Elevated high-sensitivity C-reactive protein levels are associated with local inflammatory findings in patients with osteoarthritis


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Summary

Objective: C-reactive protein (CRP) has been associated with disease progression in patients with osteoarthritis (OA), but the reasons for this remain unclear. We hypothesized that higher CRP would be related to local inflammatory findings in the joints of patients with OA.

Methods: Plasma and synovial membrane specimens from 54 OA patients undergoing total hip or knee arthroplasty or arthroscopy were obtained. Synovial fluid was obtained from 25 of these patients. Hematoxylin and eosi stained synovial membrane sections were scored for degree of inflammatory cell infiltration. Plasma high-sensitivity CRP (hsCRP) levels, and serum and synovial fluid interleukin (IL)-6 and IL-1 levels were measured by enzyme-linked immunosorbent assay.

Results: Fifty-seven percent of patients with idiopathic OA had inflammatory infiltrates within the synovial membrane. The mean hsCRP level in patients with inflammatory infiltrates was significantly higher than those without inflammation (4.7 ± 5.0 mg/L vs 1.7 ± 3.6 mg/L, P = 0.003). There were significant correlations between hsCRP levels and synovial fluid IL-6 (r = 0.64, P = 0.0006), degree of synovial inflammatory infiltration (r = 0.43, P = 0.002), and body mass index (r = 0.31, P = 0.02). Multivariate analysis indicated that only degree of inflammatory infiltrate was significantly associated with hsCRP level (P = 0.026).

Conclusion: These results suggest that systemic hsCRP levels reflect synovial inflammation in OA patients, perhaps by means of synovial IL-6 production. Future studies are needed to clarify how these infiltrates and their products may contribute to disease pathogenesis.

Key words: Synovium, C-reactive protein, Interleukin-6, Inflammation.

Introduction

Traditionally, C-reactive protein (CRP) has been used to distinguish systemic inflammatory disorders such as rheumatoid arthritis (RA) from “noninflammatory” diseases such as osteoarthritis (OA). More recently, with the introduction of high-sensitivity CRP assays (hsCRP), which can detect CRP levels that are an order of magnitude lower than traditional assays, low-level elevations in CRP have been observed in diseases where there is a local, low-grade inflammatory component. A good example of this is coronary artery disease, where systemic hsCRP levels have been shown to be independent predictors of cardiac risk1-4 and are thought to reflect the local inflammatory process within the atheromatous plaque and the vessel wall5,6. However, beyond being simply a biomarker of inflammation, CRP may reflect or contribute to molecular mechanisms of disease states. For example, CRP production by hepatocytes, the main source of this acute-phase reactant, appears to be regulated primarily by the proinflammatory cytokines interleukin (IL)-6 and IL-1. Furthermore, CRP itself may have important immune-modulating functions as it has been shown to have multiple roles in innate immune responses and tissue injury, and has the ability to activate the complement system, and enhance phagocytosis via opsonization (reviewed in Ref.7). The net effect of CRP, at least in studies of endotoxic shock, appears to be antinflammatory perhaps via enhanced IL-10 production8. Others9,10 have suggested that lower levels of CRP may enhance inflammation in chronic, subclinical inflammatory states such as obesity and atherosclerosis – might enhance inflammation by activating endothelium, and mediating leukocyte recruitment and proinflammatory cytokine synthesis10,11.

Multiple studies have demonstrated that hsCRP is modestly elevated in the plasma of patients with OA compared to age-matched controls12-15. While hsCRP levels in RA plasma are typically ≥15 mg/L, levels in OA typically range from 3 to 8 mg/L. Additionally, these levels are elevated when compared with the largest general population study (n = 8592), where the median value for hsCRP was 1.3 mg/L (25th–75th percentile: 0.6–2.9)16.

