Type I collagen degradation does not diminish with RA disease duration

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Abstract

Objective—To assess the relation between type I collagen degradation and the duration of rheumatoid arthritis (RA).

Methods—The serum concentrations of cross linked carboxyterminal telopeptide of type I collagen (ICTP) measured earlier in a community based series (90 patients) and a hospital based series (59 patients) were re-evaluated with reference to the duration of RA.

Results—The serum ICTP showed a positive correlation with the duration of the disease in the hospital based series ($r_s=0.40$, $p<0.01$) but not in the community based one ($r_s=0.18$, $p=0.10$).

Conclusions—Type I collagen degradation predominantly reflecting pathological bone destruction does not seem to diminish in longstanding RA.

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Plain radiographs are considered the gold standard for measuring joint destruction in rheumatoid arthritis (RA). Erosions in peripheral joints are one of the most characteristic features of RA. Changes are easy to see, and they provide a permanent record. Progression of the disease can be measured objectively by serial radiographs, usually with anteroposterior views of hands and feet.¹

The progression of radiographic changes in a number of inception cohorts has been followed up for up to five to eight years, but only limited information is available of longer follow up. Rasker and Cosh assessed the radiographic damage of metacarpophalangeal and wrist joints after 15 years.² Another long term study dealing with radiographic progression was carried out by Scott *et al.*³ More recently, three further studies have been published.^{4–6} The criteria used in these studies were seldom fully comparable with each other.

Overall, the studies suggest that the most rapid advance in radiographic damage occurs during early disease.¹ The curve of radiological damage ranges from a linear one in the early stages of the disease to a more level rate of progression at the later stages. Yet there is great variation in the type of progression between individual patients.⁵ A key question is whether the apparent changes in RA progression are actually artefactual and related to the ceiling effects inherent in radiographic readings.⁶ In addition, one limitation of radiographic studies is that they focus on the same joint areas, such as hands and feet, over time, though the disease process usually afflicts several joint areas with variable severity.

In recent years there has been an effort to develop biochemical tests to assess tissue destruction, such as degradation of cartilage and bone. One such test is radioimmunoassay for the carboxyterminal telopeptide of type I collagen (ICTP)⁷ applicable to serum and synovial fluid. As recently reviewed, a number of prospective and cross sectional studies of both early and advanced RA have recorded raised serum ICTP concentrations in patients with RA and shown significant correlations between the ICTP concentration and radiographic joint damage.⁸ We have now re-examined the data of two earlier study series^{9 10} to answer the question: Does the degradation of type I collagen vary during the course of RA?

Patients and methods

Of the series of patients with RA re-evaluated for this study, one was community based and the other hospital based.^{9 10} The former series consisted of 90 consecutive patients with RA (31 men, 59 women), who were the subjects of a study on the medicosocial aspects of rheumatic diseases carried out in 1989–91 in the Kuusamo area, northern Finland, with 18 000 inhabitants.⁹ The patient population included approximately 85% of all subjects with RA in the area. The mean age of the patients was 58.7 years and the mean duration of the disease 15.3 (range 1.5–40) years. Forty five (76%) of the women were postmenopausal.

The hospital based series comprised 59 patients with RA (20 men, 39 women), who had been treated in three rheumatology units in Finland.¹⁰ The mean age of the patients was 58.1 years and the mean duration of the disease 13.5 (range 0.5–58) years. Thirty one (79%) of the women were postmenopausal.

ICTP was measured by equilibrium radioimmunoassay⁷ with reagents supplied by Orion Diagnostica (FIN-90460 Oulunsalo, Finland).

The data were recorded and calculated on a personal computer using the SOLO statistical software. Mann-Whitney test, λ^2 statistics, and Spearman's rank correlation coefficient test were used as appropriate.

Results

The serum ICTP concentration correlated positively with the duration of the disease in the hospital based series ($r_s=0.40$, $p<0.01$), but not in the community based series ($r_s=0.18$, $p=0.10$) (fig 1). There was also a correlation between age and ICTP in the hospital based series ($r_s=0.47$, $p<0.001$), but not in the community based one ($r_s=0.08$, $p=0.44$). The median ICTP values for the community based and hospital based series were 4.5 (range 1.9–

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Figure 1 Relation between serum carboxyterminal telopeptide of type I collagen (ICTP) and disease duration in two series of patients with rheumatoid arthritis: (A) a community based one ($r_s=0.18$, $p=0.10$) and (B) a hospital based one ($r_s=0.40$, $p<0.01$).

14.5) and 5.3 (1.1–24.2) $\mu\text{g/l}$, respectively. Neither series showed any significant differences in serum ICTP between men and women. There was also a closer correlation between ICTP and markers of disease activity, such as C reactive protein and the joint swelling score, in the hospital based series ($r_s=0.59$, $p<0.001$; $r_s=0.65$, $p<0.001$, respectively) than in the community based one ($r_s=0.40$, $p<0.001$; $r_s=0.38$, $p<0.001$, respectively).

Discussion

Type I collagen accounts for about 90% of the organic matrix of bone. Tests reflecting its degradation have proved to be useful in assessing bone metabolism.¹¹ Several immunoassays have been developed for structures involving the ICTP, and they give different results, depending on their immunochemical specificity for the size of the antigen and the maturity of the cross links.¹¹ Also the enzymes digesting

type I collagen are important. Normal osteoclastic bone collagen degradation is mediated by cathepsin K, which destroys the ICTP antigenicity.¹¹ Thus increased concentrations of serum ICTP reflect other routes of collagen degradation, most likely those mediated through matrix metalloproteinases.

The ICTP assay has turned out to be a reliable marker for increased type I collagen degradation in situations that include local destruction of bone tissue, such as multiple myeloma,¹² bone metastases from carcinomas,¹³ and both early and advanced RA.⁸ On the other hand, the circulating ICTP antigen levels do not reflect accelerated or retarded physiological bone resorption, such as is seen in the postmenopausal state or during the use of oestrogen replacement therapy.¹⁴ No good methods are available for measuring the breakdown products of type II (cartilage) collagen.

In the work described here we reanalysed the serum ICTP data from two cross sectional series of patients with RA, one of them community based⁹ and the other hospital based.¹⁰ Serum ICTP showed a positive correlation with the duration of the disease in the hospital based series but not in the community based one. Over time some patients with RA go on to have remission and are unlikely to be encountered in hospital based series. Instead, patients with persistently active, severe joint disease—that is, with disease characteristics known to be reflected in the serum ICTP level⁹—accumulate among hospital patients. On the other hand, a selective loss of severe cases probably occurs with time in the community based series owing to excess mortality associated with RA. Accordingly, in this study a more pronounced correlation was found between serum ICTP and markers of disease activity in the hospital based series than in the community based one.

The ICTP concentrations are higher in children than in adults. The manufacturer of the test kit recommends the same reference values for the whole adult age range, though a marginal increase in serum ICTP takes place in women after the menopause.¹⁴ We used ICTP values without any correction. Perhaps the difference between a patient's ICTP concentration and that of controls matched for age and sex might provide a more accurate estimate of pathological bone resorption. However, no large control series with an age distribution similar to that of our patients with RA was available.

As it now stands, our data are in accordance with the view that pathological bone resorption does not diminish in longstanding RA. Wolfe and Sharp similarly reached the conclusion that radiographic damage occurs in RA at a constant rate.⁶

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