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Age affects joint space narrowing in patients with early active rheumatoid arthritis

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ABSTRACT

Background: Joint space narrowing (JSN) in rheumatoid arthritis (RA) may be a manifestation of (primary) osteoarthritis becoming more prominent with age. We investigated the severity and predictors of JSN progression among different age groups.

Methods: 10-year follow-up data of the BeSt study, a randomised controlled treat-to-target trial in early RA were used. Annual X-rays of hands and feet were scored using the Sharp/van der Heijde score (SHS). Subgroups were defined by age at baseline: ≥55, ≥40<55 and <40 years. JSN progression predictors were assessed by Poisson regression.

Results: Baseline JSN scores (median (IQR)) were higher in patients ≥55 (2.0 (0.0–6.0)) compared with the other age groups: 1.0 (0.0–3.0) ≥40<55 and 0.3 (0.0–3.0) <40, p<0.001. After 10 years, total JSN and SHS were similar in all age groups. In patients ≥55 the mean erythrocyte sedimentation rate (ESR) over time (relative risk 1.02 (95% CI 1.00 to 1.03)) and the combined presence of rheumatoid factor and anticitrullinated protein antibodies (RF+/ACPA+) (3.27 (1.25–8.53)) were significantly correlated with JSN progression. In patients <40 the baseline swollen joint count (SJC; 1.09 (1.01–1.18)) and ESR over time (1.04 (1.02–1.06)) were significantly associated.

Conclusions: At baseline, patients with RA ≥55 years had more JSN than younger patients but after 10 years JSN scores were similar between age groups. Independent risk factors for JSN progression were baseline SJC and ESR over time in patients <40, RF +/ACPA+ and ESR over time in patients ≥55 years. This suggests that mechanisms leading to JSN progression are related to (residual) rheumatoid inflammation and vary between age groups. These mechanisms remain to be elucidated.

Trial registration numbers: NTR262, NTR265.

Key messages

What is already known about this subject?

- Joint space narrowing (JSN) in rheumatoid arthritis may be a manifestation of (primary) osteoarthritis becoming more prominent with age.
- Older rheumatoid arthritis patients have higher damage scores in early disease, partly caused by more JSN.

What does this study add?

- JSN scores at baseline are higher in older age groups, particularly in the proximal interphalangeal joints.
- After 10 years no statistical difference in JSN scores between age groups is observed; however, risk factors for JSN progression differ between age groups.

How might this impact on clinical practice?

- JSN in older patients in early rheumatoid disease might be a manifestation of primary osteoarthritis and should be interpreted with caution.

INTRODUCTION

Joint damage in rheumatoid arthritis (RA) causes progressive disability in patients.[1] Synovial inflammation activates an immune process that causes articular cartilage degradation leading to joint space narrowing (JSN) and excessive local bone resorption and inadequate bone formation resulting in bone erosions.[2 3] Presence and progression of bone erosions and JSN can be scored using plain radiographs of hands and feet using the Sharp/van der Heijde score (SHS).[4] It is well known that joint damage progression is a result of continued high disease activity.[5] Thus, scoring progression of radiographic damage may affect how efficacy of treatment is interpreted, and can influence therapeutic decisions.

However, progression of JSN, and probably to a lesser extent of erosions, may also be a manifestation of primary osteoarthritis (OA) becoming more prominent with increasing age. Lawrence *et al*[6] showed age-related increases in radiographic OA in both women

(prevalence OA of 7.6% in those aged ≥15<24 vs 97% in patients >65) and men (prevalence OA of 9.4% in those aged ≥15<24 vs 97% in patients >65). OA progression seems to be relatively slow but more frequent and more severe OA progression in the distal and proximal interphalangeal joints of older patients was reported previously.[7 8] No definite clinical progression risk factors for radiographic OA progression are known. More painful joints and more self-reported pain appear to increase radiographic OA progression.[9]

Older patients with RA are shown to have a higher baseline damage score. Khanna *et al*[10] showed that this was mainly due to more JSN, and this associated with features of hand OA. However, Mangnus *et al*[11] showed that the difference between different age groups could not be fully explained by JSN. Others reported that patients with a higher age at onset were more often anticitrullinated protein antibodies (ACPA) positive and had more erosions at baseline, and also higher disease activity scores (DASs) and higher erosion scores during the first 2 years of treatment.[12 13] Still others showed that in advanced RA, older patients had more JSN than younger patients.[14]

We hypothesised that JSN progression may show a different pattern in older than in younger patients with RA. In addition, predictors of JSN may be different between these age groups, due to primary OA becoming more prominent with increasing age. We aimed to identify and compare age-specific baseline risk factors for the development of JSN in patients who participated in the BeSt study, a multicentre randomised clinical trial. Patients with early RA were treated according to one of four dynamic treatment strategies all aiming a low disease activity (DAS≤2.4). Patients were followed for 10 years and radiographs of hands and feet were obtained annually to score the bone erosions and JSN by the SHS.

