The Relationship Between Function and Disease Activity as Measured by the HAQ and DAS28 Varies Over Time and by Rheumatoid Factor Status in Early Inflammatory Arthritis (EIA). Results from the CATCH Cohort[§]

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Abstract: *Objective*: To investigate the relationship between function and disease activity in early inflammatory arthritis (EIA).

Methods: Canadian Early Arthritis Cohort (CATCH) (n=1143) is a multi-site EIA cohort. Correlations between the Health Assessment Questionnaire Disability Index (HAQ) and DAS28 were done at every 3 months for the first year and then at 18 and 24 months. We also investigated the relationship between HAQ and DAS28 by age (<65 versus ≥65) and RF (positive *vs* negative).

Results: Mean HAQ and DAS28 scores were highest at the initial visit with HAQ decreasing over 24 months from a baseline of 0.94 to 0.40 and DAS28 scores decreasing from 4.54 to 2.29. All correlations between HAQ and DAS28 were significant at all time points (p<0.01). The correlations between HAQ and DAS28 were variable over time. The strongest correlation between HAQ and DAS28 occurred at initial visit (most DMARD naive) (n=1,143) and 18 months (r=0.57, n=321) and 24 months (r=0.59, n=214). The baseline correlation between HAQ and DAS28 was significantly different than correlations obtained at 3, 6, and 12 months (p=0.02, 0.01, and 0.01, respectively). Age did not change the association between HAQ and DAS28 {<65 years old (r=0.50, n=868) versus ≥65 (r=0.48, n=254), p=0.49}. The correlation between HAQ and DAS28 was stronger with RF+ patients (r=0.63, n=636) *vs* RF negative (r=0.47, n=477), p=0.0043

Conclusion: Over 2 years in EIA, HAQ and DAS both improved; correlations at time points were different over 2 years and RF status affected the correlations.

Keywords: HAQ, early RA, disease activity, DAS, cohort, correlation, longitudinal.

SIGNIFICANT FINDINGS

1. The relationship between DAS and HAQ in early inflammatory arthritis is strongest at first visit to an ERA clinic but varies even in follow-up over 3 months to 2 years.

2. The relationship between DAS and HAQ varies by age and RF status.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disease that can result in progressive joint damage and significant functional impairment [1]. Disease-modifying anti-rheumatic drugs (DMARDs) have been shown to slow disease progression more effectively with early intervention than when started in more advanced disease, thus illustrating the importance of identifying RA early in its disease course [2-4]. With the recent publication

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of the 2010 ACR/EULAR criteria for RA, a new classification system now exists that identifies earlier stages of disease activity rather than relying on its late-stage features [5]. Earlier diagnosis will enable earlier implementation of disease-suppressing therapy to prevent or minimize undesirable disease sequelae, and has been shown to improve long-term outcomes particularly when combined with tighter control strategies (i.e. targeting to achieve disease remission or low disease activity states) [6].

The objective of this study was to investigate the relationship between disease activity and functional capacity in early inflammatory arthritis (EIA) using data collected from the Canadian Early Arthritis Cohort (CATCH). Disease activity was assessed using the Disease Activity Score (DAS28), while functional capacity was determined using the Health Assessment Questionnaire Disability Index (HAQ). Our goal was to determine correlations between HAQ and DAS28 scores over time in EIA using a contemporary cohort where the amount of joint damage would be substantially less than a prevalent RA cohort and possibly less than historical RA cohorts due to earlier diagnosis and institution of DMARD therapy. We also investigated the relationship between HAQ and DAS28 in older and younger subjects and in those who were RF positive or negative to determine the effects of age and RF status on this relationship.

Due to the inconsistency of the correlations that have been made in the past, our goal was to clarify the relationship between disease activity and functional capacity with particular focus on the early stages of inflammatory arthritis. Through comparison of correlations between HAQ and DAS28 at different stages in EIA (namely, 0, 3, 6, 9, 12, 18, and 24 months), we sought to determine how tightly these outcome measures were connected in a population with a relatively short duration of symptoms who had not yet accrued significant joint damage. This could provide a clearer understanding of overall health status and functional outcome in patients with early rheumatoid arthritis and how the relationship varies over time.

