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BRIEF REPORT

Walking Disabilities in Association With Tenosynovitis at the Metatarsophalangeal Joints: A Longitudinal Magnetic Resonance Imaging Study in Early Arthritis

Yousra J. Dakkak,  Fenne Wouters,  Xanthe M. E. Matthijssen,  Monique Reijnierse, and Annette H. M. van der Helm-van Mil

Objective. The relationship between functional disability and magnetic resonance imaging (MRI) inflammation has been studied for the hands, but has not been well established for the feet, even though walking difficulties are common. Therefore, our objective was to study whether walking difficulties were associated with MRI inflammation at metatarsophalangeal (MTP) joints in early arthritis patients, at diagnosis and during 24 months of follow-up.

Methods. A total of 532 consecutive patients presenting with early arthritis reported on the presence and severity of walking difficulties (Health Assessment Questionnaire question 4a, scale 0–3), and underwent unilateral contrast-enhanced MRI of MTP joints 1–5 at baseline. In total, 107 patients had clinical and MRI data at follow-up (4, 12, and 24 months). MRI inflammation (synovitis, tenosynovitis, and osteitis) was scored in line with the Rheumatoid Arthritis Magnetic Resonance Imaging Scoring system. At baseline, the association of walking disability with MRI inflammation was assessed using regression. Longitudinally, the association between a change in walking disability with a change in MRI inflammation was studied with linear mixed models.

Results. At baseline, 81% of patients with walking disabilities had MRI inflammation at MTP joints, versus 68% without walking disabilities ($P < 0.001$). Total MRI inflammation (i.e., the sum of tenosynovitis, synovitis, and osteitis) was associated with severity of walking disability ($\beta = 0.023$, $P < 0.001$). Studying the MRI features separately, tenosynovitis, synovitis, and osteitis were all univariably associated with severity of walking disability ($P < 0.001$, $P < 0.001$, and $P = 0.014$, respectively). In multivariable analysis, the association was strongest for tenosynovitis. During follow-up, a decrease in MTP inflammation was associated with a decrease in walking disability ($\beta = 0.029$, $P = 0.001$); in multivariable analyses only, tenosynovitis was independently associated ($\beta = 0.073$, $P = 0.049$).

Conclusion. Of the different inflamed tissues in MTP joints, predominantly MRI-detected tenosynovitis was associated with walking disabilities. Likewise a reduction in tenosynovitis related to a decrease in walking disabilities. These results increase our understanding of the involvement of tenosynovitis in walking disabilities in early arthritis.

INTRODUCTION

Rheumatoid arthritis (RA) is a disease that involves the small joints of the hands and feet. The focus in research, however, has primarily been on the hands (1), though 80% of patients report disease-related foot problems and 71% report walking difficulties (2). These difficulties have an important impact on the quality of life of patients that is often underestimated by clinicians (3) and is

associated with clinical factors such as inflammation, pain, and duration of disease (2,3).

Magnetic resonance imaging (MRI) is increasingly used in RA research, as it sensitively detects inflammation, defined as tenosynovitis, synovitis, and osteitis. The association between walking difficulties and MRI inflammation has not been fully explored for the forefoot. Two previous reports have included MRI data of the metatarsophalangeal (MTP) joints, but these were not

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SIGNIFICANCE & INNOVATIONS

- Walking disability at diagnosis is associated with magnetic resonance imaging (MRI) inflammation at metatarsophalangeal joints; this association was strongest for tenosynovitis.
- A treatment-induced decrease of MRI inflammation, particularly tenosynovitis, is associated with a reduction in walking disabilities.
- This study increases our understanding of the nature of walking impairments in early arthritis.

contrast-enhanced, and tenosynovitis at the MTP joints was not included (4,5). Additionally, the reports were cross-sectional and thus did not study whether change in MRI inflammation over time related to change in disability.

Therefore, with the aim to increase our understanding of the role of inflammation at the MTP joints in functional disability, we set up a cross-sectional and longitudinal study in early arthritis patients to evaluate the association of walking disabilities with MRI inflammation, defined as tenosynovitis, synovitis, and osteitis at the MTP joints.

