

Rheumatology 2020;59:3106–3108

doi:10.1093/rheumatology/keaa082

Advance Access publication 16 March 2020

The value of the squeeze test for detection of subclinical synovitis in patients with arthralgia suspicious for progression to RA

Rheumatology key message

- A positive squeeze test in clinically suspect arthralgia is associated with presence of subclinical synovitis.

SIR, The squeeze test (or compression test) is often used to quickly screen for arthritis in MCP and MTP joints. A positive test is traditionally assumed to indicate presence of synovitis [1]. Previous studies in early arthritis indeed showed that a positive squeeze test was associated with presence of swollen MCP and MTP joints, as well as with local MRI-detected inflammation [2]. The sensitivity of the test, with MRI-detected synovitis as reference, was 31–33% [2]. The field of early arthritis is moving towards identifying patients at risk for RA in the phase of arthralgia. MRI-detected subclinical inflammation has been shown to be predictive for RA development; of all inflammatory features, tenosynovitis had the strongest association [3]. We here aimed to assess if a positive squeeze test in patients with clinically suspect arthralgia (CSA) is associated with subclinical inflammation. We specifically hypothesized that it is associated with subclinical synovitis, in line with the original assumption of the test being a measure of synovitis. MRI-detected tenosynovitis was also studied, because we assumed that tenosynovitis at MCP or MTP level may also produce pain upon compression. Finally, we studied the association of the test with progression to inflammatory arthritis (IA).

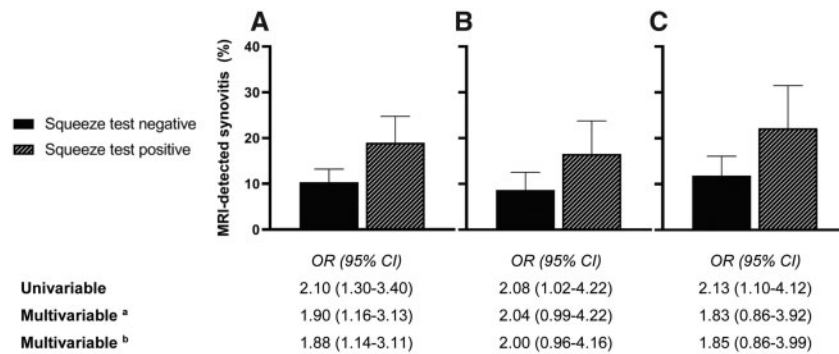
Between April 2015 and October 2018, 315 patients were consecutively included in the Leiden CSA cohort; details are provided in the Supplementary material, section 'Methods', available at *Rheumatology* online. Inclusion criteria were recent-onset (<1 year) arthralgia of small joints and a clinical suspicion for progression to RA, which means that according to the pattern recognition of the rheumatologist at first visit, imminent RA was more likely than other diagnoses, as described previously [4]. All patients gave written informed consent. The study was approved by the local medical ethical committee. At baseline the squeeze test was performed; compression across the knuckles of MCP and MTP joints with the force of a firm handshake, as described previously [2]. Unilateral contrast-enhanced 1.5T MRI of MCP (2–5) and MTP (1–5) joints was also made at baseline and scored by two trained readers for synovitis (according to RAMRIS [5]) and tenosynovitis (according to Haavardsholm *et al.*

[6]). MRI scores were dichotomized with data from age-matched symptom-free controls as reference. A detailed scanning and scoring protocol and information on dichotomization is provided in the Supplementary material, section 'Methods', available at *Rheumatology* online. Follow-up ended when patients developed clinically apparent IA (determined at physical examination), or else after 2 years. Associations of the squeeze test and MRI data (data of same extremity at baseline) were studied with generalized estimating equations, to account for the fact that in every patient a hand and a foot was assessed. The association of the squeeze test with IA development was determined using Cox regression.

