

Exercise is Effective for Disease Activity Control with Various Effects on Entheses: An Ultrasound-Based Study

Maroua Slouma^{1,2}, Siwar Ben Dhia^{1,2}, Lobna Kharrat^{1,2}, Celia Bellagha^{1,2}, Hedia Bellali^{2,3}, Imen Gharsallah^{1,2}

¹ Department of Rheumatology, Military Hospital, Tunis, Tunisia

² University of Tunis El Manar, Tunis, Tunisia

³ Department of Epidemiology, Habib Thameur Hospital, Tunis, Tunisia

CORRESPONDING AUTHOR:

Siwar Ben Dhia
Department of Rheumatology
Military Hospital
Bab Alioua Street
Tunis, Tunisia 1007
E-mail: siwarbendhia@gmail.com

DOI:

10.32098/mltj.02.2024.16

LEVEL OF EVIDENCE: 4C

SUMMARY

Introduction. The effect of physical activity on disease activity and enthesitis in patients with spondyloarthritis is unknown. We aimed to describe clinical and enthesitis features and disease activity of spondyloarthritis patients and to assess the association between physical activity and disease activity.

Methods. We conducted a cross-sectional study including consecutive patients followed for radiographic axial spondyloarthritis. For each patient, we performed ultrasonography of entheses and assessed disease activity. Physical activity level was assessed using the University of California and Los Angeles (UCLA) activity scale and the Tegner activity scale.

Results. We examined 518 entheses in 37 patients. There were 29 men (78%) and 8 women (22%). The mean age was 44.62 ± 12.31 years. Exercise was performed in 51% of patients. The median (IQR 25%-75%) UCLA activity scale was 4 (4-5) and the median (IQR 25%-75%) Tegner physical activity scale was 3 (3-5). Exercise was associated with a lower risk of disease activity (OR 0.123, $p = 0.022$, 95%CI 0.020-0.742). We didn't find a significant difference in enthesitis ultrasound characteristics between the patients practicing or not practicing exercise. Patients doing exercise had a significantly lower risk of having ≥ 3 ultrasonographic enthesophytes and plantar aponeurosis enthesophytes. Nevertheless, those who engage in physical activity have a significantly higher risk of hypoechoogenicity in the lateral epicondylar tendons.

Conclusions. Our study showed that exercise was associated with lower clinical disease activity. Physical activity can be responsible for ultrasonographic tendon insertion damage, but it doesn't accentuate the structural damage. The promotion of physical activity should be considered a healthcare priority.

KEY WORDS

Physical activity; exercise; entheses; ultrasonography; spondyloarthritis.

INTRODUCTION

Radiographic axial Spondyloarthritis (SpA), also called ankylosing spondylitis, is a chronic rheumatic disease affecting typically young men. Its prevalence ranges between 0.2% and 1.6% (1). Sacroiliac joints and spine involvement are the main characteristic features of SpA (2). It can be responsible for pain, stiffness, and disability.

The inflammation of entheses, also called enthesitis, is believed to be the central lesion in SpA (3). Entheses are skeletal anchorage points of the tendon, ligament, and joint capsule (4).

The pathophysiology of enthesitis is not fully elucidated, pro-inflammatory cytokines (IL-17, IL-22, and IL-23) and metalloproteinases seem to be involved in this disease (5-8).

Enthesitis can be asymptomatic or responsible for inflammatory pain (9). Ultrasonography (US) can detect subclinical enthesitis (10-13) and reveal early enthesal abnormalities (14, 15).

The therapeutic management of axial and enthesal manifestations is based on non-steroidal anti-inflammatory drugs (NSAIDs) and biological Disease-Modifying Anti-Rheumatic drugs (bDMARDs). The treatment goal is to achieve remission or at least low disease activity (16).

Several scores are used to assess axial disease activity and clinical and US entheses involvement. Data regarding the relationship between physical activity and disease activity and entheses scores in SpA patients are scarce.

The effect of physical activity on SpA disease activity and enthesitis is unknown.

The aim of this study was to assess the association between physical activity, disease activity, and ultrasonographic enthesal abnormalities in SpA patients.

METHODS

Patients

We conducted a cross-sectional study including consecutive patients followed for SpA and recruited from the outpatient clinic of the rheumatology department.

Inclusion criteria

We included patients fulfilling the Assessment of SpondyloArthritis International Society (ASAS) 2009 criteria (17).

Non-inclusion criteria

Non-inclusion criteria were SAPHO (Synovitis-Acne-Pustulosis-Hyperostosis-Osteitis) syndrome and crystal-induced arthritis.

Clinical assessment

The following patients' and SpA characteristics were collected: age, gender, body mass index (BMI), age of SpA onset, disease duration, extra-articular manifestations (uveitis, psoriasis, inflammatory bowel disease (IBD), pulmonary involvement, cardiac involvement, renal involvement, and osteoporosis), comorbidities according to the European League Against Rheumatism (EULAR) (18), and therapeutic management (NSAIDs, conventional synthetic DMARDs (csDMARDs), and bDMARDs).

Disease activity was assessed using Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) (19) and the Ankylosing Spondylitis Disease Activity Score (ASDAS_{CRP}) (20). Active disease corresponds to an ASDAS_{CRP} higher than 2.1 or BASDAI higher than 4.

