

Ultrasound assessment of subclinical enthesitis in Ankylosing Spondylitis patients

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Abstract

Background: spondylarthritis (SPA) is a class of inflammatory illnesses that mostly affect the spine and other joints. While synovitis develops as a result of pro-inflammatory cytokines secreted from the enthesis, enthesitis can be the fundamental pathology.

Aim: To assess subclinical enthesitis in Ankylosing Spondylitis patients using musculoskeletal ultrasound with Madrid scan and to find its relation to the acute phase reactant.

Patients and methods: This research contained 50 Ankylosing spondylitis patients and 50 control. CBC, ESR, CRP and BASDAI was applied to define disease activity. Ultrasound assessment using Madrid score was applied to measure subclinical enthesitis at 6 pairs of enthesis. The study has been conducted in the Rheumatology & Rehabilitation department Al Hussain University Hospital.

Results: Subclinical enthesitis were found at 34.8% of cases with significant correlation to erythrocyte sedimentation rate and C-reactive protein compared to the control group.

Conclusion: The total Madrid score demonstrated good diagnostic accuracy for distinguishing AS cases from controls and helped in early detection and management of Ankylosing spondylitis to prevent further complications.

Keywords: Ankylosing Spondylitis; Subclinical Enthesitis; Musculoskeletal ultrasound

1. Introduction

Ankylosing spondylitis, psoriatic arthritis, reactive arthritis, enteropathy arthritis, and undifferentiated spondylarthritis are among the inflammatory disorders that fall under the umbrella of "spondylarthritis" (SPA).¹ These diseases mostly affect the spine and other joints. Even though each ailment is unique, they all have traits in common, such as inflammatory arthritis of the joints and spine.²

Enthesitis, or inflammation at the locations where tendons and ligaments connect to bone, is a prominent pathological characteristic of SPA.³ Enthesitis may be the predominant anomaly in ankylosing spondylitis, but synovitis may develop as a result of pro-inflammatory cytokines generated from the enthesis.⁴

In clinical terms, "active" enthesitis is defined as tenderness and/or swelling at the site of an enthesis. It can be formally evaluated using

tools like the Leeds Enthesitis Index and the Maastricht Ankylosing Spondylitis Enthesitis Score, among others.⁵ Ultrasound imaging offers an advantage over clinical examination (CE) as it allows direct visualization of the enthesis and its components with high sensitivity and specificity.⁶

The ultrasound features of active inflammation and structural changes have been included in the definition of enthesopathy by the Outcome Measures in Rheumatology (OMERACT). Enteritis might be present in patients diagnosed with Ankylosing spondylitis, and these subclinical enthesitis might elevate ESR and CRP.⁷

This study aimed to assess subclinical enthesitis in Ankylosing Spondylitis patients using musculoskeletal ultrasound with Madrid scan and to find its relation to the acute phase reactant.

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2. Patients and methods

This research was a case – control observational research includes 50 cases diagnosed with Ankylosing spondylitis regarding The Assessment of Spondylarthrititis International Society (ASAS) criteria and without any history of pain at the enthesis. and 50 age- and gender-matched healthy controls.

Ethical issues: The study will get started following the permission of the protocol by the Local Research Committee, the Studies Committee, and the Research Ethics Committee of our University, in accordance with the following: The research's goals, procedures, and length must be stated clearly. The confidentiality of data and results for all participants in the research will be preserved by maintaining data anonymity and restricting access to the research team only. The Research Ethics Committee is available for any future inquiries related to the research. Any potential risks associated with the local laws were rapidly managed by the researcher; therefore, only publicly available research was utilized in this research. Copyrights and other ethical considerations of each published site will be considered, as this review depends on published literature.

Inclusion criteria: Cases diagnosed with Ankylosing spondylitis according to The Assessment of Spondylarthrititis International Society (ASAS) criteria (Rudwaleit, 2009), with disease duration above 3 months and age above 18 years old.

Exclusion criteria: Symptomatic enthesitis, BMI above 30, Recent History of severe trauma to any site of enthesis included in the study, History of surgery at any site of enthesis included in the study, Recent Corticosteroid injection at the examined structure.

Methods

After approval from the Scientific Research and Ethics Committee of the Rheumatology and Rehabilitation Department, Al-Azhar University Hospital, the methodology of the research will be explained to the patients, and verbal informed consent will be obtained. All patients will be exposed to the following: Full History taking, Disease activity of Ankylosing spondylitis patients will be measured by using the Disease Activity BASDAI index, clinical examination, CBC, ESR, and CRP will be measured for all candidates. MSUS will be done on both case and control groups to find any sign of Enthesitis based on the OMERACT definition of enthesitis, which includes: Enhanced thickness at enthesis, Doppler signal at insertion, Hypo echogenicity, Calcifications/ enthesophytes, Erosions. Utilizing Madrid Sonography enthesitis index (MASEI) at:

distal Achilles tendon bilaterally, proximal plantar fascia bilaterally, brachial triceps tendons bilaterally, distal quadriceps tendon bilaterally, distal and proximal patellar ligament bilaterally. With PDUS and GSUS, every item received one point, except for calcification (scored as zero, one, two, or three) and erosion and Doppler signal (scored as zero or three). The overall potential score for both sides (twelve entheses) is 136.

