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ORIGINAL ARTICLE

Gender differences in Iranian patients with ankylosing spondylitis

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Abstract Inequalities in features and severity of ankylosing spondylitis (AS) have been noticed between men and women, suggesting a possible influence of gender on disease phenotypes. Comparing disease features and characterization of gender differences in clinical features and medications could help elucidate the potential influence of gender on the severity of AS in patients. This study aims to assess the influence of gender on disease patterns in Iranian patients with AS. Three hundred and twenty patients diagnosed with primary AS were assessed for demographic variables, clinical manifestations, HLA status, disease severity, functional capacities, quality of life, and treatment status. Sixty-seven women and 253 men were included corresponding to a male to female ratio of 3.78:1. Both groups were similar regarding ethnicity, positive family history, and juvenile onset AS. HLA-B27 was more frequent among males (78.3 vs. 55.2 %; $p < 0.001$). There was a higher proportion of female patients with overall enthesitis ($p < 0.05$). Extra-articular manifestations and treatment modalities presented similar frequencies in both genders. No difference in gender-associated diagnostic delays was observed. Female disease was at least as severe as male disease, and in some aspects, females presented with more severe disease. Despite a relatively similar disease profile, we observed a higher rate of enthesitis among women. Together with the equally high rate of disease activity indices in both genders, these findings indicate an overall longer delay to diagnosis in our country. Early detection and specialized care would be of great practical importance.

Keywords Ankylosing spondylitis · Clinical features · Drug therapy · Gender · HLA-B27 · Iran

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Introduction

Ankylosing spondylitis (AS) is a chronic systemic inflammatory disease of joints and entheses that can progress to significant functional disability. It primarily affects the axial skeleton and is also associated with peripheral joint involvement and extra-articular manifestations. Initially considered as a disease predominantly affecting the male gender, the profile has changed over time and AS has been recognized as an important cause of disability among females as well. A male to female ratio of 2–3:1 has been reported in this regard [1].

With increased recognition of the disease in women, inequalities in features and severity have been noticed between men and woman, suggesting a possible influence of gender on disease phenotypes and severity. Comparing disease features of AS in women and men and characterization of gender differences in clinical features and medications could help elucidate the potential influence of gender on the severity of AS in patients.

Due to the availability of effective treatments for AS, it is essential for physicians to be aware of the distinctive features and treatment options of this disorder in the population. The aim of this study was to assess the influence of gender on

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disease patterns in Iranian patients with AS. We assessed differences in clinical characteristics, biological features, disease severity, quality of life, and medical treatments.

Patients and methods

Patients

Patients diagnosed with primary AS were recruited from the "Iranian AS Society" database. The Iranian AS Society, a member of the Ankylosing Spondylitis International Federation (ASIF) founded in 1993, consists of patients from around Iran [2]. Contact information was obtained through which the patients were asked whether they were willing to participate in a follow-up survey. Out of 402 selected patients, 320 completed the study. Patients from all over the country were referred to the Rheumatology Clinic at Shariati Hospital, Tehran, Iran (a national tertiary referral center) for further evaluation by a rheumatologist. The study was performed between May 2010 and June 2011.Written informed consent was obtained from all patients after informing them about the study purposes. The study was approved by the ethics committee of Tehran University of Medical Sciences.

Assessment criteria and data collection

On clinic admission, a diagnosis of AS was confirmed according to the modified New York criteria [3]. An investigator administered questionnaire was employed for data collection. Demographic data consisted of age, sex, and ethnic origin. Clinical data included age at symptom onset, age at diagnosis, and diagnostic delay. Age at symptom onset was defined as the time when the first symptom, whether axial disease, peripheral arthritis, or enthesitis, developed. Diagnostic delay was defined as the interval between the patient's initial spondyloarthritic symptom and a correct diagnosis of AS [4].

Additionally, detailed information regarding past medical history, family history, medications, peripheral arthritis, enthesitis, and extra-articular manifestations was obtained. A positive family history was defined as having a first- or second-degree relative with AS. Peripheral arthritis was defined as presence of swelling and/or restricted movement in at least one peripheral joint and/or history of previous swelling in at least one peripheral joint confirmed by a rheumatologist or orthopedist. Enthesitis was defined as inflammation and/or pain of enthesis at the following sites: calcaneal insertion of the Achilles tendon; the cervical, thoracic, and lumbar spinous processes; the greater trochanter of the femur; medial and lateral condyles of the femur; pelvic region including iliac crests, anterior superior iliac spines, ischial tuberosities, and posterior superior iliac spines; and chest wall including the manubriosternal joint and costochondral joints. Extra-articular manifestations included uveitis, inflammatory bowel disease, cutaneous manifestations, heart involvement which mainly included aortic insufficiency, lung abnormalities, and renal involvement.

