Entheseal Changes in Response to Age, Body Mass Index, and Physical Activity: An Ultrasound Study in Healthy People

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ABSTRACT. ***Objective.*** We aimed to investigate the prevalence of ultrasonographic (US) lesions in healthy entheses and contributing factors.

Methods. US scans were performed on 960 entheses of 80 healthy subjects. Factors contributing to entheseal changes were investigated with regression analysis.

Results. Thickening (20.4% of the entheses) and enthesophytes (23.1%) were the most common inflammatory and structural damage lesions, respectively. Age ($p < 0.001$), male sex ($p = 0.003$), body mass index (BMI; $p = 0.001$), and high physical activity ($p = 0.007$) were independent predictors of enthesitis scores on US.

Conclusion. The effects of age, sex, BMI, and physical activity on the entheses need to be considered when differentiating disease from health. (First Release May 1 2020; J Rheumatol 2020;47:968–72; doi:10.3899/jrheum.190540)

Key Indexing Terms:
ENTHESIS ULTRASOUND HEALTHY SUBJECTS

Enthesitis is a characteristic lesion in spondyloarthritis (SpA). Physical examination may underestimate the prevalence of enthesitis, thus leading to increased use of ultrasound (US) for more objective assessments[1,2,3]. However, US can detect minimal changes in healthy people. A study on healthy people found that synovial proliferation and/or effusion can be seen in 9% of the healthy joints[4]. For enthesitis, previous US studies demonstrated multiple elementary lesions in the entheses in healthy control arms[3,4]. It is therefore essential to accurately define entheseal abnormalities in healthy subjects.

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The objective of our study was to determine the prevalence of entheseal abnormalities on US in healthy subjects (for a population without inflammatory arthritis) and to analyze how sex, obesity, age, and physical exercise affect the frequency and severity of entheseal lesions. This information would be helpful to define what is normal in specific populations (e.g., the elderly and/or obese), to be able to discriminate from disease.

MATERIALS AND METHODS

Advertisements were hung on the hospital walls to identify candidates without any history of or current rheumatological diseases, persistent joint pain, swelling, trauma, or surgery within the last year. After excluding 7 participants who had rheumatological disease or a suspicion based on a rheumatologist's assessment, and 1 who had recent joint surgery, 80 participants were recruited. The participants were mostly people working at the hospital or their relatives, or spouses/friends who had visited patients in the hospital. Ethics approval was obtained from the Ottawa Health Science Network Research Ethics Board (20170660-01H) and all participants gave informed consent. Demographic data were collected including age, sex, weight, and height. The International Physical Activity Questionnaire, Long Form, Past 7 Days (IPAQ) was used to categorize the physical activity levels[5]. The rheumatological assessment was performed by an experienced rheumatologist (DS) to rule out any inflammatory arthritis[6].

Ultrasound protocol. All participants had a US scan on the same day of clinical assessment by an experienced rheumatologist in musculoskeletal US (SB). All scans were performed using a MyLab ClassC (Esaote), with a 6–18 MHz linear probe. Power Doppler settings were standardized with a pulse repetition frequency of 500 Hz and low wall filter.

The following entheses were included: insertions of triceps tendon, quadriceps tendon, achilles tendon, and plantar fascia, and origin and insertion of patellar tendon. The elementary lesions were based on the definition of the Outcome Measures in Rheumatology in Clinical Trials (OMERACT)

group including hypoechogenicity, thickening, Doppler signals, enthesophytes, erosions, and calcifications[7]. All lesions were scored on a scale between 0 to 3, similar to previous publications, and has been tested for its reliability and discrimination of diseases [psoriatic arthritis (PsA), psoriasis, ankylosing spondylitis, inflammatory bowel disease vs healthy controls; details given in Supplementary Table 1, available from the authors on request.][1,3,8]. Inflammation (hypoechogenicity, thickening, Doppler) and damage (calcifications, enthesophytes, and erosions) scores were calculated. A total score was obtained by adding these 2 scores (range 0–216).

