Ultrasound Characteristics of the Achilles Tendon in Tophaceous Gout: A Comparison with Age- and Sex-matched Controls

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ABSTRACT. ***Objective.*** To investigate the frequency and distribution of characteristics of the Achilles tendon (AT) in people with tophaceous gout using musculoskeletal ultrasound (US).

Methods. Twenty-four participants with tophaceous gout and 24 age- and sex-matched controls without gout or other arthritis were recruited. All participants underwent a greyscale and power Doppler US examination. The AT was divided into 3 anatomical zones (insertion, pre-insertional, and proximal to the mid-section). The following US characteristics were assessed: tophus, tendon echogenicity, tendon vascularity, tendon morphology, entheseal characteristics, bursal morphology, and calcaneal bone profile.

Results. The majority of the participants with tophaceous gout were middle-aged men (n = 22, 92%) predominately of European ethnicity (n = 14, 58%). Tophus deposition was observed in 73% (n = 35) of tendons in those with gout and in none of the controls ($p < 0.01$). Intratendinous hyperechoic spots ($p < 0.01$) and intratendinous power Doppler signal ($p < 0.01$) were more frequent in participants with gout compared to controls. High prevalence of entheseal calcifications, calcaneal bone cortex irregularities, and calcaneal enthesophytes were observed in both gout participants and controls, without differences between groups. Intratendinous structural damage was rare. Hyperechoic spots were significantly more common at the insertion compared to the zone proximal to the mid-section ($p < 0.01$), but between-zone differences were not observed for other features.

Conclusion. US features of urate deposition, tophus, and vascularization are present throughout the AT in patients with tophaceous gout. Despite crystal deposition, intratendinous structural changes are infrequent. Many characteristics observed in the AT in people with tophaceous gout, particularly at the calcaneal enthesis, are not disease-specific. (First Release August 1 2017; J Rheumatol 2017;44:1487–92; doi:10.3899/jrheum.170203)

Key Indexing Terms:
GOUT ACHILLES TENDON TOPHI ULTRASOUND

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Gout is a form of inflammatory arthritis caused by monosodium urate (MSU) crystal deposition[1]. Gout can clinically manifest as acute inflammatory arthritis, tophus formation, joint damage, and altered tendon and ligament structure and function[2]. Tophus formation has been identified as a risk factor for the development of musculoskeletal disability and the mechanical obstruction of joint movement, and is linked to a reduction in quality of life[3,4].

The Achilles tendon (AT) is involved in everyday activities, including walking, and is the main plantarflexor in gait. Alteration to the internal structure of the tendon by the degenerative process reduces the tendon's ability to respond to load, and subsequently predisposes to further injury. The presence of MSU crystals in the AT has been previously reported[5,6,7]. In a dual-energy computed tomography (CT) study, 1 in 4 people with tophaceous gout had evidence of urate crystal deposition affecting the AT, with 38% of these having only nonentheseal involvement, 40% having both entheseal and nonentheseal involvement, and 22% with only entheseal involvement[6].

Imaging provides important insights into the pathology of gout. Ultrasound (US) has been used to assess and characterize urate deposition, structural damage, and inflammation in terms of synovitis and tenosynovitis in people with gout[8,9]. The aim of our current study was to investigate the frequency and distribution of US characteristics of the AT in people with tophaceous gout compared to age- and sex-matched controls.

MATERIALS AND METHODS

Participants. Twenty-four participants with tophaceous gout were recruited from rheumatology outpatient clinics at the Auckland District Health Board, Auckland, New Zealand, together with 24 age- and sex-matched control participants recruited from public advertising of Auckland University of Technology (AUT) staff. This sample size is similar to previous imaging studies of foot disease in gout[10]. Participants with tophaceous gout fulfilled the 1977 American Rheumatism Association classification criteria for gout[11] and were to have clinical evidence of at least one palpable tophus. Participants with gout were excluded if they were experiencing an episode of acute arthritis at the time of the study visit. The study was approved by the AUT Ethics Committee (AUTEC 13/100). All participants provided written informed consent prior to entry into the study. Demographic data were obtained from all participants including age, sex, ethnicity, body mass index, current medications, and medical history. Additionally, gout disease characteristics were documented for participants with gout including disease duration and flare history, serum urate, and tophus count.