Disease-specific measurements

For the assessment of disease severity and functional capacities, a protocol based on the Assessment of SpondyloArthritis International Society (ASAS) core set [5] was used: Disease activity was assessed by Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) [6]; Disease function was assessed by Bath Ankylosing Spondylitis Functional Index (BASFI) [7]; Spinal damage or deformity was assessed by Bath Ankylosing Spondylitis Metrology Index (BASMI) [8]; Nocturnal back pain, total back pain, patient global disease activity score, and the Bath Ankylosing Spondylitis Global Score (BAS-G) for the effect of the disease on well-being of the patients for the last week or the last 6 months [9] were assessed by numerical rating score (NRS). The questionnaires had previously been validated in Farsi [10]. The Ankylosing Spondylitis Quality of Life (ASQoL) questionnaire was used for the assessment of quality of life, varying from 0 to 18 [11].

Laboratory tests

Laboratory tests including an erythrocyte sedimentation (ESR) rate and C-reactive protein (CRP) were recorded for each patient. HLA-B27 status was determined and subtyping was performed by PCR amplification with sequence specific primer (PCR-SSP) method using "Olerup SSP^{TM} HLA-B*27 Kit" (Olerup SSP AB, Sweden). PCR was performed on an ABI2720 thermal cycler (Applied Biosystems, USA). PCR products that were visualized in 2 % agarose gel under UV illumination following ethidium bromide staining and documented by photography. HLA typing was performed in the research laboratory of Rheumatology Research Center, Tehran University of Medical Sciences.

Statistical analysis

Statistical analysis was performed on Statistical Package for the Social Sciences version 16 (SPSS, Chicago, IL, USA). Patient data was presented as mean and standard deviation for continuous variables and as frequency and percentage for categorical variables. A t test was used to detect significant differences between men and women for continuous variables. For categorical variables, a chi-square or Fisher's exact test was used to determine gender-related differences. Logistic regression was utilized to assess the association between gender and disease parameters. A p value of less than 0.05 was considered as the level of significance.

Results

A total of 320 patients (67 women, 253 men) were included in this study. The ratio of male to female patients was 3.78:1. Both groups were similar regarding ethnicity with no significant difference between patients coming from various Iranian ethnic backgrounds. A positive family history of AS was reported in a higher percentage of women, yet there were no significant differences in the rates of positive familial history between the genders. The percentage of the juvenile onset cases was found to be 11.9 % among men and 7.5 % among women which did not reach statistical significance. HLA-B27 was significantly more frequent among males (78.3 vs. 55.2 %; $p<0.001$) (Table 1). As demonstrated in Table 1, the mean age, age at symptom onset and diagnosis, delay in diagnosis, and disease duration were greater in women; however, there was no statistically significant difference between the genders in age, delay in diagnosis, or disease duration.

There were a significantly higher proportion of female patients with overall enthesitis ($p<0.05$), among whom involvement of the chest wall and thoracic spine tended to be more common. The gender difference in enthesitis persisted after adjusting for potential confounding factors including disease duration, age of disease onset, age of symptom onset, and presence of arthritis (adjusted odds ratio and 95 % confidence interval of 2.57 (1.22–5.41, $p=0.013$). The rate of overall articular involvement was similar in both groups. Women were more likely to have elbow joint involvement, but the overall peripheral disease values did not reach statistical significance. Regarding the extra-articular manifestations and diseases, uveitis and inflammatory bowel disease were the most frequent findings. Skin and visceral including heart, lung, and kidney involvement were not frequent in our study population. All extra-articular manifestations presented similar frequencies in both genders. Considering treatment modalities, a statistically similar proportion was observed in both genders (Table 2).