Clinical assessment of enthesitis was performed using the Maastricht Ankylosing Spondylitis Enthesitis Score (MASES), Spondyloarthritis Research Consortium of Canada Enthesitis Index (SPARCC), and Leeds Enthesitis Index (LEI).

Physical activity and exercise evaluation

Physical activity is any bodily movement that increases energy expenditure above resting levels. However, exercise, is a subset of physical activity that is planned, structured and repetitive: jogging, biking, playing football or tennis, weightlifting, *etc.* (21).

Physical activity was assessed using the University of California and Los Angeles (UCLA) and the Tegner activity scales. UCLA activity scale is a 10-item scale including 10 descriptive activity levels ranging from wholly inactive and dependent on others (level 1), to regular participation in impact sports such as jogging or tennis (level 10) (22, 23).

Tegner activity scale is an 11-item scale with activity levels ranging from 0 (sick leave or disability) to 10 (competitive sports (national elite)) (24).

The patients were also asked to estimate the weekly duration of exercise and of physical activity.

Biological assessment

Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels were measured.

Ultrasonography assessment

A board-certified rheumatologist trained in ultrasonography performed the US examination. The rheumatologist was blinded for clinical data. The US evaluation was performed using a Mindray DC-70 device equipped with a 6-16 MHz linear transducer. The US was carried out after 15 minutes of rest at a room temperature maintained at 20 °C.

We explored the entheses of the quadriceps tendon (QT), proximal patellar tendon (PPT), distal patellar tendon (DPT), calcaneal tendon (CT), plantar aponeurosis (PA), lateral epicondyles (LET), and triceps tendon (TT).

For each patient, we calculated the following ultrasonographic enthesitis assessment scores: Spanish Enthesitis Index (SEI) (25), Glasgow Ultrasound Enthesitis Scoring System (GUESS) (12), and Madrid Sonographic Enthesitis Index (MASEI) (11).

The entheses were assessed according to the Outcome Measures Rheumatoid Arthritis Clinical (OMERACT) recommendations (26), which means 2 mm of the insertion of the bony cortex on both longitudinal and transversal axes. For each entheses, we specified the presence or not of enthesophyte, hypoechogenicity, calcification, or bony erosion.

Evaluated US abnormalities were:

- US tendon insertion damage: visualized as a thickened tendon or structural changes of the tendon insertion (hypoechoic or loss of its fibrillated appearance). The following cut-offs were used to define a thickened tendon: 5.29 mm for the CT, 4.4 mm for the PA, 6.1 mm for QT, 4 mm for both PPT and DPT (12), 4.3 for TT (11), and 3 mm for LET (27).
- Structural damage corresponds to enthesophytes, calcifications, or erosions.
- A power Doppler (PD) was evaluated at the bony insertion of the enthesis and was scored as a binary item (negative if absent and positive if any signal was present).

Statistical analyses

Statistical analyses were performed using Statistical Package for Social Sciences (SPSS) version 23. Quantitative variables were tested for normal distribution using the Shapiro-Wilk test.

We compared means of independent series using the independent samples Student T test for normally distributed variables. We performed the Mann-Whitney test to compare continuous variables with non-normal distribution. The Chi-square test was performed to assess the association between two categorical variables. As the number of patients was higher than 30, correlations between the tendon thickening and clinical or biological parameters were tested by Pearson's correlation coefficient. The prevalence ratio (PR) was used to quantify the link between independent variables and physical activity or high disease activity. We performed a stepwise backward binary logistic regression to identify risk factors independently associated with high disease activity (25) and US abnormalities associated with physical activity.

For this study, we included parameters that were significantly associated within the univariate analysis and those having

a P-value < 0.20. All statistical tests were two-sided, and the level of statistical significance was set up at (P-value < 0.05).

Ethical consideration

This study was approved by the ethics committee of the Military Hospital of Tunis (Local Person Protection Committee, Military Hospital of Tunis. Number protocol: 81/2020/CLPP - date of approval: November 10, 2020). It was conducted according to the Declaration of Helsinki. Each participant signed consent after explaining the aims and methods of the study.

RESULTS

Patients' characteristics

A total number of 518 entheses was assessed. We included 37 patients (29 men (78%) and 8 women (22%)). The mean age was 44.6 ± 12.3 years. The mean BMI was 26.5 ± 4.1 kg/m². Using BASDAI, 23 patients had active disease.

Clinical and biological characteristics are summarized in **table I**.

Physical activity characteristics

Fifty-one percent of patients practiced exercises.

Aerobic exercise was performed by 49% of patients (n = 19) (walking: 27%, jogging: 8%, football: 5%, biking: 3%, handball: 3%, and fitness exercise: 3%). Anaerobic exercise (weightlifting) was performed by only one patient. Variations of UCLA physical activity scale and Tegner activity scale are represented in the **figure 1**.

Physical activity characteristics are summarized in **table I**.

