Ultrasound imaging for the rheumatologist XXVIII. Impact of sonographic knee joint involvement in recent-onset inflammatory polyarthritis

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ABSTRACT

Objective. *To assess the impact of the knee joint inflammation, detected by ultrasonography (US), on functional disability in patients with recent-onset inflammatory polyarthritis (IP).*

Methods. *We included patients who had IP for less than 12 months and who had more than 5 swollen joints. All patients were assessed clinically at baseline. US was used to identify joint inflammation at multiple joint sites including: hands, wrists, elbows, shoulders, knees, ankles and feet. Joint group involvement was defined when at least one joint showed intra-articular signs of inflammation (synovial fluid abnormalities and/or synovial hypertrophy), according to the OMERACT definitions. Functional disability was measured using the health assessment questionnaire (HAQ) score. All patients with complete clinical and US data were included in the analysis.*

Results. *Patients with US knee involvement showed more active and severe disease at baseline. The mean difference of HAQ between patients with and without US knee inflammation was 0.42 (95%CI 0.22, 0.62; p<0.001). This difference was still clinically and statistically significant even after controlling for disease extension and pattern of joint involvement. US shoulder involvement was also significantly and independently associated with higher mean HAQ scores.*

Conclusion. *US knee involvement is associated with higher disability in IP at first presentation. US is a good tool to help in the differentiation of patients with recent-onset IP with different disease severity.*

Introduction

Although a number of effective drugs and therapeutic strategies are available for treating inflammatory polyarthritis (IP), including rheumatoid arthritis (RA), the early diagnosis and identification of reliable prognostic indicator remain an ongoing challenging (1, 2).

Several studies have focused on demographic, serological, genetic and radiographic variables as diagnostic and prognostic factors for IP (3-6). The extent and sites of joint involvement are regarded as additional diagnostic and prognostic factors (7-9).

A few studies have investigated the impact of clinical involvement of the knee joint in IP, including RA. Overall, these studies indicate that patients with early IP, including RA, have a more severe disease in terms of functional disability and worse functional prognosis (10-12). These results indicate that patients with IP who have clinical involvement of the knee joint represent a subset of patients with more severe disease. However, it is known that clinical examination is far from accurate when it comes to identifying joint inflammation compared to more sensitive and specific radiological techniques, such as musculoskeletal ultrasonography (US) (13-15). US is well demonstrated to be a valid and reliable tool for the assessment of joint inflammation and therefore could be used to sub-stratify IP patients with different disease severity (16-20).

In this work we systematically applied US to identify joint inflammation at the knee joint site in patients with recent-onset IP in order to investigate the impact of knee joint involvement on outcome such as functional disability. For this purpose we included a sample

of patients with recent-onset IP from an inception cohort of early arthritis and we cross-sectionally analysed the baseline association between US knee involvement and the health assessment questionnaire (HAQ) score.

Materials and methods

Setting and participants

Patients with IP and with symptom duration less than 12 months were included in the study. All subjects gave written consent. For the purpose of this study we only included patients with RA or undifferentiated polyarthritis who had at least 5 swollen joints on the 44-joint count at baseline evaluation.

Baseline data from patients with complete US examination were used for the cross-sectional analyses.

Patient assessment

The clinical assessment included: tender and swollen joint count (TJC, SJC) on 44 and 28 joints, visual analogue scale (VAS) for pain, patient's global assessment (PGA), physician's global assessment (PhGA) and global health assessment (GH). Disease activity was assessed using the disease activity score (DAS) on 28-joint count (21). Laboratory tests included rheumatoid factor (RF), anti-citrullinated peptide antibodies (ACPA), erythrosedimentation rate (ESR) and C-reactive protein (CRP). Functional disability was assessed by the Italian version of the HAQ (22).

The American College of Rheumatology (ACR; formerly the American Rheumatism Association) 1987 criteria for RA (23) were applied cross-sectionally at baseline.

Musculoskeletal ultrasonography

US assessment was performed blindly by a single experienced operator, using a Logiq 9 (General Electrics Medical Systems, Milwaukee, WI) with multifrequency linear probes (8-14 MHz) according to the European League Against Rheumatism (EULAR) guidelines (24). The scanning protocol of metacarpophalangeal (MCP), proximal interphalangeal (PIP) wrist, knee, elbow, shoulder, ankle and metatarsophalangeal (MTP) joints was performed as detailed elsewhere (25).

