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## Changes in serum levels of cartilage and bone markers in early osteoarthritis of the knee

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Osteoarthritis (OA) is characterized by progressive destruction of articular cartilage with concomitant changes in subchondral bone. Attempts to reveal pathophysiologic mechanisms are hampered by the lack of instruments for early diagnosis. We have therefore initiated a prospective study of individuals aged 35–55 years with long-standing knee pain to identify means to diagnose OA in its early phases and to monitor the progression of the disease by using novel biochemical and imaging techniques (Petersson et al. 1993).

In an attempt to delineate differences in tissue specific molecular fragments in serum between individuals with or without radiographic evidence of OA, sequential measurements of cartilage and bone markers in sera of individuals with knee pain were performed. The serum concentrations were correlated to presence of radiographic and bone scintigraphic changes in the knee joints at the 3-year follow-up.

### Materials and methods

Individuals with chronic knee pain (>3 months during the last 12 months) were identified using a questionnaire sent to a random sample of the population in a community in southern Sweden (Petersson et al. 1993). Initially 279 out of 2000 individuals were identified as having chronic knee pain. Of these, 204 accepted clinical and radiographic examination. In this report, 38 individuals were randomly selected for follow-up. Baseline radiographs and serum samples were available. Serum samples were drawn at follow-up 3 years after inclusion. Plain radiographs were taken under weight-bearing conditions and bone scintigraphic examination using technetium labeled

diphosphonate was performed at follow-up on both knee joints on the same day as serum was drawn. The radiographs were graded according to Ahlbäck for tibiofemoral OA (Ahlbäck 1968) and by an arbitrary scale for patellofemoral OA. The scintigraphy was visually evaluated using an arbitrary scale. All evaluations were done without knowledge of clinical data.

Serum samples were analyzed for cartilage oligomeric matrix protein (COMP), bone sialoprotein (BSP), and the keratan sulfate (KS) found primarily in the proteoglycan aggregate by specific immunoassays (Saxne and Heinegård 1992, Saxne et al. 1995, Poole et al. 1990). The Spearman correlation coefficient was used for calculating correlations and the Wilcoxon matched pair's test for comparisons between serum levels at baseline and at follow-up. P-values < 0.05 were considered significant.

### Results

Twenty-three subjects had radiographic signs of OA at the 3-year follow-up (6 in the tibiofemoral compartment, 14 in the patellofemoral compartment and 3 in both compartments). Fifteen subjects had normal radiographs after 3 years. Scintigraphic abnormalities were detected in 25 cases. In 7 of these no radiographic changes were seen.

The serum concentrations of COMP at follow-up correlated significantly ( $p < 0.001$ ) with the grades of the scintigraphy findings at follow-up ( $r_s = 0.56$  for all subjects,  $r_s = 0.65$  for the subjects with radiographic OA). The serum concentrations of BSP or KS did not correlate with the scintigraphic findings.

The serum concentrations of the tissue specific molecular markers at baseline or at follow-up did not

discriminate between the groups. However, serum COMP and serum BSP increased ( $p < 0.001$ ) in the group with radiographic OA at follow-up, but remained unchanged in the group having normal radiographs at follow-up. The KS levels did not change in any of the groups.

### Discussion

The correlation between serum levels of COMP and bone scintigraphic uptake in early OA patients is consistent with a close connection between changes in cartilage and bone metabolism in the pathogenesis of OA. This finding confirms and extends the observations of a previous study where patients with established OA and positive bone scintigraphic findings had higher serum COMP levels than those with negative scintigraphy (Sharif et al. 1995).

The other important finding of this study is the increasing serum levels of COMP and BSP in the majority of patients who at follow-up showed radiographic evidence of OA. The value of serum COMP as an indicator of knee OA is consistent with the findings in the previous study (Sharif et al. 1995). The increasing serum concentrations of both COMP and BSP may reflect the increased matrix turnover in cartilage and bone in early OA. Somewhat surprisingly, we did not find any alterations in the serum levels of KS, which has been suggested to be a potential marker of OA (Thonar et al. 1992). Since the baseline radiographs only focused on the tibiofemoral joint space and the radiographic technique was somewhat different to the one used at follow-up, we selected the subjects without knowledge of the result of the baseline examination. In fact, 13/23 patients with radio-

graphic OA at follow-up already at baseline had joint space narrowing in the tibiofemoral joint space, whereas 10/23 had normal radiographs at baseline. Thus, the study has shown that serum levels of both COMP and BSP increase in individuals with early OA, but it is obvious that this increase may occur both before and after tibiofemoral joint space narrowing can be visualized radiographically. Thus, this study suggests, but does not establish a prognostic value for these variables in the development of OA in patients with chronic knee pain.

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## Elevation of plasma hyaluronan and urinary pyridinoline in mouse collagen induced arthritis

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We have previously reported the elevation of plasma hyaluronan (HA) and urinary pyridinoline (PYD) in rat models of arthritis (1,2). Elevation of plasma HA has been linked to the hypermetabolic response of the synovium (3). Urinary pyridinoline cross links reflects the breakdown of collagen type I and type II from bone and cartilage (4,5). Because the mouse collagen induced arthritis model exhibits many characteristics of rheumatoid arthritis (RA), including pan-

nus and bone erosions (6), we examined the time dependent changes of these two markers in this model and the effect of a therapeutic agent on PYD excretion. In this report, we discuss for the first time the elevation of these markers in a mouse type II collagen induced arthritis model.

### Methods

Arthritis was induced by the intradermal injection of