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Research article

Cytokines as a predictor of clinical response following hip arthroscopy: minimum 2-year follow-up

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ABSTRACT

Hip arthroscopy in patients with osteoarthritis has been shown to have suboptimal outcomes. Elevated cytokine concentrations in hip synovial fluid have previously been shown to be associated with cartilage pathology. The purpose of this study was to determine whether a relationship exists between hip synovial fluid cytokine concentration and clinical outcomes at a minimum of 2 years following hip arthroscopy. Seventeen patients without radiographic evidence of osteoarthritis had synovial fluid aspirated at time of portal establishment during hip arthroscopy. Analytes included fibronectin–aggrecan complex as well as a multiplex cytokine array. Patients completed the modified Harris Hip Score, Western Ontario and McMaster Universities Arthritis Index and the International Hip Outcomes Tool pre-operatively and at a minimum of 2 years following surgery. Pre and post-operative scores were compared with a paired *t*-test, and the association between cytokine values and clinical outcome scores was performed with Pearson's correlation coefficient with an alpha value of 0.05 set as significant. Sixteen of seventeen patients completed 2-year follow-up questionnaires (94%). There was a significant increase in pre-operative to post-operative score for each clinical outcome measure. No statistically significant correlation was seen between any of the intra-operative cytokine values and either the 2-year follow-up scores or the change from pre-operative to final follow-up outcome values. No statistically significant associations were seen between hip synovial fluid cytokine concentrations and 2-year follow-up clinical outcome assessment scores for those undergoing hip arthroscopy.

INTRODUCTION

Femoroacetabular impingement (FAI) is being increasingly recognized as a common cause of hip pain in the young, active patient population [1–6]. Longitudinal studies have demonstrated that the presence of FAI increases the risk of developing osteoarthritis (OA) [7, 8] through the abnormal static and dynamic stresses applied to the labrum and cartilage [9–11]. Treatment options for FAI vary widely [12–14] and are typically dependent upon symptoms, amount of OA present and osseous anatomy.

Multiple studies have demonstrated that the presence of radiographic OA results in suboptimal improvement in outcome scores following hip arthroscopy for FAI [15–18]. Magnetic resonance imaging (MRI), frequently used in the work up and evaluation of patients who are potential candidates for FAI surgery, has variable sensitivity and specificity in the identification of cartilage lesions [19–22]. In the absence of radiographic OA, however, arthroscopic surgery to address cartilage and labral pathology as well as abnormal femoral and acetabular contour has proven

effective at improving clinical outcome scores and allowing athletes to return to play [23–25].

Despite promising results, the revision rate after hip arthroscopy has been shown to be as high as 6.3% [26]. While residual deformity is the most common reason for revision hip arthroscopy [26], there has recently been an increased emphasis on biological factors leading to suboptimal outcomes following hip arthroscopy. Ross *et al.* compared three-dimensional hip morphology of symptomatic hips prior to revision arthroscopy to the three-dimensional morphology of a cohort of patients not requiring a revision arthroscopy. Residual deformities were present in 45 of 50 patients (90%) in the cohort undergoing revision arthroscopy [27]. Dwyer *et al.* [28] examined a cohort of 182 patients who had undergone revision arthroscopy and noted that the location of chondral damage was an important predictor of revision arthroscopy. Other studies investigating the clinical response following intra-articular anesthetic injection or the relationship between femoral anteversion and symptom resolution following arthroscopy for FAI found no correlation [29, 30]. Several basic science and clinical experiments have provided evidence for the role of proinflammatory molecules in the development of arthritis. Scuderi *et al.* [31] identified a protein complex of fibronectin and aggrecan that was present in patients with a painful meniscal tear that was absent in asymptomatic controls. Our group previously reported the presence of an elevated cartilage breakdown product [fibronectin–aggrecan complex (FAC)] in patients with cartilage damage noted at the time of hip arthroscopy. Fibronectin, a large glycoprotein, and its proteolytic fragments have demonstrated to be chondrolytic toward cultured cartilage explants in *in vitro* studies [32, 33] and after injection into the knee joints of animal models [32, 34, 35]. Aggrecan is a high-molecular-weight proteoglycan component of the articular cartilage extra-cellular matrix [36]. Fibronectin, by way of catabolic cytokines, has been demonstrated to cleave aggrecan, thereby leading to cartilage degradation and joint disease [32].