While hsCRP is a nonspecific marker of inflammation and thus of limited use as a diagnostic marker of OA, recent
studies have demonstrated that hsCRP may have clinical and prognostic significance. Increased hsCRP levels in sera have been associated with disease progression as well as with clinical severity in OA. Recently, it was demonstrated that elevations in hsCRP may reflect events that precede, but ultimately lead to, radiographic progression in OA. In addition, elevated hsCRP has been found to be associated with severity of pain in OA. However, the mechanistic link between elevated hsCRP levels and disease activity remains unclear.

The purpose of this study was to investigate the relationship between systemic hsCRP levels and local synovial membrane inflammatory infiltrates in OA. We hypothesized that elevated hsCRP levels would be associated with synovial membrane inflammation in patients with idiopathic OA. In addition, as both IL-6 and IL-1 are known to promote production of CRP by hepatocytes, we predicted that elevated systemic or synovial fluid levels of these two cytokines might be associated with hsCRP and inflammatory infiltrates in OA.

**Materials and methods**

**PATIENTS**

Fifty-four patients with primary OA who were undergoing total hip or knee arthroplasty or arthroscopy for treatment of OA were identified for this study at a single musculoskeletal specialty hospital. These were consecutive patients presenting for surgery, and all met ACR criteria for idiopathic OA. Early OA was defined as a Kellgren–Lawrence (K–L) score of ≤2 and no intraoperative evidence of full-thickness chondral wear. Advanced OA was defined as K–L score >2 and intraoperative evidence of full-thickness chondral loss. Advanced stage patients satisfied both radiographic and clinical ACR classification criteria, and early patients satisfied clinical classification criteria. All patients with congenital malalignment; clinical, intraoperative, or pathologic evidence of previous trauma; avascular necrosis or inflammatory arthropathy were excluded. In addition, patients with insulin-requiring diabetes, diabetes requiring more than one oral hypoglycemic agent, coronary artery disease, history of myocardial infarction, history of tobacco use, or recent infection were also excluded. Although not a strict exclusion criteria, none of the patients reported a history of asthma or were taking any medications for pulmonary disease, with the exception of one patient who was taking inhaled bronchodilators. These are comorbidities which may influence hsCRP levels and thus confound results.

This study was approved by the Institutional Review Board at Hospital for Special Surgery.

**CLINICAL AND RADIOGRAPHIC DATA**

Demographic data, current medications, physical findings, and intraoperative findings were recorded. Radiographic K–L scores were determined by a blinded, experienced musculoskeletal radiologist.

**SYNOVIAL TISSUE, JOINT FLUID AND SERUM SAMPLES**

Blood and tissue specimens were obtained from the 54 patients at the time of surgery. Six patients underwent bilateral total joint replacement; in these cases, only the left side was analyzed. In patients undergoing knee surgery, synovial samples were obtained from the suprapatellar region, abutting the cartilage of the femoral trochlea. Samples from hip cases were obtained from the medial femoral neck in a juxtachondral region. All tissue samples were fixed in formalin, paraffin-embedded, and stained using standard hematoxylin and eosin (H&E) technique. In addition, synovial fluid specimens were obtained from 25 patients, all of whom had advanced disease. Synovial fluid aspiration was performed just prior to surgical arthroscopy. In cases where inadequate amounts of joint fluid were obtained, the joint was lavaged with 10 cc of normal saline and re-aspirated. Blood samples were obtained at the beginning of each case and the plasma was stored at −70°C.

