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The influence of synovial inflammation and hyperplasia on symptomatic outcomes up to 2 years post-operatively in patients undergoing partial meniscectomy

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SUMMARY

Objective: Synovitis is associated with pain and other symptoms in patients with knee osteoarthritis (OA), and in patients with meniscal tears even in the absence of radiographic OA. Patients undergoing arthroscopic partial meniscectomy were followed for 2 years to determine whether synovitis predicts post-operative symptoms.

Design: Thirty-three patients scheduled for arthroscopy were recruited for this pilot study. Symptoms were assessed using a knee pain scale, the Lysholm score, and the short form-12 (SF-12®) pre-operatively and at 16 weeks, 1 year and 2 years post-operatively. Synovial inflammation and hyperplasia were graded on surgical biopsies. Linear mixed effects models were tested to determine whether inflammation or hyperplasia is associated with outcome scores over time.

Results: Lysholm scores and SF-12® physical component sub-scores were worse pre-operatively in patients with inflammation (Lysholm: 52.42 [95% confidence interval (CI) 42.37, 62.47] vs 72.38 [66.03, 78.72], $P < 0.001$; SF-12: 36.81 [28.26, 45.37] vs 46.23 [40.14, 52.32], $P < 0.05$). Up to 2-years post-operatively, patients with inflammation achieved mean scores similar to those without inflammation. As a result, the mean improvement in Lysholm scores was 13.01 [1.48–24.53] points higher than patients without inflammation, $P = 0.03$. 33% (4/12) of patients with inflammation still had fair to poor Lysholm scores 2 years after surgery compared to 7% (1/15, P=0.14) without inflammation. No association between hyperplasia and symptoms was noted.

Conclusions: In this pilot study of patients undergoing partial meniscectomy, synovial inflammation was associated with worse pre-operative symptoms, but not with poorer outcomes in the first 2 years post-arthroscopy. Larger cohorts and longer follow-up should be pursued to confirm this relationship, and determine if the initial response is sustained.

Introduction

Osteoarthritis (OA) is a disease in which multiple joint structures are compromised, including cartilage, meniscus, bone, and synovial membrane[1]. Structural alterations seen on plain radiographs, specifically osteophytes and joint space narrowing, can be identified in approximately 34% of the United States population over age 65, but in only about half are structural changes accompanied by pain and dysfunction[2]. Importantly, pain and related symptoms are associated with more rapid structural progression[3]. Therefore understanding factors responsible for symptom development are essential to identify patients at risk of greater morbidity and disability, and to identify modifiable disease targets for therapeutic intervention.

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Multiple investigators have demonstrated the association of patient-reported symptoms such as pain with presence and severity of synovitis in patients with OA[4]. Synovitis also is associated with objective measures of knee joint dysfunction including walking and stair climbing times[5]. We have reported that the relationship between synovitis and symptoms applies to patients at risk for OA, but without radiographic signs of OA structural alterations, based on the analysis of a cohort of patients with meniscal tears undergoing meniscectomy[6].

In young sports-participants, traumatic meniscal tears are among the most common knee joint derangements and these tears are associated with an increased risk of OA development[7]. But the most common meniscal derangements are degenerative meniscal tears[8] which can occur in the setting of pre-existing OA and are also associated with risk of disease progression[7]. Patients with meniscal tears, with or without concomitant OA, often seek surgical intervention due to a variety of symptoms (pain, locking, stiffness, inability to participate in specific activities). In fact, there are close to 1 million arthroscopic meniscal procedures performed in the US annually[9], although meniscal derangement itself has not consistently been associated with pain[10–12].

The present longitudinal pilot study was designed to test the hypothesis that synovitis detected at the time of surgery predicts poorer symptomatic outcomes after arthroscopic meniscectomy. This study was conducted on patients with meniscal tears but with normal pre-surgical knee radiographs. Patient-reported knee symptoms were measured at three post-operative time points using the Lysholm score[13], short form-12 (SF-12®) health surveys[14], and a knee pain scale. The pre-operative characteristics and relationship with baseline Lysholm scores of these patients have been previously published[6]. Here, we report analysis of the relationship between synovitis measured at the time of surgery, and knee symptoms using three outcome measures up to 2 years post-operatively.

