Clinically suspect arthralgia: unraveling the development of rheumatoid arthritis

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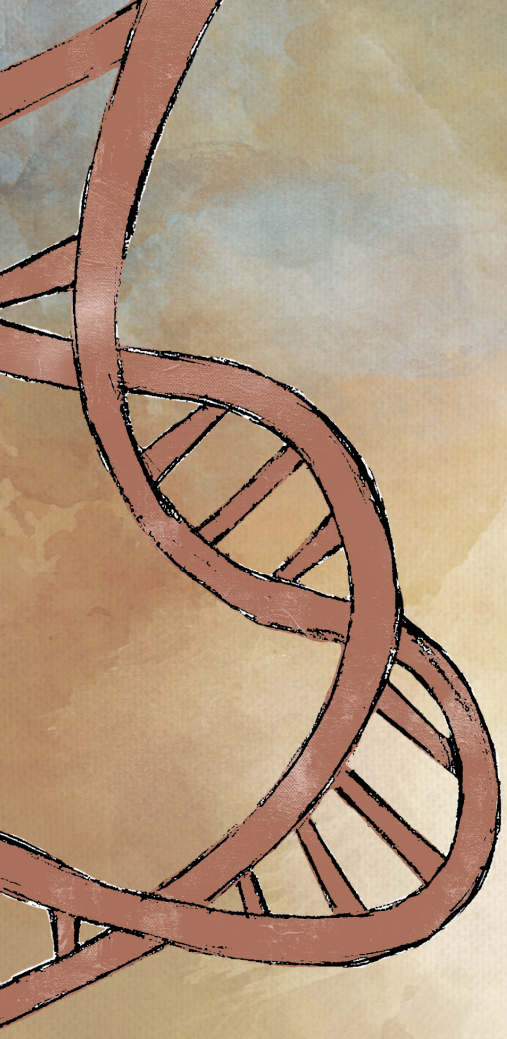

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The value of the squeeze test for detection of subclinical synovitis in patients with arthralgia suspicious for progression to RA

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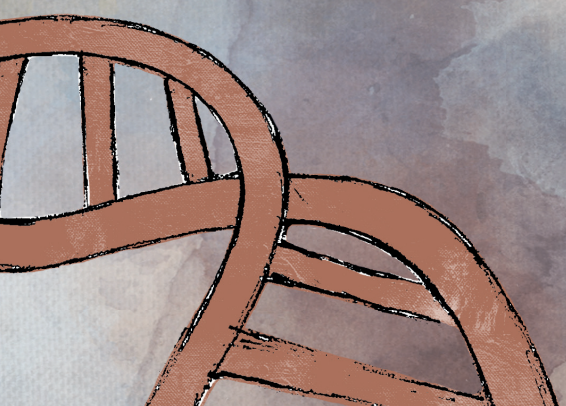
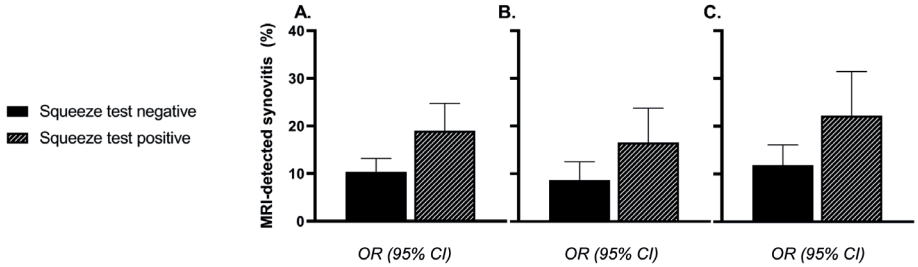


