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Early clinical and imaging features of rheumatoid arthritis: towards a more complete picture

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Chapter 8

Which inflamed tissues explain a positive metatarsophalangeal squeeze test? A large imaging study to clarify a common diagnostic procedure

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ABSTRACT

Objectives. The squeeze test of metatarsophalangeal (MTP) joints is frequently used, because it is easy and cheap. It is traditionally perceived as a test for synovitis. Besides classic intra-articular synovitis, also tenosynovitis and intermetatarsal bursitis (IMB) represent synovial inflammation, albeit juxta-articularly located. Both are frequently present in RA and occasionally in other arthritides. Therefore, we hypothesised that tenosynovitis and IMB contribute to a positive MTP squeeze test.

Methods. A cross-sectional study design was used. 192 early arthritis patients and 693 clinically suspect arthralgia (CSA) patients underwent the MTP squeeze test and forefoot MRI at first presentation. MRI measurements in age-matched healthy controls were used to define positivity for synovitis, tenosynovitis and IMB. Logistic regression was used.

Results. In early arthritis patients synovitis (OR 4.8 (95%CI 2.5–9.5)), tenosynovitis (2.4 (1.2–4.7)) and IMB (1.7 (1.2–2.6)) associated with MTP squeeze test positivity. Synovitis (3.2 (1.4–7.2)) and IMB (3.9 (1.7–8.8)) remained associated in multivariable analyses. Of patients with a positive MTP squeeze test, 79% had synovitis or IMB: 12% synovitis, 15% IMB and 52% both synovitis and IMB. In CSA patients, subclinical synovitis (3.0 (2.0–4.7)), tenosynovitis (2.7 (1.6–4.6)) and IMB (1.7(1.2–2.6)) associated with MTP squeeze test positivity, with the strongest association for synovitis in multivariable analysis. Of positive MTP squeeze tests, 39% had synovitis or IMB: 10% synovitis, 15% IMB and 13% both synovitis and IMB.

Conclusion. Besides synovitis, IMB contributes to pain upon compression in early arthritis, presumably due to its location between MTP joints. This is the first evidence showing that MTP squeeze test positivity is not only explained by intra- but also juxta-articular inflammation.

KEY MESSAGES

- Juxta-articular synovial inflammation (tenosynovitis and/or intermetatarsal bursitis) is frequently present in RA and occasionally in other arthritides.
- Positivity of the MTP squeeze test in early arthritis is explained not only by intra-articular synovitis but also intermetatarsal bursitis.
- Clinicians may consider that the MTP squeeze test not only tests for intra-articular but also juxta-articular inflammation.

INTRODUCTION

The squeeze test of metacarpophalangeal (MCP) and metatarsophalangeal (MTP) joints is frequently used in clinical practice to assist diagnosis of arthritis and for disease monitoring, since it is easy, cheap and time-efficient: it consists of simply tangentially compressing the MCPs or MTPs and is positive when this is unduly painful.[1-5]

For proper interpretation of diagnostic tests it is essential to know what causes positive results. Traditionally, a positive squeeze test is interpreted as a sign of synovitis at compressed joints. Previous imaging studies in early arthritis and arthralgia patients indeed demonstrated an association with synovitis.[6-8] However, recent imaging studies have also demonstrated that, besides intra-articular synovitis, juxta-articular synovitis also occurs in two forms in the forefoot: intermetatarsal bursitis (IMB) which represents inflammation of the synovium-lined intermetatarsal bursae, and tenosynovitis which represents inflammation of the sheaths around flexor/extensor tendons at small joints.[9-11] IMB and tenosynovitis are strongly associated with RA and occasionally present in other arthritides.[9] Whilst the contribution of local inflammation at MCP joints to positivity of the squeeze test was studied extensively, the contribution of IMB to MTP squeeze test positivity is unknown and the contribution of tenosynovitis was only partially studied.[7]

Thus, our comprehension of the frequently used MTP squeeze test requires updating. We hypothesised that IMB and tenosynovitis contribute to MTP squeeze test positivity. A large MRI study in early arthritis and clinically suspect arthralgia (CSA) patients was performed to assess this.

