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Ultrasound-detected synovitis with power Doppler signal is associated with severe radiographic damage and reduced cartilage thickness in hand osteoarthritis

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SUMMARY

Objectives: To examine ultrasound (US) features of synovitis in hand osteoarthritis (OA) joints, and to evaluate their relationship with radiological damage severity and US-detected cartilage thickness.
Methods: US examination was carried out on 14 joints of both hands of 25 patients with symptomatic hand OA (HOA) and 10 age- and sex-matched control subjects. US-detected features were: synovial hypertrophy, effusion, power Doppler signal (PDS), cartilage thickness. Conventional hand radiographs were scored utilizing the Kellgren–Lawrence and Kallman systems. HOA patients were divided into two subsets: non-erosive and erosive.
Results: Among the three groups of subjects studied, erosive OA showed the highest values of radiological scores and the highest prevalence of US-detected synovitis. Joints positive for US synovitis features (above all PDS) had higher radiological scores and lower cartilage thickness, while joints with X-ray detected central erosions [the hallmark of erosive HOA were more likely to present PDS positivity. US measured cartilage thickness inversely correlated with radiological damage scores.
Conclusions: US-detected synovitis is present in about 10% of HOA finger joints and is associated with more severe radiological damage and reduced cartilage thickness. PDS and cartilage thickness (mm) may represent two innovative additional information tools provided by ultrasonography in HOA evaluation.

Introduction

Hand osteoarthritis (OA) is one of the three most common subsets of OA, particularly in the Western world, hip and knee OA being the other two[1]. So far, hand OA (HOA) diagnosis has relied on clinical (pain and finger joint nodes) and radiological methods[2]. Conventional radiological investigations can evaluate only one compartment involved in OA: subchondral bone, while only indirect information can be retrieved about the other two compartments: articular cartilage and the synovial membrane. The role of cartilage as a target and a protagonist of OA pathology has traditionally been acknowledged, but strong clinical and histopathologic evidence also supports the role of synovial inflammation[3,4]. The lack of direct information about cartilage and synovium from conventional radiology and the intertwined pathological abnormalities in the three compartments of OA joints have recently prompted the use of more sensitive imaging techniques to study OA at different skeletal sites. Both magnetic resonance (MR) and ultrasound (US) imaging have demonstrated the presence of synovial inflammation, even in the absence of clinically detectable signs of inflammation[5–7]. In addition to synovitis detection, MR imaging (MRI) is useful for bone erosion and bone oedema evaluation: both types of bone damage are associated with structural disease progression and worse prognosis[8–10]. Conversely, US imaging has recently been enhanced with the power Doppler signal (PDS) which detects synovial vascularization and allows for a better staging of synovial inflammation, as clearly demonstrated in rheumatoid arthritis (RA) hand joints[11].

Therefore, with the use of US imaging we can both detect synovitis (investigating synovial hypertrophy, effusion and

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hypervascularization by PDS) and measure cartilage thickness, as recently demonstrated by Möller *et al*.[12]

In our study, we evaluated US detectable synovitis and cartilage thickness in finger joints from HOA and control subjects. In addition, US features of synovitis were correlated with the degree of conventional radiographic damage as assessed utilizing the Kellgren–Lawrence (K&L) and Kallman scores at single joint level[13,14].

Since HOA can present with an inflammatory and erosive pattern, characterized by more severe symptoms and perimenopausal onset, we evaluated two HOA patient groups, one with non-erosive and the other with erosive patterns, both defined by conventional radiology[15].

Patients and methods

Patients

Both hands of 35 subjects were examined by US. In 25, HOA was diagnosed according to ACR classification criteria[16]. These patients were seen consecutively in our outpatient rheumatology clinic; in 13 patients an erosive pattern was identified by conventional radiology (i.e., by the presence of the classic central erosion pattern – gull wing or saw-tooth appearance – in at least two joints). Control subjects were randomly selected from people attending our outpatient clinic for minor, non-specific complaints: these subjects had no finger joint pain and/or tenderness and no finger nodes; therefore they were classified as clinically normal controls (NC).

