Joint involvement in RA starts predominantly in the hands: functional, clinical and imaging studies in clinically suspect arthralgia and during progression to RA

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ORIGINAL RESEARCH

Joint involvement in RA starts predominantly in the hands: functional, clinical and imaging studies in clinically suspect arthralgia and during progression to RA

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ABSTRACT

Objectives It is unknown whether rheumatoid arthritis (RA) starts in hands or feet. To investigate this, we performed functional, clinical and imaging studies during progression from clinically suspect arthralgia (CSA) to RA. Additionally, we studied whether functional disabilities of hands/feet at CSA onset contribute to predicting RA development.

Methods 600 patients with CSA were followed for clinical inflammatory arthritis (IA) during median follow-up of 25 months, during which 99 developed IA. Functional disabilities were measured at baseline/4/12/24 months with the Health Assessment Questionnaire Disability Index (HAQ); HAQ items assessing hand disabilities and foot disabilities were selected. The course of disabilities towards IA development (here considered as t=0) was depicted by increasing incidences and analysed using linear mixed models. To evaluate robustness of findings, tender hand/foot joints and subclinical joint inflammation (measured with CE-1.5TMRI) of hand/foot were additionally studied. Associations between disabilities at CSA presentation (here t=0) and future IA development were studied using Cox regression in the total CSA population.

Results During IA development, hand disabilities occurred earlier and more frequently than foot disabilities. Despite both hand disabilities and foot disabilities rose significantly towards IA development, hand disabilities were more severe during this course (mean difference over time: 0.41 units, 95% CI 0.28 to 0.55, p<0.001, on a range 0–3). Similar to functional disabilities, tender joints and subclinical joint inflammation occurred earlier in the hands than feet. In the total CSA population, a single HAQ question on difficulties with dressing (hand functioning) was independently predictive for IA development: HR=2.2, 95% CI 1.4 to 3.5, p=0.001.

Conclusion Evaluation of functional disabilities, supported by clinical and imaging findings, revealed that joint involvement starts predominantly in the hands during RA development. Additionally, a single question on dressing difficulties adds value to risk stratification in patients with CSA.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Although rheumatoid arthritis (RA) at diagnosis is characterised by arthritis of the small joints of the hands and feet, it is unknown whether joint involvement in RA starts in hand-joint or foot-joint groups.

WHAT THIS STUDY ADDS

⇒ Longitudinal evaluation of functional disabilities in patients with clinically suspect arthralgia (CSA) towards RA development revealed that involvement of hands occurred earlier and more frequently than of feet.

⇒ Similar findings were done for evaluating the presence of tender joints and subclinical joint inflammation in hands and feet.

⇒ Decreased hand functioning (especially a single question on difficulties with dressing) was predictive for progression from CSA to RA and adds value to risk stratification in patients with CSA.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These novel findings advance our understanding of the trajectory of RA development and may impact the clinical care of patients with arthralgia.

INTRODUCTION

Rheumatoid arthritis (RA) is typically characterised by symmetric arthritis of the small joints.[1–3] Although at the time of RA diagnosis arthritis often manifests in the joint groups of the hands and feet, the course in which joint involvement has developed is unknown. More specifically, while at the time of diagnosis hand-joint and foot-joint groups can both be affected, it is undetermined whether joint involvement predominantly starts in hand-joint and/or foot-joint groups. Unravelling

this knowledge gap may increase our understanding of joint involvement during the earliest phases of developing RA.

Research in the last decade has shown that clinically suspect arthralgia (CSA) often precedes the development of clinical arthritis and RA. In addition, studies in CSA have revealed that subclinical joint inflammation generally starts before occurrence of clinical arthritis, and also associates with symptoms and signs in CSA.[4–6] Moreover, it has been demonstrated that physical functioning, as measured with the Health Assessment Questionnaire Disability Index (HAQ), can be impaired in the phase of CSA.[5] However, longitudinal studies in CSA are scarce and the trajectory of joint involvement during progression from CSA to RA remains to be elucidated. This at-risk stage provides a unique setting to increase our understanding of developing RA, especially when several parameters for joint involvement (eg, functional, clinical, imaging) are evaluated.

In patients with CSA, severe impairments (total HAQ score ≥1) have been associated with an increased risk for progression to RA. Moreover, previous work in a walk-in early recognition outpatient clinic (a '1.5-lines setting') showed that a single question on physical functioning (difficulties with dressing) was as discriminative for the presence of arthritis at physical examination as the total HAQ (≥1).[7] However, in CSA, it has not been investigated whether assessing only hand disabilities and/or foot disabilities can be equally informative as the total HAQ on future arthritis development. Asking a single question could be helpful for risk stratification in clinical practice where filling out full questionnaires is frequently considered less practical.

With the ultimate goal to increase comprehension of the trajectory of RA development, we aimed to investigate the course of involvement of hands and feet according to functional disabilities during progression from CSA to RA. To verify robustness of findings, the course of joint involvement prior to inflammatory arthritis (IA) was also assessed by presence of tender joints at physical examination and presence of subclinical joint inflammation on MRI of hands and feet. Second, in order to examine the applicability of hand disabilities and foot disabilities in the clinical practice, we studied whether questions assessing functional disabilities in hands or feet contribute to predicting progression from CSA to RA.