US image acquisition. The US examination was performed at the AUT Horizon Scanning Clinic by a single musculoskeletal radiologist (BA) who was blinded to the participants' diagnostic group. A Philips iU22 unit equipped with a broadband 12-14MHz linear probe was used. All settings were standardized to optimize visualization of superficial and deep structures of the AT. Greyscale scanning used a dynamic range of 40–50dB and a gain of 60dB. Power Doppler settings used a pulse repetition frequency of 500Hz, and a low wall filter of 42Hz, with the color gain increased to the highest value not generating signal under the bony cortex and optimized for low flow. All participants assumed a prone position during scanning with the knee fully extended for optimal visualization of the AT. Bilateral systematic longitudinal and transverse imaging of the enthesis and body of the AT were conducted in greyscale and power Doppler modes in accordance with the Outcome Measures in Rheumatology US task force[9].

US image interpretation. All images were stored in a picture archiving and communications system (PACS). Six months following the completion of all data acquisition, the static US images were reviewed by a single radiologist (BA) with over 20 years of experience in musculoskeletal imaging for features of urate deposition, inflammation, structure, and damage. All characteristics assessed within the AT were also recorded with respect to their location in accordance with the following 3 divisions: zone 1 (insertional zone): calcaneal enthesis to 2 cm proximal; zone 2 (pre-insertional): 2 cm to 6 cm proximal to calcaneal enthesis; and zone 3 (proximal to mid-section): 6 cm proximal to enthesis to myotendinous junction of the gastrocnemius. The 3 zones were defined from previous work on the AT that indicated a relative zone of hypovascularity within 2 cm to 6 cm proximal to the calcaneal insertion[12,13]. All US characteristics were defined in accordance with standardized definitions as follows.

Features of urate deposition. Intratendinous tophi were defined as the presence of hyperechoic heterogeneous or homogeneous lesions with poorly defined contours surrounded by an anechoic halo[14] and were recorded for each zone of the AT. Intratendinous hyperechoic spots were defined as bright foci consistent with either aggregate formation on the collagen fibril or calcified tophi (relative to the tendon fibers), with or without acoustic shadow, seen in 2 perpendicular planes[7,15] within the AT. Additionally, intratendinous focal hyperechoic areas were defined as a lack of the homogeneous fibrillar pattern with loss of the tightly packed echogenic lines after correcting for anisotropy[15]. The presence of tophi within the retrocalcaneal bursa were also recorded and defined as aggregates located in the bursa that were heterogeneous and hyperechoic (relative to subdermal fat) with poorly defined margins with or without areas of acoustic shadowing[7]. Additionally, the presence of bursal snowstorm was recorded if echogenic aggregates were observed within the bursa[16].

Features of inflammation. Tendon vascularity was assessed within each zone of the AT and defined as the presence of the power Doppler signal[17]. The enthesis of the AT, defined as the area within 2 mm of the bony cortex, was also assessed for the presence of vascularity using the same definition[15]. Retrocalcaneal bursitis was defined as a bursa with a well-defined compressible, anechoic, or hypoechoic area inside with maximal diameter larger than 2 mm as viewed in the longitudinal plane[18]. Bursal size was also recorded using digital calipers and bursal size score graded using a semiquantitative scale (0 = < 2 mm, 1 = between 2–4 mm, and 2 = > 4 mm)[17]. Bursal vascularity was defined as the presence of power Doppler activity within the bursa[17].

Features of structure and damage. AT entheseal thickness was measured on a longitudinal scan at the insertion of the deeper margin of the AT into the calcaneal bone using digital callipers[19]. AT thickness was also scored on a semiquantitative scale (1 = < 5.3 mm, 2 = 5.3–6.3 mm, and 3 = > 6.3 mm)[17]. AT length was also measured at the insertion of the deeper margin into the calcaneal bone using digital callipers[20]. A partial tendon tear was defined as a focal discontinuity[21] while a complete tendon rupture was defined as a complete loss of tendon substance[22], both of which were visualized with the US beam exactly perpendicular to the tendon to avoid anisotropy. Bone erosions were defined as a cortical breakage with a step-down contour defect, seen in 2 perpendicular planes, at the insertion of the enthesis to the bone[23] and graded on a 3-grade semiquantitative scale (0 = no bone erosion, 1 = between 0.1 and 2 mm, and 2 = > 2 mm)[17]. Bone cortex irregularities were defined as a loss of the normal regular bone contour without any clear sign of enthesophyte and/or erosion[15]. Enthesophytes were defined as a step up of bony prominence at the end of the normal bone contour, seen in 2 perpendicular planes, with or without acoustic shadow[15]. The presence of calcifications at the AT enthesis was defined as intratendinous hyperechoic spots[15].