Statistical analysis. Group comparisons for US scores and frequency of elementary lesions were made using the 2-tailed t test, Mann-Whitney U test, or chi-square test, as appropriate. The correlations between the total enthesitis scores and various demographic and lifestyle factors were evaluated using Spearman correlation analysis. Selection of variables for inclusion in the multivariable regression model was based on the univariate analysis with a significance level below p = 0.20. The final multivariable linear regression to predict US scores included age, sex, smoking status, body mass index (BMI), and physical activity as covariates. The sonographer's intra-rater reliability was tested on 62 static images prior to the study. Statistical analysis was performed using SPSS (version 22.0, IBM Corp.).

RESULTS

Fifty participants (62.5%) were female and mean (SD) age was 45.0 (16.1) years. Thirty-two participants (40.5%) were ever smokers. The majority were overweight (35.4%) or obese (17.7%). Forty-three participants (54.4%) reported high physical activity with IPAQ. Three patients had type 2 diabetes and 8 had osteoarthritis (OA; Supplementary Table 2, available from the authors on request). The intraobserver agreement for the US assessment was very good to excellent (interclass coefficient values: inflammation score 0.850; damage score 0.910; total US score 0.960).

Frequency, location, and severity of elementary lesions on ultrasound. Regarding inflammation, thickening was the most frequent lesion, found in 86.3% (69/80) of the participants, in 20.4% (196/960) of the entheses (Table 1). It was more commonly seen on the patellar tendon origins (70%) and insertions (46.2%). Doppler signals were detected in 10% of the participants, in 1.1% (11/960) of the entheses (Achilles, n = 6; triceps, n = 3; and patellar tendon, n = 2). Grade 3 Doppler signals were detected in only 1 enthesis (Achilles), the remaining being grade 1 or 2 (Supplementary Table 3, available from the authors on request).

Enthesophytes were the most common lesions to show damage, detected in 87.5% (70/80) of participants and 23.1% (222/960) of the entheses. Erosions were detected in 6.25% of the participants and in 7 entheses (Supplementary Table 3).

Inflammation, damage, and total US scores. Mean inflammation [5.5 (5.6)], damage [5.4 (5.4)], and total scores [10.9 (10.2)] per participant were calculated (Supplementary Table 4, available from the authors on request). Smokers had higher inflammation, damage, and total scores, similar to participants who were exercising more (Supplementary Table 5, available from the authors on request; and Figure 1). Males had higher scores than females [15.73 (11.6) vs 8.06 (8.2), p = 0.001]. The total US scores correlated with age (r = 0.561, p < 0.001; Figure 1) and BMI (r = 0.344, p = 0.022; Supplementary Table 6, available from the authors on request).

The highest total US scores per anatomical site were seen at the Achilles enthesis [mean (SD) 2.85 (3.92)], followed by quadriceps (2.46 (3.68)] and patellar tendon origins [2.07 (2.20); Supplementary Table 4, available from the authors on request]. BMI correlated only in lower extremity tendons (Achilles, distal patellar, and quadriceps tendons; Supplementary Table 6). US scores generally increased with age with the exception of origin and insertions of patellar tendon. Males had higher US scores at triceps tendon, quadriceps, distal patellar, and Achilles enthesis than females (data not given).

Linear regression analysis for the US scores. In multiple linear regression, age, male sex, and BMI predicted the inflammation, damage, and total US scores. High physical activity was also found as a risk factor for damage and total US scores (Table 2).

DISCUSSION

Our study demonstrates that healthy subjects have frequent lesions at entheses on US, correlating with age and BMI as well as higher scores in males, smokers, and participants with high physical activity. Our data help to understand how factors associated with poor prognosis in SpA may also affect the healthy enthesis and support the need to define cutoffs for findings that are truly specific for inflammatory enthesitis.

Both inflammatory and structural damage signs can be seen in healthy people; however, some features are seen less frequently. Doppler signals were the least frequent inflammatory lesion, detected in 8 participants. Only 3 were on more than 1 site (2 sites), and 1 was severe. Similarly, erosions were seen in 5 participants, with only 2 in 2 sites and 1 severe. Therefore, healthy people may have entheseal changes that are usually limited to 1 anatomical site and are mild/moderate in severity. In addition, the combination of these pathologies may be more suggestive of a disease, but the discrimination between health and disease would require a study design that includes both groups.

