Ultrasonography-detected subclinical inflammation in patients with hand osteoarthritis and established rheumatoid arthritis: a comparison between two different pathologies using the same ultrasound examination protocol

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Abstract:

Objectives:

A recent review of ultrasound (US) studies in osteoarthritis (OA) showed very limited data about hand OA. Previous US studies in patients with OA described a degree of overlap between the US appearance of rheumatoid arthritis (RA) and OA joints. This study aimed to assess the US features of subclinical inflammation in RA and hand OA, using the same US examination protocol.

Methods

A retrospective, cohort study compared patients with established RA (n=224) and hand OA (n=73), with respect of several demographic, clinical, laboratory and US parameters. We used a 22 hand joint US examination protocol (wrists, metacarpophalangeal and proximal interphalangeal joints bilaterally - OMERACT scoring system) for all patients.

Results

Subclinical joint inflammation in the context of equivocal clinical examination was found in 9.6% OA patients compared to 46.4% in RA ($p = 0.0001$), despite the fact that there was no significant difference between the degree of chronic joint swelling (synovial hypertrophy grade 2 and 3, $p = 0.75$ and $p = 0.11$, respectively). The presence of osteophytes was more common in patients with hand OA, as expected ($p = 0.0001$).

Conclusions

Our study findings reflected differences between the incidence and characteristics of subclinical inflammation in patients with RA and OA, which can be helpful in patients with equivocal clinical examination or history of both diseases. In our study, almost one in ten patients with hand OA had active synovitis, while almost one in two patients with RA had uncontrolled inflammation in at least one joint.

Background:

The diagnosis of hand OA is based on a combination of both the clinical and imaging features and the assessment of risk factors, clinical associations and outcomes (Zhang et al., 2009). The American College of Rheumatology (ACR) clinical classification criteria for hand OA are frequently used as diagnostic criteria. In the context of characteristic clinical picture and absence of additional features of other inflammatory arthritides, the diagnostic of hand OA is straightforward (Altman, 1990)

The main challenges encountered by the clinician relate to the difficulty in confidently diagnosing hand OA when there is no univocal clinical picture, and patients describe inflammatory hand pains. In the absence of established Heberden and Bouchard nodes and/or bony enlargement, and characteristic involvement of proximal and distal interphalangeal joints (PIPs and DIPs), thumb base, index and middle metacarpophalangeal joints (MCPs), the early diagnosis of hand OA becomes more difficult. The EULAR initiative was designed to help clinicians diagnose hand OA rather than classifying it, by identifying clinical subsets, which help differentiate OA from other hand joint pathology (Zhang, 2009). A Framingham analysis of incidence of hand OA showed an age-standardised prevalence of 44.2% in women and 37.7% in men (Haugen, 2011), suggesting a significant possibility of overlap of OA with other joint pathology.

In terms of imaging hand OA, it is widely accepted that radiography is the gold standard, and that other imaging techniques are rarely indicated for diagnosis (EULAR recommendation 9) (Zhang, 2009). Recent studies evaluated the role of ultrasound (US) examination of hand joints for diagnosis and prediction of disease progression in hand OA. In a large general population study, hand OA was

detected by US in a proportion of up to 70%, and was more frequently found at the DIP level (Abraham, 2014).

In comparison to OA, the role of US in the early diagnosis and periodic follow-up of patients with rheumatoid arthritis (RA) is well established. It has been shown that US can improve the sensitivity of ACR 2010 classification criteria for RA (Nakagomi, 2013), helping clinicians decide which patients should be started on treatment. US parameters could also help predict which patients are likely to respond to biologic therapy (Ellegaard, 2011), and were sensitive to change following intra-articular injection with steroids (Terslev, 2003).

In a real-life context, clinicians face the difficulty of differentiating between the most frequent two types of inflammatory arthritis that affects hands: RA and OA (Haugen, 2011); in particular when the clinical examination is equivocal. Our study aimed to investigate the usefulness of a standardised US examination protocol for hand joints in differentiating subclinical RA from OA, in patients with equivocal clinical examination. In addition, we explored which simplified hand US scores perform better for every disease taken separately.

