conclusion, this cross-sectional study in AS patients definitely indicates that bone loss occurs in AS and many factors independently influence this. It also indicates that increased bone turnover, lack of exercise, inflammation, and low vitamin D levels are important in the pathophysiology of AS-related osteoporosis. Furthermore, sCTX and OC Z-scores seem to be valuable markers to detect bone loss in AS. Combining biochemical BTM and BMD measurements may be useful to identify AS patients with osteoporosis in daily clinical practice whereas lumbar spine BMD measured by DXA, may be overestimated due to osteoproliferation in patients with advanced AS

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