Interobserver reliability. To assess interobserver agreement of the US characteristics, randomly selected images from 12 participants with gout and 12 controls were uploaded to PACS and were independently scored by a second musculoskeletal radiologist (TH) with over 25 years of clinical experience, who was blinded to all clinical details and US scores from the first radiologist. Reliability was determined using the κ statistic. Values of 0 to 0.2 were considered poor, 0.2 to 0.4 fair, 0.4 to 0.6 moderate, 0.6 to 0.8 good, and 0.8 to 1.0 excellent[24].

Statistical analysis. Participant characteristics were described as mean (SD) or frequency (%). Because US characteristics were nested within participants (i.e., assessed bilaterally and within 3 zones), a general estimating equation (GEE) approach was used to determine whether there were significant differences between the gout and control groups for both the binary and continuous US characteristics. Between-zone differences in the US characteristics were also analyzed within the GEE models. All tests were 2-tailed, and p values < 0.05 were considered significant. Data were analyzed using SPSS V.20 (SPSS).

RESULTS

The participant demographic and clinical characteristics are shown in Table 1. The majority of the participants with tophaceous gout were middle-aged (mean 61.9 yrs old), men (n = 22, 92%), and predominately of European ethnicity (n = 14, 58%). There were more participants of European ethnicity in the control group (p < 0.01). Participants with tophaceous gout had longstanding disease with a mean (SD) serum urate level of 0.37 (0.11) mmol/l. Hypertension and cardiovascular disease were significantly more frequent in participants with

Table 1. Participant demographic and clinical characteristics. Values mean (SD) unless otherwise specified.

Characteristic	Gout, n = 24	Control, n = 24	p
Age, yrs	61.9 (12.0)	61.7 (12.3)	0.95
Male sex, n (%)	22 (92)	22 (92)	0.99
Ethnicity, n (%)			
European	14 (58)	23 (96)	< 0.01
Māori	1 (4)	1 (4)	
Pasifika	6 (25)	0 (0)	
Asian	3 (13)	0 (0)	
BMI, kg/m^2	31.1 (4.1)	26.3 (5.1)	0.01
Disease duration, yrs	17.4 (11.9)	—	—
Age at first episode, yrs	44.3 (18.8)	—	—
Flares in preceding 3 mos	1.2 (1.5)	—	—
Hypertension, n (%)	17 (71)	7 (29)	< 0.01
Cardiovascular disease, n (%)	8 (33)	2 (8)	0.03
Type 2 diabetes, n (%)	7 (29)	2 (8)	0.07
Diuretic use, n (%)	9 (38)	9 (38)	1.00
Urate-lowering therapy, n (%)	22 (92)	—	—
Foot tophus count	2.2 (3.3)	—	—
Total tophus count	7.2 (7.4)	—	—
Serum urate, mmol/l	0.37 (0.11)	—	—

BMI: body mass index.

tophaceous gout ($p < 0.01$ and $p = 0.03$, respectively). The majority of participants with gout were treated with urate-lowering therapy (n = 22, 92%).

Interreader reliability. Interobserver reliability demonstrated that κ values were excellent for intratendinous tophus (κ = 0.91), intratendinous focal hyperechoic areas (κ = 1.00), intratendinous hyperechoic spots (κ = 0.93), intratendinous power Doppler signal (κ = 0.87), tendon tears (κ = 1.00), entheseal focal hyperechoic areas (κ = 1.00), entheseal calcifications (κ = 0.92), entheseal vascularity (κ = 0.84), bursal snowstorm appearance (κ = 1.00), bursal power Doppler signal (κ = 1.00), and calcaneal bone erosions (κ = 1.00). Kappa values were good for calcaneal bone cortex irregularities (κ = 0.77) and calcaneal enthesophytes (κ = 0.68).

US features of urate deposition. The presence of intratendinous tophus was significantly more common in the participants with gout compared to the controls (n = 35 tendons, 73% vs n = 0 tendons, 0%, respectively; $p < 0.01$; Table 2). Intratendinous hyperechoic spots were also more common in participants with gout compared to controls (n = 39 tendons, 81% vs n = 9 tendons, 19%, respectively; $p < 0.01$). Intratendinous focal hyperechoic areas, intrabursal tophus, and bursal snowstorm appearance were uncommon and could not be analyzed statistically using the GEE model.