As the presence of OA has shown to negatively affect outcomes, it is possible that further detection of cartilage or inflammatory pathology not evident on imaging or conventional work up methods may assist in predicting clinical response to arthroscopic intervention and therefore help in determining the optimal surgical candidates.

The purpose of this study was to determine whether hip synovial fluid cytokine concentrations correlated with post-operative clinical outcomes at a minimum of 2 years following hip arthroscopy for FAI. We hypothesized that those with increased cytokine values would demonstrate lower clinical outcome scores.

MATERIALS AND METHODS

Institutional review board approval was received and informed consent was obtained from each study participant. Seventeen patients who underwent hip arthroscopy for FAI and whom we previously reported cytokine values were targeted for inclusion. These patients were recruited from the arthroscopic arm of our previous study in which we evaluated the cytokine concentrations in hips of those patients undergoing either hip arthroscopy or arthroplasty. Inclusion criteria for this cohort and the previous arthroscopic cohort included age greater than 18 years, signs and symptoms of hip pain as well as imaging results consistent with FAI and those patients electing to undergo hip arthroscopy. Exclusion criteria included radiographic evidence of OA, history of prior trauma to the involved hip or history of inflammatory arthritis. Patients were recruited between June 2011 and July 2012. All patients presented with the complaint of hip pain and underwent a thorough work-up (history, physical exam, radiographs and MRI, when applicable). Patients were offered surgical intervention after a documented trial and failure of non-operative treatment and clinical response following a diagnostic intra-articular anesthetic injection.

Age, gender and medical comorbidities were recorded at presentation. Each patient completed patient reported clinical outcomes questionnaires prior to surgery [modified Harris Hip Score (mHHS), Western Ontario and McMaster Universities Arthritis (WOMAC) Index, and the International Hip Outcomes Tool (iHOT-33)] and at a minimum of 2 years following surgical intervention for FAI. For follow-up on the mHHS, patients were asked whether they had any limitations of motion. If they responded that their motion was normal, maximum scores were given for this section of the mHHS. Intra-operative findings recorded included articular cartilage and labrum status, and operative procedure(s) performed included microfracture, labral repair and/or labral debridement. These procedures were performed at the discretion of the treating surgeon. Standard practice at the time of this investigation was to perform microfracture for full-thickness cartilage defects greater than 7 mm from the acetabular rim, labral debridement when intra-substance labral tearing was present and labral repair when chondrolabral separations were present.

Hip arthroscopy was performed in the supine position on a fracture table. Each patient was prepped and draped and traction was applied to the operative leg. The anterolateral portal was established with an 18-gauge spinal needle placed over a guide wire under fluoroscopic guidance. After the camera was placed in the anterolateral portal, the spinal needle was introduced to establish the posterolateral

portal, which was visualized piercing the posterolateral capsule and entering the joint. After portal establishment, synovial fluid was obtained by injecting 10 ml of sterile normal saline intra-articularly and aspirating back the fluid. The fluid was injected under pressure and allowed to wash around the joint. All lavasate was collected prior to being placed into 2-ml tubes with 130 μl of protease inhibitor (Roche Diagnostics, Indianapolis, IN) and dissolved in phosphate-buffered saline solution (0.045 tablet/ml sample) at a pH of 7.4. The tubes were then frozen at − 80°C until cytokine analysis was performed.