METHODS

Patients

We longitudinally studied patients with CSA who were consecutively included between April 2012 and May 2020 in the Leiden CSA cohort and who developed clinical IA or had at least 1-year follow-up. The Leiden CSA cohort is an inception cohort including patients with arthralgia of the small joints (metacarpophalangeal (MCP), proximal interphalangeal (PIP), wrist or metatarsophalangeal (MTP)) for less than 1 year that is considered suspicious for progression to RA according to the rheumatologist (online supplemental data S1).[4] Patients were excluded if arthritis was already present at baseline or if the rheumatologist considered another explanation for the arthralgia (eg, osteoarthritis or fibromyalgia) more likely than imminent RA. For the current study, 109 patients with CSA were excluded because of participation in the TREAT EARLIER trial that entailed a 50% chance of methotrexate use.[8]

Outcome IA development

Patients in the CSA cohort were followed for 2 years for development of IA, defined as joint swelling at physical examination by the rheumatologist. Follow-up visits were performed at 4, 12 and 24 months after baseline. If patients perceived increased symptoms between the follow-up visits, they were seen at the outpatient clinic to verify whether the outcome of IA was achieved. Development of IA entailed the end of the CSA study. During follow-up, patients with CSA were not treated with DMARDs (including corticosteroids). Among those that developed IA and thus achieved the main outcome of the CSA cohort, RA was defined as a clinical diagnosis and fulfilling 1987 and/or 2010 RA criteria and/or start of DMARD treatment at the moment of IA development.[9 10] Patients who did not develop IA (and per definition also not RA) during follow-up were studied in separate analyses.

Functional disabilities

Functional disabilities were assessed using the HAQ, which patients completed at every study visit. The HAQ comprises 20 questions that cover eight categories of functional disabilities: dressing and grooming, arising, eating, walking, hygiene, reach, grip and activities of daily living. Every category is scored on a range of 0–3, with 0 indicating no disabilities and 3 indicating inability to perform a task.[11 12] The total HAQ score is calculated by the average score of all eight categories. In the current study, functional disabilities involving the hands were selected and defined by the average of the HAQ categories 'dressing and grooming', 'eating' and 'grip' (range of this average 0–3). This will be referred to as the HAQ hand domain. Functional disabilities involving the feet were assessed by the HAQ category 'walking' (range 0–3). This will be referred to as the HAQ foot domain. Although the other HAQ categories (arising, hygiene, reach and usual activities) may also involve hand functioning and foot functioning, large joints are predominantly involved in performing these tasks. Therefore, we did not categorise these HAQ categories as mainly involving hand joints or foot joints.[13]

Tender joints

Physical examination of tender joints (68 tender joint counts) was performed at every visit by a trained research nurse. Presence of tender joints in hands (wrists, MCPs (1–5) and PIPs (1–5), together considered as hand-joint

groups) and feet (MTPs (1–5); together summed as foot-joint groups) was studied.

Subclinical joint inflammation

At study entry and moment of IA development, patients underwent a unilateral contrast-enhanced 1.5T MRI of hand and foot on the side with the most symptoms, or the dominant side when symptom severity was symmetrical. Wrist, MCP (2–5) and MTP (1–5) joints were evaluated for subclinical joint inflammation (sum of synovitis, tenosynovitis and osteitis) and were scored according to the RA MRI scoring system and the Haavardsholm method (online supplemental data S2 and S3).[14 15] Since inflammation on MRI can also be detected in symptom-free individuals from the general population, subclinical joint inflammation was considered present, only if a similar severity at the same location occurred in less than 5% of age-matched symptom-free individuals, as done previously.[16] Thus, used cut-off values for MRI-detected inflammation were based on normal variation present in the general population. By incorporating these cut-off values, we corrected for variation of MRI-detected findings in the symptom-free population, especially among the elderly aged. Previous research showed that using this reference when defining abnormal MRI increased specificity of MRI-detected inflammation without influencing the sensitivity.[17] Detailed information on MRI-detected inflammation in symptom-free individuals can be found elsewhere.[16]

Statistical analyses

The course of hand involvement and foot involvement in patients with CSA that developed IA was studied retrospectively using repeated measurements of HAQ, tender joints and MRI. In these analyses, the date of IA development was considered t=0 and the measurements done at preceding visits were studied at a continuous time scale. For the research question on the predictive value of functional disabilities on future IA development, HAQ at CSA baseline (here t=0) was analysed in the total CSA population.

The incidence of hand disabilities (HAQ hand domain >0) and foot disabilities (HAQ foot domain >0) towards IA development were depicted by time (months) prior to IA. The course of the severity of hand disabilities and foot disabilities over time was analysed with time before IA development as independent variable using linear mixed models (LMM), after testing which shape of the model best fitted the data. Similarly, the incidence of presence of tender hand/foot-joint groups at physical examination and presence of MRI-detected joint inflammation in the hand/foot was additionally depicted.

