

Serum YKL-40 concentrations in patients with early rheumatoid arthritis: relation to joint destruction

Julia S. Johansen¹, John R. Kirwan², Paul A. Price³, and Mohammed Sharif²

¹Department of Rheumatology, Hvidovre Hospital, University of Copenhagen, Denmark; ²Rheumatology Unit, University of Bristol Division of Medicine, Bristol Royal Infirmary, United Kingdom; and ³Department of Biology, University of California San Diego, La Jolla, CA, USA.

Objective: YKL-40 is a secretory glycoprotein of chondrocytes, synovial cells, macrophages, and neutrophils. The aims were to determine serum YKL-40 in patients with early rheumatoid arthritis (RA) and seek associations with early joint erosions.

Methods: YKL-40 was measured by ELISA in serum samples collected every three months for 36 months from patients with early RA. The patients were treated with DMARDs and some were allocated to additional prednisolone.

Results: Serum YKL-40 was higher in RA patients compared with controls (98 vs. 42 µg/l, $p < 0.001$). The mean serum YKL-40 during the study correlated with the progression in Larsen score (Pearson's test: $p = 0.004$). Patients with a persistently high serum YKL-40 had larger progression in Larsen score compared with patients with normal serum YKL-40 (median progression: 7 vs. 0, $p = 0.003$).

Conclusion: These data suggest that elevated serum YKL-40 is related to progression in joint destruction in early RA patients.

Key words: YKL-40, HC gp-39, early rheumatoid arthritis, Larsen score, bone erosions, C-reactive protein

Biochemical markers of joint tissue metabolism and disease activity in patients with rheumatoid arthritis (RA) would be very useful for monitoring the varying disease course (1). Currently it is desirable to identify patients at risk of more aggressive disease and increased likelihood of having progressive joint destruction early in the course of the disease in order to treat these patients more intensively with disease modifying anti-rheumatic drugs (DMARDs). Until now measurements of the acute phase response, serum C reactive protein (CRP) and the erythrocyte sedimentation rate (ESR), have been the most widely used serological parameters for long term monitoring of disease activity and severity of RA (2–4). However, differences exist between clinical inflammation and the level of ESR and serum CRP, and these parameters can be normal in patients with apparently active joint inflammation (2,4). Furthermore, progression in Larsen score and development of bone erosions in the hands of patients with early RA can occur independently of clinical symptoms and the acute phase response (5,6). New markers reflecting other aspect of disease activity in RA are therefore of clinical importance.

YKL-40, also called human cartilage glycoprotein-39 (HC gp-39), is a mammalian member of family 18 glycosyl hydrolases (7–10) and is secreted by several cell types present in the arthritic joint. YKL-40 is a major protein secreted by chondrocytes

in vitro (8,10,11) and *in vivo* YKL-40 is detected in the chondrocytes located in the upper and middle layer of cartilage from arthritic knee joints (12). Activated macrophages secrete YKL-40 *in vitro* (13–15) and *in vivo* YKL-40 expression are found in synovial macrophages from RA patients (12,13,16), and the protein is exocytosed from the specific granules of activated neutrophils (17). YKL-40 is a heparin and chitin-binding lectin (9,14) without chitinase activity (8,10,14) and has a known gene sequence (15). The exact physiological function of YKL-40 is unknown, but it has recently been reported that YKL-40 is a growth factor for connective tissue cells (18). Interestingly YKL-40 may be a target of the T-cell-mediated immune response in RA (19–22). YKL-40 derived peptides that are predicted to bind to DRB1*0401 with the aid of a DRB1*0401 peptide-binding motif is selectively recognized by peripheral blood mononuclear cells (PBMC) from RA patients, whereas little proliferative responses of PBMC from healthy controls are found (22). Furthermore, there is a correlation between the degree of the proliferative responses of PBMC and the number of tender and swollen joints and the modified disease activity score of the patients (22). Immunization of BALB/c mice with the YKL-40 protein induced a chronic relapsing inflammatory polyarthritis, which could be delayed and suppressed by intranasal administration of YKL-40 peptides prior to immunization (19,21). Murine type II collagen induced arthritis could also be suppressed by intranasal administration of human recombinant YKL-40 (21).