**ESTABLISHMENT OF SYNOVIAL GRADING SYSTEM**

To evaluate the performance of an OA histologic grading system developed at our institution (E. DiCarlo, unpublished observations) we reviewed 755 H&E stained synovial tissue specimens from surgical patients at our institution with both a clinical (determined by the operating surgeon) and pathologic (determined by the evaluating pathologist) diagnosis of OA. Synovial inflammation was graded as absent (only scattered mononuclear cells), very low grade (0–1 perivascular focal mononuclear cell aggregates per low power field), low grade (multiple perivascular lymphocytic aggregates per low power field or detritus associated with giant cells), or high grade (both perivascular and diffuse lymphocytic or lymphoplasmacytic infiltrates) (see Fig. 1). Synovial specimens reviewed were obtained from 297 total hip arthroplasty cases, 317 total knee arthroplasty cases, and 141 arthroscopic procedures of the knee and included patients with both primary and secondary OA. The demographics of the 755 patients included in this retrospective review are shown in Table I. For the arthroplasty cases, synovial low- or high-grade inflammation was present in 53.2% of hip (48.5% low grade, 4.7% high grade) and 45.4% of knee cases (41.6% low grade, 3.8% high grade). In arthroscopy cases, low- or high-grade inflammation was present in 42.5% (41.1% low grade, 1.4% high grade). Overall, there was no difference in the prevalence of synovitis between patients undergoing arthroplasty and those undergoing arthroscopy. The prevalence of synovitis in this large cohort of OA patients was consistent with previous, smaller histologic studies, in which approximately 45–55% of patients with either early or advanced OA showed evidence of synovial inflammation.

After validating our scoring system in this large cohort, H&E stained sections from the 54 patients in our study were then classified using this scoring system. Slides were reviewed by the same musculoskeletal pathologist blinded to patient information.

**MEASUREMENT OF hsCRP, IL-6, AND IL-1β**

An hsCRP enzyme-linked immunosorbent assay (ELISA) kit (Hemagen Diagnostics, Inc., Columbia, MD) was utilized with a lower-limit of detection of 0.5 mg/L. Patient plasma was diluted according to the manufacturer’s directions. As a control, plasma was also collected from nine nonage-matched healthy volunteers, and from seven patients with RA who satisfied ACR classification criteria. IL-1β and IL-6 ELISA kits (R&D systems, Minneapolis, MN) were used to measure both systemic and synovial fluid cytokine levels. To correct for the unknown dilution of
synovial fluid in cases where the joint was lavaged, urea concentrations in both joint fluid and serum were obtained and the dilution factor was calculated in accordance with the technique described by Kraus et al.24.

**STATISTICAL ANALYSIS**

Nonparametric tests were chosen based on the non-Gaussian distribution of the data. The Mann-Whitney t-test was performed to evaluate differences between two groups. When comparing more than two groups, a Kruskal-Wallis test was performed. Fisher’s exact test was used to compare categorical variables. Spearman’s correlation coefficients were calculated in the univariate analyses. Multivariate analysis was performed by using forward stepwise regression.

**Results**

**PATIENT DEMOGRAPHICS**

Fifty-four patients were identified for the cross-sectional study. Two patients were excluded from the study: one patient due to histologic findings of avascular necrosis and one patient due to histologic findings of inflammatory arthropathy. The average age of the 52 patients was 63.2 years old (median = 64, range 43–79), and 29 (56%) were females (Table II). Twenty-seven patients had hip OA while 25 patients had knee OA. Nine of the 52 patients (17%) were classified as early OA as described above. The remaining 43 patients (83%) had advanced OA. All patients classified as advanced OA had undergone total joint arthroplasty. Only one arthroscopy patient was classified as advanced OA, based on intraoperative evidence of full-thickness cartilage wear; the remaining arthroscopy patients were classified as early OA.

**PREVALENCE OF INFLAMMATORY INFILTRATES IN OA PATIENTS**

Twenty-two patients (43%) with idiopathic OA had no histologic evidence of significant synovial inflammatory infiltrates (17 classified as absent and five as very low grade; see Materials and methods), 26 patients (50%) had low-grade inflammatory infiltrates, and four patients (7%) had high-grade inflammatory infiltrates. There were three patients with synovial detritus associated with giant cells that were regarded as having low-grade inflammation despite having no discrete mononuclear cell infiltrates.

