



Effect of Inflammatory Biomarkers on Patient Symptomatic State at Time of Knee Chondroplasty

Tristan J. Elias,^{*†} MD, Erik Haneberg,^{*‡} BS, Richard Danilkowicz,[§] MD, Navya Dandu,^{||} MD, Johnathon R. McCormick,^{*} MD, Alexandra Walker,^{*} BS, Zachary Wang,^{*} BS, Kevin Credille,[¶] MD, Jay Amin,^{*} BS, Brian J. Cole,^{*} MD, MBA , and Adam B. Yanke,^{*#} MD, PhD 

Investigation performed at Rush University Medical Center, Chicago, Illinois, USA

Background: In patients undergoing knee arthroscopy for chondral defects, the influence of cytokines on patient pain and function is not fully understood.

Purpose: 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 (PROMs) and defect characteristics.

Study Design: Case series; Level of evidence, 4.

Methods: Patients undergoing arthroscopic chondroplasty for knee cartilage defects were assigned preoperative Knee injury and Osteoarthritis Outcome Score (KOOS) and International Knee Documentation Committee (IKDC) Subjective Knee Forms. All patients received a successful synovial fluid aspiration just before initiation of the arthroscopic procedure, and concentrations of 11 cytokines of interest were measured. The number of defects, total defect area, and International Cartilage Regeneration & Joint Preservation Society (ICRS) grades were recorded based on intraoperative assessment. Univariate correlation testing was used to assess significance between cartilage defect characteristics, PROM scores, and cytokine concentrations. The Akaike information criterion was used to select the best-fit multivariate regression model to determine the primary influence on baseline PROMs.

Results: A total of 60 patients age 18 to 55 years were included. Matrix metalloproteinase 1 (MMP-1) had a positive correlation with number of defects treated ($P = .016$) and negative correlation with KOOS Quality of Life (QOL) subscale scores ($P = .035$; $R^2 = 0.173$). Vascular endothelial growth factor (VEGF) was positively correlated with defects treated ($P = .005$) and negatively correlated with KOOS Symptoms scores ($P = .035$; $R^2 = 0.225$). The treatment of multiple defects was an independent predictor of elevated interleukin 1 α (IL-1 α) ($P = .002$; $R^2 = 0.202$). C-C chemokine ligand 2 (CCL-2) was positively correlated with multiple defects ($P = .012$) and negatively with KOOS QOL ($P = .016$; $R^2 = 0.173$). Female sex was correlated with higher concentrations of MMP-3 ($P = .007$; $R^2 = 0.144$), fibroblast growth factor 2 (FGF-2) ($P = .012$; $R^2 = 0.178$), and bone morphogenetic protein 2 (BMP-2) ($P = .008$; $R^2 = 0.169$). BMP-2 was negatively correlated with KOOS Symptoms ($P = .019$). The primary driver of preoperative KOOS Symptoms scores on multivariate analysis was VEGF ($P = .023$; $R^2 = 0.120$). Similarly, KOOS QOL was independently correlated with MMP-1 concentration ($P = .045$; $R^2 = 0.079$).

Conclusion: Elevated MMP-1 was the primary driver of worse preoperative KOOS QOL scores on multivariate analysis, more so than defect characteristics. Similarly, worse preoperative KOOS Symptoms scores were more strongly correlated with elevated VEGF concentrations rather than defect ICRS grades. Other individual factors such as a larger number of defects and female sex were independently correlated with a more inflammatory synovial profile of the patient.

Keywords: knee; cartilage; inflammation; cytokines; chondroplasty; synovial fluid

Articular cartilage defects are a prevalent pathology, present in >60% of knees undergoing arthroscopy, and have

the potential to cause joint effusions, pain, and mechanical symptoms similar to knee osteoarthritis.²⁰ Given the poor vascularity of articular cartilage and limited proliferative capacity of chondrocytes after injury, focal damage to cartilage generally leads to further degenerative changes, progression of pain and disability, and eventual osteoarthritis of the joint.^{17,21}

Arthroscopic knee chondroplasty is commonly performed as the first-line surgical treatment for chondral defects <2 cm².^{15,18,30} Considered safe and minimally invasive, chondroplasty can be an effective initial treatment for these lesions; however, the procedure has variable progression to cartilage transplant.^{1,5,6,43,46,48} Yanke et al⁴⁸ found that preoperative magnetic resonance imaging (MRI) findings, structural characteristics, and baseline patient-reported outcome measures (PROMs) can help predict which patients may progress to early osteochondral allograft transplantation. However, little is known about how the inflammatory microenvironment of the knee contributes to the patient symptomatic state at time of chondroplasty and how this may contribute to patient-specific care and potentially lead to earlier, less invasive interventions for patients.

Synovial fluid cytokines are a popular area of research as potential biomarkers as they relate to ligamentous and meniscal injuries and their progression to posttraumatic osteoarthritis.^{22,32,45} The microenvironment of the knee has been shown to change in the setting of intra-articular injuries, with alterations in concentrations of cytokines affecting gene expression or the recruitment of growth factors and inflammatory cells.^{4,10,26,29,31,33,36} The extracellular matrix (ECM) of healthy cartilage undergoes a degree of turnover to maintain homeostasis; therefore, changes in the balance of catabolic and anabolic biomarkers and their correlation to clinical measures are important targets for understanding the factors affecting patients' clinical status and outcomes.³⁵ Cuéllar et al¹³ found that higher concentrations of interleukin 6 (IL-6) and monocyte chemoattractant protein 1 (MCP-1) at time of knee arthroscopy were correlated with persistent pain at final follow-up, whereas elevated matrix metalloproteinase 3 (MMP-3) concentrations were correlated with worse baseline pain scores. The Cleveland Clinic Sports Knee Group (CCSKG)¹¹ found that both patient characteristics and structural damage such as synovitis may predict patients' pain and function before knee arthroscopy. However, Cuéllar et al included patients undergoing arthroscopy for any cause, including ligamentous injury, and the CCSKG did not include analysis of synovial biomarkers and their contribution to patient symptomatic state.

Therefore, the purpose of this study was 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 PROMs and defect characteristics. We hypothesized that inflammatory biomarkers would contribute to patients' subjective pain and functional status when controlling for confounders and that synovial fluid cytokine concentrations would be related to both patient characteristics and structural defect characteristics.

METHODS

Patient Selection

A query was performed of a prospectively maintained database for patients undergoing isolated arthroscopic knee chondroplasty between January 2018 and December 2020 at a single institution with 1 of 2 senior surgeons (B.J.C. and A.B.Y.). All eligible patients had previously consented for a prospective study that involved intraoperative synovial fluid aspiration of the operative knee. The study was approved by the institutional review board. Exclusion criteria included age <18 or >55 years, osteoarthritis of Kellgren-Lawrence grade 3 or higher on preoperative radiographs, and history of inflammatory arthropathy (eg, rheumatoid arthritis). Advanced arthritic changes to the joint and inflammatory conditions were excluded due to the possible confounding effects of these disease states on potential for improvement in patient-reported outcomes.^{12,19} Additionally, inflammatory arthropathy conditions traditionally have an altered microenvironment driven by synovium and thus are not expected to be altered by chondroplasty. To be included, patients must have undergone a successful aspiration, completed preoperative PROMs, and had a preoperative MRI study.