Increased levels of YKL-40 in serum and synovial fluid are found in patients with active RA (7,12,23–25) or severe osteoarthritis (7,12,26) com-

Julia S. Johansen, Department of Rheumatology 232, Hvidovre Hospital, Kettegård Alle 30, DK-2650 Hvidovre, Denmark.
E-mail: julia.johansen@post3.tele.dk

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pared to normal subjects. A relation exists between the level of YKL-40 in serum and synovial fluid with 10–20 fold higher values in synovial fluid (7,12). Serum YKL-40 concentrations change according to disease activity in RA patients and may provide information different from the conventional markers of inflammation ESR and serum CRP (7,12,23–25). We found in a one year longitudinal study of patients with RA that patients with a persistently elevated serum YKL-40 were at risk of radiological disease progression as determined by the Larsen score (24).

The objects of the present study were to determine serum YKL-40 concentrations in a new cohort of patients with early RA and to seek associations with progression in the Larsen score and joint erosions over 3 years.

Materials and methods

Patients: Seventy-six patients, aged 23–68 years, with early RA (i.e. disease duration of < 2 years) were included in the present study. The patients took part in the randomized, double-blind, placebo-controlled “Arthritis and Rheumatism Council Low-Dose Glucocorticoid Study” (27,28). All patients fulfilled the ACR classification criteria for RA (29). Further details about this study and the clinical outcome in these patients have been published previously (27,28,30). A total of 128 patients were included in the original study, but appropriate handling of serum specimens and sufficient serum was only available for YKL-40 analysis from 76 of these 128 patients in the first year, from 71 for the second year and from 64 for the last year of the 3 year study period. The patients included in our analysis were marginally more severely affected clinically (e.g. pain 1.59 vs. 1.44; HAQ 1.40 vs. 1.05) but there was no significant difference between the prednisolone and placebo groups. In addition, there were no significant differences between the x-ray values of those included or not included in our analysis nor those in the prednisolone and placebo groups. Thus the sub-group of patients used in this study is likely to be a good representation of the original 128 patients. At inception the patients had active RA defined as six or more painful joints, three or more joints with active synovitis, early morning stiffness for > 20 min and a CRP concentration in serum > 10 mg/l. Patients with malignant disease or liver disease were not included, and none of the patients had signs of bacterial infections at the time of blood sampling. The patients were randomized to receive 7.5 mg of prednisolone (n = 35) or an identical placebo (n = 41) in addition to conventional anti-rheumatic therapy. The prednisolone therapy was discontinued after 2 years without unblinding the study, and follow-up con-

tinued for further 12 months. Approximately three quarter (75%) of the patients received treatment with DMARDs during the study. Most frequently used DMARDs were sulphasalazine (30%), penicillamine (32%), gold (7%), methotrexate (5%), and hydrochloroquine (1%). The majority of the patients (77%) also received non-steroidal anti-inflammatory drugs (NSAIDs). There were no differences in the distribution of drug treatments between the two study groups and the proportion of patients on MTX treatment were similar to other studies at the same time in the early nineties.

X-ray: Radiographs of the hands and wrists were taken at entry and after 2 and 3 years. All available radiographs were read and scored under blind conditions by the same experienced radiologist and rheumatologist as described elsewhere (27,28). Each hand was classified as erosive or non-erosive and each finger and wrist joint was then scored according to the method of Larsen et al. (31).

Clinical outcomes: Clinical disease activity were assessed every 3 months and included the following measurements: Disability (measured by the Health Assessment Questionnaire (HAQ score) (32), joint inflammation (measured by an articular index of tender and swollen peripheral joints weighted for joint size (33)), and the acute phase response (measured by serum CRP).

