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ORIGINAL REPORT

PREDICTION OF WALKING DISABILITY BY DISEASE-RELATED FACTORS IN PATIENTS WITH RHEUMATOID ARTHRITIS

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Objective: **To investigate the relationship between disease-related factors and walking disability in different phases of rheumatoid arthritis; and to predict future walking disability in rheumatoid arthritis, using disease-related factors assessed 2 years after diagnosis.**

Methods: **A cohort of 848 newly diagnosed patients with rheumatoid arthritis was followed up for a maximum of 8 years. Walking disability and several disease-related and demographic factors were recorded during follow-up. A logistic regression model was used to study associations between walking disability and these factors at different time points. A multilevel logistic regression model for longitudinal data was used to predict walking disability during follow-up from potential predictors at year 2.**

Results: **Global pain and disease activity were consistently related to walking disability at almost every time point. Significant predictors of future walking disability were: walking disability, knee pain, global pain, the passage of time during follow-up, and age.**

Conclusion: **Global pain and disease activity are related to walking disability during the first 8 years of RA. Walking disability, knee pain, and global pain at 2 years follow-up predict walking disability later in the disease. In addition, the risk for walking disability increases during the disease process and with higher age at diagnosis.**

Key words: rheumatoid arthritis; walking ability; prediction; disease-related factors.

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INTRODUCTION

Walking disability is common in rheumatoid arthritis (RA). In a recent longitudinal study by our research group, walking disability was present in 57% of patients at initial disease presentation, and varied by around 40% from year 1 to year 8 as measured by the walking subscale of the Health Assessment Questionnaire (HAQ) (1).

Factors associated with walking disability throughout the course of RA have rarely been studied. Disease-related impairments of the lower extremities, such as pain, swelling, joint damage, decreased muscle strength and limited joint mobility, are thought to be associated with walking disability in RA. However, associations between disease-related impairments and walking disability have been investigated in only one study (2). In that cross-sectional study of patients with RA, with a mean disease duration of 6 years (range 0–44 years), global pain, swollen joints of the lower extremities and knee flexion were associated with the HAQ walking subscale.

Factors associated with general functional disability (as expressed by the HAQ total score) have been studied more frequently. Disease-related factors, such as disease activity, joint damage and rheumatoid factor, but also factors such as gender, age, psychological status, muscle strength and comorbidities, were found to be associated with functional disability (3–13). There is evidence that the association between disease-related factors and functional disability varies depending on the phase of RA. In early disease (disease duration < 5 years), functional disability was found to be related to disease activity in particular. In established disease (disease duration > 5 years) functional disability was found to be related mainly to joint damage (4, 12, 13). The question arises as to whether such differences in associations can also be found when relating walking disability and specific disease-related factors in RA.

To date, the predictors of walking disability are unknown. Both patients and clinicians value the ability to predict future walking disability, because knowledge of predictors may be important for planning (conservative) treatment aimed at reducing the level of walking disability. The purpose of the present study was to determine simple, easily accessible predictors that allow the prediction of walking disability in clinical practice.

The aims of the present study were: (*i*) to investigate the relationship between disease-related factors and walking disability in different phases of rheumatoid arthritis (RA); and (*ii*) to predict future walking disability in RA, using disease-related factors assessed 2 years after diagnosis.

METHODS

Study design

Since 1995, patients in The Netherlands aged 18 years and older with recent onset arthritis (peripheral arthritis of more than 2 joints and symptom duration of less than 3 years) have been included in an Early Arthritis Cohort (EAC) (14). This cohort was established in 1995 to study a wide variety of arthritis research topics, including the presence and course of the signs and symptoms of the disease process. Patients who were already treated with Disease-modifying antirheumatic drugs (DMARDs), as well as patients with crystal synovitis, osteoarthritis, psoriatic arthritis and spondylarthropathy were excluded. By May 2007 a total of 1622 patient had been followed up. Among other measurements, patients' disease activity, joint damage by scoring radiographs, and functional disability have been assessed at different time points. For the present study all patients fulfilling the 1987 American College of Rheumatology (ACR; formerly the American Rheumatism Association) criteria for RA (15) at baseline and/or at 1 year after inclusion were selected. Data of annual assessments were used, with a maximum of 8 years of follow-up.