Flowchart and baseline characteristics are shown in the Supplementary material (Supplementary Fig. S1 and Supplementary Table S1, available at *Rheumatology* online). Fifty-one per cent of CSA patients had a positive squeeze test in MCP or MTP joints. In univariable analyses a positive test was associated with local subclinical synovitis [odds ratio (OR) 2.10 (95% CI 1.30–3.40), Fig. 1A] and tenosynovitis [OR 1.68 (95% CI 1.05–2.68); Supplementary Table S2, available at *Rheumatology* online]. In multivariable analyses including both inflammatory features only synovitis remained significant [OR 1.90 (95% CI 1.16–3.13), Fig. 1A], also after further correction for age and gender (Fig. 1A, Supplementary Table S2, available at *Rheumatology* online). Thus, a positive squeeze test is a measure of subclinical synovitis, with a sensitivity of 44% (95% CI 33–55%) and specificity of 72% (95% CI 68–76%). When analysing MCP and MTP joints separately, the squeeze test was also associated with subclinical synovitis [OR 2.08 (95% CI 1.02–4.22) and 2.13 (95% CI 1.10–4.12), respectively, in univariable analyses; Fig. 1B and C, Supplementary Table S2, available at *Rheumatology* online].

A positive squeeze test in patients with CSA was not associated with IA development in Cox regression adjusted for age, gender, CRP and ACPA-status [hazard ratio (HR) 1.57 (95% CI 0.77–3.19); Supplementary Table S3, available at *Rheumatology* online]. This is consistent with the finding that subclinical synovitis was not associated with IA development in multivariable analysis adjusted for age, gender, CRP, ACPA status and subclinical tenosynovitis [HR 1.40 (95% CI 0.59–3.31)], whilst tenosynovitis was associated [HR 4.94 (95% CI 2.03–12.06); Supplementary Table S4, available at *Rheumatology* online].

The squeeze test is known for its association with synovitis in patients with clinically manifest arthritis. This study is the first to investigate the association with subclinical inflammation in the phase of CSA. We demonstrated that a positive test was indeed associated with presence of subclinical synovitis. The sensitivity was 44%; this indicates that subclinical synovitis was frequently missed by

Fig. 1 Squeeze test and MRI-detected synovitis in (A) MCP and MTP joints, (B) MCP joints and (C) MTP joints

Subclinical inflammation was considered present if the inflammatory feature was uncommon in symptom-free controls, i.e. present in <5% of symptom-free controls at the same location and in the same age category (<40, 40–59, ≥60). Error bars represent 95% CI. ^aAdjusted for tenosynovitis. ^bAdjusted for tenosynovitis, age and gender. OR: odds ratio.

the squeeze test. For certainty on presence of subclinical synovitis imaging could be used. However, whilst MRI is more sensitive for detection of subclinical synovitis, it is also invasive and costly. In contrast, the squeeze test is easy to perform and free of costs, and therefore it can provide value as a first screening tool.

The squeeze test of the MCPs is, in combination with other clinical characteristics, part of the EULAR definition of arthralgia suspicious for progression to RA. This definition serves to identify this group of arthralgia patients and to distinguish them from arthralgia with other causes [7, 8].

A positive squeeze test *within* CSA was not significantly associated with IA development. This may seem counter-intuitive, as we have shown that it is a test for subclinical synovitis and subclinical inflammation is predictive for IA. However, this is explained by the fact that the latter association is mainly driven by tenosynovitis, as was shown previously [3]. Also in current data synovitis was not significantly associated with IA development, in contrast to tenosynovitis.

In sum, the squeeze test is a simple test that, when positive in CSA, doubles the probability of presence of subclinical synovitis.

Funding: This work was supported by the European Research Council (ERC) under the European Union's Horizon 2020 research and innovation programme (Starting grant, agreement No 714312), and the Dutch Arthritis Society.

Disclosure statement: The authors have declared no conflicts of interest.

Supplementary data

Supplementary data are available at *Rheumatology* online.