PATIENTS AND METHODS

Participants and design

The BeSt (Dutch acronym for treatment strategies) a multicentre, randomised clinical trial included 508 patients with recent-onset active RA (1987 revised American College of Rheumatology criteria[15]) and a symptom duration ≤2 years. All participants gave written informed consent and the Medical Ethics Committee of each participating centre approved the study protocol.

Patients were randomised into four treatment strategies: (1) sequential monotherapy; (2) step-up combination therapy; (3) initial combination therapy with methotrexate, sulfasalazine and prednisone; and (4) initial combination therapy with methotrexate and infliximab. Treatment adjustments were made every 3 months aiming at a DAS<2.4. If DAS was ≤2.4 for 6 months, treatment could be tapered to maintenance dose, and if then DAS<1.6 was achieved for another 6 months, medication was discontinued. Once the DAS was ≥1.6 treatment was restarted. Details of the BeSt study have been published elsewhere.[16 17]

Methods of measurement

At baseline, rheumatoid factor (RF) status was evaluated. ACPA status was determined afterwards by the anticyclic citrullinated peptide test in available stored baseline serum samples. Health assessment questionnaires (HAQs)[18] and the DAS were assessed at baseline and every 3 months for 10 years. Baseline and annual radiographs, up to 10 years, of hands and feet were collected and were scored, by two independent readers, blinded for patient identity and time order, using the SHS.[4]

Statistical analysis

Median age at baseline in our population was 54.9 years. Based on this median, and considering the unlikelihood of OA in patients <40 years old[6] three arbitrary subgroups were created: 'group <40' comprising patients aged <40 years, 'group ≥40<55' with patients ≥40 years but <55 years and 'group ≥55' with patients ≥55 years old at baseline. Baseline characteristics were compared with the multinomial variable 'age group' by the χ^2 test, one-way analysis of variance and Mann-Whitney U test. Pairwise comparisons between the age groups were performed with the χ^2 test, t-test and Kruskall-Wallis test. Mean SHS, erosion and JSN (progression) scores after 10 years were compared between groups using one-way analysis of variance, with robust SE estimation and p values because of the skewed non-normal distributions.

After 10 years, DAS and HAQ were known for 292/508 patients, and radiographs were available for 278/508 patients. To avoid bias due to missing data, multiple imputation techniques were performed. The imputed values are based on all radiographs in the study, and are consequently less sensitive to one measurement error or picture of low quality. To improve resemblance to the normal distribution, annual JSN and erosion scores were log-transformed before imputing. The imputation model incorporated the baseline variables: age, sex, body mass index (BMI), smoking status, randomisation arm, RF status, ACPA status, log-transformed erosion and narrowing score, HAQ score and the components of the DAS. Annual log-transformed erosion and narrowing scores, 10-year HAQ scores and biannual DAS were also included in the imputation model.

SHS and JSN scores are always whole non-negative numbers and therefore, JSN progression scores are integers. In our study, only 2.2% of the progression scores were negative; hence, JSN progression is approximately a count. Furthermore, 37% of the patients had zero JSN progression. For regression modelling of the JSN progression, we used robust Poisson regression after setting the negative progressions to zero. This regression method assumes that the covariates have a multiplicative effect on the mean progression scores, but remains valid if the Poisson regression is violated. We report the