Due to the small number of patients classified as either very low grade (five patients) or high grade (four patients), comparisons were made between OA patients without significant inflammatory infiltrates (absent or very low grade) and those with inflammatory infiltrates (low and high grade). As shown in Table II, there was no difference in the prevalence of synovial infiltrates between the early OA group (5/9 patients or 56%) and the advanced group (25/43 or 58%, Relative risk (RR) = 0.94, P = 1.0). The percentage of patients with synovial infiltrates did not differ in patients with hip or knee OA (RR = 1.11, P = 0.79). Slightly more women than men exhibited synovial infiltrates (62% of female patients vs 52% of male patients), but this difference was not statistically significant (RR = 1.26, P = 0.6). No statistically significant differences were seen in age (Mann-Whitney P = 0.39), body mass index (BMI) (P = 0.25), or radiographic score (P = 0.00) between patients with and without synovial infiltrates, although there was a nonsignificant trend toward higher BMI in the group with inflammatory infiltrates [Fig. 2(C)], largely due to the effect of one outlier with a BMI of 60.45.

**PLASMA hsCRP LEVELS IN OA PATIENTS AND RELATIONSHIP TO SYNOVIAL HISTOLOGY AND PATIENT DEMOGRAPHICS**

The mean hsCRP level in plasma from all the patients with OA was 3.4 ± 4.7 mg/L; mean age = 63.2 ± 8.1. As expected, this was significantly greater than the hsCRP level
in our small group of young controls (0.29 ± 0.60 mg/L, \( P = 0.007 \); mean age 33.2 ± 5.6), but much lower than levels seen in a group of seven RA patients undergoing knee or hip arthroplasty (11.2 ± 6.2 mg/L, \( P = 0.002 \); mean age 63.5 ± 12.1). Within the OA group, the mean hsCRP level in the patients with inflammatory infiltrates was significantly higher compared to the patients without inflammation (4.7 ± 5.0 mg/L vs. 1.7 ± 3.6 mg/L, \( P = 0.003 \) [Fig. 2(A)]. In addition, hsCRP levels had a moderately strong and statistically significant correlation with the degree of inflammatory infiltration (\( r = 0.42, P = 0.0015 \), Table III). We found a modest statistically significant correlation between hsCRP level and BMI (\( r = 0.31, P = 0.02 \), consistent with the clinical literature (Table III), but BMI did not correlate with degree of synovial infiltration (\( r = 0.18, P = 0.20 \)).

There were no significant associations between hsCRP levels and radiographic findings or age.

**IL-6 and IL-1β Levels in OA Patients and Relationship to Local Histology**

Measurable plasma levels of IL-6 were detected in 36 of the 52 OA patients, and were not significantly different than controls (1.47 ± 5.2 pg/ml vs. 1.0 ± 1.7 pg/ml, \( P = 0.6 \)). Synovial fluid was available for cytokine measurement in a subset of 25 advanced OA patients. The average synovial fluid IL-6 level in this subgroup of patients was 88.02 ± 124.74 pg/ml. When these patients were stratified according to the presence or absence of synovial inflammation, the mean synovial fluid IL-6 level in the group without inflammation was lower (41 ± 42 pg/ml) than that of the group with inflammation (141 ± 169 pg/ml), but the difference was not statistically significant (\( P = 0.12 \), Fig. 2(B)). There was, however, a trend toward a statistically significant correlation between the synovial fluid IL-6 level and the grade of inflammatory infiltrate (\( r = 0.39, P = 0.05 \)).

Synovial fluid IL-1β levels did not differ significantly between those patients with and those without synovial inflammation (2.5 ± 1.5 pg/ml vs. 3.8 ± 2.6 pg/ml, \( P = 0.2 \)).

**Relationship of Systemic hsCRP Levels to Synovial Fluid IL-6 and IL-1β**

Patients were dichotomized to a low hsCRP group (defined as hsCRP < 3 mg/L) and a high hsCRP group (\( > 3 \) mg/L) to allow for comparison of local cytokine levels. The cutoff level of 3 mg/L was chosen based on two large-scale population-based studies of hsCRP levels and cardiovascular risk\(^{16,25} \). Mean synovial fluid IL-6 level in the high hsCRP group was significantly elevated compared with the low hsCRP group (206.9 ± 176.7 pg/ml vs. 35.1 ± 44.6 pg/ml, \( P = 0.001 \)) [Fig. 3(A)]. In contrast, there was no significant difference in synovial fluid IL-6 levels (3.4 ± 2.2 pg/ml vs. 2.9 ± 2.3 pg/ml, \( P = 0.8 \)) between the two groups. A strong and statistically significant correlation was found between systemic hsCRP levels and synovial fluid IL-6 level in these 25 OA patients (\( r = 0.64, P = 0.0006 \), Table III and Fig. 3(B)), but not synovial fluid IL-1β level (\( r = 0.05, P = 0.8 \)).

