

THE EFFECT OF SEX ON RESPONSE TO TNF INHIBITORS IN A SAMPLE OF IRAQI
PATIENTS WITH AXIAL SPONDYLOARTHRITIS: A SINGLE CENTER STUDY

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ABSTRACT

Background: Axial Spondyloarthritis (axSpA) is a chronic inflammatory rheumatic disease predominantly affecting the axial skeleton. Tumor Necrosis Factor- α (TNF- α) inhibitors have revolutionized management, but sex-specific variations in treatment response remain under-investigated in Middle Eastern populations. **Objectives:** To evaluate the effect of sex on baseline disease profiles, functional status, and prospective clinical response to TNF inhibitors at 3 and 6 months among Iraqi axSpA patients. **Subjects and Methods:** A single-center prospective observational study was conducted at the Rheumatology Unit, Baghdad Teaching Hospital (November 2022 to April 2023). Two hundred patients with axSpA meeting ASAS classification criteria (130 males, 70 females) receiving continuous anti-TNF therapy were evaluated. Clinical measures including Erythrocyte Sedimentation Rate (ESR), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), and Bath Ankylosing Spondylitis Functional Index (BASFI) were assessed at baseline, 3 months, and 6 months post-treatment. Results: Male patients demonstrated significantly higher rates of radiographic disease (76.9% vs. 37.1 %, $p < 0.001$), HLA-B27 positivity (36.9% vs. 18.6%, $p = 0.007$), and smoking history (63.1 % vs. 7.1 %, $p < 0.001$). Conversely, females presented with higher rates of non-radiographic axSpA (62.9%), obesity (40.0% vs. 33.1 %, $p = 0.04$), and concomitant csDMARD use (38.6% vs. 9.2%, $p < 0.001$). Both sexes exhibited significant clinical improvement from baseline to 6 months ($p < 0.001$). However, female sex was associated with persistently higher residual disease activity (BASDAI at 6 months: 3.1 ± 1.4 vs. 2.4 ± 1.1 , $p = 0.001$), worse functional capacity (BASFI at 6 months: 3.3 ± 1.3 vs. 2.7 ± 1.4 , $p = 0.01$), and elevated inflammatory markers (ESR at 6 months: 21.9 ± 5.8 vs. 14.2 ± 11.8 mm/h, $p < 0.001$). **Conclusions:** Although TNF inhibitors are clinically effective in both sexes, Iraqi female axSpA patients present with higher baseline disease burden, greater functional impairment, and attenuated therapeutic response over 6 months compared to males.

KEYWORDS: Axial Spondyloarthritis, TNF Inhibitors, Sex Differences, BASDAI, BASFI, Iraq.

1. INTRODUCTION

Axial Spondyloarthritis (axSpA) is a chronic inflammatory arthritis that primarily involves the sacroiliac joints and the axial skeleton. It encompasses two clinical subsets: radiographic axSpA (r-axSpA or Ankylosing Spondylitis) and non-radiographic axSpA (nr-axSpA), distinguished by the presence or absence of structural sacroiliitis on plain radiographs. Historically considered a male-dominant disease due to the emphasis on advanced radiographic ankylosis, recent epidemiological criteria established by the Assessment of Spondylo Arthritis international Society (ASAS) have recognized a nearly equal sex prevalence, particularly in

nr-axSpA cohorts.

Biologic Disease-Modifying Antirheumatic Drugs (bDMARDs), specifically Tumor Necrosis Factor- α (TNF- α) inhibitors, have transformed axSpA management by suppressing systemic inflammation, alleviating pain, improving spinal mobility, and halting structural damage progression. Despite their efficacy, substantial heterogeneity in therapeutic response exists. Emerging global evidence suggests that sex plays a critical role in disease expression and biological drug survival. Female patients frequently report greater subjective disease activity, persistent fatigue, and higher

visual analog scale pain scores despite lower objective inflammatory markers and structural damage compared to males.

In Iraq, data regarding sex-specific clinical phenotypes and prospective treatment outcomes under TNF- α inhibition remain limited. Socioeconomic factors, diagnostic delays, metabolic comorbidities, and variation in HLA-B27 expression across populations may further modify treatment responses. Therefore, this prospective study was designed to investigate the effect of sex on baseline clinical and laboratory characteristics, as well as therapeutic response outcomes across a 6-month follow-up period in Iraqi patients with axSpA.