Table 1 Baseline characteristics in the different age groups

	Group <40 n=81	Group ≥40<55 n=179	Group ≥55 n=248	p Value
Age, mean±SD, years	33±6	49±5	66±8	
Women, n (%)	61 (75)	125 (70)	157 (63)	0.10
Smoking, no (%)	25 (30)	78 (44)	74 (30)	0.01
BMI, mean±SD	24.4±4.3	26.6±4.5	26.1±3.8	0.001
Time from diagnosis to inclusion, median weeks (IQR)	1.6 (0.7–3.1)	2.4 (1.0–5.3)	2.7 (1.0–4.7)	0.004
Symptom duration, median weeks (IQR)	26.1 (13.4–57.9)	24.6 (15.3–56.1)	22.4 (13.3–44.3)	0.25
RF positive, n (%)	53 (65)	123 (69)	153 (62)	0.32
ACPA positive, n/total n (%)	43/78 (55)	116/169 (69)	132/226 (58)	0.05
DAS, mean±SD	4.4±0.9	4.3±0.8	4.5±0.9	0.12
HAQ score, 0–3 scale, mean±SD	1.3±0.7	1.4±0.6	1.4±0.7	0.49
CRP, mean±SD	35.4±43.2	32.8±41.9	41.1±43.2	0.14
ESR, mean±SD	37.1±25.4	34.7±25.7	45.8±28.4	<0.001
Ritchie Articular Index	14 (9–20)	13 (10–17)	13 (9–18)	0.53
Swollen joint count	14 (10–18)	12 (9–18)	14 (10–19)	0.06
Total SHS (0–448 scale)				
Median (IQR)	1.0 (0.0–3.0)	1.0 (0.0–4.5)	2.5 (1.0–7.4)	<0.001
Mean±SD	2.4±3.7	3.1±4.9	5.0±6.8	
Erosion score, 0–280 scale				
Median (IQR)	0.0 (0.0–0.3)	1.0 (0.0–3.0)	0.0 (0.0–1.0)	<0.001
Mean±SD	0.5±1.4	0.9±2.6	1.1±2.0	
JSN score, 0–168 scale				
Median (IQR)	0.3 (0.0–3.0)	1.0 (0.0–3.0)	2.0 (0.0–6.0)	<0.001
Mean±SD	1.9±2.9	2.2±3.2	3.9±5.5	
Treatment strategy				
Sequential monotherapy, n (%)	19 (24)	51 (29)	56 (23)	0.52
Step-up therapy, n (%)	18 (22)	47 (26)	56 (23)	
Initial combination therapy with prednisone, n (%)	22 (27)	45 (25)	66 (27)	
Initial combination therapy with infliximab, n (%)	22 (27)	36 (20)	70 (28)	

ACPA, anticitrullinated protein antibodies; CRP, C reactive protein; DAS, disease activity score; ESR, erythrocyte sedimentation rate; HAQ, health assessment questionnaire; JSN, joint space narrowing; RF, rheumatoid factor; SHS, Sharp/van der Heijde score.

exponentiated regression coefficients, which are interpreted as ratios of means (relative to the reference category for categorical predictors, or corresponding to a one unit increase for numerical predictors). When analyses were carried out separately for each age group, we applied Bonferroni correction to adjust for multiple testing.

In the multivariate analysis, RF status and ACPA status were coded into one variable because both antibodies are frequently present in the same patients and consequently their influence is confounded by the effect of the other antibody. Since treatment strategy is randomly allocated, it does not confound the effect of other variables and was therefore not included in the multivariate models. All risk factors with a p value <0.2 were entered in the multivariate models with Bonferroni correction to correct for multiple testing. Accordingly, predictor variables with p values <0.0167 were considered significant, 98.33% CIs are given, and only predictor variables with univariate p values <0.066 were entered in the multivariate model. Since we selected our regression variables carefully, we did not remove the determinants from the multivariate analysis when they did not attain significance. Analyses were performed with SPSS V.20.0.

RESULTS

Baseline

In the BeSt study, 508 patients were included, 81 (16%) aged <40, 179 (35%) aged ≥40<55 and 248 (49%) aged ≥55. Mean age at baseline was 33, 49 and 66 in the three age groups, respectively. Table 1 shows the baseline characteristics of the three age groups.

The variables that were statistically significantly associated with the multinomial variable 'age group' (<40, ≥40<55 and ≥55) showed statistically significant differences when compared pairwise between age groups. Thirty per cent, 44% and 30% of the three age groups participants were noted as 'smokers' at baseline (group ≥40<55 vs group ≥55, p=0.004). Mean BMI was 24.4 in group <40, 26.6 in group ≥40<55 (group <40 vs group ≥40<55, p<0.001) and in 26.1 in group ≥55 (group <40 vs group ≥55, p=0.001). Erythrocyte sedimentation rate (ESR) was higher in group ≥55 compared with group <40 (mean 46 vs 37; p=0.01) and group ≥40<55 (mean 46 vs 35; p<0.001). Time from diagnosis was lower in group <40 compared with group ≥40<55 and group ≥55 (p=0.002 and p=0.004, respectively).