METHODS

Subjects

Data was collected from patients (n=1,143) enrolled into the Canadian Early Arthritis Cohort (CATCH) study. CATCH is an observational, prospective "real world" cohort of patients with early inflammatory arthritis (EIA) at 15 sites recruited since July 2007. Inclusion criteria were age >16 years, between 6 weeks and 12 months of persistent synovitis, and ≥2 swollen joints or 1 swollen metacarpophalangeal or proximal interphalangeal joint with ≥1 of the following: positive rheumatoid factor, positive anti-cyclic citrullinated peptide (anti-CCP), morning stiffness >45 minutes, response to nonsteroidal anti-inflammatory drugs, or painful metatarsophalangeal squeeze test. The majority of CATCH patients were recruited from the high population provinces, mainly Ontario and Quebec. All patients signed informed consent after reading a letter of information that was approved by either a central or institutional ethics board.

Patients were evaluated at baseline and at subsequent visits according to standard protocol. Treatment was left to the discretion of the treating physician and, included any combination of disease-modifying anti-rheumatic drug (DMARD) therapy and corticosteroids (prednisone doses of ≤10 mg daily were allowed). Therapy was adjusted at every visit with the aim of disease remission, defined as zero swollen joints. Virtually all the patients start DMARDs at first visit or shortly thereafter except those who decide not to (refuse, want to become pregnant, etc) or those with relative contraindications such as severe comorbidities or current infection. Patients are enrolling ongoing in this incident cohort and thus many people have met only one or two follow up times and the vast majority have not dropped out or been lost to follow up. We analyzed completers at each visit.

Validated Outcome Measures

Outcome measures were assessed at each visit (i.e. at baseline, 3, 6, 9, 12, 18, and 24 months). The HAQ was assessed as a measure of functional limitation. The HAQ has been found to be reproducible and validated as a reliable measurement for self-assessment [10]. Disease activity was assessed using the modified Disease Activity Score (DAS28). Previous studies comparing DAS and DAS28 have shown that modified 28-joint counts discriminate disease activity just as well as more comprehensive joint counts [11].

Statistical Analysis

We tested differences in measures of RA activity (DAS28) and functional impairment (HAQ). Pearson's correlation coefficients were calculated for HAQ and DAS28 at baseline, then every 3 months for the first year, and every 6 months in the second year. Both parametric and non-parametric statistics were calculated to help compare our results to previous studies. The data were stratified by patient age (≥65 versus <65 years old), and again in an exploratory analysis by RF status (positive versus negative) to determine if the relationships were different in early inflammatory arthritis. ANOVA was used to determine whether the HAQ and DAS28 varied among different groups at different time points. Statistical analyses were performed using SPSS software, version 18 for Mac (SPSS, Chicago, IL). P values less than 0.05 were considered statistically significant. Analyses were done for all patients in the cohort and repeated for the subset that had 24 months of complete follow up.

Competing Interests

RESULTS

Baseline demographic characteristics and clinical information regarding the 1,143 patients in the CATCH

cohort are illustrated in Table **1**. Overall, the mean age of the patients at baseline was 52.2 ± 15.8, of whom 71.2% were female. The mean duration of symptoms at study entry was 6.3 months. Follow up data for patients present at each visit was available for 518 patients during the first 12 months and 214 patients during the entire 24-month period. Mean and median values of HAQ and DAS28 for the 214 patients who completed 24 months of follow up were similar to corresponding visit values for the entire CATCH cohort (data not shown). Mean HAQ and DAS28 scores were highest at the initial visit (see Fig. **1**). Mean HAQ scores decreased over time from a baseline of 0.94 to 0.40 at 24 months. Mean DAS28 scores decreased over time from a baseline of 4.53 to 2.29 at 24 months. Both scores decreased over time after initiation of therapy indicating both an improvement in functional capacity and decreased joint inflammation.