Three subanalyses were performed on functional disabilities of hands and feet. First, as a sensitivity analysis, the course of functional disabilities prior to development of IA was repeated in patients who developed RA. Second, LMM analyses on the course of hand disabilities and foot disabilities towards IA development were stratified for anticitrullinated protein antibodies (ACPA-)status (anti-CCP2, EliA CCP, Phadia, the Netherlands, positive if ≥7 U/mL) and for autoantibody-positivity (defined as ACPA-positivity and/or IgM rheumatoid factor-positivity (RF; positive if >3.5 U/mL). Third, to verify robustness of results, a more stringent definition of hand disabilities was used (HAQ hand domain ≥1) for assessing the incidence of hand disabilities towards IA development.

Additionally, the course of functional disabilities involving hands and feet in patients with CSA without IA development was studied using separate LMM analyses.

Predictive value of the total HAQ, HAQ hand domain, HAQ foot domain and a single HAQ question on difficulties with dressing at CSA presentation, with future IA development was studied using Cox regression analyses in the total CSA population.

Analyses were performed using SPSS V.25 and STATA V.16. Two-sided p values of <0.05 were considered statistically significant.

RESULTS

Patient characteristics at CSA baseline

Baseline characteristics of the CSA population (n=600) are shown in table 1. Twenty-two per cent was ACPA and/or RF-positive, the total HAQ score was 0.7±0.5, and 42% of patients had tender hand joints without tender foot joints, 37% had tender hand and foot joints, while 8% of patients had tender foot joints without tender hand joints. The start of complaints was most often located in the upper extremities (67%), followed by both the upper and lower extremities (17%) and only lower extremities (10%). During follow-up (median duration 25 months IQR 17–26), 99 patients developed IA. Baseline data on HAQ were present in 524 patients. Baseline characteristics were largely similar in patients with and without baseline data on HAQ (online supplemental table S1).

The eight HAQ categories at presentation with CSA are shown in figure 1, according to progression to IA. Patients with CSA who progressed to IA had more severe disabilities in hand functioning and in other activities, but not with walking disabilities, than patients with CSA who did not progress to IA.

Functional disabilities involving hands and feet towards IA development

At the time of IA development more patients had developed hand disabilities than foot disabilities (81% vs 42%). Considering IA development as t=0 and evaluating all HAQ measurements during the months prior to IA development, we observed that hand disabilities occurred at an earlier timepoint than foot disabilities (figure 2A). When studying the severity of disabilities (range 0–3 both for hands and for feet), data revealed that disabilities involving the hands rose with 0.25 units/year, 95% CI 0.04 to 0.45, p=0.019 towards IA development. Disabilities involving the feet increased as well (0.29 units/year, 95% CI 0.08 to 0.50, p=0.008). The slopes for increase in

Table 1 Baseline characteristics of included patients with CSA

	All patients (n=600)	Patients developing IA* (n=99)	Patients not developing IA (n=501)
Female	469 (78)	71 (72)	398 (79)
Age in years	44±13	47±13	43±12
Symptom duration in days	137 (68–310)	143 (61–364)	134 (68–296)
ACPA-positive and/or RF-positive	133 (22)	56 (57)	77 (15)
ACPA-positive	79 (13)	46 (47)	33 (7)
RF-positive	115 (19)	52 (53)	63 (13)
CRP increased (≥5 mg/L)	130 (22)	34 (34)	96 (19)
ESR increased†	88 (15)	27 (27)	61 (12)
HAQ	0.7±0.5	0.8±0.6	0.6±0.5
Hand-domain >0	402 (67)	74 (75)	328 (66)
Foot-domain >0	175 (29)	33 (33)	142 (28)
TJC-68	5 (2–10)	5 (2–8)	5 (2–10)
TJC group‡			
TJC: hands+ feet-	252 (42)	41 (41)	211 (42)
TJC: hands- feet+	47 (8)	8 (8)	39 (8)
TJC: hands+ feet+	221 (37)	36 (36)	185 (37)
TJC: hands- feet-	72 (12)	12 (12)	60 (12)
Complaints started in joints§			
Upper extremities	402 (67)	61 (62)	341 (68)
Lower extremities	58 (10)	12 (12)	46 (9)
Upper and lower extremities	99 (17)	19 (19)	80 (16)
MRI inflammation present¶			
Hand	208 (35)	68 (69)	140 (28)
Foot	76 (13)	31 (31)	45 (9)

Data are n (%), mean±SD or median (IQR).
*88 patients met the definition for RA at moment of IA development, of whom 55 (63%) were autoantibody positive.
†ESR was considered elevated with a reference for age and sex (<50 years: male >15 mm/hour, female >20 mm/hour; >50 years: male >20 mm/hour, female >30 mm/hour).
‡TJC of the hands involved bilaterally: wrist, MCP joints 1–5, PIP joints 2–5 and IP joints of the thumb. TJC of the feet involved bilaterally: the MTP joints 1–5.
§The joints in which symptoms started were registered by the rheumatologist.
¶Subclinical joint inflammation on MRI in hand (MCP joints and wrist) and foot (MTP joints) was dichotomised per feature of inflammation (synovitis, tenosynovitis, osteitis) and per location; if the inflammation score of any feature was higher than present at the same location in <5% of age-matched symptom-free individuals, the joint was considered positive for inflammation.
ACPA, anticitrullinated protein antibody; CRP, C reactive protein; CSA, clinically suspect arthralgia; ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire Disability Index; IP, interphalangeal; MCP, metacarpophalangeal; MTP, metatarsophalangeal; PIP, proximal interphalangeal; RA, rheumatoid arthritis; RF, rheumatoid factor; TJC, tender joint count.

hand disabilities and foot disabilities did not differ from each other (p=0.55). Despite a roughly similar increase over time, hand disabilities were more severe than foot disabilities during this course (figure 3, mean difference over time of 0.41 units (95% CI 0.28 to 0.55, p<0.001)). When correcting the course of functional disabilities for age, similar differences between hands and feet were observed (online supplemental figure S1).

