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Assessment of Fracture Risk and its Predictors in Patients with Axial Spondyloarthritis using the Fracture Risk Assessment (FRAX) Algorithm

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Abstract

Background: Ankylosing spondylitis (AS) is a chronic inflammatory disease primarily affecting the axial skeleton. Increased prevalence of low bone mineral density in patients with AS has been reported by studies but data on fracture risk in these patients is scarce. The present study was undertaken to find the risk of fracture and predictors of fracture risk in patients with Axial spondyloarthritis (AxSpA) using FRAX algorithm.

Methods: 40 consecutive adult patients with AxSpA attending the Rheumatology clinic of our Institute were included in this cross-sectional observational study. Bone Mineral Density (BMD) was measured at femur neck, lumbar spine and forearm, and T-scores were taken. FRAX score was calculated using FRAX calculator for Indian cohort and results showed 10-year probability of major osteoporotic and hip fractures in percentage.

Results: Out of total 40 patients, 34 (85%) were males, and 6 (15%) were females with a mean age of 34.98 ± 9.29 years and a mean disease duration of 5.14 ± 4.47 years. Osteoporosis was found in 17 patients (42.5%) at lumbar spine, 10 (25%) at forearm, and 6 (15%) at femur. Overall prevalence of OP in the study population was 55%. The mean FRAX score for major osteoporotic fracture was 1.53 ± 1.04% and for hip fracture 0.54 ± 0.82%. On multivariate analysis, femur BMD showed independent association with risk of major osteoporotic fracture; while age, BASDAI and femur BMD with the risk of hip fracture.

Conclusion: Prevalence of osteoporosis was high in AxSpA patients. Though a trend of higher FRAX score was seen with loss of BMD, its absolute values did not exceed prescribed cut-off for intervention. The independent predictors for the risk of fracture in AxSpA patients were age, BASDAI and low BMD at femur neck.

Key words: Axial spondyloarthritis, ankylosing spondylitis, osteoporosis, FRAX.

Introduction

Axial spondyloarthritis (AxSpA) is an immune-mediated chronic inflammatory arthritis predominantly involving the spine and/or the sacro-iliac joints. It shows a strong association with HLA B-27 and mainly affects young males. AxSpA include ankylosing spondylitis (AS) and non-radiographic spondyloarthritis depending on the presence or absence of radiographic sacro-iliitis. The hallmark of AS is syndesmophytes formation and ankylosis of spine and sacroiliac joint leading to pain and severe disability.

Increased prevalence of low bone mineral density (BMD) in patients with AxSpA has been reported in studies with a reported prevalence ranging from 19% to 62% for osteoporosis (OP) in AxSpA[1,2]. The pathogenesis of OP in AS is, perhaps, multifactorial involving different mechanisms at different stages of disease[3]. Risk of radiographic or clinical vertebral fracture is increased in AS even in early disease[4,5]. Literature about the risk of fracture is limited but suggests increased prevalence of vertebral fracture in AS with loss of BMD. The prevalence of vertebral fracture is 0 - 20% in various studies; however, most of them remain unrecognised[6].

DEXA is a cost-effective, easily available test with low radiation, rapid scan time, and reproducible results[7] and has become the gold standard in clinical practice to assess BMD in different patient populations including AS. FRAX is a web-based algorithm (www.shef.ac.uk/FRAX) designed to calculate the 10-year probability of major osteoporosis related fractures and hip fracture in men and women based on easily obtained clinical risk factors and bone mineral density[8]. Though, FRAX tool has been used for fracture risk assessment in Rheumatoid arthritis (RA) patients by some authors, such data in AxSpA is scarce.

The present study was done to assess the risk of fracture and to determine its predictors in AxSpA patients using FRAX algorithm.

Material and methods

40 consecutive patients aged > 18 years and diagnosed

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with AxSpA as per ASAS criteria[9], attending the Rheumatology clinic of our institute were included in this cross-sectional observational study. Patients with chronic liver or renal disease, hypogonadism, or those taking treatment for osteoporosis were excluded.

