The correlation between ultrasound-detected synovitis of small joints and the clinical disease activity in patients with rheumatoid arthritis

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Research article

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Abstract

Background: Rheumatoid arthritis (RA) is chronic inflammatory arthritis with multi-joint involvement, especially small synovial joints in hands and feet. So far, the synovitis of which joint in hands or feet is better correlated with clinical disease activity indices is unknown; the correlation of synovitis detected by ultrasound in an individual joint with global disease activity is unclear either.

Objectives: To explore the correlation between the ultrasound-detected synovitis in metacarpophalangeal (MCP), metatarsophalangeal (MTP), proximal interphalangeal (PIP) joints and the clinical disease activity indices in patients with RA.

Methods: 30 joints, including bilateral MCP, PIP and MTP, were scanned for synovitis by ultrasound, semi-quantitatively scored for gray scale(GS) and power Doppler(PD). The correlation between Disease Activity Score-28 joints(DAS28), Simplified Disease Activity Index (SDAI), Clinical Disease Activity Index (CDAI) and ultrasound-detected synovitis score in each joint was assessed using Spearman's rank correlation test.

Results: 211 RA patients were included in this study. The whole GS scores of all MCP joints showed highest correlation with all clinical disease activity indices (r=0.403-0.452, p<0.01), followed by PIPs (r=0.318-0.331, p<0.01) and MTPs (r=0.277-0.301, p<0.01). Likewise, the whole PD scores of all MCP joints also showed highest correlation with the disease activity (r=0.332-0.396, p<0.01), followed by PIPs (r=0.211-0.242, p<0.01), and MTPs (r=0.198-0.222, p<0.01). The highest correlation of GS score with DAS28-ESR (r=0.411, p<0.01), DAS28-CRP (r=0.459, p<0.01), SDAI (r=0.444, p<0.01) was observed in MCP3 joint, while with CDAI (r=0.421, p<0.01) in MCP2 joint. The highest correlation of PD score with DAS28-ESR (r=0.353, p<0.01), DAS28-CRP (r=0.399, p<0.01), CDAI (r=0.368, p<0.01), SDAI (r=0.377, p<0.01) was in MCP5 joint.

Conclusions: The ultrasound-detected synovitis at MCP joints, especially MCP2, MCP3, and MCP5 joints, was best correlated with composite disease activity of RA, in contrast to PIP and MTP joints. MCP joints should take greater weight in clinical disease activity assessment.

Background

Rheumatoid arthritis (RA) is chronic inflammatory arthritis with multi-joint involvement, especially small synovial joints in hands and feet. Composite disease activity score (DAS), such as DAS28[1], Simplified Disease Activity Index (SDAI), Clinical Disease Activity Index (CDAI)[2, 3], which are widely applied in clinical practice include tender joint count (TJC) and swollen joint count (SJC) as important parameters. But neither tender joint nor swollen joint in feet is included in aforementioned clinical indices, although synovitis in these joints are often found in early RA[4], especially by sensitive imaging modalities such as ultrasound or magnetic resonance imaging. Moreover, each involved joint takes the same numerical weight in these indices, although neither the frequency nor severity of synovitis is evenly distributed among different joints[5].

Assessment of clinical disease activity is key for treat to target strategy in RA. Overlook of joint tenderness and swelling in feet may underestimate the actual severity of inflammation in some RA patients. Ultrasonography has been proved to be more sensitive and objective in detecting joint inflammation than physical examination. Previous studies on selection of specific joint sets assessed by ultrasound ever evaluated the correlation of ultrasound scores with clinical composite disease activity indexes, but came to different conclusions [6–8]. So far, the synovitis of which joint in hands or feet is better correlated with clinical disease activity is unknown; the correlation of synovitis in an individual joint with global disease activity is unclear either. Trying to answer these questions, we set out to study the correlation of ultrasound-detected synovitis in metacarpophalangeal (MCP), metatarsophalangeal (MTP) or proximal interphalangeal (PIP) joints with clinical disease activity in patients with RA.

