

Gender Differences in Clinical and Radiological Features Amongst Patients with Axial Spondyloarthritis

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ABSTRACT

Objective: To identify gender based clinical and radiological differences in patients with axial spondyloarthritis.

Study Design: Comparative, cross-sectional study.

Place and Duration of Study: Rheumatology Department, Fauji Foundation Hospital, Rawalpindi Pakistan, from June to Dec 2021.

Methodology: 100 patients (50 males and 50 females) were selected, who were diagnosed with axial spondyloarthritis according to Assessment of Spondylarthritis International Society criteria. Demographic data, clinical characteristics, Bath Ankylosing Spondylitis Disease Activity Index, Bath Ankylosing Spondylitis Functional Index, X-ray and magnetic resonance imaging findings of sacroiliac joints were recorded. Gender groups were compared using Student t-test, chi square and regression analysis.

Results: The mean age was 35.32±8.66 in males and 35.46±9.28 in females. Females had higher involvement of cervico-thoracic region (OR= 4.82, $p = 0.01$, 95% CI: 0.96-24.06), peripheral arthritis (OR= 3.18, $p = 0.007$, 95% CI: 0.13-0.72), delay in diagnosis (OR= 3.55, $p < 0.001$, 95% CI: 2.23-5.67), enthesitis (OR= 4.37, $p = 0.001$, 95% CI: 0.09-0.53). The mean Bath ankylosing spondylitis disease activity score was higher in females (OR= 1.36, $p = 0.002$, 95% CI: 1.12-1.64). Mean Bath ankylosing spondylitis functional index was 5.22±2.3. Smoking in males had a significant correlation with disease. Males had more severe radiographic involvement.

Conclusion: Females with axial spondyloarthritis are found to have a higher disease activity, more frequent cervico-thoracic pain, peripheral arthritis and enthesitis as compared to males. Males have more advanced radiographic involvement of sacroiliac joint.

Keywords: Axial Spondyloarthritis (axSpA), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), Enthesitis, Peripheral Arthritis, Sacroiliac Joint (SIJ), Uveitis.

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INTRODUCTION

Spondyloarthritis is a term for chronic inflammatory diseases involving the sacroiliac joints, spine and peripheral joints.¹ It is associated with significant morbidity and impaired quality of life if not timely diagnosed and treated. It can affect spine, peripheral joints, entheses, other organ systems like eyes, heart and lungs. Axial spondyloarthritis (axSpA) is a subtype that predominantly involves the axial skeleton. It is sub-classified into non-radiographic axSpA (without radiographic or x-ray changes) and ankylosing spondylitis (with radiological signs of sacroiliitis).²

While most rheumatic diseases affect the female gender predominantly, ankylosing spondylitis was traditionally believed to be a disease affecting the male population in a much larger ratio (10:1) for a long

time. Emerging research indicates a change in the gender-based prevalence.³ A recent data has reported the ratio to be 1.03:1 in Switzerland³ and now there is evidence of roughly equal occurrence of non-radiographic axSpA in both genders.⁴ The affected females tend to have different clinical and radiological presentations of axSpA as compared to males, which is likely due to difference in their physiology, hormones, pain mechanisms, immune responses and gene expression.⁵

International clinical data shows that females with axSpA have more common involvement of the peripheral joints,⁶ enthesitis^{1,7} and higher disease activity score.⁸ The males on the other hand have more severe radiologic involvement and progression of the disease.⁶

There is paucity of research on axSpA in our female population. Limited literature exists locally regarding the clinical and radiological features of axSpA in natives. This study can potentially increase

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awareness in clinicians regarding gender-based axSpA features in our population, so that timely referrals to rheumatologists are done to decrease diagnostic delay and mitigation of disease burden and morbidity can be achieved.

METHODOLOGY

This cross-sectional comparative study was carried out in the outpatient Rheumatology department at Fauji Foundation Hospital Rawalpindi from June to December 2021. Formal approval of the ethical review board letter Ref No. 550/RC/FFH/RWP Dated 31/05/2021 was taken. Sample size was calculated using WHO calculator, using confidence interval 95%, margin of error, power of 80% (mean BASDAI of 3.9 ± 1.9 in males and 5 ± 2 in females).⁹ Estimated sample size was 100 (50 males and 50 females). Patients were selected by non probability consecutive sampling technique, from rheumatology OPD after taking informed verbal consent.