Tender joints at physical examination of hands and feet towards IA development

To verify the findings, other measures of hand involvement and foot involvement were assessed in patients with CSA towards IA development. We therefore studied if hand-joint groups (wrists, MCPs and PIPs) and foot-joint groups (MTPs) were tender on physical examination. Also in this analysis, hand involvement occurred earlier and more often than foot involvement (figure 2B).

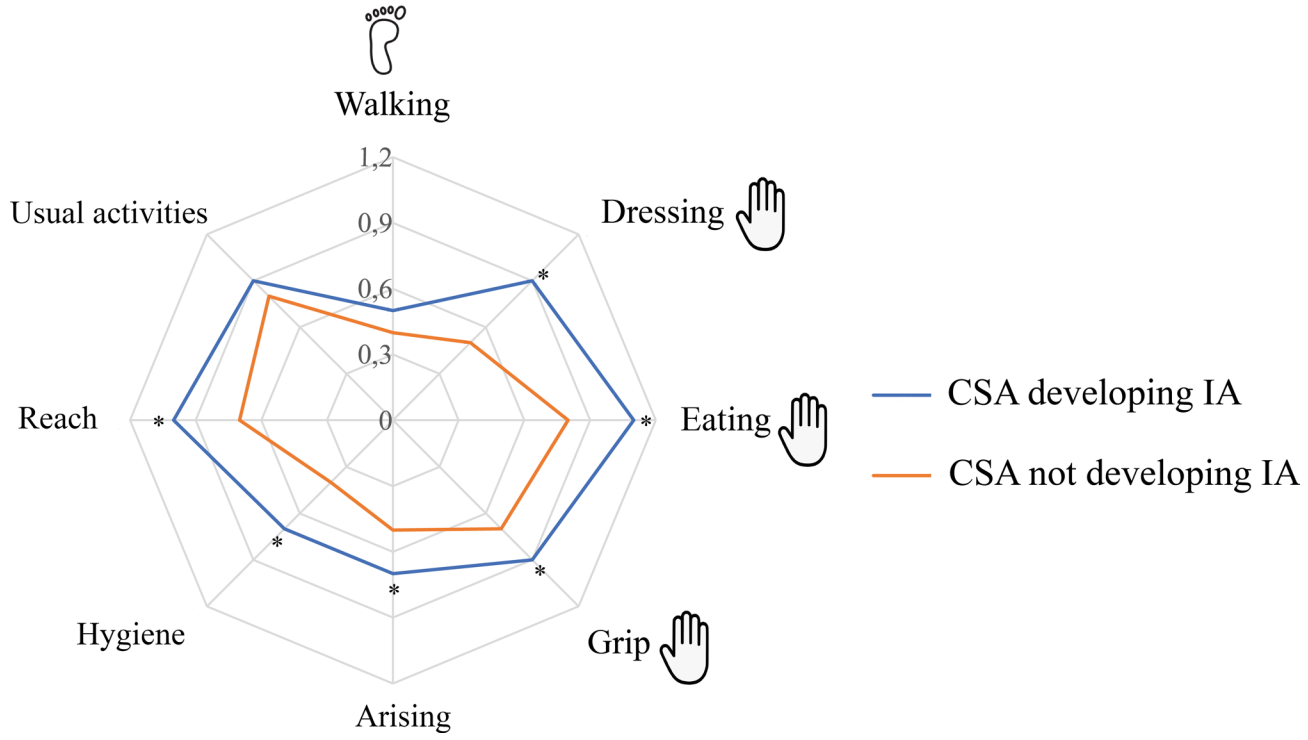

Figure 1 HAQ categories of functional disabilities at presentation with clinically suspect arthralgia. Depicted are the mean scores of the eight HAQ categories at presentation with clinically suspect arthralgia, separately for patients developing and not developing inflammatory arthritis. *Statistically significant differences between the two groups. CSA, clinically suspect arthralgia; HAQ, Health Assessment Questionnaire Disability Index; IA, inflammatory arthritis.

Subclinical joint inflammation in hand and foot towards IA development

To further substantiate these findings, we also studied the presence of subclinical joint inflammation in the hand (MCPs) and foot (MTPs) joints detected with MRI in patients with CSA before and at IA development. Again, an earlier and more frequent involvement of hand than foot was observed (figure 2C).

In 86/99 patients who developed IA during follow-up, IA occurred in at least one of the hand joints (wrists, MCPs and/or PIPs) according to the physical examination by the rheumatologist at the moment of IA development. From the remaining 13 patients without IA in the hand joints, 9 patients had arthritis in the forefeet, 2 patients in the elbow and 2 patients in the knee.

