CHARACTERIZATION OF PATHOLOGY OF KNEE MENISCI: CORRELATION OF RADIOGRAPHIC, GROSS, HISTOLOGIC, BIOCHEMICAL, AND MOLECULAR MEASURES OF DISEASE

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Introduction: Meniscal pathology is an extremely prevalent problem, which inevitably leads to osteoarthritis and associated pain, swelling, and disability. Relatively little data are available regarding the molecular, biochemical, and histologic aspects of meniscal disease. Optimizing diagnosis, prevention, and treatment for meniscal pathology is limited by this incomplete understanding. Therefore, the overall goal of our research is to comprehensively characterize pathology of the knee menisci so that diagnostic, treatment, and clinical outcomes of meniscal problems can be optimized. Our strategy is to comprehensively assess meniscal pathology and correlate clinical and basic science data in pursuit of finding clinically relevant answers for this common problem in people.

Methods: IRB approval and informed patient consent were obtained before collecting menisci from patients undergoing total knee arthroplasty (TKA) and reviewing their medical records. Twenty-three patients met inclusion criteria. Twenty-seven knees (14 right, 13 left) comprised the affected group and 6 aged “normal” knees were used as controls. All meniscal tissue was harvested and subjectively scored for gross pathology. Each meniscus (medial and lateral) was separated into the corresponding anterior, medial, and posterior sections, when present. Each section was divided into 3 portions: one portion was processed for histology, and the other two were stored for biochemical and molecular analyses. A histologic scoring system was developed and used to assess cell and matrix composition, as well as pathologic changes. The portion stored for biochemical analyses was used to determine glycosaminoglycan (GAG) content, collagen (HP) content, and water content. RNA was extracted from the portion designated for molecular analyses. Using total RNA, relative expression levels were determined by real time PCR analysis for genes involved in synthesis (collagens 1, 2, 3, 4, and 6, aggrecan, decorin), degradation (matrix metalloproteinases (MMP-1,-2,-3,-9,-13), aggrecanases (ADAMTS 4, 5)), anti-degradation, tissue inhibitors of metalloproteinases (TIMP-1, -2, -3), and signaling (interleukin 1-beta, inducible nitric oxide synthase (iNOS), and cyclooxygenases (COX-1, -2)) using a housekeeping gene (β-actin) as a standard. Weight-bearing, anterior-posterior radiographic views were used to determine joint space measurements for lateral and medial compartments, and were subjectively scored for osteoarthritic changes. Data were compared for statistically significant differences using an ANOVA, t-test (continuous data) or rank sum test (categorical data). Outcome measures were compared to determine the presence and strength of correlations using a Pearson Product Moment test or Spearman Rank Order test. Significance was set at \( p < 0.05 \).

Results: The affected TKA patients involved in this study had a mean age of 60.2 years (range 36-81), and the aged controls had a mean age of 77 (range 64-87). Affected menisci had significantly (\( p<0.001 \)) more severe gross and histologic pathology than controls (Fig. 1).

![Figure 1. Histologic appearance of affected and control menisci](image)

Collagen content was significantly higher (300.0 +/- 7.8 vs. 77.5 +/- 3.7 ug/mg) for affected knees compared to the control group. GAG content was significantly higher (37.8 +/- 1.8 vs. 20.0 +/- 2.3 ug/mg) and water content was significantly higher (73.2 +/- 0.7 vs. 39.0 +/- 0.7 %) for the affected knees compared to controls (Fig 2). GAG and water content were also significantly higher (43.5 +/- 2.5 vs. 32.3 +/- 2.3 ug/mg) and (75.3 +/- 0.7 vs. 71.2 +/-), respectively, for the medial side compared to the lateral side.

![Figure 2. Biochemical data comparing affected and control menisci](image)

A significant (\( r=0.61 \)) positive correlation was present between gross and histologic scores. A significant (\( r=0.55 \)) positive correlation was present between gross and radiographic scores. A significant (\( r=-0.59 \)) negative correlation was present between gross score and joint space. Histologic scoring categories had significant (\( r=0.53 \)) positive correlations with each other. Histologic scores had significant but weak (\( r=-0.38 \)) negative correlation with joint space and significant but weak (\( r=0.36 \)) positive correlation with radiographic scores. Correlations among histologic categories and GAG and collagen content were significant, but weak (\( r<0.4 \)). Correlation between histologic scores and water content was significant (\( r=0.64 \)). The correlation between the GAG content and water content was significant (\( r=0.42 \)). The radiographic scores had a significant but weak (\( r<0.4 \)) positive correlation with GAG content and water content, and had a significant but weak (\( r<0.4 \)) negative correlation with collagen content. The histologic scores had a weak (\( r<0.4 \)) but significant positive correlation with Col 1, 3, 6, and MMP 13, along with a significant and moderately strong (\( r=-0.41 \)) negative correlation with MMP 3. Col 1, 2, 3, and 6 had significant (\( r>0.81 \)) positive correlations with each other. MMP 2 also had significant (\( r>0.88 \)) positive correlations with Col 1, 2, 3, and 6.

Discussion: These data suggest the following: (1) Gross and histologic evaluation of menisci consistently depict severity of pathology and correlate well; (2) Gross and histologic assessment of menisci readily and accurately distinguish affected from control; (3) The amount and severity of pathology differs between medial and lateral menisci by clinical (gross and radiographic) and basic science (histology, biochemical) measures of disease; (4) Strong and significant correlations exist between basic science and clinical measures of disease; (5) In vitro measures of meniscal pathology have potential value for understanding disease mechanisms and predicting clinical disease. Therefore, continuation of this research is warranted in order to increase numbers for affected and control groups, assess more types of pathology, and more fully characterize meniscal disorders at both the basic science and clinical levels. Characterizing and distinguishing meniscal pathology fully will allow us to optimize diagnosis and prediction of disease course in patients and beneficially affect prevention and treatment strategies.

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