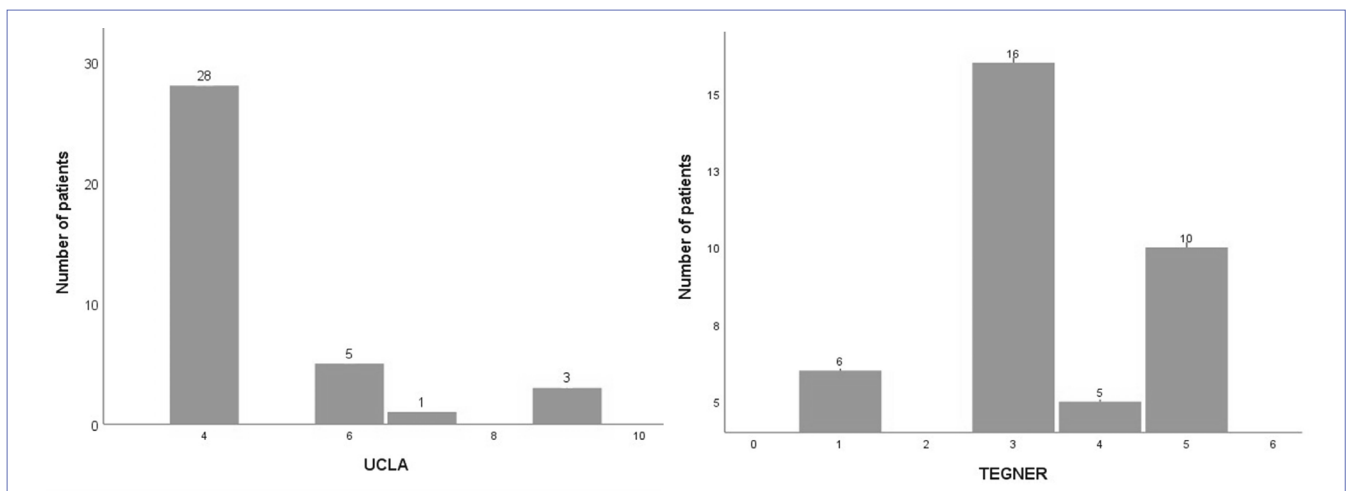


Figure 1. Variation of UCLA physical activity scale and Tegner activity scale.

Table I. SpA patients' characteristics.

Variables	
Clinical characteristics	
Age at onset, mean \pm SD years	38.1 \pm 11.3
Disease duration, median (IQR 25%-75%), years	5.3 (3 – 14)
BASDAI, mean \pm SD	4.5 \pm 2.2
ASDAS _{ESR} , mean \pm SD	3.2 \pm 1.3
ASDAS _{CRP} , mean \pm SD	3 \pm 1.2
Extra-articular manifestations, n (%)	15 (41)
Comorbidities, n (%)	19 (51)
Treatment	
NSAIDs n (%)	23 (92)
Continuous NSAIDs n (%)	12 (32)
bDMARDs n (%)	10 (27)
Biological characteristics	
CRP, median (IQR 25%-75%), mg/L	8 (4 - 33.5)
ESR, median (IQR 25%-75%), mm	28 (11 - 66.5)
Clinical assessment of enthesitis	
Painful entheses, median (IQR 25%-75%)	5 (2-12)
MASES, median (IQR 25%-75%)	2 (0.5-5)
LEI, median (IQR 25%-75%)	1 (0-2)
SPARCC, median (IQR 25%-75%)	2 (0-4.5)
Ultrasound assessment of enthesitis	
SEI, mean \pm SD	12.46 \pm 3.79
GUESS, mean \pm SD	9.62 \pm 3.86
MASEI, mean \pm SD	25.76 \pm 9.79
Physical activity characteristics	
Patients doing exercises, n (%)	19 (51)
Weekly duration of exercise, median (IQR 25%-75%), hours	0.75 (0-3.5)
Weekly duration of physical activity (IQR 25%-75%), hours	3 (1.9 - 7)
UCLA activity scale, median (IQR 25%-75%)	4 (4-5)
Tegner physical activity scale, median (IQR 25%-75%)	3 (3-5)

Values are expressed as mean \pm SD (standard deviation); n: subjects number; BMI: Body mass index; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; ASDAS: Ankylosing Spondylitis Disease Activity Score; CRP: c-reactive protein; ESR: erythrocyte sedimentation rate; NSAIDs: Non-steroidal anti-inflammatory drugs; bDMARDs: biological disease-modifying anti-rheumatic drugs; MASES: Maastricht Ankylosing Spondylitis Enthesitis Score; SPARCC: Spondyloarthritis Research Consortium of Canada Enthesitis Index; LEI: Leeds Enthesitis Index; SEI: Spanish Enthesitis Index; GUESS: Glasgow Ultrasound Enthesitis Scoring System; MASEI: Madrid Sonographic Enthesitis Index UCLA: University of California and Los Angeles activity scale; IQR: interquartile range.

Clinical and US entheses characteristics

Fourteen patients had > 3 US enthesophytes. As shown in **table II**, US entheses abnormalities were frequent. The CT entheses was the most affected, followed by the PA in the lower limbs. Enthesophytes affecting LET and TT were found in 57% of patients.

Structural damages were found mainly in QT, CT, and PA. The median number of painful entheses was 5 (IQR: 2-12) entheses. The median (IQR 25%-75%) MASES, LEI, and SPARCC were 2 (0.5-5), 1 (0-2), and 2 (0-4.5), respectively. The mean SEI, GUESS, and MASEI were 12.4 \pm 3.7, 8.2 \pm 3.8, and 25.7 \pm 9.7, respectively.