Methods:

Patient recruitment

This is a real-life, cross-sectional study, which evaluated patients referred to our US rheumatology outpatient clinics, presenting with inflammatory sounding hand joint pains during the interval from January 2012 to August 2015. The data was collected from the department data base, which included all the patients referred to have an US scan of their joints for different reasons (to help with their diagnosis of different types of hand arthropathy, to exclude ongoing inflammation in patients already diagnosed with RA, who experienced more pain or unexplained increased inflammatory markers in the context of equivocal clinical examination for hand joint synovitis, etc.). For each patient, a set of demographic, clinical and laboratory measurements was recorded at the time of the scan, as well as their provisionary diagnosis. In this period, we scanned 73 patients with OA and 224 patients RA. Patients diagnosed with both RA and significant hand OA (as established by US and Xrays), or other type of associated joint pathology (such as crystal related arthropathy, psoriatic arthritis, etc.) were excluded from this study. Where any information had not been recorded in the outpatient clinic proforma that was generated in the US clinic at the time of clinical and US examination, the records were completed by consulting the patient electronic hospital records. No inclusion or exclusion criteria were applied for the selection of patients, as all the patients with RA or OA referred by their consultant to have an US scan of their hand joints were included in our study analysis without exception.

Because we captured data collected during the US clinics, we are fully aware that patients with definite clinical OA of DIP joints or obvious clinical synovitis in the context of RA who in the opinion of their clinicians did not need an additional US examination, were not captured in this study. We used the ACR hand OA and 2010 ACR/EULAR RA classification criteria for diagnosing OA and RA, respectively.

Disease assessment

We used the same set of reported outcomes and clinical and laboratory parameters for all the patients, to ensure homogeneity of the collected data. We collected information about disease duration (in months), clinical joint examination findings including tender joint count (TJC) and swollen joint count (SJC), as well as a patient reported global assessment score (GVAS).

Additional data about the high sensitivity C-reactive protein (hsCRP), erythrocyte sedimentation rate (ESR), presence of rheumatoid factor (RF), anti citrullinated cyclic peptides antibodies (ACPA) and anti-nuclear antibodies (ANA) was also collected at the time of the scan.

Treatment details

For each patient, a detailed record was compiled of their medication at the time of the ultrasound scan, including paracetamol and NSAIDs, disease-modifying drugs (DMARDs), biologic therapies and steroids, either oral or intramuscular depot injection.

Ultrasound examination

We used an established protocol of US examination of hands comprising flexor tendons and 22 joint assessments (dorsal longitudinal and transverse views of wrists, MCP and PIP joints), which is standard of practice for our US clinics. We assessed 22 hand joints in every patient, irrespective of their hand symptoms, using the OMERACT scoring system for US examination.

US examination was performed using an Logiq S8 US machine (GE Medical Systems Ultrasound and Primary Care Diagnostics, Wauwatosa, WI, USA), equipped with a multi-frequency linear matrix array transducer (6-15 MHz). B-mode and Power Doppler (PD) machine setting are optimised and standardised for all US examinations. The settings used were: B-mode frequency 11-15 MHz depending on the depth of the anatomical area, Doppler frequency 7.5-15, depending on the depth of anatomical area; low wall filters and pulse repetition frequency around 800 Hz. Because of the small number of joints with PD signal (only patients with equivocal clinical examination were referred for an US examination of their hands for the suspicion of subclinical inflammation), we did not report separately

the grades of PD signal in the comparison table (Table 2), but they have been used to generate the total PD score for every patient.

We recorded information about synovial hypertrophy (SH) grade, presence of erosions, PD signal, joint effusion, osteophytes and tendon abnormalities. We calculated the total PD score per patient as a sum of the different PD grades found at the 22 joint examination; we calculated the SH scores in a similar fashion.

Statistical analysis

All data was transferred and collated from paper questionnaires to a Microsoft Excel spreadsheet. Using IBM SPSS Statistics 22 for further analysis and statistical tests, descriptive statistics were used to explore the patients with seropositive RA and OA further, using mean and standard deviations (SD) and median with inter-quartile ranges (IQR) depending on the data distribution. Mann-Whitney U test was implemented to compare different joint scoring systems for both OA and RA. A p-value of <0.05 was considered a statistically significant result.