The first AS symptom was inflammatory back or hip pain in 48 (71.6 %) women versus 195 (78 %) men and peripheral arthritis in 8 (12 %) women versus 36 (14.4 %) men. Compared to men, women had lower CRP (10.6±15.09 vs. 18.7±24.19 mg/L, $p<0.001$) yet similar ESR (18.6±15.42 vs. 17.6 ±17.14 mm/h, $p=0.719$) values. Mean weight and height were lower in women but body mass index values were similar in both groups. Both men and women had similar nocturnal back pain scores but women had a higher total score compared to men. Global disease activity index and well-being of the patients as assessed by BAS-G for the last week or the last 6 months were similar among genders (Table 2).

Table 1 Baseline characteristics of ankylosing spondylitis patients in Iran by gender. Results are represented as mean±SD unless otherwise specified

Characteristics	Women ($n=67$)	Men ($n=253$)	p Value
Age (years)	39.5±10.03	37.6±10	0.19
Age at symptom onset (years)	24.3±7.73	22.2±7.14	0.041*
Age at diagnosis (years)	33±9.49	30.2±8.97	0.025*
Diagnostic delay (years)	8.8±8.51	8±7.22	0.464
Disease duration (years)	15.6±10	15.5±9.29	0.96
Weight (kg)	68.9±12.67	76.5±14.88	<0.001*
Height (cm)	158.5±7.31	170.5±7.9	<0.001*
Body mass index (kg/m^2)	27.5±5.35	26.4±5.14	0.108
Ethnicity			0.328
Fars	31 (46.3 %)	126 (49.8 %)	
Turk	20 (29.9 %)	77 (30.4 %)	
Kurd	9 (13.4 %)	16 (6.3 %)	
Lor	5 (7.5 %)	18 (7.1 %)	
Other	2 (3 %)	16 (6.3 %)	
Positive family history of AS	22 (32.8 %)	74 (29.2 %)	0.569
Juvenile onset AS	5 (7.5 %)	30 (11.9 %)	0.325
HLA-B27 positive	37 (55.2 %)	198 (78.3 %)	<0.001*

HLA human leukocyte antigen

* Statistically significant

BASDAI, BASFI, and BASMI items

The individual and total BASDAI and BASFI items and scores expressed as means and standard deviations for the men and women separately, and the statistical significance are shown in Tables 3 and 4. No differences were present between women and men in any of the items of BASDAI questionnaire. Women had greater difficulty than men in climbing up steps without a handrail (BASFI-7, 4.6 vs. 3.2, respectively) and doing full day's activities (BASFI-10, 5.25 vs. 4 respectively). On comparing metrological indices, women showed lower scores in all the items contributing to an overall lower BASMI score (3.4 vs. 4.2, respectively); however, differences in intermalleolar and cervical rotation scores did not reach statistical significance (Table 5). Moreover, as depicted in Table 2, men had a higher finger to floor distance, lower lumbar rotation, and similar chest expansion compared to women.

Quality of life

ASQoL scores according to gender are presented in Table 6. Overall values were higher but not statistically significant among women; however, a significantly higher proportion of women complained of feeling like crying, struggling to do jobs around the house, having to stop to rest, getting tired easily, and getting frustrated.

Table 2 Clinical characteristics of ankylosing spondylitis patients in Iran by gender. Results are represented as mean±SD or number (percentage)

