High prevalence of ultrasound-defined enthesitis in patients with metabolic syndrome

Comment on: How normal is the enthesis by ultrasound in healthy subjects?

Di Matteo A. *et al*.

Sirs,

We read with great interest the paper recently published in your journal by Dr Di Matteo and colleagues, in which they tested the recent Outcome Measures in Rheumatology (OMERACT) definition for the ultrasound (US) diagnosis of enthesitis in healthy subjects questioning the possibility of a low discriminant power of the above cited definition (1). This US definition requires entheseal inflammatory abnormalities, while ipervascularisation and structural damages are not mandatory (2). The authors evaluated various lower limb entheses of 82 healthy subjects with US applying OMERACT's filter to diagnose "active" enthesitis (entheseal thickening, hypoechogenicity and power Doppler signals). The results of the study demonstrated a high prevalence of signs of "active" enthesitis (in 34.1% out of 82 subjects, and in 8.4% out of 820 entheses) and a correlation with age and body mass index (BMI) (1). These prevalences are comparable or higher than the prevalences reported in previous studies in which different US definitions of enthesitis were applied, thus questioning the discriminant power of the recent OMERACT's US definition of enthesitis (3-5).

In this context we are applying the above cited OMERACT US definition of enthesitis on various groups of patients, with the aim to compare the prevalences of enthesitis in different pathologies. Here we report preliminary data about US-defined enthesitis in patients with metabolic syndrome.

A group of 50 consecutive outpatients visited for mechanical low back pain, between February 2019 and September 2019 in Rheumatology Unit of Siena (20 males, 30 females, mean age 58 years) and all fullfilling International Diabetes Foundation (IDF) criteria for metabolic syndrome (6), were also evaluated with multi-site bilateral US entheseal examination (shoulders, elbows, hips, knees and heels) by an expert rheumatologist sonographer, blinded to the patient's conditions. Each patient underwent bilateral dynamic B-mode and power Doppler (PD) US examination of twelve entheseal sites: acromial deltoid insertion, supraspinatus, lateral and medial elbow epicondyles, triceps, trochanteric enthesis, quadriceps and patellar tendon, ileo-tibial tract, Achilles tendon and plantar fascia. US was performed using Esaote MyLab Twice machine equipped with 6–18 MHz transducer and standardised B-mode and Doppler settings, which were optimised for all examinations. Doppler parameters were pulse repetition frequency within 500–750 Hz and Doppler frequency within 7–11.1 MHz. An enthesis was studied as the 2 mm zone of soft tissue adjacent to the bone cortex, based on OMERACT's filter (2). Enthesitis was defined, for each site, when only mandatory inflammatory lesions (enthesis thickening and hypoechogenicity) were present. Power Doppler (PD) intra-entheseal signal was recorded as sign of active enthesitis. Structural abnormalities (erosions, enthesopytosis/calcification) were also recorded. Inflammatory and structural changes were scored as a whole when present (score 1) or absent (score 0). The sum of entheses with inflammatory and structural damage was recorded and defined as "global inflammatory score" and "global structural damage score" for each patient. The prevalences of enthesitis