Table II. US entheses abnormalities.

US abnormalities		Quadriceps tendon enthesis	Proximal insertion of the patellar tendon	Distal insertion of the patellar tendon	Calcaneal tendon	Plantar aponeurosis	Lateral epicondyle tendon	Triceps tendon
Tendon damage at its bone insertion	Tendon damage*, n (%)	34 (92)	19 (51)	30 (81)	36 (97)	36 (98)	26 (70)	30 (81)
	Thickening, (mm)	6.9 ± 0.8 [†]	4 (3.7 - 4.5)	4.4 (4.1 - 4.8)	4.9 ± 0.8 [†]	5 (4.6-5.5) [†]	4.1 ± 0.6	5.1 ± 1.1 [†]
	Thickened tendon, n (%)	27 (73)	17 (46)	29 (78)	15 (41)	35 (95)	11 (30)	30 (81)
	Hypo echogenicity, n (%)	25 (68)	5 (14)	20 (46)	32 (87)	17 (46)	21 (57)	13 (35)
	Loss of the fibrillated appearance	11 (30)	2 (5)	5 (14)	12 (32)	8 (22%)	7 (19)	1 (3)
Structural damage	Structural damage**, n (%)	26 (70)	8 (22)	11 (30)	34 (92)	29 (78)	29 (78)	27 (73)
	Enthesophytes, n (%)	25 (68)	6 (16)	6 (16)	30 (81)	21 (57)	21 (57)	12 (32)
	Calcifications, n (%)	12 (32)	3 (8)	13 (35)	13 (35)	13 (35)	14 (38)	18 (49)
	Erosions, n (%)	1 (3)	1 (3)	2 (5)	2 (5)	11 (30)	3 (8)	9 (24)
PD signal		2 (5)	1 (3)	1 (3)	3 (8)	11 (30)	7 (19)	1 (3)

US: ultrasonography; PD: power Doppler; p: significance value; *presence of a thickened tendon and/or hypoechoic appearance and/or loss of the fibrillated appearance of the tendon; **presence of calcifications; enthesophytes; or erosions; n: subjects' number; SD: standard deviation; values are expressed as mean ± standard deviation; [†]values are expressed as median (interquartile range).

Relationship between physical activity and clinical characteristics of the disease

As shown in **table III**, patients who performed exercise had a significantly lower disease activity, mean number of painful entheses, and lower clinical enthesis scores.

We found that exercise was associated with a lower risk of disease activity (PR: 0.288, p = 0.01, 95%CI 0.096-0.866).

As shown in **table IV**, negative correlations were found between the weekly duration of exercise and the following parameters: BASDAI, number of painful entheses,

Table III. Association between disease activity, entheses scores, and exercise.

	Exercise		P-value
	No (n = 18)	Yes (n = 19)	
BASDAI	5.4 ± 1.9	3.5 ± 2	0.004
ASDAS _{CRP}	3.4 ± 1.1	2.6 ± 1.1	0.05
ASDAS _{ESR}	3.7 ± 1.1	2.8 ± 1.3	0.04
CRP	39.6 ± 58.5	16.1 ± 20.1	0.107
ESR	48.7 ± 37.4	34.7 ± 30	0.217
Painful entheses	9.1 ± 6.4	3.9 ± 4.5	0.008
MASES	4.2 ± 3.2	1.7 ± 1.8	0.016
LEI	2.1 ± 1.9	0.9 ± 1.2	0.04
SPARCC	4.2 ± 3.5	1.7 ± 2.9	0.011
SEI	12.3 ± 4	12.6 ± 3.6	0.781
GUESS	10.1 ± 4	9.2 ± 3.8	0.513
MASEI	26.7 ± 10.8	24.9 ± 8.9	0.590

Values are expressed as mean ± SD (standard deviation); n: subjects' number; p: significance value; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; ASDAS: Ankylosing Spondylitis Disease Activity Score; CRP: C-reactive protein; ESR: Erythrocyte Sedimentation Rate; MASES: Maastricht Ankylosing Spondylitis Enthesitis Score; SPARCC: Spondyloarthritis Research Consortium of Canada Enthesitis Index; LEI: Leeds Enthesitis Index; SEI: Spanish Enthesitis Index; GUESS: Glasgow Ultrasound Enthesitis Scoring System; MASEI: Madrid Sonographic Enthesitis Index; NS: not significant.

SPARCC, and MASES. A negative correlation was also found between the weekly duration of physical activity and MASES. No correlations were found between these parameters and UCLA or Tegner activity scales.

In the multivariate study, we found that high disease activity was associated with increased inflammatory biomarkers (OR 6.565, $p = 0.04$, 95%CI 1.092-39.459). Nevertheless, exercise was associated with a lower risk of disease activity (OR 0.123, $p = 0.022$, 95%CI 0.020 -0.742).

Relationship between physical activity and ultrasonographic characteristics

Triceps tendon thickening, the SEI, and thickening of the distal insertion of the patellar tendon were significantly higher in patients performing physical activity (triceps tendon's thickening: 4.20 ± 0.62 vs 3.7 ± 0.3 mm, $p = 0.044$; SEI of the distal insertion of the patellar tendon: 2.5 ± 1.4 vs 1.1 ± 1.1 , $p = 0.03$, and thickening of the distal insertion of the patellar tendon: 4.6 ± 0.7 vs 3.9 ± 0.3 , $p = 0.02$). The thickness of the lateral epicondyle entheses was also posi-

tively correlated with weekly duration of physical activity as shown in **table IV**.