Sir, The squeeze test (or compression test) is often used to quickly screen for arthritis in metacarpophalangeal (MCP)- and metatarsophalangeal (MTP)-joints. A positive test is traditionally assumed to indicate presence of synovitis.[1] Previous studies in early arthritis indeed showed that a positive 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 rheumatoid arthritis (RA) in the phase of arthralgia. MRI-detected subclinical inflammation has been shown 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-October 2018 315 patients were consecutively included in the Leiden CSA-cohort, details are provided supplementary. 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] 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[6]). MRI-scores were dichotomized with data from age-matched symptom-free controls as reference. A detailed scanning and scoring protocol and information on dichotomisation is provided supplementary. 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 supplementary (Supplementary Figure 1, Supplementary Table 1). 51% 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 (OR 2.10 (95%CI 1.30-3.40), Figure 1A) and tenosynovitis (OR 1.68

Figure 1. Association between the squeeze test and subclinical MRI-detected synovitis studied in A) MCP- and MTP-joints, B) MCP-joints only and C) MTP-joints only



	OR (95% CI)	OR (95% CI)	OR (95% CI)
Univariable	2.10 (1.30-3.40)	2.08 (1.02-4.22)	2.13 (1.10-4.12)
Multivariable [a]	1.90 (1.16-3.13)	2.04 (0.99-4.22)	1.83 (0.86-3.92)
Multivariable [b]	1.88 (1.14-3.11)	2.00 (0.96-4.16)	1.85 (0.86-3.99)

[a] Adjusted for tenosynovitis
[b] Adjusted for tenosynovitis, age and gender
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.
MCP: metacarpophalangeal, MTP: metatarsophalangeal, OR: odds ratio, CI: confidence interval

(1.05-2.68), Table S2). In multivariable analyses including both inflammatory features only synovitis remained significant (OR 1.90 (1.16-3.13), Figure 1A), also after further correction for age and gender (Figure 1A, Supplementary Table 2). Thus, a positive squeeze test is a measure of subclinical synovitis, with a sensitivity of 44% (95%CI 33-55) and specificity of 72% (68-76). When analysing MCP- and MTP-joints separately, the squeeze test was also associated with subclinical synovitis (OR 2.08 (1.02-4.22) and 2.13 (1.10-4.12) respectively in univariable analyses; Figure 1B-C, Supplementary Table 2).

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 (HR 1.57 (0.77-3.19), Supplementary Table 3). 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 (0.59-3.31), whilst tenosynovitis was associated (HR 4.94 (2.03-12.06), Supplementary Table 4).

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 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, 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 counterintuitive, 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 is 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.

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Supplementary File 1 – Detailed description of methods

Patients

Between April 2015 and October 2018 315 patients were consecutively included in the Leiden Clinically Suspect Arthralgia (CSA)-cohort. Inclusion criteria were recent-onset (<1 year) arthralgia of small joints and 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 (e.g. osteoarthritis, fibromyalgia). Per definition, patients were excluded if arthritis was detected upon physical examination. At baseline visits physical examination was performed, questionnaires filled, blood samples taken and MRI performed. Physical examination included the squeeze test that was performed by rheumatologists; compression across the knuckles of metacarpophalangeal (MCP)- and metatarsophalangeal (MTP)-joints with the force of a firm handshake, it was considered positive if tenderness was induced, as described previously.[1] In line with national guidelines for general practitioners in the Netherlands, patients with suspected arthralgia or arthritis were referred to our outpatient clinic without antibody testing.[2] Therefore antibody status was mostly unknown during inclusion in the CSA-cohort, which took place at the first visit to the outpatient clinic. Thus at the time of the squeeze test rheumatologists were blind to this information. The MRI was made and scored blinded to any clinical data and rheumatologists were never informed on MRI-findings. Follow-up visits were scheduled at 4, 12 and 24 months. When necessary, for instance in case of an increase of symptoms or when patients experienced joint swelling, additional visits were planned. Follow-up ended when patients developed arthritis (determined at physical examination of joints by the treating rheumatologist), or else after 2 years. The cohort has been described in detail previously.[3]

During follow-up treatment with disease-modifying antirheumatic drugs (DMARDs, including steroids) was not allowed. However, CSA-patients with MRI-detected subclinical inflammation could participate in a randomized double-blind placebo-controlled trial (RCT; Treat Earlier, trial registration number: NTR4853), studying the effect of Methotrexate in preventing progression to RA. This RCT is still ongoing; patients enrolled in this trial (n=79) were excluded from longitudinal follow-up in the CSA cohort (Supplementary Figure 1).