Simultaneously, Guldberg-Møller, *et al* published a study on healthy entheses which found similar frequency of elementary lesions in healthy people, some lesions being more frequent in men and increasing with age; however, the overall scores of inflammation and damage were not reported[9]. In our study, in addition to the similar frequency of elementary lesions, we were able to find the link between those factors and the US scores by analyzing the overall scores.

Our study has some limitations. The choice of the entheseal sites was made based on the literature, and focusing

Table 1. Defining elementary lesions at entheses sites according to age groups.

Entheses Sites	Elementary Lesions	Age ≤ 50 Yrs, n = 51	Age > 50 Yrs, n = 29	Total, n = 80, n (%)
Quadriceps tendon				
	Hypoechogenicity (H)	0	19	19 (23.7)
	Thickening (T)	4	10	14 (17.5)
	H and T	0	8	8 (10.0)
	Power Doppler	0	0	0
	Enthesophyte	12	20	32 (40.0)
	Calcification	0	3	3 (3.75)
	Erosion	0	1	1 (1.25)
Proximal patellar tendon				
	Hypoechogenicity (H)	0	1	1 (1.25)
	Thickening (T)	34	22	56 (70.0)
	H and T	0	1	1 (1.25)
	Power Doppler	0	0	0
	Enthesophyte	3	4	7 (8.75)
	Calcification	1	1	2 (2.50)
	Erosion	0	0	0
Distal patellar tendon				
	Hypoechogenicity (H)	9	5	14 (17.5)
	Thickening (T)	24	13	37 (46.2)
	H and T	5	4	9 (11.25)
	Power Doppler	1	1	2 (2.50)
	Enthesophyte	8	9	17 (21.5)
	Calcification	7	2	9 (11.2)
	Erosion	0	3	3 (3.75)
Achilles tendon				
	Hypoechogenicity (H)	1	11	12 (15.0)
	Thickening (T)	0	6	6 (7.50)
	H and T	0	3	3 (3.75)
	Power Doppler	0	4	4 (5.0)
	Enthesophyte	36	27	63 (78.7)
	Calcification	2	2	4 (5.0)
	Erosion	0	0	0
Plantar fascia				
	Hypoechogenicity (H)	0	2	2 (2.50)
	Thickening (T)	6	12	18 (22.5)
	H and T	0	1	1 (1.25)
	Power Doppler	0	0	0
	Enthesophyte	0	6	6 (7.50)
	Calcification	0	0	0
	Erosion	1	1	2 (2.50)
Triceps tendon				
	Hypoechogenicity (H)	3	5	8 (10.0)
	Thickening (T)	0	2	2 (2.50)
	H and T	0	0	0
	Power Doppler	1	2	3 (3.75)
	Enthesophyte	10	12	22 (27.5)
	Calcification	1	2	3 (3.75)
	Erosion	0	0	0

on the upper extremity may reveal different results. The high frequency of thickening suggests the need to reassess the normal values of the thicknesses. Although diabetes mellitus or OA may challenge the definition of our healthy population, we have not excluded these participants because that would cause a selection bias for increasing with age. However, we have repeated the multivariable analysis excluding these participants, and that revealed the same factors as being significant. We tested only for factors that we could foresee being significant. Our sample size was not big enough to investigate for other comorbidities, and with a higher number of participants, more factors can be identified/tested. Finally, there is not a universally agreed scoring method for enthesitis. The OMERACT group has recently published a scoring method that is currently under investigation for its sensitivity to change[10]. The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) is also working on an enthesitis tool to be used