**Multivariate Analysis**

Multiple linear regression analysis was performed to examine the association between hsCRP levels, BMI, and histologic infiltrates. In this model, hsCRP was the dependent variable, while age, BMI and degree of inflammatory infiltrate were independent covariates. Because hsCRP was not normally distributed, the data were transformed by taking the inverse of (hsCRP + 0.5). Using this model, only degree of inflammatory infiltrate was significantly associated with hsCRP level (\( \hat{P} = 0.026 \)). As IL-6 was only measured in a subset of patients, it could not be entered into this multivariate model.

**Discussion**

Most investigations into the pathogenesis of OA have focused on the degeneration of articular cartilage and associated changes in the subchondral bone. However, changes in the synovium also occur. Small studies have described synovial mononuclear cell infiltration in approximately 50% of patients with both early and end stage disease\(^{21–23} \). Smith et al. suggested that synovitis is more characteristic of end stage disease\(^{26} \). Smaller studies have observed that CD4+ and CD68+ infiltrates may be even more pronounced in early OA\(^{27} \). The definition of early OA and synovitis in these reports differs, perhaps leading to the divergent conclusions. Although the majority of patients in the current study were undergoing joint arthroplasty for advanced disease, 57% of all the patients with OA had evidence of histologic synovitis regardless of whether disease was classified as advanced or early. This is consistent with data from the majority of reports as well as the large-scale retrospective review of 755 patients done to assess our synovial grading system.

Assessing the prevalence of synovitis is difficult due to the possibility of sampling error. Arthroscopic and histologic studies have shown that synovitis is more focal in OA compared to RA, specifically more pronounced in the juxtacondral regions\(^{28} \). A strength of this study is that we systematically sampled synovium from a standard juxtacondral area. With this standardized sampling method, we saw no significant differences in the prevalence of synovial inflammation in knee OA regardless of the actual

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**Table II**

Characteristics of the 52 patients with OA according to presence or absence of synovial inflammation

<table>
<thead>
<tr>
<th></th>
<th>Whole group (n = 52)</th>
<th>+ Inflammation (n = 30)</th>
<th>– Inflammation (n = 22)</th>
<th>P-value</th>
</tr>
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<tr>
<td>Median age (range)</td>
<td>64 (43–79)</td>
<td>64.00 (43–79)</td>
<td>65.50 (49–78)</td>
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<tr>
<td>Median BMI (range)</td>
<td>28.50 (19.9–60.45)</td>
<td>29.63 (19.90–60.45)</td>
<td>27.45 (20.60–39.05)</td>
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<tr>
<td>Median K–L score (range)</td>
<td>3 (0–4)</td>
<td>3 (0–4)</td>
<td>3 (0–4)</td>
<td>1.00</td>
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<tr>
<td>Female</td>
<td>29 (56%)</td>
<td>19 (60%)</td>
<td>11 (50%)</td>
<td>0.65</td>
</tr>
<tr>
<td>Male</td>
<td>23 (44%)</td>
<td>12 (40%)</td>
<td>11 (50%)</td>
<td>0.79</td>
</tr>
<tr>
<td>Hip</td>
<td>27 (52%)</td>
<td>15 (50%)</td>
<td>12 (54%)</td>
<td>0.79</td>
</tr>
<tr>
<td>Kneee</td>
<td>25 (48%)</td>
<td>15 (50%)</td>
<td>10 (46%)</td>
<td>0.79</td>
</tr>
<tr>
<td>Early</td>
<td>9 (17%)</td>
<td>5 (17%)</td>
<td>4 (18%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Advanced</td>
<td>43 (83%)</td>
<td>25 (83%)</td>
<td>18 (82%)</td>
<td></td>
</tr>
</tbody>
</table>

*P-values from Mann–Whitney test. | P-values from Fisher’s exact test.
compartmental localization of disease (data not shown).