2. PATIENTS AND METHODS

Study Design and Setting: A single-center prospective observational cross-sectional study was conducted at the Rheumatology Consultation Clinic and Medical Rehabilitation Unit of Baghdad Teaching Hospital, Medical City Complex, Baghdad, Iraq. Patient recruitment and clinical follow-up spanned a 6-month period from November 2022 to April 2023. Ethical authorization was obtained from the Research Ethics Committee of the College of Medicine, University of Baghdad (Approval No. 136, dated October 1, 2023). Informed verbal consent was obtained from all participants prior to enrollment.

Patient Cohort and Eligibility Criteria: A total of 200 consecutive adult patients (≥ 18 years) diagnosed with axSpA according to the ASAS classification criteria were included. Inclusion required continuous anti-TNF therapy for at least 6 months with verified medical compliance and complete baseline, 3-month, and 6-month follow-up clinical records. Patients with active infections, overlap connective tissue diseases, malignancy, prior biologic treatment failures, or missing longitudinal data were excluded.

3. RESULTS

Table 3.1: Demographic Characteristics and Risk Factor Profiles Stratified by sex (n=200).

This table outlines the background socioeconomic, anthropometric, and environmental risk factor distributions among male and female axial spondyloarthritis patients.

Parameter / Category	Overall Sample (n=200)	Male Cohort (n=130)	Female Cohort (n=70)	p-value
Age (Years), Mean $\pm$ SD	38.4 $\pm$ 11.2	37.9 $\pm$ 10.8	39.3 $\pm$ 12.0	0.41
Unemployed / Housewife (%)	72 (36.0%)	14 (10.8%)	58 (82.9%)	<0.001 *
Urban Residence (%)	152 (76.0%)	98 (75.4%)	54 (77.1%)	0.78
BMI Brackets				0.04*
Normal Weight (<25.0 kg/m ²)	52 (26.0%)	38 (29.2%)	14 (20.0%)	
Overweight (25.0–29.9 kg/m ²)	77 (38.5%)	49 (37.7%)	28 (40.0%)	
Obese (≥ 30.0 kg/m ²)	71 (35.5%)	43 (33.1%)	28 (40.0%)	
Smoking Status (Current) (%)	87 (43.5%)	82 (63.1%)	5 (7.1%)	<0.001 *

Data Collection and Clinical Metrics: Standardized interview protocols and physical examinations were performed. Demographic variables included age, sex, residence, occupational status, body mass index (BMI), smoking status, disease duration, and family history. Clinical subtype (r-axSpA vs. nr-axSpA), HLA-B27 status, baseline peripheral joint involvement, and concomitant csDMARD use were documented. Therapeutic regimen details (Etanercept, Infliximab, Adalimumab) were recorded. Disease activity and physical function were evaluated at baseline, 3 months, and 6 months using.

- **Erythrocyte Sedimentation Rate (ESR):** Measured in mm/1st hour via Westergren method.
- **Bath Ankylosing Spondylitis Disease Activity Index (BASDAI):** A self-reported 0–10 scale measuring fatigue, spinal pain, joint pain/swelling, localized tenderness, and morning stiffness. A score ≥ 4.0 indicates active disease.
- **Bath Ankylosing Spondylitis Functional Index (BASFI):** A 0–10 scale assessing physical disability across 10 activities of daily living.

Statistical Analysis: Data were analyzed using IBM SPSS Statistics version 27.0. Continuous variables were expressed as mean $\pm$ standard deviation (SD), and categorical variables as absolute numbers and percentages. The Chi-square test (χ^2) and Fisher's exact test evaluated categorical differences between sexes. Independent sample.

t-tests compared continuous clinical variables between males and females at baseline, 3 months, and 6 months. Repeated measures ANOVA assessed longitudinal changes across timepoints. Statistical significance was set at $p < 0.05$.

Table 3.2: Baseline clinical phenotypic features and genetic markers according to sex (n=200).

Comparison of disease subtype classifications, disease duration, family history, and genetic status between male and female study participants.