Patients doing exercise had a significantly lower risk of having ≥ 3 US enthesophytes (PR: 0.22; 95%CI 0.3-0.9, $p = 0.031$) and PA enthesophyte (PR: 0.188; 95%CI 0.04-0.87, $p = 0.026$).

Patients doing physical activity had a higher risk of hypoechogenicity in the distal insertion of the patellar tendon (PR: 2.88; 95%CI 1.75-4.5, $p = 0.004$). A higher UCLA activity scale was found in patients with loss of the fibrillar aspect of the DPT (6 ± 2.73 vs 4.56 ± 1.18 , $p = 0.047$).

Lower UCLA was found in patients with structural damage lesions of the QT (4.42 ± 1.13 vs 5.54 ± 2.01 , $p = 0.038$) and TT enthesitis (4.34 ± 1.09 vs 5.72 ± 1.95 , $p = 0.09$).

Lower Tegner activity scale was found in patients with the following US abnormalities: loss of the fibrillar aspect of EPL (2.5 ± 1.3 vs 3.58 ± 1.26 , $p = 0.04$) and with TT calcification (2.71 ± 1.48 vs 3.73 ± 1.09 , $p = 0.022$).

Besides, a negative correlation was found between MASEI and UCLA activity index ($r = -0.326$, $p = 0.049$). However, Tegner activity scale was positively correlated with the thickness of the PPT ($r = 0.349$, $p = 0.034$).

Table IV. Correlations between clinical and ultrasonographic characteristics and physical activity characteristics.

	Age	Weekly duration of exercise	Weekly duration of physical activity	UCLA activity scale	Tegner Physical Activity scale
BASDAI	0.313	-0.363*	-0.121	-0.199	-0.107
ASDAS ESR	0.247	-0.196	-0.009	-0.167	-0.105
ASDAS CRP	0.267	-0.155	0.140	-0.084	0.032
number of painful entheses	0.284	-0.425**	-0.321	-0.281	-0.274
SPARCC	0.373*	-0.414*	-0.292	-0.242	-0.270
MASES	0.121	-0.401*	-0.326*	-0.291	-0.183
LEI	0.329*	-0.323	-0.189	-0.206	-0.128
SEI	0.247	0.295	0.286	-0.183	0.126
GUESS	0.379*	-0.097	0.058	-0.196	0.080
MASEI	0.450**	0.032	0.159	-0.326*	-0.010
Tendon thickness					
QT	0.332*	0.258	0.045	0.169	0.086
PPT	0	0.147	-0.093	0.019	0.349*
DPT	-0.015	0.039	0.061	-0.048	0.108
CT	0.343*	-0.029	0.131	-0.158	0.200
PA	0.209	0.006	0.246	0.050	-0.016
LET	0.124	0.378*	0.306	0.119	-0.138
TT	0.213	0.114	0.172	-0.146	-0.018

Data are presented as r of Pearson correlations; * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; ASDAS: Ankylosing Spondylitis Disease Activity Score; ESR: Erythrocyte Sedimentation Rate; CRP: C-reactive protein; MASES: Maastricht Ankylosing Spondylitis Enthesitis Score; SPARCC: Spondyloarthritis Research Consortium of Canada Enthesitis Index; LEI: Leeds Enthesitis Index; SEI: Spanish Enthesitis Index; GUESS: Glasgow Ultrasound Enthesitis Scoring System; MASEI: Madrid Sonographic Enthesitis Index; QT: Quadriceps tendon entheses; PPT: Proximal insertion of the patellar tendon; DPT: Distal insertion of the patellar tendon; CT: Calcaneal tendon; PA: Plantar aponeurosis; LET: Lateral epicondyle tendon; TT: triceps tendon; UCLA: University of California and Los Angeles activity scale.

In the multivariate study, we found that exercise was associated with a lower risk of having ≥ 3 enthesophytes (OR 0.213, $p = 0.036$, 95%CI 0.05-0.90).

DISCUSSION

We attempted to assess the association between physical activity, disease activity, and ultrasonographic enthesal abnormalities in SpA patients.

Our study showed that patients who performed regular exercise had significantly lower disease activity. However, UCLA and Tegner activity scales were not correlated with disease activity.

There are controversial results regarding the effect of physical activity on disease activity and enteses. Two clinical trials assessed the effect of physical activity on psoriatic arthritis patients. No adverse events related to exercise or inflammatory flares of disease had been reported (28, 29). However, in Häkkinen's study, inflammatory flare occurred in six psoriatic arthritis patients in the exercise group and five patients in the control group leading to a temporary stoppage of the protocol (30). In their systematic review, Kessler *et al.* emphasize the widespread benefits of physical activity on psoriatic arthritis patients regarding functional capacity, general well-being, fatigue, and quality of life (31). In a study including SpA patients, the authors demonstrated that a 3-month combined home exercise associating range-of-motion, strengthening, and aerobic exercise was more effective than range-of-motion home exercise alone in terms of aerobic capacity and functional ability assessed using Bath Ankylosing Spondylitis Functional Index (BASFI) (32).