Methods

Patients

Patients with RA who fulfilled the 2010 ACR/EULAR classification criteria[9] was consecutively enrolled from rheumatology clinic of Peking University First Hospital between February 2016 and August 2017. Both clinical and ultrasound data of all patients were collected and analyzed. Those patients who were younger than 18 or with other comorbidities which could interfere with the disease activity assessment, for instance, other inflammatory arthritis, history of joint trauma or replacement, obvious joint deformity, were excluded. This study was conducted in accordance with the Declaration of Helsinki and was approved by local ethics committee. The informed consent was obtained from each patient before enrollment.

Joint assessment

Thirty-eight joints including bilateral shoulders, elbows, wrists, knees, MCPs, PIPs and MTPs were assessed for tenderness and swelling by a rheumatologist who was blinded to both clinical and ultrasound data. Clinical disease activity was measured in each patient by DAS based on 28 joint count and erythrocyte sedimentation rate (DAS28-ESR), DAS based on 28 joint count and C-reactive protein (DAS28-CRP), CDAI, and SDAI.

US assessment

A high-end ultrasound machine (LOGIQ E9, GE company) with corresponding linear probe (ML 6–15) was applied to scan 30 peripheral joints (bilateral MCP1-5, PIP1-5 and MTP1-5) for each patient, using both gray scale (GS) and power Doppler (PD). All ultrasound scan was performed by a ultrasonographer who has 10-years' relevant experience. The scanning and interpretation of lesions were based on the published literatures of OMERACT (Outcome Measures in Rheumatology Clinical Trials)[10]. Synovitis was assessed by semi-quantitative scoring systems (0–3) proposed by Szkudlarek et al[11]. The physical and ultrasound assessment of joints were blindly performed on the same visiting day.

Statistical analysis

Statistical analysis was performed with SPSS 21.0. For the descriptive analyses, continuous variables were presented as mean and standard deviation (SD) if normally distributed, and median and interquartile range (IQR) if non-normally distributed. The Spearman's rank correlation coefficient (r) was calculated between DAS28-ESR, DAS28-CRP, SDAI, or CDAI, and ultrasound GS and PD score in each hand and foot joint, respectively. P values < 0.05 were considered statistically significant.

Results

Demographics and clinical characteristics of patients

211 patients with RA were enrolled in this study. The demographics and clinical characteristics were illustrated in Table 1. Their mean age was 51.8 years, with median disease duration of 60 months. Most patients were female (177, 84.3%) and seropositive (73.8% RF positive and 87.7% ACPA positive). The median numbers of tender joint and swollen joint based on 30 joint count (bilateral MCPs, PIPs and MTPs joints) were 4 (2, 10) and 3 (1, 6), respectively. The mean (SD) DAS28-ESR and DS28-CRP were 4.59 ± 1.51 and 4.18 ± 1.39. The median (IQR) CDAI and SDAI were 17.0 (9.5, 26.25) and 17.8 (10.43, 28.82), indicating medium to high disease activity.

Table 1

Demographics and clinical characteristics of 211 RA patients

Clinical features	Values
Age (years), mean ± SD	51.82 ± 13.45
Female, n (%)	177 (84.3)
Disease duration (months), median (IQR)	60 (18, 127.5)
Positive RF, n (%)	135 (73.8)
Positive anti-CCP, n (%)	121 (87.7)
TJC-30, median (IQR)	4 (2, 10)
SJC-30, median (IQR)	3 (1, 6)
ESR (mm/h), median (IQR)	28 (16, 52.5)
CRP (mg/L), median (IQR)	9.9 (4.33, 31.70)
PGA (mm,0-100 scale), median (IQR)	50 (30, 70)
EGA (mm,0-100 scale), median (IQR)	40 (20, 60)
DAS28-ESR, mean ± SD	4.59 ± 1.51
DAS28-CRP, mean ± SD	4.18 ± 1.39
CDAI, median (IQR)	17.0 (9.5, 26.25)
SDAI, median (IQR)	17.80 (10.43, 28.82)
HAQ DI, median (IQR)	0.40 (0.15, 0.80)