PATIENTS AND METHODS

Patients. Between June 2013 and July 2017, 604 consecutive patients newly presenting with clinical confirmed arthritis of ≥ 1 joint and a symptom duration of < 2 years who were naive to disease-modifying antirheumatic drugs (DMARDs) were included in the Leiden Early Arthritis Cohort. The cohort is extensively described elsewhere (6). In short, at baseline, 4 months, 12 months, and yearly thereafter, information was obtained from physical examination, laboratory tests, questionnaires including the Health Assessment Questionnaire (HAQ), and MRI. Included patients were treated in routine care.

Of 604 patients at baseline, 65 had missing HAQ data and 7 had insufficient MRI images. The remaining 532 were studied. A flow chart is shown in Supplementary Figure 1, available on the *Arthritis Care & Research* website at <http://onlinelibrary.wiley.com/doi/10.1002/acr.24452/abstract>. From August 2010 until February 2015, follow-up MRIs were performed in patients with the initial diagnosis of RA or undifferentiated arthritis. From the 532 with complete baseline MRI and HAQ data, follow-up MRI results were available for 107 patients (see Supplementary Table 1, available on the *Arthritis Care & Research* website at <http://onlinelibrary.wiley.com/doi/10.1002/acr.24452/abstract>). The Early Arthritis Cohort was approved by the local medical ethics committee (#P10.108). Informed consent was obtained. The data sets analyzed during the current study are available from the corresponding author on reasonable request.

Assessment of walking disability. The HAQ is a well-validated, widely used questionnaire on functional disability that consists of 20 questions covering different categories of functional activities (4), including 2 questions on walking: question 4a: “are you able to walk outdoors on flat ground?” and question 4b: “are you able to climb up 5 steps?” They are answered as 0 = no difficulty, 1 = some difficulty, 2 = much difficulty, and 3 = unable to do. Question 4a was used as the primary measure of walking disability, because walking outdoors on flat ground was assumed to importantly involve forefoot mechanics. Question 4b was used as an alternative measure in a subanalysis, as climbing stairs was assumed to assess not only forefoot mechanics, but also other joints such as ankle and knee mechanics. Data on walking disability were available at baseline and at 12 and 24 months. The HAQ also evaluates equipment dependency, like walking sticks. Equipment dependency can be the result of disability in different domains, such as the knee or hip. To avoid the introduction of noise, equipment dependency was therefore not incorporated in the analyses, although excluding this dependency from the evaluation can potentially lead to an underestimation of the severity of walking disability.

MRI. Unilateral contrast-enhanced MRI of MTP joints 1–5 of the more painful side, or the dominant side in case of symmetric symptoms, was performed with a 1.5T extremity MRI (General Electric). Baseline MRI was obtained ≤ 2 weeks after the first presentation and before DMARD initiation, with follow-up MRIs at 4, 12, and 24 months. MRIs were scored for tenosynovitis, synovitis, osteitis, and erosions at MTP joints 1–5, in line with the Rheumatoid Arthritis Magnetic Resonance Imaging Scoring system, with researchers blinded from any clinical data. A detailed description is given in Supplementary Appendix A, available on the *Arthritis Care & Research* website at <http://onlinelibrary.wiley.com/doi/10.1002/acr.24452/abstract> (7–9). Total MRI inflammation was defined as the total sum of the semiquantitative scores of tenosynovitis (range 0–30), synovitis (range 0–15), and osteitis (range 0–30) at MTP joints. Follow-up MRI was scored in known time order. Reliability of scoring was excellent (intraclass correlation coefficient ≥ 0.92). Additional information is given in Supplementary Appendix A and Supplementary Figure 2, available on the *Arthritis Care & Research* website at <http://onlinelibrary.wiley.com/doi/10.1002/acr.24452/abstract>).

Statistical analysis. At baseline the association between walking difficulties and total MRI inflammation was assessed using linear regression, with severity of walking disability as the outcome. Although erosions were expected to be infrequent at the time of diagnosis, they were also studied in relation to walking disability. Next, the association of tenosynovitis, synovitis, and osteitis was assessed separately. Univariable and multivariable analyses were performed: multivariable analyses adjusted for the simultaneous presence of different types of MRI inflammation,

because these 3 features often co-occur, and in a separate analysis for the following clinical features: age, 66 swollen joint count (SJC), and C-reactive protein (CRP) level. We adjusted for these factors because they may associate with walking disability and MRI inflammation, and to elucidate whether MRI inflammation is associated with walking disability regardless of the level of systemic and local inflammation (CRP level and SJC, respectively) (6,10). The analyses were repeated for the presence of walking disability as a dichotomous outcome using logistic regression.