Jennings *et al.* found that aerobic exercise associated with stretching or stretching alone could improve the functional capacity of SpA patients (33).

In a metaanalysis including twenty-six trials with a total of 1,286 patients followed for inflammatory rheumatic diseases, the authors demonstrated a beneficial effect of physical activity on disease activity scores (Standardized Mean Difference (SMD): 0.19, 95%CI 0.05-0.33, $p < 0.01$), joint damage (SMD: 0.27, 95%CI 0.07-0.46, $p < 0.01$), and ESR (SMD: 0.20, 95%CI 0.0-0.39, $p = 0.04$) (34).

We did not find a significant difference in ESR and CRP between patients with or without physical activity. Nevertheless, patients doing exercise had a significantly lower disease activity.

This finding highlights that physical activity can be considered a non-pharmacological treatment for the management of spondyloarthritis. Therefore, regular physical activity, including cardiorespiratory fitness, muscle strength, flexibility, and neuromotor performance, is highly recommended for patients with inflammatory diseases (35).

Data regarding the effects of physical activity on enteses involvement in patients with SpA are scarce. Our study showed that physical activity was associated with a lower clinical enthesitis score. Besides, negative correlations were found between the weekly duration of exercise and the following parameters: number of painful enteses, SPARCC, and MASES. These correlations were not found with UCLA and Tegner activity scales.

A negative correlation was also found between the weekly duration of physical activity and MASES. These results highlight the beneficial effect of physical activity on clinical enteses scores.

To our knowledge, the link between physical activity and US enthesitis score has not been studied in axial spondyloarthritis patients. We did not find a significant difference in US scores between patients doing or not doing exercise.

In a study including 84 patients followed for psoriatic arthritis, patients reporting avoidance of activity had lower MASEI (β : -1.71, 95%CI -3.1 to -0.32) than those who did not (36). Triceps tendon thickening, SEI, and thickening of the distal insertion of the patellar tendon were higher in patients performing physical activity. Patients doing physical activity had also a higher risk of hypoechogenicity in the lateral epicondyle tendons.

Bakirci *et al.* showed that US changes within the enthesitis of healthy subjects were associated with physical activity (β : 4.41, 95%CI 1.25-7.58, $p = 0.007$). Thickening was the common lesion, affecting mostly the patellar tendon insertions (37).

This result suggests that biomechanical forces on the enthesitis can be responsible for US enteses abnormalities without any signs and symptoms.

The effect of physical activity on enteses depends on the type and amount of exercise.

The onset of sports-related enthesopathy seemed to be due to muscle contraction rather than the amount of exercise (38).

Ozone *et al.* showed that, unlike concentric contraction-dominant exercises, eccentric contraction-dominant exercise can be responsible for sports-related enthesopathy-like morphological changes via the activation of transforming growth factor- β superfamily pathway in enthesitis (39).

In our study, patients with loss of the fibrillar aspect of the DPT had significantly higher UCLA activity scale. This score was, however, negatively correlated with MASEI. A lower Tegner activity scale was found in patients with loss of the fibrillar aspect of EPL and with TT calcification.

Interestingly, we found that patients doing exercise had a lower risk of having ≥ 3 US enthesophytes and plantar aponeurosis enthesophyte.

These results suggest that physical activity can be responsible for US tendon insertion damage due to biomechan-

ical forces on the enthesis. However, physical activity did not accentuate the structural damage. It could even prevent structural damage.

This study highlights an association between physical activity, disease activity, and clinical and ultrasonographic entheseal abnormalities. However, a cause-effect relationship between exercise and disease activity cannot be readily established. Indeed, it is unclear whether patients with low disease activity practice exercise because their state of health allows it or whether those who practice exercise have lower disease activity because of the beneficial effect of physical activity on disease. In fact, our study had some limitations that included the small sample size and the consequently low statistical power (the statistical power of our study was 9.086% based on normal approximation and 4.278% based on normal approximation with continuity correction).

CONCLUSIONS

Our study showed that patients who exercise had significantly lower disease activity. These findings suggest that physical activity could be considered a non-pharmacological treatment for the management of spondyloarthritis and can be recommended for these patients. We also found that

physical activity was associated with a lower clinical enthesitis scores. It can be responsible for ultrasonographic tendon insertion damage, but it doesn't accentuate the structural damage. The promotion of physical activity could be considered a healthcare priority.

FUNDINGS

None.

CONTRIBUTIONS

MS: ultrasonography performance, writing – original draft. SBD, LK: writing – original draft, data collection. HB, CB: data analysis. IG: conceptualization.

DATA AVAILABILITY

Data are available under reasonable request to the corresponding author.

CONFLICT OF INTERESTS

The authors declare that they have no conflict of interests.