Abbreviations: RF rheumatoid factor, anti-CCP anti–Cyclic Citrullinated Peptide, TJC-30 tender joint count in bilateral MCPs, PIPs and MTPs joints, SJC-30 swollen joint count in bilateral MCPs ,PIPs and MTPs joints, ESR erythrocyte sedimentation rate, CRP C-reactive protein, PGA patient's global assessment, EGA evaluator's global assessment, DAS28 Disease Activity Score in 28 joints, CDAI Clinical Disease Activity Index, SDAI Simplified Disease Activity Index, HAQ DI Health Assessment Questionnaire disability index.

Frequencies and distribution of synovitis detected by ultrasound

A total of 6330 joints were assessed by ultrasound, using both GS and PD. The number of joint with GS synovitis was much higher than with PD synovitis [1622 (25.6%) vs. 814 (12.9%), $p < 0.05$]. The highest frequency of GS synovitis appeared in MTP2 joint (61.1%), followed by MTP1 (47.4%) and MCP2 joint (41.7%), while the highest frequency of PD synovitis appeared in MCP2 joint (29.4%), followed by MTP1 (25.6%) and MCP3 joint (22.7%). The GS and PD synovitis was least found in PIP joints. The frequencies

and distribution of gray scale and power Doppler synovitis in hand and foot joints was illustrated in Fig. 1.

The correlation between synovitis score and clinical composite disease activity score

The whole GS scores of MCPs (MCP1-5) joints showed highest correlation with the disease activity ($r = 0.403–0.452$, $p < 0.01$), including DAS28-ESR, DS28-CRP, CDAI and SDAI, followed by PIPs ($r = 0.318–0.331$, $p < 0.01$) and MTPs ($r = 0.277–0.301$, $p < 0.01$). Similarly, the whole PD scores of MCPs also showed highest correlation with the disease activity ($r = 0.332–0.396$, $p < 0.01$), followed by PIPs ($r = 0.211–0.242$, $p < 0.01$) and MTPs ($r = 0.198–0.222$, $p < 0.01$). At an individual joint level, GS score was overall better correlated with disease activity than PD score, except for MCP5 joint. Among the 30 joints, the highest correlation of GS score with DAS28-ESR ($r = 0.411$, $p < 0.01$), DAS28-CRP ($r = 0.459$, $p < 0.01$), SDAI ($r = 0.444$, $p < 0.01$) was observed in MCP3 joint, and the highest correlation of GS score with CDAI ($r = 0.421$, $p < 0.01$) was observed in MCP2 joint(Table 2). Similarly, the best correlation of PD score with DAS28-ESR ($r = 0.353$, $p < 0.01$), DAS28-CRP ($r = 0.399$, $p < 0.01$), CDAI ($r = 0.368$, $p < 0.01$), SDAI ($r = 0.377$, $p < 0.01$) was observed in MCP5 joint. On the contrary, the lowest correlation of GS ($r = 0.166–0.199$, $p < 0.01$) as well as PD ($r = 0.134–0.143$, $p < 0.01$) score with clinical disease activity was in PIP1 joint(Table 3).

Table 2

Correlation coefficient between GS score in each hand/foot joint and clinical disease activity indices

Joint	DAS28-ESR	DAS28-CRP	SDAI	CDAI
MCP1	0.207*	0.234**	0.259**	0.253**
MCP2	0.382**	0.381 **	0.398**	0.421**
MCP3	0.411**	0.459**	0.444**	0.393**
MCP4	0.335**	0.360**	0.386**	0.372**
MCP5	0.368**	0.374**	0.405**	0.365**
PIP1	0.173*	0.166 *	0.199*	0.196*
PIP2	0.224*	0.219**	0.242*	0.235**
PIP3	0.235**	0.209*	0.232**	0.233**
PIP4	0.273**	0.269**	0.279**	0.282**
PIP5	0.286**	0.265**	0.291**	0.274**
MTP1	0.218 **	0.235**	0.257**	0.234**
MTP2	0.206 *	0.223**	0.202**	0.180*
MTP3	0.287**	0.254**	0.261**	0.262**
MTP4	0.220 **	0.203*	0.213**	0.217 **
MTP5	0.179*	0.155	0.151	0.149

