BENHA MEDICAL JOURNAL bmj

Print ISSN 1110-208X

Online ISSN 2357-0016

Original article

Planter Entheseal involvement in Rheumatoid arthritis patients

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Received: 26 May 2024

Accepted:23 August 2024

Abstract

Introduction: Although enthesopathy is considered a common feature of Spondyloarthritis (SpA) but also it is one of the impacts of Rheumatoid Arthritis (RA) on the musculoskeletal system (MSK), this study elucidates the frequency of planter enthesopathy in RA patients. **Aim of the work:** is to determine the occurrence of planter entheseal involvement in RA patients using musculoskeletal ultrasound (MSUS) and to elucidate its association with disease activity and autoantibodies. **Subject and methods:** planter entheses were assessed cross-sectionally in 60 RA patients and 60 age and sex matched apparently healthy volunteers. Clinical and laboratory data were collected to assess disease activity using Disease Activity Score-28 (DAS-28), Real-time ultrasonography was performed for detection of planter enthesopathy, and abnormalities were quantified using the Madrid Sonography Enthesitis index (MASEI). **Results:** Clinical enthesitis was found in 58 of 120 examined persons, with significant prevalence of planter US enthesopathy in RA patients 30%. Ultrasound (US) examination revealed the presence of one or more abnormalities (entheseal thickening, enthesophytes, erosions, structural abnormalities, PD), with significant association regarding Disease activity score & Entheseal thickness and PD Signal. But insignificant associations regarding Disease activity score & other US findings. Insignificant associations were detected between ultrasound findings and autoantibodies (RF ,ACCP). **Conclusions:** Higher frequency of planter enthesopathy among RA patients, evidenced by clinical and ultrasonographic features. The presence of enthesitis in RA might represent a potential marker for disease activity.

Key words: RA, MSUS , Planter enthesitis

Introduction

Rheumatoid arthritis (RA), one of the systemic autoimmune diseases is characterized by chronic synovitis and progressive joint destruction leading to decline in functional capacity, eventual work disability, and reduced quality of life (QoL) (1). Musculoskeletal system (MSK) involves multiple joints, tendon sheaths, and bursae (2). As a result of synovitis and bone inflammation (osteitis), the disease leads to progressive destruction of hyaline cartilage, bone, and soft tissue (3). However, the literature on entheseal pathology in RA has been rather scarce, believed to be secondary to articular synovial inflammation and based on the involvement of synovial membrane lining the tendon sheaths and the bursae (4).

Enthesopathy is associated with inflammation at the site of tendons or ligaments in the bone (5).

Imaging studies are more sensitive and specific than clinical examination in the diagnosis of enthesitis, and even US might be superior to MRI in detection of early signs of enthesopathy (6).

Ultrasound gives a detailed information about active and chronic lesions affecting the entheses (7). Also, US being a real-time examination, it allows the lateral sweep of the transducer for identification of the thickest section through the plantar fascia (8).

Planter enthesopathy is considered one of planter heel pain syndromes. Plantar aponeurosis (PA) is a fascial structure that originated from the calcaneus and traversed the foot to insert onto the base of each metatarsal bone (9).

Aim of the work: The aim of this study was to determine the occurrence of planter entheseal involvement in rheumatoid arthritis (RA) patients using MSUS and to elucidate its association with disease activity and autoantibodies.

Subjects and methods:

This cross-sectional study was carried out on two groups; group 1: sixty RA patients diagnosed according to the 2010 American College of Rheumatology/European League Against Rheumatism classification criteria for rheumatoid arthritis (ACR/EULAR) (10) recruited from Benha University Hospitals ; Rheumatology, Rehabilitation and Physical Medicine outpatients' clinic and inpatients' department in the period from March to August 2022 (6 months), group 2: sixty apparently healthy subjects recruited from the hospital personnel and relatives of other patients as a control group. Patients with previous knee or ankle surgery, patients diagnosed with psoriasis or inflammatory bowel disease or overlapping with SPA, were excluded. The nature of the current study was discussed with all participants, and from each participant, an informed consent was obtained before inclusion, and all procedures performed were in accordance with the ethical standards of the Benha University Medical Ethical Review Board **(MS 37-2-2022)** and with the 1964 Helsinki declaration ethical standards.