Table 1. **Baseline Characteristics of CATCH Study Participants**

Characteristic	Value
Age (years), mean ± SD	52.2 ± 15.8
Female sex, no. (%)	815 (71.2)
Duration of symptoms (months) ± SD (Range)	6.3 ± 3.7
HAQ score, mean ± SD	0.94 ± 0.72
DAS28 score, mean ± SD	4.53 ± 1.99
RF positive, no. (%)	636 (57.1)
Anti-CCP positive, no. (%)	424 (60.0)
Tender joint count (TJC28) ± SD	8.19 ± 6.82
Swollen joint count (SJC28) ± SD	7.42 ± 6.28
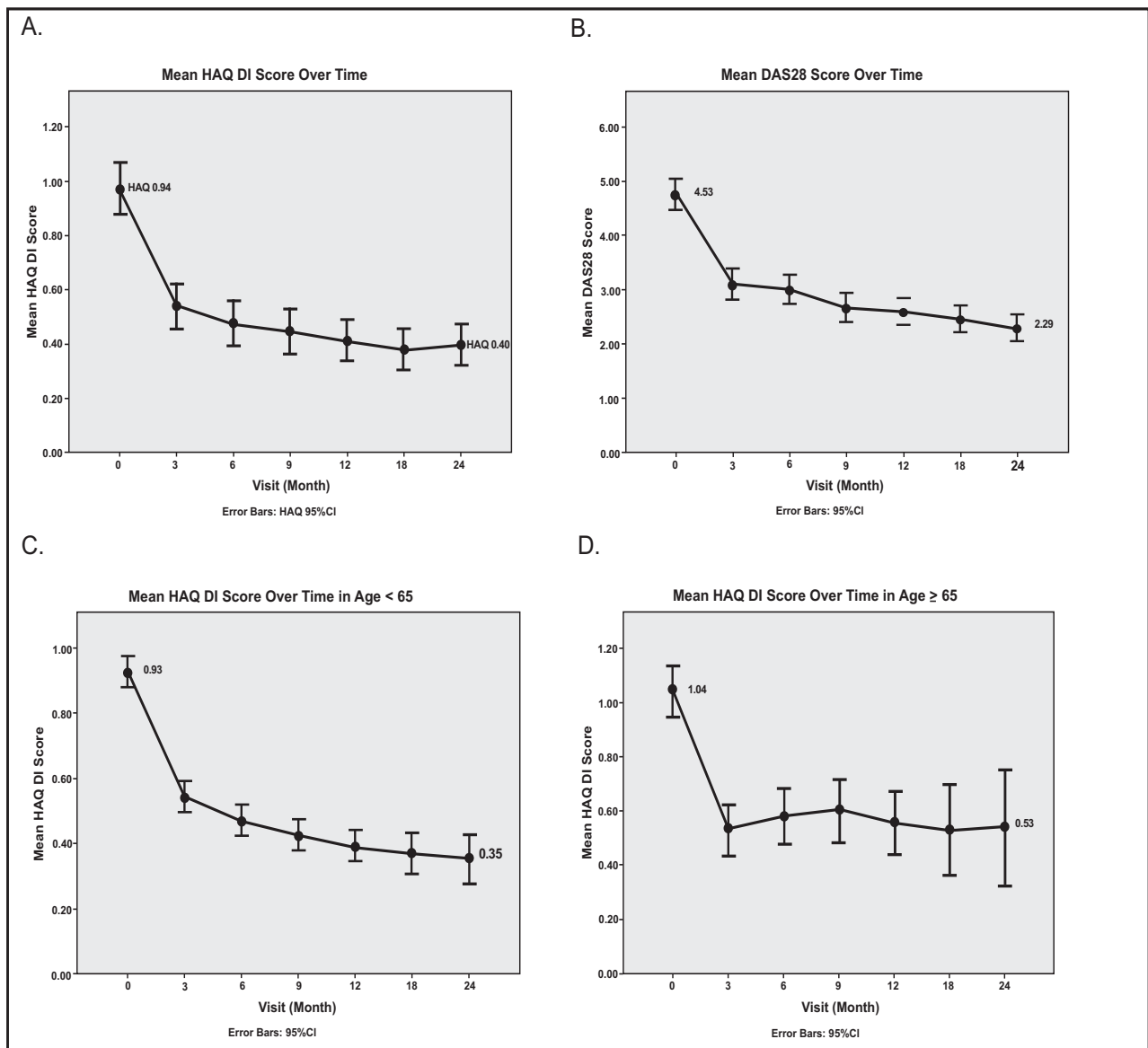
Fig. (1). Mean HAQ scores (**A**) and Mean DAS28 scores (**B**) over time. Outcome measures were assessed at each visit (i.e. at baseline and then every 3 months for the first year and every 6 months for the second year). Panels (**C**) and (**D**) show Mean HAQ scores over time subdivided by age.

