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Predictors of radiological progression and changes in hand bone density in early rheumatoid arthritis

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Objective. **To identify predictors for radiological and functional outcome and bone loss in the hands in early rheumatoid arthritis (RA) during the first 2 yr of disease and to study the relationship between these variables.**
Methods. **An inception cohort of consecutively recruited patients was examined at baseline and after 12 and 24 months using X-rays of hands and feet, clinical [28-joint count, Health Assessment Questionnaire (HAQ), global visual analogue scale (VAS), grip strength] and laboratory (erythrocyte sedimentation rate, C-reactive protein, markers of bone formation and resorption) measurements and dual-energy X-ray absorptiometry measurements of the hands.**
Results. **Joint destruction increased significantly during the study, with the Larsen score at baseline as the strongest predictor. Radiological progression and bone loss over 24 months were significantly retarded in patients responding to therapy. The effects of the shared epitope and initial high inflammatory activity on radiological progression were overridden by the therapeutic response. Radiological progression correlated significantly with bone loss. Global VAS, Larsen score and HAQ at inclusion significantly predicted change in HAQ over time.**
Conclusions. **Radiological progression and bone loss were retarded by early therapeutic response. Bone loss was related to radiological progression.**

The development of erosions and disability have been used as outcome measures in rheumatoid arthritis (RA). Several reports have observed that the clinical and radiological courses of RA may follow diverging paths [1, 2]. Measures of joint swelling, tenderness and function and laboratory-derived parameters which reflect synovial inflammation have shown demonstrable improvement in many patients whilst articular damage continues [3, 4]. Peri-articular osteoporosis in joints occurs earlier than erosions, but cannot be quantified accurately using plain radiography. Dual-energy X-ray absorptiometry (DXA) is an established technique for measuring axial and appendicular bone mineral density (BMD) [5–7]. Several studies have shown a decrease in peri-articular and axial bone mass that correlated with disease activity in early RA [8–10]. Inflammatory mediators, particularly cytokines, from inflammatory cells are the most likely cause of osteoporosis in RA [11–13]. Markers of bone formation [serum osteocalcin [14–16] and serum type 1 procollagen carboxyterminal propeptide (PICP) [16]] and bone resorption [serum cross-linked carboxyterminal telopeptide of type I collagen (ICTP, a marker of type I collagen degradation) [16–19] and serum type I collagen C-telopeptide breakdown products [15]] have been related to radiological progression, systemic inflammatory activity and osteoporosis in RA.

In this study of the first 2 yr of disease in early RA, we wanted to find markers for monitoring the process of local synovitis. Radiological progression was compared

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with DXA measurements of the hands of patients with early RA. We also wanted to identify predictors for these outcome assessors and for functional progression.

Materials and methods

Patients

Forty-three patients (30 women and 13 men) with early arthritis (i.e. patients who had been symptomatic for <12 months), fulfilling the American College of Rheumatology criteria for the classification of RA [20], were consecutively included in the study and followed for 2 yr. All 43 patients completed the study. The age at onset of disease (mean $\pm$ S.D.) was 49 ± 14.6 yr (range 21–75) for female patients and 56 ± 11.3 yr (39–74) for males. The duration of symptoms at inclusion in the study was 7.5 ± 2.5 months (3–12). Fifteen women were postmenopausal, and six of these were receiving hormone replacement therapy (HRT). Thirty-nine of the patients were seropositive for rheumatoid factor (RF) according to the Waaler-Rose method. Twenty-seven patients were HLA-DR4-positive, four had the DRB1*0404 allele, 18 had DRB1*0401 and five had both alleles. These two alleles were defined as shared epitopes. Furthermore, eight patients were HLA-DR1-positive.