Clinical and laboratory profile: All patients were subjected to: Clinical evaluation: *, Through history taking, *Complete clinical examination * Clinical assessment of plantar enthesopathy by (Inspection: for redness, swelling at the inferior pole of the calcaneus and Palpation: for tenderness, swelling).

*Laboratory investigations that included CBC, ESR, CRP, Liver enzymes, Kidney functions. *Immunological investigation (RF–ACCP) by immunofluorescence technique. *Assessment of disease activity using Disease Activity Score-28 (DAS-28) (11). *Radiological evaluation in the form of plain X-ray of both hands and both feet *Assessment of disease disability using the HAQ (health assessment questionnaire) as a comprehensive measure of outcome in RA patients and scored (0-3) for the four possible responses for the Disability Index questions (12). *Real-time ultrasonography was performed for detection of planter enthesopathy: using an liner high frequency 6-15 MHz probe on LOGIQ P9, made in Korea ultrasound machine. Abnormalities were quantified using the Madrid Sonography Enthesitis index (MASEI) and an enthesopathy score was calculated for each patient giving a possible maximum total score of 22. Patients diagnosed with bilateral planter enthesitis, the most sever one is the one that was scored and was examined by MSUS.

Statistical analysis:

All statistical calculations were performed using the statistical package for the social science, version 2١ (SPSS, Chicago, IL, USA). Quantitative variables were described in the form of mean ± standard deviation (SD) when normally distributed and median (range) when not normally distributed. Qualitative variables were described as number and percent. The Mann-Whitney U test was used for comparison of non-normally distributed quantitative variables. Qualitative variables were analyzed using $\chi 2$ (chi square) test or Fisher's exact test when the expected frequency was less than 5. P value$\leq$0.05 is considered significant and $\leq$0.01 was considered highly significant.

Results:

Demographic characteristics of the studied groups showed no statistically significant differences between patients and the control group regarding age, sex distribution and BMI. The disease's duration ranged between 1 year and 30 years with a mean of 9.6±7.3 years among RA patients group.

Clinical planter Enthesitis was positive in (58 /120); in cases group 43 patients had positive planter enthesitis (71.7%) and 17 patients had negative planter enthesitis (28.3%),while in control group only 15 persons had positive tender planter enthesitis(25.0%), There is a highly significant difference as regarding clinical planter enthesitis**(P <0.001)(Table 1).**

Regarding different ultrasonographic findings between cases and the control group, there was a statistically significant difference regarding bone erosion(P=0.01), while there were insignificant differences regarding the presence of Enthesophytes(P=0.8), positive PD

signal(P=0.1) and abnormal aponeurosis structure(P=0.1) (Table 2).

Regarding planter entheses assessment using MSUS; there is a highly significant difference between RT&LT planter Enthesis regarding presence of thickened Planter Enthesis in both cases and control group (P<0.001)(Figure 1) with a mean thickness of (4.4 ±0.81),(3.71 ±0.73) for cases and control group on the Right side respectively. and a mean of (4.4 ±0.84), (3.69 ±0.78) for cases and control group on the Left side respectively.

Ultrasonographic finding of planter fascia in RA patients were distributed as fellow **;** 8 patients (6.7)% had calcaneal bone erosion, 12 patients(10%) had calcifications in their aponeurosis at the calcaneal region ,4 patients (3.3%) had positive signal with PD , 12 patients (10%) had abnormal aponeurosis structure **(Figure 2)**.

Regarding DAS-28 of the involved RA patients, 2 patients had low disease activity (3.3%) status, 36 patients had moderate disease activity (60 %), 22 patients had high disease activity (36.6 %), no patients were in remission.