In both the HOA and control groups, people with positive rheumatoid factor or psoriasis or a history of psoriasis in first degree relatives were excluded. In addition, subjects with signs or symptoms suggestive of connective tissue disease, other inflammatory arthritides or inflammatory bowel diseases were also excluded from the study. Finally, a history of gout and chondrocalcinosis (calcium pyrohosphate deposition disease) were also considered as exclusion criteria.

All subjects gave written informed consent and approval from the ethics committee of our institution was obtained.

Methods

Anteroposterior X-ray examination of both hands was performed in all subjects within 1 week of the US examination and the radiological involvement of the single joints was graded according to the K&L and Kallman score systems. All images were blinded for identifying data and the radiological scoring was performed by two rheumatologists who were unaware of the US results: both operators had experience in radiological scoring of the hand and together they evaluated all the X-ray films or DVDs.

US joint examination was performed using light pressure and a large quantity of visible scanning gel between the transducer and the skin. Patients were in a comfortable position with their hands completely relaxed in order to avoid movement artifacts and with the finger joints in a neutral position, but extended and flexed as required to visualise pathology. We used the same model (Acuson Antares Siemens apparatus) and machine setting (11.4 MHz, 30 dB/DR60, MapE/VEOff, RS3/SCOff) for all patients and controls.

Longitudinal and transverse US examination was performed on both hands on the volar and dorsal sides using a multi-frequency linear transducer (VFX 13–5 MHz, 18 fps; TIS 1.2/TIB 1.2). Measurements were conducted to the depth of 20 mm. Power Doppler settings were standardised with a lower pulse repetition frequency (305 MHz) and a Doppler frequency of 8 MHz; wall filters were set at the lowest value (F1). Colour priority was maximised to evaluate vessels that were not visible on gray-scale (GS). We set the colour gain by turning up the Doppler gain until random noise was encountered and then it was lowered until the noise disappeared (3–4 dB).

The following joints were examined: metacarpophalangeal (MCP) 1–5, proximal interphalangeal (PIP) 1–5 and distal interphalangeal (DIP) 2–5 joints.

Synovial inflammation was characterized by evaluating synovial hypertrophy (present/absent) and joint effusion (present/absent) using gray-scale ultrasonography (using the Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) definitions developed for RA) and PDS, defined as a signal within a region of GS synovitis, was assessed as present/absent (we did not use the semi-quantitative scale because of the low intensity of PDS in almost all the joints evaluated)[17]. Structural pathology was investigated by evaluating cartilage thickness (mm, assessed as a well-defined anechogenic or homogeneously hypoechogenic band between the chondrosynovial and osteochondral margins) (Fig. 1)[18]. Cartilage thickness was measured in the longitudinal scan, with hands on a dorsal side and joints flexed as far as possible[12]. Joints with ankylosis were excluded from US evaluation.

Examination was performed by a single ultrasonographer experienced in musculoskeletal US who was blinded to patient radiographic data.

Statistical analysis

Statistical analysis was performed using the standard software packages SPSS 17.0 (SPSS Inc., Chicago, IL, USA) and the SAS System for Windows release 8.0.

The study was dimensioned using information from previous studies[19], and a pilot study.

We considered PDS positivity as the least frequent US synovitis variable in the general population (NC but also HOA patients).

The end point was to observe any relationship between joints with the presence of PDS and radiological severity measured by Kallman's score (we did not choose the K&L because of its limited range of values). Therefore, we conducted a pilot study, the results of which were used in a power analysis to obtain the sample size. So with a power >0.8 and $\alpha = 0.05$ the minimum sample size was of 36 joints (18 with and 18 without PDS). On the basis of results from a recent study[19], we can assume that the frequency of PDS positivity would be around 7% in finger joints of HOA patients, so we needed at least 257 joints (which corresponds to about 10 patients, evaluating 28 joints per patient) to reach 18 PDS positive joints.

