Ultrasound pathology of the entheses in an age and gender stratified sample of healthy adult subjects: a prospective cross-sectional frequency study

J. Guldberg-Møller[1], L. Terslev[2], S.M. Nielsen[1], M.J. Koenig[1,3], S.T. Torp-Pedersen[1,4], A. Torp-Pedersen[1], R. Christensen[1], H. Bliddal[1], K. Ellegaard[1]

[1]The Parker Institute, Bispebjerg and Frederiksberg Hospital, Frederiksberg, Denmark;
[2]Center for Rheumatology and Spine Diseases, Rigshospitalet, Glostrup, Denmark;
[3]Department of Radiology, Herlev-Gentofte Hospital, Hellerup, Denmark;
[4]Department of Radiology, Rigshospitalet Glostrup, Glostrup, Denmark.

Abstract

Objective

Ultrasound (US) examination of the entheses is increasingly used. However, little is known about US findings in the entheses in asymptomatic persons. The aim of this study was to investigate the appearance of US signs in the entheses of the lower limb in asymptomatic subjects.

Methods

We recruited 64 subjects, eight women and eight men whose ages covered four decades, from 20 to 60 years. None had tendon or joint disease in the lower limbs. Participants were examined by a rheumatologist and blood samples were collected to rule out enthesis pathology. The enthesis of the dominant leg were examined with grey-scale and Doppler US to evaluate increased thickness, changed structure, enthesophytes/calcifications, erosions, and colour Doppler signal.

Results

Ultrasound examination of 320 entheses was made. At enthesis level, elementary lesions were seen at 73 (22.8%) sites, at subject-level 47 (73.4%) persons showed elementary lesions, in 27 (57%) only one enthesis was affected. Doppler activity was seen in four sites, three at the quadriceps insertion. Most common US elementary lesion was enthesophytes at the Achilles and quadriceps tendon insertion. A tendency towards more elementary lesions was seen in men, and a slight increase was seen with increasing age, however, not statistically significance.

Conclusion

Our findings suggest that US can be used to diagnose/examine subjects in adulthood for pathological changes in the entheses; however, caution should be taken regarding enthesophytes of the quadriceps and Achilles tendon.

Key words
ultrasound, entheses, healthy subjects

Jørgen Guldberg-Møller, MD
Lene Terslev, PhD
Sabrina M. Nielsen, MSc
Merete J. Koenig, PhD
Søren T. Torp-Pedersen, MD
Arendse Torp-Pedersen, MD
Robin Christensen, PhD
Henning Bliddal, DMSc
Karen Ellegaard, PhD

Please address correspondence to:
Dr Karen Ellegaard,
The Parker Institute,
Bispebjerg and Frederiksberg Hospital,
Nordre Fasanvej 57,
DK-2000 Frederiksberg, Denmark.
E-mail: karen.ellegaard@regionh.dk

Received on January 17, 2018; accepted in revised form on July 2, 2018.

Funding: this study was supported by The Danish Rheumatism Association and the Oak Foundation.

Competing interests: L. Terslev has received speakers fees from Abbvie, Janssen, Pfizer, Novartis, MSD, UCB, and GE;
the other authors have declared no competing interests.

Introduction

Enthesitis is defined as inflammation affecting the enthesis. The enthesis is defined as the area of the attachment of the tendons, ligaments and capsules into the bone, and all structures in the area are part of the enthesis (1). Ultrasound (US) examination of the enthesis is increasingly used in order to document pathological changes in, *e.g.* spondyloarthritis (SpA), and various scoring systems have been developed (2-5). Grey-scale (GS) US is used to assess morphological changes and Doppler US to assess increased blood flow as part of the inflammatory process. The OMERACT Ultrasound Working Groups have validated the following US elementary components of enthesitis: hypoechogenicity, increased thickness, enthesophytes/calcifications, erosions, and Doppler activity <2mm from the enthesis (6, 7). Most research in US examination of the enthesis is conducted on patients with axial SpA and psoriatic arthritis (PsA), however little is known about whether similar US enthesis signs can be found in asymptomatic subjects. Inflammation-like changes have been observed in the Achilles tendon and in the joints of hands and feet in healthy subjects (8-10). By consequence, it is relevant to investigate the occurrence and distribution of US detected elementary lesions in healthy subjects to optimise the use of US examination of the enthesis for diagnostic purposes and to increase the validity of US examination for diseases characterised by pathology in the entheses.