Synovial Fluid Collection and Proteomic Analysis

Aspirations were taken intraoperatively with the patient supine under sterile conditions before the initiation of

#Address correspondence to Adam B. Yanke, MD, PhD, Rush University Medical Center, 1611 W Harrison St, St 300, Chicago IL 60612, USA (email: Adam.yanke@rushortho.com; cartilage.restoration@rushortho.com).

*Rush University Medical Center, Chicago, Illinois, USA.

†UTMB Health, Galveston, Texas, USA.

‡Case Western Reserve University, Cleveland, Ohio, USA.

§Emory University, Atlanta, Georgia, USA.

||Allegheny General Hospital, Pittsburgh, Pennsylvania, USA.

*Houston Methodist, Houston, Texas, USA.

Submitted June 4, 2025; accepted January 11, 2026.

One or more of the authors has declared the following potential conflict of interest or source of funding: A.B.Y. is a paid consultant for AlloSource, JRF Ortho, Patient IQ, and Icarus; is an unpaid consultant for Sparta Biomedical and Stryker; holds stock or stock options with Sparta Biomedical, Stryker, and Icarus; and is an associate editor for *AJSM*. B.J.C. receives research support from Aesculap/B.Braun, Arthrex, and *Operative Techniques in Sports Medicine*; is on the editorial or governing board for *American Journal of Sports Medicine*; is a paid consultant for Arthrex; receives IP royalties from Arthrex and *Journal of the American Academy of Orthopaedic Surgeons*; is a board or committee member for the Arthroscopy Association of North America; holds stock or stock options in Elsevier Publishing and Ossio; is on the editorial or governing board of JRF Ortho; receives other financial or material support from the National Institutes of Health (NIAMS & NICHD); receives publishing royalties or financial or material support from Ossio. This work was supported by Vericel.

TABLE 1
Roles of the Synovial Fluid Biomarkers Analyzed^a

Biomarker	Role	Lower Limit, pg/mL	Upper Limit, pg/mL
MMP-1	Collagenase that degrades triple-helical fibrillar collagen that is fundamental in bone and ligaments. ⁹	42.96	10,440
MMP-3	Small protease that degrades segments of the ECM. Its active form is a marker of synovial inflammation and cartilage turnover in inflammatory joint diseases. ⁹	71.73	17,430
EGF	Stimulates transcription of growth-related genes, helps maintain the superficial cartilage layer, and prevents osteoarthritis initiation. ²⁴	8.85	2150
VEGF	Induces ECM remodeling, angiogenesis, and bone formation. Increased expression has been shown to correlate with increased osteoarthritis severity. ⁴²	6.71	1630
PDGF-BB	Promotes mesenchymal cell proliferation and cartilage matrix production. ²⁸	12.18	2960
FGF-2	Degrades articular cartilage via upregulation of matrix-degrading enzyme production and inhibition of proteoglycan synthesis. ¹⁶	1.40	340
IL-1 α	Stimulates the synthesis and recruitment of numerous biomarkers and enzymes involved in articular inflammation and cartilage destruction. ²³	4.77	1160
BMP-2	Stimulates chondrogenesis through the proteoglycan synthesis and ECM turnover. ⁷	0.00	3470
CCL-2	Recruits monocytes to induce inflammation and cartilage damage in osteoarthritis. ³⁸	28.68	6970
CCL-5/RANTES	Chemokine that attracts leukocytes to propagate inflammation and cartilage destruction in osteoarthritis. ²	16.95	4120
Aggrecan	Large proteoglycan that contributes to cartilage's structural integrity. ⁴¹	324.86	78,940

^aBMP-2, bone morphogenetic protein 2; CCL-2, C-C chemokine ligand 2; CCL-5, C-C chemokine ligand 5/RANTES; EGF, epidermal growth factor; FGF-2, fibroblast growth factor 2; ECM, extracellular matrix; IL-1 α , interleukin 1 α ; MMP-1, matrix metalloproteinase 1; MMP-3, matrix metalloproteinase 3; PDGF, platelet-derived growth factor; VEGF, vascular endothelial growth factor.

arthroscopy. Aspiration was performed from the superolateral approach with an 18-gauge needle after skin preparation with alcohol swab and subcutaneous injection of 10 mL of 2% lidocaine. Synovial fluid samples were centrifuged, and the supernatant was stored at -80°C until analysis. The synovial fluid samples were analyzed for the following inflammatory biomarkers with multiplex enzyme-linked immunosorbent assay: interleukin 1 α (IL-1 α), epidermal growth factor (EGF), vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), fibroblast growth factor 2 (FGF-2), C-C chemokine ligand 2 (CCL-2), C-C chemokine ligand 5/RANTES (CCL-5), bone morphogenetic protein 2 (BMP-2), matrix metalloproteinase 1 (MMP-1), MMP-3, and aggrecan. These synovial biomarkers were chosen given their known roles in cartilage degeneration as well as their presence in commercially available testing kits (Table 1). The samples were digested 1:1 with 3 mg/mL hyaluronidase before execution of the assay in accordance with the manufacturer's protocol. A minimum of 3 μL was required for analysis. Samples were run in duplicate with normalization to the total aspirate volume but were not normalized to total protein concentration or any factor other than aspirate volume. Samples were analyzed on a FlexMAP 3D system (Luminex) using xPONENT software (Version 4.3.229.0). Analytes were measured using a Human Magnetic Luminex 2-Plex kit (R&D Systems; LXSAHM-02) and a Human Magnetic Luminex 9-Plex kit (R&D Systems; LXSAHM-09). Upper and lower limits of detection are included in Table 1.

Patient-Reported Outcome Measures

Patients were assigned preoperative International Knee Documentation Committee (IKDC) and Knee Injury and Osteoarthritis Outcome Score (KOOS) subjective forms, including Activities of Daily Living (ADL), Pain, Quality of Life (QOL), Sports, Symptoms, and Joint Replacement (JR) subscales. All questionnaires were administered via a secure web-based platform, and study personnel did not assist patients during completion. Patients were asked to record how long they had experienced symptoms before their operative date and what prior injections, if any, they had received to the operative knee.

Defect Characteristic Measurements

The number of defects, total defect area, and macroscopic International Cartilage Regeneration & Joint Preservation Society (ICRS) grades were recorded based on intraoperative assessment.⁸ A single orthopaedic surgery senior resident (J.R.M.) reviewed each patient's preoperative MRI scan to assign an Area Measurement and Depth & Underlying Structures (AMADEUS) score.²⁵ This scoring system assigns a total score between 0 and 100 based on subcategories assessing cartilage defect size, defect depth/morphology, and subchondral bone quality, with lower total scores representing more severe defects.²⁵ MRI measurements were performed manually within the hospital's Picture Archiving and Communication System.

