Elevation in Circulating Biomarkers of Cartilage Damage and Inflammation in Athletes With Femoroacetabular Impingement

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Background: Femoroacetabular impingement (FAI) is one of the most common causes of early cartilage and labral damage in the nondysplastic hip. Biomarkers of cartilage degradation and inflammation are associated with osteoarthritis. It was not known whether patients with FAI have elevated levels of biomarkers of cartilage degradation and inflammation.

Hypothesis: Compared with athletes without FAI, athletes with FAI would have elevated levels of the inflammatory C-reactive protein (CRP) and cartilage oligomeric matrix protein (COMP), a cartilage degradation marker.

Study Design: Controlled laboratory study.

Methods: Male athletes with radiographically confirmed FAI (n = 10) were compared with male athletes with radiographically normal hips with no evidence of FAI or hip dysplasia (n = 19). Plasma levels of COMP and CRP were measured, and subjects also completed the Short Form–12 (SF-12) and Hip Disability and Osteoarthritis Outcome Score (HOOS) surveys.

Results: Compared with controls, athletes with FAI had a 24% increase in COMP levels and a 276% increase in CRP levels as well as a 22% decrease in SF-12 physical component scores and decreases in all of the HOOS subscale scores.

Conclusion: Athletes with FAI demonstrate early biochemical signs of increased cartilage turnover and systemic inflammation.

Clinical Relevance: Chondral injury secondary to the repetitive microtrauma of FAI might be reliably detected with biomarkers. In the future, these biomarkers might be used as screening tools to identify at-risk patients and assess the efficacy of therapeutic interventions such as hip preservation surgery in altering the natural history and progression to osteoarthritis.

Keywords: C-reactive protein; cartilage oligomeric matrix protein; osteoarthritis; HOOS; SF-12

The hip is the second most common site of osteoarthritis (OA), and 10% of the population experiences pain, limited function, and disability because of hip OA. Femoroacetabular impingement (FAI) is one of the most common mechanisms that lead to the development of early cartilage and labral damage in the nondysplastic hip. The development of symptomatic hip injury in the nonarthritic hip is related to the underlying structure of the hip joint combined with the applied mechanical loads. While the combination of dynamic and static factors that affect the mechanics of the hip joint are complex, the most common structural deformities are a loss of femoral head-neck offset (“cam”), focal or global acetabular overcoverage (“pincer”), and combined impingement deformity. These anatomic abnormalities of the proximal femur and/or acetabulum result in repetitive collisions occurring during dynamic hip motion that lead to regional loading of the femoral head-neck junction against the acetabular rim, which can precipitate labral injury, chondral delamination,
and a degenerative cascade of more extensive, nonfocal intra-articular injury. The severity of the labral and associated cartilaginous injury often depends on the duration of the untreated injury, suggesting the importance of early diagnosis and treatment.

Several studies have established that the surgical treatment of FAI is an effective, reliable, and safe method to relieve pain and improve function at short- to mid-term follow-up in patients without significant OA. Using 3D models based on computed tomography scans, we and others have demonstrated an improvement in in vivo hip kinematics after surgical correction of FAI. While FAI decompression improves the in vivo kinematics, no studies have correlated specific prognostic indicators of OA with successful treatment of FAI by hip preservation surgery. In addition, the literature does not provide support for prophylactic surgical intervention in asymptomatic individuals, because an alteration in the natural history or progression of OA after FAI surgery has not been established with the available short- and mid-term follow-up.

Many biomarkers of inflammation and cartilage turnover have been used to study the progression of OA. Cartilage oligomeric matrix protein (COMP) is a connective tissue extracellular matrix (ECM) protein that binds several other ECM proteins and helps to organize collagen II–rich matrices. COMP also circulates in the blood and is a marker of cartilage turnover, with increased levels of COMP associated with joint inflammation and OA. C-reactive protein (CRP) is a biological marker that is associated with inflammation, and there is a correlation between increasing CRP levels and the severity of OA.