There was a statistically significant correlation between entheseal thickness with DAS-28 **(r=0.310, P=0.016)**, and HAQ **(r=0.257, P-0.047) (Table 3).**

Regarding the association between ultrasonographic findings in patients with different disease activity status, we found a statistically significant association regarding DAS and PD Signal **(p=0.03)**, while there was a statistically insignificant association regarding DAS and other US findings [bone erosion **(p=0.2)** , enthesophyte **(p=0.2)** , structural abnormality**(p=0.4)**].

Significant positive correlations were found between MASEI score and age, BMI, and disease duration **(p=00.03,0.015, 0.01)** respectively **(Table 4).**

There was a statistically significant association between DAS -28 and PD Signal **(P=0.03)** , while there were a statistically insignificant associations regarding DAS-28 and other US findings.(bone erosion, enthesophyte, structural abnormality) **(P=0.2 ,0.2 ,0.4)** respectively **(Table 5).**

Among patients with positive RF; 11.4% had bone erosion ,11.4 % had Enthesophytes, 5.7% had PD signal and 14.3% had structural abnormality. While in patients with negative RF;16% had bone erosion,12% had Enthesophytes, 8% had PD signal and 16% had structural abnormality) with statistically insignificant associations between these ultrasound findings and RF**(Table 6)**.

Among patients with positive ACCP;13.3% had bone erosion, 15.6 % had Enthesophytes , 8.9% had PD signal and 15.6% had structural abnormality. While in patients with negative ACCP;13.3 % had bone erosion, 13.3% had structural abnormality, no patients had Enthesophytes or PD signal with statistically insignificant associations between with these ultrasound findings and ACCP **(Table 6)**.

Among patients with normal BMI 30% of them had Enthesophytes and 10% had PD

signal. While in patients showed overweight 18.9% had bone erosion, 5.4% had Enthesophyte ,5.4% had PD signal and 21.6% had structural abnormality. While obese patients; 7.7% had bone erosion, 15.4% had Enthesophyte ,7.7% had PD signal and 7.7% had structural abnormality with insignificant associations between these ultrasound findings and BMI**.**

In between US findings there were statistically significant associations between the age and both of bone erosion and structural Abnormality **(p=0.001 ,0.007)** respectively. While there were insignificant associations between the Age and both of Enthesophyte and PD signal **(p=0.7 ,0.1)** respectively**.**

Among the studied RA patients, 71.7% of RA patients were on regular steroid in a dose ranging from 5 to 20 mg/day, 51.7 % of them were on regular Methotrexate , 58.3 % of them were on regular Hydroquine , 13.3% of them were on regular Leflunamide , 46.7% them were on regular Sulfasalazine, 13.3 % of them were on regular Biologic therapy.

Table (1): Comparison of the study groups regarding Clinical Enthesitis:

		Cases (n=60)		**Control (n=60)**		**Total**		**X^2**	**p-value**
		No.	%	No.	%	No.	%		
Clinical Enthesitis	N	17	28.3%	45	75.0%	62	51.7%	24.3	<0.001*
	P	43	71.7%	15	25.0%	58	48.3%		
Total		60	100.0%	60	100.0%	120	100.0%		

Table(2):comparison between the studied groups regarding MSUS findings:

		Cases (n=60)		Control (n=60)		Total		X^2	**p-value**
		No.	%	No.	%	No.	%		
Bone erosion	N	52	86.7%	60	100.0%	112	93.3%	6.6	0.01*
	P	8	13.3%	0	0.0%	8	6.7%		
Enthesophyte/ calcification	N	53	88.3%	55	91.7%	108	90.0%	0.1	0.8
	P	7	11.7%	5	8.3%	12	10.0%		
PD signal	N	56	93.3%	60	100.0%	116	96.7%	2.3	0.1
	P	4	6.7%	0	0.0%	4	3.3%		
Structural Abnormality	N	51	85.0%	57	95.0%	108	90.0%	2.3	0.1
	P	9	15.0%	3	5.0%	12	10.0%		

Table (3): Correlation between entheseal thickness, DAS and HAQ

	r	p-value
DAS	0.310	0.016*
HAQ	0.257	0.047*

DAS= Disease activity score, HAQ: Health assessment questionnaire.

