Serological Bone Markers and Joint Damage in Early Polyarthritis

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ABSTRACT. ***Objective.*** To investigate the relationship between osteocalcin (OC), a marker of bone formation, and the recently developed serum marker of bone resorption, ß-C-telopeptide (ß-CTx), and radiographic damage in patients with early oligo- and polyarthritis.

Methods. Patients with peripheral arthritis of ≥ 2 joints and < 2 years of symptom duration were studied. The OC and ß-CTx concentrations at baseline were correlated with disease activity and radiographic damage at baseline, and with radiographic progressive disease after 2 years (delta Sharp/van der Heijde score ≥ 5). The additional value of serum bone metabolism markers to predict radiographic progressive disease was compared to that of established prognostic factors by multivariate logistic regression analysis.

Results. Two hundred seventy-nine patients (67% female; median age 56 yrs, range 18–83) were included in the study, of whom 73% were diagnosed with rheumatoid arthritis (RA). Baseline levels of ß-CTx ($p < 0.05$) were significantly correlated with baseline radiographic damage whereas OC was not. ß-CTx was also significantly ($p < 0.001$) related to measures of disease activity like erythrocyte sedimentation rate, C-reactive protein, and the disease activity score DAS28. Radiographic progressive disease after 2 years corresponded univariately with increased levels of ß-CTx ($p < 0.001$), but not with OC. In multivariate analysis, ß-CTx was not superior to other measures of radiographic progressive disease such as autoantibodies and disease activity.

Conclusion. Increased serum levels of the bone turnover marker ß-CTx are associated with radiographic damage at baseline and radiographic progression after 2 years. However, ß-CTX is less predictive than markers already in use. (J Rheumatol 2004;31:1491–6)

Key Indexing Terms:
BONE TURNOVER MARKERS JOINT DAMAGE EARLY POLYARTHRITIS

Rheumatoid arthritis (RA) is a chronic inflammatory disease that causes joint damage such as bony erosions and loss of cartilage even within the first 2 years after disease onset[1,2]. In the long term, this joint damage often results in functional disability[3,4].

A number of studies showed that early and aggressive treatment of RA with disease modifying antirheumatic drugs (DMARD) suppresses the inflammation process and limits joint destruction[5-9]. Therefore, it is important to recognize those patients who will deteriorate rapidly at an early stage.

Prognostic markers for a severe outcome of early RA mentioned in previous studies include female sex[10,11], serum IgM-RF positivity[12-14], high initial radiographic damage[12,14,15], a high number of swollen joints[16], and other markers of disease activity[13,17-19]. Combinations of these predictors reach a maximum accuracy of 82% in predicting mild or progressive disease[14]. Unfortunately, this percentage is not sufficient for decision-making at the individual level.

The predictive value of bone metabolism markers for the development of radiological joint damage is not explored thoroughly yet. In general, bone metabolism is a continuous process of bone resorption and bone formation.

Until recently, it was not possible to measure bone resorption in serum reliably. Measurement of bone resorption in serum is not only more convenient for both patients and laboratory personnel than measurement of urinary excretion, but is also more accurate, as serum markers have lower spontaneous variability and greater precision. Nowadays it is possible to detect C-telopeptide (CTx) concentrations in serum independent of the time of day. In a trial observing the effect of bisphosphonates, it was suggested that the coefficient of variation of serum ß-CTx was lower than other bone markers, e.g., urinary N-terminal telopeptide (NTx)[20].

Bone metabolism is influenced by RA, either directly by the inflammatory process itself, or by indirect effects such as immobilization or the use of corticosteroids[21]. Several

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studies have shown that bone resorption was increased by disease activity in RA[22-26]. However, data on bone formation in RA are conflicting: both high and low levels have been reported[27,28]. Because markers of bone metabolism might not only reflect generalized bone loss, but also local damage (erosions), we investigated the relationship between markers of bone turnover and radiologically detectable joint damage.