MRI scanning and scoring protocol

Contrast-enhanced MRI was made of MCP(2-5)- and MTP(1-5)-joints of the most painful side (in case of equally severe symptoms on both sides, the dominant side was scanned). MRI was performed on a MSK-extreme 1.5T extremity MRI system (GE,

Wisconsin, USA) using a 145mm coil for the foot and a 100mm coil for the hand. The patient was positioned in a chair beside the scanner, with the hand or foot fixed in the coil with cushions.

In the hand (MCP-joints 2-5) the following sequence was acquired before contrast administration: T1-weighted fast spin-echo (FSE) sequence in the coronal plane (repetition time (TR) 575 ms, echo time (TE) 11.2 ms, acquisition matrix 388×288, echo train length (ETL) 2). After intravenous injection of gadolinium contrast (gadoteric acid, Guerbet, Paris, France, standard dose of 0.1 mmol/kg) the following sequences were obtained: T1-weighted FSE sequence with frequency selective fat saturation (fatsat) in the coronal plane (TR/TE 700/9.7ms, acquisition matrix 364×224, ETL 2), T1-weighted FSE fatsat sequence in the axial plane (TR/TE 570/7.7 ms; acquisition matrix 320x192; ETL 2).

The obtained post-contrast sequences of the forefoot (MTP-joints 1-5) were: T1-weighted FSE fatsat sequence in the axial plane (TR/TE 700/9.5ms; acquisition matrix 364x224, ETL 2) and: T1-weighted FSE fatsat sequence in the coronal plane (perpendicular to the axis of the metatarsals) (TR/TE 540/7.5ms; acquisition matrix 320x192, ETL 2).

Field-of-view was 100mm for the hand and 140mm for the foot. Coronal sequences of the hand had 18 slices with a slice thickness of 2mm and a slice gap of 0.2mm. Coronal sequences of the foot had 20 slices with a slice thickness of 3mm and a slice gap of 0.3mm. All axial sequences had a slice thickness of 3mm and a slice gap of 0.3mm with 16 slices for the MCP-joints and 14 for the MTP-joints.

All joints were scored semi-quantitatively according to the validated RA MRI scoring system (RAMRIS). Synovitis was scored on a range 0-3 based on the volume of enhancing tissue in the synovial compartment (none, mild, moderate, severe).[4] Similar to methods described by Haavardsholm et al. the tenosynovitis-score was based on the thickness of peritendinous effusion or synovial proliferation with contrast enhancement (normal, <2mm, 2-5mm, >5mm (range 0-3)).[5]

Scoring was performed independently by two trained readers. Interreader and intrareader intraclass correlation coefficients were ≥0.91 and ≥0.92, respectively.

Mean scores from both readers were used, in case of disagreement between readers the lowest score was used. Then, as MRI-detected subclinical inflammation also can be present in the general population, scores were dichotomized with MRI-data of symptom-free controls as reference (n=193, as published previously).[6] Patients were

considered positive for an inflammatory feature (synovitis or tenosynovitis) if the feature (with the observed severity) was present in <5% of symptom-free controls at the same location and in the same age category (<40, 40-59, ≥60).

Outcome

The main outcome for longitudinal analyses was development of clinically apparent inflammatory arthritis (IA), determined by the rheumatologist (who was blinded to MRI-data but not to other general laboratory investigations including auto-antibody status) at physical examination.