Characteristics	Women ($n=67$)	Men ($n=253$)	p value
Clinical data			
Enthesitis	55 (82.1 %)	174 (68.8 %)	0.032*
Cervical	16 (23.9 %)	44 (17.4 %)	0.226
Thoracic	36 (53.7 %)	96 (37.9 %)	0.02*
Lumbar	39 (38.2 %)	115 (45.5 %)	0.063
Pelvic	23 (34.3 %)	69 (27.3 %)	0.257
Heel	3 (4.5 %)	13 (5.1 %)	1
Chest wall	21 (31.3 %)	48 (19 %)	0.029*
Greater trochanter	7 (10.4 %)	24 (9.5 %)	0.813
Knee	1 (1.5 %)	5 (2 %)	1
Arthritis	32 (47.8 %)	128 (50.6 %)	0.68
Peripheral joint involvement	16 (23.9 %)	37 (14.6 %)	0.07
Elbow	6 (9 %)	7 (2.8 %)	0.023*
Wrist	4 (6 %)	7 (2.8 %)	0.251
Hand	4 (6 %)	9 (3.6 %)	0.483
Foot	3 (4.5 %)	6 (2.4 %)	0.4
Knee	6 (9 %)	20 (7.9 %)	0.780
Ankle	8 (11.9 %)	16 (6.3 %)	0.123
Root joint involvement	32 (47.8 %)	127 (50.2 %)	0.723
Shoulder	13 (19.4 %)	39 (15.4 %)	0.431
Hip	20 (29.9 %)	99 (39.1 %)	0.162
Extra-articular manifestations			
IBD	5 (7.5 %)	19 (7.5 %)	0.99
Uveitis	9 (13.4 %)	40 (15.8 %)	0.631
Cardiovascular	1 (1.5 %)	4 (1.6 %)	0.717
Pulmonary	2 (3 %)	4 (1.6 %)	0.609
Renal	1 (1.5 %)	1 (0.4 %)	0.376
Skin	2 (3 %)	12 (4.7 %)	0.528
Activity/functional index			
ESR (mm/h)	18.6±15.42	17.6±17.14	0.719
CRP (mg/L)	10.6±15.09	18.7±24.19	<0.001*
Nocturnal back pain	5±3.13	4.4±3	0.141
Total back pain	5.3±2.99	4.4±2.81	0.019*
Patient global disease activity score	4.9±2.85	4.4±2.77	0.199
BAS-G for last week	5.2±2.92	4.6±2.97	0.129
BAS-G for the last 6 months	5.5±2.7	5.1±2.86	0.3
Chest expansion (cm)	3.9±2.02	4.3±1.9	0.09
Finger to floor (cm)	10±11.95	21.2±14.45	<0.001*
Lumbar rotation (degrees)	73.6±22.96	60.6±28.36	<0.001*
Medications			
NSAID	53 (79.1 %)	201 (79.4 %)	0.951
Sulfasalasine	34 (50.7 %)	132 (52.2 %)	0.835
Prednisolone	17 (25.4 %)	63 (24.9 %)	0.937
Intra-articular corticosteroids	9 (13.4 %)	22 (8.7 %)	0.244
Etanercept	5 (7.5 %)	15 (5.9 %)	0.65
Infliximab	3 (4.5 %)	9 (3.6 %)	0.72
Anti-TNF	6 (9 %)	21 (8.3 %)	0.871
Methotrexate	15 (22.4 %)	54 (21.3 %)	0.852

IBD inflammatory bowel disease, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *BAS-G* Bath Ankylosing Spondylitis Global Score, *NSAID* nonsteroidal anti-inflammatory drug, *TNF* tumor necrosis factor

* Statistically significant

Table 3 Comparison of disease activity as assessed by BASDAI scores in Iranian males and females with ankylosing spondylitis

	Sex	Number	Mean±SD	*p* value
BASDAI (total score)	Women	67	5±2.23	0.187
	Men	253	4.6±2.45	
BASDAI-1 (overall fatigue/tiredness)	Women	67	5.81±2.676	0.103
	Men	253	5.18±2.825	
BASDAI-2 (overall neck, back, or hip pain)	Women	67	6.28±3.009	0.116
	Men	253	5.62±3.096	
BASDAI-3 (overall pain/swelling of joints)	Women	67	4.36±2.896	0.189
	Men	253	3.82±3.243	
BASDAI-4 (level of discomfort in areas tender to touch)	Women	67	4.63±3.428	0.359
	Men	253	4.21±3.311	
BASDAI-5 (severity of morning stiffness)	Women	67	4.70±3.172	0.77
	Men	253	4.83±3.085	
BASDAI-6 (duration of morning stiffness)	Women	67	3.60±2.839	0.961
	Men	253	3.62±2.940	

BASDAI Bath Ankylosing Spondylitis Disease Activity Index

Discussion

Previous studies have shown distinct differences in the prevalence and clinical manifestation of AS between women and men [1, 12]. However, the exact pathogenesis of AS is still unknown and both sex and gender factors may have contributions in this regard. Differences in sex (i.e., genetic, hormonal, and other phenotypic differences) or gender (i.e., society- or culture-related differences in physical activity, delay in diagnosis, environmental influences, infections, and smoking) or a combination of both could contribute to this matter [13]. In order to make better diagnostic and treatment decisions for AS patients, it is necessary to be familiar with socio-cultural as well as phenotypic differences in disease patterns between genders. This is the first published study focusing on gender differences of Iranian patients with AS and provides valuable information regarding the potential influence of sex or gender on clinical expression and severity of this this disease. Larger national studies involving patients from a community cohort or nationwide patient registry are required to determine gender differences and AS prevalence more precisely in Iran.