The aim of the treatment was to achieve remission, using the disease-modifying anti-rheumatic drug(s) (DMARDs) which the physician regarded most suitable with respect to the clinical situation. During the study, 40 (93%) of the patients were receiving DMARD treatment for more than 6 months either as monotherapy or combination therapy. Thirty-four were treated with methotrexate as monotherapy or combination therapy, 22 with sulphasalazine, 11 with azathioprine and seven with gold in oral or parenteral form. Chloroquine and cyclosporin were only used in combination therapy, in six cases and one case respectively. At inclusion, eight patients were being treated with oral corticosteroids ($\leqslant 10$ mg/day), and a total of 17 patients (40%; five men and six pre- and six postmenopausal women) were treated with oral corticosteroids for at least 12 months during the study. Corticosteroids were used as treatment in those patients with high inflammatory activity [median DAS28 (disease activity score for 28 joints) 6.1, range 4.6–8.2]. Three patients were treated with an NSAID (non-steroidal anti-inflammatory drug) alone during the study period. Thirteen patients were non-smokers, 12 were ex-smokers and 18 were smokers at entry to the study.

Methods

The patients were examined radiographically and by DXA at inclusion in the study and after 12 and 24 months. The clinical and routine laboratory data were recorded every 6 months during the study. In 14 patients (four males and five premenopausal and five postmenopausal females) the first DXA examination was performed 6 months after inclusion. Because there were no differences between DXA values in the other patients examined at inclusion and at 6 months, the 6-month values were used as inclusion values in these 14 patients. The clinical examination included a 28-joint count for tender and swollen joints and assessment with a global visual analogue scale [VAS; EULAR (European League Against Rheumatism) criteria] [21], grip strength (Grippit instrument; AB Detektor, Göteborg, Sweden [22]) and the Health Assessment Questionnaire (HAQ) [23]. The DAS28 was calculated [24]. Therapy response was determined according to EULAR response criteria [25]. The area under the curve (AUC) for C-reactive protein (CRP) was calculated according to Matthews *et al.* [26].

The erythrocyte sedimentation rate (ESR mm/h, Westergren method) and blood levels of CRP (mg/l) were determined at every time point. Serum was sampled at inclusion for analysis of bone markers osteocalcin (ng/l), ICTP (ng/l) and PICP (ng/l) at inclusion, and was stored at -80°C until assayed. Osteocalcin was measured using a commercially available immunoradiometric assay (Nichols Institute Diagnostics, San Juan Capistrano, CA, USA), whilst ICTP and PICP were measured by radioimmunoassay (RIA) (Orion Diagnostica, Espoo, Finland). The class II DRB1* (15 subtypes) alleles were identified by PCR-SSP (polymerase chain reaction with sequence-specific primers) using low-resolution primers from Dynal (Oslo, Norway). DNA from the samples was extracted with DTAB/CTAB [27].

Radiographs of the hands, wrists and feet were assessed by one radiologist and graded according to the modified Larsen score [28]. Bone mineral content (BMC) and BMD of the hands were estimated by one examiner using DXA (Lunar DPX-L; Lunar Corp., Madison, WI, USA). The proximal limit of the hand was a line through the base of the metacarpal bones. The coefficient of variation in healthy individuals between different BMD measurements was 1.1%. Healthy individuals (five men and 11 women, comprising six pre-menopausal and five post-menopausal women) were assessed as controls for BMC and BMD of the hands. The patient data for DXA measurements are presented as the mean of the right and left hands.

Statistics

Differences in continuous data from different time points were analysed with the Wilcoxon signed rank test and Friedman two-way analysis of variance by ranks, and between groups with the Mann–Whitney *U*-test and the Kruskal–Wallis test. Variations over time between groups were analysed by analysis of variance for repeated measurements (StatView version, 4.51, Abacus Concepts, Inc., Berkeley, CA, USA). Categorical data were analysed with the χ^2 test. Correlation between the variables was analysed with Spearman's rank correlation. The calculations were performed using SPSS (SPSS for Windows, version 10.0; Chicago, IL, USA). All P values refer to two-sided tests; P values less than 0.05 were considered significant. Radiological score as a dependent variable in logistic regression analysis was dichotomized into qualitative variables (higher or lower than the median value). The variables included in multiple regression analysis were selected from the results of correlation analyses and from clinical presumptions.