The choice of inflammatory molecules assayed was representative of typical molecules observed in a variety of inflammatory conditions. The synovial fluid biomarkers measured were FAC, interferon-γ, interleukin (IL)-6, IL-1 receptor (IL-1RA), IL-1b, monocyte chemoattractant protein-1, eotaxin, macrophage inflammatory protein-1β, interferon-inducible protein 10, platelet-derived growth factor-BB, regulated upon activation normal T cell expressed and presumably secreted, tumor necrosis factor-α, and vascular endothelial growth factor. Following the protocol established by the manufacturer, the concentrations were determined through the use of a panel of human multiplex inflammatory cytokines and the BioPlex 200 System (Bio-Rad Laboratories, Hercules, CA). The assay was performed through the use of antibody linked polystyrene beads with various fluorophore levels and has been validated against standard enzyme-linked immunosorbent assays (ELISA) [37]. The relative concentration of each sample of each cytokine was compared with standard positive and negative control concentrations provided by the manufacturer. FAC concentration was reported as optical density as determined by the use of a heterogeneous sandwich ELISA [31].

Pre and post-operative questionnaire scores were compared with a paired *t*-test and the association between intra-operative cytokine concentration and post-operative questionnaire score was performed with Pearson's correlation coefficient (SPSS v.21, IBM Incorporated, Sommers, NY). An alpha value of 0.05 was set as significant.

RESULTS

Follow-up clinical outcome scores for 16 of the 17 patients (94%) were available at a minimum of 2-year follow-up. The cohort consisted of 4 males and 12 females with an average age of 38.9 ± 11.2 years at the time of operation. The mean follow-up time was 2.49 ± 0.27 years. Of the 16 patients available for follow-up, 6 patients underwent both cheilectomy and acetabuloplasty, 4 underwent acetabuloplasty, 2 underwent cheilectomy only and 4 underwent neither acetabuloplasty nor cheilectomy but rather had labral debridement or repair, chondroplasty or capsular plication. Seven underwent a labral repair, nine underwent labral debridement and three underwent microfracture. No patients that provided 2-year follow-up had undergone interval operations on the operative hip.

Table I. Cytokine values in hip synovial fluid

Cytokine	*Mean*	*SEM*
FAC (OD)	1.052	0.361
IFN-γ (ρg/ml)	29.047	14.155
IL-6	37.853	20.534
IL-1RA	879.174	512.799
IL-1b	1.273	0.661
MCP-1	28.110	9.854
Eotaxin	7.915	4.661
MIP-1β	5.001	0.828
IP-10	171.073	43.704
PDGF-BB	262.348	159.806
RANTES	318.478	90.539
TNFα	62.043	34.918
VEGF	140.264	40.863

TNF, tumor necrosis factor; RANTES, regulated upon activation normal T cell expressed and presumably secreted; IP-10, interferon-inducible protein 10; MIP, macrophage inflammatory protein; MCP, monocyte chemoattractant protein; IFN, interferon; VEGF, vascular endothelial growth factor; SEM, standard error of the mean; OD, optical density; PDGF-BB, platelet-derived growth factor-BB.

Statistically significant pre-operative to post-operative improvement was seen in mHHS ($P < 0.0001$), WOMAC ($P < 0.0001$) and iHOT-33 ($P < 0.0001$) scores. The mean mHHS improved from 61.9 to 82.5 {mean difference = 20.6 [95% confidence interval (CI) 13.6–27.6]}, WOMAC scores improved from 42.7 to 16.4 (mean difference = −26.3 [95% CI 17.8–34.8]) and iHOT-33 scores improved from 44.6 to 83.4 (mean difference = 38.9 [95% CI 29.4–48.4]). The mean cytokine values for the entire cohort are listed in Table I. Figure 1 demonstrates the mean analyte concentration compared with measured iHOT-33 score.

No significant correlation was seen between any of the synovial fluid cytokine values and the 2-year follow-up outcome scores. No significant correlation was found between any cytokine value and the difference between pre-operative and post-operative questionnaire scores.