To assess whether a change in the severity of walking disability was associated with a change in MRI inflammation, linear mixed models were used. First, the association was studied for total MRI inflammation with walking disability as the outcome. Subsequently, tenosynovitis, synovitis, and osteitis were assessed separately. Also here analyses were performed univariably and multivariably, adjusting for the simultaneous presence of different types of MRI inflammation and for clinical features. Linear mixed models have the advantage that all patient information is used, including for those who had missing data, as this method assumes that missing outcomes can be estimated using available measurements.

RA patients may have more severe inflammation, potentially influencing the relationship between walking difficulties and MRI inflammation. Therefore, as a subanalysis, the analyses between walking difficulties and MRI inflammation at baseline and during follow-up were repeated in the subgroup of RA patients (clinical diagnosis and fulfilment of 1987 or 2010 criteria at 2 weeks).

We prioritized walking difficulties in the main analyses. As a subanalysis we analyzed whether MRI inflammation at MTP joints could possibly also be related to difficulty climbing stairs. Therefore, analyses were repeated with difficulty climbing stairs as the outcome.

RESULTS

Patient characteristics. Of 532 patients with baseline data, the mean age was 58 years, 60% were female, and the mean symptom duration was 10 weeks. Walking disability was present in 202 patients (38%). This finding was comparable in the subgroup of patients who were studied longitudinally. Patient characteristics are shown in Supplementary Table 1, available on the *Arthritis Care & Research* website at <http://onlinelibrary.wiley.com/doi/10.1002/acr.24452/abstract>.

Walking disability and MRI-detected inflammation at baseline.

Mean MRI scores and the results from regression analyses are shown in Tables 1 and 2. At baseline, more severe walking disabilities were associated with more severe total MRI inflammation ($\beta = 0.023$, $P < 0.001$). The severity of walking disability was associated with tenosynovitis, synovitis, and osteitis scores in univariable analyses ($P < 0.001$, $P < 0.001$, and $P = 0.014$, respectively). In a multivariable analysis that included all 3 features, the effect size was largest for tenosynovitis ($\beta = 0.042$, $P = 0.060$). In a separate multivariable analysis, the results for total MRI inflammation and tenosynovitis were adjusted for clinical features (age, SJC, and CRP level); MRI inflammation and tenosynovitis remained associated with walking disability ($P = 0.014$ and $P = 0.042$, respectively). Walking disability was not associated with erosion scores ($P = 0.18$). In additional multivariable analyses, the results for total MRI inflammation and tenosynovitis were adjusted for clinical features and MRI-detected erosions that revealed similar results ($\beta = 0.014$, $P = 0.026$ for MRI inflammation and $\beta = 0.035$, $P = 0.047$ for tenosynovitis, results not shown in tables). Next the association of the

Table 1. Severity of walking disability and the association between MRI-detected inflammation at the MTP joints and walking-disability at disease presentation in 532 early arthritis patients*

	Total inflammation score†	Tenosynovitis score	Synovitis score	Osteitis score	Erosion score
MRI score, mean $\pm$ SD‡					
Disability positive	4.6 $\pm$ 6.3	1.3 $\pm$ 2.2	1.6 $\pm$ 2.1	1.7 $\pm$ 3.2	0.7 $\pm$ 1.1
Disability negative	2.7 $\pm$ 4.1	0.7 $\pm$ 1.4	1.0 $\pm$ 1.5	1.1 $\pm$ 2.1	0.6 $\pm$ 0.9
Univariable analysis					
β (95% CI)	0.023 (0.01, 0.03)	0.064 (0.03, 0.1)	0.063 (0.03, 0.1)	0.029 (0.02, 0.05)	0.043 (-0.02, 0.1)
<i>P</i>	<0.001	<0.001	<0.001	0.014	0.18
Multivariable analysis					
MRI features§					
β (95% CI)	–	0.042 (-0.02, 0.09)	0.026 (-0.02, 0.08)	0.007 (-0.02, 0.04)	–
<i>P</i>	–	0.06	0.27	0.66	–
Clinical features¶					
β (95% CI)	0.015 (0.00, 0.03)	0.036 (0.00, 0.07)	–	–	–
<i>P</i>	0.014	0.042	–	–	–

* Assessed using linear regression. 95% CI = 95% confidence interval; MRI = magnetic resonance imaging; MTP = metatarsophalangeal.