REFERENCES

1. Stolwijk C, van Onna M, Boonen A, van Tubergen A. Global Prevalence of Spondyloarthritis: A Systematic Review and Meta-Regression Analysis. *Arthritis Care Res (Hoboken)*. 2016;68(9):1320-31. doi: 10.1002/acr.22831.
2. Sieper J, Poddubnyy D. Axial spondyloarthritis. *Lancet*. 2017;390(10089):73-84. doi: 10.1016/S0140-6736(16)31591-4.
3. Shamji MF, Bafaquh M, Tsai E. The pathogenesis of ankylosing spondylitis. *Neurosurg Focus*. 2008;24(1):E3. doi: 10.3171/FOC/2008/24/1/E3.
4. Schett G, Lories RJ, D'Agostino M-A, et al. Enthesitis: from pathophysiology to treatment. *Nat Rev Rheumatol*. 2017;13(12):731-41. doi: 10.1038/nrrheum.2017.188.
5. Slouma M, Kharrat L, Tezegdenti A, et al. Increased serum interleukin 22 levels in patients with axial spondyloarthritis. *Expert Rev Clin Immunol*. 2023;19(1):123-9. doi: 10.1080/1744666X.2023.2142563.
6. Slouma M, Abbess M, Kharrat L, et al. Ultrasonography of heel entheses in axial spondyloarthritis patients: frequency and assessment of associated factors. *J Ultrasound*. 2023;26(1):185-92. doi: 10.1007/s40477-022-00715-x.
7. Slouma M, Bouzid S, Dhahri R, et al. Matrix Metalloproteinases; A Biomarker of Disease Activity and Prognosis in Spondyloarthritis: A Narrative Review. *Curr Rev Clin Exp Pharmacol*. 2023;18(1):31-8. doi: 10.2174/277243281766620113112809.
8. Slouma M, Kharrat L, Tezegdenti A, Dhahri R, Ghazouani E, Gharsallah I. Pro-inflammatory cytokines in spondyloarthritis: a case-control study. *Expert Rev Clin Immunol*. 2024;1-9. doi: 10.1080/1744666X.2024.2304080.
9. Weinreb JH, Sheth C, Apostolakos J, et al. Tendon structure, disease, and imaging. *Muscles Ligaments Tendons J*. 2014;4(1):66-73.
10. D'Agostino M-A, Said-Nahal R, Hacquard-Bouder C, Bras-seur J-L, Dougados M, Breban M. Assessment of peripheral enthesitis in the spondylarthropathies by ultrasonography combined with power Doppler: a cross-sectional study. *Arthritis Rheum*. 2003;48(2):523-33. doi: 10.1002/art.10812.
11. de Miguel E, Cobo T, Muñoz-Fernández S, et al. Validity of enthesitis ultrasound assessment in spondyloarthropathy. *Ann Rheum Dis*. 2009;68(2):169-74. doi: 10.1136/ard.2007.084251.
12. Balint PV, Kane D, Wilson H, McInnes IB, Sturrock RD. Ultrasonography of enthesal insertions in the lower limb in spondyloarthropathy. *Ann Rheum Dis*. 2002;61(10):905-10. doi: 10.1136/ard.61.10.905.
13. Kristensen S, Christensen JH, Schmidt EB, et al. Assessment of enthesitis in patients with psoriatic arthritis using clinical examination and ultrasound. *Muscles Ligaments Tendons J*. 2016;6(2):241-7. doi: 10.11138/mltj/2016.6.2.241.
14. D'Agostino MA, Breban M. Ultrasonography in inflammatory joint disease: why should rheumatologists pay attention? *Joint Bone Spine*. 2002;69(3):252-5. doi: 10.1016/s1297-319x(02)00394-9.
15. Wiell C, Szkudlarek M, Hasselquist M, et al. Power Doppler ultrasonography of painful Achilles tendons and entheses in