Ethical issues

The data was collected as standard of practice. The study analysed retrospectively the results of the US examinations of patients seen in our US clinics over a defined period of time. The local ethics committee appreciated that the data collected in this study was standard of practice in our department and no ethical approval or patient's consent were required as no patient information was used for teaching or new intervention research. The results of our study analysis had no impact on the clinical management of patients and their confidentiality was maintained. Our US clinic data base that generated the results reported in this paper supports our department periodic service evaluation activities.

RESULTS:

Patient demographics

We compared the two groups of interest, comprising 73 patients with OA and 224 patients with RA. The mean age of patients was greater in the OA group (60.6±9.9) than the RA group (53.8± 15.3) (P <0.05). We found a similar proportion of female patients (80.8%) in the OA group and the RA group (81.3%). A proportion of 73.6% of RA patients (165 patients) were treated with DMARDs and 29% (65 patients) with biologics at the time of the US scan. None of the hand OA patients included in our study were treated with DMARDs (Table 1).

Table 1 shows the differences in patients' demographics between the OA and RA patients

Table 1:

Disease	OA (N=73)	RA (N=224)	*P* value
Duration of the disease in months	Median: 12 IQR: 60	Median: 42 IQR: 117	**0.006**
Percentage of patients on NSAIDs and painkillers at the time of the scan	13.7%	10.3%	**<0.0001**
CRP	Median:1.15 IQR: 3.4	Median: 1.9 IQR: 4.9	**0.03**
ESR	Median: 5 IQR: 11	Median: 9 IQR: 20	0.116
SJC	0.52 ± 1.33 Median: 0.00 IQR: 0.00	2.52 ±3.33 Median:1.00 IQR: 4.00	**<0.0001**
TJC	4.15 ±7.65 Median: 0.00 IQR: 5.00	8.09 ± 7.94 Median: 6.00 IQR: 11	**<0.0001**
Pain score	2.5 ± 4.1 Median: 0.00 IQR: 50.0	4.5 ± 3.1 Median: 50.00 IQR: 50.00	**<0.0001**

To assess the level of consistency between the SJC, GVAS and TJS scores for both groups of patients, the Cronbach's alpha statistical test was applied. There was a low consistency between these three assessments for the RA group (α=0.308), and a very poor correlation between clinical examination and patients' reported outcomes for the OA group (α = -0.022).

We investigated the differences between the US assessments patients with RA vs. OA, and as expected, chronic inflammatory features and PD signal were more frequently recorded in patients with RA. As all the patients referred for an US scan had equivocal clinical examination and required an US scan to help with their disease activity assessment or diagnosis, the number of joints with inflammatory changes or OP was rather small; therefore, we reported the median values of the number of joints with a particular US finding (Table 2). As the patients included in our study had rather subclinical inflammation in the context of both RA and OA, we also reported the percentage of patients with no evidence of a certain US abnormality as this was a frequent encounter (zero values).

Table 2 shows the difference between the US features found at the US examination of hands of patients with OA vs. RA.

Table 2:

Disease	OA (N=73)	RA (N=224)	*P* value
Number of joints with SH grade 1	Median: 0.00 IQR: 2	Median: 1 IQR: 3	**0.014**
	Percentage of patients with no joints with SH grade 1:		
	60.3	43.3	
Number of joints with SH grade 2	Median: 0.00 IQR: 3	Median: 0.00 IQR: 3	0.75
	Percentage of patients with no joints with SH grade 2:		
	54.8	51.3	
Number of joints with SH grade 3	Median: 0 IQR: 1	Median: 0 IQR: 2	0.11
	Percentage of patients with no joints with SH grade 3:		
	68.5	56.7	

Number of joints with PD signal	Median: 0 IQR: 0	Median: 0 IQR: 2	**P<0.0001**
	Percentage of patients with no PD signal:		
	90.4	53.6	
Number of joints with OP	Median: 7 IQR: 8	Median: 1 IQR: 3	**P<0.0001**
	Percentage of patients with no joints with OP:		
	15.1	44.6	
Number of joints with erosions	Median: 0 IQR: 4	Median: 2 IQR: 8	**0.002**
	Percentage of patients with no erosions:		
	57.5	29.9	

Comparison between the US parameters in patients with OA and RA

As the patients included in our study did not have definite clinical picture of hand OA or active synovitis associated with RA, we have also been interested in reporting both the differences between the numbers of patients with present (non-zero values) and absent (zero values) US features between the two patient groups.