Statistical Analysis

All statistical analyses were performed with RStudio (Version 1.2.1335; R Foundation for Statistical Computing). Nonparametric tests were used to avoid assumptions of normality. Univariate Spearman rank correlation testing was used to assess significance between continuous data for demographic characteristics, cartilage defect characteristics, PROM scores, and cytokine concentrations. Mann-Whitney *U* tests or Kruskal-Wallis tests were used for categorical variables. The Akaike information criterion (AIC) was used to select the best-fit multivariate linear regression model that offered the greatest amount of variation using the fewest possible independent variables. Given our sample size of 60 and the statistical assumption that a minimum of 15 observations per predictor were considered sufficient for analysis, we input the 4 independent variables found to be most significantly associated with PROM scores on univariate testing into a multivariate analysis to control for confounders. Only PROMs with at least 2 significant univariate correlations to aspirate cytokines were included on multivariate regression analysis. This was repeated for each cytokine to evaluate what variables most influence these synovial biomarkers. All testing was 2-sided, and significance was set at $P < .05$.

RESULTS

Patient Demographic Characteristics

A total of 60 patients who underwent arthroscopic knee chondroplasty between January 2018 and December 2020 with a successful synovial fluid aspiration and baseline PROM scores were included for analysis. Of these, 33 patients (55%) were male, the mean age of the cohort was 33.0 ± 8.3 years (range, 19.3-55.6 years), and the mean body mass index was 28.9 ± 6.4 (range, 17.7-48.7). A total of 29 (48.3%) patients underwent some concomitant procedure. Sixteen patients received concomitant partial meniscectomy, 5 patients received microfracture or osteochondritis dissecans drilling, and 11 patients received concomitant loose body excision, synovectomy, or fat pad excision. Single chondral defects were detected in 38 patients, and 22 patients had multiple chondral defects. In total, the sample entailed 30 patellar, 28 trochlear, 21 medial femoral condyle, 11 lateral femoral condyle, and 2 lateral tibial plateau lesions, for a total of 92 chondral lesions treated with chondroplasty.

The mean duration of symptoms before surgery was 3.8 ± 4.7 years (range, 2 months to 22 years). Nonoperative treatment with injections was pursued with 43 of the 60 patients. Of these 43 patients, 21 patients had a single injection, 14 patients had 2 injections, 4 patients had 3 injections, and 4 patients had ≥ 4 injections. Stratifying preoperative injections by type, 23 patients received steroid, 7 patients received hyaluronic acid, 9 patients had multiple injections with at least 1 steroid and 1 hyaluronic acid injection, and 4 patients had injection regimens with at least 1 injection being platelet-rich plasma. The mean

time from the last injection to arthroscopy date was 7.8 ± 11.9 months. Of the 60 patients, 31 received at least 1 surgery before the chondroplasty that qualified them for inclusion in this study. Prior surgeries included anterior cruciate ligament (ACL) reconstruction, medial collateral ligament (MCL) repair, meniscectomy, meniscal repair, chondroplasty, microfracture, medial patellofemoral ligament (MPFL) reconstruction, and tibial tubercle osteotomy.

Cytokine Correlations

Results from univariate correlation testing of the independent variables of interest against inflammatory and chondrogenic biomarkers from intraoperative synovial fluid aspirations are presented in Table 2.

MMP-1 and MMP-3. Higher concentrations of MMP-1 were significantly correlated with lower baseline KOOS Symptoms ($P = .026$; $\rho = -0.30$) and KOOS QOL ($P = .025$; $\rho = -0.31$) scores. MMP-1 was additionally positively correlated with total defect area on intraoperative assessment ($P = .012$; $\rho = 0.34$) and the number of defects ($P = .035$). MMP-3 was significantly correlated only with patient sex, being found in higher concentrations in female compared with male patients ($P = .014$).

VEGF, EGF, and FGF-2. Higher concentrations of VEGF were correlated with worse baseline KOOS JR ($P = .017$; $\rho = -0.32$) and KOOS Symptoms ($P = .002$; $\rho = -0.41$) scores, a larger total defect area ($P = .009$; $\rho = 0.352$), and a larger number of cartilage defects ($P = .002$), including when evaluated as a binary value of single versus multiple defects ($P = .004$). Synovial EGF was only positively correlated with AMADEUS score on preoperative MRI ($P = .042$; $\rho = 0.27$). FGF-2 concentrations were higher in female patients ($P = .014$) and patients who did not require a concomitant procedure at time of chondroplasty ($P = .020$).

CCL-2. Elevated synovial CCL-2 was correlated with lower preoperative KOOS ADL scores ($P = .049$; $\rho = -0.27$) and the treatment of multiple chondral defects ($P = .015$).

IL-1 α and Aggrecan. Elevated IL-1 α and aggrecan were both correlated with worse preoperative KOOS QOL scores ($P = .017$, $\rho = -0.32$ and $P = .032$, $\rho = -0.29$, respectively). IL-1 α was additionally higher in patients being treated for multiple defects ($P = .037$).

BMP-2. BMP-2 concentration was found to be significantly higher in female patients ($P = .040$). No other significant correlations were found.

PDGF and CCL-5. No significant correlations were found between PDGF or CCL-5 and the variables of interest.

Patients who received an injection before surgery exhibited significantly lower baseline MMP-1 concentrations compared with those who did not (median 7416 vs 13,914; $P = .016$), whereas no other cytokines differed between groups (Appendix Table A1, available in the online version of this article).

Among patients who received an injection, time from injection to surgery was inversely correlated with aggrecan concentration (Spearman $\rho = -0.36$; $P = .03$). The

TABLE 2
Univariate Correlation Testing Against Inflammatory and Chondrogenic Biomarkers
From Intraoperative Synovial Fluid Aspiration^a