The analysis of patients was carried out using the One Way Analysis of Variance (ANOVA) with the Scheffè *post-hoc* pairwise test (normally distributed and homoschedastic variables) or the Kruskal–Wallis and the Mann–Whitney test with Bonferroni correction for multiple comparison (for the other continuous variables) to investigate differences in means among and between groups. The Pearson's chi square or the Fisher exact test was utilized to investigate differences in frequency distribution. Quantitative variables were expressed as mean $\pm$ standard deviation (SD).

The analysis of joints was always carried out adjusted for patients as random effect and the adjusted means were estimated *via* the Lsmeans PROC MIXED SAS procedure. Quantitative variables were expressed as the mean and a 95%confidence interval (CI) of the mean (95%CI). The SAS proc mixed procedure was used to compare means and percentages among joints from NC, non-EHOA and erosive HOA (EHOA) patients and between groups.

The logistic regression *via* the SAS NLMIXED procedure was used to assess differences in frequency distribution between the dicotomic variables. The results are expressed as Odds ratio (OR) (95% CI) and Wald statistic *P* value. The correlation between cartilage thickness and the K&L or Kallman scores was performed *via* the General Linear Model (GLM) SAS procedure using the partial eta[2] (a

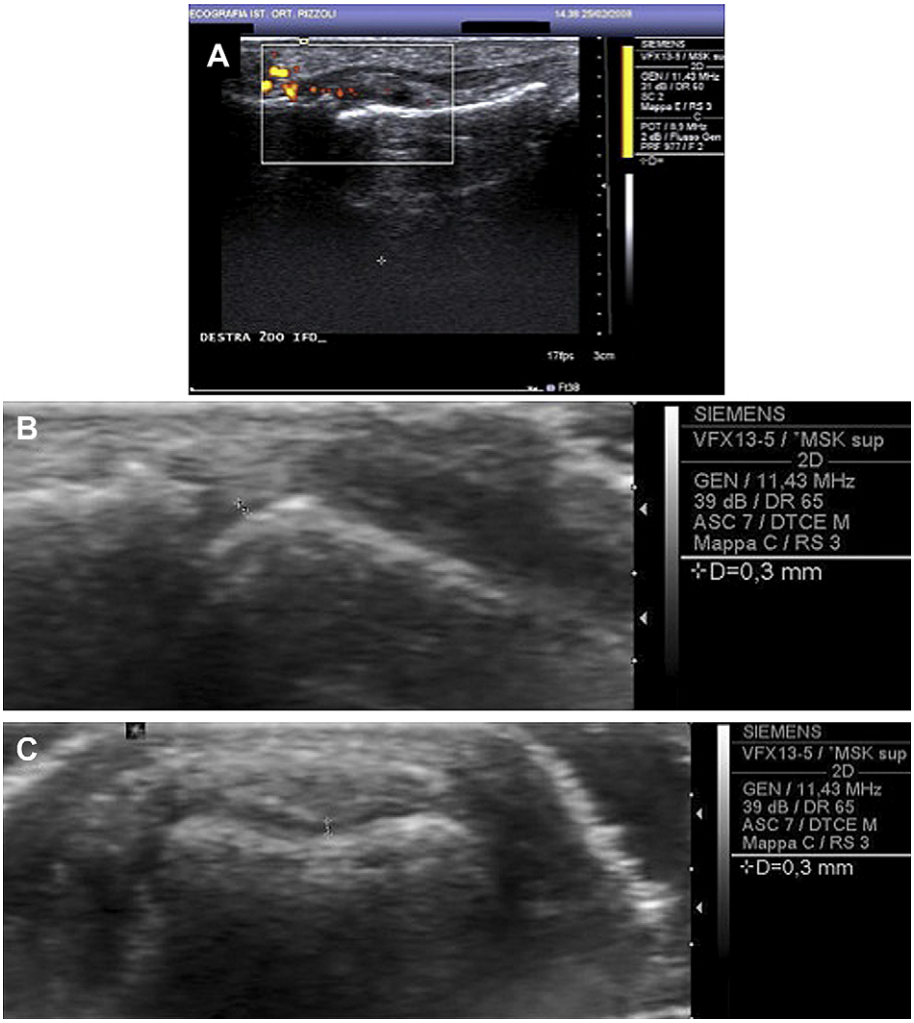

Fig. 1. Longitudinal US image of the second right PIP joint shows the presence of PDS (A). Cartilage thickness measurement in the third right PIP joint in the longitudinal (B) and transverse (C) views (caliper position is presented).

correlation coefficient which estimates the percentage of variability of cartilage thickness explained by the radiological scores values).

