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INTRODUCTION: In established OA, the presence of synovial inflammation (synovitis) is associated with pain and progression of disease. We previously demonstrated that synovitis was also a frequent finding associated with pre-operative symptom severity in patients undergoing arthroscopic partial meniscectomy, even in the absence of radiographic OA changes. Synovial inflammation was also associated with a specific pattern of chemokine expression (IL-8, CCL5, CCL19 and CCR7). Despite no radiographic disease, 80% of these patients had evidence of early-stage cartilage degeneration when examined intra-operatively. Here we present the longitudinal follow-up of these patients to test whether synovial inflammation present at the time of surgery predicts post-surgical knee symptoms up to 2 years post-operatively.

METHODS: Patients and Outcomes: Thirty-three patients scheduled for arthroscopic meniscectomy with a history of knee injury and without radiographic evidence of OA were recruited from the Orthopedic practices at the New England Baptist Hospital. Intra-operative evidence of early-stage OA cartilage degeneration was documented in 80% of these patients using the Outerbridge score. Pre-operative symptoms were measured utilizing the Lysholm score (a patient-administered questionnaire measuring knee-specific symptoms and dysfunction) and have been reported previously. Lysholm questionnaires were readministered post-operatively at 16 weeks, 1 year and 2 years. A total of 28 patients completed the 2 year follow-up. Assessment of synovitis: Synovial biopsies were taken at the time of surgery. Inflammation was scored on Hematoxylin & Eosin stained sections using our published semi-quantitative scoring system (1). This scoring system is based on increasing perivascular mononuclear cell infiltration. Synovial lining hyperplasia was assessed separately. We used a linear mixed effects model to study whether synovitis impacted Lysholm scores over time, adjusting for age (centered at 45), BMI (centered at 27), gender and cartilage Outerbridge score. Chemokine expression analysis: Synovial total RNA was extracted using routine methods, and chemokine (IL-8, CCL5, CCL19, CCR7) expression determined by quantitative real-time polymerase chain reaction (RT-PCR) in twelve patients.

RESULTS:

Figure 1: Lysholm scores over the 2 year follow-up in patients undergoing arthroscopic meniscectomy. There were significant improvements from the pre-operative Lysholm scores at all three post-operative time points (Kruskal-Wallis p<0.0001), with a mean (+/-SD) improvement of 27 (+/-16) points at 2 years. At two years, all but five patients had Lysholm scores ≥ 80.

Figure 2: Lysholm scores in patients with inflammation (n=12, squares) and patients without inflammation (n=16, circles). As previously reported (1), patients with synovitis had, lower preoperative Lysholm scores.

Adjusting for age, BMI, gender and cartilage Outerbridge score, synovitis was associated with greater improvement in Lysholm scores over time (p=0.003 at 16 weeks, p=0.026 at one year, and p=0.030 at two years). The average 2-year Lysholm scores did not differ significantly between patients with and without inflammation (p=0.31). However, four of the five patients with 2-year post-operative Lysholm scores below 80 exhibited synovitis.

Table 1: Associations between chemokine mRNA relative expression (RE) levels and post-operative improvement in Lysholm scores.

<table>
<thead>
<tr>
<th>RE</th>
<th>Change from Pre-operative Lysholm scores</th>
<th>16 weeks</th>
<th>1 year</th>
<th>2 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-8</td>
<td>r = 0.529</td>
<td>r = 0.096</td>
<td>r = 0.411</td>
<td></td>
</tr>
<tr>
<td></td>
<td>p = ns</td>
<td>p = ns</td>
<td>p = ns</td>
<td></td>
</tr>
<tr>
<td>CCL5</td>
<td>r = 0.437</td>
<td>r = 0.198</td>
<td>r = 0.402</td>
<td></td>
</tr>
<tr>
<td></td>
<td>p = ns</td>
<td>p = ns</td>
<td>p = ns</td>
<td></td>
</tr>
<tr>
<td>CCL19</td>
<td>r = 0.704</td>
<td>r = 0.205</td>
<td>r = 0.850</td>
<td></td>
</tr>
<tr>
<td></td>
<td>p = 0.050</td>
<td>p = ns</td>
<td>p = 0.004</td>
<td></td>
</tr>
<tr>
<td>CCR7</td>
<td>r = 0.704</td>
<td>r = 0.587</td>
<td>r = 0.790</td>
<td></td>
</tr>
<tr>
<td></td>
<td>p = 0.016</td>
<td>p = ns</td>
<td>p = 0.002</td>
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</tbody>
</table>

r = Spearman correlation coefficient. ns = non-significant p-value (<0.05). Similar to histologic synovitis, inflammation measured by synovial mRNA levels of CCL19 and CCR7 were also associated with greater improvements in Lysholm scores at both the 16 week and 2 year post-operative time points.

DISCUSSION: In this cohort of patients with pre-radiographic OA undergoing arthroscopic partial meniscectomy, synovitis identified histologically did not predict worse Lysholm scores up to 2 years post-operatively. Instead, patients with inflammation, measured both histologically and by expression of CCL19 and CCR7, demonstrated greater symptom improvement post-operatively which was significant up to two-years. Our results indicate that patients with detectable synovitis may be more responsive to surgical and other therapeutic interventions up to two years post-operatively. As the majority of these radiographically normal patients did well in the follow-up period, the ability to distinguish patients who develop progressive knee symptoms was limited. Of note, four of twelve (30%) of patients with synovitis demonstrated 2-year Lysholm scores lower than 80, compared with one of sixteen (6%) of patients without synovitis. This suggests that larger numbers and longer follow-up may be needed to identify patients who develop progressive knee symptoms after surgical intervention for meniscal tears.

SIGNIFICANCE: Risk factors for poor post-operative outcomes or progression to symptomatic knee OA after meniscectomy are not completely understood. This small pilot study did not support a strong relationship between the presence of synovial inflammation and greater symptom levels at two-years post-arthroscopy. However, results suggest that longer follow-up is needed to better identify patients with progressive symptoms.

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