Increased serum C reactive protein may reflect events that precede radiographic progression in osteoarthritis of the knee

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Abstract

Objective—Raised serum C reactive protein (CRP) and hyaluronate (HA) concentrations predict the progression of knee osteoarthritis (OA) in the long term but the consistency of these relations with time is unknown. The purpose of this work was therefore to determine if raised CRP and HA at entry and three years before entry (−3 years) predict radiological progression of knee OA in a group of patients between entry and five years.

Methods—Knee radiographs from 90 patients with knee OA at entry and five years follow up were assessed for progression of disease over five years. The concentrations of serum CRP and HA were measured at entry (n=90) and also in 40 serum samples available from −3 years. Odds ratios (OR) for predicting progression were calculated by logistic regression.

Results—Serum CRP at entry was not predictive of progression between entry and five years (OR 1.12, 95% CI 0.81, 1.55) but serum CRP at −3 years was predictive of progression (OR 1.90, 95% CI 1.01, 3.28). Serum HA concentration at entry predicted progression between entry and five years (OR 2.32, 95% CI 1.16, 4.66).

Conclusion—These results are consistent with previous reports relating to HA, and suggest that raised serum CRP reflects events that precede a period of later radiographic progression in knee OA. However, because of the large overlap between groups, the serum CRP or HA concentration are not good predictors of individual patient progression and have a poor sensitivity and specificity.

Table 1  Demographic and clinical characteristics of the patients

<table>
<thead>
<tr>
<th></th>
<th>Entry (n=90)</th>
<th>−3 Years (n=40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age* (y)</td>
<td>65.2 (9.9)</td>
<td>65.0 (9.7)</td>
</tr>
<tr>
<td>BMI* (kg/m²)</td>
<td>27.7 (5.0)</td>
<td>26.6 (4.9)</td>
</tr>
<tr>
<td>Proportion male (%)</td>
<td>39</td>
<td>35</td>
</tr>
<tr>
<td>Proportion moderate or severe pain (%)</td>
<td>68</td>
<td>75</td>
</tr>
<tr>
<td>Proportion with Kellgren and Lawrence grade &gt;2 (%)</td>
<td>50</td>
<td>35</td>
</tr>
</tbody>
</table>

*Mean (SD).

Table 2  Serum CRP and HA concentrations at entry

<table>
<thead>
<tr>
<th>Serum concentration at entry (n=90)</th>
<th>Serum concentration at entry (n=40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absolute values</td>
<td>Ln values</td>
</tr>
<tr>
<td>-----------------</td>
<td>-----------</td>
</tr>
<tr>
<td>CRP (mg/l)</td>
<td>Mean 6.78</td>
</tr>
<tr>
<td>HA (ng/ml)</td>
<td>Mean 133.09</td>
</tr>
</tbody>
</table>

Figure 1  Serum CRP and serum HA concentrations in all patients (n=90) at entry.

RESULTS

Table 1 shows the demographic and clinical characteristics of the patients. There were 55 women and 35 men, mean age 65 years. Kellgren and Lawrence scores of 1, 2, 3 and 4 were present in 22, 24, 27 and 17 patients respectively. Of the 90 patients, 38 progressed and 52 did not progress. The demographic, clinical and radiographic variables for the subset of 40 patients for whom serum samples were available at −3 years were similar to group as a whole at entry (see table 1).

Table 2 gives the mean CRP and HA values for the patients and individual values for all 90 patients at entry are illustrated in figure 1. At entry the CRP concentrations of the 40 patients (for whom serum samples were also available at −3 years) was higher than the full set of 90 patients but this was not statistically significant (p=0.162). Serum HA values of the two groups were similar at entry (see table 2).