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Accepted 4 February 2020

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Rheumatology 2020;59:3108–3109
 doi:10.1093/rheumatology/keaa085
 Advance Access publication 17 March 2020

The effect of reducing systemic inflammation on serum urate

Rheumatology key message

- Decreasing systemic inflammation leads to an increase in serum urate.

SIR, urate is a product of the metabolic breakdown of purine nucleotides, and raised serum urate (hyperuricaemia) is the primary cause of the inflammatory arthritis gout. During gout flares it is well established that serum urate (SU) concentrations decrease and up to 49% of patients have levels within normal reference ranges [1, 2]. This has been hypothesized to be related to the systemic inflammatory response rather than the gout disease process itself. Waldron and colleagues demonstrated a significant reduction in SU when patients without gout had major surgery [3]. This leads to the consideration of the inverse situation when systemic inflammation is suppressed. It is therefore of interest to assess how SU may be affected by a significant reduction in inflammation, as occurs in patients with active rheumatic disease who commence potent immunosuppressants.

An analysis was performed using a database of adult patients from a rheumatology service who had been commenced on a biologic disease modifying anti-rheumatic drug (bDMARD). Included patients were started on the bDMARD while known to the clinic and completed at least 3 months of uninterrupted therapy. There were no patients with gout in the cohort. SU, at least one of inflammatory markers CRP or ESR, and renal function results

were required to be available from within 3 months prior to, and 3–6 months after, commencement of the bDMARD. Exclusion criteria included inadequate records of commencement, no SU or inflammatory markers available within the specified time frames, or intercurrent illness at the time of specimen collection. Paired *t* test analysis was performed comparing SU, inflammatory markers, and renal function before and after initiation of the bDMARD. Ethics approval was granted by the local institutional ethics committee (the Royal Brisbane & Women’s Hospital Human Research Ethics Committee; HREC/2018/QRBW/45944).

Records of 289 patients were examined, with 108 of these meeting inclusion criteria; 63% of the patients were female, and the median age of participants was 54.5 years (IQR 42–61 years). The indication for bDMARD use was RA (63%), psoriatic arthritis (24.1%) ankylosing spondylitis (12%) and other inflammatory disease (0.9%). The bDMARDs used were predominantly tumour necrosis factor inhibitors (85%) with a small number of patients receiving one of five other bDMARDs.

After commencement of bDMARD therapy, mean SU increased from 0.286 to 0.305 mmol/l; see Table 1. CRP and ESR were also significantly reduced and renal function was unchanged. These results provide evidence that SU significantly increases following commencement of potent immunosuppression. In this cohort we have also provided evidence of a coincident significant reduction in CRP and ESR supporting the assertion of a reduction in systemic inflammation. Taken together with the observation of decreases in SU in gout flare and in elective surgery, this supports a two-way relationship between the level of systemic inflammation and SU. The mechanism behind this relationship remains unclear, but may be related to changes in the fractional excretion of urate possibly precipitated by an alteration in the inflammatory milieu [1, 4].

The increase in SU with immunosuppression could also contribute to the coexistence of hyperuricaemia or gout in patients with systemic inflammatory disorders who receive effective therapies. A large recently reported cohort of RA patients (*n* = 1999) had a 6.1% prevalence of co-existent gout, higher than expected from the general population [5, 6]. Whilst decreases in SU during gout flare have been long observed, this is the first demonstration that the phenomenon also occurs in reverse. Future work could focus on demonstrating a possible difference in fractional

TABLE 1 Laboratory results prior to and after commencing biologic disease modifying anti-rheumatic drugs

	<i>n</i>	Prior	Post	<i>P</i>
Serum urate (0.12 - 0.45 mmol/l)	108	0.286	0.305	0.00025
CRP (<5 mg/l)	108	24.8	10.2	<0.00001
Erythrocyte sedimentation rate (1 - 20 mm/h)	100	34.7	19.4	<0.00001
eGFR (>90 ml/min/1.73 m ²)	108	84.8	84.0	0.23

eGFR: estimated glomerular filtration rate.