There was no statistically significant difference between the RA and OA groups of patients when we compared the number of patients with zero values for certain US parameters (osteophytes, PD signal or erosions), as expected, as the majority of patients did not have obvious clinical features of OA or clinical synovitis (Table 3). However, Mann Whitney test comparison between the numbers of patients with at least one joint with SH grade 3 showed significant difference between RA and OA groups when we excluded the patients with no SH grade 3 in any of their joints, suggesting that if significant SH is present, the patients are more likely to have RA than OA. As expected, the number of osteophytes in the wrists, MCP and PIP joints was significantly higher in patients with OA.

Table 3 compared the proportion of OA and RA patients with different US features (present vs. absent)

Table 3:

OA vs. RA	Proportion of patients with absent US features	Chi-squared test for comparison OA vs. RA	Mean rank of US score	Mann Whitney test for comparison OA vs. RA
SH grade 2	54.8% vs. 51.3%	0.2634	14.5 vs. 47.5	Z score: 0.952 *P* = 0.171
SH grade 3	68.5% vs. 56.7%	P = 0.608	7.83 vs. 39.8	Z score: 2.665 ***P* = 0.00491**
Positive PD signal	91.8% vs. 53.6%	3.182	2.4 vs. 39.9	Z score: -7.89 **P=0.00067**
Osteophytes	15.1% vs. 44.6%	P =0.0745	29.6 vs. 51.2	Z score: -5.8797 ***P* <0.001**
Erosions	57.5% vs. 29.9%	34.5	14.0 vs. 71.3	Z score: 1.2234 *P* = 0.111

Discussion:

Our study compared the ability of a comprehensive 22 joint US examination protocol to detect subclinical inflammation in two different categories of patients with hand arthropathies, RA and OA. Hand US examination facilitated the diagnosis of hand OA (by excluding mimicking pathology) and assessed for the presence of subclinical inflammation in both disease groups. The patients included in this study were referred by their clinicians to have an US scan of their hands for a clinical reason (e.g. disparity between RA associated symptoms and clinical evidence of synovitis; lack of correlation between inflammatory markers, patient reported outcomes and physician assessment of disease activity; to confirm active inflammation in certain joints that can be amenable to intraarticular injections in hand OA; or to provide re-assurance that there was no superimposed inflammatory pathology in patient with hand OA, etc.) .

Our study results showed that inflammatory markers were not useful in differentiating the group of patients with subclinical RA and hand OA on the whole; however, the patients with RA had more swollen and tender joints and higher pain scores than the patients with OA (as expected in the context of a longstanding inflammatory disease). US parameters that helped differentiating between hand OA and RA were: the presence of PD signal and erosions (more frequently found in patients with RA) and osteophytes (more frequently found in patients with OA). Interestingly, US detected SH was not different in terms of frequency of joints affected and grading between the two groups; however SH grade 3 was more frequent in patients with RA vs. OA, but only when patients with some degree of chronic swelling were compared.

Previous studies showed that erosive hand OA was associated with US detectable inflammatory changes in the affected joints (Mancarella, 2010). We found only one previous study assessing comparatively patients with either hand OA or RA. This study compared the ability of US and photo optical imaging to detect inflammatory changes in patients with PIP joint OA, and patients with RA, when compared with healthy volunteers (Amitai, 2015).