The correlations between the HAQ score and the DAS28 are shown in Table **2**. Pearson correlations were significant at all measured time intervals (p<0.01). Correlations between HAQ and DAS28 varied over time, the strongest occurred at the first visit (r=0.53, n=1143), at which point many of the patients were still untreated. Strong correlations were again noted at 18 months (r=0.57, n=321) and at 24 months (r=0.59, n=214). At 6, 9, and 12 months the correlation was weaker (r=0.41, 0.30, and 0.40, respectively). The baseline correlation between HAQ and DAS28 was significantly different than correlations obtained at 3, 6, and 12 months (p=0.02, 0.01, and 0.01, respectively), but not statistically significantly different from values obtained at 18 and 24 months (p=0.54 and 0.43, respectively).

Table 2.   Correlations Between HAQ and DAS28 Over Time

Visit (Months)	No. of Patients	Pearson's Correlation Coefficient	P-Value[†] (Comparison to Previous Visit)
0	1,143	0.53[*]	-
3	900	0.43[*]	0.020
6	725	0.41[*]	0.812
9	581	0.30[*]	0.040
12	518	0.40[*]	0.105
18	321	0.57[*]	0.017
24	214	0.59[*]	0.828

[*]Correlations between HAQ and DAS28 are significant at the 0.01 level (2-tailed). Note the N decreases as many patients have not achieved long enough follow up.
[†] P-values compare correlation coefficient for HAQ and DAS28 at specified visit to correlation obtained at preceding visit.

Patients who were RF+ had consistently higher mean HAQ and DAS28 scores throughout the disease course (see Fig. **2**). The correlation between HAQ and DAS28 was statistically significantly stronger with RF+ patients (r=0.63, n=636) than RF negative patients (r=0.47, n=477), p=0.0043. Age did not change the association between HAQ and DAS28. Patients aged ≥65 years had a slightly weaker correlation (r=0.52) overall than younger patients (r=0.55), although the result was not statistically significant (p=0.49). Over the disease course, HAQ scores in the older age group remained consistently elevated in comparison to those for younger patients (see Fig. **2**).

DISCUSSION

Over a two-year study period of patients with early inflammatory arthritis, we found that functional capacity and disease activity both improved after initiation of treatment. Our findings differ from previous studies that have found worsening functional capacity over the course of RA despite stable disease activity; however, our follow up was relatively short [7]. This finding may reflect improved response to therapeutic treatment options that have become available in the last decade, as well as more aggressive treatment strategies than in older reports. It is difficult to determine if the HAQ and DAS relationship that decreases over time is due to variability in the response to treatment in addition to the variability between subsets such as RF positive and negative patients.