Abbreviations: MCP metacarpophalangeal, MTP metatarsophalangeal, PIP proximal interphalangeal, DAS28 Disease Activity Score in 28 joints, ESR erythrocyte sedimentation rate, CRP C-reactive protein, CDAI Clinical Disease Activity Index, SDAI Simplified Disease Activity Index.

* $p < 0.05$, ** $p < 0.01$.

Table 3

Correlation coefficient between PD score in each hand/foot joint and clinical disease activity indices

Joints	DAS28-ESR	DAS28-CRP	SDAI	CDAI
MCP1	0.155	0.191*	0.183*	0.188*
MCP2	0.274**	0.286**	0.307**	0.342**
MCP3	0.340**	0.399**	0.377**	0.348**
MCP4	0.301**	0.331**	0.351**	0.344**
MCP5	0.353**	0.375**	0.372**	0.368**
PIP1	0.141	0.142	0.143	0.134
PIP2	0.186*	0.198*	0.192*	0.184*
PIP3	0.167*	0.148	0.146	0.144
PIP4	0.168*	0.167*	0.152	0.153
PIP5	0.164*	0.173*	0.163*	0.156*
MTP1	0.204*	0.229**	0.236**	0.206**
MTP2	0.174*	0.172*	0.150	0.152
MTP3	0.242**	0.228**	0.211*	0.228**
MTP4	0.169*	0.165*	0.145	0.147
MTP5	0.141	0.120	0.094	0.094

Abbreviations: MCP metacarpophalangeal, MTP metatarsophalangeal, PIP proximal interphalangeal, DAS28 Disease Activity Score in 28 joints, ESR erythrocyte sedimentation rate, CRP C-reactive protein, CDAI Clinical Disease Activity Index, SDAI Simplified Disease Activity Index.

* $p < 0.05$; ** $p < 0.01$.

Discussion

Synovitis with multiple joint involvement is the prominent features of RA. At present, all the involved joints are handled equally in evaluating the clinical disease activity by all composite scores. Although some proposed simplified US scoring systems had shown good correlation with composite clinical disease activity indices, the correlation between US-defined synovitis at an individual joint level with global clinical disease activity has not been sufficiently explored. Besides, the role of synovitis in MTP joints, which are not included in 28-joint count, is controversial. Kapral T et al considered absence of MTP joints in clinical disease activity assessment would not impair its validity since patients with feet involvement reported higher patient's global assessment[12]. Whereas, Wechalekar MD et al

demonstrated that even subclinical synovitis in foot joints was predictive for disease relapse, bone damage progression and functional impairment[13].

In this study, synovitis score defined by both GS and PD ultrasound in MCP joints showed the highest correlation with all clinical composite disease activity indices. At single joint level, MCP3, MCP5 and MCP2 joints displayed the best correlation between GS score and most clinical disease activity indices. The MCP joints also showed higher correlation coefficient between PD score and clinical disease activity indices, except for MCP1 joint. In our previous study of developing a simplified ultrasound scoring system in RA, MCP2, MCP3 and MCP5 joints were also identified as their highest frequencies of both positive GS and PD synovitis, and their highest sensitivity and negative predictive value among all the wrist and hand joints [14]. Both studies suggested that MCP joints are most frequently involved and most representative of synovitis among all small joints of hand and foot in RA patients, especially MCP2, MCP3 and MCP5 joints. In contrast, GS synovitis was most frequently detected in MTP2 joint (61.1%), followed by MTP1, but PD synovitis was relatively less detected in MTP joints compared to MCP joints. The correlations of synovitis with clinical disease activity indices were generally lower in MTP joints than MCP joints. The phenomenon was not only confined to RA patients[15]. Higher prevalence of effusion and synovitis in forefoot joints than in wrist or finger joints was also identified in healthy individuals[16]. Synovitis in MTP3 joint seemed to be better correlated with clinical disease activity among all MTP joints, in spite of higher frequency of GS and PD synovitis in MTP1 and MTP2 joints. Hiraga also found that the mean length of hypoechoic synovial area was largest in MTP1 and MTP2, and decreased towards the MTP5 joint in asymptomatic healthy subjects [17]. Our result further indicated that GS synovitis in MTP1 and MTP2 joints may be largely caused by mechanical stress instead of RA, and MCP joints should contribute more in clinical disease activity assessment compared to MTP and PIP joints.