Furthermore, there were no differences in the prevalence of infiltrates according to Kellgren–Lawrence scores. This suggests that synovial inflammation may identify an OA subset rather than merely reflect a stage of disease progression.

There is an increasing literature suggesting that synovitis may contribute to symptoms and to cartilage damage in patients with OA. At least two studies have demonstrated that magnetic resonance imaging (MRI) evidence of synovitis is associated with pain in knee OA. Most interestingly, a prospective arthroscopic study of 420 patients with primary medial compartment knee OA demonstrated that patients with synovitis had more chondropathy at baseline, and more progressive cartilage loss after 1 year. On the molecular level, serum hyaluronic acid, believed to originate primarily from inflamed synovium, is elevated in OA and correlates with a functional capacity score. Otterness et al. investigated the use of disease markers as a means to distinguish the presence of OA. They demonstrated low CRP high CRP

\[ r = 0.64, p = 0.0006 \]

Due to the non-Gaussian distribution, data were plotted on log-10 axes. 0.6 was added prior to log transformation to account for zero values.

Table III

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Correlation coefficient (r)</th>
<th>P-value</th>
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</thead>
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<tr>
<td>Synovial fluid IL-6</td>
<td>25</td>
<td>0.64</td>
<td>0.0006</td>
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<tr>
<td>Inflammatory grade</td>
<td>52</td>
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</tr>
<tr>
<td>Body mass index</td>
<td>52</td>
<td>0.31</td>
<td>0.02</td>
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<tr>
<td>Kellgren–Lawrence score</td>
<td>43</td>
<td>0.07</td>
<td>0.67</td>
</tr>
<tr>
<td>Age</td>
<td>52</td>
<td>0.09</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Fig. 2. (A) hsCRP levels in 52 OA patients with synovial inflammation compared to those without inflammation. Synovial inflammation was defined as having either low-grade or high-grade synovial lymphocytic infiltrates as described in Fig. 1. Mean ± standard deviation (SD) in patients without inflammation was 1.7 ± 3.6 mg/L, while in those with inflammation it was 4.7 ± 5.0 mg/L (P = 0.001). (B) Synovial fluid IL-6 levels in 25 advanced OA patients with synovial inflammation compared to those without inflammation. In patients without inflammation mean IL-6 was 41 ± 42 pg/ml, while in those with inflammation it was 141 ± 169 pg/ml (P = 0.07, ns). (C) BMI in patients with and without synovial inflammation. Median (interquartile range) BMI in patients without synovial inflammation was 27.45 (24.80–32.63). In patients with synovial inflammation median BMI was 29.63 (25.40–34.26, P = 0.25) including an outlier with BMI of 60.45, and 29.05 (25.40–33.87, P = 0.3) excluding this outlier. This outlier was included in all analyses, as its exclusion did not change any results significantly.

Fig. 3. (A) Synovial fluid IL-6 levels in advanced OA patients with low (≤3 mg/ml) vs high (>3 mg/ml) hsCRP levels. Those in the low hsCRP group had a mean ± SD IL-6 level of 35 ± 45 pg/ml, compared with 207 ± 177 pg/ml in the high hsCRP group (P = 0.001). (B) Correlation of plasma hsCRP levels, and synovial fluid IL-6 levels. Statistical analysis yielded a Spearman r = 0.64 and P = 0.0006. Due to the non-Gaussian distribution, data were plotted on log-10 axes. 0.6 was added prior to log transformation to account for zero values.
that inflammatory molecular markers defined significant differences between patients with OA and control populations.