The aim of this study was to assess the appearance of grey-scale and Doppler US signs in the entheses of the lower limb in a sex- and age-stratified group of "healthy" participants with asymptomatic entheses by assessing the structures proposed by the OMERACT US working group (7).

Materials and methods

This prospectively designed descriptive study was performed and reported in accordance with the recommendations of the 'STrengthening the Reporting of OBservational studies in Epidemiology' (STROBE) guidelines (11). The study protocol was pre-specified and written in Danish, and the original protocol is available from the corresponding author upon request; the Statistical Analysis Plan (SAP) was prepared after data collection, but before any analyses were done (SAP is available online as Appendix 1).

Participants, recruitment and ethics

The study group was formed from 64 apparently healthy participants recruited from the Copenhagen General Population Study/The Copenhagen City Heart study (12). For each decade from 20 years to 60 years, a random sample of 25 subjects was chosen at first, and supplementary samples were made until eight women and eight men in each decade were included. The volunteers were interviewed by a third party for inclusion and exclusion criteria, without any involvement of the investigators.

The inclusion criteria were: age between 20 and 60 years and no history of tendon disease in the lower extremities. The exclusion criteria were: clinical signs of enthesitis, present or previous tendon/enthesis disease in the lower extremities; more than eight hours sport activities per week at any time; inflammatory systemic disease; pregnancy; and important medical conditions (*e.g.* diabetes mellitus, severe heart, lung or kidney diseases).

The study was approved by the local ethics committee (KF 01-149/03) and informed consent was obtained from the participants before inclusion.

Questionnaires

The participants were asked about present and previous injuries from tendons/entheses, tendon problems in close family, smoking and alcohol habits, workload (sedentary/physically active) and sport activities. Furthermore, the Norwegian versions of the Victorian Institute of Sport Assessment (VISA) scale were filled in by all participants (13, 14). This is an index used to assess severity of pathology in both knee and Achilles tendons, the scores are ranging from 0 to 100, where 100 represent no problems and 0 extreme problems.

Table I. Characteristics of study population registered according to gender and decade.

Variable	Gender	Age 20-29 (n=14) [a]	Age 30-39 (n=16)	Age 40-49 (n=16)	Age 50-59 (n=16)	Total (n=62)
Age (years), median (IQR)	M	28.2 (27.5;28.9)	36.3 (34.7;37.7)	47.8 (46.4;48.4)	53.8 (52.1;56.0)	39.8 (30.2;49.7)
	F	27.9 (26.6;29.0)	34.5 (33.8;35.8)	44.8 (43.1;49.2)	56.8 (55.7;57.3)	
BMI (kg/m^2), mean (SD)	M	23.9 (2.7)	25.6 (4.9)	26.5 (4.6)	27.1 (2.7)	24.1 (3.7)
	F	22.3 (2.2)	20.8 (1.8)	23.6 (1.8)	22.4 (3.1)	
Smoker, n (%)	M	1 (13%)	2 (25%)	2 (25%)	3 (38%)	17 (27%)
	F	1 (13%)	1 (13%)	3 (38%)	4 (50%)	
Tendon problems in closest family, n (%)	M	0 (0%)	1 (13%)	0 (0%)	1 (13%)	4 (6%)
	F	0 (0%)	0 (0%)	1 (13%)	1 (13%)	
Former muscle sprain, n (%)	M	2 (25%)	1 (13%)	2 (25%)	3 (38%)	9 (14%)
	F	0 (0%)	0 (0%)	1 (13%)	0 (0%)	
Workload - sedentary, n (%)	M	6 (75%)	7 (88%)	5 (63%)	6 (75%)	45 (70%)
	F	4 (50%)	5 (63%)	7 (88%)	5 (63%)	
Sports active						
Light <1 hour per week, n (%)	M	4 (50%)	2 (25%)	3 (38%)	1 (13%)	16 (25%)
	F	2 (25%)	1 (13%)	1 (13%)	2 (25%)	
Moderate 1-3 hours per week, n (%)	M	1 (13%)	4 (50%)	3 (38%)	4 (50%)	27 (42%)
	F	2 (25%)	4 (50%)	5 (63%)	4 (50%)	
Vigorous >3 hours per week, n (%)	M	2 (25%)	2 (25%)	2 (25%)	3 (38%)	19 (30%)
	F	3 (38%)	3 (38%)	2 (25%)	2 (25%)	
VISA knee score (0-100) <100, n (%)	M	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (2%)
	F	0 (0%)	0 (0%)	1 (13%)	0 (0%)	
VISA achilles score (0-100) <100, n (%)	M	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	F	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Blood screening - abnormal, n (%)[c]	M	1 (13%)	1 (13%)	2 (25%)	0 (0%)	8 (13%)
	F	0 (0%)	2 (25%)	0 (0%)	2 (25%)	
Clinical findings - abnormal, n (%)[d]	M	1 (13%)	4 (50%)	0 (0%)	1 (13%)	12 (19%)
	F	1 (13%)	3 (38%)	1 (13%)	1 (13%)	