Results

The clinical and laboratory data for the patients at inclusion and at 12 and 24 months are presented in Tables 1 and 2. At inclusion, the median number of swollen and tender joints was 6.0 and 4.0 respectively. Thirty-one (72%) of the patients had joint erosions at inclusion. The median Larsen score was 8.0 and the median number of joints with erosions was 3.0 (Table 1). DAS28 improved significantly during the study for both females and males ($P<0.01$–0.001), with no significant difference between the sexes. The numbers of good or moderate responders (EULAR criteria) at 6, 12 and 24 months were 26, 26 and 29 respectively [25]. The serum level of ICTP was significantly increased in both

TABLE 1. Clinical and radiological variables at inclusion and at 12 and 24 months in 43 patients with early RA [median (interquartile range)]

Variable	Inclusion	12 months	24 months	P[a]
DAS28	4.6 (4.1–5.7)	3.3 (2.4–4.2)	3.4 (2.2–4.2)	<0.0001
Swollen joint count	6.0 (3.0–12.0)	2.0 (0.25–5.8)	2.0 (0.0–5.8)	<0.0001
Tender joint count	4.0 (1.0–10.5)	1.0 (0.0–4.0)	1.0 (0.0–4.0)	<0.0001
Larsen score	8.0 (0.50–18.0)	22.5 (12.0–32.0)	27.5 (18.0–43.0)	<0.0001
Number of joints with erosions[b]	3.0 (0.25–8.8)	10.0 (6.0–16.0)	13.0 (8.2–19.5)	<0.0001
HAQ	0.69 (0.25–1.00)	0.32 (0.00–0.72)	0.32 (0.00–0.75)	<0.01

[a]Friedman's test was used for test differences within individuals during the study period.
[b]Joints with erosions are defined as those having a Larsen score $\geqslant 2$.

TABLE 2. Bone markers at inclusion in 43 patients with early RA [mean (95% confidence limits)]

	This study		Reference values[a]	
	Females ($n=30$)	Males ($n=13$)	Females	Males
Osteocalcin (ng/l)	20.0 (15.7–24.2)	22.4 (17.9–27.0)	18.7 (6.8–30.0)[b]	22.5 (11.1–32.2)[b]
PICP (ng/l)	114 (101–127)	131 (108–155)	109 (50–170)[b]	112 (38–202)[b]
ICTP (ng/l)	4.5*** (3.9–5.0)	4.3*** (3.3–5.2)	2.8 (1.6, 5.0)[c]	2.4 (1.3–5.2)[c]

[a]According to manufacturer.
[b]Mean (95% confidence limits).
[c]Mean (0.025 and 0.975 fractiles).
***$P<0.001$, patients *vs* controls.

female and male patients compared with the cited reference values provided by the manufacturer, and correlated with the number of swollen joints ($r_s=0.592$, $P<0.05$) and tender joints ($r_s=0.700$, $P<0.05$) in premenopausal females. Osteocalcin and PICP were within the range of reference values (Table 2).

Radiological examinations

At inclusion, Larsen score was significantly higher in males compared with females ($P<0.05$). Furthermore, the Larsen score increased significantly over time in both male ($P<0.001$) and female ($P<0.0001$) patients (Fig. 1). At inclusion, postmenopausal females had a higher Larsen score than premenopausal females ($P<0.05$), and the score increased significantly in both groups ($P<0.01$ and $P<0.001$ respectively) throughout the study (Fig. 1). The differences at inclusion between males and pre- and postmenopausal females remained significant throughout the study. There was significantly ($P<0.01$) less progression during the second year. However, after stratifying for sex and menopausal status, the differences did not reach statistical significance in the subgroups. DAS28, CRP, HAQ score, number of swollen joints and Larsen score at inclusion correlated with Larsen score and with the number of joints with erosions at 24 months (Table 3). The Larsen score at 24 months correlated significantly with radiological progression at 24 months ($r_s=0.619$, $P<0.01$). The change in Larsen score over 24 months did not correlate with any variables at inclusion.