Biochemical analysis: Blood samples were taken at entry and every 3 months during the 3 year study period. The serum was separated from the blood cells within 3 hours and stored at –70°C until analysis was performed. Serum CRP was determined by an in-house capture ELISA (34), serum hyaluronate by an inhibition ELISA (35), serum amino-terminal propeptide of type III procollagen (PIIINP) was determined by radioimmunoassay (RIA-gnost PIIIP; CIS bio international UK Ltd., High Wycombe, UK), serum keratan sulfate was measured by an inhibition ELISA (36), serum osteocalcin was measured by immunoradiometric assay (ELISA-OSTEO; CIS bio international UK Ltd.), and the proenzyme forms of stromelysin 1 (promatrix metalloproteinase 3 (proMMP-3)) was measured by ELISA (37). Further details about these assays and results are described elsewhere (30). The serum YKL-40 concentration was determined by a two-site, sandwich-type enzyme-linked immunosorbent assay (Quidel, Mountain View, CA, USA) (23) using streptavidin-coated microplate wells, a biotinylated-Fab monoclonal capture antibody, and an alkaline phosphatase-labeled polyclonal detection antibody. The source of the YKL-40 antigen used for standards and production of antibodies were purified from the conditioned medium of the human osteosarcoma cell line MG63. The detection limit is 20 µg/l and the intra-assay

and inter-assay variations were < 4.3% and < 5.3%, respectively. To eliminate the inter-assay variation samples from each patient were analyzed in the same assay.

Healthy volunteers: The normal range of serum YKL-40 was determined in 191 healthy age-matched volunteers with a mean age of 46 years (range 23–68 years). They were all healthy, were not taking any medicine, and had no clinical signs or symptoms of cancer, joint, liver, metabolic or hormonal disease (26). Potentially, serum YKL-40 may vary with time. Therefore, the normal variation in serum YKL-40 levels was evaluated in 30 healthy women with an age between 24–62 years. They had serum samples collected five times with seven days intervals, and subsequently after 3 years serum samples were again collected five times with seven days intervals from 21 of these women.

Statistical analysis: The statistical analysis was performed with Sigma Stat (SPSS Inc. Chicago, IL, USA). Results are given as median and range. Comparison between groups was performed by the non-parametric Mann-Whitney test and comparison between two related samples was performed by the Wilcoxon test. Correlation analysis between the different parameters were calculated by the Spearman rho test. P values less than 0.05 were considered significant. The course of the changes in serum YKL-40 and serum CRP were expressed in time integrated values and the area under the curve (AUC) (38) was determined using 9 time points covering the first 2 years and 13 time points for the whole 3 year study period, since serum YKL-40 and CRP concentrations were determined every third month. Pearson's test and Fisher's Exact test were used to evaluate if a relationship existed between progression in Larsen score and serum YKL-40 and CRP.

Results

Serum YKL-40 in relation to disease activity. Baseline clinical and demographic features of the patients are presented in Table I. The median serum YKL-40 level in patients with early RA (median 98 µg/l (range 21–408)) was significantly higher than the level in healthy age-matched controls (42 µg/l (20–184), $p < 0.001$). Forty nine per cent of the patients had elevated serum YKL-40 (i.e. > 102 µg/l, the upper 95th percent confidence limit of healthy age-matched subjects). 89% percent of the patients at baseline had high articular indices score (i.e. ≥ 100) and serum YKL-40 in these patients were higher compared to patients with low articular indices score (i.e. < 100) (106 vs. 73 µg/l, $p = 0.090$). Forty patients became inactive during the 3 year study period (i.e. they had no tender or swollen joints). Serum YKL-40 was

Table I. Baseline demographic, clinical and radiographic characteristics of the patients.