Detailed history regarding inflammatory back pain (IBP), joint pain, extra-articular symptoms, and treatment were obtained. History of fracture in self or parents was taken. Detailed musculoskeletal examination was done and disease-specific measures like Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI) and Bath Ankylosing Spondylitis Metrology Index (BASMI) were estimated. HLA B-27, ESR, haemogram, liver and kidney function tests, and X-rays of pelvis, spine and peripheral joints, as indicated, were done. BMD was measured by densitometer (HOLOGIC, INC. 35 CROSBY DRIVES BEDFORD, Model ASY-00409) at 3 sites: left femur neck, lumbar spine (L_1 to L_4) and non-dominant forearm; and values of T-score were obtained.

As per WHO criteria, BMD was classified on the basis of T-score of femur neck/lumbar spine/forearm as below:-

Osteoporosis	:	T-score < -2.5
Osteopenia	:	T-score < -1 and > -2.5
Normal bone density	:	T-score > -1

The FRAX scores were calculated using FRAX calculator for Indian cohort. The results were obtained in % as 10-year probability of major osteoporotic fracture or hip fracture. The WHO task force has identified eight individual risk factors for fracture (entered in a questionnaire form in FRAX calculator), independent of BMD and they have added country-specific fracture incidence rate for each country to these risk factors to give a 10-year probability of fracture. According to the National Osteoporosis Foundation (NOF) recommendation, 10-year probability of major osteoporotic fracture > 20% and hip fracture > 3% is considered to be significant for intervention[10,11].

Results

Out of 40 patients, 34 (85%) were males and 6 (15%) were females with a mean age of 34.98 ± 9.29 years and disease duration of 5.14 ± 4.47 years. The Mean BMD of femur, lumbar spine and forearm were -1.5 ± 0.82 gm/cm^2, -2.2 ± 1.23 gm/cm^2 and -1.99 ± 1.19 gm/cm^2 respectively. The mean BMD of lumbar spine was the lowest among the three sites, followed by forearm and femur. BMD of femur was normal in 9 (22.5%), whereas osteopenia in 25 (62.5%) and osteoporosis in 6 (15%) patients was seen. Lumbar spine showed osteoporosis in 17 (42.5%) patients, osteopenia in 14 (35%) patients, and normal BMD in 9 (22.5%) patients. DEXA scan of forearm showed osteopenia in 23 (57.5%) patients, osteoporosis in 10 (25%) patients while BMD was normal in 7 (17.5%) patients. Thus, osteoporosis was seen in 42.5% for spine, 25% for forearm and 15% for femur. Overall, the prevalence of osteoporosis in our study was 55% (22 out of 40 patients had osteoporosis at least at one site). The mean of FRAX score for major osteoporotic fracture was 1.53±1.04 % (0.8 - 6.3 %). The FRAX for hip fracture was 0.54 ± 0.82% (0 - 4%). We found only one patient with a ten- year hip fracture risk of > 3% and no patient had a ten-year risk of a major osteoporosis-related fracture of > 20%.

Table I: Patient characteristics between the groups on the basis of BMD T-score/

Patient characteristics	Normal BMD (N = 9)	Osteopenia (N = 25)	Osteoporosis (N = 6)	P - value
Age (years)	37 ± 9.8	32.32 ± 7.99	43 ± 9.7	0.027
*Sex (male)	7 (78%)	23 (92%)	4 (67%)	0.233
Disease duration (years)	2.92 ± 2.78	4.94 ± 4.07	9.33 ± 5.85	0.019
Height (cm)	163.11 ± 5.75	165.76 ± 7.01	161 ± 4.65	0.225
Weight (kg)	64.11 ± 13.11	61.16 ± 11.49	56.83 ± 7.94	0.49
BMI (kg/m^2)	24.42 ± 4.2	22.75 ± 2.87	22.02 ± 3.31	0.313
Chest expansion (cm)	4.12 ± 0.88	4.25 ± 0.91	3.63 ± 0.51	0.298
*Uveitis	2 (22%)	3 (12%)	0	0.440
*Current smoker	1 (11%)	6 (24%)	1 (17%)	0.692
BASDAI	3.57 ± 1.68	3.67 ± 1.28	4.72 ± 1.86	0.262
BASFI	3.28 ± 1.3	3.48 ± 1.32	4.23 ± 0.95	0.341
BASMI	2.73 ± 1.91	3.14 ± 1.87	4.5 ± 1.44	0.177
ESR (mm/hr)	21.22 ± 11.32	25.56 ± 9.44	34 ± 6.2	0.049
FRAX score for Major osteoporotic fracture	0.97 ± 0.16	1.29 ± 0.23	3.45 ± 1.73	< 0.001
FRAX score for hip fracture	0.1 ± 0.09	0.3 ± 0.19	2.03 ± 1.29	< 0.001