We have reviewed the literature for previous correlations between HAQ and DAS over time and identified studies conducted approximately a decade ago looking at more advanced rheumatoid arthritis using a Medline search for HAQ and DAS and RA and relationship or correlation, and reviewing papers that were relevant and their references. Our search yielded an inconsistent relationship between functional capacity and disease activity with the relationship varying over time and between papers (see Table **3**).
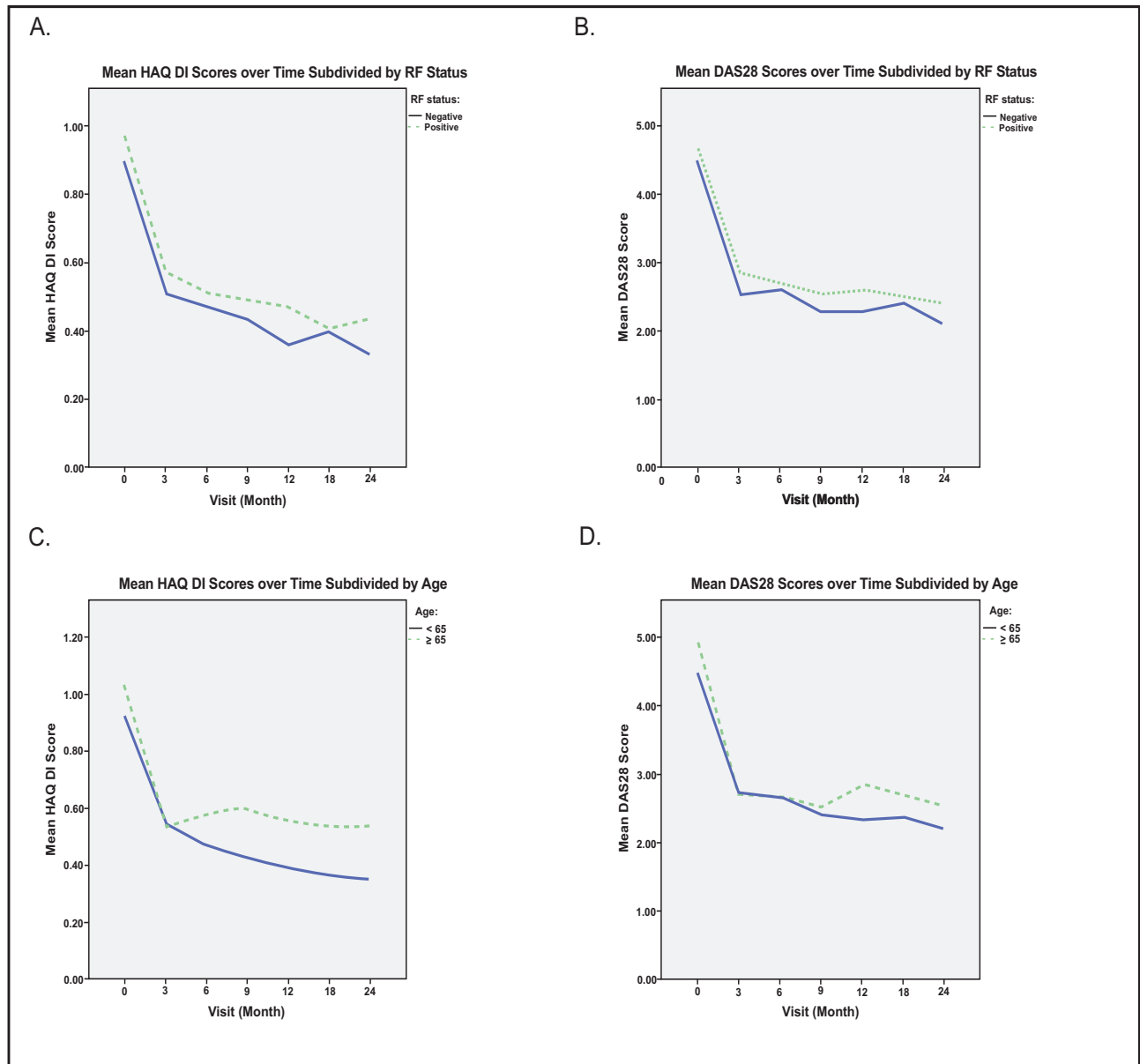
In a nine-year, open, prospective study population of 378 patients with early RA started in 1985, Welsing, *et al.* found the HAQsability index correlated significantly with DAS scores especially prior to the development of permanent joint damage [7]. Functional capacity was most influenced by disease activity and joint inflammation in early disease, permanent joint damage was the predominant factor in more advanced disease [7]. Another study suggested that disease activity is the major determinant of the HAQ score [8]. Although worsening joint destruction contributed to a decline in functional capacity over the years, it was never the sole determinant of the HAQ score. Likewise, data from the TEMPO trial published in 2006 showed that the severity of disease activity over 1 year in patients with active RA (disease duration 6 months to 20 years) was strongly correlated with greater functional disability as measured by the HAQ [9].

Most of the patients studied had mild or no significant damage as these were early onset but we did not have the Xrays scored which is a limitation. A study by Drossaers-Bakker, *et al.* found variations to be reflective of changing disease activity [8].