The variance components analysis was used to determine the effect of US synovial hypertrophy, joint effusion and PDS positivity on cartilage thickness variance.

The US intra-reader reliability for each joint was obtained in two measurements, at basal and at 12 weeks from the first US evaluation. Radiological intra-reader reliability was obtained by re-reading, at 12 weeks, the X-rays of the first consecutive 15 subjects, carried out at basal. We utilized the Intraclass Correlation Coefficient (ICC) for cartilage thickness, the K&L and Kallman radiological scores values, the Cohen's kappa coefficient (k) for synovial hypertrophy, joint effusion, PDS. Values >0.8 were considered as excellent[17]. Any P value < 0.05 was considered statistically significant.

Results

A total of 35 subjects underwent X-ray and US scanning of both hands. Demographic data from control subjects and patients are shown in Table I.

We analysed 971 joints by US (nine were excluded for ankylosis); all joints were assessed by K&L and 770 by Kallman's scoring systems (Kallman's score does not take into account the metacarpophalangeal joints).

Radiological findings

We observed a significant progressive increase of both radiological scores from NC to EHOA (Table II). In the 971 joints examined, 49 (5%) showed a classic central erosion pattern (48 in EHOA and one in a non-EHOA subset). Eroded joints had higher values of K&L and Kallman scores compared to non-eroded joints: K&L: 4 (3–4) vs 1 (1–2), $P = 0.0004$; Kallman: 9 (7–9) vs 4 (3–5),

Table I
Demographic subset data of NC and patients

	NC ($N = 10$)	Non-EHOA ($N = 12$)	EHOA ($N = 13$)	P Value
Women, % (n)	80 (8)	83 (10)	100 (13)	0.36†
Age (yrs), mean ± SD (95%CI)	66.8 ± 9.0 (60.3–73.3)	67.0 ± 7.5 (62.2–71.8)	63.9 ± 8.2 (59.0–68.9)	0.59‡
Disease duration (yrs), median (25th–75th percentiles)	–	6 (3–13)	7 (4–13)	0.79*
BMI, mean ± SD (95%CI)	24.9 ± 3.4 (22.5–27.3)	25.8 ± 4.7 (22.8–28.7)	25.2 ± 2.9 (23.4–26.9)	0.85‡

N: Number of subjects.
* Mann–Whitney test.
† Pearson Chi Square test.
‡ One Way ANOVA test.

Table II
Radiological and US characteristics of the joints of NCs and patients

	NC ($n=279$)	Non-EHOA ($n=332$)	EHOA ($n=360$)	One Way ANOVA	NC vs non-EHOA	NC vs EHOA	Non-EHOA vs EHOA
K&L, mean (95%CI)	0.79 (0.58–1)	1.3 (1.1–1.5)	1.8 (1.6–1.9)	<0.0001	0.001	<0.0001	0.002
Kallman, mean (95%CI)	3.20 (2.63–3.77)	4.6 (4.1–5.1)	5.8 (5.3–6.3)	<0.0001	0.0013	<0.0001	0.003
Syn. Hyperthr., % (95%CI)	7.5 (3.6–11.4)	9.3 (5.8–12.8)	13.3 (9.8–16.8)	0.06	–	–	–
Joint effusion, % (95%CI)	6.8 (3.0–11.0)	9.3 (6.0–13.0)	12.5 (9.2–15.8)	0.08	–	–	–
PDS, % (95%CI)	0.4 (0.0–3.0)	6.3 (3.9–8.7)	10.0 (7.6–12.4)	<0.0001	0.002	<0.0001	0.04
Cartilage (mm), mean (95%CI)	0.41(0.36–0.46)	0.39 (0.35–0.43)	0.31 (0.27–0.35)	<0.0001	0.46	0.002	0.01

n: Number of joints examined.