In patients with early oligo- and polyarthritis, we investigated the correlation of the baseline levels of osteocalcin (OC), a marker of bone formation, and the recently developed serum marker of bone resorption, ß-CTx, with the baseline radiographic damage as well as radiographic progression after 2 years. Further, the correlation between markers for bone metabolism and measures of disease activity was studied. Finally, we compared the value of bone metabolism markers with other predictive variables for radiographic damage.

MATERIALS AND METHODS

Patients. Patients included in the study were referred to a large rheumatology outpatient clinic between September 1995 and April 1998, and were aged 18 years or older with peripheral arthritis of at least 2 joints and less than 2 years' symptom duration. Excluded were patients with bacterial, psoriatic or crystal-induced arthritis, reactive arthritis, spondyloarthropathy, osteoarthritis, sarcoidosis, or systemic autoimmune diseases. Patients were diagnosed with RA based on the clinical diagnosis of an experienced rheumatologist at baseline; the remainder of the patients were considered to have undifferentiated oligo- or polyarthritis (UPA). All patients received nonsteroidal antiinflammatory drugs (NSAID) at the first visit to the clinic. Two weeks after inclusion patients were treated with either hydroxychloroquine (HCQ) or sulfasalazine, which was dependent on disease activity. The sequence of subsequent therapy was methotrexate (MTX) followed by aurothioglucose.

Disease variables. At baseline we measured demographic characteristics, time of onset of complaints (defined as persistent pain and/or swelling of a joint), and a disease activity score [DAS28, based upon erythrocyte sedimentation rate (ESR) and number of painful and number of swollen joints (both by 28 joint count)], patient global assessment by visual analog scale (VAS)[29], C-reactive protein (CRP), anticyclic citrullinated peptide (anti-CCP) antibodies[30], IgM rheumatoid factor (IgM-RF), damage score on radiographs of hands and feet[15], and the functional status by the validated Dutch version of the Health Assessment Questionnaire (HAQ)[31].

Bone formation was assessed by the osteocalcin level in serum (N-MID osteocalcin kit, Roche Diagnostics Nederland BV, Almere, The Netherlands) and bone resorption by type 1 collagen CTx breakdown products in serum (ß-CrossLaps kit; Roche Diagnostics). Both assays were performed on an Elecsys 2010 analyser (Roche Diagnostics) according to the instructions of the manufacturer. Both assays had intra- and interassay coefficients of variation of less than 5%. These were independent from the time of measurement.

Outcome at 2 years was defined by radiographic joint damage. Joints were scored for erosion and joint space narrowing according to the method of Sharp/van der Heijde[32]. The maximum achievable radiological score was 448. An experienced rheumatologist (DvS), who was blind to the clinical status of the patients, scored the radiographs. The radiographs were read in pairs with a known time sequence. Radiographic progression, expressed as the Sharp/van der Heijde change score, was computed by subtracting the initial radiographic damage score from the 2-year score.

As postmenopausal state in early RA is predictive for joint destruction, menopausal status in female patients was determined. Because no data on the menopausal status of the women were available, an arbitrary division was made by considering all women older than 45 years as postmenopausal.

Statistical analysis. Spearman's rank correlation coefficient test was used to analyze the relationship between ß-CTx, OC level at entry, traditional markers, and the baseline radiographic damage and radiographic progression. Spearman's correlation coefficients were calculated between ß-CTx and OC levels and measures of disease activity (ESR, CRP, anti-CCP+, IgM-RF+, DAS28, and HAQ).

Secondly, the predictive value of the serum level of these bone metabolism markers was compared with other variables for progressive erosive disease. Therefore, the patients were divided into an erosive and nonerosive group at baseline and into a radiographic progressive and mild disease group after 2 years. Erosive disease at baseline was defined as baseline Sharp/van der Heijde score ≥ 5; the remainder was denoted as nonerosive. Radiographic progressive disease was defined as Sharp/van der Heijde change score after 2 years ≥ 5, the remainder was classified as mild[33]. Univariate analyses were performed with Student's t test for differences in baseline disease variables between erosive and nonerosive disease and progressive and mild radiographic disease, respectively. Subsequently, clinically relevant baseline characteristics were entered into 2 separate forward stepwise logistic regression analyses. All analyses were carried out with SPSS 10.0.