US features of inflammation. Intratendinous power Doppler signal was more prevalent in participants with tophaceous gout compared to control participants (n = 39 tendons, 81% vs n = 9 tendons, 19%, respectively; $p < 0.01$; Table 3). No differences were found for entheseal vascularity between participants with gout and controls (n = 10 tendons, 21% vs n = 7 tendons, 15%, respectively; $p = 0.65$). Retrocalcaneal bursitis and bursal Doppler signal were uncommon and could not be analyzed statistically using the GEE model.

Table 2. Features of urate deposition. Values are n/N (%) unless otherwise specified.

Ultrasound Characteristic	Gout, n = 48 Tendons	Controls, n = 48 Tendons	p
Intratendinous tophus	35/48 (72.9)	0/48 (0.0)	< 0.001
Intratendinous hyperechoic spots	39/48 (81.2)	9/48 (18.7)	< 0.01
Intratendinous focal hyperechoic areas	5/48 (10.4)	2/48 (4.2)	*
Intrabursal tophus	0/48 (0.0)	0/48 (0.0)	*
Bursal snowstorm appearance	1/24 (4.2)	0/23 (0.0)	*

*Could not be analyzed because of low frequency of the ultrasound characteristic.

US features of structure and damage. Figure 1 illustrates (a) intratendinous urate deposits that appear as hyperechoic bands (arrows) on collagen fibrils in the mid-portion of the AT; (b) intratendinous tophus deposition to the proximal zone of the AT (arrows); and (c) intratendinous vascularization to the mid-portion of the AT (arrows). Partial tears were observed in 2 tendons (4%) in participants with gout and in none of the controls, while neither group demonstrated AT ruptures (Table 4). There was no significant difference in mean tendon thickness (4.7 mm vs 4.3 mm; $p = 0.85$) or mean tendon length (57.9 mm vs 57.3 mm; $p = 0.90$) between participants with gout and controls. The presence of entheseal calcifications (n = 28 tendons, 59%; vs n = 19 tendons, 40%; $p = 0.43$), calcaneal bone cortex irregularities (n = 13 tendons, 27%; vs n = 9 tendons, 19%; $p = 0.43$), or calcaneal enthesophytes (n = 33 tendons, 69%; vs n = 29 tendons, 60%; $p = 0.64$) was not significantly different between tophaceous gout and control groups.

Owing to the similarities in the tendon thickness and calcaneal bone erosion scores between groups, these variables could not be analyzed using the GEE model.

US features by AT zone. No significant differences were found for intratendinous tophus presence ($p = 0.07$) and intra-

Table 3. Features of inflammation. Values are n/N (%) unless otherwise specified.

Ultrasound Characteristic	Gout, n = 48 Tendons	Controls, n = 48 Tendons	p
Intratendinous Doppler signal	39/48 (81.2)	9/48 (18.7)	< 0.01
Entheseal Doppler signal	10/48 (20.8)	7/48 (14.6)	0.65
Retrocalcaneal bursitis	0/48 (0.0)	0/48 (0.0)	*
Bursal size score, mm			
< 2	22/24 (91.7)	23/23 (100)	*
2–4	2/24 (8.3)	0/23 (0.0)	
> 4	0/24 (0.0)	0/23 (0.0)	
Bursal Doppler signal	7/48 (14.6)	0/48 (0.0)	*

*Could not be analyzed because of low frequency of the ultrasound characteristic.