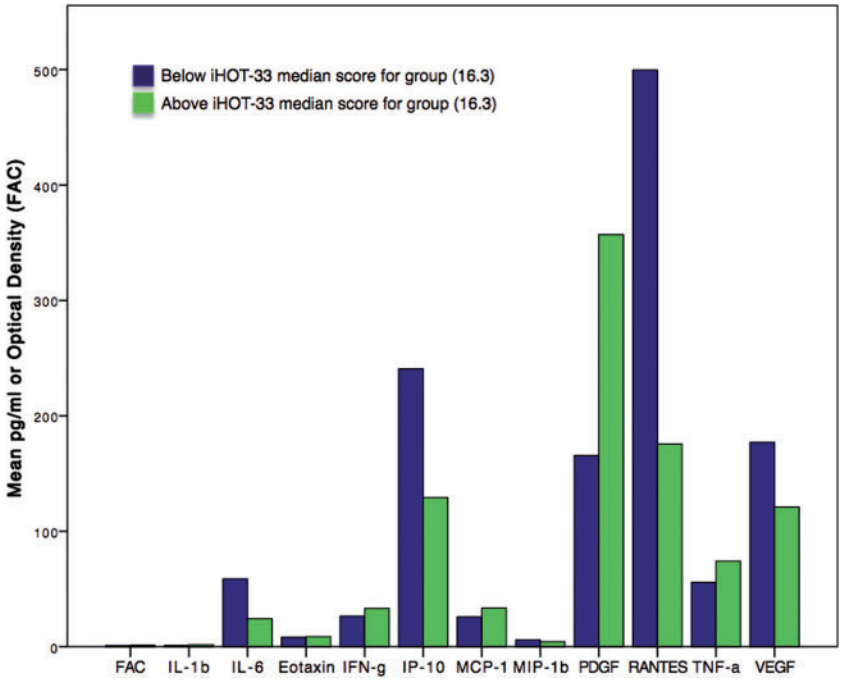

Fig. 1. Mean concentration of all analytes broken down by patient groups. Patients were dichotomized into groups with a score below (blue) and above (green) the median iHOT-33 value of the entire cohort.

DISCUSSION

This investigation sought to determine whether synovial fluid cytokine concentrations correlated with clinical outcomes at a minimum of 2 years following hip arthroscopy for FAI. The hypothesis of increased cytokine concentrations correlating to decreased clinical outcomes (or less improvement in outcome scores) was not supported by the data and no statistically significant relationship was found between these measures.

The number of arthroscopic hip operations continues to increase with the improved understanding of FAI as a cause of hip pain. Radiographic evidence of severe preoperative OA has been repeatedly shown to be associated with worse clinical outcomes [15–18]. Although arthroscopy for FAI in patients with hip pain and without radiographic evidence of OA has overall been effective at improving pain and clinical outcome scores, a subset of these patients do not achieve optimal outcomes.

There are many potential reasons for a lack of optimal clinical outcomes following hip arthroscopy. The most commonly cited cause of sub-optimal clinical outcome is residual or incomplete correction of bony deformity [27, 38–40]. It is possible that OA of the hip at the time of the initial FAI operation may be underreported, as these studies report those undergoing revision hip arthroscopy. Patients with persistent hip pain after arthroscopic FAI surgery, in the realm of hip OA, often are treated with hip arthroplasty and thus not included in these aforementioned revision hip arthroscopy series. Unaddressed hip instability is yet another recognized cause of failed hip arthroscopy [40, 41] and cadaveric studies examining capsular and labral contributions to hip instability highlight the importance of addressing and managing capsular defects [42, 43].

Additionally, early cartilage damage or joint inflammation, which may not be detectable by radiography or MRI, may also contribute to poor post-operative outcomes. In an investigation of patients requiring revision hip arthroscopy, the presence of chondral damage on the anterior acetabulum was a positive predictor for revision arthroscopy [28]. Patients with evidence of mild chondral damage of the anterior acetabulum were nearly two times more likely to undergo revision, while those with moderate to severe chondral damage on the anterior acetabulum were 1.5 times more likely to undergo revision [28]. Of note, the presence of chondral damage to the femoral head and superior, lateral and posterior acetabulum were not predictive of revision.