Inclusion Criteria: We included patients who fulfilled the Assessment of SpondyloArthritis international Society ASAS classification criteria for inflammatory back pain¹⁰ and axial spondyloarthropathy.¹¹

Exclusion Criteria: Following patients were excluded; failed to give consent or had other defined spine pathology.

The data included clinical and demographic features, like age, gender, education, marital status, comorbid, duration of delay in diagnosis, smoking status, predominant region of back pain, presence of peripheral arthritis, enthesitis, uveitis and family history of spondylarthritis. Disease activity was calculated using Bath Ankylosing Spondylitis Disease Activity Index¹²(BASDAI; NRS range 0–10) and functional limitation was assessed with Bath Ankylosing Spondylitis Functional Index¹³(BASFI; NRS range 0–10). The radiographic (x-ray) findings of sacroiliac joints were recorded. Sacroiliitis was graded from 0(normal)-4(fusion) as per New York criteria.¹⁴ MRI of the sacroiliac joints was also performed to detect early features of axSpA, like bone marrow oedema.

Statistical Analysis was performed using Statistical Package for the social sciences (SPSS) version 23.00. Mean±standard deviation and frequencies were calculated for continuous and categorical variables respectively in each gender. Association of the study variables with gender was

assessed by regression analysis. Univariate regression analysis was performed keeping gender as the dependent variable and other study variable as independent factors. Only variables with significant *p*-value were entered in multivariate regression. *P*-value of <0.05 was considered statistically significant.

RESULTS

Total 100 patients were analyzed including 50 males and 50 females. Mean age of the patients was 35.39 ± 8.93 years, with minimum of 15 and maximum 56 years. Both study groups had comparable age range. Similar trend was observed for educational status of the two groups. Two thirds of the study patients were educated more than 10th grade, with equal proportions of males and females in this category. 21(21%) of the study subjects were smokers, males constituting the majority 15/21(71.42%) of them. More than half of the patients had inflammatory back pain (IBP) in both upper and lower spine, whereas females had higher involvement of cervico-thoracic region.

X-ray of the SIJ was normal in 19(19%) of the patients, constituting non-radiographic spondyloarthropathy (nr-axial SpA). Among these non-radiographic SpA patients, 11(57.8%) were females. Data about HLA-B27 was available for 58 patients. 34(58.62%) had positive HLA-B27. Out of these 19(55.8%) were males and 15(44.11%) females. Mean BASDAI was 4.73 ± 2.31 , being higher in females. Table-I shows the distribution of study variables in the population.

X-ray grading of the study population is shown in Figure-1.

MRI findings are depicted in Figure-2.

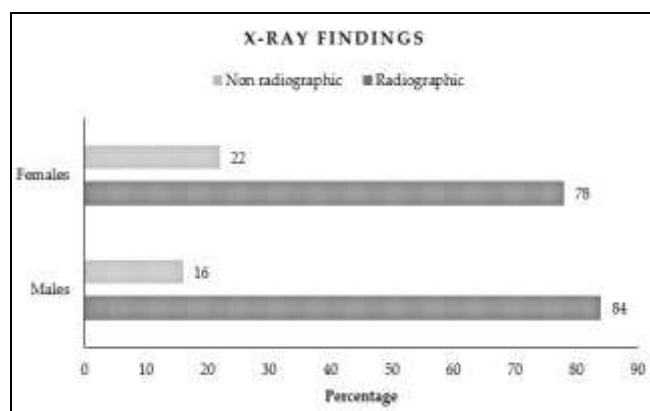


Figure-1: Findings of X-ray Pelvis

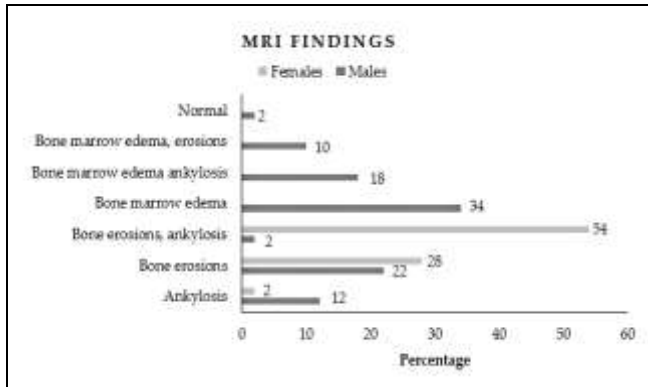


Figure-2: Distribution of MRI changes in study groups.

Most common findings were bone marrow edema and erosions both alone and in combination. MRI was normal in 1% patients.