While COMP and CRP have a well-established role in tracking the progression of early cartilage breakdown and inflammation and in patients with OA, it is not known whether they are altered in the presence of FAI before the establishment of more advanced degenerative OA. We hypothesized that athletes with FAI would have elevated levels of biomarkers of inflammation and cartilage catabolism. To test this hypothesis, we measured the levels of COMP and CRP in male athletes with FAI and compared these findings with the levels of COMP and CRP in activity-matched and age-matched male athletes with normal hips (as shown by radiography).

MATERIALS AND METHODS

Subjects

This study was approved by the University of Michigan Medical Center Institutional Review Board. All subjects provided informed consent before participating in the study. Subjects were recruited from our sports medicine clinic or from flyers placed around campus. The inclusion criteria for the control group (referred to here as “FAI–”) included physically active male athletes, 18 to 40 years of age, with radiographically normal hips (absence of FAI and dysplasia) and negative anterior impingement and flexion, adduction, and internal rotation (FADIR) manual tests. Subjects were excluded from the control group if they had a history of hip pain, lower extremity injury, major medical illnesses, or musculoskeletal diseases. The inclusion criteria for the experimental group (referred to as “FAI+”) included symptomatic physically active male athletes, 18 to 40 years of age, with radiographically confirmed presence of cam-type, pincer-type, or mixed FAI lesions and with positive anterior impingement and FADIR manual tests. The exclusion criteria for the experimental group were a history of hip surgery, hip dysplasia, significant hip joint chondral degeneration (greater than Tönnis grade 1), other lower extremity injury not related to FAI, major medical illnesses, or musculoskeletal diseases. The presence or absence of cam, pincer, or mixed FAI lesions on AP, frog lateral, or Dunn lateral radiographs was determined by a board-certified and fellowship-trained musculoskeletal radiologist according to the guidelines of Ganz et al.

Measurement of Biomarkers

Approximately 3 mL of blood was collected from an antecubital vein into a K2-EDTA tube. Blood was spun down at 1000 g for 10 minutes, and plasma was removed and stored at −80°C until use. Plasma samples were analyzed in duplicate with enzyme-linked immunosorbent assays for COMP (R&D Systems, Minneapolis, Minnesota) and ultrasensitive CRP (Calbiotech, Spring Valley, California) in a SpectraMax plate reader (Molecular Devices, Sunnyvale, California). Assays were conducted according to the instructions from the manufacturer.

Questionnaires

All subjects completed the Short Form–12 (SF-12) survey to evaluate general health, the Hip Disability and Osteoarthritis Outcome Score (HOOS) questionnaire to evaluate hip-specific function, and the Tegner scale to evaluate physical activity level.

Statistical Analyses

Results are presented as mean ± standard deviation. Prism 5.0 (GraphPad Software, LaJolla, California) was used to analyze results. Differences between groups were tested using Student t tests (α = 0.05).

RESULTS

To determine whether athletes with FAI have elevated levels of biomarkers of cartilage degradation and inflammation and differences in SF-12 and HOOS scores, we recruited subjects who were matched for age, activity, and body mass index and who had radiographically confirmed absence of FAI (Table 1) to serve as a healthy control group. Compared with controls, athletes with FAI had a 24% increase (P = .04) in circulating levels of COMP (Figure 1) and a 276% increase (P < .001) in circulating levels of CRP (Figure 2). We also asked each subject to complete the SF-12 and HOOS questionnaires. Athletes...
TABLE 1

| Characteristics of Subjects Without Femoroacetabular Impingement (FAI–) and Subjects With FAI (FAI+)\(^a\) |
|-----------------|-----------------|
| FAI–            | FAI+            |
| No. of subjects | 19              | 10              |
| Age, y          | 22.3 ± 3.4      | 23.1 ± 6.4      |
| Tegner activity level | 7.7 ± 1.0      | 7.3 ± 2.9      |
| Body mass index, kg/m\(^2\) | 24.8 ± 2.6      | 26.5 ± 3.5      |

*Values are presented as mean ± standard deviation. No significant differences between FAI– and FAI+ subjects were noted for any of these categories.