METHODS

Patients

We studied 192 early arthritis patients from the Leiden Early Arthritis Clinic (EAC) cohort, which enrolls patients with clinically apparent early arthritis (symptom duration <2 years; including RA as well as other arthritides). Secondly, 567 CSA patients from the Leiden CSA cohort were studied, which concerns patients presenting with recent onset (<1 year) arthralgia of small joints with increased risk of RA development according to the clinical expertise of their rheumatologist. In addition, we studied 126 CSA patients at baseline participating in the TREAT EARLIER trial, a randomised controlled trial testing whether methotrexate prevents progression to clinical arthritis in CSA patients with subclinical MRI inflammation (synovitis, tenosynovitis and/or osteitis).

All three cohorts were described previously.[12-14] Importantly, CSA excludes patients with clinically apparent arthritis, or in whom another cause of the arthralgia (e.g. osteoarthritis, fibromyalgia) was more likely. Patients were included regardless of auto-antibody status. We consecutively included all patients who underwent forefoot MRI and the MTP squeeze test (online Supplementary Data S1 presents details on inclusion, including a flowchart).

The study was conducted in compliance with the Helsinki Declaration. All patients provided written informed consent.

Squeeze test

In each cohort, at baseline the MTP squeeze test was performed, which was positive when compression of the MTP joints was unduly painful. Assessors were blinded for MRI scores, providing unbiased outcome assessment.

MRI scanning and scoring

Contrast-enhanced 1.5T-MRI was made of the MTP joints on the side with most symptoms, or the dominant side when symptom severity was symmetrical. Details on MRI scanning and scoring are presented supplementary (online Supplementary Data S2).

In short, IMB was considered present in case of bursal contrast-enhancement in the superior intermetatarsal space (with or without rim-enhancement) on ≥ 2 consecutive slices in the axial and coronal plane, as described previously.[10] At each intermetatarsal space, IMB presence and its dorsoplantar dimension in millimeters were recorded. In addition, MRIs were evaluated for synovitis and tenosynovitis in line with the RA MRI scoring system (RAMRIS).[15]

Inter- and intra-reader reliability (intraclass correlation coefficients (ICCs); ≥ 0.85 for IMB, ≥ 0.84 for tenosynovitis, ≥ 0.90 for synovitis) were published previously.[10,15] MRI readers were blinded for clinical data.

To prevent false positivity, positivity for MRI-features was defined using healthy controls as a reference.[16,17] IMB, synovitis or tenosynovitis were deemed present only if scored in a severity that was present at the same location in $< 5\%$ of age-matched healthy controls. Reference scores were acquired from 193 healthy controls who were scanned using the same MRI machine and scan protocol previously.[18]

Statistical analyses

Logistic regression assessed associations of IMB, tenosynovitis and synovitis with MTP squeeze test positivity. Multivariable logistic regression models adjusted for sex

and simultaneous presence of inflammation features by entering IMB, synovitis and tenosynovitis presence at the MTP joints as separate independent variables. Nagelkerke R^2 was used to assess the explained variance in MTP squeeze test positivity.

IBM-SPSS (v25) was used. Two-sided p-values <0.05 were considered statistically significant.

RESULTS

Patients

192 early arthritis and 693 CSA patients were studied. The MTP squeeze test was positive in 27% of early arthritis patients and 29% of CSA patients. Patient characteristics are presented in Table 1 (online also available as Supplementary Table S1).

Table 1. Patient characteristics

	Cohort 1 Early arthritis n = 192	Cohort 2 CSA n = 567	Cohort 3 CSA n = 126
Age in years, mean \pm SD	57 \pm 15	44 \pm 13	47 \pm 11
Female, n (%)	102 (53)	425 (75)	82 (65)
Symptom duration in weeks, median (IQR)	9 (4–22)	20 (9–44)	30 (19–47)
TJC, median (IQR)	3 (2–5)	5 (2–9)	4 (2–9)
SJC, median (IQR)	3 (1–7)	0	0
ACPA-positive, n (%)	45 (23)	78 (14)	32 (25)
RF-positive, n (%)	60 (31)	110 (19)	36 (29)
Increased CRP (\geq 5 mg/L), n (%)	113 (59)	128 (23)	36 (29)
Presence of MRI inflammation at \geq 1 MTP joint			
Synovitis, n (%)	70 (36)	71 (13)	23 (18)
Tenosynovitis, n (%)	55 (29)	47 (8)	11 (9)
Intermetatarsal bursitis, n (%)	73 (38)	126 (22)	22 (17)
Positive MTP squeeze test, n (%)	52 (27)	156 (28)	45 (36)

Cohort 1: Leiden Early Arthritis Clinic

Cohort 2: Leiden CSA cohort

Cohort 3: TREAT EARLIER trial participants not included from the Leiden CSA cohort

