LETTERS TO THE EDITOR

Increased type I collagen degradation is associated with a need for total joint replacement surgery in rheumatoid arthritis

Much work has been done to find biochemical tests that could reflect disease processes in rheumatoid arthritis (RA) more precisely than the traditional laboratory tests. Such tests include markers of bone and cartilage metabolism.[1]

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 by a radioimmunoassay of a cross linked carboxyterminal telopeptide of type I collagen (ICTP)[2] might be useful in diseases involving connective tissue degradation, such as RA. We recently tested ICTP, used as a serum test, in a community based RA series of 90 patients with a mean (SD) disease duration of 15·3 (8·7) years.[3] Thirty nine (43%) of the patients had increased serum concentrations of ICTP and the test discriminated between patients with signs of aggressive disease and milder cases.[3] We have followed the subjects of the series for three years, looking for important morbidity events, such as destruction of large joints (hip and knee) indicated by a need for total joint replacement surgery (TJRS). Patients who died early during the follow up were excluded.

During the follow up of three years, nine (26%) of the 35 patients with initial serum ICTP values above the upper limit of the reference range (4·6 μg/l) required TJRS of at least one joint (six of them underwent two, and one underwent three operations) compared with one (2%) of the 50 patients who had normal serum concentrations of ICTP ($p = 0·001$) (table). Thus increased serum ICTP among patients with advanced RA seems to discriminate between cases with destructive joint disease, and a further need for TJRS, and milder cases.

Interestingly, in the present series, increased C reactive protein (CRP) had an equivalent prognostic power as to a further need of TJRS. We did not make sequential analyses of the above laboratory tests for this study, but it has been shown that even when current drug treatment reduced the acute phase response, radiographic progression continued.[4] The few data on increased serum ICTP reported previously were similar.[5]

In this series of patients with advanced RA, an increase in serum ICTP was associated with progressive disease course as judged by need for TJRS. Ideally, measurement of outcome in RA should estimate the outcome of disease during the early reversible stages and the later stages. In our previous series of early RA, an increased serum ICTP was also a risk factor for a more erosive disease course.[5] Thus a combination of measurement of serum ICTP, and more traditional measures used in clinics, such as the number of swollen joints and CRP, could serve as prognostic indicators for cases requiring the most aggressive treatments.

SARI ÅMAN
MARKKU HAKALA
Department of Internal Medicine, University of Oulu, FIN-90220 Oulu, Finland

LEILA RISTELI
Department of Medical Biochemistry

JUHA RISTELI
Department of Clinical Chemistry

Correspondence to: Dr Sari Åman.

1 Peel N, Eastell R, Russell G. Markers of bone and collagen breakdown in early inflammatory arthritis. *Baillieres Clin Rheumatol* 1992; **6**: 351–72.
2 Risteli J, Elomaa I, Niemi S, Novamo A, Risteli L. Radioimmunoassay for the pyridinoline cross-linked carboxyterminal telopeptide of type I collagen: a new serum marker of bone collagen degradation. *Clin Chem* 1993; **39**: 635–40.
3 Hakala M, Risteli L, Manelius J, Nieminen P, Risteli J. Increased type I collagen degradation correlates with disease severity in rheumatoid arthritis. *Ann Rheum Dis* 1993; **52**: 866–9.
4 Scott D, Coulton B, Bacon P, Popert A. Methods of x-ray assessment in rheumatoid arthritis: a re-evaluation. *Br J Rheumatol* 1985; **24**: 31–9.
5 Paimela L, Leirisalo-Repo M, Risteli L, Hakala M, Helve T, Risteli J. Type I collagen degradation product in serum of patients with early rheumatoid arthritis. Relationship to disease activity and radiological progression in a 3-year follow-up. *Br J Rheumatol* 1994; **33**: 1012–6.