Table (4): Correlation between MASEI and different variables:

	Correlation coefficient(r)	**p-value**
Age	0.371	0.003*
BMI	0.37	0.015*
Disease Duration	0.331	0.01*

Table (5): Comparison between RA patients with different disease activity status regarding MSUS findings

	Low activity (n=2)		**Moderate activity (n=35)**		**High activity (n=23)**		**X^2**	**p-value**
	No.	%	No.	%	No.	%		
Bone erosion	1	50.0%	5	14.3%	2	8.7%	2.8	0.2
Enthesophyte /Calcification	0	0.0%	2	5.7%	5	21.7%	3.7	0.2
PD signal	0	0.0%	0	0.0%	4	17.4%	6.9	0.03*
Structural Abnormality	1	50.0%	5	14.3%	3	13.0%	2.1	0.4

Table (6): Relation between RF /ACCP results and US findings:

Characteristics	**RF**				**X^2**	**p-value**
	Positive		**Negative**			
	No.	**%**	**No.**	**%**		
Bone erosion	4	11.4%	4	16%	0.3	0.6
Enthesophyte /Calcification	4	11.4%	3	12%	0.1	0.9
PD signal	2	5.7%	2	8%	0.1	0.7
Structural Abnormality	5	14.3	4	16%	0.1	0.9
Characteristics	**ACCP**				**X^2**	**p-value**
	Positive		**Negative**			
	No.	**%**	**No.**	**%**		
Bone erosion	6	13.3%	2	13.3%	---	---
Enthesophyte/Calcification	7	15.6%	0	0.0%	2.6	0.1
PD signal	4	8.9%	0	0.0%	1.4	0.2
Structural Abnormality	7	15.6%	2	13.3%	0.1	0.8

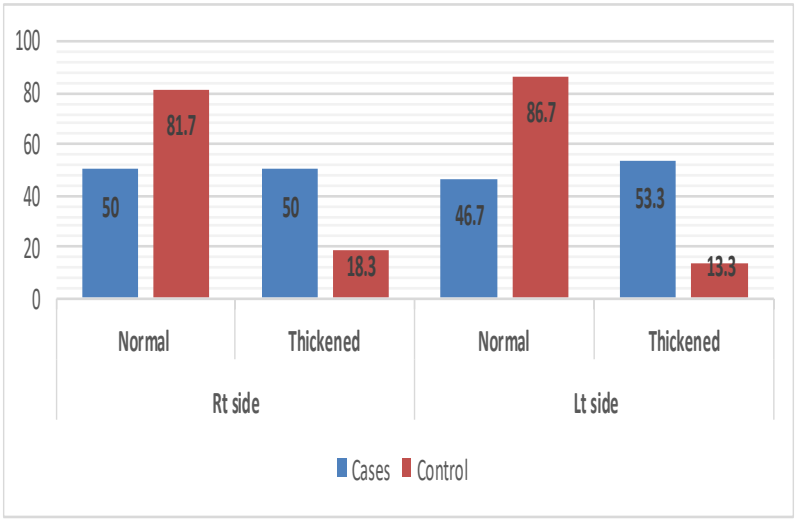

Figure (1): Comparison of study groups regarding presence of thickened Planter Enthesis