Table 3 shows the odds ratios for predicting disease progression. Raised serum CRP measured at entry does not identify those patients who will progress. By contrast, serum CRP at −3 years is predictive of progression in OA from entry to five years (p=0.042). Serum HA...
is increased at both time points in those who show progression. At −3 years this is of borderline statistical significance (p=0.067) but at entry it is significant (p=0.016). To illustrate these findings, the individual serum concentrations of CRP and HA for the 40 patients in whom measurements at entry and −3 years are available are shown in relation to disease outcome in figures 2 and 3. Because of the large overlap between groups, the serum CRP or HA concentration is not a good predictor of individual patient progression. The sensitivity and specificity for CRP at −3 years (cut off 9.65 mg/l) was 38% and 85%, at entry CRP had no predictive power. Those for HA at −3 years (cut off 117.3 ng/ml) were 46% and 87% and at entry (cut off 150.0 ng/ml) were 38% and 89%.

Discussion
There have been a number of reports demonstrating associations between biochemical markers measured in serum and disease severity and outcome in OA. Although CRP has traditionally been seen as “normal” in OA, sensitive assays show that it is raised in many patients but is below the level usually detected in hospital chemical pathology departments. Increased serum CRP and HA have been shown to predict progression of disease in two previous cohort study reports. The results presented here confirm that raised serum HA is predictive of an immediate period of progression of knee OA. They show that serum HA is also predictive of progression if measured three years before. In contrast, serum CRP was not predictive of progression when measured immediately before a five year progressive period, but was predictive of that progression when measured three years in advance. Because of the large overlap between groups, the serum CRP or HA concentration are not good predictors of individual patient progression and have a poor sensitivity and specificity. However, the data provide an insight into potential pathological mechanisms.

This is a convenience sample of patients presenting with knee OA at one time and being assessed at another, raising the possibility that selection bias might be influencing the CRP values and their changes. However, the principal finding of our study is that measurements of CRP at one time point are related to radiographic progression over a distant (three years ahead) and prolonged (the subsequent five years) period. Even if the cause of the raised CRP was also the cause of the presentation to the rheumatologist (for example, it may be related to an inflammatory episode), that does not detract from the conclusion that serum CRP reflects events that precede a subsequent period of cartilage loss.

In this study, progression on radiographs represented principally joint space narrowing and hence loss of articular cartilage in the medial compartment. The results are consistent with previous studies of these markers in OA and were statistically significant when age and BMI were taken into account. This has been the case even though patellofemoral
disease has not been assessed in these cohorts of patients. The presence and progression of patellofemoral disease will serve to cloud the link to serum marker measurements. Furthermore, CRP and HA measurements were available in a relatively small number of patients and they may have OA at other sites as well as the knee joint. Nevertheless, our findings are statistically significant and suggest that a raised serum CRP reflects events that precede a subsequent period of cartilage loss. This implies that some events associated with cartilage loss begin before others.

Raised CRP may be related to other pathological findings. For example, increased serum CRP (measured using a similar sensitive method) has been found in patients with cardiovascular diseases. However, this group consisted of patients aged between 50 and 59 years, an age group where OA is common. It is therefore conceivable that the raised CRP concentrations in this group is attributable to preclinical OA and that an increase of serum CRP (when other intercurrent diseases associated with raised CRP is absent) may identify subjects who will develop OA. Further longitudinal studies of biochemical markers in this type of patients would explore the usefulness of serum CRP and HA as prognostic markers.

Our earlier studies found that abnormal bone scintigraphy correlate with subsequent cartilage loss. Bone scans that showed active uptake in the knee identified patients with about a 50% chance of radiological progression (as defined in this study) over the following five years, while a negative scan virtually ruled out such progression. This may suggest that bone reaction is an integral part of the pathological processes related to cartilage loss. Moreover, the results indicate that activation of bone metabolism occurs, like raised serum CRP concentrations, out of phase with the loss of cartilage. These data raise the possibility that a variety of joint tissues are involved in the pathogenesis of tibiofemoral OA, and that they become active in the disease process in a phasic pattern.