The results of the multiple regression analysis (adjusted for sex and for age at inclusion) presented in Table 4 indicate that the response to therapy at 6 months, shared epitope and initial values of Larsen score, CRP and

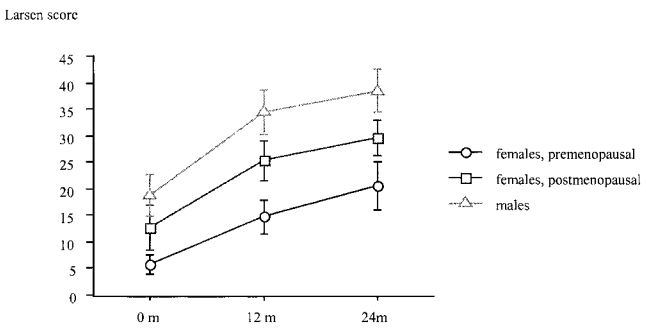

FIG. 1. Changes in Larsen score during 24 months in 43 patients with early RA. The Larsen score at onset was significantly higher in males and progression was significant in all three groups.

number of swollen joints were independently associated with radiological progression after 24 months compared with baseline, and explained 53.3% of its variation. In simple regression analysis, only a good therapeutic response at 6 months was significantly associated with radiological progression. In another multiple regression analysis with the same covariates and Larsen score at 24 months as the response variable, the covariates reached the same significance and 73.3% of the variation in Larsen score was explained (data not shown). A good response to therapy at 6 and at 12 months significantly predicted protection against radiological progression at 24 months (Table 5).

DXA examinations

The BMC and BMD values at inclusion were significantly higher (BMC, $P<0.001$; BMD, $P<0.01$) for

TABLE 3. Spearman rank correlation coefficients between different variables at inclusion and the radiological and functional outcome and bone mass of hands at 24 months in 43 patients with early RA

Variable	Radiological outcome		BMD (g/cm^2)	HAQ
	Larsen score	No. of joints with erosions		
DAS28	0.430**	0.380*	−0.106	0.459**
CRP (mg/l)	0.345*	0.400**	−0.337*	0.349*
HAQ	0.465**	0.459**	0.009	0.515***
Global VAS (mm)	0.257	0.249	−0.087	0.493**
Swollen joint count	0.394*	0.370*	−0.124	0.319*
Tender joint count	0.300	0.233	0.080	0.242
Grip strength[a] (mm Hg)	−0.240	−0.273	0.502**	−0.203
Larsen score	0.584***	0.638***	−0.127	0.385*
Number of joints with erosions	0.541***	0.611***	−0.119	0.403**

[a]Measured with Grippit [22].
*$P<0.05$; **$P<0.01$; ***$P<0.001$.

TABLE 4. Results of simple and multiple regression analyses with radiological progression at 24 months as dependent variable in 43 patients with early RA

Variable	Simple regression[a]			Multiple regression[a]		
	β	95% CI	P	β	95% CI	P
Therapeutic response at 6 months						
Good	−12.423	−23.718, −1.129	0.032	−14.639	−24.220, −5.058	0.004
Intermediate	−5.756	−14.905, 3.392	0.210	−11.226	−19.800, −2.653	0.012
None (reference)						
Shared epitope present (reference = absent)	5.721	−2.585, 14.027	0.172	9.279	1.882, 16.677	0.016
Larsen score	−0.196	−0.498, 0.106	0.196	−0.422	−0.739, −0.104	0.011
Swollen joints	0.328	−0.318, 0.974	0.311	0.685	2.159E–02, 1.349	0.043
HAQ	6.605	−1.252, 14.462	0.097	3.069	−6.823, 12.961	0.531
CRP (mg/l)	0.147	−3.677E–02, 0.331	0.114	0.182	−1.63E–02, 0.380	0.071

[a]$R^2=0.533$; R^2 adjusted = 0.387.
CI, confidence interval.