We observed that increasing degree of synovial infiltration correlated with elevated plasma hsCRP levels in idiopathic OA. This suggests that the elevated hsCRP levels seen in these patients may reflect local inflammation within the joint. Both in vitro and in vivo studies have demonstrated that IL-6 is the chief regulator of CRP production by hepatocytes. Therefore, we assessed IL-6 levels in both joint fluid and plasma to evaluate this potential molecular link between local synovitis and CRP production. In the subset of patients with advanced OA from whom we had joint fluid, we found consistently detectable levels of IL-6 in the synovial fluid, but very low or undetectable levels in plasma consistent with previous reports. Given the known mechanistic relationship between CRP and IL-6, this suggests that IL-6 produced in the affected joint may in part be responsible for the elevations in systemic hsCRP seen in this population of patients. Studies in inflammatory arthritis have demonstrated an association between synovial fluid IL-6 levels and circulating levels of CRP, however, in idiopathic OA this association has not been previously reported. It has been proposed that IL-6 produced at local sites is cleared rapidly from the circulation, and may accumulate within the liver to induce an acute-phase protein response. It is possible that this mechanism is active in both a subset of OA and inflammatory arthritis.

Another potential stimulus of CRP production by hepatocytes is IL-1. This cytokine appears to work synergistically with IL-6 to promote CRP production in vitro. IL-1 is produced by synovium and cartilage of patients with OA, and is thought to play a central role in promoting articular cartilage catabolism. We found no association between synovial fluid IL-1β levels and either hsCRP levels or synovial inflammation grade. It is possible that other factors prevent IL-1 from influencing CRP production in vivo, in contrast to our prediction based on in vitro data.

Many cell types within the joint are capable of producing IL-6 including synovial fibroblasts, synovial T cells, and articular chondrocytes. The present study does not address which cell type(s) is the predominant source, but we did observe a correlation between synovial fluid IL-6 and inflammatory cell infiltrates. This suggests that in this group of patients, the majority of the IL-6 is produced by the inflammatory cells themselves, or synovial fibroblasts activated by the inflammatory cells. A recently published study of 51 RA patients undergoing knee surgery found similar associations of synovial fluid IL-6 levels and synovial inflammatory infiltration, consistent with the results presented here. These same associations found in a disease long considered noninflammatory and fundamentally different from RA is of considerable interest.

It is well known that hsCRP levels may be influenced by age and obesity. As expected, we observed a correlation between hsCRP levels and BMI in patients with OA, consistent with results from large studies of cardiovascular risk indicators. However, our multivariate analysis suggests that our results are unlikely to be attributable to weight alone, as only synovial inflammatory grade was significantly associated with hsCRP levels. We saw no association between BMI and degree of inflammation, and the nonsignificant trend toward increased BMI in patients with synovial infiltrates could largely be explained by one outlier. Furthermore, we saw no association between systemic IL-6 levels and either hsCRP ($r = 0.09, P = 0.56$) or BMI ($r = -0.004, P = 0.97$) in this group of patients.

We did not observe a correlation between age and hsCRP levels in our patients, in contrast to many epidemiological studies. The association of age with hsCRP levels may be indirect through various comorbid conditions (excluded in this study) that also increase with age. In spite of the potential pathogenic mechanisms of OA that have been identified in this study, this nonspecificity of CRP limits its clinical utility as a disease marker.

In conclusion, we have identified a relationship among elevated plasma levels of hsCRP, elevated synovial fluid levels of IL-6 and the presence of chronic synovial inflammation in patients with idiopathic OA. Taken together with results from studies linking elevated hsCRP with more rapid disease progression and pain, these data suggest that OA patients with synovial inflammation and elevated hsCRP may form a subgroup of patients with a more aggressive form of disease. In addition to the complex interactions between biomechanics and altered cartilage metabolism that initiate OA, synovial inflammation may be an additional mechanism contributing to disease pathogenesis in a subset of patients. Elucidation of the cellular mechanisms that account for IL-6 production and inflammation in the synovial membrane of some OA patients may add to our understanding of pathogenesis and allow identification of patients who may benefit most from more aggressive antiinflammatory therapy.

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