$P=0.0002$. The ICC value for intra-reader reliability for the K&L score at a single joint was 0.985 (0.983–0.988), and for the Kallman score it was 0.988 (0.986–0.990).

Ultrasonographic features in the three groups of subjects

The distribution of US-detected synovitis features in MCP, PIP and DIP joints from the three subject groups is presented in Table III.

Features of synovial inflammation were also observed in NC (mainly synovial hypertrophy and effusion) but were more prevalent in the OA groups, PDS showing the highest significance (Table II). Cartilage thickness showed a significant progressive decrease from NC to EHOA (Table II).

The intra-observer reliability for the presence of US-detected dicotomic synovial hyperthrophy and joint effusion was excellent with k values of 0.910 (95%CI: 0.843–0.977) and 0.943 (95%CI: 0.888–0.998), respectively; for dicotomic PDS, it was almost excellent with a k value of 0.864 (95%CI: 0.748–0.979); the ICC for cartilage thickness was excellent with a value of 0.926 (95%CI: 0.906–0.941).

Ultrasonographic features and radiographic damage

An increased PDS positivity was found in joints with radiological central erosion (RCE), while other features of synovitis were not significantly increased in eroded joints. Cartilage thickness was significantly lower in eroded joints (Table IV).

Among US-detected synovitis features only PDS positivity was associated with more severe radiological damage (Table V).

A significant negative correlation between cartilage thickness and radiographic scores was found (Fig. 2).

Relationships between US features of synovitis and cartilage thickness

In univariate analysis, joints with PDS positivity compared to joints without PDS positivity more frequently showed the presence of synovial hypertrophy (22% vs 4.1%, $P=0.0002$), joint effusion (37.9% vs 8.0%, $P=0.0004$), and lower cartilage thickness (mean ± SD: 0.24 mm ± 0.20 vs 0.37 mm ± 0.23, $P=0.0004$).

In multivariate analysis (variance component analysis), considering all US variables, PDS was the only synovitis feature significantly correlated to cartilage thickness.

The mean (95%CI) cartilage thickness was 0.25 (0.19–0.31) mm in the joints with PDS positivity and 0.37 (0.33–0.41) mm in the joints without PDS positivity.

Table III
Number and distribution of joints with joint effusion, synovial hyperthrophy and PDS positivity in the three groups of subjects

	Groups	Joint effusion ($n=95$)	Synovial hyperthrophy ($n=100$)	PDS ($n=58$)
MCP	0	7	7	0
	1	13	13	6
	2	10	11	7
PIP	0	9	9	0
	1	10	10	4
	2	16	16	13
DIP	0	3	5	1
	1	8	8	11
	2	19	21	16

n: Total number of joints with joint effusion, synovial hyperthrophy and PDS positivity.
0: NC.
1: non-EHOA.
2: EHOA.

Discussion

In this study, we detected US features of GS synovitis in about 10% of HOA joints. Synovitis had been widely evaluated and assessed in OA patients utilizing clinical, imaging and histological methods. Various percentages and degrees of synovial inflammation have been found and correlated to disease severity and progression mainly in knee OA patients[5].

In HOA, synovial inflammation could only be evaluated by clinical means but more recently also by means of US and MRI investigations[6,10,20,21].

The main aim of this study was to evaluate the relationship between US-detected synovitis and the degree of radiological damage both at patient group and single joint levels.

Therefore, we compared three groups of subjects with different degrees of radiological changes in the joints of their hands. Our group of control subjects had no clinical signs or symptoms of HOA but showed US signs of synovitis in a small percentage of the joints (mainly synovial hypertrophy and effusion): US-detected synovitis features progressively increased in the groups with non-EHOA and EHOA, PDS appearing as the most OA specific synovitis feature.

The presence of synovitis features in NC joints was somewhat surprising. We would like to point out that, to our knowledge, no data about US features in normal aging hands have been published to date. In addition, we cannot exclude that some cases among NC were in a very early stage of HOA.