Abbreviations: CSA = clinically suspect arthralgia; SD = standard deviation; IQR = interquartile range; TJC = tender joint count (68 joints); SJC = swollen joint count (66 joints); ACPA = anti-citrullinated protein antibodies; RF = IgM rheumatoid factor; CRP = C-reactive protein; MRI = magnetic resonance imaging; MTP = metatarsophalangeal; TREAT EARLIER = Treat Early Arthralgia to Reverse or Limit Impending Exacerbation to Rheumatoid arthritis

Early arthritis patients

In early arthritis patients synovitis (OR 4.8 (95%CI 2.5–9.5)), tenosynovitis (2.4 (1.2–4.7)) and IMB (1.7 (1.2–2.6)) on MRI associated with MTP squeeze test positivity (Table 2; online also available as Supplementary Table S2). Synovitis (3.2 (1.4–7.2)) and IMB (3.9 (1.7–8.8)) remained independently associated with MTP squeeze test positivity in multivariable analyses adjusted for sex and simultaneous presence of MRI features. Tenosynovitis was not independently associated with MTP squeeze test positivity (0.8 (0.3–1.8)). Although we did not anticipate that osteitis would contribute to a positive MTP squeeze test, the multivariable analyses were repeated including osteitis as well. This showed similar results for synovitis, IMB and tenosynovitis, and no significant association for osteitis.

Table 2. The relation between presence of synovitis, tenosynovitis or intermetatarsal bursitis on forefoot MRI and positivity of the MTP squeeze test

	Univariable OR (95%CI)	Multivariable [#] OR (95%CI)
Early arthritis patients (cohort 1)		
Synovitis	4.8 (2.5–9.5)	3.2 (1.4–7.2)
Tenosynovitis	2.4 (1.2–4.7)	0.8 (0.3–1.8)
Intermetatarsal bursitis	5.5 (2.8–11.0)	3.9 (1.7–8.8)
CSA patients (cohort 2)		
Synovitis	2.6 (1.6–4.4)	2.0 (1.1–3.6)
Tenosynovitis	2.8 (1.5–5.1)	1.7 (0.8–3.4)
Intermetatarsal bursitis	1.7 (1.1–2.6)	1.2 (0.8–2.0)
CSA patients (cohort 3)		
Synovitis	4.6 (1.8–11.9)	4.1 (1.5–11.5)
Tenosynovitis	2.3 (0.7–8.1)	1.3 (0.3–5.9)
Intermetatarsal bursitis	2.1 (0.8–5.2)	1.2 (0.4–3.7)
All CSA patients (cohorts 2 & 3)		
Synovitis	3.0 (2.0–4.7)	2.5 (1.5–4.1)
Tenosynovitis	2.7 (1.6–4.6)	1.5 (0.8–2.9)
Intermetatarsal bursitis	1.7 (1.2–2.6)	1.2 (0.8–1.8)

[#] Adjusted for sex and presence of the other two MRI inflammation features

Cohort 1: Leiden Early Arthritis Clinic

Cohort 2: Leiden CSA cohort

Cohort 3: TREAT EARLIER trial participants not included from the Leiden CSA cohort

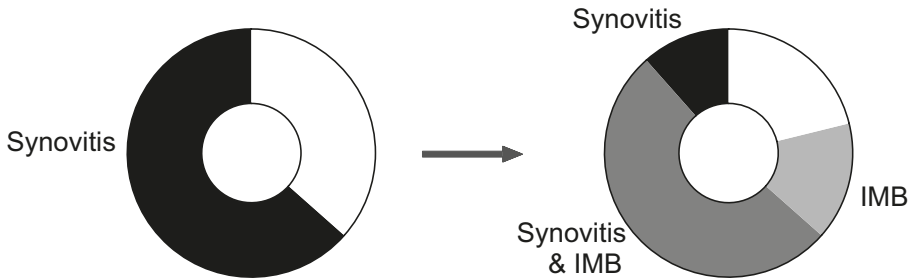
Abbreviations: MRI = magnetic resonance imaging; MTP = metatarsophalangeal; OR = odds ratio;

CI = confidence interval; CSA = clinically suspect arthralgia;

