Longitudinal Serum and Urine Proteomic Signatures Predict Early Cartilage Change in MRI Following Arthroscopic Partial Meniscectomy

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Introduction: Arthroscopic partial meniscectomy (APM) is one of the most common orthopedic procedures, yet postoperative outcomes vary considerably. A subset of patients develops relatively rapid degenerative cartilage changes, and the underlying mechanisms remain unclear. Systemic biomarkers in serum and urine offer a minimally invasive means to monitor longitudinal molecular changes[1]; however, their dynamic association with APM outcomes remains underexplored. Early cartilage changes can be detected at short-term follow-up using high resolution MRI [2]. The objective of this study was to characterize proteomic changes in serum and urine samples from patients undergoing APM. We hypothesized that early postoperative proteomic changes would stratify patients at risk for early cartilage degeneration.

Methods: This pilot exploratory study initially enrolled 15 patients with isolated meniscus tears who underwent arthroscopic partial meniscectomy (APM). Five patients were lost to follow-up, leaving 10 patients (7 males and 3 females) with complete 1-year follow-up data. Each patient underwent morphologic MRI[3] and provided serum and urine samples at four time points: day of surgery (DOS), 2 months (T2), 6 months (T6), and 12 months (T12) postoperatively. Proteomic profiling was performed using high-resolution Liquid Chromatography–Tandem Mass Spectrometry (LC-MS/MS) with label-free quantification (LFQ). Patients were classified into early cartilage change or no early cartilage change groups based on predefined MRI criteria at T12 (An increase in Modified Noyes Score ≧ 1). Within each group, early postoperative changes were identified by comparing T2 to DOS using $|\log_2 FC| \geq 1$ and $p < 0.05$ as the primary threshold. Baseline (DOS) between-group differentially expressed proteins (DEPs) were evaluated and overlaps with early-change proteins were descriptively summarized to highlight candidates with potential early predictive value. To test whether candidate proteins exhibited different longitudinal trajectories between groups, we conducted linear mixed-effects models with a subject-level random intercept and fixed effects for group, time (categorical), and their interaction. The group×time interaction was the primary parameter of interest; a significant interaction indicates divergent trajectories over 1 year. Effect sizes with 95% confidence intervals were reported. Given the exploratory, small-sample design, analyses were restricted to candidate proteins and false discovery rate values were provided as supportive information.

Results: Baseline demographics and clinical characteristics were comparable between both groups, with no statistically significant differences. Although not statistically significant, study group(group with cartilage change at 12 months) patients exhibited a higher proportion of males (83% vs. 50%) and a higher prevalence of persistent synovitis at 12 months (67% vs. 25%). Proteomic profiling revealed distinct sets of surgery-sensitive proteins when comparing DOS to T2 within each outcome group. In serum, 12 proteins showed significant changes in the early cartilage change group (study group) and 66 in the no-change group (control group). In urine, 19 proteins changed significantly in the study group and 61 in the control group. To identify candidate biomarkers with potential early predictive value, we examined the intersection of surgery-sensitive proteins with baseline (DOS) between-group differences. At the same time, we searched the literature to determine whether these proteins had previously been associated with osteoarthritis (OA), synovitis, inflammation, or oxidative stress. In serum, three proteins emerged: VCP (valosin-containing protein), CFL1 (Cofilin-1), and S100A4. VCP decreased significantly from DOS to T2 in the control group and was also differentially expressed at DOS, consistent with its reported roles in cytoskeletal organization and stress responses. CFL1 and S100A4 both decreased significantly at T2 in both groups, although neither showed baseline differences; CFL1 has been implicated in cytoskeletal dynamics, and S100A4 has been linked to inflammatory cartilage degradation. In urine, two notable proteins were identified: CCL2 (Chemokine(C-C motif) ligand 2) and DCN (decorin**)**. Both increased significantly from DOS to T2 in control group, and also differentially expressed at DOS. CCL2 (MCP-1) is a well-established chemokine implicated in synovitis, while DCN regulates collagen fibrillogenesis and has been associated with cartilage degeneration. However, longitudinal mixed-effects modeling did not reveal significant group × time interactions over 12 months.

Discussion: This exploratory study demonstrates the feasibility of systemic proteomic profiling to identify surgery-sensitive proteins following APM and highlights several candidates with potential relevance to early cartilage outcomes. Importantly, VCP, CFL1, and S100A4 in serum, as well as CCL2 and DCN in urine, displayed early postoperative changes and are supported by prior evidence linking them to osteoarthritis-related inflammation or cytoskeletal remodeling. Although these proteins did not exhibit significant long-term trajectory differences, their early postoperative responsiveness may nonetheless provide predictive insights and underscore their potential utility as biomarkers of increased risk for subsequent cartilage degeneration. In conclusion, distinct serum and urine protein signatures were associated with early MRI-based cartilage changes at one year, suggesting potential prognostic value. These findings warrant validation in larger cohorts with statistical correction for multiple testing.

Significance: Identification of early systemic proteomic markers may enable postoperative risk stratification and inform management strategies to prevent progression of cartilage degeneration in at-risk patients.

Reference: 1) Ewing, Michael A et al. Am J Sports Med. 2022 (PMID: 35834869). 2) Collins, Jamie E et al. Arthritis Care Res. 2020 (PMID: 30932360). 3) Argentieri, Erin C et al. J Orthop Res.2024 (PMID: 39177306).

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