Pairwise age group comparison of the variables not statistically significantly associated with 'age group' was

Table 2 Outcomes 10 years after randomisation

	Group <40 n=81	Group ≥40<55 n=179	Group ≥55 n=248	p Value <40 vs ≥40<55	p Value <40 vs ≥55	p Value ≥40<55 vs ≥55
DAS over time, mean±SD	2.0±0.7	2.0±0.6	2.1±0.6	0.68	0.57	0.18
ESR over time, mean±SD	17.2±12.3	17.8±11.6	22.1±16.1	0.73	0.01	<0.01
Total SHS, 0–448 scale						
Median (IQR)	4.1 (1.2–12.5)	6.5 (2.0–15.5)	7.0 (3.0–15.5)	0.69	0.57	0.75
Mean±SD	15.0±32.4	13.5±20.3	12.9±17.1			
SHS progression						
Median (IQR)	2.7 (0.0–7.0)	3.0 (0.5–11.7)	2.5 (0.5–8.4)	0.54	0.19	0.15
Mean±SD	12.6±31.0	10.4±18.5	7.8±15.9			
Erosion score, 0–280 scale						
Median (IQR)	1.0 (0.0–3.8)	1.3 (0.3–5.0)	1.5 (0.5–4.0)	0.91	0.37	0.07
Mean±SD	4.9±13.0	5.1±9.6	3.6±6.5			
Erosion progression						
Median (IQR)	0.8 (0.0–3.0)	1.0 (0.0–4.0)	0.8 (0.0–2.1)	0.93	0.20	0.02
Mean±SD	4.3±12.7	4.2±8.1	2.5±6.2			
JSN score, 0–168 scale						
Median (IQR)	3.0 (0.5–8.0)	4.0 (1.0–10.0)	5.3 (2.0–11.5)	0.48	0.73	0.47
Mean±SD	10.1±20.4	8.4±12.4	9.4±12.0			
JSN progression						
Median (IQR)	1.0 (0.0–5.0)	1.9 (0.0–7.5)	1.8 (0.0–5.5)	0.36	0.20	0.49
Mean±SD	8.2±19.3	6.2±11.6	5.4±11.2			

DAS, disease activity score; ESR, erythrocyte sedimentation rate; SHS, Sharp/van der Heijde score; JSN, joint space narrowing.

performed, but showed no statistically significant differences between groups except for DAS and swollen joint count (SJC; data not shown). Age group <40 had similar baseline DAS and SJC compared with groups ≥40<55 and ≥55. Group ≥40<55 had lower DAS compared with group ≥55 (4.3 vs 4.5; p=0.04) and a lower baseline SJC compared with group ≥55 (median (IQR): 12 (9–18) vs 14 (10–19); p=0.02). More patients were ACPA positive in group ≥40<55 than in group <40 (68% vs 55%; p=0.05) and group ≥55 (68% vs 58%; p=0.05). Both ACPA and RF were present in 46%, 60% and 48% of the patients in group <40, group ≥40<55 and group ≥55, respectively.

All baseline radiographic scores were similar in group <40 and group ≥40<55. Baseline SHS was higher in group ≥55 (median 2.5, IQR 1.0–7.4) compared with the other groups (group <40: 1.0 (0.0–3.0); group ≥40<55: 1.0 (0.0–4.5); p<0.001). Baseline erosion scores were higher in group ≥55 compared with group ≥40<55 (1.0 (0.0–3.0) vs 0.0 (0.0–1.0); p=0.006) and group <40 (0.0 (0.0–0.3); p<0.001). Also, more patients in group ≥55 had JSN≥0.5 (70% vs 50% in group <40; p=0.001; and 55% in group ≥40<55; p=0.002) and the median JSN score was higher compared with the other groups (2.0 (0.0–6.0) in group ≥55 vs 0.3 (0.0–3.0) in group <40 and 1.0 (0.0–3.0) in group ≥40<55; p<0.001). JSN in the proximal interphalangeal joints increased with age: (mean±SD) 0.1±0.5 (median (IQR) 0.0 (0.0–0.0)) in group <40, 0.2±0.5 (0.0 (0.0–0.0)) in group ≥40<55 and 0.4±0.9 (0.0 (0.0–0.5)) in group ≥55 (<40 vs ≥40<55 p=0.06; <40 vs ≥55 p=0.001; ≥40<55 vs ≥55 p=0.02). This trend was not observed in the metacarpophalangeal joints. JSN scores in metacarpophalangeal joints are higher in group ≥55 compared with group ≥40<55 (0.6 ±1.2 (0.0 (0.0–1.0)) vs 0.4±0.9 (0.0 (0.0–0.0)), p=0.01) but not compared with group <40 (0.5±0.9 (0.0 (0.0–1.0)); <40 vs ≥55, p=0.51).