Patient selection

A total of 848 (52%) patients fulfilled the ACR criteria for RA within the first year and were included in the study. All of these patients had at least a baseline measurement. The duration of follow-up varied between patients, as patients have been included from 1995 through May 2007. A total of 682 patients had a follow-up of 1 year, 341 patients had a follow-up of 4 years, and 121 patients had a full follow-up of 8 years. Our earlier report on the same cohort analysed drop-out from the cohort. The most common reasons for dropping out were: insufficient time ($n = 81$), moving to another area ($n = 46$), and disease remission ($n = 37$).

Drug treatment decisions were made by the rheumatologists according to clinical practice standards.

Measures

Dependent variable.

• Walking disability: for the assessment of walking disability one category of the Health Assessment Questionnaire (HAQ) disability index (16), i.e. walking (walking outdoors on flat ground, climbing up 5 steps), was used. The HAQ walking subscale (HAQ-walking) produces a score between 0 (no disability) and 3 (severe disability). Walking disability was regarded as absent if the score = 0 and as present if the score ≥ 1. The dichotomized score was used in the analyses.

Independent variables.

• Pain and swelling of joints of the lower extremity. Pain by palpation and the presence or absence of swelling of joints were assessed by a trained clinical research assistant. For the present study measurements of pain and swelling of the lower extremity, including the number of painful and swollen metatarsophalangeal (MTP) joints (range 0–10 for both pain and swelling) and pain and swelling of the knee joints (range 0–2 for both pain and swelling) were used. Pain in these joints was regarded as absent if the score for pain was 0 and present if the score ≥ 1. The same approach was used for swelling. The dichotomized scores (score 0 vs score ≥ 1) were used in the analyses.

• Joint damage of MTP and interphalangeal (IP) joints. For a subgroup of patients with a follow-up of at least 2 years ($n = 539$ at baseline), joint damage of the hands and feet on radiographs was assessed by 2 trained rheumatologists using the Sharp/van der Heijde method (17). The consensus between the 2 rheumatologists was high (Pearson's correlation of 0.84, $p < 0.01$, calculated for a subgroup of 67 radiographs). The score for the feet included a score for erosions (range 0–10 per joint) and a score for joint space narrowing (range 0–4 per joint) of the 10 MTP joints and the 2 IP joints of the big toes. Therefore, the total score for erosion in both feet ranges from 0 to 120 and the total score for joint space narrowing in both feet ranges from 0 to 48. Erosion of the feet was regarded as absent if the score for erosion was 0 and present if the score ≥ 1. The same approach was used for joint space narrowing. The dichotomized scores (score 0 vs score ≥ 1) were used in the analyses.

• Other variables. Gender, age at baseline, the absence (= 0) or presence (= 1) of IgM rheumatoid factor, symptom duration at baseline, the disease activity score that includes a 28-joint count and the erythrocyte sedimentation rate (mm/h) (DAS28; range 2–10) (18) and global pain assessed on a 100-mm visual analogue scale (VAS), were recorded.

Statistical analysis

Descriptive statistics were calculated for basic demographic and disease-related characteristics of the patients at baseline. Descriptive statistics of potential predictors of walking disability at 2 years follow-up were also calculated. The choice for predictors at 2 years follow-up was made because medication is supposed to be adjusted at that time.

Univariate logistic regression analyses at baseline and 2, 4, 6 and 8 years follow-up were performed with the dichotomized score of the HAQ-walking subscale as the dependent variable. Independent variables were: knee pain, knee swelling, MTP pain, MTP swelling, forefoot erosion, and forefoot joint space narrowing. These scores were dichotomized for their use in the analyses (0 = absent and 1 = present). Other independent variables were: gender, age at baseline (per 10 years), symptom duration at baseline, rheumatoid factor, VAS global pain (per 10 mm) and DAS28. Multivariate logistic regression models were constructed at 0, 2, 4, 6 and 8 years. p was set at < 0.20 for entering the models. Backwards selection using the likelihood ratio statistic of $p < 0.05$ to stay in the model was used to select the best variables.