<u>Demographic</u>	
Female/male	55/21
Age, years	48 (23–68)
Disease duration, years	1.3 (0.2–2.0)
Rheumatoid factor present	67%
<u>Measurement of disease activity*</u>	
Pain Score	1.6 (0.2–3.0)
Articular index #	213 (0–467)
HAQ score	1.5 (0.1–2.9)
Serum CRP, mg/l	20 (9–198)
Serum YKL-40, µg/l	98 (21–408)
<u>Radiographic</u>	
Number of patients with Larsen score >0	39
Number of patients with bone erosions	34

#An index of tender and swollen peripheral joints weighted for joint size (33). *Values are medians (range).

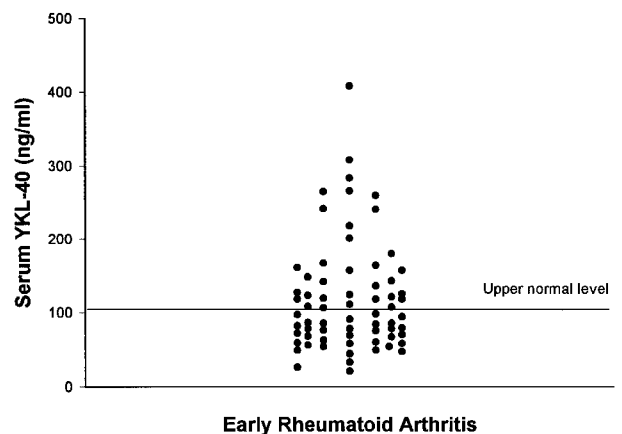


Fig. 1. Individual serum levels of YKL-40 in patients with early RA before treatment with DMARD or prednisolone. The median serum YKL-40 and the 95th percentile value of healthy age-matched subjects is 42 µg/l and 102 µg/l, respectively.

decreased (– 14%, $p = 0.003$) at the time when the patients were inactive compared to the previous serum YKL-40 concentration at a time when the patient had signs of synovitis. If these inactive patients later had signs of clinical relapse (i.e. an articular indices score > 0), serum YKL-40 increased (+ 38%, $p = 0.003$) compared to the level when the patients were inactive. Patients who remained active with high articular indices score (i.e. ≥ 100) during the study had unchanged serum YKL-40.

Changes in serum YKL-40 during treatment with NSAIDs and DMARDs only or in combination with prednisolone. The patients were included in a 2 year double-blind, placebo-controlled study comparing treatment with NSAIDs and DMARDs only or in combination with low dose of prednisolone (i.e. 7.5 mg p.o./day) for 2 years followed by one year without prednisolone. The base-line serum YKL-40

was similar in both treatment groups. There were no significant differences between the changes in serum YKL-40 in the two treatment groups during the 3 year study. Serum YKL-40 levels were only significantly decreased compared to the initial value at 6 months ($p=0.014$) and 30 months ($p=0.048$) in patients treated with DMARDs only and at 9 months ($p=0.008$) in the group treated with DMARDs in combination with prednisolone. Twenty two patients were treated for at least 24 months with sulphasalazine. Serum YKL-40 was decreased in these patients after 3 months (-17% , $p<0.003$) compared to baseline values and remained significantly decreased ($p=0.04$ to $p=0.001$) during the sulphasalazine treatment. After 24 months of treatment with sulphasalazine serum YKL-40 was decreased by 29% ($p<0.001$). Twenty two patients were treated for at least 24 months with penicillamine and they had unchanged serum YKL-40 (except at 6 months). Only a few patients were treated for at least 12 months with other DMARDs and the effects on serum YKL-40 were therefore not evaluated. The mean variation in serum YKL-40 in the patients during the 3 year study period was 31% and significantly higher than the normal variation of 5% ($p<0.001$) in serum YKL-40 levels in 30 healthy female controls.