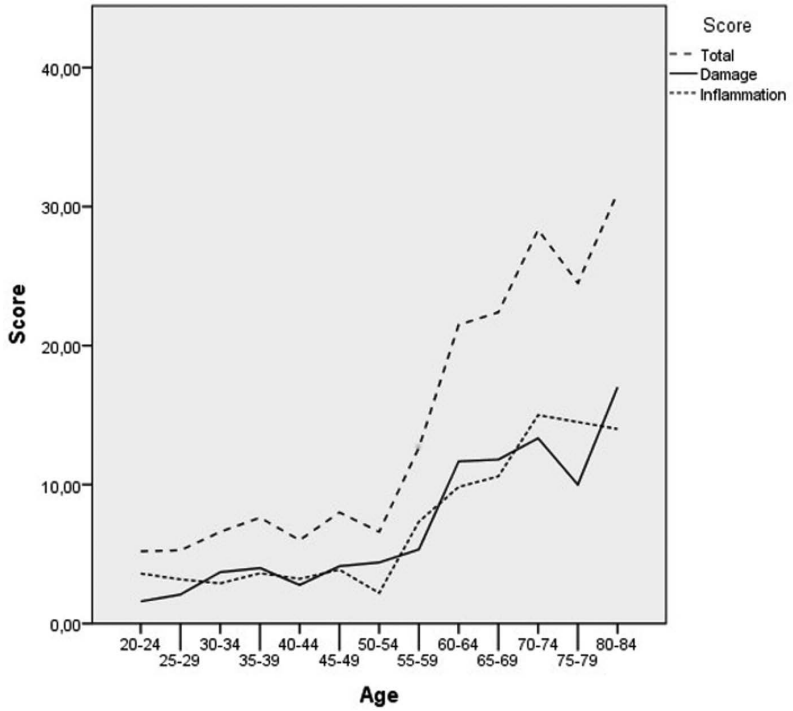

Figure 1. The effect of age on enthesitis scores as revealed by ultrasound.

Table 2. Multivariate regression results of the factors affecting ultrasound scores.

	Inflammation Score		Damage Score		Total Score	
	B (95% CI)	p	B (95% CI)	p	B (95% CI)	p
Variables						
Intercept	**–13.2 (–19.3 to –7.1)**	**< 0.001**	**–12.0 (–17.7 to –6.4)**	**< 0.001**	**–25.3 (–35.3 to –15.2)**	**< 0.001**
Age	0.17 (0.10–0.23)	**< 0.001**	0.18 (0.13–0.24)	**< 0.001**	0.35 (0.25–0.46)	**< 0.001**
Sex (men vs women)	2.73 (0.78–4.68)	**0.007**	2.3 (0.49–4.1)	**0.014**	5.05 (1.82–8.28)	**0.003**
Smoking (ever vs never)	–0.046 (–2.0 to 1.97)	0.963	–0.10 (–1.9 to 1.7)	0.916	–0.14 (–3.46 to 3.16)	0.930
BMI	0.35 (0.13–0.57)	**0.002**	0.26 (0.05–0.46)	**0.014**	0.61 (0.24–0.97)	**0.001**
Physical activity (high vs low and moderate)	1.89 (–0.022 to 3.80)	0.053	2.5 (0.73–4.3)	**0.006**	4.41 (1.25–7.58)	**0.007**
	Observations: 76		Observations: 76		Observations: 76	
	R^2/adjusted R^2: 0.500/0.465		R^2/adjusted R^2: 0.547/0.515		R^2/adjusted R^2: 0.599/0.571	

Significant differences are in bold face. BMI: body mass index.

for diagnostic purposes in PsA, and preliminary work has been published[11,12]. We have used a slightly different scoring method, which has been used in multiple studies previously and the validity has been tested. Also, the elementary lesions used in our study are identical to the aforementioned tools, based on the elementary lesions defined by the OMERACT group. The work by GRAPPA and OMERACT will identify a universally accepted tool to be used for diagnosis and responsiveness, respectively.

Our study demonstrated US changes within the enthesis, associated with older age, higher BMI, physical activity, and sex. These results support the effect of biomechanical forces on the enthesis, not necessarily reflecting a pathology leading to any symptoms.

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The results of our study have been presented at meetings of the American College of Rheumatology (ACR; abstract number 1194, 2018) and the Canadian Rheumatology Association (POD-12, 2019) and the abstracts are/will be published in congress proceedings (*Arthritis and Rheumatology*, vol. 70, Suppl 9, 2018, ACR/ARHP Annual Meeting Abstract Supplement), and *The Journal of Rheumatology*.

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