Multilevel logistic regression analysis for longitudinal data (19) was performed with the dichotomized score of the HAQ-walking subscale from years 3 to 8 as the dependent variable. Potential predictors at year 2 were: walking disability, knee pain, knee swelling, MTP pain, MTP swelling, forefoot erosion, forefoot joint space narrowing, DAS28, VAS global pain (per 10 mm) and rheumatoid factor. In addition, gender, age at baseline (per 10 years), and the passing of time during follow-up were included as predictors. For the interpretability of the last predictor (time), years 3 to 8 were recoded into years 0 to 5. Interactions between time and the final predictors were analysed by forming interaction terms. A significance level of $p < 0.05$ was used to stay in the model. Odds ratios (ORs) with 95% confidence intervals were calculated for the final predictors.

All analyses were performed using SPSS (version 15.0), except for the multilevel logistic regression analysis for longitudinal data, which was performed using Stata (version 10.0; procedure xtmelogit with 30 adaptive quadrature points).

RESULTS

Descriptive analyses

Baseline patient characteristics are shown in Table I. Walking disability was present in 57% of the patients.

Values of potential disease-related predictors of walking disability at 2 years follow-up are shown in Table II. Data for 558 patients were present at year 2. The prevalence of patients with walking disability decreased to 36%. At clinical examination, 45% of patients had pain in at least one MTP joint, compared with 15% of patients who had pain in at least one knee joint. On radiographs, 39% of patients had at least one erosion of the forefoot. The mean DAS28 decreased to 3.2 (SD 1.3).

Associations with walking disability at various time points

In the univariate logistic regression analyses at 0, 2, 4, 6 and 8 years, the following variables were associated with HAQ-

Table I. *Patient characteristics at baseline (n = 848)*

Characteristics	Value
Female, %	69
Age, years, mean (SD)	55.2 (14.2)
Duration of symptoms, median (IQR)	0.0 (0.0–1.0)
Rheumatoid factor positive, %	51.3
DAS28, mean (SD)	5.2 (1.2)
Walking disability present, %	57

IQR: interquartile range; DAS28: disease activity score in 28 joints; SD: standard deviation.

Table II. *Values of potential disease-related predictors at 2 years follow-up*

	Value	*n*
Walking disability present, %	36.4	492
Knee pain present, %	15.4	558
Knee swelling present, %	7.9	558
MTP pain present, %	44.8	558
MTP swelling present, %	37.5	558
Forefoot erosion present, %	39.3	517
Forefoot joint space narrowing present, %	28.6	517
DAS28, mean (SD)	3.2 (1.3)	525
VAS-global pain, mean (SD)	29.9 (24.4)	532

n: number of patients evaluated; MTP: metatarsophalangeal joint; DAS28: disease activity score in 28 joints; VAS: visual analogue scale; SD: standard deviation.

walking at $p < 0.20$ at all time points: knee pain, MTP pain, MTP swelling, DAS28 and VAS-global pain. Knee swelling was associated with HAQ-walking at 0, 2, 4 and 6 years, age and gender at 4 years only, and rheumatoid factor at 6 years only (at $p < 0.20$). For the multivariate logistic regression analyses per time point these variables were entered in the model. The results of the multivariate analyses are shown in Table III. Only variables that showed a significant association with HAQ-walking are presented. VAS-global pain was associated with HAQ-walking at every studied time point during the first 8 years of RA. DAS28 was associated with HAQ-walking at every studied time point, except for year 8. Knee pain, knee swelling, MTP pain, and age were associated with HAQ-walking at one or more time points. Forefoot erosion and forefoot joint space narrowing were not significantly associated with HAQ-walking at any studied time point.