Statistical Test Used	Independent Variable	PDGF	CCL-5	MMP-3	MMP-1	EGF	VEGF	IL-1 α	FGF-2	CCL-2	BMP-2	Aggrecan
Spearman correlation	IKDC	$P = .616$	$P = .749$	$P = .781$	$P = .091$	$P = .616$	$P = .828$	$P = .670$	$P = .380$	$P = .938$	$P = .824$	$P = .575$
Spearman correlation	KOOS Pain	$\rho = -0.073$	$\rho = -0.047$	$\rho = -0.041$	$\rho = -0.244$	$\rho = -0.074$	$\rho = -0.032$	$\rho = -0.062$	$\rho = -0.128$	$\rho = -0.011$	$\rho = -0.033$	$\rho = -0.084$
Spearman correlation	KOOS Symptoms	$P = .307$	$P = .323$	$P = .886$	$P = .175$	$P = .295$	$P = .063$	$P = .411$	$P = .976$	$P = .143$	$P = .712$	$P = .756$
Spearman correlation	KOOS ADL	$\rho = -0.142$	$\rho = 0.137$	$\rho = -0.020$	$\rho = -0.187$	$\rho = -0.145$	$\rho = -0.254$	$\rho = -0.114$	$\rho = 0.004$	$\rho = -0.202$	$\rho = -0.051$	$\rho = -0.043$
Spearman correlation	KOOS Sports	$P = .739$	$P = .592$	$P = .493$	$P = .026^b$	$P = .885$	$P = .002^b$	$P = .293$	$P = .225$	$P = .349$	$P = .295$	$P = .555$
Spearman correlation	KOOS QOL	$\rho = 0.046$	$\rho = 0.075$	$\rho = 0.095$	$\rho = -0.302$	$\rho = 0.020$	$\rho = -0.406$	$\rho = -0.146$	$\rho = 0.168$	$\rho = -0.130$	$\rho = 0.145$	$\rho = -0.082$
Spearman correlation	KOOS JR	$P = .332$	$P = .291$	$P = .539$	$P = .095$	$P = .325$	$P = .070$	$P = .356$	$P = .706$	$P = .049^b$	$P = .960$	$P = .472$
Spearman correlation	Total defect area	$\rho = -0.135$	$\rho = 0.146$	$\rho = -0.086$	$\rho = -0.230$	$\rho = -0.137$	$\rho = -0.249$	$\rho = -0.128$	$\rho = -0.053$	$\rho = -0.269$	$\rho = -0.007$	$\rho = -0.100$
Spearman correlation	AMADEUS Score	$P = .628$	$P = .568$	$P = .817$	$P = .057$	$P = .430$	$P = .100$	$P = .442$	$P = .974$	$P = .476$	$P = .851$	$P = .906$
Spearman correlation	ICRS grade	$\rho = -0.067$	$\rho = -0.080$	$\rho = 0.032$	$\rho = -0.261$	$\rho = -0.110$	$\rho = -0.226$	$\rho = -0.107$	$\rho = 0.005$	$\rho = -0.099$	$\rho = -0.026$	$\rho = -0.016$
Spearman correlation	Age	$P = .252$	$P = .256$	$P = .577$	$P = .025^b$	$P = .208$	$P = .260$	$P = .017^b$	$P = .393$	$P = .121$	$P = .320$	$P = .032^b$
Spearman correlation	No. of defects treated (single/multiple)	$\rho = -0.159$	$\rho = -0.157$	$\rho = -0.078$	$\rho = -0.306$	$\rho = -0.174$	$\rho = -0.156$	$\rho = -0.324$	$\rho = -0.118$	$\rho = -0.214$	$\rho = -0.138$	$\rho = -0.293$
Spearman correlation	Sex (female/male)	$P = .518$	$P = .583$	$P = .851$	$P = .121$	$P = .739$	$P = .049^b$	$P = .324$	$P = .729$	$P = .122$	$P = .809$	$P = .656$
Spearman correlation	Concomitant procedure (yes/no)	$\rho = 0.089$	$\rho = 0.076$	$\rho = -0.026$	$\rho = -0.211$	$\rho = 0.046$	$\rho = -0.266$	$\rho = -0.136$	$\rho = 0.048$	$\rho = -0.211$	$\rho = 0.033$	$\rho = -0.061$
Kruskal-Wallis	No. of defects treated (single/multiple)	$P = .362$	$P = .216$	$P = .340$	$P = .012^b$	$P = .593$	$P = .009^b$	$P = .051$	$P = .153$	$P = .205$	$P = .735$	$P = .469$
Mann-Whitney U	Sex (female/male)	$\rho = -0.125$	$\rho = -0.170$	$\rho = -0.123$	$\rho = 0.340$	$\rho = -0.074$	$\rho = -0.352$	$\rho = -0.267$	$\rho = -0.197$	$\rho = -0.175$	$\rho = -0.047$	$\rho = 0.101$
Mann-Whitney U	Concomitant procedure (yes/no)	$P = .503$	$P = .174$	$P = .531$	$P = .273$	$P = .042^b$	$P = .532$	$P = .997$	$P = .220$	$P = .843$	$P = .301$	$P = .634$
Mann-Whitney U	No. of defects treated (1/2/3/4)	$\rho = 0.091$	$\rho = 0.184$	$\rho = 0.085$	$\rho = -0.149$	$\rho = 0.273$	$\rho = -0.085$	$\rho = 0.000$	$\rho = 0.167$	$\rho = -0.027$	$\rho = 0.141$	$\rho = -0.065$
Mann-Whitney U	Concomitant procedure (yes/no)	$P = .091$	$P = .106$	$P = .768$	$P = .426$	$P = .152$	$P = .600$	$P = .308$	$P = .148$	$P = .453$	$P = .518$	$P = .251$
Mann-Whitney U	Concomitant procedure (yes/no)	$\rho = -0.232$	$\rho = -0.222$	$\rho = -0.041$	$\rho = 0.111$	$\rho = -0.216$	$\rho = 0.073$	$\rho = -0.141$	$\rho = -0.106$	$\rho = 0.104$	$\rho = -0.091$	$\rho = -0.159$
Mann-Whitney U	Concomitant procedure (yes/no)	$P = .966$	$P = .309$	$P = .791$	$P = .116$	$P = .593$	$P = .077$	$P = .069$	$P = .638$	$P = .715$	$P = .513$	$P = .180$
Mann-Whitney U	Concomitant procedure (yes/no)	$\rho = 0.006$	$\rho = -0.134$	$\rho = -0.035$	$\rho = 0.205$	$\rho = 0.070$	$\rho = -0.230$	$\rho = -0.237$	$\rho = -0.062$	$\rho = 0.048$	$\rho = -0.086$	$\rho = 0.175$
Mann-Whitney U	Concomitant procedure (yes/no)	$P = .788$	$P = .957$	$P = .763$	$P = .076$	$P = .167$	$P = .004^b$	$P = .037^b$	$P = .825$	$P = .015^b$	$P = .282$	$P = .213$
Mann-Whitney U	Concomitant procedure (yes/no)	$P = .772$	$P = .999$	$P = .856$	$P = .035^b$	$P = .719$	$P = .002^b$	$P = .058$	$P = .725$	$P = .065$	$P = .226$	$P = .282$
Mann-Whitney U	Concomitant procedure (yes/no)	$P = .677$	$P = .298$	$P = .014^b$	$P = .647$	$P = .494$	$P = .712$	$P = .443$	$P = .014^b$	$P = .791$	$P = .040^b$	$P = .443$
Mann-Whitney U	Concomitant procedure (yes/no)	$P = .888$	$P = .767$	$P = .092$	$P = .747$	$P = .830$	$P = .930$	$P = .148$	$P = .020^b$	$P = .577$	$P = .587$	$P = .239$

^aRho >0 (green highlight) represents a positive correlation, whereas rho <0 (red highlight) represents negative correlation. ADL, Activities of Daily Living; AMADEUS, Area Measurement and Depth & Underlying Structures; BMP-2, bone morphogenetic protein 2; CCL-2, C-C chemokine ligand 2; CCL-5, C-C chemokine ligand 5/RANTES; EGF, epidermal growth factor; FGF-2, fibroblast growth factor 2; ICRS, International Cartilage Regeneration & Joint Preservation Society; IKDC, International Knee Documentation Committee; IL-1 α , interleukin 1 α ; JR, Joint Replacement; KOOS, Knee injury and Osteoarthritis Outcome Score; MMP-1, matrix metalloproteinase 1; MMP-3, matrix metalloproteinase 3; PDGF, platelet-derived growth factor; QOL, Quality of Life; VEGF, vascular endothelial growth factor.