Subanalyses on functional disabilities of hands and feet

Three subanalyses were performed for the data on hand disabilities and foot disabilities.

First, the incidence of hand disabilities and foot disabilities in patients with RA development (n=88) was similar to what was observed in the total group of patients developing IA (online supplemental figure S2A). The finding that hand disabilities were more severe than foot disabilities was also similar in patients developing RA (mean difference over time 0.41 units (95% CI 0.27 to 0.55, p<0.001)); online supplemental figure S2B).

In addition, analyses were stratified for ACPA status (online supplemental figure S3). In both ACPA groups, hand disabilities and foot disabilities increased towards IA development, and hand disabilities were more severe in these groups as well. However, this difference was the largest in ACPA-negative disease (mean difference over time: 0.57 units (95% CI 0.38 to 0.76, p<0.001) in ACPA-negative vs 0.20 units (95% CI 0.15 to 0.39, p<0.035) in ACPA-positive disease). Stratification for autoantibody-positivity showed similar results (online supplemental figure S2B).

Finally, even when using a more stringent definition of hand disabilities (HAQ hand domain ≥1, meaning that a minimal score of one was required for every category of hand disabilities ('dressing and grooming', 'eating' and 'grip')), hand disabilities occurred earlier and more frequently than foot disabilities (online supplemental figure S4). With this, we accounted for the fact that the hand domain of the HAQ contains more questions than the foot domain.

Functional disabilities in patients with CSA not progressing to IA

For comparison, the course of hand disabilities and foot disabilities was studied in the 501 patients who did not develop IA during follow-up. During a median follow-up of 25 (15–26) months, 77% of patients (n=385) had two or more serial HAQ measurements. Functional disabilities involving hands and feet decreased significantly over time, thus showing improvement (figure 4). Also, in these patients, hand disabilities were more severe than foot disabilities, but the difference was smaller than was observed in the patients that progressed to IA (mean

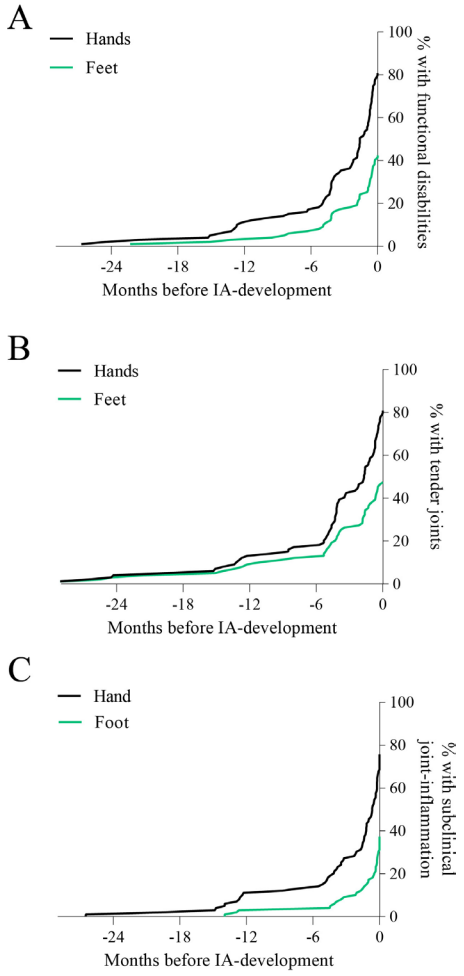

Figure 2 Increasing incidence of (A) functional disabilities, (B) tender joints and (C) subclinical joint inflammation in hands and feet in patients with CSA during the trajectory towards development of inflammatory arthritis. (A) Lines depict the increasing incidence of functional disabilities involving the hands and feet prior to development of inflammatory arthritis (considered as t, 0), including all HAQ measurements. Hand disabilities and foot disabilities were defined as a score >0 on the hand domain and foot domain of the HAQ, both having a range of 0–3. In this analysis, 63% of patients had one HAQ measurement and 31% had repeated HAQ measurements prior to IA development. (B) Lines depict the increasing incidence of tender joints in hands (wrists, MCPs and PIPs) and feet (MTPs) at physical examination prior to development of inflammatory arthritis (considered as t, 0). Tender joints in hands and feet were analysed dichotomously (TJC hands >0 and TJC feet >0). In this analysis, 65% had one TJC assessment and 35% had repeated TJC assessments prior to IA development. (C) Lines depict the increasing incidence of subclinical joint inflammation on contrast-enhanced 1.5TMRI of the hand and foot prior to IA development (considered as t, 0). Out of 99 patients with CSA with IA development, MRI at presentation with CSA was present in 92% and in 51% at IA development. The raw data on functional disabilities, tender joints and subclinical joint inflammation are presented in online supplemental figure S5. CSA, clinically suspect arthralgia; HAQ, Health Assessment Questionnaire Disability Index; IA, inflammatory arthritis; MCP, metacarpophalangeal; MTP, metatarsophalangeal; PIP, proximal interphalangeal.

difference over time in non-progressing patients=0.19 units (95% CI 0.15 to 0.22, p<0.001)).

