Increased type I collagen degradation correlates with disease severity in rheumatoid arthritis

Markku Hakala, Leila Risteli, Jorma Manelius, Pentti Nieminen, Juha Risteli

Abstract

Objectives—To assess the extent and clinical significance of type I collagen degradation in rheumatoid arthritis (RA).

Methods—Serum samples from 90 consecutive patients with RA from a cross-sectional population-based study and 90 age- and sex-matched controls were analysed with the new assay of cross-linked carboxyterminal telopeptide of type I collagen (ICTP).

Results—Patients with RA had significantly higher concentrations of ICTP than the controls. ICTP correlated strongly with measures of impairment in RA, such as the erosive state of joint disease (ES) (r = 0.57, p < 0.001) and Keitel function test (KFT) (r = 0.49, p < 0.001), and more weakly with various disease activity markers. When erythrocyte sedimentation rate (ESR), ES or KFT were used as indicators of disease severity among the patients with disease duration over five years, ICTP distinguished the more serious RA from milder cases.

Conclusions—Elevated serum concentrations of ICTP are common in RA and are associated with signs of aggressive disease.

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Most of the laboratory tests that are currently used for assessing the condition of patients with rheumatoid arthritis (RA) reflect inflammatory activity rather than tissue destruction.1 3 Only the end result of the latter, that is, loss of joint space and bone erosions, can be seen on radiographs.4 The impairment and disability caused by RA is closely related to connective tissue degradation, and the search continues for laboratory tests that could monitor the activity of this process.1 2 4

Type I collagen accounts for about 90% of the organic matrix of bone, and is also the major matrix protein in tendons, ligaments and soft connective tissues. Thus assessment of its breakdown might have a use in diseases with connective tissue degradation, such as RA. At present, the activity of type I collagen breakdown can only be estimated by assays that are based on the use of urine samples. These include the assay of the imino acid 4-hydroxyproline and that for the pyridinoline and deoxypyridinoline crosslinks which have also been tested in patients with RA,6 but have not been established in routine clinical work. In this study we use a new serum marker for the degradation of this collagen type, the cross-linked carboxyterminal telopeptide of type I collagen (ICTP),7 in a cross-sectional population-based outpatient series of RA patients.

The validity of ICTP as an indicator of bone resorption has been verified in high/low turnover bone diseases by histomorphometric studies.7 Serum levels of ICTP also increase in the presence of local bone destruction, such as in patients with multiple myeloma.8 We wanted to test whether in RA type I collagen degradation is accelerated so that it leads to elevated concentrations of ICTP in the blood and, if so, which characteristics of the disease it is associated with.

Patients and methods

Patients

We studied 90 consecutive patients with RA,9 31 men and 59 women, who had been included in a population-based study on medicosocial aspects of rheumatic diseases, carried out in 1989–91 in the Kuusamo area, Northern Finland, with 18 000 inhabitants.10 The patient population of our study included approximately 85% of all subjects with RA in the area, thus representing the whole spectrum of the disease from mild to severe. Ninety age- and sex-matched mobile subjects without overt joint or bone diseases were selected as controls from the same geographical area.

The mean (SD) age of the patients was 58.7 (11.2) years, and the duration of the disease 15.3 (8.7) years. Five of the 90 patients did not use any medication for RA, 16 had non-steroidal anti-inflammatory drugs (NSAIDs) as the only treatment, 64 used slow-acting anti-rheumatic drugs (SAARDs) and 5 peroral corticosteroids. In addition, 23 of the 64 patients with SAARDs were also on peroral corticosteroids. The corticosteroid dose was in all cases ≤10 mg prednisolone. This was an outpatient series; none of the 90 patients needed permanent treatment in a nursing home or were bedridden or permanently in a wheelchair.

