Synovial Fluid Biomarker Alternatives: Can Plasma and Urine Samples Shed Light on the Post-Traumatic Intra-articular Microenvironment?

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INTRODUCTION: Injuries to the meniscus and anterior cruciate ligament (ACL) alter knee anatomy and disrupt normal kinematics. More recent studies have also demonstrated the changes to the joint microenvironment with recruitment of both pro- and anti-inflammatory cytokines as a result of an injury. With the ability to be quantitatively measured and the potential for longitudinal tracking, biomarkers have been hailed as a potential means of following pathology progression and treatment response. While synovial fluid biomarker analysis can provide a description of the intra-articular microenvironment, arthrocentesis is a procedure not without complications. The purpose of this study was to analyze the association of plasma and urine biomarkers with synovial fluid biomarkers that have previously shown to be markers of the post-injury intra-articular response.

METHODS: This institutional review board approved study was a retrospective review of a prospectively collected database of patients enrolled between February 2012 and September 2017. Patients undergoing primary knee arthroscopy were invited to provide synovial fluid, blood, and urine samples prior to surgery. Informed consent was obtained from all patients. Indications for surgery in this cohort included ACL tear, meniscus tear, recurrent patellofemoral instability, and osteochondral defect. The concentration of 10 synovial fluid biomarkers was measured. The biomarkers were selected based on previous studies and consisted of RANTES, IL-6, MMP-3, MIP-1β, TIMP-1, TIMP-2, IL-1Ra, VEGF, MCP-1, and bFGF. Plasma and urine biomarkers were selected based on the previously demonstrated association with inflammatory processes and cartilage degradation. Plasma was analyzed for the concentration of RAGE, CTX-I (CrossLaps), and CRP. Urine was analyzed for the concentration of beta CTX and CTX-II (CartiLaps). Samples were analyzed using a multiplex magnetic bead immunoassay. Spearman correlations and log-transformed Pearson correlations of the concentration of synovial fluid and plasma/urine biomarkers were performed. Post-hoc analysis using Bonferroni correction was performed to account for multiple testing.

RESULTS: One hundred and fifty one patients were included in the analysis. Forty three patients (28.5%) had combined ACL and meniscus tears, 18 patients (11.9%) had isolated ACL tears, 76 patients (50.3%) had isolated meniscus tears, and 14 patients (9.3%) had chondral lesions with intact soft tissue. Mean age for all patients was 41.43 +/- 13.50 years. Due to the non-parametric nature of biomarker concentrations, the associations between biomarkers was first analyzed using a series of Spearman correlations. There were several moderate and strong positive correlations between synovial fluid biomarkers. The strongest associations were between VEGF and MCP-1 ($r = 0.78$, $p < 0.001$), VEGF and MIP-1β ($r = 0.70$, $p < 0.001$), VEGF and IL-6 ($r = 0.67$, $p < 0.001$), and IL-6 and MCP-1 ($r = 0.68$, $p < 0.001$). There were significant negative correlations between bFGF and IL-6 ($r = -0.43$, $p < 0.001$), MCP-1 ($r = -0.43$, $p < 0.001$), MMP-3 ($r = -0.37$, $p < 0.001$), MIP-1β ($r = -0.39$, $p < 0.001$), TIMP-1 ($r = -0.37$, $p < 0.001$), and VEGF ($r = -0.52$, $p < 0.001$). There was a significant negative correlation between plasma CRP and synovial fluid RANTES ($r = -0.21$, $p = 0.016$). There was a significant positive correlation plasma CRP and synovial fluid TIMP-2 ($r = 0.19$, $p = 0.030$). However, after Bonferroni correction, there were no statistically significant Spearman correlations between synovial fluid biomarkers and biomarkers in plasma or urine. The association between biomarker levels was also analyzed by log-transforming the data and performing Pearson correlations. There were no statistically significant log-transformed Pearson correlations between synovial fluid biomarkers and biomarkers in plasma or urine.

DISCUSSION: The utilization biomarkers found in blood and urine plays a well-established role in the diagnosis and treatment of many diseases. The ease and limited skill required in the collection of plasma and urine samples make them ideal targets worth investigating as alternatives or complements to synovial fluid biomarker analysis. However, the changes in the molecular milieu following knee injury are largely contained within the intra-articular space. Our analysis demonstrated no association between the tested plasma or urine biomarkers and synovial biomarkers that have been shown to accurately reflect post-injury changes.

SIGNIFICANCE/CLINICAL RELEVANCE: In the post traumatic knee, there is no substitute for synovial fluid biomarker analysis. While blood and urine samples are significantly easier to collect and can help to provide the orthopaedic surgeon with a more global perspective on a patient's inflammatory status, an assessment of the intra-articular microenvironment requires an evaluation of the synovial fluid and associated mediators in direct contact with the injury site.

Figure 1: Correlogram demonstrating strength of Spearman correlation between all biomarkers tested. * denotes a statistically significant correlation after Bonferroni correction.