Relation between serum YKL-40 and other markers of disease activity. At base-line no correlations were found between serum YKL-40 and different biochemical parameters of synovial inflammation (serum CRP, PIIINP, hyaluronate, and proMMP-3), cartilage metabolism (serum keratan sulphate and proMMP-3), and bone formation (serum osteocalcin). During the 3 year study period significant, albeit low, correlations were found between serum YKL-40 and CRP (highest Spearman's $\rho=0.52$), PIIINP (highest $\rho=0.39$), and proMMP-3 (highest $\rho=0.39$) at several time points (Table II). At a number of time points weak correlations were found between serum YKL-40 and serum hyaluronan, keratan

sulphate, osteocalcin, HAQ score and the articular joint index. There was no correlation between serum YKL-40 and age ($\rho=0.17$).

Serum YKL-40 in relation to progression in Larsen score and bone erosions. At baseline thirty nine patients had a Larsen score ≥ 1 and 34 patients had bone erosions. Although there was a trend towards higher serum YKL-40 in those patients with erosions at baseline, there was no statistically significant difference in the baseline serum YKL-40 between patients with radiological signs of joint destruction (i.e. bone erosions or Larsen score ≥ 1) and patients with no radiological signs of RA (110 vs. 84 $\mu\text{g/l}$, $p=0.106$). Baseline serum CRP were significantly higher in patients with baseline joint destruction compared to patients with normal joints (30 vs. 11 mg/l , $p=0.01$). Baseline levels of serum YKL-40 and CRP were not related to the progression in Larsen score or development of new bone erosions during the following 2 and 3 years.

Thirty-six patients had a Larsen score of 0 at baseline and 21 (58%) of these patients developed joint destruction during the study. These patients had a significantly higher mean serum YKL-40 level (based on the 13 measurements taken with 3 months interval) than patients with no progression in Larsen score (105 vs. 73 $\mu\text{g/l}$, $p=0.004$) (Table III). Twenty one patients developed bone erosions (from 0 at baseline) and they had higher mean serum YKL-40 ($p=0.031$) during the study than patients with non-erosive RA. The mean serum CRP level was not higher in patients who developed joint destruction than patients without progression (Table III). The mean serum PIIINP, proMMP-3, hyaluronan, and keratan sulphate levels were not higher in patients with development of joint destruction compared to patients without progression (data not shown).

A significant correlation was found between the mean serum YKL-40 level and the progression in Larsen score during the study (The first 2 years:

Table II. Correlations between serum YKL-40 and other biochemical parameters of disease activity or joint destruction in patients with early RA.

	Time (months)												
	0	3	6	9	12	15	18	21	24	27	30	33	36
CRP	-	0.35 ^b	0.35 ^b	0.52 ^c	0.38 ^b	0.24 ^a	0.28 ^a	0.45 ^c	-	0.48 ^c	0.36 ^b	0.28 ^a	0.41 ^b
PIIINP	-	0.35 ^b	0.25 ^a	0.39 ^c	0.28 ^a	-	0.32 ^b	0.25 ^a	-	-	-	-	0.28 ^a
ProMMP-3	-	0.39 ^c	0.34 ^b	0.33 ^b	0.33 ^b	0.33 ^b	-	-	-	0.31 ^a	-	0.32 ^a	-
Hyaluronan	-	-	0.25 ^a	-	-	0.30 ^a	0.28 ^a	-	-	-	-	-	-
KS	-	-	-0.31 ^b	-	-	-	-	-	-	-	-	-	-0.27 ^a
Osteocalcin	-	-	0.36 ^a	0.30 ^a	-	-	-	-	0.36 ^a	-	-	-	-
HAQ score	-	0.25 ^a	0.31 ^b	-	0.29 ^a	-	-	-	-	0.26 ^a	-	-	0.27 ^a
Articular Index	-	-	-	0.23 ^a	-	-	-	-	-	-	-	-	-

Values are Spearman's ρ . a= $p<0.05$; b= $p<0.01$; c= $p<0.001$; - =non significant. CRP =C-reactive protein; PIIINP =N-propeptide of type III procollagen; proMMP-3 =pro matrix metalloproteinase 3 (stromelysin 1); KS =keratan sulfate.