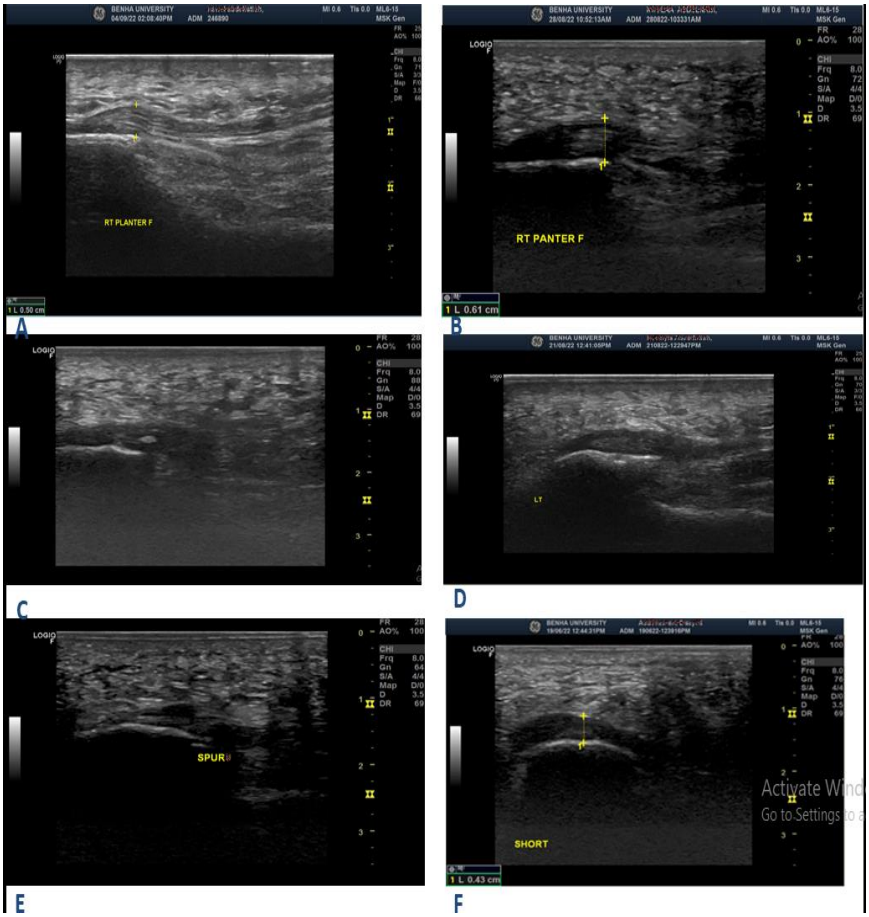

Figure (2): Long views: A) Increased entheseal thickness with preserved fibrillar appearance, B) Increased thickness with pathological echogenicity, C) Entheseal enthesophyte, D) Step down sign of calcaneal bone erosion, E) Calcaneal spur, F) Short axis of mildly increased planter entheseal thickness

Discussion:

There is limited data regarding US evaluation of enthesitis in RA. Thus, it is necessary to evaluate enthesopathy in RA using US (13). Currently, this work studied Planter Entheseal involvement in rheumatoid arthritis patients.

This work revealed positive clinical planter enthesitis in 43 RA patients (71.7%) and 17 patients had negative planter enthesitis (28.3%), This was different from a study that found the least affected site was the plantar fascia among RA patients (14), this gap could be explained by different selected groups between both studies. In the same study, 3% of RA patients only had calcaneal bone erosion , and we found calcaneal erosions in 6.7 % of RA patients with significant difference between cases and the control group (P=0.01) , this may be due to different sample size and different disease durations.

In the present study; significant occurrence of planter US enthesopathy in RA patients 30% , similar to other that showed significant prevalence of US enthesopathy in 33.3%(15).

Our study showed a highly significant difference between RA patients and controls regarding RT&LT planter entheseal thickness (P<0.001), while another study showed no significant difference between RA and control groups as regarding thickened planter enthesis (13).

In our study there was a statistically significant difference regarding bone erosion between cases and control (P=0.01) and insignificant difference regarding the presence of enthesophytes (P=0.8), positive PD signal(P=0.1) and abnormal aponeurosis structure(P=0.1), although, another study showed that there were statistically insignificant difference regarding bone erosion (P=0.08) and the presence of Enthesophytes (P=0.14) .and significant difference regarding positive PD signal, highly significant difference regarding abnormal aponeurosis structure (P=0.004) between cases and control groups (13), This discrepancy could be attributed to different sample size.

Our study showed a statistically significant correlation between entheseal thickness and DAS (P=0.016), statistically significant association between DAS & PD Signal (P=0.03). And insignificant association regarding DAS & other US findings.