RESULTS

Two hundred seventy-nine consecutive patients with early oligo- and polyarthritis were included in the study (Table 1). At baseline, 73% were diagnosed with RA (69% according to the American College of Rheumatology criteria for RA[34]), 37% were IgM-RF positive, and 22% showed erosions in hands, feet or both.

During the first year of followup, 89% of the patients were treated with DMARD: sulfasalazine (59%), MTX (28%), HCQ (29%), and aurothioglucose (1%). Prednisone was used by 29 (10%) patients as well. Bisphosphonates were used by 10% of the patients, as in The Netherlands these medicines are prescribed by protocol when corticosteroids are used.

The presence of radiographic damage at baseline was positively correlated with serum levels of anti-CCP+, ESR, CRP ($p < 0.01$), IgM-RF+, and ß-CTx ($p < 0.05$), but not with OC. Radiographic progression after 2 years correlated significantly with ß-CTx, anti-CCP+, IgM-RF+, ESR, CRP, and DAS28 score ($p < 0.01$) and not with OC (Table 2a).

To investigate whether a relationship existed between ß-CTx, OC, and variables of disease activity, a correlation test was used. Levels of ß-CTx correlated significantly with ESR, CRP, the DAS28 score ($p < 0.001$), number of swollen

Table 1. Baseline demographic characteristics of the 279 patients with early oligo- and polyarthritis.

Age (yrs) median (range)	56 (18 to 83)
Female, %	67
Postmenopausal women (% of total cohort)	47
Duration of complaints (mos), median (range)	3.5 (0.4 to 24)
Diagnosis RA, %	73
IgM RF+, %	37
Erosive disease (Sharp score ≥ 5), %	22

Table 2a. Correlation between bone metabolism markers, traditional markers, and radiographic progressive disease in 279 patients with early oligo- and polyarthritis. Values are Spearman correlation coefficients.

Variable	Erosive Disease at Baseline†	Radiographic Progressive Disease after 2 years††
ß-CTx	0.15*	0.18**
Osteocalcin	NS	NS
ESR	0.19**	0.36**
CRP	0.18**	0.34**
IgM-RF+	0.14*	0.41**
Anti-CCP+	0.22**	0.49**
DAS28 score	NS	0.26**

* $p < 0.05$; ** $p < 0.01$. † Erosive disease at study start: baseline Sharp/van der Heijde score ≥ 5 points. †† Radiographic progressive disease: Sharp/van der Heijde score after 2 years ≥ 5 points. Mild disease: Sharp/van der Heijde change score after 2 years < 5 points.

Table 2b. Correlation between bone metabolism markers (osteocalcin and ß-CTx) and baseline variables of disease activity in 279 patients with early oligo- and polyarthritis. Values are Spearman correlation coefficients.

	ß-CTx	Osteocalcin
ESR	0.24*	NS
CRP	0.19*	NS
IgM RF+	NS	NS
Anti CCP+	NS	NS
DAS28 score	0.19*	NS
HAQ	0.18**	NS

* $p < 0.001$; ** $p < 0.01$.

joints, and HAQ score ($p < 0.01$). OC was not correlated with any of these disease activity variables (Table 2b).

To assess the predictive value of the bone metabolism markers with other predictive variables for erosive disease, the patients were divided into a nonerosive (n = 218; 78%) and an erosive group (n = 61; 22%) at baseline. A second analysis was performed after separation of the radiographic mild (n = 184; 66%) from the progressive group (n =95; 34%) (Table 3) after 2 years of disease.

No differences between the groups were found in disease duration or sex (data not shown). Patients with erosive disease at entry were significantly older, postmenopausal, more often anti-CCP positive ($p < 0.001$) and IgM-RF positive, and showed higher mean ESR levels ($p < 0.01$) and a worse mean functional status ($p < 0.05$) compared to patients with nonerosive disease at study start. Further, mean ß-CTx and OC levels were significantly higher ($p < 0.05$) in the erosive disease group compared to the nonerosive group (Table 3).