Predictive value of functional disabilities at CSA baseline and future IA development

In order to examine the applicability of hand disabilities and foot disabilities in clinical practice, we studied whether functional disabilities of hands/feet in CSA contribute to predicting progression to IA. In line with previous literature, also in these data, a total HAQ ≥1 was associated with an increased risk for IA development: HR=2.0, 95% CI 1.3 to 3.1, p=0.001. Analyses of hand disabilities and foot disabilities separately showed that a HAQ hand domain ≥1 was also associated with IA development (HR=1.9, 95% CI 1.3 to 3.0, p=0.003), in contrast to HAQ foot domain ≥1 (HR=1.2, 95% CI 0.8 to 1.8, p=0.40). Moreover, a single HAQ question on any difficulties with dressing (scored ≥1) was associated with future progression to IA: HR=2.2, 95% CI 1.5 to 3.5, p<0.001, and its effect estimate was thus comparable to the total HAQ ≥1 (figure 5). Presence of any difficulties with dressing remained predictive for IA development after adjustment for age, sex, elevated CRP (≥5 mg/L), ACPA and RF: HR=2.2, 95% CI 1.4 to 3.5, p=0.001.

DISCUSSION

Knowledge of the earliest stages of RA development can be obtained by studying an 'at-risk stage'. We aimed to study the course of joint involvement in the hands and feet in patients with CSA during progression to RA or non-conversion. Although it was known that functional disabilities, pain and subclinical joint inflammation already occur in the stage of CSA, it was unidentified in which joints these signs of joint involvement start. We showed that functional disabilities involving the hands started earlier than foot disabilities and that hand disabilities were more severe than foot disabilities during the trajectory towards IA/RA. In addition, similar findings were obtained for hand involvement and foot involvement when analysing tender joints and subclinical joint inflammation. By incorporating functional, clinical and imaging findings, this study is the first suggesting that joint involvement is more prominent and starts earlier in the hands than in the feet in CSA that evolves to RA. These data assist in understanding the processes of development of RA and its burden for the patient.

Literature on the stage of classified RA showed that patients with ACPA-negative RA have more functional disabilities than patients with ACPA-positive RA.[18] Our study revealed that functional disabilities increased towards IA development in both ACPA groups and that the difference between hand disabilities and foot disabilities during IA development was larger in ACPA-negative CSA. These data suggest that a predominant start in the hands is more prevalent in ACPA-negative than in ACPA-positive disease. This would also be in agreement with a previous study in patients presenting with CSA reporting

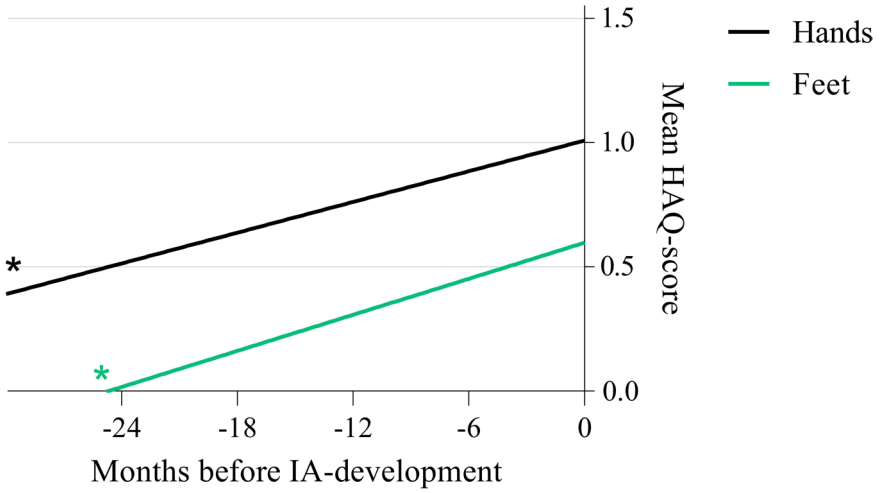

Figure 3 Severity of functional disabilities (mean HAQ score) involving hands and feet in patients with CSA during the trajectory towards development of inflammatory arthritis. Lines depict the course of functional disabilities involving the hands (average of dressing, eating, grip; range 0–3) and feet (walking; range 0–3), derived from linear mixed model analyses and including all HAQ measurements prior to development of inflammatory arthritis. In these analyses, the moment of inflammatory arthritis is considered as t, 0. *Statistically significant increases in mean HAQ scores. CSA, clinically suspect arthralgia; HAQ, Health Assessment Questionnaire Disability Index; IA, inflammatory arthritis.

more symptoms in the upper extremities only in ACPA-negative patients, and with a study at RA diagnosis showing more frequent arthritis in the hands without foot involvement in ACPA-negative RA.[18 19] Differences in underlying pathophysiology of ACPA-positive and ACPA-negative disease in relation to functional disabilities and location of inflammation remains subject for future research.