Outcomes after 10 years

The 10-year follow-up characteristics are shown in table 2. Average DAS over time was similar in all groups. ESR over time was higher in group ≥55 (mean 22) compared with the other groups (mean 17 <40 and mean 18 in group ≥40<55; p=0.01 group <40 vs ≥55, p<0.01 group ≥40<55 vs ≥55). After 10 years of follow-up none of the mean radiographic scores differed between the age groups but JSN≥0.5 was found more often in group ≥55 (90%) compared with group <40 (75%) and in group ≥40<55 (80%; p=0.001 and p=0.008, respectively).

SHS progression was similar in all groups (2.7 (0.0–7.0); 3.0 (0.5–11.7); 2.5 (0.5–8.4)). Erosion progression scores were higher in group ≥40<55 compared with group ≥55 (1.0 (0.0–4.0) vs 0.8 (0.0–2.1); p=0.02). JSN progression did not differ statistically significantly between the age groups: (mean±SD) 8.2±19.3 (median (IQR) 1.0 (0.0–5.0)) in group <40, 6.2±11.6 (1.9 (0.0–7.5)) in group ≥40<55 and 5.4±11.2 (1.8 (0.0–5.5)) in group ≥55. Scores at 10 years and progression scores are

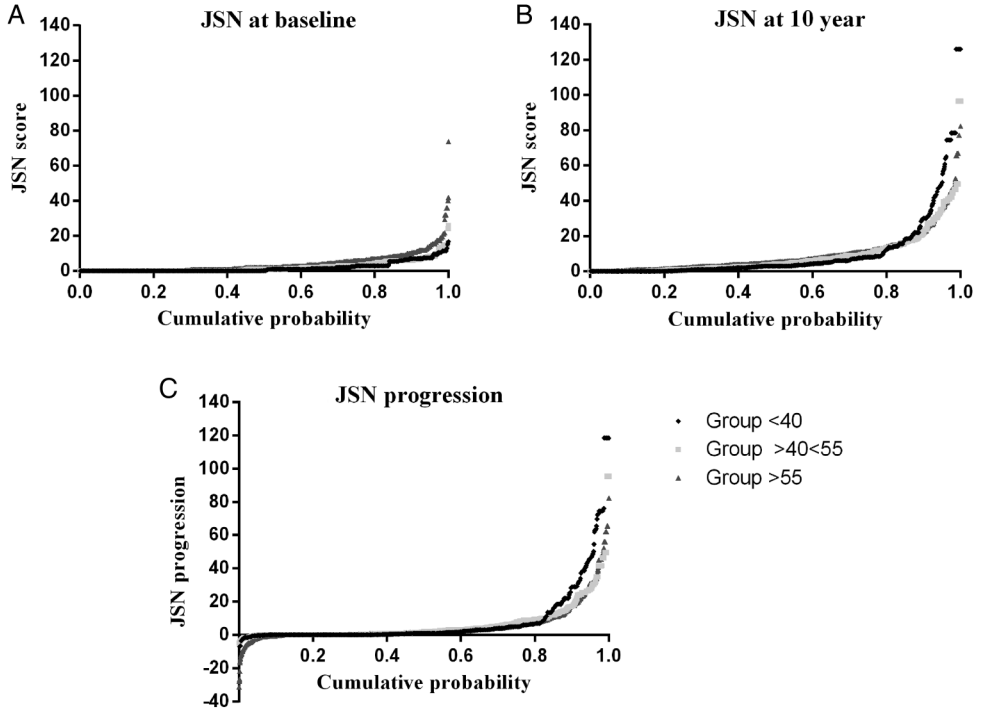

Figure 1 Probability plots JSN score at baseline (A), 10 years (B) and progression (C) for the different age groups (darkest dots: group <40, lightest dots group ≥40<55, intermediate dots: group ≥55; uploaded as a separate file). JSN, joint space narrowing.