Sample size: The study will be conducted on 50 Ankylosing spondylitis patients with and 50 controls, with a total of 600 entheses. Sampling method: Non-random sampling. Type of the study: Case-control observational study. Study setting: This study will be performed, and the patients will be recruited from the Rheumatology and Rehabilitation department at Al-Azhar University. Interpretation of statistics: The gathered data has been examined, encoded, and organized utilizing the Statistical Package for the Social Sciences (IBM Corp., 2017). IBM SPSS Statistics for Windows, Version 25.0. Armonk, New York: IBM Corporation. Data have been presented, and appropriate analyses have been conducted based on the type of data acquired for each parameter. The Shapiro-Wilk test has been conducted to assess the normality of the distribution of data. Mean and standard deviation for quantitative data. Percentage and frequency of qualitative data. The Student's T Test was utilized to evaluate the statistical significance of the difference between the means of the two research groups. The Mann-Whitney (U test) has been utilized to evaluate the statistical significance of a distinction in a non-parametric variable between two research groups. The Chi-Square test has been utilized to examine the association between two qualitative parameters. Correlation analysis: To assess the strength of association between two quantitative variables. The ROC Curve (receiver operating characteristic) serves as an effective tool for assessing the specificity and sensitivity of quantitative diagnostic measures that classify cases into two distinct groups. 3 The optimal cutoff point has been determined to optimize the AUC value. An AUC above 0.9 signifies excellent accuracy, 0.7–0.9 represents moderate accuracy, 0.5–0.7 reflects low accuracy, and 0.5 represents a chance result. A p-value is considered significant if less than 0.05 at a confidence interval 95%.

3. Results

The current research involved 50 cases diagnosed with Ankylosing Spondylitis (AS) and 50 age- and gender-matched healthy controls. The primary objective was to assess the presence of subclinical enthesitis using musculoskeletal ultrasound and correlate these findings with clinical and laboratory parameters, including

disease duration, BASDAI score, and inflammatory markers like CRP and ESR. Ultrasound findings were analyzed based on the Total Madrid Score.

Table 1. Subclinical Enthesitis Findings in Ankylosing Spondylitis Patients

CATEGORY	N - %
TOTAL EXAMINED ENTHESES	600 entheses
NUMBER OF ENTHESES WITH SUBCLINICAL ENTHERSITIS	209 entheses
PERCENTAGE OF SUBCLINICAL ENTHERSITIS	34.8%

According to Subclinical Enthesitis Findings in Ankylosing Spondylitis Patients, 209 out of 600 examined entheses (34.8%) have been identified as having subclinical enthesitis.

Table 2. Total Madrid Score Among Study Groups

	CASES (N=50)	CONTROLS (N=50)	TEST, P-VALUE
TOTAL MADRID SCORE	10.90 ± 11.26	0.36 ± 1.10	Z: 6.218, p < 0.001*
MEDIAN (MIN-MAX)	6.50 (0.00-39.00)	0.00 (0.00-4.00)	

Z: Mann whitnry test, * for significant p value (<0.05)

The total Madrid score, used to assess the severity of enthesitis, was significantly higher in the AS group (10.90 ± 11.26) compared to controls (0.36 ± 1.10, p<0.001). (Figure 1)

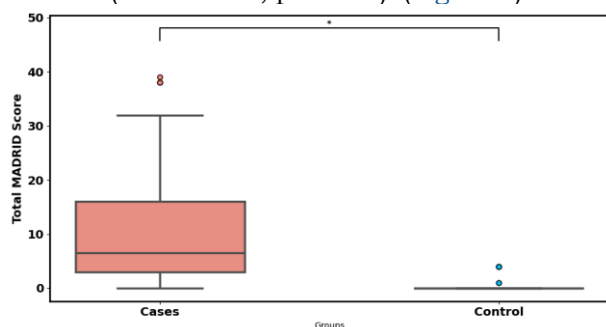


Figure 1. Comparison between studied groups according to total madrid score.

Table 3. Diagnostic performance of Total Madrid Score for discrimination between cases from control.