In addition, the more severely damaged joints (i.e., joints with RCE) showed more frequent US signs of synovitis and conversely, joints with US-detected synovitis had significantly higher radiological

Table IV
US findings (synovitis and cartilage thickness) in joints with and without RCE

	Joints with RCE ($n=49$)	Joints without RCE ($n=922$)	OR (95%CI)	P Value
Synovial hypertrophy, % (n)	16.3 (8)	10.0 (92)	1.84 (0.76–4.4)	0.17*
Joint effusion, % (n)	16.3 (8)	9.4 (87)	1.96 (0.81–4.73)	0.13*
PDS, % (n)	20.4 (10)	5.2 (48)	5.70 (2.24–14.52)	0.0003*
Cartilage thickness (mm), mean (95%CI)	0.17 (0.10–0.24)	0.38 (0.35–0.40)	–	<0.0001†

n: Total number of joints with or without RCE.
* Logistic regression (with patient random effect).
† One Way ANOVA (with patient random effect).

Table V
Radiological scores in joints with and without US features of synovitis

	K&L, mean (95%CI)	Kallman, mean (95%CI)
Joints with synovial hypertrophy	1.5 (1.2–1.7)	4.8 (4.2–5.4)
Joints without synovial hypertrophy	1.3 (1.1–1.5)	4.6 (4.1–5.1)
P Value	0.12	0.27
Joints with effusion	1.3 (1.2–1.4)	4.9 (4.3–5.5)
Joints without effusion	1.4 (1.2–1.7)	4.6 (4.1–5.1)
P Value	0.11	0.17
PDS positive joints	2.0 (1.7–2.3)	5.8 (5.1–6.5)
PDS negative joints	1.3 (1.1–1.4)	4.5 (4.1–5.0)
P Value	<0.0001	<0.0001

Test: One Way ANOVA with patient as random effect (mean and 95%CI corrected for patient random effect).

damage scores. Therefore, an association between US signs of synovitis and more severe joint damage was found in this study.

Radiological scores of joint damage rely mainly on joint space narrowing (i.e., cartilage thinning and damage) and on bone overgrowth (i.e., osteophytes): both lesions take some time to manifest while synovial inflammation can appear more rapidly and be short lived[22]. Thus, a cross sectional study like ours is not suitable for addressing the question of the role of synovitis in the pathogenesis of the features of radiological damage.

It is well known that in inflammatory HOA, Heberden and Bouchard nodes show inflammatory characteristics in the early stages of their formation which subsequently require some time to recede[22]. The patients we studied were not in the early stages of the disease and, in addition, we did not evaluate the clinical signs of joint inflammation since the aim of the study was related to radiological damage. Nonetheless, Keen *et al*. recently evaluated US signs of synovitis in HOA and their relationship to symptoms: these authors demonstrated that symptomatic joints were more likely to show US signs of synovitis. In addition, their patients were younger and therefore in the earlier phase of disease. It is interesting to note that in their study the prevalence of synovitis, but not of PDS positivity, was higher than in our study (synovitis: 46% vs 9–13%; PDS: 7% vs 6–10%)[21]. Furthermore, having only evaluated patients with EHOA, Vlychou *et al*. found frequent ultrasonographic evidence of inflammation with a distribution of PDS positivity among MCP, PIP and DIP joints similar to what was found in our HOA series[23]. Lacking any age-matched control group, the authors of this study could not elaborate about the disease specificity of their findings or about the role of synovial inflammation in the pathogenesis of joint damage.

Evaluation of bone erosions and osteophytes by MRI or US has already been carried out. Iagnocco *et al*. demonstrated a good concordance between US and radiography in detecting central erosions[24], while utilizing MRI, Graigner *et al*. found that central or marginal erosions were present in 80% of examined patients, thus suggesting that almost all HOAs are erosive[10]. Furthermore, these authors found synovitis-like tissue associated with many of the marginal erosions. It has to be noted that the majority of the patients studied were in an early stage of disease (symptoms duration up to 12 months). Vlychou *et al*. also evaluated bone erosions and osteophytes, finding that US examination is a more sensitive imaging modality compared to conventional radiography[23].

