Inflammation is a feature of the disease process in early knee joint osteoarthritis

Sir, Traditionally osteoarthritis (OA) has been considered a process involving a disturbance of the normal balance between degradation and repair in the articular cartilage and subchondral bone. In contrast to rheumatoid arthritis where inflammation, both local and systemic, is a key feature, OA is considered a primarily non-inflammatory condition. The clinical signs of low-grade inflammation that are seen in some patients, representing later stages of the process, have been thought to reflect secondary events in the joint. This view has been questioned and in a recent review arguments in favour of inflammation being of major importance in OA pathophysiology were presented [1]. In support, in established OA, low-level increases in serum C-reactive protein (CRP) have been reported [2, 3].

To examine the role of inflammation in early knee OA, we determined serum CRP in individuals with knee pain at baseline and after 3 yr and correlated the levels to the presence of radiographic OA as defined below after 3 yr. We also correlated serum CRP to serum cartilage oligomeric matrix protein (COMP) to investigate further the role of COMP as a cartilage marker and examine the relationship between CRP and COMP as markers for different pathophysiological features [4].

The examined individuals have been described including the COMP results [5]. Thirty-eight individuals with chronic knee pain (> 3 months at inclusion) were monitored over a 3-yr period and divided into two groups, those who after 3 yr had normal radiographs (n = 15) and those who showed joint-space narrowing in the tibiofemoral (joint space < 3 mm) and/or the patellofemoral joint (joint space < 5 mm) (n = 23) [6, 7]. For comparison, sera from 20 healthy blood donors were examined. There was no significant age difference between the three groups. The median (range) age of the individuals with positive radiographs was 49 yr (39–54), for the individuals with knee pain with negative radiographs 44 yr (37–54) and for the blood donors 44 yr (37–55). There were 10 male and 10 female blood donors. Of the persons developing positive radiographs, 14 were female and nine male and of the persons with only knee pain, three were female and 12 were male.

Serum COMP was measured by inhibition enzyme-linked immunosorbent assay (ELISA) using a polyclonal antiserum [4]. Serum CRP was quantified by a sensitive sandwich ELISA (detection limit < 0.05 mg/l) developed using commercially available reagents. Immunoplates C96 Maxisorp (NUNC, Copenhagen, Denmark) were coated by a dilution of rabbit anti-human CRP antibodies (DAKO A-073, Copenhagen, Denmark) and dilutions of human serum CRP-calibrator (DAKO X-0923, Copenhagen, Denmark) were used for constructing a standard curve. Sheep anti-human CRP
antibodies conjugated with alkaline phosphatase (Biogenesis, 1707–0504, Poole, UK) were used for detection. The inter- and intra-assay variations were less than 5% and dilutions of sera were parallel with the standard curve.

The results of the CRP and COMP analyses are shown in Fig. 1. Serum CRP was already increased in the radiograph-positive patients at baseline both compared with individuals with knee pain without radiographic changes at the 3-yr follow-up and with blood donors ($P < 0.01$ vs both groups, Mann–Whitney U-test). The differences remained at the 3-yr follow-up ($P < 0.01$ vs individuals with only knee pain). In sharp contrast, serum COMP levels at baseline in the early OA group did not differ significantly from the levels in the other groups, but increased during the 3-yr period ($P < 0.001$ for the difference between the two measurements, Wilcoxon’s matched pairs analysis). Importantly, in individuals with only knee pain, the COMP levels remained unchanged. Corroborating the different serum pattern of CRP (increased concentrations in first sample) and COMP (increasing concentrations over 3 yr) in these groups, we found no significant positive correlation between these variables in any of the groups at any time point (Spearman’s correlation test) in line with recent findings [8].

Increased serum CRP in early phases of OA suggests the presence of low-grade inflammation, which supports a pathophysiological role of inflammation at early stages of the disease process. This inflammation may possibly change the sensitivity of the cartilage to low-grade trauma. Increasing serum COMP, not correlating with serum CRP, in early OA most likely reflects altered cartilage turnover. The findings thus support that inflammation is a component of the early events leading to clinical OA, preceding the initial events in the cartilage as indicated by serum COMP levels.

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![Fig. 1. (A) Serum CRP and (B) serum COMP in blood donors](image)

**Fig. 1.** (A) Serum CRP and (B) serum COMP in blood donors ($n = 20$), in individuals with knee pain having normal knee joint radiographs at follow-up ($n = 15$) and in individuals with knee pain having radiographic changes compatible with osteoarthritis at follow-up ($n = 23$). Serum levels of CRP and COMP in the former groups at baseline and at the 3-yr follow-up are shown. The horizontal bars denote the median for each group. For details, see text.