While our study showed important findings of the trajectory of IA and RA development, it also raises the question why hand joints are affected earlier than foot-joint groups. Further unravelling of the associated mechanisms may increase our understanding of the pathophysiology of RA development. Currently, this remains speculative. Hand joints and foot joints are different with respect to exposed mechanical forces; whereas mechanical forces in the feet are related to weight-bearing, in the hands, these are mostly related to movement without a major influence of weight-bearing. Physical (work) load has been reported as risk factor for autoantibody-positive and autoantibody-negative RA, but the type of mechanical forces in relation to this risk is unexplored.[20] The differences in hand involvement and foot involvement are robust since we observed this difference in three measures. In addition, the evaluation of functional disabilities of hands and feet was normalised at a scale 0–3 each and thereby not dependent on a higher number of HAQ items for hands and feet. Furthermore, the steepness of the lines indicating progression was similar in hands and feet (figure 3), implying that foot disabilities just started later. Another

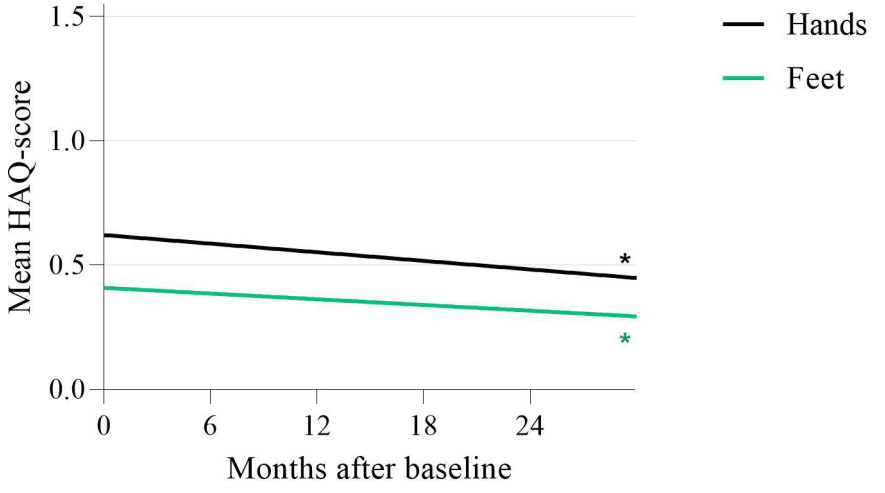

Figure 4 Functional disabilities involving hands and feet in CSA who did not develop inflammatory arthritis. Lines depict the average course of functional disabilities involving the hands (dressing, eating, grip) and feet (walking) after baseline in patients with CSA who did not develop arthritis, derived from linear mixed model analyses. *Statistically significant decreases in mean HAQ scores. CSA, clinically suspect arthralgia; HAQ, Health Assessment Questionnaire Disability Index.

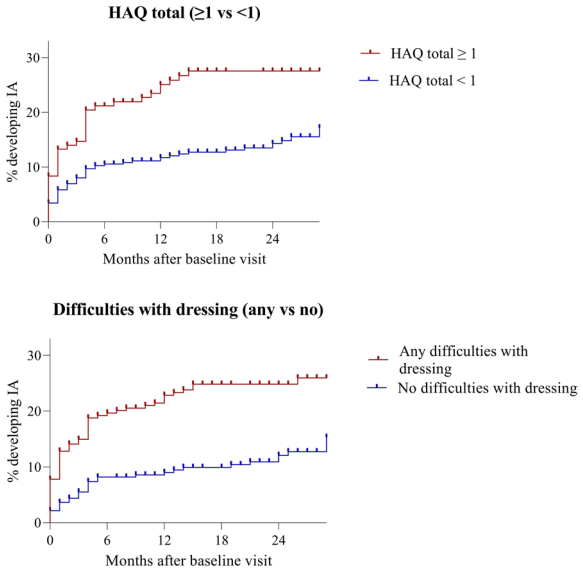

Figure 5 A total HAQ score ≥1 is similarly associated with IA development as the presence of difficulties with dressing retrieved from a single HAQ question. Progression from CSA to inflammatory arthritis, according to the total HAQ and a single HAQ question on difficulties with dressing. HAQ, Health Assessment Questionnaire Disability Index; IA, inflammatory arthritis.

explanation could simply be the difference in number of joints that was considered involvement of the hands in our analyses (wrists, MCPs and PIPs, total of n=22 joints bilaterally) and feet (MTPs, total of n=10 joints bilaterally). Thus, the 'chance' of a hand joint being the first inflamed joint is then higher than the 'chance' for a foot joint. Further studies are needed to investigate possible mechanisms underlying the observed predominance of hands and time order in hand involvement and foot involvement.

Although other pre-RA cohorts may differ in inclusion criteria (symptoms and/or antibodies) and imaging modalities (ultrasound or MRI), it is interesting to compare our findings to previous studies in pre-RA. Nam *et al* studied ultrasound findings in ACPA+individuals with musculoskeletal symptoms and observed that 27%–79% of patients had evidence of GS in one of the MTP joints, compared with 10%–52% of patients in the wrist, MCP or PIP.[21] For PD, these percentages of patients were 1–8 and 2–22, respectively. An important difference with our analyses is that we studied patients with pre-RA longitudinally towards IA development and not only at presentation with symptoms. We therefore could study the development of joint involvement during the trajectory of developing RA. Additionally important to remark is that there are multiple studies on joint involvement at physical examination at the moment of clinical arthritis, but these studies also differ from our study, as these results describe the moment of RA diagnosis and not the pre-RA phase.[18 21 22]