[a] Data was missing for one woman and one man in the decade 20-29 for all variables except for age and gender.
[b] More than 14 items alcohol per week for women and 21 items for men.
[c] None had increased inflammatory markers - other increased values were of no relevance.
[d] Hypermobility and/or flatfoot.

Clinical examination and blood tests

The anterior knee tendons, the Achilles tendon and the fascia plantaris were examined. Functional tests were made and pain and enlargement of the tendons or the peritendinous tissues were evaluated by palpation. All the examinations were performed by an experienced rheumatologist (HB).

Blood was analysed for: haemoglobin, plasma creatinine, plasma sodium, plasma potassium, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), plasma alkaline phosphatase, and plasma alanine aminotransferase.

Ultrasound

Ultrasound examinations were performed with a Logiq 9 (GE Medical, Milwaukee, WI, USA) using a ML 6–15 MHz transducer. The same fixed colour Doppler pre-set was used. The pre-set was optimised for assessing inflammatory flow according to current recommendations (15). Only the dominant leg was examined (classified according to the dominant arm). Ultrasound examinations were performed by a physician experienced in musculoskeletal ultrasound (MJK).

The following US features were evaluated: increased thickness, changed structure including hypoechogenicity between fibres, enthesophytes/calcifications, erosions, and colour Doppler activity <2mm from the enthesis. Five insertion areas were evaluated on US: 1. the quadriceps tendon at the base of the patella, 2. The patellar tendon at apex patella, 3. The patellar tendon at the insertion on tuberositas tibiae, 4. Achilles tendon at the insertion on calcaneus, 5. Fascia plantaris at the insertion on calcaneus. No colour Doppler examinations were performed at the fascia plantaris insertion, as the heal pad absorbs Doppler signal.

The knee tendons were examined with the subjects in supine position and the tendons of the foot in the prone position. The grey-scale US of the knee was performed with the knee in a 20 degree flexed position, obtained with a 10 cm pad under the knee. The Doppler examination was made with the knee fully extended in order to obtain the maximum flow (16). The Achilles tendon and the fascia plantar aponeurosis were examined with the ankle in neutral position with the foot hanging relaxed

Table II. Findings of US elementary lesions according to gender and decade.