Table 3 Univariate Poisson regression analysis per age group

	Group <40 RR (95% CI)	Group ≥40<55 RR (95% CI)	Group ≥55 RR (95% CI)
Baseline smoking	0.83 (0.16 to 4.23)	1.18 (0.60 to 2.32)	2.00 (1.11 to 3.58)
BMI<25	Ref	Ref	Ref
BMI>25<30	0.91 (0.22 to 3.82)	0.58 (0.37 to 1.50)	1.12 (0.58 to 2.14)
BMI>30	0.28 (0.05 to 1.66)	0.74 (0.19 to 1.73)	1.19 (0.50 to 2.87)
Ritchie Articular Index	1.00 (0.94 to 1.06)	0.95 (0.89 to 1.01)	0.98 (0.93 to 1.03)
Swollen joint count	**1.11 (1.02 to 1.21)**	0.97 (0.93 to 1.01)	1.01 (0.98 to 1.05)
JSN	**1.17 (1.01 to 1.35)**	1.06 (0.99 to 1.14)	1.00 (0.94 to 1.07)
Erosions	1.13 (0.90 to 1.41)	**1.06 (1.01 to 1.12)**	1.02 (0.89 to 1.15)
RF−/ACPA−	Ref	Ref	Ref
RF+/ACPA−	1.65 (0.28 to 9.82)	3.31 (0.93 to 11.75)	1.47 (0.48 to 4.47)
RF−/ACPA+	2.78 (0.48 to 16.15)	1.76 (0.54 to 5.79)	2.52 (0.84 to 7.54)
RF+/ACPA+	**5.39 (1.25 to 23.15)**	**3.41 (1.33 to 8.71)**	4.19 (1.58 to 11.07)
RF−	Ref	Ref	Ref
RF+	2.81 (0.90 to 8.77)	**2.88 (1.40 to 5.96)**	2.63 (1.31 to 5.28)
ACPA−	Ref	Ref	Ref
ACPA+	**3.79 (1.21 to 11.89)**	2.02 (0.94 to 4.33)	3.39 (1.58 to 7.28)
Average ESR over time	1.04 (1.00 to 1.08)	**1.02 (1.00 to 1.04)**	1.02 (1.01 to 1.03)
Sequential monotherapy	Ref	Ref	Ref
Step up to combination therapy	0.44 (0.07 to 2.79)	1.29 (0.56 to 3.02)	0.81 (0.34 to 1.93)
Initial combination therapy with prednisone	0.89 (0.20 to 3.93)	0.77 (0.36 to 1.64)	0.93 (0.38 to 2.25)
Initial combination therapy with infliximab	**0.20 (0.04 to 0.95)**	0.49 (0.19 to 1.27)	0.84 (0.36 to 2.00)

Bold typeface represents risk factors that attained significance.
95% CI, 98.33% (Bonferroni correction) CI; ACPA, anticitrullinated protein antibodies; BMI, body mass index; Erosions, erosion score (SHS); ESR, erythrocyte sedimentation rate; JSN, joint space narrowing; RF, rheumatoid factor; RR, relative risk; SHS, Sharp/van der Heijde score.

shown in figure 1. While the median progression scores are higher in the oldest groups, JSN progression scores are more skewed to the right (higher progression scores) in the youngest group, as reflected by a higher mean and higher SD in that group.

Predictive factors for JSN progression

Univariate risk factors that were statistically significantly associated with JSN progression in group <40 were JSN at baseline (relative risk (IQR); 1.17 (1.01–1.35)), baseline SJC (1.11 (1.02–1.21)), ACPA+ (3.79 (1.21–11.89)), RF+/ACPA+ (5.39 (1.25–23.15)) and average ESR over time (1.04 (1.00–1.08); table 3) and initial combination therapy with infliximab was protective against JSN progression compared with sequential monotherapy (0.20 (0.04–0.95)). In group ≥40<55, erosions at baseline (1.06 (1.01–1.12)), RF+ (2.88 (1.40–5.96)), RF+/ACPA+ (3.41 (1.33–8.71)) and average ESR (1.02 (1.00–1.04)) were correlated with JSN progression. Also, initial combination therapy with infliximab (0.49 (0.19–1.27)) compared with sequential monotherapy tended to protect against JSN progression in group ≥40<55. In group ≥55, smoking (2.00 (1.11–3.58)), RF+ (2.63 (1.31–5.28)), ACPA+ (3.39 (1.58–7.28)), RF+/ACPA+ (4.19 (1.58–11.07)) and average ESR (1.02 (1.01–1.03)) were statistically significantly related to JSN progression. Treatment strategies were not correlated with JSN progression in group ≥55.