Table 4 Comparison of functional outcomes as assessed by BASFI scores in Iranian males and females with ankylosing spondylitis

	Sex	Number	Mean±SD	*p* value
BASFI (total score)	Women	67	4.3±2.41	0.246
	Men	251	3.8±2.65	
BASFI-1 (putting on socks)	Women	67	2.90±3.452	0.39
	Men	253	3.29±3.334	
BASFI-2 (bending forward from waist)	Women	67	3.40±3.389	0.117
	Men	253	4.17±3.594	
BASFI-3 (reaching up to a high shelf)	Women	67	3.67±3.475	0.256
	Men	253	3.15±3.299	
BASFI-4 (getting up from armless chair)	Women	67	3.16±3.122	0.784
	Men	253	3.28±3.220	
BASFI-5 (getting up from floor)	Women	67	5.93±3.470	0.099
	Men	253	5.13±3.531	
BASFI-6 (standing unsupported)	Women	67	3.72±3.406	0.164
	Men	253	3.09±3.255	
BASFI-7 (climbing steps without handrail)	Women	67	4.63±3.550	0.003*
	Men	252	3.21±3.351	
BASFI-8 (looking over shoulders)	Women	67	4.78±3.575	0.471
	Men	252	4.42±3.639	
BASFI-9 (doing physically demanding activities)	Women	67	5.07±2.851	0.129
	Men	251	4.42±3.204	
BASFI-10 (doing full day's activities)	Women	67	5.25±2.782	0.002*
	Men	252	4.01±3.007	

BASFI Bath Ankylosing Spondylitis Functional Index

* Statistically significant

Table 5 Comparison of metrological indices as assessed by BASMI scores in Iranian males and females with ankylosing spondylitis

	Sex	Number	Mean±SD	*p* value
BASMI (total score)	Women	67	3.4±1.58	0.001*
	Men	251	4.2±1.88	
Lateral lumbar flexion (cm)	Women	67	12.4±5.37	0.003*
	Men	251	10±5.98	
Lateral lumbar flexion (score)	Women	67	4.2±2.54	0.002*
	Men	251	5.4±2.9	
Tragus-to-wall (cm)	Women	67	14.7±3.98	<0.001*
	Men	251	18.4±6.48	
Tragus-to-wall (score)	Women	67	2.1±1.35	<0.001*
	Men	251	3.4±2.1	
Lumbar flexion (modified Schober) (cm)	Women	67	3.8±1.74	0.04*
	Men	251	3.2±2.15	
Lumbar flexion (modified Schober) (score)	Women	67	5.1±2.52	0.014*
	Men	251	6.1±2.77	
Intermalleolar distance (cm)	Women	67	96.8±21.8	0.937
	Men	251	96.5±22.4	
Intermalleolar distance (score)	Women	67	2.7±1.96	0.674
	Men	251	2.8±2.09	
Cervical rotation (degrees)	Women	67	66.9±19.99	0.069
	Men	251	61.4±22.46	
Cervical rotation (score)	Women	67	2.6±2.37	0.133
	Men	251	3.2±2.56	

BASMI Bath Ankylosing Spondylitis Metrology Index

* Statistically significant

As compared to recent reports with male to female ratios of as low as 2:1 [13, 14], we found a male predominance of 79 % demonstrating a male to female ratio of 3.78:1 which concurs with previous reports on Iranian [15] and some Asian [16, 17] patients with AS. However, even higher gender ratios have been reported among Asian nations [18, 19]. We do not know whether this higher male to female ratio is a specific feature among the Asian population. Having been conducted at single centers and referral hospitals, most of the Asian studies are prone to selectively recruiting patients with more severe symptoms. Our study included patients from different ethnicities across the country and is one of the largest studies conducted in Iran; therefore, it might be more representative than the previous studies.

Gender categories of our study population showed similar sociodemographic characteristics; the two groups were balanced considering ethnicity, age, and body mass index. The possible impact of such factors on disease outcome has been of question and subject to previous studies [20, 21].