*Continuous variables have been presented as mean ± SD. *Categorical variables have been presented as numbers with percentages in brackets.*

Patient characteristics were compared after dividing them into 3 groups based on the BMD T-score of femur. Age, disease duration, ESR as well as FRAX score for major osteoporotic and hip fractures were higher in patients with osteoporosis (P value < 0.05). However, sex, anthropometric measurements, BASDAI, BASFI, BASMI, uveitis, and smoking status were comparable between the groups.

Univariate regression analysis was done for FRAX score with different variables to determine the factors associated with fracture risk in these patients. It was found that higher age, disease duration, BASDAI, BASFI, BASMI and lower femur BMD were associated with risk of major osteoporotic fracture or hip fracture. High ESR was associated with risk of

hip fracture only. These factors were then included for Multivariate regression analysis to determine the independent risk factors for major osteoporotic fracture or hip fracture.

Table II: Univariate analysis of FRAX score for major osteoporotic fracture and hip fracture.

	Major osteoporotic fracture		Hip fracture	
	Standardised Beta-co-efficients	P value	Standardised Beta-co-efficients	P value
Age (yrs)	.422	.007	.412	.008
Male gender	-.153	.347	-.115	.479
Disease duration (yrs)	.501	.001	.469	.002
Body mass index				
Normal				
Underweight	.124	.446	.161	.322
Overweight	-.151	.351	-.154	.341
Obese	-.086	.596	-.089	.584
Weight (kg)	-.051	.753	-.046	.780
Height (cm)	-.095	.558	-.083	.613
Chest expansion (cm)	-.289	.071	-.276	.085
Uveitis	-.197	.223	-.175	.280
Current smoker	.071	.662	.117	.474
BASDAI	.361	.022	.398	.011
BASFI	.332	.036	.330	.037
BASMI	.428	.006	.423	.007
ESR (mm/hr)	.311	.051	.318	.045
Femur BMD (gm/cm^2)	-.755	<.001	-.748	<.001
Lumbar-spine BMD (gm/cm^2)	-.213	.187	-.243	.132
Forearm BMD (gm/cm^2)	-.284	.076	-.276	.085

Table III: Multivariate linear regression for FRAX score for major osteoporotic fracture.

	Beta	P - value
Age (yrs)	.246	.055
Duration (yrs)	.078	.549
BASDAI	.249	.093
BASFI	-.037	.774
BASMI	.029	.824
Femur BMD (gm/cm^2)	-.591	<.0001

On multivariate regression analysis, only femur BMD was found as the independent predictor for major osteoporotic fracture. With the decrease in femur BMD by 1 gm/cm^2, FRAX for major osteoporotic fracture increases by 0.755 units (p value < .0001).

Table IV: Multivariate linear regression for FRAX score for hip fracture.

	Beta	P - value
Age (yrs)	.276	.034
Duration (yrs)	.035	.793
BASDAI	.337	.030
BASFI	-.071	.594
BASMI	.000	.998
ESR (mm/hr)	-.019	.869
Femur BMD (gm/cm^2)	-.600	< .0001

On multivariate regression analysis, age, BASDAI and femur neck BMD were found to be independent predictors of hip fracture. With the decrease in femur BMD by 1 gm/cm^2, FRAX for hip fracture increases by 0.595 units (p value < .0001). Similarly, hip fracture risk increases by 0.024 units (p value = .034) and by 0 .186 units (p - value .030) for 1 unit increase in age and BASDAI respectively.