Risk factors with a p value <0.067 were entered in the multivariate analysis per age group (table 4). In the

Table 4 Multivariate Poisson regression analysis per age group

Group <40	RR (95% CI)
Baseline JSN	1.07 (0.95 to 1.22)
Swollen joint count	**1.09 (1.01 to 1.18)**
RF−/ACPA−	Ref
RF+/ACPA−	1.80 (0.29 to 11.25)
RF−/ACPA+	3.14 (0.34 to 28.66)
RF+/ACPA+	4.00 (0.88 to 18.08)
Time average ESR	**1.04 (1.02 to 1.06)**
Group ≥40<55	
Baseline JSN	1.02 (0.95 to 1.10)
Baseline Erosions	1.04 (0.98 to 1.10)
Ritchie Articular Index	0.96 (0.89 to 1.03)
Swollen joint count	1.00 (0.95 to 1.10)
RF−/ACPA−	Ref
RF+/ACPA−	2.67 (0.76 to 9.39)
RF−/ACPA+	1.28 (0.37 to 4.43)
RF+/ACPA+	2.65 (0.95 to 7.38)
Time average ESR	1.01 (0.99 to 1.04)
Group ≥55	
Smoking at baseline	1.46 (0.81 to 2.63)
RF−/ACPA−	Ref
RF+/ACPA−	1.33 (0.45 to 3.98)
RF−ACPA+	2.31 (0.75 to 7.10)
RF+/ACPA+	**3.27 (1.25 to 8.53)**
Time average ESR	**1.02 (1.00 to 1.03)**

Bold typeface represents risk factors that attained significance.
95% CI, 95% CI after Bonferroni correction; ACPA, anticitrullinated protein antibodies; Erosions, erosion score (SHS); ESR, erythrocyte sedimentation rate; JSN, joint space narrowing; RF, rheumatoid factor; RR, relative risk; SHS, Sharp/van der Heijde score.

multivariate Poisson regression, in group <40 baseline SJC (1.09 (1.01–1.18)) and average ESR (1.04 (1.02–1.06)) were independently associated with JSN progression. In group ≥40<55 none of the risk factors were significantly correlated, but the influence of the combined presence of RF and ACPA showed a trend (4.00 (0.88–18.10)). In group ≥55 the 10-year average ESR (1.02 (1.00–1.03)) and the combined presence of RF and ACPA (3.27 (1.25–8.53)) were significantly associated with JSN progression. If only baseline variables were incorporated in the multivariate model, similar results were yielded; however, the influence of the combined presence of RF and ACPA in group ≥40<55 attained significance (data not shown).

DISCUSSION

Radiographic damage progression, as potential cause of permanent disability, is an important target for preventive therapy and one of the main determinants of successful treatment in patients with RA. However, in some patients with RA primary OA, represented by JSN may contribute to radiographic joint damage progression. Previous cross-sectional studies[10–12 14] have shown that older patients with RA had higher damage scores than younger patients with RA at baseline, partly explained by higher JSN.[10 11] In addition, radiographic OA is more often present in older patients and progression is more frequent and more severe in older patients. Risk factors for OA progression differ from risk factors for RA progression.[6–8]

We hypothesised that older patients with RA also show more JSN progression over time than younger patients, because progression in JSN is caused by both RA and OA, and that progression of JSN was associated with different risk factors in different age groups.

To investigate our hypothesis, we compared the severity of JSN between the age groups and tried to identify age group-specific risk factors in a cohort of patients with recent onset RA (1987 criteria), who were treated to target DAS≤2.4 over the course of 10 years, with three-monthly DAS calculation and treatment adjustments, and radiographs of hands and feet taken at baseline and yearly thereafter. JSN scores were derived from the SHS.

As expected, we found that patients with RA of ≥55 years old showed JSN more often and more severe JSN at baseline than younger patients. It was shown that while damage to the proximal interphalangeal joints at baseline increases with age, damage to the metacarpophalangeal joints does not. Older patients had higher ESR, higher SJC, higher DAS and a higher baseline erosion score suggesting that in older patients there was more rheumatoid inflammation. After 10 years, there were no statistically significant differences between the age groups in the amount of JSN progression, but JSN progression was more skewed to the right in the youngest group, as reflected by a higher mean and higher SD in that group. Risk factors for JSN progression were only slightly different in the three age groups. In patients ≥55 years, the presence of RF and ACPA and a high ESR as marker for systemic inflammation over time were independent risk factors for JSN progression. Also in patients <40 years, high inflammatory activity, represented by baseline SJC and ESR over time, was independently associated with JSN progression, but the presence of autoantibodies was not. In the >40 ≤55 years age group there were no independent predictors for JSN progression.

