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 radiographic 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 pannus 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

acid soluble native type II collagen into mice. On day 17, the mice were injected with LPS. Disease severity was evaluated by scoring each paw from 0 to 3 and then adding all 4 paw scores (7). Blood drawn from the eye orbit was used to obtain plasma. The levels of HA in the plasma were measured by an ELISA (8). In preliminary studies, we found the same levels of HA in blood drawn by either cardiac puncture or orbital bleeding. Urine was drawn directly from the bladder. PYD levels (expressed as nM pyridinoline/mM creatinine) were quantitated using assay kits from Metra Biosystems (Palo Alto, CA, USA).

Results and Discussion

Using LPS as a disease enhancer has increased the number of responders (incidence) to nearly 100% by day 21. This has also decreased the experimental variability so that the measurement of paw scores better reflects the progression of the disease severity. The onset of the disease was evident on day 21 and peaked on day 24 (Figure 1A). Plasma HA was elevated on day 21 and also reached the peak level on day 24, about 10 times above normal levels (Figure 1B). Though the disease severity dropped after day 24, it still remained high. Plasma HA dropped more dramatically than the paw scores, and between days 35 to 45 the HA level was elevated only 50 to 100% above normal. Interestingly, we found that mouse plasma HA was 100 times higher than what we have encountered in other species. For example, in normal rat serum HA is 25–50 ng/ml, and in rats with adjuvant arthritis it is elevated to 150–300 ng/ml. The normal mouse HA level, as determined by our assay, was 5,300 ± 520 ng/ml, and with arthritic mice the peak level was 57,200 ± 4,400 ng/ml (mean ± SE)

As the disease progressed in the arthritic mice, there was a net increase in the urinary PYD. There was no significant change in the PYD levels on day 15, but it was elevated ~2–4-fold on days 24 and 45. The PYD levels were highest on day 24 when the paw score was also the highest. In one recent study, PYD levels on day 45 were 285 ± 20 in diseased animals vs. 77 ± 6 in the normal mice (mean ± SE). Cyclophosphamide, a therapeutic agent in RA, completely blocked the disease as indicated by paw score and lowered the elevated PYD excretion by 79% ($p < 0.001$).

Conclusions

In utilizing markers for evaluating disease, it is important to recognize the time-dependent changes in specific joint tissues. Animal models allow for a well controlled tracking of these markers. We found a dramatic increase in HA at the initiation of a persistent arthritis. This work is consistent with the clinical observation that plasma HA is prognostic for RA (9). PYD cross links also increased with onset of arthritis and remained elevated. Urinary PYD allows for the monitoring of the catabolism of collagen from the arthritic joints and can be used to show this aspect of drug efficacy.

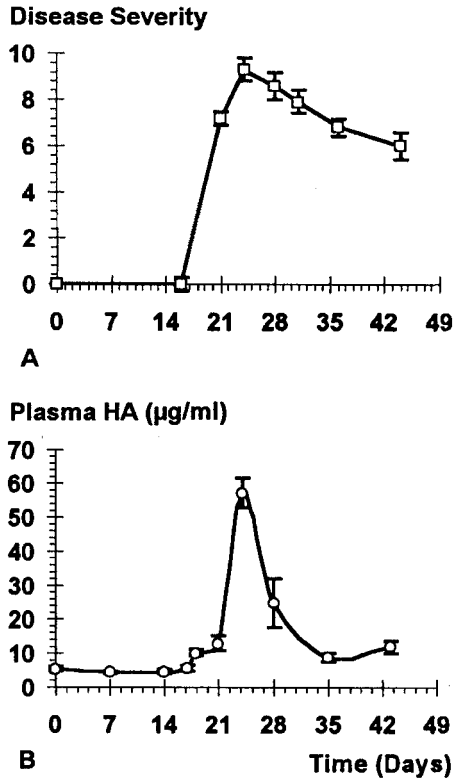

Figure 1. Time dependent changes of Disease Severity, (A); and Plasma HA, (B); in the mouse collagen induced arthritis. Values are mean ± SE for 6 to 8 mice.

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Intra-articular and circulating levels of type I and III collagen markers in inflammatory and degenerative joint disease

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In a chronic inflammatory disease as rheumatoid arthritis, the local processes in the affected tissues lead to destruction of the joint. When estimating the inflammatory activity in rheumatic joint diseases, a major problem is the rather unspecific and indirect character of the biochemical and the crude character of the clinical measures used.

As more specific markers of the local pathological processes, metabolites from the collagen turnover have been introduced (Risteli 1990, Hørslev-Petersen, 1988).

The object of our study was to investigate the relation between circulating and local levels of type I and III metabolites, and whether the local concentrations reflect the local processes in the knee joint.

Materials

The aminoterminal propeptide of type III procollagen (PIIINP) as a marker of type III collagen formation, the carboxyterminal propeptide of type I procollagen (PICP) as a marker of type I collagen formation and the crosslinked carboxyterminal telopeptide of type I collagen (ICTP) as a marker of type I collagen degradation were measured in eleven patients (6 females and 5 males) with chronic knee synovitis (13 knees) who underwent chemical synovectomy by intraarticular osmic acid (osmium tetroxide). Collagen markers were analysed by commercially available radioimmuno assays. (Orion Diagnostica, SF-90460, Oulunsalo, Finland). Standard radiograph of the affected knee was taken prior to treatment. Conventional clinical and biochemical evaluations were performed.

Results (Table)

The circulating levels of PIIINP and ICTP were sig-

Table. Values given as median with interquartile range in ng/ml

	PIIINP		ICTP		PICP	
	serum	synovial fluid	serum	synovial fluid	serum	synovial fluid
All patients n = 13						
Before osmic acid	4.0 (2.9–4.7)	854 (600–1380)	5.4 (3.4–7.8)	17 (13–22)	172 (105–225)	1030 (790–1660)
After osmic acid (t30)	3.9 (2.6–4.9)	1118 (1030–3160)	4.9 (3.5–8.4)	20 (12–55)	155 (106–222)	1375 (1170–2270)
Remission group n = 7						
Before osmic acid	3.7 (2.6–4.4)	850.6 (587–929)	4.6 (3.3–7.6)	15 (13–22)	172 (105–185)	1030 (740–1660)
After osmic acid (t30)	3.1 (2.1–4.4)	–	4.0 (3.4–7.8)	–	145 (93–225)	–
Relapse group n = 6						
Before osmic acid	4.5 (3.3–5.2)	1254 (600–2580)	7.6 (5.4–8.0)	18 (12–40)	168 (96–248)	1235 (870–2470)
After osmic acid (t30)	4.8 (3.9–5.1)	1118 (1030–3160)	7.5 (4.9–8.8)	20 (12–55)	187 (114–222)	1375 (1170–2270)