In our study, it appears the strongest correlation between HAQ and DAS28 in the first year occurred at the initial visit, at which point most of the patients were still untreated. Therefore, we conclude there is a correlation between functional capacity and disease activity that appears to be strongest at disease onset, but remains strong over the course of EIA.

Stronger correlations between HAQ and DAS28 were observed with RF positive patients and with younger patients. Rheumatoid factor has previously been shown to be predictive of RA development in EIA [12]; it also serves as a prognostic marker as its presence is associated with both more severe disease and radiographic joint erosions. Because RF is a risk factor of joint damage, early control of disease activity, particularly in this subset would likely improve long-term functional outcome.

The lack of correlation between HAQ and DAS28 in older patients may be due to factors other than disease activity, whereby comorbidities may contribute to impairment of functional capacity. Residual functional limitation during clinical remission may be attributed to disease-related damage, and has been identified as an irreversible component of the HAQ in later stages of the disease whereas the component of functional limitation affected by active inflammation is considered reversible [13]. In contrast with more advanced RA, our cohort represented patients with new onset inflammatory arthritis whose erosive joint damage was theoretically minimal. Maintaining good functional capacity in these patients through correction of reversible causes (i.e. control of disease activity) is the main goal of treatment.

A.

Mean HAQ DI Scores over Time Subdivided by RF Status

C.

Mean HAQ DI Scores over Time Subdivided by Age

B.

Mean DAS28 Scores over Time Subdivided by RF Status

D.

Mean DAS28 Scores over Time Subdivided by Age

Fig. (2). Mean HAQ and DAS28 scores over time subdivided by RF status and age. (**A**) Mean HAQ scores over time subdivided by RF status. (**B**) Mean DAS28 scores over time subdivided by RF status. (**C**) Mean HAQ scores over time subdivided by age. (**D**) Mean DAS28 scores over time subdivided by age. Outcome measures were assessed at each visit (i.e. at baseline and then every 3 months for the first year and every 6 months for the second year).

When interpreting outcome measures such as the HAQ, various sources of functional limitation should be considered such as normal aging and OA [13]. Combining the HAQ with other clinical measures, such as the DAS28 and mTSS (i.e. modified total Sharp score, a validated measure of joint space narrowing and joint erosion), helps to overcome this obstacle and identify the cause of functional disability.

Both disease activity and functional impairment are related to work disability even at baseline visit in early RA [14]. Higher disease activity, older age, female sex, and positive rheumatoid factor status have previously been shown to be predictors of a worse functional capacity, independent of the DAS [7].

Our study has other limitations. The disease duration and follow up are relatively short. In addition, the majority of patients included in this study have not yet completed two years of follow up; however, we have very little missing data and a very low drop-out rate and our completers are comparable to the entire cohort in their baseline characteristics.

In conclusion, by studying early inflammatory arthritis, we were able to test the stability of the initial correlations of HAQ and DAS28. With earlier identification of RA patients, validated outcome measures that have been used to monitor disease activity and functional limitation in the past can now be applied to a patient population at an earlier stage in the disease course. The HAQ and DAS28 are important tools to monitor disease progression, and both are necessary with

every patient encounter to help elucidate the cause of functional impairment in early RA and to provide a clearer understanding of overall health status and functional outcome in patients with rheumatoid arthritis.

Table 3.   Published Correlations Between HAQ and DAS

Published Study	Time Period	Correlation Coefficient	P Value or (95% C.I.)
Prevoo, *et al.* (1995)[i]	6-year period	0.38	p < 0.05
Drossaers-Bakker, *et al.* (1999)[ii]	Baseline	0.68	p < 0.001
	Year 3	0.51	p < 0.001
	Year 6	0.79	p < 0.001
	Year 12	0.61	p < 0.001
Sokka, *et al.* (2000)[iii]	Baseline	0.45	p < 0.001
Welsing, *et al.* (2001)[iv]	Baseline	0.40	(0.28, 0.51)
	Year 3	0.40	(0.27, 0.51)
	Year 6	0.79	(0.71, 0.85)
	Year 9	-0.02	(-0.27, 0.22)
Van der Heijde, *et al.* (2006)[v]	52-week period	0.64	p < 0.0001

[i.]*Pearson correlation coefficient* for 324 patients with recent-onset RA (ACR criteria, disease duration < 1 year) from 2 clinics followed for 6 years between 1985 and 1994 [11].