For athletes with FAI a 22% reduction \((P < .001)\) in the SF-12 PCS but no change \((P = .11)\) in the SF-12 MCS (Figure 3). For the HOOS questionnaire, athletes with FAI had a 21% reduction \((P < .001)\) in pain subscale scores, a 30% reduction \((P < .001)\) in symptoms scores, a 17% decrease \((P = .001)\) in activities of daily living scores, a 39% decrease \((P < .001)\) in sport and recreation scores, and a 40% reduction \((P < .001)\) in hip-related quality of life scores (Figure 4).

DISCUSSION

The purpose of this study was to determine whether athletes with symptomatic FAI had elevated biomarkers of cartilage degeneration and inflammation. In the current study, COMP and CRP levels were significantly higher in athletes with FAI compared with age- and activity-matched athletes without FAI. Additionally, we identified that athletes with FAI had reduced SF-12 PCS scores and significant reductions in all of the HOOS subscale scores. These results suggest that biochemical changes occur within the joints of patients with FAI that may contribute to the subsequent development of OA.

Hip OA is one of the most severe and frequent disabilities in the elderly population, and primary hip arthroplasties represent a quarter of the total joint replacement surgeries performed annually.\(^2\) Developmental dysplasia, slipped capital femoral epiphyses, and Legg-Calvé-Perthes disease have long been strongly associated with the development of OA later in life, but these conditions are responsible for less than 10% of primary hip arthroplasties.\(^28\) The mechanisms that lead to the development of the majority of hip OA cases remain largely unknown.\(^20,28\) Recently, Ganz and colleagues\(^4,17,18\) put forth a theory that the anatomic abnormalities of the proximal femur and/or acetabulum in patients with FAI result in regional loading of the femoral head-neck junction against the acetabular rim, leading to labral injury, chondral delamination, and a degenerative cascade of more extensive, nonfocal intra-articular injury. Anatomic simulations,\(^6,26\) whole body kinematics,\(^12\) and T2-weighted MRI studies\(^3,9\) strongly support a connection between FAI and the development of OA.

COMP is a glycoprotein found in articular cartilage that helps to stabilize and align type II collagen molecules. When articular cartilage is broken down, COMP is released into the circulation, which makes it a useful biomarker for monitoring cartilage damage. In this study, athletes with FAI had a 22% reduction \((P < .001)\) in circulating COMP levels compared with control athletes \((FAI–, n = 19)\), while athletes with femoroacetabular impingement \((FAI+, n = 10)\) had an elevation in circulating COMP levels. Values are mean ± SD. *Significantly different from FAI– \((P = .04)\).

![Figure 1](image1.png)

**Figure 1.** Circulating levels of cartilage oligomeric matrix protein (COMP). Compared with control athletes \((FAI–, n = 19)\), athletes with femoroacetabular impingement \((FAI+, n = 10)\) had an elevation in circulating COMP levels. Values are mean ± SD. *Significantly different from FAI– \((P = .04)\).

![Figure 2](image2.png)

**Figure 2.** Circulating levels of C-reactive protein (CRP). Compared with control athletes \((FAI–, n = 19)\), athletes with femoroacetabular impingement \((FAI+, n = 10)\) had an elevation in circulating CRP levels. Values are mean ± SD. *Significantly different from FAI– \((P < .001)\).
marker of cartilage degeneration. Circulating levels of COMP are elevated in patients with radiographically apparent OA and increase as the OA burden increases. While no specific reference values for COMP are available for younger subjects to assess the risk of developing OA, the increased COMP levels in athletes with FAI compared with age- and activity-matched asymptomatic controls provide the first biochemical evidence to support a potential connection between FAI and OA and provide support for the use of biomarkers as a diagnostic and screening tool for FAI.