males compared with females and for premenopausal compared with postmenopausal females (BMC, $P<0.05$; BMD, $P<0.01$). As the BMC and BMD values were highly correlated at the various time points, only the BMD values were used in the analyses. The data relating to BMD values of the hands at inclusion and at 12 and 24 months are presented in Table 6. The BMD for the entire group of female patients decreased significantly during the study period, by 2.8% ($P<0.01$). When stratified for menopausal status, it was significant only in postmenopausal females, although there was a decrease in premenopausal females (Table 6). Because we used the 6-month data as inclusion data in 14 individuals, we compared the measurements in all patients at 6, 12 and 24 months, and obtained the same results. There was no significant difference between patients receiving and not receiving HRT (data not shown). The decrease in the postmenopausal group was significantly larger than in the healthy matched controls ($P<0.01$). There was a significant difference in BMD between pre- and postmenopausal females over time (0–24 months, $P<0.0001$).

Grip strength at inclusion correlated with BMD at 24 months and CRP at inclusion correlated inversely with BMD at 24 months (Table 3). For CRP, the correlation was confined to males ($r_s=-0.755$, $P<0.01$). In males and premenopausal females the levels of osteocalcin at inclusion correlated inversely with BMD at 24 months ($r_s=-0.591$, $P<0.05$ and $r_s=-0.516$, $P=0.07$ respectively). No variable at inclusion correlated with the change in BMD over time. There was a weak correlation between the accumulated number of tender and swollen joints in the hands over time and loss of BMD in postmenopausal females ($r_s=-0.550$,

TABLE 5. Response to therapy[a] in relation to Larsen score at 24 months in 43 patients with early RA (logistic regression analysis)

Response to therapy	Coefficient	OR	95% CI	P
6 months				
Good	−2.303	0.100	0.013, 0.781	0.028
Moderate	−1.427	0.240	0.049, 1.177	0.079
12 months				
Good	−1.792	0.167	0.031, 0.904	0.038
Moderate	−0.118	0.889	0.186, 4.244	n.s.
24 months				
Good	−0.742	0.476	0.102, 2.230	n.s.
Moderate	0.251	1.286	0.286, 5.774	n.s.

[a]Response criteria according to EULAR 28 [25].
OR, odds ratio; CI, confidence interval; n.s., not significant.

TABLE 6. DXA variable (BMD, g/cm^2) at inclusion, at 12 and at 24 months in 43 patients with early RA [median (interquartile range)]

Variables	Inclusion	12 months	24 months	*P*
Males ($n=13$)	0.461 (0.427–0.502)	0.448 (0.431–0.493)	0.459 (0.433–0.495)	n.s.
Premenopausal females ($n=15$)	0.429 (0.419–0.457)	0.418 (0.402–0.471)	0.417 (0.399–0.457)	n.s.
Postmenopausal females ($n=15$)	0.395 (0.380–0.407)	0.400 (0.362–0.411)	0.386 (0.353–0.403)	<0.01

n.s., not significant.

TABLE 7. Results of multiple regression analysis with change in BMD g/cm^2 between inclusion and 24 months[a] as dependent variables in 43 patients with early-onset RA

Variable	β	95% CI	*P*
Therapeutic response at 6 months			
Good	−1.952E–02	−3.669E–02, −2.358E–03	0.027
Intermediate	−1.655E–02	−3.222E–02, −8.849E–04	0.039
None (reference)			
CRP (mg/l)	1.825E–04	−5.535E–05, 4.203E–04	0.127
Osteocalcin (ng/l)	5.684E–04	2.968E–06, 1.134E–03	0.049

The model was adjusted for gender, menopausal status and smoking habits.
Inclusion values of CRP and osteocalcin were used.
[a]$R^2=0.350$, R^2 adjusted $=0.164$.