^bSignifies a statistical association between independent and dependent variable for Spearman correlation tests or a statistical difference in cytokine concentration between groups for Kruskal-Wallis and Mann-Whitney U testing (yellow highlight).

remaining cytokine concentrations were not correlated with time from injection (Appendix Table A2, available online).

Finally, symptom duration demonstrated no significant associations with baseline cytokine concentrations (Appendix Table A3, available online).

Baseline PROMs

Results from univariate correlation testing of baseline PROMs against patient demographics and lesion characteristics are presented in Table 3. The correlations between PROMs and synovial biomarkers can again be found in Table 2.

Of the evaluated PROMs, only KOOS Symptoms (MMP-1, VEGF) and KOOS QOL (MMP-1, IL-1 α , aggrecan) were found to correlate with at least 2 intraoperative cytokine concentrations. KOOS Symptoms score was also found to be negatively correlated with articular defect size ($P = .002$; rho = -0.43) and was significantly worse in patients

treated for multiple defects (mean score, 46.05 \pm 7.89) compared with those treated for a single lesion (56.73 \pm 20.46; $P = .016$).

IKDC and KOOS Sports scores had no significant correlations to any studied variable including cytokine concentrations. Better KOOS Pain scores preoperatively were significantly correlated with smaller sized lesions ($P = .022$; rho = -0.32). Similarly, higher KOOS ADL scores were also correlated with smaller total defect areas ($P = .015$; rho = -0.34) in addition to fewer lesions requiring treatment (continuous scale, $P = .045$; binary scale, $P = .012$). KOOS JR was negatively correlated with total defect area ($P = .011$; rho = -0.35), and better scores were associated with fewer lesions treated (single defect, 58.28 \pm 15.29; multiple defects, 51.01 \pm 11.30; $P = .038$).

Clinically, patients who received an intra-articular injection preoperatively reported significantly better baseline KOOS QOL scores (median 25.0 vs 15.6; $P = .006$), whereas no differences were observed in IKDC or KOOS Pain, Symptoms, ADL, or Sports scores (Appendix Table A4, available online).

TABLE 3
Univariate Correlation Testing Between Patient-Reported Outcome Measures and Patient/Defect Characteristics^a

Statistical Test Used	Independent Variable	IKDC	KOOS Pain	KOOS Symptoms	KOOS ADL	KOOS Sports	KOOS QOL	KOOS JR
Spearman correlation	Total defect area	$P = .231$ $\rho = -0.320$	$P = .022^b$ $\rho = -0.430$	$P = .002^b$ $\rho = -0.430$	$P = .015^b$ $\rho = -0.340$	$P = .130$	$P = .645$	$P = .012^b$ $\rho = -0.350$
Spearman correlation	AMADEUS score	$P = .600$	$P = .668$	$P = .429$	$P = .586$	$P = .432$	$P = .669$	$P = .707$
Spearman correlation	ICRS grade	$P = .474$	$P = .879$	$P = .602$	$P = .701$	$P = .956$	$P = .173$	$P = .911$
Kruskal-Wallis	No. of defects treated (1/2/3/4)	$P = .504$	$P = .254$	$P = .121$	$P = .045^b$	$P = .312$	$P = .969$	$P = .135$
Mann-Whitney <i>U</i>	No. of defects treated (single/multiple)	$P = .214$	$P = .080$	$P = .016^b$	$P = .012^b$	$P = .092$	$P = .819$	$P = .038^b$
Mann-Whitney <i>U</i>	Sex (female/male)	$P = .144$	$P = .405$	$P = .821$	$P = .678$	$P = .161$	$P = .727$	$P = .427$
Mann-Whitney <i>U</i>	Concomitant procedure (yes/no)	$P = .936$	$P = .519$	$P = .747$	$P = .938$	$P = .972$	$P \geq .999$	$P = .641$

^aADL, Activities of Daily Living; AMADEUS, Area Measurement and Depth & Underlying Structures; ICRS, International Cartilage Regeneration & Joint Preservation Society; IKDC, International Knee Documentation Committee; JR, Joint Replacement; KOOS, Knee injury and Osteoarthritis Outcome Score; QOL, Quality of Life.

^bSignifies a statistical association between independent and dependent variable for Spearman correlation tests (red highlight for negative correlation, $\rho < 0$) or a statistical difference in cytokine concentration between groups for Kruskal-Wallis and Mann-Whitney *U* testing (yellow highlight). Only correlations reaching significance have their rho values listed.

Among patients who received an injection, time from injection to surgery was not associated with PROM scores (Appendix Table A5, available online). Similarly, symptom duration demonstrated no significant associations with PROM scores across all domains (Appendix Table A6, available online).

Multivariate Analysis

The 2 PROMs that were found to be significantly correlated with at least 2 cytokines were KOOS Symptoms and KOOS QOL. For KOOS Symptoms, the 4 independent variables in AIC best-fit analysis were total defect area, VEGF, number of defects, and MMP-1 concentration. The best-fit model for multivariate regression included VEGF concentration and total defect area, with VEGF retaining significance as the variable independently correlated with KOOS Symptom score ($P = .023$), as shown in Table 4.

The AIC best-fit model for KOOS QOL score included MMP-1 and ICRS grade. MMP-1 concentration was found to be significantly correlated with KOOS QOL score ($P = .045$), more so than ICRS grade.

Cytokines that were found to have significant correlations on multivariate testing were MMP-3 (female sex, $P = .007$), MMP-1 (number of defects, $P = .012$, and KOOS QOL score, $P = .016$), VEGF (number of defects, $P = .005$, and KOOS Symptoms score, $P = .035$), IL-1 α (number of defects, $P = .035$), FGF-2 (female sex, $P = .012$), CCL-2 (number of defects, $P = .012$, and KOOS QOL, $P = .016$), and BMP-2 (female sex, $P = .008$, and KOOS Symptoms, $P = .019$).

DISCUSSION

The most important finding of this study was that VEGF was the primary driver of preoperative KOOS Symptoms score in patients undergoing arthroscopic knee chondroplasty on multivariate analysis. Similarly, KOOS QOL was independently correlated with MMP-1 concentration in this patient population. In the case of both PROMs, multivariate regression analysis determined that these synovial fluid cytokines played a larger role in patient symptomatic state than demographic or articular cartilage defect characteristics.