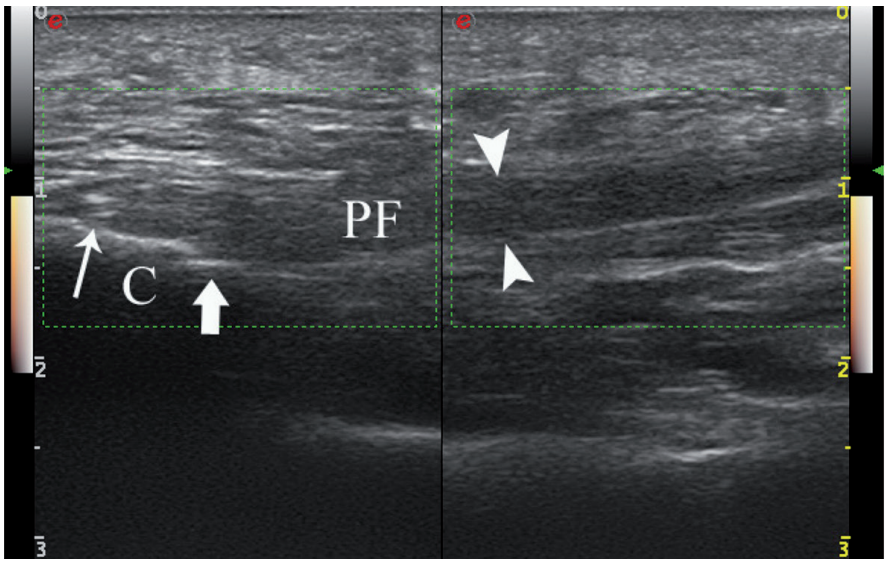

Fig. 1. Enthesopathy with midportion tendinosis of plantar fascia.
Subcalcaneal sagittal scan in an obese patient with metabolic syndrome. Hypoechoic thickening of the plantar fascia (PF) enthesis and fascial midportion (between the arrowheads), with a calcaneal spur (arrow) and calcifications (thin arrow) on the calcaneal (**C**) surface; this pattern could be defined enthesitis by the recent OMERACTs definition, as these abnormalities occur within 2 mm from bone surface. However the midportion of the plantar fascia appears heterogeneously hypoechoic and thickened, with ill-defined margins, suggesting a diagnosis of plantar fascia tendinosis due to biomechanical overload and dysmetabolic pathology. This pattern should be defined tendinosis with enthesopathy.

Table I. Clinical characteristics of patients and correlations with US findings.

	US findings	LEI	WHO obesity classes	Type II diabetes	Sex (male/female)	Age
Patients'characteristics		0.44 (SD 0.644, range 0-2)	1.3 (0.8391 SD, range 0-2)	15 patients	20/30	58.2 (7.53 SD, range 45-78)
Global inflammatory score	1.4 (SD 1.1, range 0-5)	r=0.3824 p=0.0061 **	r=0. r=5521 p=0 p=0.0001 **	p=0.5054 ns	p=0.1486 ns	p=0.0592 ns
Global structural damage score	2.54 (SD 2.15, range 0-8)	r=0.4239 p=0.0022 **	r=0.5788 p<0.0001 **	p=0.5722 ns	p=0.1478 ns	p=0.2329 ns
Power Doppler	6 entheses (1% of 600)	p=0.0759	p=0.5255	p=0.0759 ns	r=0.4523 p=0.0010 **	p=0.4077 ns
Erosions	2 entheses (0.33 % of 600)	p=0.3321	p=0.6859	p=0.3321 ns	p=0.0799 ns	p=0.1131 ns

Data are expressed as mean (standard deviation SD, and range), if not otherwise specified. The non-parametric Spearman rank test was applied to correlate variables.
The level of statistical significance was set at a p-level of 0.05. *p<0.05, **p<0.01. US: ultrasound; LEI: Leeds Enthesitis Index; WHO: World Health Organisation.

in dysmetabolic patients were thus calculated, and global scores were also correlated with some characteristics of the group study: BMI and related WHO obesity classes, presence of type II diabetes, sex and age. The Leeds Enthesitis Index (LEI) was also applied in each patient (7). Statistical analyses were performed using InStat GraphPad (laYolla California) statistical package.

We demonstrated a high prevalence of US-defined enthesitis in dysmetabolic patients (38 patients, 76% out of 50 patients, 70 enthesitis, 11% out of 600 entheses). Power Doppler signals, indicative of "active" enthesitis were reported in 6 patients (12% out of 50 patients, 1% out of 600 entheses). Moreover, in 41 patients (82% out of 50 patients) and 127 entheses (2.1% out of 600 entheses) structural damages have been found. A significant positive correlation has been found between global inflammatory and structural damage scores and both obesity classes (p=0.0001 and p<0.0001, respectively) and LEI (p=0.0061 and p=0.0022, respectively). Entheseal erosions, although rare (0.33% of entheses), were significantly more frequent in males (p=0.001) (Table I).

Our data confirm the correlation of entheseal pathology with obesity (1, 8) and LEI (7), as reported in previous studies. Moreover, the high prevalences of US-defined enthesitis in dysmetabolic patients, using the most recent OMERACT's definition, suggest a low specificity of this definition. As correctly proposed by Di Matteo and collegues, a more specific definition of enthesitis should comprise a combination of grey-scale and PD findings. In particular, erosions and PD signal should be differently weighted, as yet proposed in a recent enthesitis score (9). In our opinion, also a revision of terminology could be useful, as many enthesitis in healthy, obese and dysmetabolic patient should be defined enthesopathy and not enthesitis (5). Another point of discussion of the recent OMERACT's definition is the limit of the US-enthesis study at 2 mm from the bone cortex. In fact, many aspecific enthesopathy are related to a more complex problems of tendinopathy, tendinosis, biomechanic overload that should be considered when a US diagnosis of enthesitis is made (5, 8) (Fig. 1). In conclusion, further studies seem to be necessary to improve the specificity of US definition of enthesitis for primary inflammatory-immunological causes of entheseal pathologies.

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Competing interests: none declared.

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