We found no significant difference between males and females for family history. A similar finding was also found in a national registry from Turkey [16]. Furthermore, a systematic cross-sectional study assessing the recurrence of spondyloarthropathies among first-degree relatives of patients revealed no gender differences suggesting a model of inheritance with no dominance variance and without sex influence [22]. Moreover, the frequency of juvenile onset AS was also similar in both genders, which is consistent with the previous studies [15, 16], in addition to a survey comparing juvenile and adult onset AS which showed no difference in sex distribution between the groups [23]. Nevertheless, despite the similar family history observed among genders, AS is considered as a highly heritable polygenic disease with environmental factors playing a role in determining susceptibility in some populations [24].

HLA-B27 is the main genetic component to AS susceptibility, and its prevalence among women with AS is equivalent to that in men [25]. We found a lower prevalence of HLA-B27 among women with AS which concurs with some other studies [17, 26]. It could be concluded that Iranian women with AS may have a lower prevalence of HLA-B27. Another possible explanation could be an overrepresentation of HLA-B27-negative female AS patients; such patients may more frequently have been referred from other hospitals and included in our study population after being unsuccessfully treated under another diagnosis.

Enthesitis was a predominant finding in our female patients. Peripheral joint involvement has been implied as a feature of female AS [1]. Yet, our overall levels of peripheral joint involvement did not attain statistical threshold. Moreover, higher frequency of enthesitis has previously been reported in patients with peripheral arthritis [27]. Although not completely supported by our findings, we could conclude that enthesitis may also be a characteristic of female patients with

Table 6 Comparison of quality of life as assessed by ASQoL scores in males and females

	Sex	Number	Mean±SD	*p* value
ASQoL (total score)	Women	65	8.5±4.42	0.212
	Men	248	7.7±5.47	
ASQoL-1 (my condition limits places I go)	Women	66	0.48±0.504	0.827
	Men	250	0.50±0.501	
ASQoL-2 (I feel like crying)	Women	66	0.74±0.441	0.006*
	Men	249	0.57±0.497	
ASQoL-3 (difficulty dressing)	Women	66	0.30±0.463	0.874
	Men	249	0.31±0.465	
ASQoL-4 (struggle to do jobs around house)	Women	66	0.59±0.495	0.015*
	Men	250	0.42±0.495	
ASQoL-5 (impossible to sleep)	Women	66	0.24±0.432	0.417
	Men	249	0.20±0.398	
ASQoL-6 (unable to join activities with friends/family)	Women	66	0.41±0.495	0.280
	Men	249	0.34±0.474	
ASQoL-7 (tired all the time)	Women	65	0.51±0.504	0.149
	Men	250	0.41±0.492	
ASQoL-8 (have to keep stopping to rest)	Women	66	0.67±0.475	0.012*
	Men	250	0.50±0.501	
ASQoL-9 (have unbearable pain)	Women	66	0.38±0.489	0.920
	Men	250	0.37±0.484	
ASQoL-10 (takes time to get going in the morning)	Women	66	0.23±0.422	0.124
	Men	250	0.32±0.467	
ASQoL-11 (unable to do jobs around house)	Women	66	0.24±0.432	0.859
	Men	250	0.23±0.423	
ASQoL-12 (get tired easily)	Women	66	0.73±0.449	0.041*
	Men	250	0.60±0.492	
ASQoL-13 (get frustrated)	Women	66	0.39±0.492	0.066
	Men	245	0.27±0.445	
ASQoL-14 (pain is always there)	Women	66	0.65±0.480	0.859
	Men	247	0.64±0.481	
ASQoL-15 (miss out on a lot)	Women	66	0.45±0.502	0.141*
	Men	248	0.56±0.498	
ASQoL-16 (difficult to wash my hair)	Women	66	0.20±0.401	0.137
	Men	248	0.12±0.322	
ASQoL-17 (my condition lets me down)	Women	66	0.68±0.469	0.525
	Men	248	0.72±0.449	
ASQoL-18 (worry about letting people down)	Women	66	0.47±0.503	0.999
	Men	248	0.47±0.500	

ASQoL Ankylosing Spondylitis Quality of Life

* Statistically significant

AS. Moreover, due to the high rate of enthesitis among our population and its predominance in females and considering the overlap of enthesitis sites with fibromyalgia tender points, we could imply that women presenting with AS may more likely be misdiagnosed as fibromyalgia syndrome contributing to a greater delay to diagnosis.

