Intra-Articular Vascular Endothelial Growth Factor and Matrix Metalloproteinase-1 are the Primary Drivers of Worse Baseline Knee Injury and Osteoarthritis Outcome Score Symptoms and Quality of Life Subscores at Time of Knee Chondroplasty

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INTRODUCTION: Biomarkers are a topic of interest in orthopaedics in the setting of osteoarthritis and patients undergoing knee arthroscopy for any reason. However, in patients undergoing knee arthroscopy for chondral defects, the influence of cytokines on patient pain and function is not fully understood. The purpose of this study is to investigate the concentrations of synovial inflammatory cytokines in patients undergoing arthroscopic chondroplasty for chondral defects in the knee and correlate those cytokine levels with baseline patient reported outcome measures (PROs) and defect characteristics. We hypothesized that the synovial cytokine environment will correlate with patient symptoms more so than baseline defect characteristics.

METHODS:

Sixty patients 18-50 years old undergoing arthroscopic chondroplasty for knee cartilage defects were enrolled. Patients were assigned preoperative Knee injury and Osteoarthritis Outcome Score (KOOS) and International Knee International Knee Documentation Committee (IKDC) Subjective Knee Forms. Preoperative magnetic resonance images were used to calculate AMADEUS (Area Measurement And Depth Underlying Structure) scores.1 All patients received a successful synovial fluid aspiration just prior to initiation the arthroscopic procedure. The number of defects, total defect area, and ICRS grades were recorded based on intraoperative assessment. Patients with concomitant procedures beyond partial meniscectomy were excluded.

Multiplex ELISA analyzed aspirations for: PDGF-BB, CCL-5/RANTES, MMP-3, MMP-1, EGF, VEGF, IL-1a, FGF-2, CCL-2, BMP-2, and aggrecan. Univariate correlation testing was used to assess significance between cartilage defect characteristics, PROs, and cytokine concentrations **(Figure 1)**. The Akaike Information Criterion (AIC) was utilized to select the best-fit multivariate regression model using the 4 most significant independent variables for each cytokine **(Figure 2)**. AIC best-fit modeling was repeated for each PRO that had at least two significant cytokine associations on univariate testing **(Figure 3)**. Significance was set at $P<0.05$.

RESULTS:

MMP-1 had a positive correlation with number of defects treated ($P=0.016$) and negative correlation with KOOS quality of life (QOL) subscores ($P=0.035$; R2 =0.173). VEGF was positively correlated with defects treated ($P=0.005$) and negatively correlated with KOOS Symptoms scores ($P=0.035$; R2 =0.225). The treatment of multiple defects was an independent predictor of elevated IL-1a ($P=0.002$, R2 =0.202). CCL-2 was positively correlated with multiple defects ($P=0.012$) and negatively with KOOS QOL ($P=0.016$, R2 =0.173). Female sex was correlated with higher concentrations of MMP-3 ($P=0.007$, R2 =0.144), FGF ($P=0.012$, R2 =0.178), and BMP-2 ($P=0.008$; R2 = 0.169). BMP-2 was negatively correlated with KOOS Symptom ($P=0.019$).

The primary driver of preoperative KOOS Symptoms scores on multivariate analysis was VEGF ($P=0.023$, R2 =0.120), influencing patient symptoms beyond defect characteristics. Similarly, KOOS QOL was independently correlated with MMP-1 concentration ($P= 0.045$, R2 =0.079), more so than ICRS grade **(Figure 3)**.

DISCUSSION AND CONCLUSION: Multivariate regression analysis revealed that elevated MMP-1 was the primary driver of worse preoperative KOOS QOL scores, more so than defect characteristics such as the number of lesions treated. Similarly, worse preoperative KOOS Symptoms scores were more strongly correlated with elevated VEGF concentrations rather than defect ICRS grades. Our study demonstrated that synovial fluid cytokines appear to be the primary drivers of patients' subjective assessments of their pain and function preoperatively.

Figure 1. Results from univariate correlation testing between PRO's, defect characteristics, demographic info, and intraoperative synovial fluid aspiration. A rho >0 represents a positive correlation, while rho <0 represents negative correlation.
* Signifies statistical significance. Red highlight = significant negative correlation. Green highlight = significant positive correlation. Yellow highlight = significant difference between groups, rho not applicable.

Figure 2. AIC best-fit modeling determined the greatest amount of variation using the fewest possible independent variables for each cytokine. Variables found to be independently significant by subsequent multivariate regression analysis are marked with bold with *.

Figure 3. Multivariate regression modeling based on AIC best-fit models for the PRO scores with at least two significant correlations to synovial cytokine concentrations based on univariate analyses. Variables found to be independently correlated with PRO scores on multivariate regression analysis are marked in bold with *.

Patient Reported Outcome Score	KOOS Symptoms	KOOS QOL
Independent Variables Analyzed	1. Total Defect Area 2. VEGF 3. Number of Defects 4. MMP-1	1. IL-1 2. MMP-1 3. Aggrecan 4. ICRS Grade
AIC Best-Fit Model (p-value)	**VEGF (0.023)*** Total Area (0.186)	**MMP-1 (0.045)*** ICRS Grade (0.151)
Adjusted R2	0.120	0.079