These results are similar to the findings of Cuéllar et al,¹³ whose study group found correlations between synovial biomarkers and baseline patient symptomatic state. However, their results found that higher concentrations of MMP-3 at the time of knee arthroscopy were correlated with baseline patient pain on visual analog scale (VAS).¹³ Interestingly, our analysis found that a different MMP biomarker, MMP-1, was significantly correlated with subjective quality of life scores, although we found an association only between MMP-3 and female sex. Differences in the findings between studies may be attributed to a variety of factors. For one, Cuéllar et al included all patients indicated for arthroscopy, which included 30 patients with ACL injury and only 5 patients (7%) with isolated cartilage injury. The inclusion of patients with concurrent ligamentous injury limits the applicability of their findings to our cohort with a narrower focus on cartilage defects and the exclusion of any inflammatory arthropathies. Additionally, the subjective PROMs used differed between studies. KOOS subjective questionnaires cover

TABLE 4
Multivariate Regression Analysis of Synovial Cytokines and Patient-Reported Outcome Measures^a

	Independent Variables Analyzed	AIC Best-Fit Model (P)	Adjusted R ²
Cytokine			
PDGF-BB	KOOS Pain; KOOS ADL; KOOS QOL; ICRS grade	KOOS ADL (.063) ICRS grade (.9612)	0.032
CCL-5	ICRS grade; AMADEUS; KOOS QOL; KOOS ADL	ICRS Grade (.563) AMADEUS (.054) KOOS QOL (.267)	0.044
MMP-3	Sex; concomitant procedure; total defect area; KOOS Symptoms	Sex (.007) ^b Defect area (.825) KOOS Symptoms (.355)	0.114
MMP-1	No. of defects; KOOS QOL; KOOS Symptoms; KOOS Sports	No. of defects (.012) ^b KOOS QOL (.016) ^b	0.173
EGF	AMADEUS; KOOS QOL; KOOS Pain; KOOS ADL	AMADEUS (.056) KOOS QOL (.141)	0.068
VEGF	No. of defects; KOOS Symptoms; defect area; KOOS JR	No. of defects (.005) ^b KOOS Symptoms (.035) ^b Defect area (.178)	0.225
IL-1 α	KOOS QOL; No. of defects; concomitant procedure; ICRS grade	No. of defects (.035) ^b KOOS QOL (.057) ICRS grade (.836)	0.095
FGF-2	Sex; concomitant procedure; ICRS grade; defect area	Sex (.012) ^b Defect area (.246) Concomitant procedure (.120) ICRS grade (.171)	0.178
CCL-2	No. of defects; KOOS QOL; KOOS JR; KOOS Pain	No. of defects (.012) ^b KOOS Symptoms (.019) ^b KOOS QOL (.016) ^b	0.173
BMP-2	Sex; No. of defects; KOOS Symptoms; AMADEUS	Sex (.008) ^b KOOS Symptoms (.019) ^b AMADEUS (.479)	0.169
Aggrecan	KOOS QOL; age; No. of defects; ICRS grade	KOOS QOL (.085) ICRS grade (.069)	0.068
Outcome			
KOOS Symptoms	Total defect area; VEGF; No. of defects; MMP-1	VEGF (.023) ^b Total defect area (.186)	0.120
KOOS QOL	IL-1 α ; MMP-1; aggrecan; ICRS grade	MMP-1 (0.045) ^b ICRS grade (0.151)	0.079

^aADL, Activities of Daily Living; AMADEUS, Area Measurement and Depth & Underlying Structures; BMP-2, bone morphogenetic protein 2; CCL-2, C-C chemokine ligand 2; CCL-5, C-C chemokine ligand 5/RANTES; EGF, epidermal growth factor; FGF-2, fibroblast growth factor 2; ICRS, International Cartilage Regeneration & Joint Preservation Society; IL-1 α , interleukin 1 α ; JR, Joint Replacement; KOOS, Knee injury and Osteoarthritis Outcome Score; MMP-1, matrix metalloproteinase 1; MMP-3, matrix metalloproteinase 3; PDGF, platelet-derived growth factor; QOL, Quality of Life; VEGF, vascular endothelial growth factor.

^bVariables found to be independently significant by multivariate regression analysis.

a wide array of questions prompting patients to assess their pain and function and have been validated in the setting of osteoarthritis and posttraumatic osteoarthritis.³⁹ The KOOS QOL subscale relies on patients' assessment of how aware they are of their knee pain and how that affects their lifestyle and confidence in that knee. Although there is inherent interplay between how patients interpret their pain and how that affects their quality of life, the correlation of MMP-3 to VAS is a different assessment than the KOOS subscales evaluated in the present study. Further, Cuéllar et al analyzed the concentrations of MMP-3 and MMP-13 but not MMP-1. Although within the same family of matrix metalloproteinases, concentrations of MMP-3 and MMP-1 have been shown to vary from one another in different disease states.²⁷

MMP-1 is known to degrade collagen types I through III and is elevated in the arthritic state but absent in synovitis alone.^{40,47} VEGF is a known proinflammatory molecule involved in angiogenesis and ECM remodeling, among other roles, that can also be upregulated by other inflammatory cytokines. Therefore, a logical assumption would be that larger cartilage defects may be associated with increased levels of MMP-1 as the cartilage further degrades, which was reflected in our data and furthermore an increase in VEGF concentrations. Consequently, as cartilage defects become larger and arthritic change more widespread, symptoms would similarly progress, which could be a potential explanation for the correlated changes seen in the KOOS scores. Although not reflected in our data, other known interactions between MMPs could be

at play in our study patients, particularly in a synergistic role. Prior literature has established the presence of MMP-9 in the knee joint in small amounts from chondrocytes but primarily from monocytes and macrophages that are increased in arthritis.³⁴ Similarly, MMP-14 is produced by a myriad of cells present in the knee and plays a role in degradation of ECM and collagen type II. Each of these MMPs has been shown to have a synergistic effect with MMP-1 in regard to cartilage degradation; however, we do not have values of these in order to assess their levels within our study.

The CCSKG¹¹ studied how patient characteristics and intraoperative findings related to PROMs in 638 patients undergoing knee arthroscopy for meniscal and cartilage origins. Their findings included a significant relationship between abnormal synovium intraoperatively and KOOS Pain scores on multivariate analysis. Although not directly collecting synovial fluid cytokines, the presence of synovitis has been shown to be an inciting event for the migration of inflammatory cytokines to the intra-articular environment.¹⁴

When we examined the relationships between patient characteristics and structural defects as they pertain to synovial cytokine concentrations, a larger number of defects and female sex were recurrently found to be significantly associated with higher concentrations of these biomarkers. Elevated concentrations of MMP-1, VEGF, CCL-2, and IL-1 α were found to have significant associations with a larger number of articular defects. Higher concentrations of MMP-3, FGF-2, and BMP-2 were all associated with female sex on multivariate analysis.

Tsuchida et al⁴⁴ demonstrated that patients with focal cartilage defects or osteoarthritis had elevated synovial concentrations of proinflammatory cytokines including IL-6, IL-13, interferon γ , and oncostatin M when compared with the synovial fluid of patients with healthy, nonsymptomatic cartilage. The investigators also analyzed the cytokine expression from cartilage tissue extracts harvested from their 3 study groups, finding VEGF concentrations to be higher in patients with cartilage damage; however, the investigators did not measure the VEGF within the synovial fluid of their patients. Pan et al³⁷ measured serum concentrations of IL-6, tumor necrosis factor α , and C-reactive protein from adults aged 50 to 80 years in Tasmania, Australia. Those investigators similarly identified that systemic IL-6 levels were associated with progressive lateral tibial plateau cartilage volume loss and worse pain over longitudinal follow-up of 10.7 years. Our study identified synovial fluid concentrations of VEGF and MMP-1 as key mediators associated with worse baseline KOOS Symptoms and QOL scores. Together, these findings support the role of VEGF and IL-6-mediated inflammatory pathways in chondral degradation and pain generation. These results support the further investigation into the link between synovial cytokine expression and its impact on PROMs.