CRP is an acute phase protein that plays a central role in initiating the systemic response to inflammation, with circulating levels rising 1000-fold or more over baseline after acute injuries or infections. While no specific reference values for CRP are available for younger subjects to assess the risk of developing OA, the increased COMP levels in athletes with FAI compared with age- and activity-matched asymptomatic controls provide the first biochemical evidence to support a potential connection between FAI and OA and provide support for the use of biomarkers as a diagnostic and screening tool for FAI.

There are several limitations to the current study. The study included male patients only and thus is not necessarily generalizable to the entire population. Several studies have reported variability in the types of FAI between sexes, with women demonstrating more pincer-type disease that is more difficult to reliably detect or characterize. There are also carry indirect health benefits associated with the surgical treatment of FAI.

Future longitudinal studies are necessary to further define the changes in these biomarkers with time and with or without corrective surgical intervention. A limitation in the use of any circulating biomarker of cartilage breakdown is the inability to identify specific joints where they originated. We attempted to aspirate synovial fluid under ultrasound guidance to correlate with serum measures, but the low volume of synovial fluid in the hip joint, along with the small amount of contaminating blood from skin and subcutaneous tissues, made it difficult to obtain sufficient quantities of clean synovial fluid for analysis. Similarly, although CRP is largely produced in the liver in response to proinflammatory signals sent from inflamed tissues, we cannot directly determine a causal link between FAI and elevated CRP levels. Recent work identified that radiographic signs of FAI were frequently observed in collegiate athletes with FAI (3.15 mg/L) would be in the low-risk category, but the mean CRP levels for control athletes (0.83 mg/L) had decreased HOOS subscale values for pain, symptoms (Symp), hip-related activities of daily living (ADL), sport and recreation (SR), and hip-related quality of life (QOL). Values are mean ± SD. *Significantly different from FAI− (P < .001).

Figure 3. Short Form–12 (SF-12) scores. Compared with control athletes (FAI−, n = 19), athletes with femoroacetabular impingement (FAI+, n = 10) had lower SF-12 PCS scores but no difference in MCS scores. Values are mean ± SD. *Significantly different from FAI− (P < .001).

Figure 4. Hip Disability and Osteoarthritis Outcome Scores (HOOS). Compared with control athletes (FAI−, n = 19), athletes with femoroacetabular impingement (FAI+, n = 10) had decreased HOOS subscale values for pain, symptoms (Symp), hip-related activities of daily living (ADL), sport and recreation (SR), and hip-related quality of life (QOL). Values are mean ± SD. *Significantly different from FAI− (P < .001).
NFL prospects, although not every athlete who showed signs of FAI had symptoms of hip or groin pain.\textsuperscript{27} Additional insight would be gained in future studies that evaluate both sexes, a wider variety of age levels, a spectrum of specific FAI subtypes and symptom levels, and additional biomarkers of inflammation and OA.

Despite the limitations of the study, our results provide the first biochemical support linking FAI with increased cartilage turnover and elevated systemic inflammation. Clinical intervention for FAI is currently indicated for symptomatic hip pain and deterioration in function, and unfortunately FAI is often diagnosed after significant chondral and labral injury has occurred.\textsuperscript{8} While anatomic, biomechanical, and now biochemical studies have linked FAI to the development of OA, prognostic indicators of OA that correlate with successful hip preservation surgery have not yet been identified. It is also not known whether prophylactic preservation surgery in asymptomatic individuals will be effective because an alteration in the natural history or progression of OA after corrective surgery for FAI has not been determined. Given the importance that biomarkers play in tracking the progression and severity of joint degeneration and inflammation in patients with OA,\textsuperscript{19,25,34} biomarkers may serve as a useful and cost-effective tool to identify at-risk FAI patients and assess the efficacy of therapeutic interventions such as hip preservation surgery in altering the natural history and progression of OA.

REFERENCES