- patients with and without spondyloarthropathy: a comparison with clinical examination and contrast-enhanced MRI. *Clin Rheumatol.* 2013;32(3):301-8. doi: 10.1007/s10067-012-2111-4.
16. Ward MM, Deodhar A, Gensler LS, et al. 2019 Update of the American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network Recommendations for the Treatment of Ankylosing Spondylitis and Nonradiographic Axial Spondyloarthritis. *Arthritis Care Res (Hoboken).* 2019;71(10):1285-99. doi: 10.1002/acr.24025.
 17. Sieper J, Rudwaleit M, Baraliakos X, et al. The Assessment of SpondyloArthritis international Society (ASAS) handbook: a guide to assess spondyloarthritis. *Ann Rheum Dis.* 2009;68 Suppl 2:ii1-44. doi: 10.1136/ard.2008.104018.
 18. Baillet A, Gossec L, Carmona L, et al. Points to consider for reporting, screening for and preventing selected comorbidities in chronic inflammatory rheumatic diseases in daily practice: a EULAR initiative. *Ann Rheum Dis.* 2016;75(6):965-73. doi: 10.1136/annrheumdis-2016-209233.
 19. Garrett S, Jenkinson T, Kennedy LG, Whitelock H, Gaisford P, Calin A. A new approach to defining disease status in ankylosing spondylitis: the Bath Ankylosing Spondylitis Disease Activity Index. *J Rheumatol.* 1994;21(12):2286-91.
 20. Lukas C, Landewé R, Sieper J, et al. Development of an ASAS-endorsed disease activity score (ASDAS) in patients with ankylosing spondylitis. *Ann Rheum Dis.* 2009;68(1):18-24. doi: 10.1136/ard.2008.094870.
 21. Metsios GS, Kitas GD. Physical activity, exercise and rheumatoid arthritis: Effectiveness, mechanisms and implementation. *Best Pract Res Clin Rheumatol.* 2018;32(5):669-82. doi: 10.1016/j.berh.2019.03.013.
 22. Amstutz HC, Thomas BJ, Jinnah R, Kim W, Grogan T, Yale C. Treatment of primary osteoarthritis of the hip. A comparison of total joint and surface replacement arthroplasty. *J Bone Joint Surg.* 1984;66(2):228-41. doi: 10.2106/00004623-198466020-00010.
 23. Zahiri CA, Schmalzried TP, Szuszczewicz ES, Amstutz HC. Assessing activity in joint replacement patients. *J Arthroplasty.* 1998;13(8):890-5. doi: 10.1016/s0883-5403(98)90195-4.
 24. Tegner Y, Lysholm J. Rating systems in the evaluation of knee ligament injuries. *Clin Orthop Relat Res.* 1985;(198):43-9.
 25. Alcalde M, Acebes JC, Cruz M, González-Hombrado L, Herro-Beaumont G, Sánchez-Pernaute O. A sonographic enthesitic index of lower limbs is a valuable tool in the assessment of ankylosing spondylitis. *Ann Rheum Dis.* 2007;66(8):1015-9. doi: 10.1136/ard.2006.062174.
 26. Balint PV, Terslev L, Aegerter P, et al. Reliability of a consensus-based ultrasound definition and scoring for enthesitis in spondyloarthritis and psoriatic arthritis: an OMERACT US initiative. *Ann Rheum Dis.* 2018;77(12):1730-5. doi: 10.1136/annrheumdis-2018-213609.
 27. Cohen MS, Romeo AA, Hennigan SP, Gordon M. Lateral epicondylitis: anatomic relationships of the extensor tendon origins and implications for arthroscopic treatment. *J Shoulder Elbow Surg.* 2008;17(6):954-60. doi: 10.1016/j.jse.2008.02.021.
 28. Thomsen RS, Nilsen TIL, Haugeberg G, Bye A, Kavanaugh A, Hoff M. Impact of High-Intensity Interval Training on Disease Activity and Disease in Patients With Psoriatic Arthritis: A Randomized Controlled Trial. *Arthritis Care Res (Hoboken).* 2019;71(4):530-7. doi: 10.1002/acr.23614.
 29. Roger-Silva D, Natour J, Moreira E, Jennings F. A resistance exercise program improves functional capacity of patients with psoriatic arthritis: a randomized controlled trial. *Clin Rheumatol.* 2018;37(2):389-95. doi: 10.1007/s10067-017-3917-x.
 30. Häkkinen A, Häkkinen K, Hannonen P. Effects of strength training on neuromuscular function and disease activity in patients with recent-onset inflammatory arthritis. *Scand J Rheumatol.* 1994;23(5):237-42. doi: 10.3109/03009749409103722.
 31. Kessler J, Chouk M, Ruban T, Prati C, Wendling D, Verhoeven F. Psoriatic arthritis and physical activity: a systematic review. *Clin Rheumatol.* 2021;40(11):4379-89. doi: 10.1007/s10067-021-05739-y.
 32. Hsieh L-F, Chuang C-C, Tseng C-S, Wei JC-C, Hsu W-C, Lin Y-J. Combined home exercise is more effective than range-of-motion home exercise in patients with ankylosing spondylitis: a randomized controlled trial. *Biomed Res Int.* 2014;2014:398190. doi: 10.1155/2014/398190.
 33. Jennings F, Oliveira HA, de Souza MC, Cruz V da G, Natour J. Effects of Aerobic Training in Patients with Ankylosing Spondylitis. *J Rheumatol.* 2015;42(12):2347-53. doi: 10.3899/jrheum.150518.
 34. Sveaas SH, Smedslund G, Hagen KB, Dagfinrud H. Effect of cardiorespiratory and strength exercises on disease activity in patients with inflammatory rheumatic diseases: a systematic review and meta-analysis. *Br J Sports Med.* 2017;51(14):1065-72. doi: 10.1136/bjsports-2016-097149.
 35. Rausch Osthoff A-K, Niedermann K, Braun J, et al. 2018 EULAR recommendations for physical activity in people with inflammatory arthritis and osteoarthritis. *Ann Rheum Dis.* 2018;77(9):1251-60. doi: 10.1136/annrheumdis-2018-213585.
 36. Wervers K, Herrings I, Luime JJ, et al. Association of Physical Activity and Medication with Entesitis on Ultrasound in Psoriatic Arthritis. *J Rheumatol.* 2019;46(10):1290-4. doi: 10.3899/jrheum.180782.
 37. Bakirci S, Solmaz D, Stephenson W, Eder L, Roth J, Aydin SZ. Enteseal Changes in Response to Age, Body Mass Index, and Physical Activity: An Ultrasound Study in Healthy People. *J Rheumatol.* 2020;47(7):968-72. doi: 10.3899/jrheum.190540.
 38. Ozone K, Kokubun T, Takahata K, et al. Structural and pathological changes in the entheses are influenced by the muscle contraction type during exercise. *J Orthop Res.* 2022;40(9):2076-88. doi: 10.1002/jor.25233.
 39. Ozone K, Minegishi Y, Takahata K, et al. Eccentric contraction-dominant exercise leads to molecular biological changes in entheses and enthesopathy-like morphological changes. *J Orthop Res.* 2023;41(3):511-23. doi: 10.1002/jor.25399.