No clear cut-off between the types of US-detected inflammatory changes that can differentiate subclinical RA from hand OA was ever established. Our study found that the median number of joints with moderate degrees of SH was similar between both diseases, and only the severe SH was more frequently encountered in patients with RA, suggesting that establishing a cut-off value based on the number of joints with SH alone to enable a differential diagnosis between the two diseases is not feasible. On the other hand, the proportion of patients with PD signal was significantly different between the two diseases (8.2% patients with hand OA and 46.4% of RA patients had active inflammation in their joints), as was the proportion of both erosions and osteophytes (42.5% in the OA group vs. 70.1% in the RA and 84.9% vs. 55.4%, respectively). This study raised awareness that chronic and active inflammatory changes are encountered in both RA and OA, although the proportion of patients with active inflammation was significantly higher in patients with RA; while the proportion of patients with chronic inflammatory changes in their joints was similar. When we compared only the RA and OA patients with SH detected by US, a higher proportion of RA patients had severe SH, finding that suggested that if there is evidence of chronic inflammation, this is likely to be more severe in RA when compared to hand OA.

US detected joint inflammation was effective in predicting the development of osteophytes (OP) in patients with hand OA in several longitudinal studies (Kortekaas, 2015). There is controversy regarding the correlation between hand pain in OA and the level of inflammation detected by US examination. Although one study found no correlation between hand pains and US detected inflammatory fea-

tures in OA (Kortekaas, 2014), another concluded that pain in OA is associated with inflammation, which can be detected by US (Kortekaas, 2010). Erosive OA was associated with more frequent US inflammatory features when compared to patients with non-erosive OA, and was also found to affect a large proportion of patients with hand OA (51% of patients with hand OA had erosions in another study) (Kortekaas, 2013). In our study, 42.5% of OA patients had erosions in at least one joint; this can be considered comparable with the previously reported data, especially when considering that patients with obvious OP and joint deformities were excluded from our cohort.

If, the presence of chronic inflammatory changes which lead to erosions is very well documented in subclinical RA (Nguyen, 2014), and previous effort attempted to establish the best US scoring systems (Naredo, 2013), less data are available for patients with hand OA. Inflammatory changes were found in joints unaffected by erosions in patients with erosive hand OA, suggesting an initial inflammatory process, or a possible systemic cause for erosive joint disease in this category of patients (Kortekaas, 2013). It was found that US evaluation of hand joints correlated with clinical symptoms in patients with hand OA, and showed improvement following US guided injections with hyaluronic acid (Klauser, 2012). It was proposed that PD signal and cartilage thickness (mm) measurements may represent two useful information tools for hand OA evaluation, which both correlated with radiographic progression (Mancarella, 2010). In our study, 9.2% OA patients and inflammatory hand pains had PD signal in their joints, and 42.5% had at least one joint with erosions, both in the context of having longstanding symptoms (IQR = 60 months).

Our cohort study could not provide any suitable information regarding the temporal relationship between the presence of PD, erosions and OP in hand OA. Even if the inflammatory features are present in OA, they are seen in a lower proportion of patients and affecting a smaller number of joints than in patients with RA. In comparison to the OA patients, in our study almost one in two RA patients (46.4%) had active inflammation in their joints.

Limitations:

Our study did not have strict inclusion criteria to ensure the homogeneity of the OA and RA cohorts analysed; the patients were included based on their clinician's decision to send them for an US scan of their hands to help with their diagnosis (in the case of OA patients) or to optimize their disease activity assessment (in the case of RA patients). We did not explore correlations between clinical examination, DAS 28 scores, disease duration or medication and different US scores, as this was beyond the scope of our study. We did not include US scores assessing DIP or CMC1 joints, since the purpose of the study was to use the same US examination protocol for all our patients.

Conclusion:

This real-life cohort study provided evidence that joint inflammatory changes detectable by US characterise both RA and hand OA. If the proportion of patients with SH was similar in our cohort study, within these subgroups of patients, the SH was likely to be more severe in RA when compared to OA. The proportion of patients with PD signal, erosions and OP differed significantly between the two disease groups, and helped with the patient diagnosis and disease activity assessment, along with clinical, laboratory and other imaging parameters. Our study also showed that almost one in ten patients with hand OA can have PD signal compared to one in two in the RA group, and that the inflammatory markers were not particularly useful in differentiating clinically equivocal RA from hand OA.

The authors declared no conflict of interest.

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