Clinical Parameter	Male Cohort (n=130)	Female Cohort (n=70)	Statistical Significance
Radiographic axSpA (r-axSpA)	100 (76.9%)	26 (37.1 %)	$\chi^2 = 30.5$, $p < 0.001$ *
Non-Radiographic axSpA (nr-axSpA)	30 (23.1 %)	44 (62.9%)	$\chi^2 = 30.5$, $p < 0.001$ *

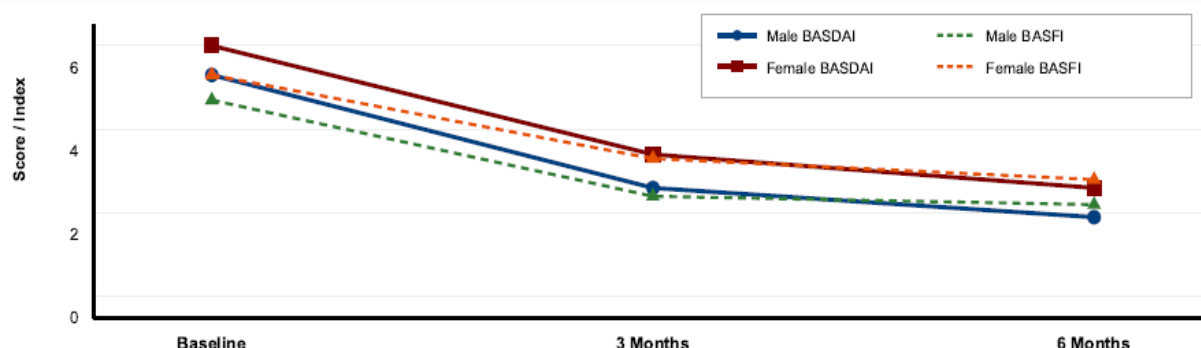
Table 3.3: Therapeutic agent distribution and concomitant csDMARD utilization by sex (n=200).

Detailed tabulation of specific anti-TNF biologic agents prescribed and accompanying synthetic DMARD co-therapies across sex cohorts.

Treatment Parameter	Overall Sample (n=200)	Male Cohort (n=130)	Female Cohort (n=70)	p-value
TNF Inhibitor Prescribed				0.70
Etanercept	118 (59.0%)	78 (60.0%)	40 (57.1 %)	
Infliximab	59 (29.5%)	37 (28.5%)	22 (31.4%)	
Adalimumab	23 (11.5%)	15 (11.5%)	8 (11.4%)	
Concomitant cs DMARD Therapy	39 (19.5%)	12 (9.2%)	27 (38.6%)	<0.001*
Methotrexate	18 (9.0%)	5 (3.8%)	13 (18.6%)	<0.001*
Sulfasalazine	21 (10.5%)	7 (5.4%)	14 (20.0%)	0.002*

Figure 3.1: Comparative longitudinal progression of ESR, BASDAI, and BASFI scores over 6 months of TNF inhibitor therapy.

Line plots illustrating time-course clinical response trajectory from baseline to 3 and 6 months stratified by sex.

**Table 3.4: Comparative baseline and prospective response parameters across 6 months of TNF inhibitor therapy (n=200). Longitudinal tracking of Inflammatory markers (ESR), Disease Activity Index (BASDAI), and Functional Index (BASFI) at baseline, 3 months, and 6 months post-treatment initiation.**

Clinical Parameter / Follow-up Interval	Male Cohort (n=130) Mean ± SD	Female Cohort (n=70) Mean ± SD	Mean Difference (95% CI)	Inter-sex p-value	Intra-sex Longitudinal p-value
Erythrocyte Sedimentation Rate (ESR, mm/1 st hr)					
Baseline	38.0 ± 23.6	37.6 ± 23.1	0.4 (-6.4 to 7.2)	0.91	<0.001 * (Both sexes)
3 Months	19.9 ± 12.4	25.0 ± 13.9	-5.1 (-8.9 to -1.3)	0.008*	
6 Months	14.2 ± 11.8	21.9 ± 15.8	-7.7 (-11.7 to -3.7)	<0.001 *	
Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)					
Baseline	5.8 ± 1.4	6.5 ± 1.2	-0.7 (-1.1 to -0.3)	<0.001 *	<0.001 * (Both sexes)
3 Months	3.1 ± 0.89	3.9 ± 1.2	-0.8 (-1.1 to -0.5)	<0.001 *	
6 Months	2.4 ± 1.14	3.1 ± 1.4	-0.7 (-1.1 to -0.3)	0.001 *	
Bath Ankylosing Spondylitis Functional Index (BASFI)					
Baseline	5.2 ± 1.1	5.8 ± 0.8	-0.6 (-0.9 to -0.3)	<0.001 *	<0.001 * (Both sexes)
3 Months	2.9 ± 1.1	3.8 ± 1.2	-0.9 (-1.2 to -0.6)	<0.001 *	
6 Months	2.7 ± 1.4	3.3 ± 1.3	-0.6 (-1.0 to -0.2)	0.01 *	