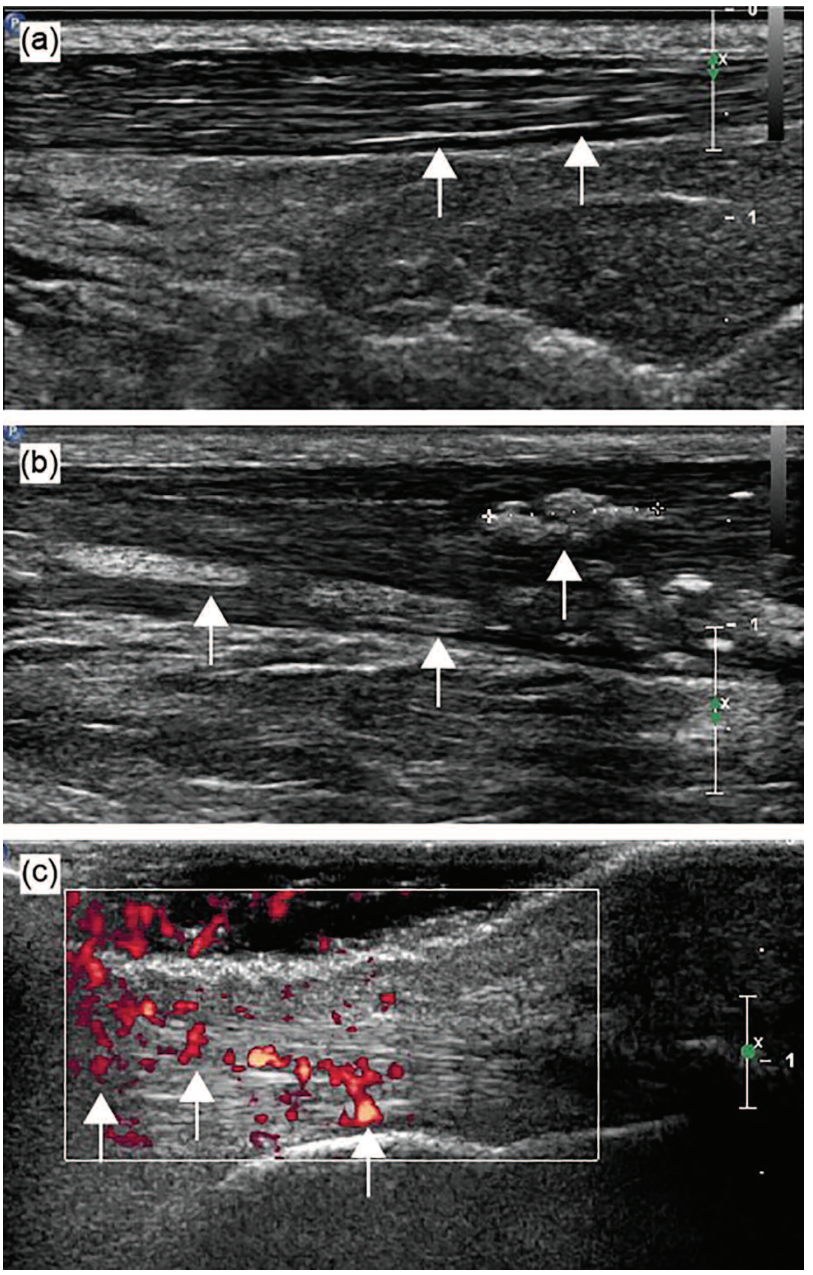

Figure 1. (a) Intratendinous urate deposits appear as hyperechoic bands (arrows) on collagen fibrils in the mid-portion of the Achilles tendon. (b) Intratendinous tophus deposition to the proximal zone of the Achilles tendon (arrows). (c) Intratendinous vascularization to the mid-portion of the Achilles tendon (arrows).

tendinous power Doppler signal ($p = 0.60$) between the 3 zones of the AT in people with tophaceous gout (Table 5). A significant difference was observed for the presence of intratendinous hyperechoic spots by AT zone ($p < 0.01$). Pairwise comparisons revealed that hyperechoic spots were significantly more common in zone 1 compared to zone 3 ($p < 0.01$).

DISCUSSION

The aim of our current study was to investigate the frequency and distribution of US characteristics of the AT in people with tophaceous gout. Our findings demonstrate that, compared with age- and sex-matched control participants, people with tophaceous gout have both disease-specific and nonspecific features, including a higher prevalence of tophus, intra-

Table 4. Features of structure and damage. Values are n/N (%) unless otherwise specified.

Ultrasound Characteristic	Gout, n = 48 Tendons	Controls, n = 48 Tendons	p
Tendon tear	2/48 (4.2)	0/48 (0.0)	*
Tendon rupture	0/48 (0.0)	0/48 (0.0)	*
Tendon thickness, mm, mean (SD)	4.7 (0.8)	4.3 (0.7)	0.85
Tendon thickness score, mm			*
< 5.3	20/24 (83.3)	23/24 (95.8)	
5.3–6.3	4/24 (16.7)	1/24 (4.2)	
> 6.3	0/24 (0.0)	0/24 (0.0)	
Tendon length, mm, mean (SD)	57.9 (19.8)	57.3 (15.6)	0.90
Entheseal calcifications, mm	28/48 (58.3)	19/48 (39.6)	0.43
Calcaneal bone erosion score			*
None	48/48 (100)	48/48 (100)	
0.1–2	0/48 (0.0)	0/48 (0.0)	
> 2	0/48 (0.0)	0/48 (0.0)	
Calcaneal bone cortex irregularities	13/48 (27.1)	9/48 (18.7)	0.43
Calcaneal enthesophytes	33/48 (68.7)	29/48 (60.4)	0.64

*Could not be analyzed because of low frequency of the ultrasound characteristic.