Methods

Patients

The study was approved by the Institutional Review Board (IRB) of the New England Baptist Hospital (NEBH), and all patients gave written, informed consent. Inclusion and exclusion criteria, as well as demographics and baseline characteristics, have been described in detail previously.[6] Briefly, thirty-three patients with a history of knee injury and a magnetic resonance imaging (MRI)-confirmed meniscal tear scheduled for arthroscopic partial meniscectomy were recruited between September 2005 and April 2009. Patients with radiographic evidence of OA (osteophytes or joint space narrowing) were excluded. There were twenty-one males and twelve females, median age was 45 interquartile range, (IQR 40–53), and median body mass index (BMI) was 26.9 (IQR 24.7–28.1). The majority (twenty-five patients) had complex meniscal tears with multiple cleavage planes consistent with degenerative type tears, and only 20% had completely normal cartilage surfaces as indicated by an Outerbridge score[15] of zero in all three knee compartments.

Synovial tissue collection and evaluation of synovitis

Knee synovial biopsies were obtained during surgery from three locations (suprapatellar pouch, medial and lateral gutters). Biopsies were taken from areas that appeared inflamed or thickened. When no inflammation was apparent, standard locations were used: femoral aspects of the gutters and the central supratrochlear region in the pouch. Biopsies from five patients were insufficient for analysis, so 28 patients contributed biopsies. Histologic features of synovitis[16] were evaluated on formalin-fixed, paraffin-embedded, hematoxylin and eosin (H&E) stained synovial membrane sections. Inflammation was evaluated on a semi-quantitative scale[6] presented in Table I, based on perivascular mononuclear cell aggregates. In addition, synovial lining hyperplasia, vascularity, fibrosis, and the presence of detritic fragments of bone and cartilage were graded independently (Table I). The grading system was adapted from multiple sources[16–19] with input from an experienced musculoskeletal Pathologist (ED). Randomly chosen subsets of synovial specimens were scored by two independent readers (ED, CRS) for assessment of inter- and intra-reader reliability. However, the final reported scores reflect those of a single reader (the experienced musculoskeletal Pathologist, ED).

Outcome scores

Symptoms were assessed using three instruments. First, Lysholm questionnaires were utilized to assess knee-specific symptoms. The Lysholm questionnaire is a clinician-developed instrument measuring symptoms including pain, swelling, limp, locking, and instability, as well as functional disability (stair climbing, squatting, use of supports). A summed score is reported on a scale of 0–100, where 100 = no symptoms/disability[13]. Second, the SF-12® health survey was utilized to measure general physical and emotional health. Physical (PCS) and mental (MCS) component summary sub-scores were calculated and expressed as norm-based standardized scores[14], with 50 equal to the population mean and 10 the population standard deviation. Finally, patients were also asked to assess their knee pain on a scale from 0 to 10 (0 = no pain). All three instruments were administered pre-operatively and at 16 weeks, 1 year and 2 years post-operatively. Thirty-one patients completed the 2-year follow-up.

Measurement of chemokine transcript levels

mRNA levels of four chemokines and one chemokine receptor (Interleukin (IL)-8, C–C Chemokine Receptor 7 (CCR7), C–C Chemokine Ligand 19 (CCL19), CCL21 and CCL5) were measured in twelve

Table I
Synovial histopathologic grading (for H&E stained sections)

1) Mononuclear inflammation:
- Grade 0 = none
- Grade 1 = mild (0–1 perivascular aggregates per field)
- Grade 2 = moderate (>1 perivascular aggregate per field ± focal* interstitial infiltration)
- Grade 3 = marked (both perivascular and widespread* interstitial aggregates)

2) Vascularity:
- Grade 0 = normal
- Grade 1 = mildly increased
- Grade 2 = markedly increased

3) Fibrosis of sublining:
- Grade 0 = absent
- Grade 1 = focal
- Grade 2 = widespread

4) Detritus:
- Grade 0 = absent
- Grade 1 = small particulate
- Grade 2 = large particulate

5) Synovial hyperplasia†:
- Grade 0 = normal (up to 2 cell layers thick)
- Grade 1 = hyperplasia I (3–4 cells thick)
- Grade 2 = hyperplasia II (>4 cell thick)

* Focal = present in <50% of the field. Widespread = present in >50% of the field.
† Hyperplasia evaluated at high power (40×). All other features evaluated at low power (5–10×).