A limitation in our study is that repeated data on disabilities, tender joints and MRI were limited to maximally three observations prior to IA development and most patients had one measurement in the pre-IA/pre-RA phase. The data presented in figure 3 were derived from plotting all measurements at the (calendar) time preceding IA/RA development. However, this may be suboptimal for the detection of time orders, since this assumes that the relation between symptoms and duration to IA development is similar for all patients with CSA. A better study design for the identification of time orders is a study with frequently repeated measures with smaller intervals in the same patients preceding the development of IA/RA. This would allow a more precise evaluation of time orders and is a subject for future research. Additionally, evaluation of functional disabilities during the trajectory of CSA in relation to the course of subclinical synovitis, tenosynovitis and osteitis would be insightful. Previous research showed that, among the different inflamed joint tissues, tenosynovitis had the strongest association with RA development and with the presence of functional disabilities and difficulties making a fist.[23–25] The course in which the different tissues in/at the joint become inflamed and explain the clinical presentation as well as the development and progression of functional disabilities, remains to be determined in future research. This would require a study with serial MRIs made at small time intervals and concomitant evaluation of physical functioning. Also, we studied the value of impairments in physical functioning within the CSA population with respect to the long-term outcome. Thus, our study was not designed to determine the ability to differentiate between different diagnoses. Finally, although RA is characterised by involvement of the small joints of hands and feet, future research could also focus on involvement of large joints in pre-RA. A previous study investigated involvement of the shoulder joint with imaging in patients with CSA and demonstrated that inflammation here was infrequent and not an early feature of RA.[26] Also, arthralgia of the knee has been reported to be present in the minority of ACPA-positive patients at risk for RA development.[27] However, a more through comparison between small and large joints involvement during RA development is a subject for future research.

One could suggest that patients with hand symptoms were more often included in the CSA cohort than patients with foot complaints only. However, rheumatologists were instructed to include patients with arthralgia of the small joints (MCP, PIP, wrist or MTP) that was suspicious for progression to RA and were not instructed to include patients based on the EULAR definition of CSA or specifically hand tests.[28] Additionally, a previous study showed that out of all individuals presenting to the outpatient clinic with arthralgia but who were not included in the CSA cohort, only 0.2% developed RA after 1 year.[29] In other words, these patients were not identified as CSA but in retrospect were 'pre-RA' at their first visit to the outpatient clinic. Even if all these few patients only had foot symptoms (this information is not known), this number would be low and unlikely to affect the reported

findings. Hence, although we cannot definitely exclude the possibility that especially patients with foot symptoms were unrecognised in our cohort and study population, we feel that this is unlikely. Additionally, referral bias by GPs is not to be expected, since the Dutch guidelines for GPs do not describe to perform specific tests at physical examination of, for example, the hands, such as the squeeze test, before referral.[30] Neither did rheumatologists give these instructions to GPs.

Additionally, questions may arise on the use of the HAQ domains in our study. First, although the hand domain and foot domain of the HAQ was based on literature, other joints than the hands and feet could also be involved in these domains (eg, elbows in eating or knees in walking).[13] Also, physical examination (tender joints) of the feet may be more difficult than of the hands. However, we validated the findings with imaging (subclinical joint inflammation on MRI). Although all three used outcomes may have advantages and disadvantages, the occurrence of comparable results in all three measures supports the findings and shows robustness of results. Second, although the HAQ was developed decades ago and the buttons on clothes and milk containers may have changed over time, it has established itself as a valuable, effective and sensitive tool for measurement of health status.[11] Our data did not suffer from historical changes since we did not perform a comparison of HAQ scores between patient groups throughout the decades. Instead, we used the same HAQ for all patients to study individual changes over time within patients. Third, the eating domain of the HAQ contains questions on eating are about cutting meat, bringing a full glass or cap to the mouth, and opening a new carton of milk or soda. Thus, this will not be influenced by jaw issues.

Although it was already known that a high HAQ is predictive for IA development and RA development, it is not often used in clinical practice as filling out a full HAQ and calculating the score may be considered less feasible. We observed that the hand domain of the HAQ was more strongly associated with IA development than the foot domain and that a single HAQ question on difficulties with dressing (clearly involving hand functioning) was an independent predictor for future IA development. Our findings in CSA are fully in line with a recent study in early arthritis revealing that a single HAQ question on difficulties with dressing was equally predictive as a total HAQ score >1.[7] Even though the HAQ was not designed for the use of its components separately, the cumulative scientific evidence about the value of this single question is encouraging, also because asking a single question is easily done in clinical practice.

In conclusion, in our CSA cohort, we observed that joint involvement starts earlier and is more severe in the hands than in the feet during RA development. The difference in hand involvement and foot involvement was observed for functional disabilities and supported by similar findings in the presence of tender joints and subclinical joint inflammation. These results may influence future research and clinical practice that could use hand assessments to risk stratify individual with joint symptoms who are considered at-risk for future RA. Further study is needed to understand this in additional populations. In addition, these findings provide novel insights in the trajectory of developing RA. Moreover, the observations on hand disabilities could also be easily translated to clinical practice as a single question on hand functioning (difficulties with dressing) is easily asked.

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