According to serum creatinine levels (normal range 60–115 μmol/l) renal function was slightly decreased in four of the patients and in one of the controls; the highest value in the patient group being 154 μmol/l. Overall serum creatinine showed a larger variance among the RA patients but the mean values did not differ between the patients and controls, 79.8 (19.1) and 80.1 (12.5) μmol/l, respectively.
CLINICAL AND RADIOLOGICAL METHODS

Physical examination was done by one of the authors (MH) and included the following assessments: duration of morning stiffness, grip strength, Ritchie articular index (RAI) with a joint swelling score. Swelling in each joint/joint group was estimated as follows: none = 0, mild = 1, moderate = 2 and severe = 3. The sum of RAI and joint swelling score was used as general activity index of RA. The Keitel function test (KFT), which involves a series of range-of-motion tasks, performed by the patient, to examine the functional capacity of the limbs and the vertebral column, was used with minor modifications, resulting in a total score from 96 (worst) to 0. KFT gives an overall picture of functional limitation in a patient and has been shown to be a reliable global measure in RA. Routine laboratory tests for assessment of disease activity were included in the study protocol and were taken in the morning (7–10 am after overnight fasting). Serum samples were stored at −20°C before analyses. Rheumatoid factor (RF) was measured with an immunoturbidometric method (Orion Diagnostica, SF-02200 Espoo, Finland), with values ≥25 IU/ml considered positive. In addition, radiographs of both hands were taken for the study.

The erosive state of the joint disease was assessed by one of the authors (JM) from posteroanterior radiographs of both hands by Larsen’s method,\textsuperscript{14} classifying MCP, (P)IP and wrist joints (indices 0–5) compared with a standard series. The Larsen indices of the wrist joints were multiplied by five.\textsuperscript{15} When all the joints referred to are fully destroyed the index of erosive state is 150.

MEASUREMENT OF SERUM ICTP CONCENTRATION

ICTP was measured in duplicate 100-µl aliquots of serum using a recently developed equilibrium radioimmunoassay\textsuperscript{6} (Orion Diagnostica, SF-90460 Oulunsalo, Finland). The standard and tracer antigens of the test are cross-linked carboxyterminal telopeptide parts of type I collagen liberated by digestion with bacterial collagenase from decalcified human femoral bone. The intra-assay variation of the ICTP assay is around 6% and the inter-assay variation less than 8%.\textsuperscript{8}

STATISTICAL ANALYSIS

The data were recorded and calculated on a personal computer using SOLO statistical software.\textsuperscript{16, 17} Student’s t test, Spearman’s rank correlation coefficient test, Chi-square statistics and Fisher’s exact probability test were used as statistical methods when appropriate.

Results

The mean (SD) concentration of the ICTP antigen in serum was higher in RA patients [52 (25) µg/L] than in the controls [31 (075) µg/L, yielding a reference interval of 16–4.6 µg/L; p < 0.001] (fig 1). ICTP correlated with age in the controls (r = 0.36, p < 0.001) but not in the patients. Thirty-nine (43%) of the patients had ICTP concentration exceeding the upper limit of the reference interval, with an equal proportion of elevated values among men and women. Four (29%) of the pre- and 22 (49%) of the postmenopausal women with RA had an elevated ICTP concentration; this difference did not reach a statistical significance.

It seemed that patients, particularly those with generalised joint disease affecting also the central joints (hip, knee, shoulder), had high levels of ICTP. Patients with total joint replacement (TJR) of large joints had higher ICTP concentrations than those without, 7.0 (2.6) and 4.8 (2.3) µg/L, respectively (p < 0.001). Fifteen (88%) of 17 patients with TJR had ICTP concentration over the reference range compared with 24 (33%) out of those without (p < 0.001).

In the whole RA group studied, the serum ICTP concentration correlated with all the common indices used in RA (table 1), the correlation being strongest with the erosive state (fig 2) and functional state (KFT). Both the RAI and joint swelling score correlated with ICTP (r = 0.32, p = 0.02; and r = 0.38, p < 0.001, respectively). Furthermore, there was a correlation between grip strength and ICTP (r = −0.34, p = 0.001). ICTP did not correlate with the duration of the disease or the joint damage.
Table Relation between ICTP* and common indices used in rheumatoid arthritis (RA) in a cross-sectional study of 90 RA patients.

<table>
<thead>
<tr>
<th></th>
<th>GAI</th>
<th>ES</th>
<th>RF</th>
<th>ESR</th>
<th>CRP</th>
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<tr>
<td>ICTP</td>
<td>0.43</td>
<td>0.57</td>
<td>0.23</td>
<td>0.99</td>
<td>0.40</td>
<td>0.49</td>
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<td>p</td>
<td>&lt;0.001</td>
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*ICTP = cross-linked carboxy-terminal telopeptide of type I collagen in serum; GAI = general activity index (sum of the scores of Ritchie articular index and joint swelling score); ES = erosive state of joint disease; RF = rheumatoid factor; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; KFT = Keitel function test.

