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### Is shoulder involvement in clinically suspect arthralgia an early feature of rheumatoid arthritis? A longitudinal ultrasound study

#### Rheumatology key message

- Subclinical tenosynovitis of the biceps tendon is not an early feature of RA in clinically suspect arthralgia patients.

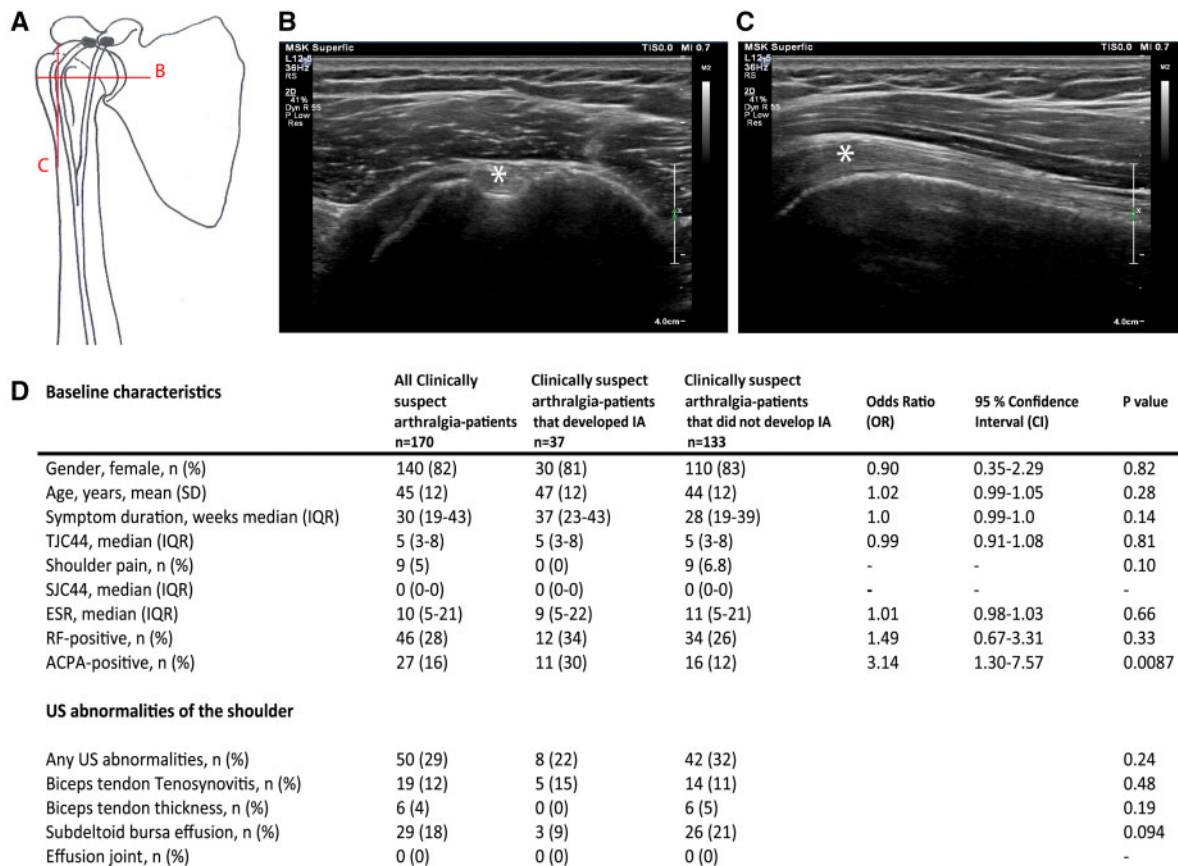
Sir, Multiple studies have demonstrated that shoulder complaints are frequent in RA [1, 2]. Recently, it has been shown that shoulder involvement is predictive of RA development in patients with undifferentiated arthritis and its value is comparable with that of small joint involvement [3]. The phase of clinically suspect arthralgia precedes the phase of clinically apparent arthritis. In this phase, subclinical tenosynovitis in small hand joints is associated with developing RA [4]. Given the similarities in predictive values between the shoulder and small joints in undifferentiated arthritis, and the predictive value of tenosynovitis in clinically suspect arthralgia, we hypothesized that tenosynovitis of the bicep tendon visualized by US is also associated with developing inflammatory arthritis (IA) in clinically suspect arthralgia patients. We examined the biceps tendon, since this is the only tendon of the shoulder that is enclosed by a synovial sheath as it passes through the bicipital groove (Fig. 1A–C) [5].