† Defined as the summed scores of tenosynovitis, synovitis, and osteitis.

‡ Mean score of MRI features in patients with walking disability (defined as Health Assessment Questionnaire [HAQ] question 4a = ≥ 1) and patients without walking disability (HAQ question 4a = 0).

§ Multivariable analyses including MRI-detected tenosynovitis, synovitis, and osteitis at the MTP joints.

¶ Multivariable analyses including swollen joint count, age at inclusion, and C-reactive protein level, performed separately for the total inflammation score and for tenosynovitis. Due to the risk of overfitting, this multivariable analysis only included variables that were most importantly associated with walking disability.

Table 2. Presence of walking disability: association between MRI-detected inflammation at the MTP joints and walking disability at disease presentation in 532 early arthritis patients*

	Presence of any inflammation†	Tenosynovitis score	Synovitis score	Osteitis score	Erosion score
MRI feature present, no. (%)‡					
Disability positive	163 (81)	91 (45)	128 (64)	117 (60)	93 (46)
Disability negative	223 (68)	105 (32)	161 (49)	165 (50)	147 (45)
Univariable analysis					
OR (95% CI)	1.08 (1.0, 1.1)	1.22 (1.1, 1.4)	1.21 (1.1, 1.3)	1.10 (1.0, 1.2)	1.12 (0.9, 1.3)
P	<0.001	<0.001	<0.001	0.013	0.23
Multivariable analysis					
MRI features§					
OR (95% CI)	–	1.15 (1.003, 1.31)	1.09 (0.93, 1.27)	1.03 (0.94, 1.12)	–
P	–	0.045	0.29	0.57	–
Clinical features¶					
OR (95% CI)	1.06 (1.02, 1.10)	1.15 (1.03, 1.28)	–	–	–
P	0.005	0.017	–	–	–

* Dichotomous outcome, association assessed using logistic regression. 95% CI = 95% confidence interval; MRI = magnetic resonance imaging; MTP = metatarsophalangeal; OR = odds ratio.

† Defined as the presence of tenosynovitis, synovitis, and/or osteitis.

‡ Presence of an MRI feature in patients with walking disability (defined as Health Assessment Questionnaire [HAQ] question 4a = ≥1) and patients without walking disability (HAQ question 4a = 0).

§ Multivariable analyses including MRI-detected tenosynovitis, synovitis, and osteitis at the MTP joints.

¶ Multivariable analyses including swollen joint count, age at inclusion, and C-reactive protein level, performed separately for the total inflammation score and for tenosynovitis. Due to the risk of overfitting, this multivariable analysis only included variables that were most importantly associated with walking disability.

3 inflammatory features was studied with the presence of walking disability as a dichotomous outcome (Table 2). This analysis revealed similar results (Tables 1 and 2).

Course of walking disability and MRI inflammation during 2 years of follow-up. Then we assessed whether a change in the severity of walking disability was associated with

a change in MRI inflammation during 2 years of follow-up (Figure 1 and Supplementary Table 2, available on the *Arthritis Care & Research* website at <http://onlinelibrary.wiley.com/doi/10.1002/acr.24452/abstract>). A decrease in total MRI inflammation was associated with a decrease in walking disability ($\beta = 0.022$, $P = 0.019$). For the separate features, a decrease in tenosynovitis and synovitis was associated with a decrease