Uveitis is reported to be the most common extra-articular manifestation of AS. Gender predilection for uveitis has been controversial, some studies showing a female predominance [28], others reporting male preponderance [29], and some finding no difference [30]. It has been implicated that as the disease progresses, this gender difference becomes less pronounced [17].

The age pattern was rather balanced among our study population; no difference in gender-associated diagnostic delays was observed in our study, which is contrary to a previous report revealing longer diagnostic delays among female patients [31].

BASDAI items mostly exceeded a cutoff of 4 which is often used to define active disease [32]. Most of the disease indices obtained in our study (BASDAI, BASFI, ASQoL, and the patient global assessment) presented similarly in the male and female patients. It has been suggested that female patients have less severe disease, resulting in less disability [33]. According to our findings, female disease was at least as severe as male disease, and in some aspects, females presented

with more severe disease, at least according to the patients' grading. However, the aforementioned measures are subjective and the pain threshold may be debatable. Moreover, laboratory markers such as CRP did not support these findings. Assessment of spinal mobility as assessed by overall BASMI and individual lateral lumbar flexion, tragus-to-wall, and lumbar flexion scores along with lumbar rotation values revealed a more significant impairment in men indicating worse axial status. A national survey of the Turkish population also came up with higher BASMI scores in males [16]. This is in concordance with a body of studies showing more spinal involvement in men [16, 34, 35] and peripheral involvement in women [1, 16, 34]. Nevertheless, chest expansion did not differ significantly between groups which may at least partially be due to the higher rate of enthesitis in the chest wall of women.

Recognizing between gender differences and its contribution to disease characteristics would aid in the diagnosis and therapeutic management of this disease. Overall, although finding several differences in disease characteristics, gender differences were less pronounced among our patients. This could partly be due to demographic and socioeconomic patterns and epidemiologic factors related to study population. Also, a systematic selection of the more severe and progressed cases may have contributed to narrowed gender difference in our patients. Milder cases of the disease mainly in rural areas with less developed health services may have remained undiagnosed and treated symptomatically without referral to a specialist. Furthermore, as previously mentioned, some gender-related aspects of the disease may become less pronounced over time with disease progression. Establishing an early diagnosis and providing appropriate and effective treatment may result in less functional damage and a better quality of life in the future.

The present study has several strengths, including a large and diverse number of AS patients recruited from across the country, random selection of patients from major sources, and the use of validated outcome measures. Even so, we must interpret our findings bearing several reservations in mind. Part of the information relating to early symptoms and clinical features was collected by patient interview with potential limitation in recall. In addition, despite the usefulness of cross-sectional studies in showing associations, it is not possible to establish a temporal relation between presumed predictors and outcome measures. Ideally, we would have started follow-up on a patient's initial diagnosis. In this regard, developing a national registry incorporating multiple referral centers would not only enable more efficient follow-up but would also provide a more accurate description of the disease pattern in Iran. Lastly, detailed radiographic scoring data, other than that confirming evidence of sacroiliitis, were not available for all of our patients, and radiologic indices were therefore not considered in this study.

Despite being a broad assessment of AS patients in our country and in spite of including a majority of Iranian ethnic origins, our results may not be fully generalized to the whole country and races. We obtained initial patient data from the national AS society which has a broad coverage throughout the country. Nevertheless, participants were referred to and evaluated in a tertiary referral center in the capital city of Tehran. Although travel and medical expenses were provided for all participants, there is underestimation of patients from far provinces which is attributable to the inherent challenges of following a large group of patients, many of whom reside in rural communities separated by large distances from specialized centers. In this regard, development of a national AS registry incorporating multiple referral centers would enable more efficient follow-up as well as more accurate description of the disease pattern in Iran.

Conclusion

This study points to gender differences of AS among a previously underreported population. Our descriptive data indicate some important clinical points regarding gender characterization. Despite a relatively similar disease profile, we observed a higher rate of enthesitis among women. Together with the equally high rate of disease activity indices in both genders, these findings indicate an overall longer delay to diagnosis in our country. Early detection and specialized care would be of great practical importance. The increased use of newer treatment modalities may alter the natural history of this disorder and demand further and broader epidemiological studies in the future.

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Disclosures None

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