Table III. Mean levels of serum YKL-40 and serum CRP during the 3 year study period according to progression in Larsen score and bone erosions of the hands in patients with no signs of joint destruction at baseline.

	Larsen score at 3 years		Mann-Whitney's test	Bone erosions at 3 years		Mann-Whitney's test
	0	≥ 1		0	≥ 1	
Serum YKL-40 (µg/l)	73 (26-117) ¹⁵	105 (20-303) ²¹	p=0.004	75 (21-247) ¹⁹	105 (20-303) ²¹	p=0.031
Serum CRP (mg/l)	12 (10-47) ¹³	19 (10-97) ²¹	p=0.208	12 (10-47) ¹⁹	19 (10-47) ²¹	p=0.056

Values are medians (range)^{number of patients}. The mean serum levels of YKL-40 and CRP during the 3 year study period are based on 13 different measurements taken at 3 months interval.

Pearson's correlation = 0.33, p = 0.006; All 3 years: Pearson's correlation = 0.36, p = 0.004). A significant correlation between the mean serum CRP level and the progression in Larsen score during the study was only found for the 3 year study period (The first 2 years: Pearson's correlation = 0.20, p = 0.103; All 3 years: Pearson's correlation = 0.29, p = 0.021). Figure 2 illustrates the frequency distribution of progression in Larsen score during the 3 years study period in relation to high or normal serum concentrations of serum YKL-40 and CRP during the study period.

Table IV shows the progression in joint destruction

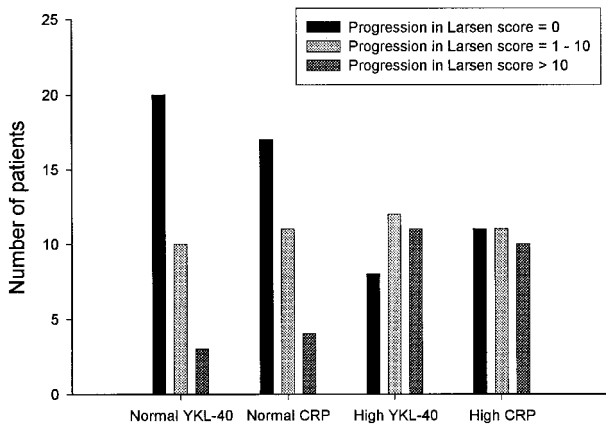


Fig. 2. Frequency distribution of progression in Larsen score during the 3 year study period in relation to serum concentrations of YKL-40 and CRP (expressed as mean values during the 3 year study).

according to the levels of serum YKL-40 and CRP. Patients with a persistently elevated serum YKL-40 (i.e. mean YKL-40 > 102 µg/l) had a significantly larger progression in Larsen score after 2 and 3 years than patients with normal serum YKL-40 (p = 0.012 at 2 years and p = 0.003 at 3 years). There was a significant difference in the development of new bone erosions after 2 years between patients with high or normal mean serum YKL-40 levels (p = 0.016). A persistently elevated CRP (i.e. mean CRP > 15 mg/l) was only related to progression in Larsen score after 3 years.

Sixty-four percent of the patients with a progression in Larsen score during the 3 year study period had a continuously elevated serum YKL-40 whereas only 28% of the patients without progression in Larsen score had a continuously elevated serum YKL-40 (Fisher's exact test: p = 0.006). Similar results were found if only the first 2 years were evaluated (Fisher's exact test: p = 0.008). Fifty eight per cent of the patients with a progression in Larsen score during the 3 year study had a continuously elevated serum CRP whereas 38% of the patients without progression in Larsen score had elevated serum CRP (Fishers exact test: p = 0.136). Similar results for serum CRP were found if only the first 2 years were evaluated (Fisher's exact test: p = 1.00). If both serum YKL-40 and CRP were determined 81% of the patients with a progression in Larsen score and 90% of the patients with a progression in

Table IV. Progression in Larsen score and bone erosions according to the mean level of serum YKL-40 and serum CRP during the study period.