The presence of joint effusion (JE) and synovial hypertrophy (SH) was identified in each joint as abnormal anechoic/hypoechoic intra-articular material according to the OMERACT definitions (26). Grey-scale (GS) synovitis was defined as the presence of JE and/or SH. JE and SH were subjectively graded from 0 to 3 (0=normal; 1=mild; 2 = moderate; 3=marked) (25, 27). GS synovitis was graded by summing the scores of both JE and SH.

Synovial power Doppler (PD) was assessed by selecting a region of interest that included the bony margins, joint space and a variable view of surrounding tissues (depending on the joint size). PD calibrations were adjusted at the lowest permissible pulse repetition frequency to maximise sensitivity and were taken as a constant for the same joint in different patients. Doppler frequency was set higher for the study of small joints and superficial tissues, and lower for deep structures. Colour gain was set just below the level that causes the appearance of noise artefacts. Flow was demonstrated in two perpendicular planes and confirmed by pulsed wave Doppler spectrum to exclude artefacts. The PD signal was subjectively graded on a semi-quantitative scale from 0 to 3 (0=absence or minimal flow; 1=mild: single vessel signal; 2=moderate: confluent vessels; 3=marked: vessel signals in >50% of the joint area) on the image with the maximal enhancement on PD (25, 28, 29).

A joint was considered involved when score 1 GS synovitis and/or PD signal were detected by US.

The involvement of each joint group (wrists, MCPs, PIPs, elbows, shoulders, knees, ankles, MTPs) was defined as the presence of at least 1 positive joint.

Statistical methods

Summary statistics of mean and standard deviation (SD) or median and interquartile range (IQR), when appropriate, were presented for continuous variables. Baseline differences between patients with and without US knee involvement were tested using the Wilcoxon's rank sum test for continuous variables and the chi-square test for categorical variables.

Only patients with complete clinical and US data at baseline were included in analysis.

To explore the relationship between the involvement of the knee and HAQ we applied linear regression. This approach allowed us to estimate the HAQ mean difference (MD) between patients with and without US knee involvement and 95% confidence interval (95%CI), even correcting for relevant confounders.

The expected violation of distributive normality of the outcome variable (HAQ) was allowed, due to the robustness of the linear regression model. To verify this, we also performed a quantile regression, and the result from the linear regression model was retained only in case of consistency of the results.

Following this approach we firstly carried out an unadjusted analysis followed by sequential adjusted analysis aimed at controlling for potential confounders and to identify the specific impact of the site of involvement on functional disability. In the first step we corrected for potential confounders such as age and sex; in the second step we also checked for the extension of joint inflammation; and in the third step also for every other specific joint site involvement.

All analyses were conducted using Stata version 11 (StataCorp, College Station, TX).

Results

Study sample

We have cross-sectionally analysed a total of 228 subjects with early-onset IP at baseline evaluation. Their main clinical characteristics are summarised in Table I. Overall, the study sample included patients median (IQR) age of 62 (51–72) years, higher prevalence of female gender (71.9%), median (IQR) symptoms duration of 3.5 months (2.3–6.5), with severe disease activity (mean (SD) DAS28 5.2 (1.8), and moderate functional disability (median[IQR] HAQ 1.250 [0.687–1.875]). The majority of patients (85.5%) were untreated with DMARDs or oral steroids at baseline.

Clinical and ultrasonographic joint involvement

Of the 228 patients, 146 (64.0%) pre-

Table I. Patients' characteristics.

	All subjects 228	US knee involvement Yes 146	US knee involvement No 82
Age, median (IQR)	62 (51–72)	62 (52–73)	60 (49–68)
Gender female, n (%)	164 (71.9)	101 (69.1)	63 (76.8)
Disease duration, median (IQR)	3.5 (2.3–6.5)	3.7 (2.3–6.4)	2.9 (2–6.5)
RF, n (%)	70 (31)	41 (28)	29 (35)
ACPA, n (%)§	54 (24)	33 (23)	21 (26)
ACR criteria, n (%)**	172 (75.4)	120 (82.2)	52 (63.4)
DAS28, mean (SD)***	5.2 (1.8)	5.4 (1.2)	4.8 (1.1)
VAS pain, median (IQR)*	57 (48–80)	60 (50–80)	53 (40–76)
VAS patient, median (IQR)***	60 (46–80)	63 (47–80)	51 (45–75)
VAS physician, median (IQR)*	45 (33–60)	49 (38-62)	40 (29–50)
VAS GH, median (IQR)	54 (50–71)	52 (50–70)	55 (50–74)
SJC44, median (IQR)***	11 (8–18)	14 (9–19)	9 (7–13)
TJC44, median (IQR)***	13 (6–18)	14 (6–19)	11 (5–18)
SJC28, median (IQR)***	9 (6–13)	10 (7–14)	6 (4–10)
TJC28, median (IQR)***	8 (3–14)	9 (4-15)	8 (3–12)
ESR, median (IQR)***	25 (14–42)	28 (16–48)	21 (11–34)
CRP, median (IQR)***	0.7 (0.3–2.4)	1.1 (0.3–3.1)	0.5 (0.3–1.3)
HAQ score, median (IQR)**	1.3 (0.7–1.9)	1.4 (0.8-2)	0.9 (0.5–1.5)