Variable	Age 20–29		Age 30–39		Age 40–49		Age 50–59		Total (n=64)	*p*-value interaction[a]	*p*-value effect of decade	*p*-value effect of gender
	M (n=8)	F (n=8)	M (n=8)	F (n=8)	M (n=8)	F (n=8)	M (n=8)	F (n=8)				
Quadriceps												
Increased tendon thickness present, n (%)	1 (13%)	0	0	0	1 (13%)	0	0	0	2 (3%)	1.000	0.406	0.088
Changed tendon structure present, n (%)	1 (13%)	0	0	0	1 (13%)	0	1 (13%)	0	3 (5%)	1.000	0.609	0.037
Enthesophyte (0-3), median (IQR)	1 (0;1)	0 (0;0)	0 (0;1)	0 (0;1)	1 (0;2)	0 (0;0)	1 (0;1)	0 (0;0)	0 (0;1)	0.343	0.905	0.026
Enthesophyte, pathology present, n (%)	4 (50%)	1 (13%)	2 (25%)	3 (38%)	4 (50%)	1 (13%)	5 (63%)	2 (25%)	22 (34%)	0.311	0.831	0.032
Doppler (0-3), median (IQR)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)	0.767	0.201	0.522
Doppler, pathology present, n (%)	1 (13%)	0	0	0	0	0	1 (13%)	1 (13%)	3 (5%)	0.783	0.195	0.538
Erosion (0-3), median (IQR)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)	NA	NA	NA
Erosion, pathology present, n (%)	0	0	0	0	0	0	0	0	0	1.000	1.000	1.000
Prox. patella lig.												
Increased tendon thickness present, n (%)	0	0	0	1 (13%)	0	0	1 (13%)	1 (13%)	3 (5%)	0.783	0.195	0.538
Changed tendon structure present, n (%)	0	0	0	1 (13%)	0	0	1 (13%)	1 (13%)	3 (5%)	0.783	0.195	0.538
Enthesophyte (0-3), median (IQR)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)	0.406[b]	0.417[b]	1.000[b]
Enthesophyte, pathology present, n (%)	0	1 (13%)	0	0	0	0	1 (13%)	0	2 (3%)	0.406	0.417	1.000
Doppler (0-3), median (IQR)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)	NA	NA	NA
Doppler pathology present, n (%)	0	0	0	0	0	0	0	0	0	1.000	1.000	1.000
Erosion (0-3), median (IQR)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)	NA	NA	NA
Erosion, pathology present, n (%)	0	0	0	0	0	0	0	0	0	1.000	1.000	1.000
Dist. patella lig.												
Increased tendon thickness present, n (%)	0	0	0	2 (25%)	2 (25%)	1 (13%)	3 (38%)	1 (13%)	9 (14%)	0.194	0.090	0.709
Changed tendon structure present, n (%)	0	0	0	1 (13%)	1 (13%)	1 (13%)	2 (25%)	1 (13%)	6 (9%)	0.600	0.184	1.000
Enthesophyte (0-3), median (IQR)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)	0.767	0.196	0.599
Enthesophyte, pathology present, n (%)	0	0	0	1 (13%)	0	0	1 (13%)	1 (13%)	3 (5%)	0.783	0.195	0.538
Doppler (0-3), median (IQR)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)	1.000[a]	0.412[a]	0.228[a]
Doppler, pathology present, n (%)	0	0	0	0	0	0	1 (13%)	0	1 (2%)	1.000	0.412	0.228
Erosion (0-3), median (IQR)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)	NA	NA	NA
Erosion, pathology present, n (%)	0	0	0	0	0	0	0	0	0	1.000	1.000	1.000
Achilles tendon												
Increased tendon thickness present, n (%)	1 (13%)	0	3 (38%)	0	1 (13%)	0	1 (13%)	0	6 (9%)	1.000	0.529	0.002
Changed tendon structure present, n (%)	0	0	0	0	0	0	0	0	0	1.000	1.000	1.000
Enthesophyte (0-3), median (IQR)	0 (0;1)	0 (0;1)	1 (1;1)	0 (0;0)	1 (0;1)	0 (0;1)	1 (0;2)	0 (0;0)	0 (0;1)	0.420	0.929	0.015
Enthesophyte, pathology present, n (%)	3 (38%)	3 (38%)	6 (75%)	1 (13%)	5 (63%)	2 (25%)	4 (50%)	2 (25%)	26 (41%)	0.296	0.962	0.010
Doppler (0-3), median (IQR)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)	NA	NA	NA
Doppler, pathology present, n (%)	0	0	0	0	0	0	0	0	0	1.000	1.000	1.000
Erosion (0-3), median (IQR)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)	1.000[a]	0.412[a]	0.228[a]
Erosion, pathology present, n (%)	0	0	0	0	1 (13%)	0	0	0	1 (2%)	1.000	0.412	0.228
Fascia plantaris												
Increased tendon thickness present, n (%)	1 (13%)	1 (13%)	2 (25%)	0	2 (25%)	1 (13%)	0	1 (13%)	8 (13%)	0.227	0.753	0.443
Changed tendon structure present, n (%)	0	1 (13%)	1 (13%)	0	1 (13%)	0	0	0	3 (5%)	0.262	0.619	0.547
Enthesophyte (0-3), median (IQR)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)	1.000[a]	0.412[a]	0.228[a]
Enthesophyte, pathology present, n (%)	0	0	0	0	0	0	1 (13%)	0	1 (2%)	1.000	0.412	0.228
Erosion (0-3), median (IQR)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)	NA	NA	NA
Erosion, pathology present, n (%)	0	0	0	0	0	0	0	0	0	1.000	1.000	1.000