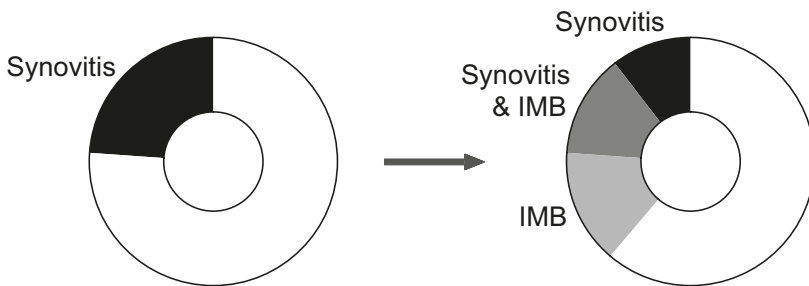
TREAT EARLIER = Treat Early Arthralgia to Reverse or Limit Impending Exacerbation to Rheumatoid arthritis

Figure 1. Presence of synovitis, IMB and simultaneous presence of synovitis and IMB in patients (A: early arthritis, B: CSA) with a positive MTP squeeze test

A. Early arthritis



B. Clinically suspect arthralgia (CSA)



Left: the situation wherein only synovitis is considered to explain test positivity.

Right: the situation wherein, in addition to synovitis, IMB is considered to explain test positivity.

The total surface of each chart represents all MTP squeeze test positive patients.

Shaded areas represents patients in whom local inflammation was detected on forefoot MRI.

Blank areas represent patients in whom test positivity is unexplained by MRI-detected inflammation.

Percentages:

A, left: synovitis = 63% **A**, right: synovitis = 12%; synovitis & IMB = 52%; IMB = 15%

B, left: synovitis = 24% **B**, right: synovitis = 10%; synovitis & IMB = 13%; IMB = 15%

Abbreviations: IMB = intermetatarsal bursitis; MTP = metatarsophalangeal; CSA = clinically suspect arthralgia.

Next, we assessed the increase in explained variance of MTP squeeze test positivity by including IMB in the multivariable model. The Nagelkerke R^2 value of the model including synovitis was 19%, which increased statistically significantly to 26% when IMB was added to the model ($p=0.001$ by likelihood-ratio test).

To visualise how often IMB and synovitis underlie a positive MTP squeeze test, frequencies of both features separately and their simultaneous presence were plotted and compared with the situation wherein only synovitis would be considered explanatory for positivity of the MTP squeeze test (Figure 1A). Of early arthritis-patients with a

positive MTP squeeze test, 63% had MRI-detected synovitis (irrespective of IMB). Of these, 52 percentage points in fact comprised synovitis combined with IMB. Additionally, 15% had IMB without synovitis. 21% of early arthritis patients with a positive MTP squeeze test did not have synovitis or IMB. Test characteristics with MRI-detected local inflammation as outcome are presented supplementary (online Supplementary Table S3).

Figure 2. Example images of the execution of the MTP squeeze test (A); IMB (B), synovitis (C) and tenosynovitis (D) on forefoot-MRI



A. The MTP squeeze test was performed as described previously by van den Bosch et al.[6] The assessor places his/her thumb and fingers laterally and medially on the patient's forefoot, at the level of the MTP joints, and applies a compressive force equivalent to a firm handshake.

B–D. Axial T1-weighted gadolinium post-contrast MR-images at the level of the metatarsal heads. Contrast-enhancement of the bursa between the 3th and 4th metatarsals is present, consistent with IMB (arrow). Contrast-enhancement of the synovium lining the 4th MTP joint is present, consistent with synovitis (arrowhead). Contrast-enhancement is present around the flexor tendon at the 2nd MTP joint, consistent with tenosynovitis (dotted arrow).

Abbreviations: MTP = metatarsophalangeal; MRI = magnetic resonance imaging; IMB = intermetatarsal bursitis.

CSA patients

In CSA patients synovitis (3.0 (2.0–4.7)), tenosynovitis (2.7 (1.6–4.6)) and IMB (1.7 (1.2–2.6)) on MRI associated with MTP squeeze test positivity (Table 2). In multivariable analyses, synovitis remained independently associated (2.5 (1.5–4.1)) whilst tenosynovitis (1.5 (0.8–2.9)) and IMB did not (1.2 (0.8–1.8)). Also here, when osteitis was added to the model this was not associated with a positive MTP squeeze test and results for synovitis, IMB and tenosynovitis were similar. Of CSA patients

with a positive MTP squeeze test, 24% had synovitis on MRI (Figure 1B). Of these, 13 percentage points also had IMB. Additionally, 15% had IMB without synovitis. 61% of early arthritis patients with a positive MTP squeeze test did not have synovitis or IMB.