The classification and quantification of cytokines within the synovial fluid of knees afflicted with articular damage have important clinical implications. Primarily, by understanding the microenvironment of a damaged and inflamed

knee, we may be able to augment the intra-articular environment preoperatively to alleviate patient symptoms as well as attenuate additional cartilage damage mediated by the inflammatory cytokines. Allen et al³ found that anti-inflammatory agents such as IL-1 receptor antagonist and doxycycline were able to attenuate the production of inflammatory cytokines in a model of intra-articular ankle fractures. Future research should be directed at determining the effects of commercially available therapeutic agents on both the intra-articular microenvironment and patient outcomes when delivered preoperatively to patients with articular defects of the knee.


Limitations


The current study is limited in that the cohort does not represent the general population. All patients included consented to arthroscopic chondroplasty due to their symptomatic state, and there was no control group of matched asymptomatic individuals with whom to compare synovial cytokine concentrations. The primary focus of the present study was cartilage defects treated with arthroscopic chondroplasty. Although we ensured that our exclusion criteria prevented the confounding of synovial cytokine concentrations by concurrent ligamentous injury, we did not exclude all patients who had any concomitant procedure. With this came 16 patients (26.67%) who had meniscal injury requiring concomitant partial meniscectomy at time of chondroplasty. However, the only variable significantly associated with concomitant procedures on univariate testing was the concentration of FGF-2, and on multivariate analysis the occurrence of a concomitant procedure no longer demonstrated an association. The study is also limited by the cytokines available in the particular test kit that was used. There are other potential cytokines of interest that could be identified with broader testing. The single surgeon imaging interpretation can also be considered a limitation of this study. Finally, the current study evaluated the cytokine concentrations and PROMs only at the time of initial knee chondroplasty. A future area of study would be to evaluate the longitudinal change in cytokine concentrations after cartilage procedures and the effects of these inflammatory on the healing environment as well as how they correlate with patient outcomes.

CONCLUSION

Elevated MMP-1 was the primary driver of worse preoperative KOOS QOL scores on multivariate analysis, more so than defect characteristics. Similarly, worse preoperative KOOS Symptoms scores were more strongly correlated with elevated VEGF concentrations rather than defect ICRS grades. Other individual factors such as a larger number of defects and female sex were independently correlated with a more inflammatory synovial profile of the patient.

ORCID iDs

Brian J. Cole  <https://orcid.org/0000-0002-4006-2113>

Adam B. Yanke  <https://orcid.org/0000-0002-9601-4217>

REFERENCES

- Abram SGF, Palmer AJR, Judge A, Beard DJ, Price AJ. Rates of knee arthroplasty in patients with a history of arthroscopic chondroplasty: results from a retrospective cohort study utilising the National Hospital Episode Statistics for England. *BMJ Open*. 2020;10(4):e030609.
- Alaaeddine N, Olee T, Hashimoto S, Creighton-Achermann L, Lotz M. Production of the chemokine RANTES by articular chondrocytes and role in cartilage degradation. *Arthritis Rheumatism*. 2001;44(7):1633-1643.
- Allen NB, Abar B, Danilkowicz RM, Kraus VB, Olson SA, Adams SB. Intra-articular synovial fluid with hematoma after ankle fracture promotes cartilage damage in vitro partially attenuated by anti-inflammatory agents. *Foot Ankle Int*. 2022;43(3):426-438.
- Anderson DD, Chubinskaya S, Guilak F, et al. Post-traumatic osteoarthritis: improved understanding and opportunities for early intervention. *J Orthop Res*. 2011;29(6):802-809.
- Anderson DE, Rose MB, Wille AJ, Wiedrick J, Crawford DC. Arthroscopic mechanical chondroplasty of the knee is beneficial for treatment of focal cartilage lesions in the absence of concurrent pathology. *Orthop J Sports Med*. 2017;5(5):2325967117707213.
- Bisson LJ, Kluczynski MA, Wind WM, et al. Patient outcomes after observation versus debridement of unstable chondral lesions during partial meniscectomy: the Chondral Lesions and Meniscus Procedures (ChAMP) randomized controlled trial. *J Bone Joint Surg*. 2017;99(13):1078-1085.
- Blaney Davidson EN, Vitters EL, Van Lent PL, Van De Loo FA, Van Den Berg WB, Van Der Kraan PM. Elevated extracellular matrix production and degradation upon bone morphogenetic protein-2 (BMP-2) stimulation point toward a role for BMP-2 in cartilage repair and remodeling. *Arthritis Res Ther*. 2007;9(5):R102.
- Brittberg M, Peterson L. Introduction to an articular cartilage classification. *ICRS Newsletter*. 1998:5-8.
- Cabral-Pacheco GA, Garza-Veloz I, Castruita-De La Rosa C, et al. The roles of matrix metalloproteinases and their inhibitors in human diseases. *Int J Mol Sci*. 2020;21(24):9739.
- Clair AJ, Kingery MT, Anil U, Kenny L, Kirsch T, Strauss EJ. Alterations in synovial fluid biomarker levels in knees with meniscal injury as compared with asymptomatic contralateral knees. *Am J Sports Med*. 2019;47(4):847-856.
- Cleveland Clinic Sports Knee Group, Knee Group, Bessette MC, Westermann RW, et al. Predictors of pain and function before knee arthroscopy. *Orthop J Sports Med*. 2019;7(5):2325967119844265.
- Cotter EJ, Weissman AC, Yazdi AA, Muth SA, Cole BJ. Arthroscopic debridement of mild and moderate knee osteoarthritis results in clinical improvement at short-term follow-up: a systematic review. *Arthroscopy*. 2025;41(2):377-389.
- Cuellar VG, Cuellar JM, Kirsch T, Strauss EJ. Correlation of synovial fluid biomarkers with cartilage pathology and associated outcomes in knee arthroscopy. *Arthroscopy*. 2016;32(3):475-485.
- Dayer JM, Burger D. Cytokines and direct cell contact in synovitis: relevance to therapeutic intervention. *Arthritis Res*. 1999;1(1):17-20.
- Dekker TJ, Aman ZS, DePhillipo NN, Dickens JF, Anz AW, LaPrade RF. Chondral lesions of the knee: an evidence-based approach. *J Bone Joint Surg*. 2021;103(7):629-645.
- Ellman MB, Yan D, Ahmadinia K, Chen D, An HS, Im HJ. Fibroblast growth factor control of cartilage homeostasis. *J Cell Biochem*. 2013;114(4):735-742.
- Frank RM, Cotter EJ, Nassar I, Cole B. Failure of bone marrow stimulation techniques. *Sports Med Arthrosc Rev*. 2017;25(1):2-9.
- Hacken BA, LaPrade MD, Stuart MJ, Saris DBF, Camp CL, Krych AJ. Small cartilage defect management. *J Knee Surg*. 2020;33(12):1180-1186.
- Hall A, Lee D, Campbell R, et al. Predictors of patient-reported outcomes after hyaluronic acid injections: effect of expectations and psychological stress. *J Am Acad Orthop Surg Glob Res Rev*. 2024;8(8):e23.00152.
- Heir S, Nerhus TK, Rotterud JH, et al. Focal cartilage defects in the knee impair quality of life as much as severe osteoarthritis: a comparison of knee injury and osteoarthritis outcome score in 4 patient categories scheduled for knee surgery. *Am J Sports Med*. 2010;38(2):231-237.
- Houck DA, Kraeutler MJ, Belk JW, Frank RM, McCarty EC, Bravman JT. Do focal chondral defects of the knee increase the risk for progression to osteoarthritis? A review of the literature. *Orthop J Sports Med*. 2018;6(10):2325967118801931.
- Irie K, Uchiyama E, Iwaso H. Intraarticular inflammatory cytokines in acute anterior cruciate ligament injured knee. *Knee*. 2003;10(1):93-96.
- Jacques C, Gosset M, Berenbaum F, Gabay C. The role of IL-1 and IL-1Ra in joint inflammation and cartilage degradation. *Vitam Horm*. 2006;74:371-403.
- Jia H, Ma X, Tong W, et al. EGFR signaling is critical for maintaining the superficial layer of articular cartilage and preventing osteoarthritis initiation. *Proc Natl Acad Sci U S A*. 2016;113(50):14360-14365.
- Jungmann PM, Welsch GH, Brittberg M, et al. Magnetic Resonance Imaging Score and Classification System (AMADEUS) for assessment of preoperative cartilage defect severity. *Cartilage*. 2017;8(3):272-282.
- Kaplan DJ, Cuellar VG, Jazrawi LM, Strauss EJ. Biomarker changes in anterior cruciate ligament-deficient knees compared with healthy controls. *Arthroscopy*. 2017;33(5):1053-1061.
- Keyszer G, Lambiri I, Nagel R, et al. Circulating levels of matrix metalloproteinases MMP-3 and MMP-1, tissue inhibitor of metalloproteinases 1 (TIMP-1), and MMP-1/TIMP-1 complex in rheumatic disease: correlation with clinical activity of rheumatoid arthritis versus other surrogate markers. *J Rheumatol*. 1999;26(2):251-258.
- Kieswetter K, Schwartz Z, Alderete M, Dean DD, Boyan BD. Platelet derived growth factor stimulates chondrocyte proliferation but prevents endochondral maturation. *Endocrine*. 1997;6(3):257-264.
- Kingery MT, Adams AC, Manjunath AK, Berlinberg EJ, Markus DH, Strauss EJ. Synovial fluid cytokine profile at the time of arthroscopy explains intermediate-term functional outcomes. *Am J Sports Med*. 2022;50(5):1261-1271.
- Krych AJ, Saris DBF, Stuart MJ, Hacken B. Cartilage injury in the knee: assessment and treatment options. *J Am Acad Orthop Surg*. 2020;28(22):914-922.
- Liu B, Goode AP, Carter TE, et al. Matrix metalloproteinase activity and prostaglandin E2 are elevated in the synovial fluid of meniscus tear patients. *Connect Tissue Res*. 2017;58(3-4):305-316.
- Mabey T, Honsawek S. Cytokines as biochemical markers for knee osteoarthritis. *World J Orthop*. 2015;6(1):95-105.
- Martin JA, Brown T, Heiner A, Buckwalter JA. Post-traumatic osteoarthritis: the role of accelerated chondrocyte senescence. *Biorheology*. 2004;41(3-4):479-491.
- Milars C, Lepetsos P, Dafou D, Potoupnis M, Tsiroidis E. Association of matrix metalloproteinase (MMP) gene polymorphisms with knee osteoarthritis: a review of the literature. *Cureus*. 2021;13(10):e18607.
- Mueller MB, Tuan RS. Anabolic/catabolic balance in pathogenesis of osteoarthritis: identifying molecular targets. *PM R*. 2011;3(6 suppl 1):S3-S11.
- Neuman P, Dahlberg LE, Englund M, Struglics A. Concentrations of synovial fluid biomarkers and the prediction of knee osteoarthritis 16 years after anterior cruciate ligament injury. *Osteoarthritis Cartilage*. 2017;25(4):492-498.
- Pan F, Tian J, Ciccitini F, Jones G. Prospective association between inflammatory markers and knee cartilage volume loss and pain trajectory. *Pain Ther*. 2022;11(1):107-119.