	High YKL-40 (>102 µg/l)	Normal YKL-40 (≤102 µg/l)	Mann-Whitney's test	High CRP (>15 mg/l)	Normal CRP (≤15 mg/l)	Mann-Whitney's test
Progression in Larsen score						
0-2 years	1.0 (0-59) ³⁵	0.0 (0-17) ³⁶	p=0.012	0.5 (0-59) ³⁸	0.0 (0-17) ³³	p=0.278
0-3 years	7.0 (0-60) ³¹	0.0 (0-19) ³³	p=0.003	6.0 (0-60) ³¹	0.0 (0-19) ³²	p=0.033
Development of bone erosion						
0-2 years	0 (0-2) ³⁴	0 (0-2) ³⁶	p=0.016	0 (0-2) ³⁸	0 (0-2) ³²	p=0.285
0-3 years	1 (0-2) ³¹	0 (0-2) ³³	p=0.089	1 (0-2) ³¹	0 (0-2) ³²	p=0.079

Values are medians (range)^{number of patients}. The mean serum levels of YKL-40 and CRP during the 2 or 3 year study period were based on 9 different measurements for the study period 0-2 years and on 13 different measurements for the study period 0-3 years for most of the patients, since the biochemical markers were measured with 3 months interval during the study.

bone erosions could be identified based on high serum YKL-40 or CRP level.

Discussion

In the study we found that serum YKL-40 was elevated compared to normal subjects for approximately 50% of the patients with clinically active early RA. Patients with clinically active disease at baseline that later became inactive had a decrease in serum YKL-40, while patients who remained clinically active had unchanged levels. Low correlations were sometimes found between serum YKL-40 and CRP, PIIINP, and proMMP-3. No correlation was found between serum YKL-40 and the articular joint score.

At baseline there was a trend towards higher serum YKL-40 levels in patients with bone erosion, but the difference between those with and those without erosions were not statistically significant. However, the mean serum YKL-40 levels in these patients with early RA during the 3 year study period were significantly related to the radiological progression of joint damage determined as the Larsen score. This is in accordance with the results of a smaller study of RA patients (disease duration < 3 years) followed for one year (24) and a large cross sectional study of patients with longer disease activity (39), but is in contrast to a small study of early RA patients where serum YKL-40 did not provide information of disease progression (40).

Our study indicates that in some patients serum YKL-40 provided information on disease activity different from that of serum CRP. Elevated serum concentration of YKL-40 was observed in some patients showing progression in the Larsen score but with normal levels of serum CRP, and normal serum YKL-40 levels were found in a few patients with elevated serum CRP. If both serum YKL-40 and serum CRP were measured, 81% of the patients with a progression in Larsen score and 90% of the patients with a progression in bone erosions could be identified. Serum YKL-40 was elevated in more of the patients with progression in bone erosions than serum CRP. One possible explanation for this observation is that the use of prednisolone, which suppresses serum CRP level, may have masked the relation between serum CRP and progression in joint destruction.

It has recently been reported that YKL-40 may be a growth factor of connective tissue cells (18). We think that YKL-40 could play a role in cartilage destruction in arthritic joints and that serum YKL-40 may reflect a combination of cartilage metabolism and a more local aspect of the inflammatory process than serum CRP in patients with early RA. Others have suggested that the articular erosive pro-

cess is at least partly driven by mechanisms other than inflammation (41). CRP is not secreted by the cells in the arthritic joint, but the serum CRP level represents a non-specific distant response by hepatocytes to mediators like interleukin-6, tumour necrosis factor, and interleukin-1 β (42). YKL-40 is not secreted by hepatocytes and a plausible explanation of the elevated serum YKL-40 levels in patients with active RA would be that the protein is secreted in excess by activated chondrocytes, macrophages and leukocytes in the arthritic joint.