The second aim of our study was to investigate the relationship between synovitis and the damage of the target tissue of the OA process: cartilage. In order to gain this information, we did not evaluate joint space narrowing but, instead, we measured cartilage thickness.

The evaluation of joint space narrowing is very subjective and operator dependent and no validated criteria have been reported: in fact, some reported descriptions of joint space narrowing criteria resemble true tautology. On the other hand, measuring cartilage thickness has already been carried out successfully in knee and HOA and we felt this approach less subjective and more consistent[25]. Möller *et al*. recently validated the US measurement of finger joint cartilage thickness studying subjects without disease and patients with RA, OA and other various forms of arthritis[12]. These authors found a positive correlation between US measured cartilage and radiographic joint space width. In addition, they found that cartilage thickness was more reduced in early symptomatic OA than in early RA, suggesting more severe and/or rapid cartilage damage in OA than in RA.

We found a significant negative correlation between US measured cartilage thickness and X-ray damage scores. The better discrimination in cartilage thickness obtained using the K&L score compared to the Kallman score is probably due to the more composite nature of the Kallman scoring system. In the latter, joint space narrowing, which is directly related to US cartilage thickness, is only one of the six variables considered, while in the K&L scoring system only two variables are considered (joint space narrowing and osteophytes), which means that joint space narrowing has a much more significant influence (50%) on the result.

Finally, synovitis as detected with PDS, was associated to significantly reduced cartilage thickness. On the basis of the results from this and previous studies of ours, we suggest that cartilage thickness measurement provided by ultrasonography represents an additional information tool regarding structural pathology. Finally, taking into account the results on the relationships between PDS and radiological damage and the findings that PDS is again the best synovitis predictor for US-detected cartilage damage, we suggest PDS evaluation is an important completion in HOA imaging.

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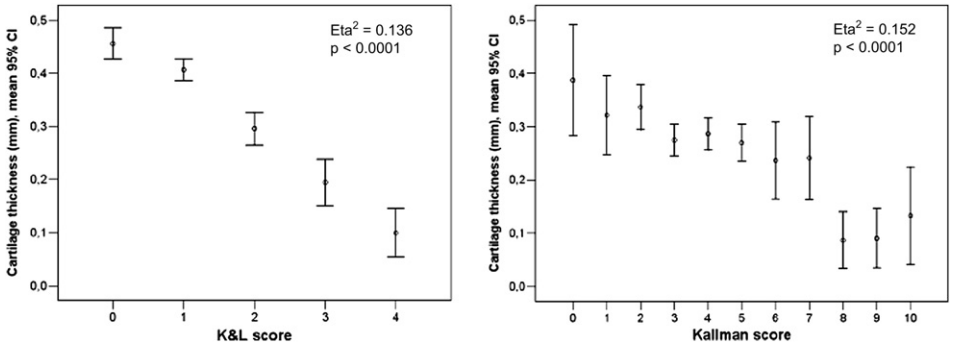

Fig. 2. Relationship between cartilage thickness (mm) and radiological scores (Kallman and K&L).

Rizzoli (Ricerca corrente) and MIUR (Rome). The study sponsor was not involved in the study design, collection, analysis and interpretation of data, in the writing of the manuscript and in the decision to submit the manuscript for publication.

Author contributions statement

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published.

Conception and design: Mancarella, Magnani, Galletti, Meliconi.

Analysis and interpretation of the data: Mancarella, Pignotti, Meliconi.

Drafting of the article: Mancarella, Pignotti, Meliconi.

Critical revision of the article for important intellectual content: Mancarella, Galletti, Pignotti, Meliconi.

Final approval of the article: Mancarella, Meliconi.

Provision of study materials or patients: Mancarella, Magnani, Addimanda.

Statistical expertise: Pignotti.

Obtaining of funding: Meliconi.

Administrative, technical, or logistic support: Mancarella, Magnani, Addimanda.

Collection and assembly of data: Mancarella, Addimanda.

Guarantor of study integrity: Meliconi.

Conflict of interest

None of the authors has any conflict of interest or disclosures to report in relation to this work.

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