[ii.]*Spearman's correlation coefficients for* 132 female patients, aged 20-50 years at first visit, followed in a 12-year prospective cohort of RA patients [8].

[iii.]*Spearman's correlation coefficient* for 141 patients with RA (1987 ACR revised criteria), median disease duration 11.8 years, minimum of 3 years [15].

[iv.]*Pearson correlations* were calculated between the HAQ and the DAS for 378 patients with recent-onset RA (disease duration < 1 year) in a prospective study started in 1985 with data collected at 0, 3, 6, and 9 years after study start [7].

[v.]*Pearson correlation coefficient:* of 682 enrolled patients, 522 completed 52 weeks of treatment. Correlation between patient reported health status measures and measures of disease activity were calculated over 52 weeks (LOCF analysis) [9].

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

ACKNOWLEDGEMENTS

REFERENCES

[1]   Jenkins JK, Hardy KJ, McMurray RW. The pathogenesis of rheumatoid arthritis: a guide to therapy. Am J Med Sci 2002; 323(4): 171-80.

[2]   van der Heide A, Jacobs JW, Bijlsma JW, *et al.* The effectiveness of early treatment with "second-line" antirheumatic drugs. A randomized, controlled trial. Ann Intern Med 1996; 124(8): 699-707.

[3]   Anderson JJ, Wells G, Verhoeven AC, *et al.* Factors predicting response to treatment in rheumatoid arthritis: the importance of disease duration. Arthritis Rheum 2000; 43(1): 22-9.

[4]   Lard LR, Visser H, Speyer I, *et al.* Early versus delayed treatment in patients with recent-onset rheumatoid arthritis: comparison of two cohorts who received different treatment strategies. Am J Med 2001; 111(6): 446-51.

[5]   Aletaha D, Neogi T, Silman AJ, *et al.* 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/ European League Against Rheumatism collaborative initiative. Arthritis Rheum 2010; 62(9): 2569-81.

[6]   Haraoui B, Pope J. Treatment of Early Rheumatoid Arthritis: Concepts in Management. Semin Arthritis Rheum 2011; 40(5): 371-388.

[8]   Welsing PM, van Gestel AM, Swinkels HL, *et al.* The relationship between disease activity, joint destruction, and functional capacity over the course of rheumatoid arthritis. Arthritis Rheum 2001; 44(9): 2009-17.

[8]   Drossaers-Bakker KW, de Buck M, van Zeben D, *et al.* Long-term course and outcome of functional capacity in rheumatoid arthritis: the effect of disease activity and radiologic damage over time. Arthritis Rheum 1999; 42(9): 1854-60.

[9]   van der Heijde D, Klareskog L, Singh A, *et al.* Patient reported outcomes in a trial of combination therapy with etanercept and methotrexate for rheumatoid arthritis: the TEMPO trial. Ann Rheum Dis 2006; 65(3): 328-34.

[10]   Bruce B, Fries JF. The Stanford Health Assessment Questionnaire: a review of its history, issues, progress, and documentation. J Rheumatol 2003; 30(1): 167-78.

[11]   Prevoo ML, van 't Hof MA, Kuper HH, *et al.* Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum 1995; 38(1): 44-48.

[12]   van der Heijde D, Desiree M, Landewe, *et al.* Joint space narrowing has a stronger impact on physical function than joint erosion: results from 8-year longitudinal analysis (Abstract). Arthritis Rheum 2010; 62(Suppl 10): 1113.

[13]   Aletaha D, Smolen J, Ward MM. Measuring function in rheumatoid arthritis: Identifying reversible and irreversible components. Arthritis Rheum 2006; 54(9): 2784-92.

[14]   Mussen L. Low prevalence of work disability (WD) in early inflammatory arthritis (EIA) and early rheumatoid arthritis: results from the catch cohort. Rheumatol Int 2013; 33(2): 457-65.

[15]   Sokka T, Kankainen A, Hannonen P. Scores for functional disability in patients with rheumatoid arthritis are correlated at higher levels with pain scores than with radiographic scores. Arthritis Rheum 2000; 43(2): 386-9.