IQR: inter-quartile range; n: numbers; SD: standard deviation. *p*-values are estimated from logistic regressions.
[a]Interaction between gender and decade. [b]*p*-values are estimated from proportional odds model for ordinal outcome variables.

over the edge of the examination table. During the US examination still-images of all the examined portions were stored. If any US changes were present carefulness was made to display these changes clearly on the stored image. No descriptions of the images were made by the person performing the US examination.

The features stored and evaluated on the US still images were the ones proposed by the OMERACT US working group (7). All images were evaluated in consensus by two investigators (KE; JGM), who both had experience in musculoskeletal US (KE 12 years and JGM 3 years).

Statistical methods

This study was designed as a descriptive cross-sectional study*; i.e.* a statistical frequency survey among healthy participants. No formalised statistical power and/or sample size was performed, however our anticipation was that a potential prevalence of US-detected abnormalities among one-in-five (20%) in each stratum would offer a significant descriptive impact. Thus within the reasonable limits of what appeared feasible, with a total sample of 64 participants – any given comparison of two independent binomial proportions (using Pearson's Chi-square statistic with a Chi-square approximation) with a two-sided significance level of 0.05 – our design have an approximate power of 80.6% if the proportions of having ultrasound pathology of the entheses are 40% and 10%, respectively (*e.g.* men *vs.* women).

The characteristics of the participants

were described for each gender and decade using descriptive statistics presenting continuous outcomes as means with corresponding standard deviations (SD), ordinal outcomes as medians with corresponding interquartile ranges (IQR), and binary outcomes as numbers with corresponding percentages.

The findings of US pathology were initially described for each gender and decade using descriptive statistics. Subsequently, data were analysed with statistical models with the fixed factors gender (man, woman), age (20–29, 30–39, 40–49, 50–59), and the corresponding interaction between these factors, in order to investigate whether mutual associations exist between these factors and findings of US pathology.

For binary outcome variables logistic regression models were used, for ordinal outcome variables, such as rating 0–3, proportional odds models were used, and for continuous variables linear models were used. No correction for multiple testing was done. All models were tested for their assumptions. All analyses were carried out using the statistical programme R (v. 3.2.3).

Results

Recruiting letters were sent to 425 subjects, of these 325 did not want to participate and 29 were excluded due to exclusion criteria, thus 71 were invited for the examination programme. Five withdrawals of consent after enrolment and in two cases, the clinical examination revealed pathology of the enthesis, which lead to exclusion before the study, finally data, except age and US examination, were missing for one man and one woman in the youngest decade. Basic characteristics of the participants are given in Table I; the average body mass index in cohort was within normal range; very few were smokers and none had alcohol habits that exceeded the limits of the Danish authorities, which is 14 items alcohol per week for women and 21 for men (no shown). No pathology related to joint and tendon was seen in the blood test in any of the included subjects and none had increased inflammatory markers in the blood. The majority of participants had sedentary work and were moderate to vigorous physically active in their leisure time (1 to >3 hours per week). Tendon problems in the near family or previous muscle sprain were only seen in 4 and 9% respectively. Only one had minor pathology in the VISA knee index score (97 point in the range from 0–100, where 100 is no complains) and none in the VISA Achilles index.