Examples of the MTP squeeze test and MRI-detected IMB, synovitis and tenosynovitis are presented in Figure 2.

DISCUSSION

The MTP squeeze test is regularly used to test for synovitis. However, recent imaging studies demonstrated that not only intra-articular synovitis but also juxta-articular synovial inflammation (IMB and tenosynovitis) is frequently present in the forefeet in RA and occasionally in other arthritides.[9,11] We hypothesised that IMB and tenosynovitis contribute to MTP squeeze test positivity. Our study showed that not only synovitis but also IMB associated independently with MTP squeeze test positivity in early arthritis. This is the first evidence that MTP squeeze test positivity is not only explained by intra- but also juxta-articular synovial inflammation.

Presumably, IMB contributes to MTP squeeze test positivity because of its location between the MTP joints. Thus, when performing the MTP squeeze test, clinicians should realise that they are not only testing for intra-articular synovitis but also for IMB, which is a form of juxta-articular synovial inflammation with high specificity for RA.[9] In patients with CSA, IMB is associated with future RA development.[17] Although the squeeze test alone may not be sufficient in detecting or excluding arthritis of MTP joints, our findings expand the scientific basis for its use as a complementary diagnostic tool as part of the total clinical evaluation of patients with suspected early arthritis.

Our findings also add to mounting evidence that juxta-articular inflammation contributes to typical symptoms and signs of arthritis, in addition to intra-articular inflammation.[10,11] Previous research showed that IMB may co-occur with higher frequencies of other imaging-depicted inflamed tissues in the forefoot and that it associates with systemic measures of inflammation and disease activity, and with functional limitations.[9,10,17,19,20] Moreover, MRI-detected IMB and tenosynovitis contribute to joint tenderness and joint swelling in early arthritis, independent from other forefoot inflammation, while this association was not found for synovitis. Together with current findings, this implies that the clinical picture of early arthritis depends not only on intra-articular but also juxta-articular synovial inflammation.

While in multivariable analyses synovitis contributed to MTP squeeze test positivity in both early arthritis and CSA patients, IMB contributed only in early arthritis and not in CSA patients. This finding, which is in line with a previous study showing that in CSA synovitis is the most important contributor to local joint tenderness,[21] may relate to the fact that most CSA patients do not develop clinical arthritis (the percentage of progression is roughly 20%). Additionally, MRI-detected subclinical inflammation is less prevalent in the phase of CSA than in early arthritis. Likewise, IMB presence was 21% in CSA patients and 38% in early arthritis patients. Possibly, IMB severity may increase during development of arthritis and does not yet reach the threshold of inducing compression pain in part of CSA patients.

In line with the complexity of forefoot anatomy, additional anatomical structures may be involved in MTP squeeze test positivity. Morton's neuroma co-occurring with IMB may have contributed to MTP squeeze test positivity. Both features can be imaged using contrast-enhanced MRI, but IMB associates with RA more strongly and has higher sensitivity for RA and for other arthritides. Smaller Morton's neuromas may be difficult to discern from IMB.[9] Therefore, the current study focused on IMB and Morton's neuroma was not assessed separately. However, to prevent interference of Morton's neuroma with IMB measurements, any plantar protrusion from the bursa that exceeded the deep transverse metatarsal ligament (the location of the plantar nerve, from which Morton's neuromas originate) was not included in IMB measurements, as reported previously.[9,10]

There were some limitations. Firstly, deviations of forefoot bones (e.g. hallux valgus and hammer toes) were not specifically accounted for as no weightbearing radiographs were available. Secondly, validated scoring methods for IMB are non-existent. Therefore, IMB was scored using an approach that was developed locally in collaboration with an MSK radiologist with >20 years of experience.[9,10] Reliability measures were reassuring (inter- and intra-reader ICCs ≥ 0.85 ; online Supplementary Data S2). Strengths of our study include the large sample size and the adjustment of MRI findings for normal variations.

In conclusion, this large cross-sectional MRI study in early arthritis and CSA patients examined the contribution of IMB and tenosynovitis to positivity of the MTP squeeze test. Although traditionally assumed to screen for synovitis, we demonstrated that also IMB contributes to positivity of the test in early arthritis patients. These findings may enhance understanding of this frequently used procedure among clinicians. Moreover, these data show that besides intra-articular synovial inflammation, juxta-articular synovial inflammation also contributes to the clinical picture and diagnostics of early arthritis and RA.

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