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Commentary

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Identification of a Novel Fibronectin-Aggrecan Complex in the Synovial Fluid of Knees with Painful Meniscal Injury

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Investigation performed at Jupiter Outpatient Medical Center, Jupiter, Florida

Background: Molecular biomarkers associated with knee pain may be useful as diagnostic modalities, prognostic indicators, and surrogate end points for therapeutic trials. The present study describes a novel complex of fibronectin and aggrecan that is present in the affected knee of patients with pain and meniscal abnormality.

Methods: The present prospective study included thirty patients with knee pain, mechanical symptoms, and magnetic resonance imaging findings that were positive for a meniscal tear who chose arthroscopic partial meniscectomy after unsuccessful nonoperative management. Synovial fluid was aspirated at the time of surgery and was assayed for the fibronectin-aggrecan complex with use of a heterogeneous enzyme-linked immunosorbent assay (ELISA). The results were compared with knee aspirates from ten asymptomatic volunteers with no pain who underwent magnetic resonance imaging of the knee.

Results: The mean optical density (and standard deviation) of the fibronectin-aggrecan complex was significantly greater in synovial fluid from knees undergoing arthroscopic surgery as compared with fluid from asymptomatic controls (13.29 ± 8.48 compared with 0.03 ± 0.09 ; $p < 0.001$). The mean age in the study group was significantly greater than in control group (46.0 ± 12.6 compared with 38.5 ± 6.0 years; $p = 0.02$), but controlling for age did not affect the results. Post hoc, an optical density cutoff value of 0.3 distinguished the study group from the control group with 100% accuracy.

Conclusions: A novel fibronectin-aggrecan complex is present in the synovial fluid of painful knees with meniscal abnormality. The fibronectin-aggrecan complex may prove to be useful as a clinical biomarker or therapeutic target. Further research is warranted to correlate functional outcome after surgery with the fibronectin-aggrecan complex and other cartilage biomarkers.

Level of Evidence: Diagnostic Level IV. See Instructions to Authors for a complete description of levels of evidence.

Protein biomarkers associated with degenerative joint disease may be useful as diagnostic tools, prognostic indicators, and surrogate end points for therapeutic trials. Inflammatory cytokines, matrix degradation products, and proteases have all been implicated in the pathophysiology of joint degeneration, which involves complex signaling among cartilage, synovium, and bone¹.

Immunoreactivity to specific cytokines, including interferon-gamma (IFN- γ), interleukin-6 (IL-6), monocyte chemoattractant

protein-1 (MCP-1), and macrophage inflammatory protein-1 beta (MIP-1 β), recently has been observed in painful knees with meniscal abnormality². There is also evidence that inflammatory cytokines are associated with fibronectin and its fragments³, which in turn are associated with aggrecan and its fragments⁴, in the pathophysiology of degenerative joint disease. In addition, it has been observed that the fragmentation patterns of aggrecan in patients with acute injury and chronic joint degeneration differ from those in healthy controls⁵.

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A commentary by Armando F. Vidal, MD, is available at www.jbjs.org/commentary and is linked to the online version of this article.

Further investigation of the IFN- γ -immunoreactivity signal observed in the previous study has revealed cross-reactivity with other biomolecules and the subsequent discovery of a novel protein-protein fibronectin-aggregan complex⁶. This complex was identified by means of proteomic analysis utilizing multiplexed-bead immunoassay, Western blots, column chromatography, and mass spectrometry of synovial fluid samples from the knees of patients with symptomatic meniscal injury. The aim of the present study was to prospectively validate this fibronectin-aggregan complex in a new series of thirty patients with meniscal abnormality as compared with control patients without pain or meniscal abnormality on magnetic resonance imaging. The immunoassay utilized in the present study was optimized on a previous and distinct set of patients, none of whom are reanalyzed here.

In the present study, the level of the fibronectin-aggregan complex in the synovial fluid from the knees of individuals with meniscal abnormality undergoing arthroscopic partial meniscectomy was measured. We hypothesized that the complex would be elevated in patients with knee pain undergoing surgery as compared with asymptomatic controls, indicating that the fibronectin-aggregan complex is implicated in the disease state.