Patients with radiographic progressive disease after 2 years were significantly more frequently IgM-RF positive and anti-CCP positive, had higher mean ESR levels and higher mean disease activity (DAS28 score), worse mean initial functional status (HAQ), and more mean radiographic damage ($p < 0.001$) at entry compared to patients with mild radiographic disease (Table 3). ß-CTx levels were significantly higher ($p < 0.001$) in the radiographic progressive group compared to the mild disease group. OC was equal among the groups (Table 3).

To determine the additional predictive value of ß-CTx and OC for baseline erosive disease or radiographic progressive disease, variables that were significantly ($p < 0.05$) associated in the univariate analysis were entered into 2 separate logistic regression models (Table 4). Variables most predictive for erosive disease at study start were anti-CCP positivity and a higher age. The model accounts for 79% of the variance. Variables most predictive for radiographic progressive disease at 2 years were anti-CCP positivity, IgM-RF positivity, higher mean baseline HAQ score, and a higher mean ESR level. The predictive value of these variables was higher than those of ß-CTx and OC. Also, this model accounted for 79% of the variance.

DISCUSSION

In a group of 279 patients with early oligo- and polyarthritis, the presence of initial radiographic damage and the radiographic progression after 2 years was associated with increased bone resorption as measured by the serum marker ß-CTx. There was no correlation with bone formation and joint damage.

The observation that radiographic progressive disease is associated with increased bone resorption is in accord with several other studies[21-23,35]. However, in our study bone metabolism was measured in serum, which is more convenient for both patients and laboratory personnel. Moreover, serum markers have lower spontaneous variability and greater precision[20].

Studies on the predictive value of markers of bone metabolism for progression of radiographic detectable joint damage are scarce. Garnero, *et al*[22] studied the relationship between a marker of synovium resorption and radiographic progression in early RA. It was concluded that high baseline levels of urinary glucosyl-galactosyl-pyridinoline (Glc-Gal-Pyd) were associated with increased risk of progression of joint destruction over one year in early RA. This association was independent of the severity of radiologic damage and inflammation at baseline. However, the additional value of bone metabolism markers above other prognostic variables was not examined. In another study, Garnero, *et al*[36] investigated the association between bone resorption and longterm radiologic progression. They concluded that high baseline levels of urinary C-terminal crosslinking telopeptide of type 1 (CTX1) independently predicts an increased risk of radiologic progression over 4 years in patients with early RA, especially those without radiologic joint damage at baseline. However, all patients from this study were diagnosed with RA and had active disease, which is not comparable with our study. Furthermore, the marker for bone resorption was measured in urine.

Table 3. Univariate analysis for erosive disease at study start and radiographic progressive disease after 2 years in 279 early oligo- and polyarthritis patients. Data are mean (SD) or median (range) unless otherwise stated.

Baseline Variables	Erosive Disease at Baseline			Radiographic Progressive Disease After 2 Years		
	Non-erosive n = 218 (78%)	Erosive† n = 61 (22%)	p	Mild n = 184 (66%)	Progressive‡ n = 95 (34%)	p
Age, yrs	54 (18-83)	64 (27-82)	***	55 (18-83)	59 (27-81)	NS
IgM RF+, %	35	57	**	24	72	***
Anti-CCP+, %	28	52	***	16	66	***
ESR, mm/h	31 (23)	40 (23)	**	28 (23)	42 (22)	***
No. swollen joints (28 JC)	7.6 (6.1)	8.8 (6.2)	NS	7.5 (6.3)	8.7 (5.8)	NS
DAS28 score	4.8 (1.3)	5.1 (1.1)	NS	4.6 (1.3)	5.3 (1.1)	***
Sharp/van der Heijde-score	—	—	—	0 (0–40)	3 (0–86)	***
HAQ score	0.8 (0.7)	1.0 (0.9)	*	0.7 (0.6)	1.1 (0.9)	***
Osteocalcin, ng/ml	22.4 (10.6)	25.6 (12.2)	*	22.9 (10.5)	23.4 (12.0)	NS
ß-CTx, ng/ml	0.29 (0.22)	0.36 (0.22)	*	0.28 (0.19)	0.37 (0.25)	***

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$. † Erosive disease at study start: baseline Sharp/van der Heijde score ≥ 5 points. ‡ Radiographic progressive disease: Sharp/van der Heijde change score after 2 years ≥ 5 points. Mild disease: Sharp/van der Heijde change score after 2 years < 5 points.