Table-I: Demographic and Clinical Features of the Study Groups

Variables	Total n=100	Males n=50	Females n=50
Age in years (Mean±SD)	35.39±8.93	35.32±8.66	35.46±9.28
Smoking	21(21%)	15(30%)	6(12%)
Education			
>10th grade	68(68%)	47(94%)	47(94%)
<10th grade	32(32%)	3(6%)	3(6%)
Family history	20(20%)	10(20%)	10(20%)
Delay in diagnosis (years)	4.89±2.34	3.12±1.31	6.66±1.72
Predominant axial pain			
Cervico-thoracic	12(12%)	2(4%)	10(20%)
Lumbosacral	33(33%)	21(42%)	12(24%)
Both	55(55%)	27(54%)	28(56%)
Peripheral arthritis	58(58%)	22(44%)	36(72%)
Hip involvement	39(39%)	24(48%)	15(30%)
Enthesitis	59(59%)	21(42%)	38(76%)
Uveitis	22(22%)	13(26%)	9(18%)
HLA B27	34(34%)	19(38%)	15(37%)
Imaging classification			
Non radiographic Ax-SpA	19(19%)	8(16%)	11(22%)
Radiographic Ax-SpA	81(81%)	42(84%)	39(78%)
BASDAI (Mean±SD)	4.73±2.31	3.98±2.15	5.49±2.24
BASFI (Mean±SD)	5.22±2.3	5.27±2.17	5.16±2.44

Ax-SpA= axial spondyloarthritis; BASDAI= Bath ankylosing spondylitis disease activity index; BASFI= Bath ankylosing spondylitis functional index.

The gender groups were compared for each of the parameters. Among demographic variables, male gender had significant association with smoking with a *p*-value of 0.03. While among the disease specific parameters, peripheral arthritis, enthesitis and cervico-thoracic pain were significantly higher in females. Gender had no considerable relation to BASFI, whereas female gender was associated with significantly higher BASDAI (OR=1.36, 95% CI 1.12-

1.64, *p*<0.01). Females were diagnosed 3.54 years later than males on average and this difference was statistically significant with a *p*-value of <0.001. Table-II shows the results of comparison between the two study groups.

DISCUSSION

Spondyloarthropathies in general and ankylosing spondylitis in specific, is associated with considerable morbidity and mortality. Two decades ago, the prevalence of spondyloarthritis was found to be roughly 0.1 per 1000 in North Pakistan¹⁵ and 0.9 per 1000 in the South¹⁶ with a male to female ratio of 3:1. The recently found prevalence of radiographic SpA is 1%.¹⁷ Another local research showed that majority of the patients presenting with inflammatory back pain and diagnosed with axial spondyloarthritis were females.¹⁸ It goes without saying that detailed history and examination is of paramount significance in young patients presenting with back ache to timely diagnose patients with ankylosing spondylitis. However, there is paucity of native data regarding gender-based clinical and radiographic differences in SpA patients.

Many female patients diagnosed with axial spondyloarthritis are currently being treated and followed in our rheumatology unit. We have observed that females are presenting with different disease manifestations and course as compared to our male population. We have focused on the gender-based and disease-specific clinical and radiological features. The parameters which were found statistically significant are discussed here.

The diagnosis of SpA is easily missed in women because of lack of awareness of the common presentations in females. Our study found that time period from symptom onset to a clinical diagnosis in SpA is later in females than in males. A meta-analysis has shown significant delay in diagnosis in women as compared to men.¹⁹ The diagnostic delay is much longer in our female cohort (6.66±1.72years). Multiple factors may contribute to this delay in diagnosis e.g., a typical presentations in females, lack of awareness of gender-specific disease features and also a poor referral system in the country²⁰ being a major hurdle for the patients in reaching rheumatologists timely. The symptoms of axial spondyloarthritis can be easily mis-diagnosed as fibro-myalgia, which is a common confounder causing the diagnosis to be missed or delayed.¹⁹ Early diagnosis leads to better outcomes, and international guidelines have stressed