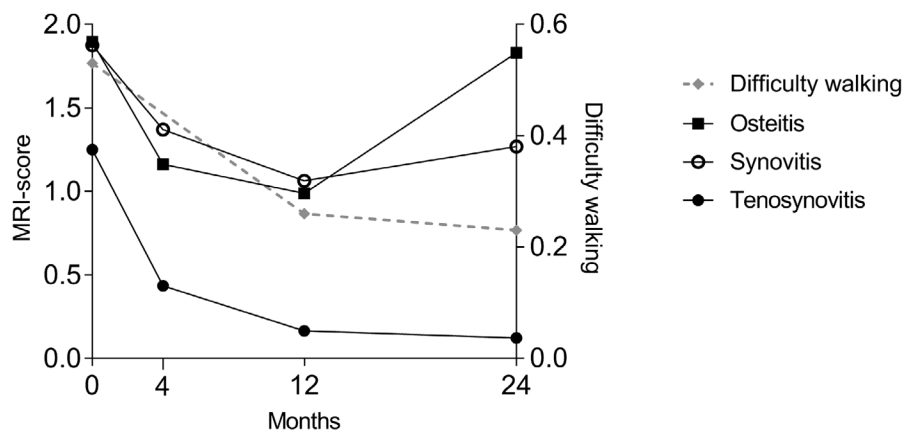


Figure 1. Difficulty walking and magnetic resonance imaging (MRI) mean scores for osteitis, synovitis, and tenosynovitis during 24 months of follow-up. Difficulty walking was assessed by the Health Assessment Questionnaire question 4a: “are you able to walk outdoors on flat ground?” Patients answered on a scale from 0 to 3 (0 = without difficulty, 1 = with some difficulty, 2 = with much difficulty, 3 = unable to do). In univariable analyses, a decrease in tenosynovitis and synovitis was associated with a decrease in walking disability ($P = 0.001$ and $P = 0.002$, respectively; see Supplementary Table 2, available on the *Arthritis Care & Research* website at <http://onlinelibrary.wiley.com/doi/10.1002/acr.24452/abstract>). In multivariable analyses that included osteitis, synovitis, and tenosynovitis, only the association for tenosynovitis remained ($\beta = 0.073$, $P = 0.049$). Follow-up MRI data were available as follows: 107, 100, 80, and 41 patients at baseline and at 4, 12, and 24 months, respectively. Data on walking difficulty were available for 107, 78, and 70 patients at baseline and at 12 and 24 months, respectively. The increase in osteitis score at 24 months was caused by missing data for patients with resolution of symptoms who were lost to follow-up at 24 months, while patients with more severe disease kept coming for follow-up (see Supplementary Figure 4, available at <http://onlinelibrary.wiley.com/doi/10.1002/acr.24452/abstract>).

in walking disability ($P = 0.001$ and $P = 0.002$, respectively, in univariable analyses), while osteitis was not statistically significant ($P = 0.058$). The association for tenosynovitis remained in multivariable analysis adjusted for synovitis and osteitis ($\beta = 0.073$, $P = 0.049$) and when adjusted for clinical features ($\beta = 0.091$, $P = 0.002$). The analyses were repeated and adjusted for baseline values, which revealed similar results for MRI inflammation ($\beta = 0.024$, $P = 0.014$) and for tenosynovitis ($\beta = 0.069$, $P = 0.034$) (Figure 2).

Subanalysis in RA patients. As a subanalysis, the association between walking difficulties and MRI inflammation at baseline was assessed in the subgroup of RA patients ($n = 192$), as RA patients may have more severe inflammation that may influence the relationship between walking difficulties and MRI inflammation (see Supplementary Table 3, available on the *Arthritis Care & Research* website at <http://onlinelibrary.wiley.com/doi/10.1002/acr.24452/abstract>). Indeed, walking difficulties were more frequently present (46% versus 38% of patients; see

