Type I collagen degradation does not diminish with RA disease duration

M Hakala, K Aho, S Åman, R Luukkainen, M Kauppi, J Risteli

Abstract

Objectives—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=0.46, p<0.01) but not in the community based one (r=0.18, p=0.10).

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

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) applicable to serum and synovial fluid. As recently reviewed, a number of prospective and case control studies 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. We have now re-examined the data of two earlier study series 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. 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. 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 (75%) 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. 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 radioimmunoassay with reagents supplied by Orion Diagnostica (FIN-90460 Oulu, Finland). The data were recorded and calculated on a personal computer using the SOLO statistical software. Mann-Whitney test, 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=0.40, p<0.01), but not in the community based series (r=0.18, p=0.10) (fig 1). There was also a correlation between age and ICTP in the hospital based series (r=0.47, p<0.001), but not in the community based one (r=0.04, p=0.44). The median ICTP values for the community based and hospital based series were 4.5 (range 1.9–42.0) and 6.0 (range 1.9–29.0) ng/ml, 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 (rₛ=0.59, p<0.001; rₛ=0.65, p<0.001, respectively) than in the community based one (rₛ=0.40, p<0.001; rₛ=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.14 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 level—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.7


14.5) and 5.3 (1.1–24.2) µg/l, respectively.

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 (rₛ=0.18, p=0.10) and (B) a hospital based one (rₛ=0.40, p<0.01).
4 Kaarela K, Kautiainen H. Continuous progression of radio-
logical destruction in seropositive rheumatoid arthritis. J
5 Graudal N, Jurik AG, de Carvalho A, Graudal H.
Radiographic progression in rheumatoid arthritis: A
long-term prospective study of 109 patients. Arthritis
6 Wolfe F, Sharp JT. Radiographic outcome of recent-onset
arthritis: A 19-year study of radiographic progression.
7 Risteli J, Elomaa I, Niemi S, Nisunen M, Risteli L. Radiol-
ogic bone destruction: cross-linked carboxyterminal
telopeptide of type I collagen: a new serum marker of
8 Åman S. Markers of collagen metabolism in the assessment
of rheumatoid arthritis—with special reference to cross-
linked carboxyterminal telopeptide of type I collagen
[thesis]. Acta Universitatis Ouluensis D Medica
9 Hakala M, Risteli L, Matukoski T, Nieminen P, Risteli J.
Increased type I collagen degradation correlates with
disease severity in rheumatoid arthritis. Ann Rheum
10 Hakala M, Åman S, Liukkaniemi E, Risteli L, Kangri M,
Niemi S, et al. Application of markers of collagen
metabolism in serum and synovial fluid for assessment of
disease process in patients with rheumatoid arthritis.
M, et al. Immunohistochemical characterization of urine
for the carboxyterminal telopeptide of human type I collagen: loss
of antigenicity by treatment with cathepsin K. Bone 2001;
28:367–73.
12 Elomaa I, Vilkkunen P, Risteli L, Risteli J. Serum
concentration of the cross-linked carboxyterminal telopep-
tide of type I collagen (ICTP) is a useful prognostic indica-
13 Arai A, Relansu M, Hietta R, Takashita D, Ogata E. Use-
of bone metabolic markers in the diagnosis and
follow-up of bone metastases from lung cancer. Br J Cancer
14 Hassager C, Risteli J, Risteli L, Christiansen C. Effect of the
monospecific and hormone replacement therapy on the
carboxy-terminal pyridinoline cross-linked telopeptide of
Type I collagen degradation does not diminish with RA disease duration

M Hakala, K Aho, S Åman, R Luukkainen, M Kauppi and J Risteli

Ann Rheum Dis 2001 60: 420-422
doi: 10.1136/ard.60.4.420

Updated information and services can be found at:
http://ard.bmj.com/content/60/4/420

These include:

References
This article cites 13 articles, 5 of which you can access for free at:
http://ard.bmj.com/content/60/4/420#BIBL

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Topic Collections
Articles on similar topics can be found in the following collections

Connective tissue disease (4253)
Degenerative joint disease (4641)
Immunology (including allergy) (5144)
Musculoskeletal syndromes (4951)
Rheumatoid arthritis (3258)

Notes