Table 5. Ultrasound characteristics by zone of tendon. Values are n (%) unless otherwise specified.

Ultrasound Characteristic	AT Zone[a]	Gout, n = 48 Tendons	p
Intratendinous tophus	Zone 1	26 (54.2)	0.07
	Zone 2	25 (52.1)	
	Zone 3	12 (25.0)	
Intratendinous hyperechoic spots	Zone 1	22 (45.8)	< 0.01[b]
	Zone 2	17 (35.4)	
	Zone 3	10 (20.8)	
Intratendinous power Doppler signal	Zone 1	17 (35.4)	0.60
	Zone 2	15 (31.2)	
	Zone 3	17 (35.4)	

[a]Zone 1: insertion; zone 2: pre-insertion; zone 3: proximal to pre-insertion. [b] Pairwise comparisons revealed a significant difference between zone 1 and zone 3 ($p < 0.01$). AT: Achilles tendon.

tendinous power Doppler signal, and intratendinous hyperechoic spots. Despite these findings, structural damage in the AT was minimal in participants with gout.

Our current study showed that tophi were present in 73% of tendons in participants with tophaceous gout, which is higher than that reported in previous imaging studies (range, 22%–34% of tendons)[5,7]. However, clinical evidence of palpable tophi was not an inclusion criterion in these prior studies, suggesting that MSU deposition within the AT may be more prevalent in patients with gout who have advanced tophaceous disease. Chhana, *et al*[25] reported that MSU crystals directly interact with tenocytes to reduce cell viability and function, and these interactions may contribute to tendon damage in people with advanced gout. Despite the frequent deposition of tophus in our current study, disruption of collagen fibrillar echotexture was rarely observed.

Our current results demonstrated tophus deposition present in all 3 zones of the AT, with the enthesis and body of the AT being the most prevalent sites. In a dual-energy CT study, Dalbeth, *et al*[6] reported that 38% of AT examined had only nonentheseal involvement, 40% had both entheseal and nonentheseal involvement, and 22% had only entheseal involvement. Intratendinous hyperechoic spots were observed significantly more often in participants with gout in all tendon zones, but significantly higher in the insertional zone. Hyperechoic spots are representative of either intratendinous aggregate formation on the collagen fibril or calcified tophi[7]. However, in agreement with Ventura-Ríos, *et al*[5], we also observed intratendinous hyperechoic spots in some control participants. Hyperechoic changes and calcifications within the AT in healthy populations may be related to biomechanical factors or asymptomatic calcific tendinopathy[26]. In participants with tophaceous gout, power Doppler signal was observed in all zones of the AT with no difference between the 3 zones. Our data show that a positive Doppler signal is not only a synovial feature in tophaceous gout, but also extends to the intratendinous structure. The high prevalence of intratendinous vascularization observed in our current study contrasts with Ventura-Ríos, *et al*[5], who reported no positive Doppler signal in the AT in participants with gout. We observed the Doppler signal was also present in control participants supporting the notion that this lesion is not exclusive to gout.

Despite the high tophus burden observed in the participants with gout, intratendinous structural damage was not a major feature. Further, we observed only minimal erosive damage at the enthesis, suggesting that the calcaneal enthesis is not a common site of bone erosion in tophaceous gout. Additionally, entheseal thickening was not a significant feature, with no differences being found between participants with tophaceous gout and controls. Calcaneal enthesophyte formation was also observed at a similar rate in both groups. Enthesophytes are commonly found in healthy individuals and therefore do not necessarily indicate disease. The presence of minimal damage together with no significant alteration in fibrillar echotexture provides further evidence that the AT may not be structurally altered in participants with tophaceous gout.

Some limitations of our present study should be taken into account. Despite the study demonstrating crystal deposition and vascularization, the scoring and definitions of elemental tendinous features in tophaceous gout are yet to be standardized and validated. Future research would benefit from validation of these features through comparison with other advanced forms of musculoskeletal imaging including dual-energy CT and magnetic resonance imaging. The cross-sectional study design did not enable the investigation of a temporal sequence of lesion development, which would

have allowed differentiation between disease-specific and age-related characteristics. Finally, the control participants were not screened for hyperuricemia, which may have influenced the US findings[10].

US features of urate deposition and vascularization are present throughout the AT in patients with tophaceous gout. Despite crystal deposition, intratendinous structural changes are infrequent. Many characteristics observed in the AT, particularly at the calcaneal enthesis, are not disease-specific to people with tophaceous gout.

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