3. DISCUSSION

This prospective single-center study highlights distinct sex-specific dimorphisms in disease characteristics and anti-TNF response trajectories among Iraqi patients with axSpA. Our findings confirm that while TNF inhibitors induce significant clinical and functional improvements in both sexes, female patients maintain persistently higher subjective disease activity (BASDAI), worse functional impairment (BASFI), and elevated residual systemic inflammation (ESR) across a 6-month treatment period.

The clinical phenotype differed markedly between sexes at baseline. Male patients exhibited a striking predominance of radiographic axSpA (76.9%), higher HLA-B27 prevalence (36.9%), and longer disease duration prior to biologic initiation. This aligns with global registry data, including the REGISPONDA and DESIR cohorts, where radiographic structural damage and syndesmophyte formation are consistently higher in males. Conversely, female patients presented predominantly with non-radiographic axSpA (62.9%) and suffered significant diagnostic delays, a phenomenon widely attributed to lower HLA-B27 positivity rates and milder radiographic sacroiliitis in females leading to delayed specialist referral.

In terms of therapeutic response, both male and female patients demonstrated highly significant reductions in ESR, BASDAI, and BASFI from baseline to 6 months ($p < 0.001$), confirming the overarching efficacy of anti-TNF agents (Etanercept, Infliximab, Adalimumab) in our Iraqi population. However, female patients recorded higher absolute scores at every evaluation interval. The baseline BASDAI in females (6.5 ± 1.2) was significantly higher than in males (5.8 ± 1.4), and this discrepancy persisted at 6 months (3.1 ± 1.4 vs. 2.4 ± 1.1 , $p = 0.001$). A similar trend was observed for functional impairment (BASFI) and ESR levels, which dropped to 14.2 ± 11.8 mm/h in males compared to 21.9 ± 15.8 mm/h in females at 6 months ($p < 0.001$).

Several biological, psychological, and lifestyle mechanisms may explain these sex discrepancies. First, elevated obesity rates among female patients in our sample (40.0% vs. 33.1% in males) likely contribute to chronic low-grade systemic inflammation and altered pharmacokinetics of biological agents. Adipose tissue secretes pro-inflammatory adipokines that can attenuate anti-TNF response. Second, central sensitization, fibromyalgia overlap, and sex-specific pain perception pathways may elevate subjective sub-items of the BASDAI (such as fatigue and diffuse enthesal pain) in women, even when objective axial inflammation is controlled. Third, socioeconomic factors—notably the high unemployment/housewife rate (82.9%) in females—may influence health-seeking behavior and treatment adherence. Interestingly, female patients

received concomitant csDMARDs at a significantly higher rate (38.6% vs. 9.2%), reflecting clinician efforts to manage persistent peripheral symptoms or co-existing soft tissue inflammation.

4. CONCLUSIONS AND RECOMMENDATIONS

5.1 Conclusions: Substantial sex-based dimorphism exists among Iraqi patients with axial spondyloarthritis. Male patients are characterized by radiographic disease, HLA-B27 expression, and longer disease duration. TNF inhibitors are highly effective across both sexes; however, female patients exhibit a relatively attenuated response, with higher residual disease activity, worse functional disability, and higher ESR levels at 6 months.

a. Recommendations

- Establish early diagnostic protocols specifically targeting non-radiographic axSpA in females presenting with chronic back pain.
- Incorporate objective inflammatory biomarkers (such as MRI sacroiliac inflammation and high-sensitivity CRP) alongside subjective index scores (BASDAI/ASDAS) to guide treatment escalation in female patients.
- Implement multidisciplinary weight management and physical rehabilitation programs to address metabolic confounders like obesity.

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