Wilcoxon signed rank sum test * $p<0.05$ ** $p<0.01$ *** $0<0.001$
RF: rheumatoid factor; ACPA: anti-citrullinated peptide antibodies; ACR: American College of Rheumatology; DAS: disease activity score; VAS: visual analogue scale; GH: global health assessment; TJC, SJC: tender and swollen joint count; ESR: erythrosedimentation rate; CRP: C-reactive protein; HAQ: health assessment questionnaire.

Table II. Musculoskeletal ultrasound findings at the knee joints.

	Grade	Joint effusion	Synovial hypertrophy	Power Doppler
Right knee, n(%)	0	96 (42.1)	189 (82.8)	217 (95.1)
	1	110 (48.2)	25 (10.9)	9 (3.9)
	2	19 (8.3)	7 (3.0)	2 (0.8)
	3	3 (1.3)	7 (3.0)	0
Left knee, n(%)	0	105 (46.0)	193 (84.6)	220 (96.4)
	1	109 (47.8)	24 (10.5)	8 (3.5)
	2	14 (6.1)	5 (2.1)	0
	3	0	6 (2.6)	0

sented with US involvement of either or both knees. US involvement was detected in 132 (57.9%) right and in 125 (54.4%) left knee joints. Involvement was symmetrical in 110 (48.2%) patients. Detailed analysis of US features of patients showed that in most of them the joint had low scores for effusion and hypertrophy. PD signal was detected in a very low percentage of patients (4.8% for the right knee and 3.5% for the left), and again with low scores (Table II).

Clinical involvement of either or both knees was found in the 47.7% patients (unilateral 33.1% and bilateral 14.6%). US was more sensitive (proportion difference = 0.16 [95%CI 0.06–0.26]) than clinical examination. Using US as reference standard clinical examination showed a low sensitivity (57.7%) and a low specificity (70.9%) for the detection of joint inflammation.

US involvement of the other joint groups was recorded: MCP in 207 (91%), MTP in 195 (85%), wrists in 177 (78%), PIP in 171 (75%), ankles in 123 (54%), elbows in 34 (15%) and shoulders in 21 (9%) patients.

Impact of US knee joint involvement on functional disability

Age, sex distribution, disease duration, autoantibody (RF and/or ACPA) distribution, tender joint count, VAS pain and GH, and previous treatment were not different between patients with and without knee US involvement. The SJC, both on 28 and 44 joints ($p<0.001$), DAS28 ($p<0.001$), PGA ($p=0.04$), PhGA ($p<0.001$), ESR ($p=0.003$), CRP ($p=0.003$) and HAQ at the baseline visit ($p=0.001$) significantly differed comparing the two groups and were higher in the group of patients with US involvement of the knee (Table I).

We focused further analysis on the relationship between HAQ US-detected knee involvement.

In the first unadjusted analysis, subjects with US knee involvement showed a significantly higher HAQ score compared to those without US knee involvement (MD 0.42 [95%CI 0.22-0.62]) (Table III). This effect was also independent of the age and gender.

Since subjects with US knee involvement showed a wider degree of disease involvement, we analysed the effect of the knee joints correcting for the number of swollen joints. On equal swollen joints, the involvement of the knee accounted for a clinically and statistically significant mean increase of the HAQ score of 0.27 [95%CI 0.07–0.47].

When including the analysis of US involvement of other joint groups in the model, presence of an affected knee still significantly influenced the HAQ score. In this model, age and the 44-swollen joint count resulted in a significant influence; another joint group with a likewise significant impact was the shoulder (Table IV).

Discussion

This study sought to determine the impact of US knee involvement on functional disability in an inception cohort of IP. This is the first study specifically investigating such relationship.

We found that involvement of the knee joint detected by US identified a subgroup of patients with a significant lower functional disability as measured by HAQ score.