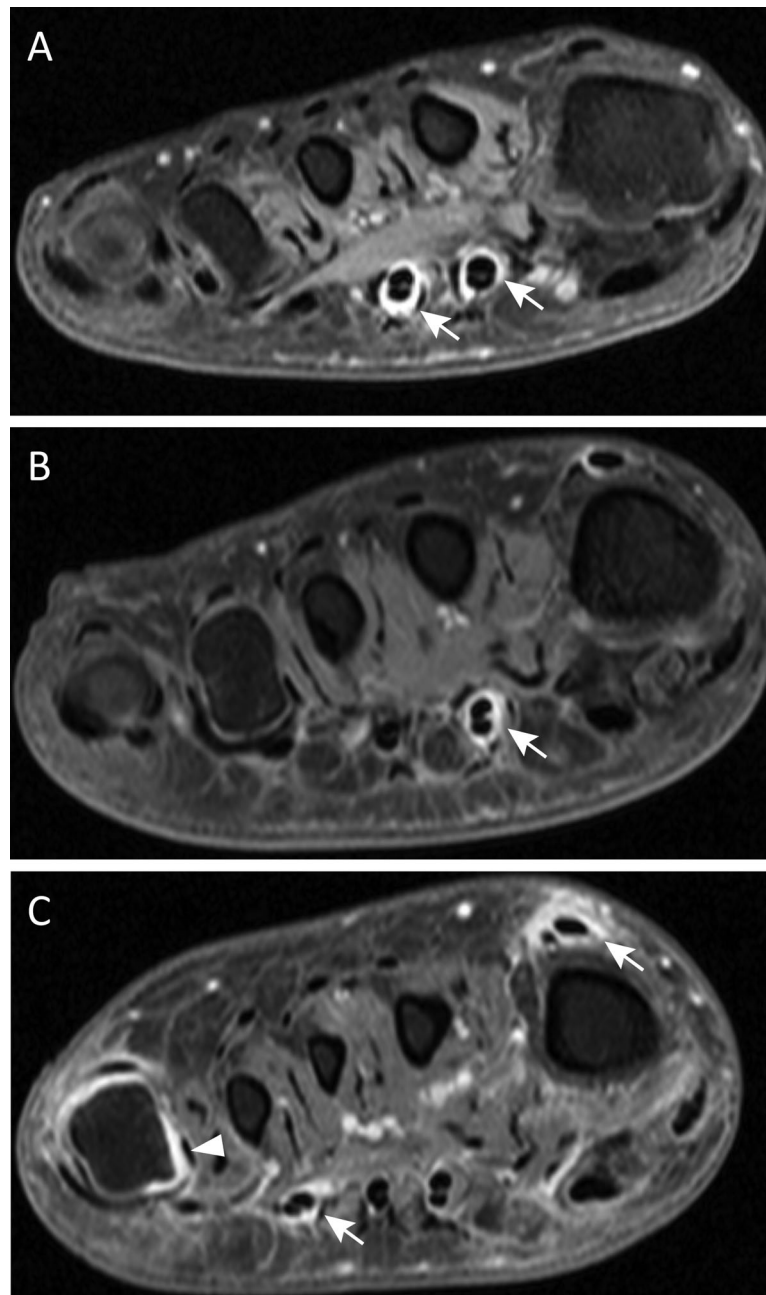


Figure 2. Examples of magnetic resonance imaging–detected tenosynovitis (arrows) in the coronal plane. **A**, Tenosynovitis of the common flexor digitorum at the 2nd and 3rd metatarsophalangeal (MTP) joint; **B**, Tenosynovitis of the common flexor digitorum at the 2nd MTP joint; and **C**, Tenosynovitis of the extensor hallucis longus and common flexor digitorum of the 4th MTP joint, with synovitis of MTP-5 (arrowhead).

Supplementary Table 1, available at <http://onlinelibrary.wiley.com/doi/10.1002/acr.24452/abstract>), and the total MRI inflammation score was higher in RA patients than in early arthritis patients with walking disabilities (6.4 versus 4.6; see Supplementary Table 3, available at <http://onlinelibrary.wiley.com/doi/10.1002/acr.24452/abstract>). Similar results were observed as in the main analyses; in multivariable analysis, the association only remained for tenosynovitis ($\beta = 0.078$, $P = 0.004$). The effect of tenosynovitis remained when adjusted for clinical features ($\beta = 0.054$, $P = 0.015$).

Next we assessed whether a decrease in walking difficulties was associated with a decrease in MRI inflammation in the subgroup of RA patients ($n = 72$) (see Supplementary Figure 3 and Supplementary Table 4, available on the *Arthritis Care & Research* website at <http://onlinelibrary.wiley.com/doi/10.1002/acr.24452/abstract>). This analysis revealed similar results, and in multivariable analysis the association only remained for tenosynovitis ($\beta = 0.097$, $P = 0.021$). The effect of tenosynovitis remained when adjusted for clinical features ($\beta = 0.12$, $P < 0.001$).

Subanalysis for difficulty climbing stairs and MRI inflammation. Finally, the analyses at baseline were repeated with difficulty climbing stairs (HAQ question 4b) as the outcome (see Supplementary Table 5, available on the *Arthritis Care & Research* website at <http://onlinelibrary.wiley.com/doi/10.1002/acr.24452/abstract>). Also here, the severity of walking disability was associated with the total MRI inflammation score ($\beta = 0.023$, $P < 0.001$). In multivariable analysis with all 3 inflammatory features, the effect was strongest for tenosynovitis ($\beta = 0.045$, $P = 0.045$).