Predictors of future walking disability

Table IV shows the final prediction model derived from the multilevel logistic regression analysis for longitudinal data. HAQ-walking during follow-up (years 3 to 8) was predicted by the following disease-related variables at year 2: HAQ-walking, knee pain and VAS-global pain. Furthermore, age and the passage of time during follow-up predicted future walking disability. A significant effect for the interaction between HAQ-walking at year 2 and time was found, which means that, for the patients with walking disability at year 2, the risk for walking disability later in the disease remained constant (OR = 0.94, 95% confidence interval (CI) 0.84–1.16), whereas, for patients without walking disability at year 2, the risk for walking disability increased over time (OR = 1.23, 95% CI 1.05–1.44). The negative value of the interaction term means a decreasing effect of HAQ-walking at year 2 over time. There was no significant effect for cohort (i.e. year of inclusion in the EAC). Furthermore, no random time effect was found.

DISCUSSION

The results show that global pain was associated with walking disability at all studied time points during the first 8 years of the disease. This finding is in accordance with other studies, in which strong associations between pain and general functional disability, both in the early and established stages of RA, were found (2, 3, 20–22). In a cross-sectional study of Häkkinen et al. (2), using RA patients with a mean disease duration of 6 years, all subdimensions of the HAQ, including the HAQ walking subscale, were associated with global pain. It can be concluded that pain makes an important contribution to both general functional disability and walking disability.

Furthermore, DAS28 (all years except for year 8), knee pain, knee swelling and MTP pain (at several time points) were associated with walking disability. This means that both global disease activity and disease activity in lower extremity joints affect walking ability.

The presence of forefoot joint damage was not associated with walking disability during the first 8 years of the disease. In line with our findings, Häkkinen et al. (2) found that forefoot joint damage was not associated with the HAQ walking subscale. General functional disability (as measured with the total HAQ score) was found to be particularly related to disease activity in early disease (disease duration < 5 years), whereas

Table III. *Results of multivariate logistic regression analyses of walking disability with significant variables at 0, 2, 4, 6, and 8 years*

Variable	Baseline (*n* = 808) OR (95% CI)	Year 2 (*n* = 482) OR (95% CI)	Year 4 (*n* = 290) OR (95% CI)	Year 6 (*n* = 123) OR (95% CI)	Year 8 (*n* = 89) OR (95% CI)
Knee pain	1.98 (1.35–2.90)		2.78 (1.30–5.95)	5.56 (1.28–24.14)	
Knee swelling	1.78 (1.21–2.63)				
MTP pain	1.47 (1.05–2.06)				2.93 (1.08–7.95)
Age/10 years			1.27 (1.00–1.61)		
DAS28	1.50 (1.28–1.76)	1.66 (1.36–1.98)	1.53 (1.16–2.03)	1.97 (1.14–3.40)	
VAS-global pain/10 mm	1.14 (1.05–1.23)	1.09 (1.00–1.21)	1.38 (1.20–1.58)	1.39 (1.10–1.76)	1.45 (1.14–1.83)

OR: odds ratio; CI: confidence interval; MTP: metatarsophalangeal joint; DAS28: disease activity score in 28 joints; VAS: visual analogue scale. Dependent variable: HAQ-walking (0,1).

Table IV. *Results of multilevel logistic regression analysis of walking disability (from years 3 to 8) with significant variables*

Variable	B	Odds ratio	95% CI OR	*p*-value
Intercept (SD)	–4.88 (2.22)	–	–	–
HAQ-walking at year 2	3.90	49.38	19.26–126.65	<0.001
Pain knee at year 2	1.08	2.95	1.13–7.01	0.014
VAS-global pain/10 mm at year 2	0.23	1.26	1.09–1.46	0.002
Age/10 years	0.26	1.30	1.01–1.67	0.043
Time*	0.21	1.23	1.05–1.44	0.010
HAQ-walking at year 2 × time	–0.27	0.76	0.59–0.99	0.044

*Time = 0 equals 3 years follow-up; dependent variable: HAQ-walking from years 3 to 8 (0,1).
B: regression coefficient; CI: confidence interval; SD: standard deviation; HAQ: Health Assessment Questionnaire; VAS: visual analogue scale.

in established disease (disease duration >5 years) functional disability was found to be related mostly to joint damage (4, 12, 13). The present study did not show this pattern for walking disability in the first 8 years of RA. This finding might be due to improvements in medication in recent years, which have resulted in better control over joint damage. The contribution of joint damage to functional disability might appear later in the disease process.