To answer our research question we used data from the SONAR study, sonographic evaluation of hands, shoulders and feet in patients presenting with inflammatory arthralgia, to identify subclinical arthritis. This was a multicentre observational cohort study. In this study, US of both shoulders was made at baseline. US abnormalities of the biceps tendon [1], the glenohumeral joint [2] and the subdeltoid bursa [3] were assessed for tenosynovitis, arthritis and bursitis. Thereafter, patients were followed for the course of 1 year (with 6-monthly visits) for the development of clinically apparent IA, which was verified by the treating physician. The medical ethics committee of Erasmus University Medical Center (Erasmus MC), Rotterdam, The Netherlands approved the study (MEC-2010–353). Furthermore, the study was assessed for feasibility by the local ethical bodies of the other two participating hospitals (Maasstad Hospital and Vlieland Hospital). All patients gave written informed consent before inclusion according to the Declaration of Helsinki. Student's *t* test and the Mann–Whitney test were used to compare baseline values. US abnormalities between groups were compared using a  $\chi^2$  test. A detailed description of the cohort, US protocol, and statistics are presented in the Supplementary Material, Methods section, available at *Rheumatology* online.

A flowchart is presented as supplementary material, available at *Rheumatology* online. No significant differences in baseline characteristics were found between included and excluded patients (Supplementary Table S1, available at *Rheumatology* online). Of the participants, 140 patients (82%) were female, the mean age was 45 years and the median symptom duration was 30 weeks (Fig. 1D). After 1 year, 37 patients (22%) had developed IA and, of those patients, 17 (46%) fulfilled the 2010 criteria for RA (Supplementary Table S2, available at *Rheumatology* online). The remaining 20 patients were diagnosed with: undifferentiated arthritis (80%), OA (15%) and PsA (5%). Shoulder pain was infrequent (5%) and only observed in the non-IA group. ACPA positivity was associated with IA development [odds ratio (OR) 3.14, 95% confidence interval 1.30–7.57,  $P = 0.0087$ ] (Fig. 1D).

Although shoulder pain was infrequent, we did find US shoulder abnormalities in 50 patients (29%, Fig. 1D). None were predictive for IA development. Subclinical tenosynovitis of the biceps tendon was present in 15% and 11% of clinically suspect arthralgia patients who, respectively, did and did not develop IA ( $P = 0.48$ ). Also, bilateral tenosynovitis was evenly distributed between both groups (6% and 6%) (Supplementary Fig. S2, available at *Rheumatology* online). A thickened biceps tendon and subdeltoid bursa effusion were also not associated with IA development ( $P = 0.19$  and  $P = 0.094$ , respectively). Joint effusion was absent (Fig. 1D). The subgroup analysis with RA as outcome showed similar results (Supplementary Table S3, available at *Rheumatology* online).

US abnormalities of the shoulder were less frequent in our study than in other studies: biceps tenosynovitis 23–44%, subdeltoid bursitis 18–67% and effusion of the

**Fig. 1** Anatomical representation of the biceps tendon and baseline characteristics including US abnormalities

(A) Anatomy of the shoulder joint and the course of the biceps tendon through the bicipital groove. The letters indicate the two perpendicular planes of the US probe for scanning the biceps tendon. (B) US of the transverse plane of the biceps tendon. (C) US of the longitudinal plane of the biceps tendon. (D) Baseline characteristics and US abnormalities at baseline in patients with clinically suspect arthralgia. Tub. Minus: tuberculum minus; Tub. majus: tuberculum majus; IA: inflammatory arthritis; TJC44: tender joint count in 44 joints; SCJ44: swollen joint count in 44 joints. White asterisk indicates biceps tendon.

joint 28–38% [6, 7]. However, these studies were performed in established RA. It is plausible that these patients had developed more abnormalities in the shoulder joint over the years due to active inflammation. On the other hand, US shoulder abnormalities are also seen in healthy individuals and prevalences vary widely. Iagnocco *et al.*, for example, showed a prevalence of 28.9%, which is comparable with our overall prevalence of 29% [8].