Statistics

First the association of a positive squeeze test (including data of hands and feet) with MRI-detected inflammation was studied with generalized estimating equations (GEE), accounting for the fact that every patient contributed both a hand and a foot to the analysis. In this analysis unilateral data (same side for MRI and squeeze test) was used. Multivariable GEE analyses were adjusted for age and gender. Subanalyses were performed for the squeeze test at only MCP- or only MTP-joints separately.

The predictive value of the squeeze test for development of IA was studied with cox regression. Time-to-event was determined as the time from inclusion until the first time IA was observed by the rheumatologist. Patients who did not develop IA were censored at the date of their 2-year visit, or, when current follow-up was shorter than 2 years, at the date of the last visit, or for patients that were still being followed at the date all medical files were last checked for IA development (28 December 2018). Multivariable cox regression was corrected for regular predictors age, gender, CRP and ACPA-status.

P-values <0.05 were considered statistically significant. IBM SPSS Statistics Version 25 was used.

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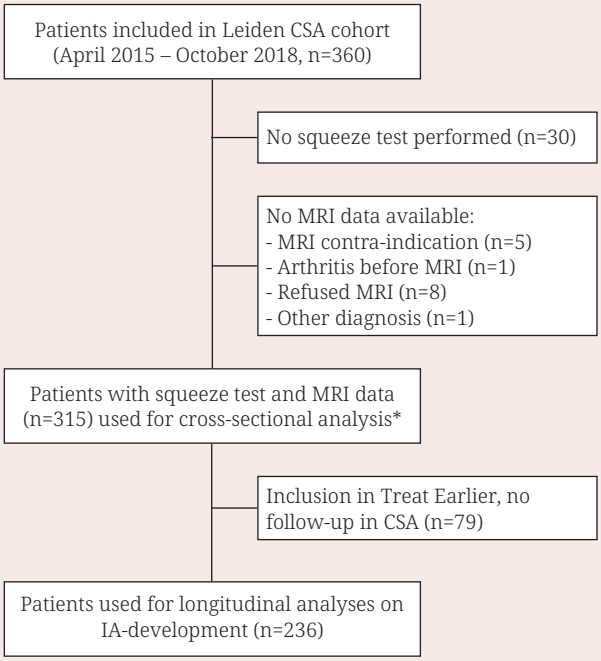
Supplementary Figure 1. Patient selection flowchart



Patients used for longitudinal analyses (n=236) had a median follow-up of 22 months (95% CI 20-24), 33 (14%) developed IA.
*11 hands or feet had no data of MRI and squeeze test at the same side and were not included in the analysis, hence the GEE included 619 extremities of 315 patients.

Supplementary Table 1. Baseline characteristics of the studied CSA-patients

	Total source population CSA-cohort (n=360)	Patients included in cross-sectional analysis: squeeze test and MRI inflammation (n=315)	Patients included in longitudinal analysis: squeeze test and IA development (n=236)
Age in years, mean (SD)	43.7 (12.4)	43.8 (12.3)	43.2 (12.0)
Female, n (%)	264 (73.3)	230 (73.0)	182 (77.1)
Symptom duration in weeks, median (IQR)	20 (8-48)	20 (9-46)	21 (10-50)
68-TJC , median (IQR)	5 (2-10)	5 (2-10)	5 (2-11)
ACPA positivity (≥7 U/mL), n (%)	52 (14.4)	46 (14.6)	31 (13.1)
RF positivity (≥3.5 IU/mL), n (%)	77 (21.4)	63 (20.0)	42 (17.8)
Increased CRP (≥5 mg/L), n (%)	77 (22.6)	66 (21.9)	41 (18.3)
Positive squeeze test MCP and/or MTP joints, n (%)	164 (49.7)	160 (50.8)	120 (50.8)
Presence of morning stiffness ≥60 minutes, n (%)	127 (36.2)	107 (35.0)	76 (32.9)
Family history positive for RA, n (%)	82 (23.2)	73 (23.3)	44 (18.8)