Materials and Methods

Subjects

Institutional review board approval was obtained for both the study group and the asymptomatic controls. The study group consisted of patients with an age of eighteen years or more who had a history of knee pain (for more than three but less than six months) and who had had unsuccessful nonoperative management involving nonsteroidal anti-inflammatory drugs, physical therapy, and activity modification. The inclusion criteria were the presence of mechanical symptoms, including locking, catching, or giving way; positive physical examination findings, including joint-line tenderness, a positive McMurray test, or a positive Steinman test; and magnetic resonance imaging (MRI) findings demonstrating a meniscal tear in a location that correlated with the findings of the physical examination. The exclusion criteria were the presence of high-grade (Kellgren-Lawrence grade-IV) osteoarthritis; a history of previous knee surgery or trauma; ligamentous incompetence on examination or magnetic resonance imaging; and a diagnosis of inflammatory arthritis, crystalline arthropathy, or rheumatologic diseases. Patients in the study group were evaluated with weight-bearing anteroposterior, lateral, and patellofemoral radiographs, which were graded according to the Kellgren-Lawrence system by the operating surgeon. The Outerbridge grade was determined at the time of arthroscopy. Patients in the control group had a negative history for knee pain or trauma and underwent magnetic resonance imaging of the knee to assess for meniscal tear, anterior cruciate ligament (ACL) tear, or high-grade cartilage injury. To avoid unnecessary radiation exposure, patients in the control group did not have radiographs. Patients and controls were recruited from the private practices of five board-certified orthopaedic surgeons specializing in arthroscopic surgery of the knee

during the period of January 2008 to March 2009 (Clinical-Trials.gov NCT01006278).

Sample Storage and Preparation

Synovial fluid was collected from the knees of all subjects by means of needle aspiration with use of a sterile technique, was placed in a sterile polypropylene tube, and was frozen at -80°C until the time of sample analysis⁶. At the time of analysis, each sample was thawed to room temperature, was treated with 5 mg/mL hyaluronidase, was clarified by means of centrifugation at 5000 g, and was filtered with use of 0.45- μm low protein binding filtration. The collected filtrate was immediately assayed as described below.

ELISA Analysis

A heterogeneous, enzyme-linked immunosorbent assay (ELISA) was developed and validated in a previous study⁶; none of the patients who were used for the development of the assay are included in the present series. This assay detects a protein complex of fibronectin and the aggregan G3 domain. Briefly, an anti-aggregan G3 domain antibody (Santa Cruz Biotechnology, Santa Cruz, California) in phosphate-buffered saline (PBS)/Tween 20/thimerosal solution was used to coat a ninety-six-well microplate. The plate was treated with bovine serum albumin (BSA) in the same buffer overnight at 4°C to block excess binding sites and then was washed six times with a PBS/Tween 20/thimerosal solution. The centrifuged and filtered sample was aliquoted at three serial dilutions in triplicate into the microplate and was incubated for one hour to facilitate binding of the complex to the immobilized antibody. After washing six times with the wash buffer, anti-fibronectin antibody labeled with horseradish peroxidase (HRP) (US Biological, Swampscott, Massachusetts) was added and incubated for one hour. After six washes, the tetramethylbenzidine (TMB) substrate (Sigma, St. Louis, Missouri) was added and the reaction product was measured on the basis of optical density (OD) at a 450-nm wavelength. Human fibronectin (BD Biosciences, San Jose, California) at 10 $\mu\text{g}/\text{mL}$ concentration was used as a negative control.

Data Analysis

Data were analyzed with use of the t test, analysis of variance, the Wilcoxon rank-sum test, and two-by-two contingency table analysis. A priori power analysis was performed. Using our sample size of thirty affected and ten unaffected individuals, and an alpha value of 0.05 assuming a very large effect size (Cohen $d = 1.1$), the power of the t test was 0.84.

Source of Funding

No extramural or intramural funding was employed or necessary for design and conception, data collection, data interpretation and analysis, or preparation of the manuscript. Biochemical assays were provided by Cytonics (Jupiter, Florida).

Results

The study group consisted of thirty knees from thirty patients who chose arthroscopic partial meniscectomy after the

TABLE I Two-by-Two Contingency Table for the Level of the Fibronectin-Aggregan Complex in the Surgical and Asymptomatic Control Groups*

	Surgery Group (no. of patients)	Asymptomatic Control Group (no. of subjects)
ELISA >0.3 OD at 450 nm	30	0
ELISA <0.3 OD at 450 nm	0	10

*The optimal optical density (OD) cutoff value of 0.3 at 450 nm was determined post hoc.

failure of nonoperative treatment, and the control group consisted of ten knees from ten asymptomatic subjects. The mean age (and standard deviation) of the study and control groups were 46.0 ± 12.6 and 38.5 ± 6.0 years, respectively. The difference was significant ($p = 0.02$; t test). There were seventeen males and thirteen females in the study group and six males and four females in the control group. The difference was not significant ($p = 0.85$; exact binomial test). No patient in the control group had magnetic resonance imaging evidence of meniscal tear, anterior cruciate ligament tear, or high-grade cartilage injury.