$P<0.05$). Analysing the patients with respect to response to therapy at 6 and 12 months, there was a significant decrease in BMD between inclusion and 24 months in the groups with a poor response ($P<0.001$, $n=13$ and $P<0.05$, $n=14$ respectively), but not in the groups with a moderate or good response. The distributions of sex and menopausal status were equal in the groups with a poor response. The results of the multiple regression model analysis with change in BMD over 24 months as the dependent variable (adjusted for gender, menopausal status and smoking habits) showed that only the therapeutic response at 6 months and the level of osteocalcin were independently associated with change in bone density (Table 7). The same result was obtained when corticosteroid treatment was added to the model. When the same analysis was performed with BMD at 24 months as the dependent variable (adjusted for smoking habits), the level of osteocalcin at inclusion, months of corticosteroid therapy, sex and menopausal status were independently associated with BMD at 24 months and explained 63.2% of its variation (data not shown). The association with CRP, measured by correlation analysis, did not remain significant in the multiple regression model. When grip strength, AUC for CRP and accumulated number of arthritis of finger joints ever were included in the model, the results were similar (data not shown).

The percentage decrease in BMD (ΔBMD) from inclusion to 24 months correlated inversely with the change in the number of eroded joints ($r_s=-0.548$, $P<0.001$) and with the change in Larsen score ($r_s=-0.552$, $P<0.001$). The correlation was similar when analysing radiological findings, graded by Larsen score, for the hands only ($r_s=-0.508$, $P<0.01$).

HAQ examinations

HAQ decreased significantly during the study (Table 1); the decrease was confined to females ($P<0.05$) when the sexes were analysed separately. However, comparison between the sexes over time did not show any significant difference between females and males. HAQ at 24 months correlated with DAS28, HAQ, global VAS and number of swollen joints at inclusion (Table 3). In multiple regression analysis, global VAS and Larsen score at inclusion contributed significantly ($P<0.01$ and $P<0.05$ respectively) to the variation in HAQ (accounting for 52.3% of it) at 24 months, adjusted for therapeutic response at 6 months, sex, age, CRP, HAQ, number of tender and swollen joints at inclusion. When the same factors were used in the model and the change in HAQ over 24 months was used as dependent variable, global VAS ($P<0.01$), Larsen score ($P<0.05$) and HAQ at inclusion ($P<0.001$) explained 62.6% of the variation in HAQ.

Discussion

An interesting finding in this small inception cohort is the clear effect of the response to therapy at 6 and 12 months on radiological findings at 24 months and on radiological progression during the first 24 months. Despite the fact that a high number of the patients already had erosions at inclusion, which correlated strongly with the radiological outcome, the significance of the response to therapy was clearly evident. Also, the radiological progression during the second year was less than that during the first year. This emphasizes the importance of getting a good response to therapy as

early as possible in patients with RA. The number of swollen joints and CRP at inclusion, as signs of disease activity, predicted radiological outcome, whereas tender joints at inclusion had low predictive value. Many previous studies of X-ray progression have, in agreement with our findings, demonstrated the predictive value of a combination of initial factors, such as joint involvement [29–32], acute-phase response [32–34] and genetic predisposition for RA [31, 32, 34]. In all but one of these studies, seropositivity for RF showed a clear correlation with X-ray progression. This could not be demonstrated in our study, probably because almost all of the patients (91%) were seropositive for RF. We did not find any correlation between signs of erosive disease at inclusion and the duration of symptoms. This is in contradiction to another study [35], in which a strong correlation between initial X-ray findings and duration of symptoms was found. In our patients with the shared epitope, the radiological progression over time did not differ significantly, in a simple regression analysis, from that observed for patients without the epitope. We believe that this may be explained by the relatively high frequency of HLA DR4 in the normal population of northern Sweden, resulting in a small contribution of the shared epitope to the disease severity. However, in a multiple regression model including other variables, the shared epitope made a significant contribution to radiological progression (Table 4). We are able to conclude, as has been suggested in another study [36], that the effect of the shared epitope on radiological progression is overridden by the therapeutic response at 6 months. Somewhat unexpectedly, a negative β value was found for the Larsen score at inclusion in the multiple regression analysis with radiological progression as dependent variable. This finding resulted from the effects of interactions of variables during the study. By correlation analysis (data not shown), we found that one of these variables was the response to therapy. Only 53.3% of the variation in radiological progression was explained by the variables tested. This suggests that there must be several other factors, not analysed in the present study, that contribute to radiological progression. Most of the covariates analysed were variables measuring inflammatory activity rather than the destructive process.