See the flowchart in Supplementary Figure 1 for the description of patient selection; patient characteristics were similar between the total source population and the studied groups, which argues against important selection bias.
CSA: clinically suspect arthralgia, SD: standard deviation, IQR: interquartile range, TJC: tender joint count, ACPA: anti-citrullinated protein antibody, RF: rheumatoid factor, CRP: c-reactive protein, MCP: metacarpophalangeal, MTP: metatarsophalangeal, RA: rheumatoid arthritis

Supplementary Table 2. Associations between the squeeze test and MRI-detected subclinical inflammation in patients with CSA

Analyses on MCP- and MTP-joints	**Negative squeeze test (n=435)**	**Positive squeeze test (n=184)**	**Univariable**	**Multivariable[a]**	**Multivariable[b]**
	Prevalence, n (%)	*OR (95% CI)*	*OR (95% CI)*	*OR (95% CI)*	
Synovitis	45 (10.3)	35 (19.0)	2.10 (1.30-3.40)	1.90 (1.16-3.13)	1.88 (1.14-3.11)
Tenosynovitis	52 (12.0)	32 (17.4)	1.68 (1.05-2.68)	1.37 (0.85-2.22)	1.46 (0.89-2.38)
Analyses on MCP-joints only	**Negative squeeze test MCP (n=207)**	**Positive squeeze test MCP (n=103)**			
Synovitis	18 (8.7)	17 (16.5)	2.08 (1.02-4.22)	2.04 (0.98-4.25)	2.00 (0.96-4.16)
Tenosynovitis	34 (16.4)	20 (19.4)	1.23 (0.67-2.26)	1.06 (0.56-2.00)	1.12 (0.60-2.09)
Analyses on MTP-joints only	**Negative squeeze test MTP (n=228)**	**Positive squeeze test MTP (n=81)**			
Synovitis	27 (11.8)	18 (22.2)	2.13 (1.10-4.12)	1.83 (0.86-3.92)	1.85 (0.86-3.99)
Tenosynovitis	18 (7.9)	12 (14.8)	2.02 (0.93-4.40)	1.42 (0.58-3.50)	1.51 (0.61-3.73)

[a] Multivariable analyses including synovitis and tenosynovitis
[b] Multivariable analyses including synovitis, tenosynovitis, age and gender
CSA: clinically suspect arthralgia, MCP: metacarpophalangeal, MTP: metatarsophalangeal, OR: odds ratio, CI: confidence interval

Supplementary Table 3. Results from multivariable analysis including the squeeze test for the development of inflammatory arthritis

	Multivariable Cox regression	
	HR (95% CI)	*p-value*
Positive squeeze test	1.57 (0.77-3.19)	0.22
Age	1.02 (0.99-1.05)	0.27
Gender	1.61 (0.73-3.55)	0.24
Increased CRP	1.69 (0.77-3.74)	0.19
ACPA positivity	7.81 (3.77-16.2)	<0.001

73% of the patients that progressed to IA fulfilled the 2010 or 1987 criteria for RA at the time of IA-development, 3% were diagnosed with psoriatic arthritis and 24% had undifferentiated arthritis. HR: hazard ratio, CI: confidence interval, CRP: c-reactive protein, ACPA: anti-citrullinated protein antibody

Supplementary Table 4. Results from multivariable analysis including MRI-detected subclinical synovitis and tenosynovitis for the development of inflammatory arthritis

	Multivariable Cox regression	
	HR (95% CI)	*p-value*
MRI-detected synovitis	1.40 (0.59-3.31)	0.45
MRI-detected tenosynovitis	4.94 (2.03-12.06)	<0.001
Age	1.00 (0.97-1.03)	0.97
Gender	1.72 (0.79-3.75)	0.18
Increased CRP	1.41 (0.65-3.06)	0.38
ACPA positivity	4.17 (1.84-9.48)	0.001

HR: hazard ratio, CI: confidence interval, CRP: c-reactive protein, ACPA: anti-citrullinated protein antibody