Other investigators studied the frequency of enthesopathy among SLE patients as an example of autoimmune disease, they reported that SLEDAI score had a highly significant positive correlation with US enthesitis (16)

Our study showed insignificant correlations between MASEI and HAQ, which agrees with another study (17) (p=0.065).

Our study showed that ; from patients with positive RF [11.4% had bone erosion (p=0.6) ,11.4 % had Enthesophytes (p=0.9) , 5.7% had PD signal (p=0.7) , 14.3% had structural abnormality (p=0.9)], while from

patients with negative RF [16% had bone erosion (p=0.6) ,12% had Enthesophyte (p=0.9) , 8% had PD signal (p=0.7) , 16% had structural abnormality (p=0.9)] and all showed statistically insignificant associations between these ultrasound findings and RF, this was similar to another study among RA patients(18).

Our study showed that; from patients with positive ACCP (13.3% had bone erosion , 15.6 % had Enthesophytes (p=0.1) , 8.9% had PD signal (p=0.2) , 15.6% had structural abnormality (p=0.8), while from patients with negative ACCP (13.3 % had bone erosion, 13.3% had structural abnormality (p=0.8), no patients had enthesophytes or PD signal. All showed statistically insignificant associations between these ultrasound findings and ACCP, that was different from another study that showed positive correlation between Anti-CCP and tenosynovitis/paratenonitis score by gray scale US(GSUS) (p = 0.023) among RA patients (19).

Our study showed 5 patients (75%) with positive ACCP and 15 patients (25%) with negative ACCP with some difference from another study that showed positive anti-CCP in 222 patients (53.21%) and negative anti-CCP in 196 patients (46.89%) among Iranian RA population (20). This difference could be attributed to different ethnicities.

Our study showed; positive highly significant correlations between MASEI and age (p=0.003*), in agreement with another study among hemodialysis patients (p=0.032) that considered the age as an important influencer of the biological milieu and tendon adaptation to mechanical loading (21).

Our result showed; positive significant correlations between MASEI and BMI (p=0.015*), positive significant correlations between MASEI and Disease Duration (p=0.01*), this was similar to what was found by Rabee et al., among the studied SLE patients (p=0.002) (22).

Although, a study showed when the body mass index (BMI) > 25 kg/m2, there is 2-fold increased risk for planter fasciitis (23), our study showed statistically insignificant associations between ultrasound findings and BMI. And this may be due to different clinical and mechanical measures of their foot and ankle function and different underlying bone & soft tissues abnormalities with different daily physical activities among the studied population.

Our study showed a significant association between the age and bone erosion (p=0.001), that was similar to what was found by another study among RA patients (18).

We found significant association between the age and structural abnormality (p=0.007), that was like what was found in a study that illustrated positive, significant, and moderately strong correlation between age (as a continuous variable) and ordinal stages, which is seen for all (fibrous and fibrocartilaginous) entheses under study (24). Also, another showed that age is an independent predictor of the thickness of the planter fascia, and age and gender are

independent predictors of echogenicity of the planter fascia (25).

Our study showed insignificant association between the Age and both of Enthesophyte and PD signal. that was different from another that showed healthy subjects had frequent lesions at entheses on US, correlated with their age and BMI (26).

This study had some limitations. First, the small sample size, variations in the clinical presentation of patients, the use of different types of therapy, different laboratory techniques. Secondly, the cross-sectional design of the study was better to be longitudinal which would allow evaluation of the predictors & their correlations and long-term outcome of planter enthesopathy in RA patients Thirdly, studying more lower limb entheses are needed for perfectly applying any of lower limb entheses scores. So, further studies are recommended to include many participants that can enhance the findings of our study.

Conclusion:

Higher frequency of planter enthesopathy among RA patients, evidenced by clinical and ultrasonographic features. The presence of enthesitis in RA might represent a potential marker for disease activity.

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To cite this article: Refaat M. El-tannawy, Nashwa I. Hashaad, Rehab M. Gabal, Hagar A. Abd El-Maksoud. Planter Entheseal involvement in Rheumatoid arthritis patients. BMFJ 2024;41(8): 616-627.