This data, however, require patients to undergo surgery to determine their status with regard to the need for revision surgery and/or post-operative outcomes. Rather, a more suitable method to determine outcomes following hip arthroscopy would be one in which surgical intervention is not required. This could come in the form of preoperative assessment of joint status through a combination

of imaging as well as cytokine profiling, which could be obtained through pre-operative aspiration potentially at the same time as a diagnostic injection or arthrogram. Our group's previous study collected hip synovial fluid from a cohort undergoing arthroscopy (those who had minimal to no radiographic OA) and another cohort undergoing arthroplasty (those who had radiographic evidence of OA) and analyzed the cytokine concentration differences between cohorts. This work identified a biomarker (FAC), which was shown to be elevated in patients undergoing hip arthroscopy for FAI when compared to those undergoing arthroplasty for OA. Additionally, it was found that those patients undergoing arthroscopy who were noted to have cartilage loss requiring microfracture at the time of operative intervention had elevated levels of FAC compared to those with less cartilage loss who did not meet the indication for microfracture [44]. This previous study did not find a relationship between biomarker concentration and pre-operative assessment scores; however, it did not study the relationship between cytokine concentration and change in outcome scores.

Although the data presented in this study do not support the ability of cytokine concentrations to predict clinical outcomes, there is potential to identify a subset of biomarkers, which will not only lead to better patient selection and pre-operative counseling but may also lead to a better understanding of hip pain and avenues by which to direct potential therapeutic targets. The ability to determine cartilage status via synovial fluid aspirate may be useful in predicting joint pathology prior to surgical intervention and therefore help to determine which patients may be most amenable to intervention for FAI.

This investigation is not without its limitations. The lack of significant correlation between cytokine values and patient reported outcome assessments may be due to the fact that 2-year follow-up may not be long enough to detect clinical differences between patients who may respond more positively to arthroscopic intervention in the hip. Dwyer *et al.* [28] reported that revision operations occurred at an average of 3.1 ± 2.8 years after the index operation. Additionally, it may be due to the large variability of cytokine concentrations that were observed between patients. While no normative data exist regarding synovial fluid cytokine concentrations in those with FAI, gene expression profiles of synovial fluid in hips with rapidly destructive coxopathy, OA, osteonecrosis and rheumatoid arthritis also demonstrated large variations in IL-1β, IL-6, IL-8 and tumor necrosis factor-α between subjects [45]. Finally, it is possible this study was underpowered to detect a significant difference in some of the attempted analyses. For example, a *post-hoc* power analysis revealed that to see a statistically significant correlation between FAC concentration and post-operative mHHS scores, 44 patients per group would have been required. To conclude that a statistically significant correlation existed between FAC and iHOT-33 scores, 58 patients per group would have been needed. Given the sample size of 17 patients, this study was not powered to detect significant correlations between FAC and clinical outcomes based on these *post-hoc* analyses. Furthermore, it is possible there was a dilutional effect that influenced the synovial fluid samples. Great care was taken to adhere to the sample collection protocol while performing the lavage and obtaining the aspirations. Despite the fact that the volume of saline injected was standardized, it is possible that the presence of a joint effusion created a dilutional effect that influenced the sample obtained. This limitation is likely minimal as no significant joint effusions were present at time of aspiration. Lastly, the presence of blood contamination in the aspirates is inevitable. Although there were no apparently grossly contaminated samples, the effect of blood and other contaminants on cytokine concentrations is not well described.

CONCLUSION

There was no correlation between synovial fluid cytokine concentrations and post-operative clinical outcome scores at a minimum of 2 years following hip arthroscopy for FAI. Larger and longer-term investigations are warranted to further evaluate the relationship of intra-operative cytokine concentration and clinical outcomes after hip arthroscopy.

FUNDING

Cytonics Inc. donated the ELISA kits and performed the cytokine analysis.

CONFLICT OF INTEREST STATEMENT

G.D.A. serves as a consultant and has stock options in Cytonics, Inc. and G.J.S. serves as President and Founder, Cytonics Inc.

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