Our previous study has shown ultrasound-detected synovitis was much less than clinically determined arthritis in PIP joints[5]. The possible mechanisms include being relatively small and superficial joints, interference by subcutaneous inflammation or osteophytes, or two-dimensional characteristic of ultrasound which may miss detection of most severe synovitis. Similar results were found in this study, therefore synovitis of PIP joints makes limited contribution to the global disease activity. In a meta-analysis [18] evaluating the diagnostic accuracy of US compared with MRI for the detection of synovitis in RA patients, the summary estimates of sensitivity and specificity were 0.64 (95% CI 0.43, 0.81)/0.93 (95% CI 0.88, 0.97) and 0.71 (95% CI 0.33, 0.93)/0.94 (95% CI 0.89, 0.97) for MCP and PIP joints, respectively. Due to the diversity of study design, the role of synovitis in PIPs in global disease activity is inclusive.

To the best of our knowledge, this is the first study exploring the correlation of ultrasound-detected synovitis at a single joint level with composite clinical disease activity in patients with RA. Knee, shoulder, elbow and wrist joints, as part of 28 joints, were not included in the ultrasound assessment was the limitation of the study. But MCP and PIP joints, which are most frequently involved in RA and account for over 70% of 28 joints, are assessed by ultrasound, thus the results are convincing.

Conclusions

The ultrasound-detected synovitis of MCP joints, especially MCP2, MCP3, and MCP5, was best correlated with composite disease activity score of RA, in contrast to PIPs and MTPs. MCP joints should take greater weight in clinical disease activity assessment than PIP joints.

Abbreviations

RA: Rheumatoid arthritis; Composite disease activity score (DAS); SDAI: Simplified Disease Activity Index; CDAI: Clinical Disease Activity Index; TJC Tender joint count; SJC: Swollen joint count; MCP: Metacarpophalangeal; MTP: metatarsophalangeal; PIP: Proximal interphalangeal; DAS28-ESR: DAS based on 28 joint count and erythrocyte sedimentation rate; DAS28-CRP: DAS based on 28 joint count and C-reactive protein; GS: grey scale; PD: power Doppler; OMERACT: Outcome Measures in Rheumatology Clinical Trials; SD: Standard deviation; IQR: Interquartile range; RF：rheumatoid factor; anti-CCP：anti–Cyclic Citrullinated Peptide; TJC-30：tender joint count in bilateral MCPs, PIPs and MTPs joints; SJC-30：swollen joint count in bilateral MCPs ,PIPs and MTPs joints; PGA：patient's global assessment; EGA：evaluator's global assessment; HAQ DI：Health Assessment Questionnaire disability index.

Declarations

Ethics approval and consent to participate

This study was approved by local ethics committee. Signed informed consent was obtained from all patients prior to inclusion.

Consent for publication

All authors gave their consent for publication.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors have declared no competing interests.

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Authors' contributions

All authors contributed substantially to the conception and design of the study and interpreted data. XRD and XYS designed the ultrasound protocol. XRD, XYS, WHX and YW collected data. XYS, and XRD analyzed data. XRD and ZLZ prepared the first draft of the report. All authors contributed to revision of the report and approved the final version.