There was no significant difference in radiological progression between the sexes, in spite of the fact that males had a higher Larsen score at inclusion in the study. In another study it was shown that postmenopausal women had a more severe radiological outcome than premenopausal women [37]. One reason that we were unable to demonstrate a difference could be the small number of patients in our study.

There was a clear correlation between bone loss in the hands and radiological progression. However, bone loss in the hands, which could be the result of local inflammation mediated by cytokines, was only correlated with inflammatory activity as measured by CRP at baseline in males. Some influence of local inflammation was suggested in the postmenopausal females by the correlation between bone loss in the hands and accumulated number of arthritis of the finger joints. However, this correlation was rather weak and the strongest predictors of bone loss in hands were the therapeutic response at 6 months and the level of osteocalcin in both sexes. One explanation for the fact that CRP did not correlate with appendicular bone loss in females could be the effect of menopausal status. Unlike the observations reported by Peel *et al.* [7] and Deodhar *et al.* [9], we could not find any convincing direct relationship between inflammatory activity and bone loss in the hands. Rather, the hand bone loss seemed to follow the same pattern as that found for axial bone loss [38, 39]. However, reduced bone loss of the hands in patients with a response to therapy at 6 and 12 months and a strong negative correlation with radiological progression indicates an indirect relationship with inflammation. Only six patients received HRT during the study, hence it was not possible to evaluate the protective role of oestrogens, nor was this the purpose of our study. The corticosteroid treatment did not seem to affect bone density but corticosteroids were given to the patients with the most active disease. We conclude that measurement of bone density of hands in this study of early RA did not give any information additional to that given by X-ray examination.

The levels of the bone formation markers osteocalcin and PICP were within normal ranges in the present study, whilst the levels of the bone resorption marker ICTP were increased. This suggests an imbalance in bone turnover leading to loss of bone mass. Baseline osteocalcin levels predicted bone loss in the hands but not the radiological outcome. Levels of ICTP and PICP at inclusion had no predictive value either on radiographic findings and outcome or on bone mass after 24 months. The finding by Åman *et al.* [19] that ICTP together with ESR and CRP could predict radiological progression was not confirmed in this study. The increase in ICTP at inclusion and its correlation with swollen and tender joints was interpreted as a result of the inflammation at that time point.

The HAQ score at inclusion correlated strongly with HAQ at 24 months, and it predicted (besides the Larsen score and global VAS at inclusion) changes in HAQ over 24 months. This finding is in line with several other studies which have shown that poor functional status at presentation is one of the best predictors of subsequent outcome [30, 40]. As our study included only 24 months of follow-up, the number of patients who developed functional disability with HAQ $\geqslant 1$ was very low. Consequently, we are unable to draw any clinically relevant conclusions concerning the HAQ score, although a follow-up period longer than 24 months would probably facilitate the interpretation. In our study, improvement in the HAQ score was confined to females; this has not been reported in previous follow-up studies on early RA [41, 42]. The Larsen score at inclusion significantly predicted HAQ outcome

at 24 months adjusted for therapeutic response at 6 months, sex and age and HAQ at inclusion. This finding is consistent with that reported in early RA by van Leeuwen *et al*. [42].

From this study we are able to conclude that radiological progression during 24 months was retarded when the patients responded to DMARD therapy at 6 and 12 months. The therapeutic response was even more evident when considered in the context of the shared epitope and inflammatory activity. Bone loss in the hand, measured by DXA, correlated with radiological progression and was most strongly predicted by the therapeutic response at 6 months and osteocalcin level. Bone loss over time was only significant in postmenopausal females. The HAQ score significantly improved in females during the study and global VAS and Larsen score at inclusion predicted HAQ at 24 months.

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