These results confirm previous reports that JSN is more prevalent and more severe in older patients with RA than in younger patients at baseline. However, contrary to our hypothesis, we did not find more JSN progression in older patients. In fact, the most severe JSN progression was observed in (a subgroup of) patients <40 years. Slow progression observed in (a subgroup of) older patients may in part represent JSN due to primary OA, which has been shown to be slowly progressive and more prevalent in older patients.[7 8 19]

This hypothesis is supported by the fact that, although ESR over time was higher in the oldest group than in the other age groups, as is observed in healthy individuals,[20] DAS over time was not, indicating that the SJCs and Ritchie Articular Index results over time were low.

RA appears to have been well suppressed in the older patients, which is also suggested by the finding that the mean erosion progression score was lower than in the other age groups. Primary OA is supposed to be relatively rare in the ≤40 years age group, but over 10 years follow-up may have progressively occurred, adding to the increased JSN progression scores due to inflammation in those patients. However, in the younger patients, erosion progression scores were also higher, suggesting that from baseline, when they had a higher SJC, over 10 years follow-up, when they had similar DAS but lower ESR, RA may have been insufficiently suppressed. That initial combination therapy in the older patients is not associated with less JSN progression may suggest that JSN progression in older patients is caused by OA which is less susceptible to the treatment with TNF inhibitors.[21] However, in older patients, the combined presence of RF and ACPA was associated with more damage progression. In general, these antibodies have been associated with a more destructive disease course in RA. A previous analysis of the BeSt study[22] showed that presence of ACPA did not affect the suppression of inflammation, but even in patients with similar low disease activity was associated with more damage progression. Why this is not found for younger patients in this study remains to be investigated, but might be explained by the smaller sample size in the age group <40.

Previous studies have looked at the possible contribution of primary OA to JSN scores in patients with RA[14 23 24] by multivariate linear analysis adjusted for age. This statistical method assumes a linearity of the relationship between age and outcome that may not exist in the oldest patients[11] and does not take into

account the non-linear interaction between some risk factors and age. By stratifying into different age groups, we could assess non-linear relations between age and risk factors. The downside of our method is a loss of power and the loss of differentiation between ages that belong in one age group. The age limits per group were set arbitrarily, in part based on the median age in the total group (55 years), the need for sufficient numbers of patients per group and the presumption that significant primary OA is unlikely in patients under 40 years old. We were able to follow patients for 10 years, whereas previous studies had shorter follow-up periods. During these 10 years all patients received treatment targeted at a DAS ≤2.4. This resulted, as previous analyses[17] have shown, in similarly well-controlled rheumatoid disease activity in all patients in the four strategy arms from 1 year onwards.

It can be argued that to distinguish primary OA from rheumatoid joint damage, one of the specific scoring methods for OA should have been used.[19] These however may also include rheumatoid joint damage in the score, and it remains unclear which is the best method to score OA progression. Instead, we looked at JSN as part of the SHS, precisely to highlight that a method to measure outcomes of RA treatment can be susceptible to overestimation of rheumatoid damage by including OA. Our hypothesis that JSN in older patients is caused by RA and OA was supported by increasing JSN at baseline in the proximal interphalangeal joints but not in the metacarpophalangeal joints. However, the potentially combined presence of rheumatoid damage and osteoarthritic features suggest that risk factors identified in our analyses might also be risk factors for both causes of JSN progression.

In conclusion, in different age groups of patients with RA, JSN scores and progression of JSN may be influenced by various factors, one of which may be primary OA in the older age groups. This may affect how radiographic scoring methods can be interpreted to represent treatment effects of antirheumatic therapy in different age groups. In all patients, inflammation should be optimally suppressed to avoid the progression of joint damage which may determine long-term functional ability. At baseline, disease seems to be more severe in older persons, but after 10 years, radiographic outcomes do not differ between age groups, implicating that progression in the younger patients might not be optimally suppressed. Finally, a possible association between inflammation and progression of OA should be further investigated by including specific OA scoring methods and by evaluation in other cohorts, as this knowledge may open a door to preventive treatment.

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