38. Raghu H, Lepus CM, Wang Q, et al. CCL2/CCR2, but not CCL5/CCR5, mediates monocyte recruitment, inflammation and cartilage destruction in osteoarthritis. *Ann Rheum Dis*. 2017;76(5):914-922.
39. Roos EM, Lohmander LS. The Knee injury and Osteoarthritis Outcome Score (KOOS): from joint injury to osteoarthritis. *Health Qual Life Outcomes*. 2003;1:64.
40. Rose BJ, Kooyman DL. A tale of two joints: the role of matrix metalloproteases in cartilage biology. *Dis Markers*. 2016;2016:4895050.
41. Roughley PJ, Mort JS. The role of aggrecan in normal and osteoarthritic cartilage. *J Exp Orthop*. 2014;1(1):8.
42. Shibuya M. Vascular endothelial growth factor (VEGF) and its receptor (VEGFR) signaling in angiogenesis: a crucial target for anti- and pro-angiogenic therapies. *Genes Cancer*. 2011;2(12):1097-1105.
43. Spahn G, Hofmann GO, Von Engelhardt LV. Mechanical debridement versus radiofrequency in knee chondroplasty with concomitant medial meniscectomy: 10-year results from a randomized controlled study. *Knee Surg Sports Traumatol Arthrosc*. 2016;24(5):1560-1568.
44. Tsuchida AI, Beekhuizen M, 't Hart MC, et al. Cytokine profiles in the joint depend on pathology, but are different between synovial fluid, cartilage tissue and cultured chondrocytes. *Arthritis Res Ther*. 2014;16(5):441.
45. Turati M, Maggioni D, Zanchi N, et al. Characterization of synovial cytokine patterns in bucket-handle and posterior horn meniscal tears. *Mediators Inflamm*. 2020;2020:5071934.
46. Weißenberger M, Heinz T, Boelch SP, et al. Is debridement beneficial for focal cartilage defects of the knee? Data from the German Cartilage Registry (KnorpelRegister DGOU). *Arch Orthop Trauma Surg*. 2020;140(3):373-382.
47. Wu H, Du J, Zheng Q. Expression of MMP-1 in cartilage and synovium of experimentally induced rabbit ACLT traumatic osteoarthritis: immunohistochemical study. *Rheumatol Int*. 2008;29(1):31-36.
48. Yanke AB, Hevesi M, Dandu N, et al. After chondroplasty, patient election to proceed with cartilage transplantation is closely and additively associated with preoperative AMADEUS (Area Measurement And DEpth Underlying Structure) grade, condylar involvement, Knee injury and Osteoarthritis Outcome Score pain score, and Veterans Rand 12-Item Health Survey physical score. *Arthrosc Sports Med Rehabil*. 2022;4(6):e1903-e1912.