AUC	95% CI	P	Cut off	Sensitivity (%)	Specificity (%)
0.861	0.777 to 0.922	<0.001*	4	70	100

AUC, area under ROC curve; CI, confidence interval

The total Madrid score demonstrated good diagnostic accuracy for distinguishing AS cases from controls, with an AUC of 0.861, a sensitivity of 70%, and a specificity of 100% at a cut-off score of 4 (p<0.001). This suggests that the Madrid score is a valuable tool for identifying subclinical enthesitis in AS patients. (Figure 2)

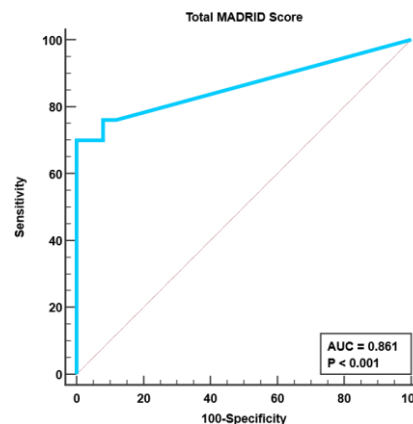


Figure 2. ROC curve of total MADRID score for discrimination between cases from control.

In the overall study population, age was significantly correlated with the Total Madrid Score, indicating that enthesitis severity tends to increase with advancing age. Hemoglobin levels showed a weak negative correlation with the Total Madrid Score, suggesting that lower hemoglobin levels may be associated with higher enthesitis severity, although the effect is relatively small. Both ESR and CRP, key markers of inflammation, were positively correlated with the Madrid Score. Among the Ankylosing Spondylitis (AS) cases, age and disease duration were strongly correlated with the Total Madrid Score. This indicates that older cases and those with longer disease duration tend to have more severe enthesitis. The BASDAI score, a measure of disease activity, was also positively correlated with the Madrid Score, showing that cases with higher disease activity tend to have more severe subclinical enthesitis. Blood parameters, including hemoglobin, platelets, and TLC, did not show significant correlations in the AS group. In the control group, there were insignificant correlations among the Total Madrid Score and most parameters, except for platelet count and TLC, which showed weak negative correlations. Interestingly, CRP had a negative correlation with the Madrid Score in the controls, although this relationship was not present in the AS group. These findings suggest that in healthy individuals, there may be minimal subclinical inflammation, as reflected by the weaker associations between inflammatory markers and enthesitis in this group. (Table 4)

Table 4. Correlation between Total Madrid Score and study parameters

	ALL SUBJECTS		CASES		CONTROL	
	Rs	p-value	rs	p-value	Rs	p-value
AGE (YEARS)	0.549	<0.001*	0.424	<0.001*	0.271	0.057
DISEASE DURATION IN YEARS	-	-	0.407	<0.001*	-	-
BASDAI	-	-	0.383	<0.001*	-	-
HEMOGLOBIN (G/DL)	-0.199	0.047*	-	0.646	0.069	0.633
PLATELETS	-0.129	0.202	-	0.900	-	0.029*

(10 ³ /μL)			0.018		0.309	
TLC (10 ³ /μL)	-0.150	0.136	-	0.639	-	0.034*
			0.068		0.300	
ESR (MM/H)	0.349	<0.001*	0.151	0.294	0.199	0.166
CRP (MG/L)	0.247	0.013*	0.036	0.803	-	0.015*
					0.341	
TSH (MIU/L)	-0.027	0.788	-	0.487	0.083	0.566
			0.101			
URIC ACID (MG/DL)	-0.062	0.542	0.119	0.412	-	0.262
					0.162	

rs: Spearman correlation coefficient, *: Significant ≤0.05

4. Discussion

The Total Madrid Score was significantly higher in the AS group (10.90 ± 11.26) compared to controls (0.36 ± 1.10, $p < 0.001$). This score serves as a critical measure for evaluating enthesitis severity and supports the notion that subclinical enthesitis is prevalent among AS patients. A total of 34.8% of examined entheses showed signs of subclinical enthesitis. The Total Madrid Score's function in clinical practice is reinforced by its ability to differentiate between AS patients and healthy controls. The results also show that ultrasonography studies can identify notable structural alterations in entheses in patients with AS, validating the importance of using scoring systems like the Total Madrid Score to monitor disease activity and guide treatment strategies effectively.⁸ Furthermore, the Total Madrid Score's association between age and disease duration indicates that patients who are older and have had their condition longer tend to have more severe enthesitis, which is consistent with the chronic nature of inflammation in ankylosing spondylitis.⁹ Inflammatory markers like ESR and CRP also showed positive correlations with the Madrid Score, reinforcing their role as indicators of disease activity.¹⁰ Age significantly correlates with the Total Madrid Score, reflecting increased enthesitis severity in older patients.¹¹ The results demonstrated that both ESR and CRP levels were positively associated with the Madrid Score, highlighting their importance in assessing inflammatory activity.¹²

Hemoglobin levels showed a weak negative correlation, suggesting that anemia may be linked to more severe enthesitis manifestations.

4. Conclusion

This study effectively demonstrates that ultrasound can reveal subclinical enthesitis in patients with Ankylosing Spondylitis. The results underscore the importance of early detection and management strategies aimed at mitigating inflammation and preventing long-term complications associated with Ankylosing Spondylitis.

Disclosure

The authors have no financial interest to declare in relation to the content of this article.

Authorship

All authors have a substantial contribution to the article

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There are no conflicts of interest.

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