Relation between serum concentrations of ICTP at the start of a three year follow up and number of total joint replacement operations

Serum ICTP concentration	*Number of operations*		
	0–12 months	*13–24 months*	*25–36 months*
Increased	4	8	5
Normal	0	0	1

There were 18 total joint replacement operations for 10 patients.
ICTP = Cross linked carboxyterminal telopeptide of type I collagen.

Polymyalgic presentation of enterovirus infection: a cause of diagnostic confusion

The cause of polymyalgia rheumatica (PMR) remains unknown. In the absence of arteritic symptoms, the diagnostic yield from temporal artery biopsy is low and, in the majority of patients, PMR remains a 'clinical' diagnosis. While the possibility of underlying temporal arteritis and expectation of rapid clinical response may prompt early recourse to steroid treatment in suspected PMR, failure to adhere closely to established diagnostic criteria[1] may lead to misdiagnosis. We report a case of enteroviral infection mimicking PMR.

A previously well 70 year old housewife was seen by her general practitioner (GP) with a 10 day history of malaise and 'burning' pain, profound early morning stiffness and weakness in the shoulder girdle, upper arms, thighs, and lower back. She volunteered difficulty in lifting her arms to brush her teeth in the morning. Her symptoms were of sudden onset and had been preceded by transient pharyngitis. She reported no rash and no joint swelling. Non-steroidal and anti-inflammatory analgesia and a course of co-amoxiclav, started three days after the onset of symptoms, produced no improvement. Five days before developing symptoms, she had come into contact with her six year old grandson who had been mildly unwell with fever and widespread vesicular rash.

Her haemoglobin was 12·6 g/dl, leucocyte count $10·3 \times 10^9$/l, platelets 645×10^9/l and erythrocyte sedimentation rate (ESR) 70 mm/1st h. On the basis of her presenting symptoms and laboratory results, a diagnosis of PMR was made by her doctor. Prednisolone 20 mg daily was started and symptoms rapidly resolved.

The patient was referred to the Rheumatology outpatient clinic, and when seen six weeks later was symptom free on prednisolone 10 mg daily. Clinical examination was normal. A full blood count, rheumatoid factor, antinuclear antibody, creatinine phosphokinase, calcium, alkaline phosphatase, thyroid function tests, and myeloma screen were normal. ESR was 10 mm/1st h.

History of exposure to viral infection and initial symptoms of pharyngitis prompted a search for a viral trigger. A significantly increased level of enterovirus specific IgM antibody was detected consistent with recent enteroviral infection. The reference laboratory assay, a *mu*-capture enzyme linked immunosorbent assay (ELISA) (98% specificity; Dr J W A Bendig, PHLS, Epsom, unpublished data) is able to detect a broad range of enteroviral infection but does not identify specific serotypes.[2] Serology for varicella, parvovirus, rubella, influenza A and B, respiratory syncytial virus (RSV) and cytomegalovirus did not reveal recent infection with these micro-organisms. Prednisolone was withdrawn uneventfully over the next 10 weeks. The patient remained well six months later.

The human enteroviruses, which include polio-, echo- and coxsackie viruses and enteroviruses 68–71, cause a range of diseases.[3] Enteroviral infection is recognised most commonly in association with mild epidemic illness in children. In Hand, Foot and Mouth disease, associated with a number of coxsackie serotypes—most commonly A16—vesicular rash is prominent and may, on occasion, be widespread, mimicking that of varicella. This patient may have been exposed to enteroviral infection through contact with her grandson. Enteroviruses are, however, common pathogens and an alternative source of infection cannot be excluded.

Whilst acute peripheral small joint synovitis, with or without spondylarthritis, accompanied by rash, fever and pleuropericarditis, can occur in coxsackie virus infection,[4] no association between PMR and enteroviral infection has been reported. In patients with PMR, levels of antibody to enterovirus,[5] in addition to those to influenza A and B, *Herpes simplex*, mumps, measles, *Mycoplasma pneumoniae*,[6] *Herpes zoster*,[7]