Earlier results from the "Arthritis and Rheumatism Council Low-Dose Glucocorticoid Study" have shown that prednisolone (7.5 mg/day) has a protective effect on joint erosion in the hand and wrist in the patients with early RA (27,28). We could not detect any difference in serum YKL-40 levels between the patients treated with low dose of prednisolone in combination with DMARDs and the patients treated with DMARDs only. It is unknown if glucocorticoids have a direct effect on the regulation of YKL-40. High doses of prednisolone (15–30 mg/day) decrease serum YKL-40 in patients with active RA, whereas no changes in serum YKL-40 were found if the patients were treated with low doses of prednisolone (5 mg/day) (24). Also high doses of intra-articular glucocorticoid injections in knee joints with synovial inflammation are followed by a decrease in serum YKL-40 concentrations (12).

In summary, the concentration of YKL-40 in serum may reflect aspects of disease pathology and outcome in patients with early RA. Some observations in the present study suggest that YKL-40 provide information different from serum CRP. YKL-40 may prove to be a new tool for estimating disease progress and studying the pathophysiology of RA.

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Announcements

Tenth Intensive Applied Epidemiology Course for Rheumatologists, 11-15 March 2002, ARC Epidemiology Unit, Manchester, UK.

No prior experience in epidemiology is required. The course is residential and is limited to 25 places. For further details and a registration form, please contact Ms Lisa McClair at <Lisa@fsl.ser.man.ac.uk >

BSR XIXth AGM 2002, 23-26 April 2002, Brighton, UK More information: www.rheumatology.org.uk

3rd International Congress on Autoimmunity, 20-24 February 2002, Geneva, Switzerland.

More information: www.kenes.com/autoim2002

New Trends in Osteoarthritis, 9-11 May 2002, Milan, Italy.

Main topics: Epidemiology, pathogenetic mechanisms and clues, clinical patterns, imaging, biochemistry, medical treatment, surgical approach and cartilage transplants, rehabilitation, social and drug related economic problems. Organizing committee: Rheumatology Unit L, Sacco Hospital, University of Milan-Italy. E-mail: osteoarthritis@oic.it

4th Central European Congress for Rheumatology, 10-12 May 2002, Vienna, Austria.

More information: www.medacad.org

International Osteoporosis Foundation—IOF World Congress on Osteoporosis, 10-14 May 2002, Lisbon, Portugal

More information: www.osteofound.org E-mail: info@iofflyon.org

5th European Conference on Systemic Lupus Erythematosus, 26-30 May 2002, Athens, Greece.

Conference web site: www.lupus2002.gr E-mail: congress@amphitriion.gr

EULAR 2002—Annual European Congress of Rheumatology, 12-15 June 2002, Stockholm, Sweden

For more information please visit: www.eular.org

10th International Conference on Behcet's Disease, 27-29 June 2002, Berlin, Germany.

Please contact e-mail: RKMCR@aol.com or website: www.behcet.ws

29th Scandinavian Congress of Rheumatology, 15-18 August 2002, Tromsø, Norway.

For more information please visit: www.29scr2002.org/

10th International Congress on Antiphospholipid Antibodies, 29 Sept–3 Oct 2002, Taormina, Sicily, Italy.

Website: www.kenes.com/aps E-mail: aps@kenes.com

OARSI World Congress on Osteoarthritis, 30 Sept–3 Oct 2002, Washington, DC, USA

Please visit: www.oarsi.org E-mail: oarsi@oarsi.org

Third International Meeting on Social and Economic Aspects of Osteoporosis and Osteoarthritis, 7-9 November 2002, Barcelona, Spain

E-mail: ypc@compuserve.com