Table-II: Results of Comparison between the Study Groups

Variables	Univariate regression analysis			Multivariate regression analysis		
	<i>p</i> -value	Odds ratio	95% confidence interval	<i>p</i> -value	Odds ratio	95% confidence interval
Age (Mean±SD)	0.94	1.002	0.96-1.05			
Smoking	0.03	0.32	0.11-0.91	0.32	0.32	0.04-2.93
Education (>10th grade)	0.53	0.76	0.33-1.76			
Family history	1	1	0.38-2.68			
Delay in diagnosis	0.000	3.56	2.23-5.67	0.00	5.28	2.37-11.76
Region of predominant axial pain (ref=Cervico-thoracic)						
Lumbosacral	0.01	0.11	0.21-0.61	0.01	0.007	0.00-0.34
Both	0.55	0.21	0.42-1.04	0.03	0.02	0.00-0.66
Peripheral arthritis	0.005	3.27	1.42-7.52	0.14	4.82	0.61-37.91
Hip involvement	0.07	0.46	0.20-1.06			
Enthesitis	0.001	4.37	1.85-10.32	0.02	13.19	1.55-112.46
Uveitis	0.34	0.63	0.24-1.63			
HLA B27	0.37	0.66	0.27-1.63			
Imaging classification (Radiographic Ax-SpA)	0.45	0.68	0.25-1.85			
BASDAI	0.002	1.36	1.12-1.65	0.006	1.95	1.21-3.13
BASFI	0.82	0.98	0.83-1.16			

Statistically significant results are depicted in bold.

Ax-SpA= axial spondyloarthritis; BASDAI= Bath ankylosing spondylitis disease activity index; BASFI= Bath ankylosing spondylitis functional index.

the importance of timely referral and treatment in SpA patients.²¹

Predominant cervical pain, wide spread pain, peripheral arthritis and enthesitis have been found more commonly in female SpA patients as compared to the males.^{22,5} Cervico-thoracic spine pain and stiffness is also significant in our female SpA patients, alongwith peripheral involvement (enthesitis, peripheral arthritis). It was observed that many women with SpA had initially presented with predominant cervical pain without lumbar involvement. Cervical pain can be easily missed as a SpA feature and misinterpreted as myalgia or fibromyalgia.¹⁹ Thus, it is important to ask young females presenting with cervical pain about morning stiffness in the neck and history of arthritis, enthesitis, extra-articular features and family history of SpA. Peripheral arthritis, predominantly involving large joints and enthesitis (inflammation of tendon insertion sites) such as Achilles tendinitis and plantar fasciitis were common features in women as compared to men with SpA and have a contributory role in increasing the disease burden. These red flags in females with inflammatory back pain should raise a high clinical suspicion of SpA.

The disease activity score was also higher in females (mean BASDAI 5.49±2.24), another cause of increased disease burden and impaired quality of life. Females have higher pain perception as compared to

males, which may lead to greater pain reporting on subjective scores. Concomitant fibro-myalgia, which is very common in women with rheumatic diseases,^{23,24} can lead to chronic wide spread pain and fatigue. This can be a factor causing over estimation of disease activity self-reported by the patient.

The male population with SpA has more advanced radiographic damage, thus making it easier to pick spondylitis merely on x-rays.⁵ The early changes of sacroiliitis, like bone marrow edema, were found on the MR imaging of sacroiliac joint performed at the same time when x-ray of these patients appeared normal, i.e., non-radiographic SpA, which been found to be more common in the female subjects of our study. International research has also appreciated a higher incidence of nr-axSpA in females.⁴ It is important to pick non-radiographic SpA because it requires treatment like ankylosing spondylitis.²⁵ Females who present with inflammatory back pain are now being screened and diagnosed more accurately for SpA in our hospital because of the easy availability of MRI, which picks up early or non-radiographic axial spondyloarthritis, which is more common in women. However, the prevalence of the radiographic SpA wasn't significantly different between our study groups.

Thus, it is prudent to screen young females having inflammatory back pain and/or SpA features (articular and extra-articular) with MR imaging of the

sacroiliac joints, even if their initial x-rays of the sacroiliac joints appear normal.

LIMITATION OF STUDY

1: BASDAI which was used for disease activity scoring is a very subjective tool and doesn't comprise of any objective measure like ESR or CRP that have been included in other disease activity assessment tools, like ASDAS.

2: nr-axSpA was found more commonly in females, however bone marrow edema and sclerosis of SIJ can also appear after pregnancy and in osteitis condensans ilii.⁴

CONCLUSION

Females tend to have different disease manifestations, such as more peripheral arthritis, enthesitis and cervical spine involvement as compared to males. This should raise awareness in clinicians to be more vigilant regarding young females presenting with these features in clinics to prevent delay in diagnosis.

Conflict of Interest: None.

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Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

IUD & AK: Data acquisition, data analysis, critical review, approval of the final version to be published.

SP & HG: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

SS & BS: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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