Comparing subjects with and without US knee involvement, we found a number of further clinical differences that could account for the increased mean HAQ score. In particular the higher number of swollen joints in patients with US knee involvement suggested that US knee involvement could be a "biomarker" of the extension of the disease rather than

identifying a subgroup of patients with a qualitatively different distribution of joint inflammation. Although adjusted analyses confirmed that swollen joints acted as confounder of the relationship between for US knee involvement and functional disability, US knee involvement retained both statistical and clinically significant effects on HAQ score. To rule out the possibility that the effect of knee involvement was due to a relationship with one or more different joint groups we also performed a multivariate analysis including all joint sites included in our US protocol, showing again significant differences between subjects with and without knee involvement.

Previous studies have focused on the impact of the clinical involvement of the knee. In a cross-sectional study on established RA, the knee involvement accounted for a valuable proportion of reported pain and functional disability scales (11). In a prospective study of an inception cohort of IP, the knee involvement resulted independently associated with future development of functional disability both in the overall population of IP and even more in the subgroup of patients who fulfilled classification criteria for RA (10). In a further cohort study of early RA, the involvement of large joint – in particular, the knee – was demonstrated to longitudinally associate with a worse radiological outcome after 12 months (12). Other studies investigating the longitudinal effect of the clinical involvement of the knee in the early phases of IP in terms of different clinical outcomes showed less consistent results. In particular, the knee involvement did not appear as a significant predictor of relevant outcomes such as the persistency of symptoms (and erosiveness) (8) and the fulfilment ACR criteria for RA (9). The study of Visser *et al*. analysed patients with early arthritis including mono- and oligoarthritis, while the study of van der Helm-van Mil *et al*. only included early undifferentiated arthritis. Selecting a population of both mono-oligoarthritis and polyarthritis is not clearly a good choice to explore the effect of knee involvement, as the intrinsic relationship between knee and monoarthritis may bias the prognostic value of the knee toward the effect of monoarthritis by itself. For this reason, we selected a population of polyarthritis who had at least 5 swollen joints (30). The particular setting of the inception cohort allowed us to investigate a homogeneous population of untreated patients.

US allowed us to easily assess multiple sites during the same session.

Our study reconfirmed the higher sensitivity of US in the detection of joint inflammation over clinical examination. Furthermore, in our study sample we detected more prevalent low US scores of knee involvement. These findings indicate that our analysis mostly investigated the effect of mild and subclinical knee involvement. As a matter of fact, although a significant effect in terms of functional disability was demonstrable also for the clinical involvement of the knee, it was weaker and disappeared when corrected for the extension of the disease (not shown). This strengthens the relevance of using US to detect subclinical joint inflammation at the knee site.

From an analysis of the effect on HAQ of different joint groups, the shoulder showed the highest impact. This finding is in keeping with the previous reported association between clinical involvement of the shoulder and risk of future structural damage in early RA (12). Conversely, it contrasts with the lack of association between shoulder involvement and disability observed in a wide population-based inception cohort of IP (10). As discussed by Wiles *et al*. this lack of evidence could be due to inaccurate clinical examination in detecting shoulder involvement. Our study therefore supports the use of US as a tool for detecting shoulder involvement in IP.

This study has some limitations. The study population did not include some specific forms of IP, such as seronegative spondyloarthropathy. This selection may limit the generalisability of our findings to the overall population of recent-onset IP. A second limitation relates to the choice of the HAQ score as an outcome measure. Since specific domains within the HAQ are devoted to knee involvement, some degree of association could be expected. Finally, US findings may be non-specific for

Table III. Crude and adjusted estimates of mean difference in HAQ between subjects with and without US knee involvement.

	Mean HAQ difference	95%CI	*p*-value
US knee	0.42	0.22–0.62	<0.0001
US knee*	0.39	0.20–0.59	<0.0001
US knee#	0.27	0.07–0.47	0.008

*adjusted for age and sex.
#adjusted for age, sex, swollen joints on 44.

Table IV. Multivariable adjusted estimates of mean difference in HAQ between subjects with and without specific joint group US involvement.

	Mean HAQ difference	95%CI	*p*-value
US knee#	0.25	0.05–0.46	0.02
US wrist#	0.11	-0.13–0.35	0.4
US MCP#	-0.10	-0.45–0.25	0.6
US PIP#	-0.09	-0.32–0.14	0.4
US elbow#	-0.10	-0.36–0.17	0.5
US shoulder#	0.56	0.23–0.89	0.001
US ankle#	0.08	-0.12–0.27	0.4
US MTP#	-0.01	-0.28–0.26	0.9

#adjusted for age, sex, swollen joints on 44.

inflammation related to polyartritis alone and could be related to degenerative processes.

In conclusion, this study confirms the impact of knee involvement on the disease severity of IP, and supports the use of US in the stratification of patients with recent-onset IP with different disease severity.

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