Table 4. Stepwise logistic regression analysis of variables predictive for erosive disease and radiographic progressive disease.

Predictor at Baseline	Erosive Disease at Baseline				Radiographic Progressive Disease After 2 Years			
	ß	SE	Odds Ratio	95% CI	ß	SE	Odds Ratio	95% CI
Constant	–4.7	1.02	—	—	–3.4	0.77	—	—
ß-CTx	NS	—	—	—	NS	—	—	—
Osteocalcin	NS	—	—	—	NS	—	—	—
ESR	NS	—	—	—	0.01	0.01	1.01	1.0 to 1.03
Anti-CCP+	1.2	0.42	3.2	1.4 to 7.4	1.9	0.39	6.9	3.3 to 14.9
IgM RF+	NS	—	—	—	0.73	0.38	2.1	1.0 to 4.4
DAS28	NS	—	—	—	NS	—	—	—
HAQ	NS	—	—	—	0.51	0.26	1.7	1.0 to 2.8
Age	0.05	0.01	1.05	1.02 to 1.08	NS	—	—	—

Åman, *et al*[35] tested the predictive value of a marker for bone resorption (cross-linked carboxyterminal telopeptide of type I collagen: ICTP) in combination with IgM-RF and CRP for radiographic disease progression (Larsen) in early RA. Although ICTP alone correlated with progressive radiological damage, it was concluded that initially elevated serum ICTP combined with high levels of IgM-RF could predict an aggressive disease course in early RA better. In our study, the bone resorption marker ß-CTx was related with radiographic progression, although IgM-RF and anti-CCP status remained rather strong predictors.

It appears that the process of bone metabolism is uncoupled in patients with RA. Bone resorption is positively associated with joint destruction as well as with disease activity, whereas bone formation is not. Other studies confirmed that bone resorption was increased in active disease[22,23,37], whereas bone formation was not[24-26]. According to Garnero, *et al*[26], bone formation was reduced in patients both with and without joint destruction, whereas resorption was increased only in patients with joint destruction in relation to disease activity.

Besides disease activity, bone resorption is influenced as well by postmenopausal status and corticosteroid therapy. Biochemical markers of bone metabolism are greatly affected by menopausal status in patients with RA as well as in controls. Osteopenia in postmenopausal women is caused by the increase in uncoupling between bone formation and bone resorption[27]. According to Kuiper, *et al*[38], postmenopausal state in early RA increases the risk of future disability and damage, especially in older patients. The negative effect of postmenopausal status on bone metabolism was also found in our cohort, as older age and postmenopausal status were associated with erosive disease at study start. Further, corticosteroid therapy decreases bone

formation and enhances bone resorption, which can lead to osteopenia[39-41]. However, the effect of corticosteroid therapy is relatively mild, as it causes only a short term negative effect on bone formation and probably also reduces bone resorption, at least partly as a result of decreased disease activity[21,24]. In our study, the effect of prednisone would be limited, as it was used by only 10% of the patients and the measurements of CTx took place at baseline.

Our study has some limitations. Instead of using only one marker for bone resorption and bone formation, a combination of markers for bone resorption and bone formation rather than a single test might increase the prognostic value to determine aggressive joint disease[35,42-45]. Further, we determined only baseline levels of markers for bone resorption and formation. Future research is needed to find out whether time-integrated values of bone metabolism markers do make a difference in predicting progressive radiographic disease. However, according to Verhoeven, *et al*[21], mainly time-integrated values of ESR explain progression of joint damage in early RA. The contribution of urinary pyridinoline excretion (a bone resorption marker) in the prediction of disease outcome may be modest, especially when markers of acute phase reaction are readily available. As radiographic progressive disease was associated with a higher mean number of DMARD used during the first year of followup, the level of bone resorption might be underestimated.

In summary, although the serological marker for bone resorption ß-C-telopeptide is predictive for radiographic joint destruction, it is not any better, and may be less predictive, than measures already in use.

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