Figure 1 is a graphical representation of the optical density for the ELISA immunoassay. The optical density of the ELISA immunoassay was 13.29 ± 8.48 for the study group, compared with 0.03 ± 0.09 for the control group. The difference was significant ($p < 0.001$; t test). The significance did not change with the use of one-way analysis of variance controlling for age or with the use of Wilcoxon rank-sum test. Table I is a two-by-two contingency table of the levels of the fibronectin-aggregan complex in the study and control groups with a cutoff value of 0.3 optical density as determined by post hoc analysis.

The mean Kellgren-Lawrence score (and standard deviation) for the thirty knees in the study group was 1.7 ± 0.7 .

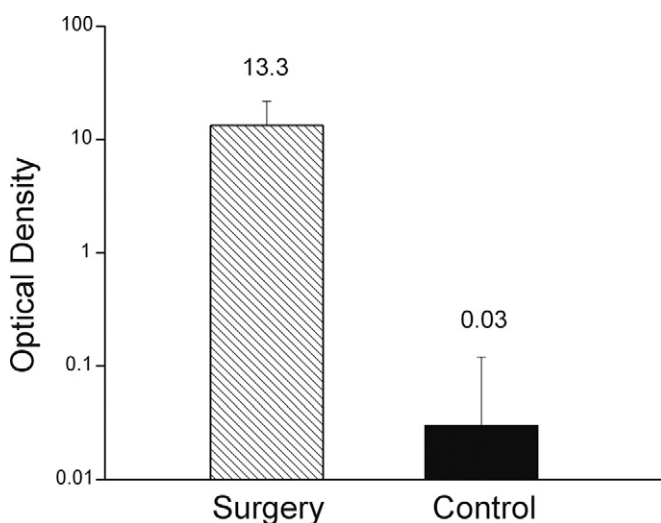


Fig. 1
Bar graph depicting the level of the fibronectin-aggregan complex in the study and control groups. The values on the y axis indicate the mean optical density at a 450-nm optical wavelength for the heterogeneous ELISA on a logarithm base 10 scale. The error bars represent the standard error of the mean.

Three knees (10%) had a Kellgren-Lawrence score of 3. The level of the complex was not correlated with the Kellgren-Lawrence score on one-way analysis of variance ($p = 0.65$). The mean Outerbridge score (and standard deviation) for the thirty knees in the study group was 1.8 ± 0.6 . Two knees (13%) had an Outerbridge score of 3. The level of the complex was not correlated with the Outerbridge score on one-way analysis of variance ($p = 0.49$).

Discussion

The current study demonstrates that a fibronectin-aggregan complex is present in the synovial fluid of painful knees with meniscal abnormality. The ELISA signal of the complex in symptomatic patients is elevated several hundredfold relative to asymptomatic control patients, and the difference is significant after controlling for age. This protein-protein complex may serve as a candidate biomarker or future therapeutic target for painful meniscal abnormality.

An increasing number of candidate biomarkers have been identified in the pathophysiology of degenerative joint diseases. In the study by Cuellar et al., lavage fluid from knee joints with painful meniscal injury demonstrated greater immunoreactivity to interferon gamma ($\text{IFN-}\gamma$), interleukin-6 (IL-6), macrophage inflammatory protein-1 beta (MIP-1 β), and monocyte chemoattractant protein-1 (MCP-1) when compared with fluid from nonpainful knees². Inflammatory cytokines have a complex relationship with fibronectin and its fragments³ and aggregan and its fragments⁴ in degenerative joint disease.

Fibronectin

Fibronectin is a large structural glycoprotein whose multiple domains form part of the cell-surface receptor for numerous ligands, including glycosaminoglycans, fibrin, collagen, and several cytokines⁷. Fibronectin and its fragments are implicated in the degeneration of synovial joints⁸ and intervertebral discs⁹, are associated with the release of cytokines in chondrolysis³, and cause the cleavage of aggregan in cartilage degeneration⁴. Therefore, fibronectin fragments may themselves be pathogenic in addition to being secondary degradation products of other pathogenic processes⁸. Based on biochemical evidence, full-length fibronectin is involved in the formation of fibronectin-aggregan complex⁶, whereas previous studies have investigated the role of fibronectin fragments, which are not bound to any other degradation product^{10,11}.

Aggrecan

Aggrecan is a cartilage proteoglycan that, together with type-II collagen, is a major extracellular structural component of articular cartilage¹². Degradation of aggrecan by aggrecanases is thought to be an important event in cartilage degeneration¹³, and numerous specific aggrecan fragments have been purified from synovial fluid¹⁴. An increase in aggrecan fragments has been observed after knee injury and in association with osteoarthritis¹⁵. Aggrecan cleavage is induced by fibronectin fragments⁴, and certain aggrecan fragments are markers of joint degeneration, which differ among inflammatory, traumatic, acute, and chronic disease states¹⁶. Fragments of the G3 domain of aggrecan, the domain implicated in the present report, differ between cartilage disease states⁵ and demonstrate age-related increases in articular cartilage¹⁷.