DISCUSSION

Walking disabilities were frequent, and in our study 38% of early arthritis patients and 46% of RA patients reported having difficulties with walking. We aimed to increase our understanding of the role of inflammation at the MTP joints in this disability and observed that the severity of inflammation at MTP joints as detected with MRI was associated with walking disabilities at diagnosis. Interestingly, although univariable analyses revealed that synovitis, tenosynovitis, and osteitis were associated with walking difficulties, and that synovitis and tenosynovitis often co-occur (risk of collinearity in multivariable analyses), in multivariable analyses including the different inflammatory lesions, tenosynovitis had the strongest association. This finding suggests that tenosynovitis not only causes walking difficulties because it co-occurs with synovitis, but that by itself it can also lead to walking difficulties in patients with early arthritis. The association of tenosynovitis with walking disability was also independent of regular measures of local and systemic inflammation (SJC and CRP level). Finally, serial MRIs revealed that a decrease of MRI inflammation was associated with a reduction in walking

disabilities and that here as well the association was strongest for tenosynovitis. These results suggest that tenosynovitis at the level of MTP joints importantly contributes to physical impairments.

These results add to the increasing evidence on the importance of tenosynovitis in early RA (11). Most of this research, however, has focused on the hands (1,4), also regarding disability. In the hands, tenosynovitis also had the strongest association. A recent study showed that of the 3 inflammatory MRI features at the MTP joints, tenosynovitis had the strongest association with early RA (12). In that report, tenosynovitis at both flexor and extensor tendons was associated with RA and occurred in 31% and 28% of RA patients, respectively, of which the most common site was extensor tenosynovitis of MTP-1, which occurred in 20% of RA patients. Our current study is the first to report on MTP tenosynovitis with respect to functional disability.

To the best of our knowledge, no longitudinal studies on walking disability in relation to imaging-detected inflammation exist in early disease. Previous studies have reported on the occurrence of walking disabilities in established RA, where walking disability remained moderate to severe during follow-up (13). We have found a decrease in walking disability from the moment of diagnosis until 2 years of follow-up. This decrease after diagnosis is most likely the result of treatment initiation. Nevertheless, after having observed that the severity of walking disabilities is associated with the severity of tenosynovitis, we see confirmation in the fact that improvement in walking is associated with a reduction in tenosynovitis.

A limitation of this study is that the HAQ is validated for integral use and not for the individual questions. Validated questionnaires that specifically study foot-related disability exist, like the Leeds Foot Impairment Score that more specifically studies impairment and activity limitation (14). The relationship of imaging-detected MTP inflammation in these different aspects of foot disability would certainly be interesting and is a subject for further research.

MTP-1 is a predilection site for degenerative disease, and part of the inflammation (synovitis, osteitis) at advanced age in MTP-1 is possibly related to osteoarthritis. However, research has also reported that tenosynovitis at MTP-1 is RA specific, and that involvement of MTP-1 is especially specific for RA in younger patients (12,15). We therefore did not exclude MTP-1 from our analyses. Although radiographic information on osteoarthritis of MTP-1 was not systematically available, we did adjust for age in our analyses, as osteoarthritis is mostly age related.

Walking disabilities in established RA can be due to inflammation but also due to damage and joint deformity. We studied patients at first presentation to the outpatient clinic and found no relation between erosions and walking disabilities. This finding is not surprising, as the prevalence of erosions, and thus the contribution to functional impairment, is low at disease onset.

Interestingly, in addition to the studied MRI features, in the forefoot, synovium-lined intermetatarsal bursae are present that can clearly be differentiated from tenosynovitis, synovitis, and osteitis, as they have no anatomical connection with MTP joints and are surrounded bilaterally by the interosseous tendons (16). Inflammation of these bursae, referred to as intermetatarsal bursitis, relates to clinical joint swelling (17) and may predict the development of foot impairment in RA patients (13). How inflammation relates to tenosynovitis, synovitis, and osteitis in respect to disability is unknown.

In conclusion, in patients with arthritis, we traditionally consider synovitis to be the cause of disability. We have shown that, additionally, tenosynovitis at the MTP joints is an important feature that needs to be considered. Appreciating this role of tenosynovitis increases our understanding of walking disabilities in patients with early arthritis and of functional disability in RA patients.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Dakkak had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Dakkak, Reijnierse, van der Helm-van Mil.

Acquisition of data. Dakkak, Wouters.

Analysis and interpretation of data. Dakkak, Matthijssen, van der Helm-van Mil.

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