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Publisher's Note

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Figures

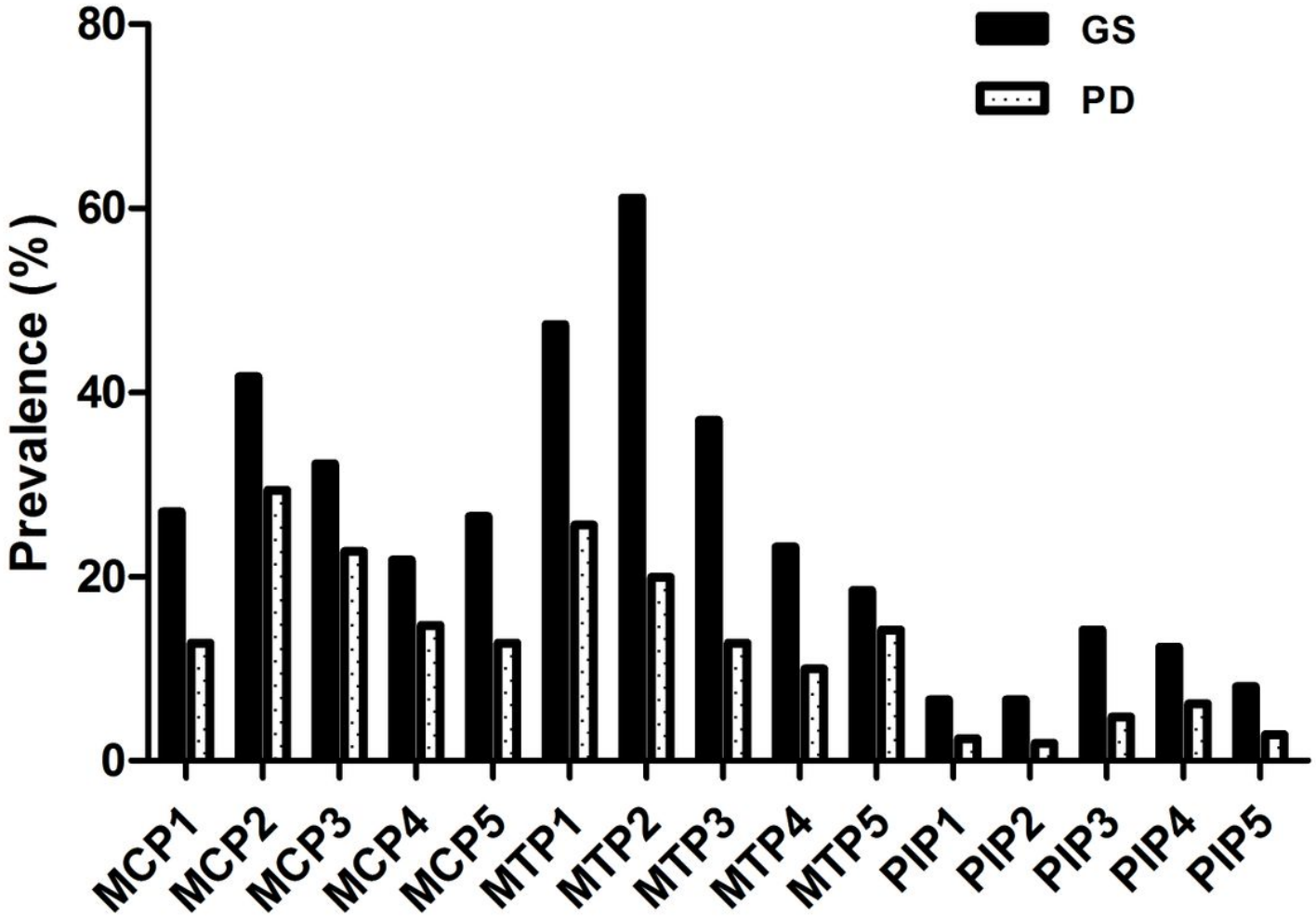

Figure 1

The frequencies and distribution of gray scale and power Doppler synovitis in hand and foot joints was illustrated