Fibronectin-Aggrecan Complex

Aggrecan is a multidomain protein in which the G3 domain contains lectin sequences¹⁸. An interaction has been identified between lectin domains and fibronectin type-III (FN III) domains of tenascins¹⁹. This known interaction of fibronectin with lectins suggests that a complex could be formed between the fibronectin and aggrecan G3 domains. In addition to the known correlations between fibronectin, aggrecan, and cytokines^{3,4}, the relationship is further complicated by apparent cross-reactivity of the complex with some commercially available anti-IFN- γ antibodies⁶. However, the currently optimized immunoassay is specific for the fibronectin-aggrecan complex and does not efficiently detect either fibronectin or aggrecan alone in the absence of the complex⁶.

The present study had several limitations. Sample acquisition by means of needle aspiration is a variable clinical procedure that may result in a small volume of aspirate, a bloody aspiration, or the aspiration of a large effusion with unknown dilution effects on the quantification of candidate biomarkers²⁰. Although the present study was prospective, calculation of the sensitivity, specificity, and cutoff value for the study group as compared with the control group was performed post hoc. A much larger prospective study is required to confirm the biomarker cutoff value and clinical performance characteristics. However, the results of the present study suggest that the cutoff value is unlikely to significantly change given the wide disparities in levels between the groups. A reference standard/positive control for the fibronectin-aggrecan complex must be synthesized on a large scale in order to generate a standard curve by which the optical density at 450-nm optical wavelength can be converted to an absolute concentration. Such a standard curve likely will exhibit a sigmoidal shape with floor and ceiling effects typical of such curves. The effects of a standardized curve, along with characterization of the limit of detection in concentration units (pg/mL), might make the apparent separation between the study and control groups in terms of optical density units look less disparate. Furthermore, outcome studies must be performed to determine if the level of fibronectin-aggrecan complex predicts surgical response to arthroscopic partial meniscectomy and debridement.

The pathophysiology of degenerative joint disease is complex, and much of the current work regarding biomarkers

focuses on osteoarthritis irrespective of meniscal degeneration²¹⁻²³. In contrast, our inclusion criteria focused on meniscal abnormality as demonstrated by magnetic resonance imaging findings that correlated with physical examination findings in the absence of end-stage osteoarthrosis on radiographs. Such meniscal tears may be degenerative in nature, possibly constituting both a cause and effect of concomitant early-stage osteoarthritis and making a definitive distinction between the two disease entities elusive²⁴. However, our goal was to isolate subjects with knees that would be widely accepted as candidates for partial meniscectomy in light of current evidence-based indications²⁵⁻²⁷ in order to identify candidate biomarkers that could be correlated with surgical outcomes in future studies.

This long-term goal of utilizing biomarkers to distinguish knees with a symptomatic meniscal tear that is likely to respond to arthroscopic debridement from knees with osteoarthritis that is unlikely to respond to arthroscopic debridement is a critical one. It is widely believed by experienced surgeons that certain patients with a degenerative knee are much more likely to respond to arthroscopic debridement than others^{28,29}. Findings that increase the probability of success when debriding a meniscal tear that is seen on magnetic resonance imaging include the presence of joint-line tenderness correlating with meniscal stress testing³⁰; normal alignment and preservation of joint space height with radiographically mild disease³¹; and the absence of concomitant risk factors, including obesity, smoking, and chronic pain³². A number of articles have synthesized the available evidence for clinical decision-making²⁵⁻²⁷.

However, the results of these observational studies must be balanced against increasing level-I evidence that arthroscopic debridement of all patients with osteoarthritis results in no outcome differences compared with nonoperative management³³. At the present time, no level-I evidence clearly demonstrates the indications for arthroscopic partial meniscectomy³⁴, and further randomized studies are required^{28,29}. In addition to the clinical and imaging findings already highlighted, continued investigation of biomarkers that sharpen surgical indications and improve the functional outcome of surgery is important²⁵. Ideally, a clinically useful biomarker will distinguish an abnormality that is likely to respond to arthroscopic debridement from either a minimal abnormality that does not require surgery or an end-stage abnormality that is beyond arthroscopic treatment. The present preliminary results indicate that the fibronectin-aggrecan complex is involved in the process by which meniscal injury results in knee pain. If these findings are confirmed in future clinical outcome studies, the fibronectin-aggrecan complex may serve as a biomarker or future therapeutic target. ■

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