A strength of the current study was that US was performed by two experienced ultrasonographers who had received training prior to the start of the study. Also, a standardized US protocol and scoring system was used for scanning. In addition, analyses on primary and secondary outcomes provided similar results.

A limitation is that the number of patients that developed IA or RA and the frequency of US abnormalities within this group were relatively low. Although this may have harboured the risk of false-negative findings, there was no tendency towards more US-detected

inflammation, even in the clinically suspect arthralgia patients who progressed to IA. Therefore, further US studies on the shoulder in clinically suspect arthralgia would not seem to be valuable.


In conclusion, subclinical tenosynovitis of the biceps tendon, visualized with US, is not an early feature of RA and is also not predictive of the development of RA. Based on these results, standard US screening of the shoulder is not necessary in clinically suspect arthralgia patients for determining their risk of developing IA.

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## Supplementary data

Supplementary data are available at *Rheumatology* online.

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## Association between celiac disease and systemic lupus erythematosus: a Mendelian randomization study

### Rheumatology key message

- Mendelian randomization study suggested celiac disease might be associated with the risk of SLE.

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SIR, Celiac disease (CeD) is an autoimmune disease characterized by immune-reaction to gluten by T lymphocytes with gastrointestinal manifestations in children. Observationally, it has been reported that a variety of other autoimmune diseases are associated with CeD [1]. Correspondingly, a few cases have been reported that CeD precedes SLE [2]. In addition, >20% of patients with CeD have anti-double stranded DNA antibody, raising the intriguing question of whether abnormal immune responses in the gut play a role in systemic autoimmune disease [3]. To examine the association between CeD and SLE, I performed two-sample Mendelian randomization (MR) using the inverse-variance weighted (IVW), MR-Egger regression and weighted median methods. A two-sample MR utilizes genetic variants as instrumental variables (IVs) for assumption about causal impact of exposure on outcome derived from different samples [4].

I used the publicly available datasets of genome-wide association studies (GWASs) for CeD GWASs (12 041 cases and 12 228 controls) of the European population as the exposure and SLE GWASs (1311 cases and 1783 controls) of the European population as the outcome [5, 6]. To improve inference, selection of genetic variants associated with CeD as IVs was based on a linkage disequilibrium  $R^2$  value of 0.001, clumping distance of 10 000 kb and  $P$ -value threshold of  $5.00 \times 10^{-8}$  (genome-wide significance). Then, I examined the association between single nucleotide polymorphisms (SNPs) and risk of SLE. Finally, by combining the results acquired from of each SNPs using MR analysis, I estimated the causal association between CeD and risk of SLE. The effect size was shown by the  $\beta$ -coefficient. I assessed heterogeneity across SNPs by Cochran's Q statistic. To explore whether single SNPs drive causal association, I performed a leave-one-out analysis. All MR analyses were performed in MR Base platform (<http://www.mrbase.org/>; App version: 1.2.2 3a435d). The R script is in the supplementary material, section 'R Script', available at *Rheumatology* online.

I obtained 11 SNPs as IVs from CeD GWASs (Supplementary Table S1, available at *Rheumatology* online). These SNPs were located at *ZNF184* (rs13195040), *HLA-DPA1* and *HLA-DPB1* (rs1431403), *CIITA* and *LOC105371080* (rs6498114), *MMEL1* (rs10752747), *LOC105375027* (rs10947460), *LOC105369519* (rs10892258), *KIAA1109* (rs13119723), *TSBP1* and *TSBP1-AS1* (rs9268303), and unknown genes (rs13030124, rs12527282 and rs9258302).