Discussion

Bone mineral density in our patients with AxSpA was estimated using DEXA scan at 3 sites: femur, lumbar spine and forearm. The overall prevalence of osteoporosis in our study was 55%. It was similar to other studies showing the prevalence of osteoporosis in AS as 19 - 62%[1,2].

In our study, BMD was reduced in the majority of patients, in spite of relatively short disease duration (mean 5.14 ± 4.47 years) and low disease activity (BASDAI of 3.8 ± 1.48). The mean BMD of lumbar spine was the lowest among the three sites, followed by forearm and femur. Similar findings were reported by Davogelaer *et al* showing a decrease in the lumbar spine BMD in mild AS[12].

Overall, the prevalence of osteopenia was more at femur (62.5%) and prevalence of osteoporosis at lumbar spine (42.5%). Vasdev *et al* also found that AS patients had significantly lower BMD at the spine and femur as compared with controls (P < 0.001); with OP in spine and femur neck seen in 28.75% and 11.54% respectively[13]. They also found increased prevalence of osteopenia at femur and osteoporosis at lumbar spine similar to our study.

In our study, the mean FRAX score for major osteoporotic fracture was 1.53 ± 1.04 % and for hip fracture 0.54 ± 0.82%. We found only one patient with a ten-year hip fracture risk of > 3%, and no patient with major

osteoporosis-related fracture of > 20% on FRAX algorithm. In the study by Meng *et al* on RA patients, OP was found in 41.1% patients, 10-year risk of hip fracture was 0.62 ± 0.11% and for major osteoporotic fracture 4.04 ± 0.83%[14]. These values were higher as compared to controls; however, both the values were below the NOF treatment cut-offs (i.e., 10-year risk of > 20% and > 3% for major osteoporotic and hip fracture respectively) in spite of the fact that RA had been included as a risk factor in FRAX algorithm, and steroid use was prevalent in RA. In our study, though a trend of increasing FRAX score was seen with reduced BMD; absolute values of FRAX scores were not found higher than cut-off set by NOF. Thus, FRAX algorithm did not appear to predict the increased fracture risk requiring intervention in Ax SpA patients. However, this observation could be due to younger age group of Ax SpA patients, small sample size, one time FRAX scoring without follow-up and FRAX calculator not considering Ax SpA as a risk factor (unlike Rheumatoid Arthritis).

To determine predictors of fracture risk in Ax SpA patients, logistic regression analysis was done between various clinical parameters and FRAX score for major osteoporotic fracture and hip fracture. On univariate analysis, age, disease duration, BASDI, BASFI, BASMI, were found to be associated with FRAX scores for hip fracture and major osteoporotic fracture ($P < 0.05$). ESR showed correlation only with FRAX score of hip fracture and not with major osteoporotic fracture. No correlation was found with sex, anthropometric measurements, uveitis, smoking and BMD of forearm and lumbar spine. On multivariate regression analysis, only femur BMD showed independent association with FRAX score for major osteoporotic fracture. However, the FRAX score for hip fracture showed age, BASDAI and femur BMD as its independent predictors. A significant negative correlation was shown between BMD of femur neck and risk of hip fracture and major osteoporotic fracture ($P < 0.05$). This finding was consistent with other studies that showed BMD of femur to be better correlated with risk of vertebral fracture[15,16]. In a meta-analysis, Cara Pray *et al* found that age, male sex, disease duration, low BMD at femoral neck were associated with the increased risk of vertebral fracture in AS while BMI, uveitis, serum ESR, BASDAI, BASFI were not significantly associated[17].

We conclude that prevalence of osteoporosis and hence fracture risk is higher in AxSpA patients despite younger age and early disease; though we could not show high FRAX scores in absolute terms. The independent predictors for increased risk of fracture in AxSpA patients are increasing age and disease activity and loss of BMD at femur neck.

The present study has several limitations. It was a small cross-sectional observational study with no controls. FRAX – as an algorithm – itself suffers from various drawbacks and limitations. It does not utilise AxSpA or BMD of sites other than femur as a factor in its calculator.

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