Present duration of morning stiffness. However, both the erosive state and KFT showed a correlation with the duration of the disease ($r = 0.44$, $p < 0.001$; and $r = 0.34$, $p = 0.002$, respectively).

To compare ICTP with disease severity we identified two groups among the patients with a disease duration longer than five years. Thirty-one patients had both erythrocyte sedimentation rate (ESR) and erosive state values above or equal to the respective median values, while in 19 both parameters were below the median. The serum ICTP concentrations were 6.6 (3.1) and 3.9 (1.2) $\mu$g/l, respectively ($p < 0.001$). A similar result was obtained when functional state was used instead of the erosive state in the division, subjects with high ESR and poor KFT ($n = 26$) having a higher ICTP concentration [6.8 (3.3) $\mu$g/l] than those with a milder disease [$n = 18$; 4.1 (1.1) $\mu$g/l, $p < 0.001$].

Neither the duration nor the cumulative dose of corticosteroid therapy correlated with ICTP. Instead, patients with corticosteroids had significantly more often elevated ICTP concentrations (>4.6 $\mu$g/l) than those without, 19/28 vs 20/62 ($p = 0.002$). However, those treated with corticosteroids had otherwise signs of aggressive disease [associated with elevated ICTP], such as a high grade of erosive state and major joint prostheses. ICTP level did not significantly differ between patient groups with various therapies (SAARDs, NSAIDs, no drug).

**Discussion**

The biochemical basis of the ICTP assay differs from that of the commonly used laboratory parameters, such as ESR and C-reactive protein, which reflect the inflammatory activity rather than tissue destruction in RA. Instead, the ICTP antigen is derived from fibrillar type I collagen, the main substance of the organic matrix of bone and soft tissues, and its release into circulation is thus a direct measure of tissue destruction. The assay does not cross-react with type II collagen, that is, it does not measure breakdown of hyaline cartilage.

In the present series, 43% of the RA patients had elevated serum ICTP concentrations. ICTP correlated strongly with measures of impairment in RA, such as erosive state (assessed from hand radiographs) and Keitel function, which both reflect the anatomical changes in joints. A weaker association was also found with markers of disease activity. This may be explained by the multipotential role of cytokines in RA. For example, both interleukin-1 (IL-1) and IL-6, besides their ability to induce hepatic synthesis of acute phase reactants, also mediate bone resorption and tissue destruction in RA. Since ICTP presumably derives from ongoing soft tissue or bone breakdown one would have expected to see more of a correlation with indices of inflammation rather than radiographic damage which reflects previous destruction. Our experience from patients with early RA is that ICTP has a close correlation with disease activity markers and that remititive therapy decreases ICTP levels (unpublished data). In the present series, most patients had SAARDs which probably modifies our result. It is known that the present drug therapy modifies more the acute phase than the chronic, destructive phase of RA.

Patients with total joint replacement, with high levels of ICTP in the present series, represent the most destructive form of RA. As RA is a polyarticular disease, elevated levels of ICTP in those who already have joint prostheses could be an indicator of ongoing destruction in other major joints. Overall central joints offer a larger area for periartricular bone loss than peripheral joints. Significant and progressive bone loss has also been documented to occur around the prosthesis.

Immobilisation is a well-known inducer of generalised bone loss leading to osteoporosis. Worsening walking time and functional grade have been shown to correlate with reductions in femoral shaft bone mass in RA. Thus a combination of systemic and local effects of RA on bone metabolism could lead to elevated ICTP concentrations in the subjects with central joint affliction. However, our patients were actively treated with a high frequency of total joint replacement surgery, and thus there was a low prevalence of major immobilisation in this series. Neither the menopausal status nor steroid usage explains increased ICTP concentrations in our RA series. When the effect of impaired renal function on ICTP becomes significant with glomerular filtration rates of about two thirds of the lower limit of the reference interval it appears that the elevated ICTP levels in our RA series cannot be explained by renal disease.

In our cross-sectional outpatient series, ICTP, a new biochemical marker of type I collagen degradation correlated more closely with measures of impairment in RA, such as radiograph and Keitel function, than those of inflammation. According to these preliminary data ICTP seems to be associated with major joint disease. This is presumably due to the large area of affected periartricular bone in such cases. Further studies are needed to test a more distinct hypothesis of elevation of ICTP in the serum of RA patients.

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