Several disease-related factors at 2 years follow-up (i.e. walking disability, knee pain and global pain), age and the passage of time during follow-up predicted walking disability later in the disease.

The odds ratio for walking disability at 2 years follow-up was high, meaning that the presence of walking disability at year 2 was a strong predictor for walking disability later in the disease. This is in accordance with the literature regarding the prediction of general functional ability, where functional ability at baseline seems to be the most consistent prognostic factor of functional ability later in the disease (14, 23–26).

Knee pain at 2 years follow-up was shown to be a predictor for future walking disability, while the presence of forefoot pain did not predict walking disability. This might indicate that involvement of the large joints of the lower extremity has more impact on walking disability than involvement of the small joints. Further research is needed to confirm this finding.

Higher global pain at 2 years follow-up predicted future walking disability. An explanation for this finding could be that pain is reported by the patient, as is walking disability. Observed disease-related factors, i.e. rheumatoid factor and DAS28, did not predict future walking disability. This finding suggests that patient-reported factors might be more relevant than observed factors for the consequences of the disease.

A higher age and the passage of time during follow-up were found to be predictors of future walking disability, meaning an increase in the risk of walking disability with age and during the disease process. Sokka et al. (27) also found age to be a factor in the progression of functional disability. They analysed longitudinal data over 5 years for changes in the HAQ scores in patients with RA and age- and sex-matched controls from the general population and concluded that progression of functional disability among patients with RA and among persons in the general population is largely explained by the ageing process (27). Finally, a significant interaction effect with time for walking disability at year 2 was found. This means that for patients with walking disability at 2 years follow-up the risk for experiencing walking disability later in the disease remained constant, whereas for patients without walking disability at year 2 the risk for walking disability increased with time.

The choice for predictors at 2 years after initial disease presentation was made as medication is supposed to be adjusted at that time. In our earlier study (1) using data of the same cohort we found an improvement in disease-related variables (i.e. walking disability, disease activity, joint pain and joint swelling) from initial presentation to 2 years follow-up. From year 2 to year 8 these values were rather stable. For this reason, we used variables at 2 years after initial disease presentation to predict walking ability.

The presence of walking disability at 2 years follow-up strongly predicted future walking disability. Thus, a patient with walking disability at 2 years of follow-up is likely also to have walking disability later during follow-up. Walking disability at 2 years follow-up is therefore a reason to consider (conservative) treatment for lower extremity impairments and walking disability, including physiotherapy and podiatry.

There are some limitations of the present study. First, no measurements of pain, swelling and joint damage in other foot joints than the forefoot joints were recorded in the Early Arthritis Cohort (EAC). The EAC also lacks measurements of hip involvement. This limits the results of the present study regarding the impact of lower extremity involvement on walking disability.

In addition, no questionnaire specifically designed to measure lower extremity functioning was used. Instead, a subscale of the HAQ was used to measure weight-bearing functioning. However, the advantage of the HAQ is that it is the most common functional measure in rheumatology, and is easily accessible in rheumatology practice. Häkkinen et al. (2) showed a high internal consistency of the walking subscale (Crohnbach's $\alpha = 0.82$, 95% 1-sided CI = 0.78). The Crohnbach's α of the HAQ-subscale in our study was 0.88 (95% CI 0.86–0.90).

Furthermore, dichotomizing the major variables used in the present study reduces the information available in these variables. On the other hand, dichotomization makes interpretation of the results easier and therefore more useful for daily practice. More details of the variables included in the present study can be found in our earlier report (1).

Finally, there are some limitations of the use of an open cohort, e.g. the drop-out rate, and the heterogeneity of medications. These limitations have been addressed extensively in

our earlier report on the same cohort (1). Selection bias due to drop-out was concluded to be minimal. Also, the heterogeneous medical treatment history of patients with RA in our cohort, with a start in 1995, has been acknowledged. Biologics were introduced, around 2001 with possible effects on the frequency of foot impairments and walking disability.

In conclusion, global pain and disease activity are related to walking disability during the first 8 years of RA, and joint damage is not. Walking disability, knee pain and global pain at 2 years follow-up predict walking disability later in the disease. In addition, the risk for walking disability increases during the disease process and with higher age.

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