The distribution of all pathological changes evaluated on US is listed in Table II. At the enthesis level, pathology was seen in 22.8% of all insertions (73 of 320) examined, at the subject-level 73.4% (47/ 64) persons showed at least one pathological finding on US examination, in 57% only one insertion was affected and in 34% two sites were affected. Only one erosion was seen and in one enthesis (Achilles insertion). Doppler activity <2 mm from the insertion was seen in four entheses of which three were in the quadriceps insertion on the patella. The most common US elementary lesion seen was enthesophytes at the insertion of the Achilles and quadriceps tendons.

Elementary lesions such as tendon thickness and calcifications in the quadriceps and Achilles tendon was seen significantly more in men. Only a slight increase in elementary lesions was seen with increasing age.

Discussion

This study aimed to investigate US detected signs of pathology in the entheses of the lower limb in a larger age-stratified cohort of healthy subjects between 20 and 60 years. US signs of pathology were seen in many sites, thus elementary lesions were seen in 73.4% of the healthy subjects. This is in accordance with the study by D'Agostino *et al*. where grey-scale entheseal involvement was seen in 52% of their healthy controls (5). Similarly, in a cohort of healthy subjects US detected synovial hypertrophy and Doppler activity in 88% of the participants (10) indicating that a cut-off between normality and pathology is needed for patients suspected of having inflammatory diseases. In accordance with this, a composite score for entheseal pathology in SpA patients, the MASEI score, suggested a score of ≥18, with a maximal score of 136 points, to distinguish between patients and healthy controls, allowing for some pathology in the healthy subjects (17). In 57% of all the healthy persons in our sample, pathology was seen in only one insertion (27/47) and the majority of elementary lesions were enthesophytes in the entheses of the quadriceps and Achilles tendons (Table II) that may be related to traction. Only one erosion was detected in one enthesis and Doppler activity less than 2 mm from the insertion (7) was found in only four entheses of which three were in the quadriceps insertion on patella.

Our results indicate that with awareness of the "normal" distribution and severity of US changes at the entheses, US examination may be a valuable part for the detection of entheseal pathology in adulthood patients. The results from both our study and the study by D'Agostino *et al*. indicate that Doppler activity and erosions in the entheses are rarely found in healthy persons (5).

We found a tendency towards an increasing number of changes in the enthesis with increasing age. This is not surprising as more and more degenerative changes will appear with increasing age. This may indicate that our results would have been different if we had also included persons from 60 to 80 years. In future studies it could be interesting to investigate the prevalence of US elementary lesion in this age group as well. This would lead to an even more valid use of US examination of the enthesis.

A limitation of our study is that most of the participants in our cohort had sedentary work and were only moderately active in their leisure time. In a sample of more active participants with this age distribution, further load on the tendons at either work or sport might have led to more frequent pathology in the entheses (18, 19). Furthermore it could be argued that the strength of our results would have been increased if the US evaluation was made at the time of US examination and not afterwards on stored images, as the evaluation on live images is more sensitive. However, it was for practical reasons, not possible in our study set-up. Also it could

be argued that it is likely that more US changes were found if older decades were included in the study, however our focus was to investigate US changes in the in enthesis in the adulthood.

The strength of our study is that this cross-sectional study was sampled from a large population study in Copenhagen, thus it can be assumed that the findings reflect the normal Danish population. Furthermore, the examinations were performed in a standardised way, with fixed US pre-sets according to best practice (15).

Conclusion

Our findings suggest that US can be used as part of the examination and diagnosis of pathological changes of the entheses in *adulthood* although with caution regarding enthesophytes of the quadriceps and Achilles tendon, as these could appear to result in more "false positives".

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