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Molecular Characterization of Articular Cartilage from Young Adults with Femoroacetabular Impingement

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Investigation performed at Washington University School of Medicine at Barnes-Jewish Hospital, St. Louis, Missouri

Background: Femoroacetabular impingement is a frequent cause of hip pain and may lead to secondary osteoarthritis, yet little is known about the molecular events linking mechanical hip impingement and articular cartilage degeneration. The first goal of this study was to quantify the expression of inflammatory cytokine and chemokine, matrix-degrading, and extracellular matrix genes in articular cartilage harvested from control hips and hips with femoroacetabular impingement and end-stage osteoarthritis. The second goal was to analyze the relative expression of these genes in articular cartilage harvested at various stages of osteoarthritis.

Methods: Cartilage samples were obtained from thirty-two hips undergoing hip preservation surgery for femoroacetabular impingement or hip arthroplasty. Three control cartilage samples were also analyzed. Specimens were graded intraoperatively with regard to the severity of cartilage damage, the radiographic osteoarthritis grade was recorded, and quantitative RT-PCR (real-time polymerase chain reaction) was performed to determine relative gene expression.

Results: Except for interleukin-1β (IL-1β) and CXCL2, the mRNA (messenger RNA) expression of all other chemokine (IL-8, CXCL1, CXCL3, CXCL6, CCL3, and CCL3L1), matrix-degrading (matrix metalloproteinase [MMP]-13 and ADAMTS-4), and structural matrix (COL2A1 [collagen, type II, alpha] and ACAN [aggregan]) genes was higher overall in cartilage from hips with femoroacetabular impingement compared with hips with osteoarthritis and normal controls. The differences reached significance (p ≤ 0.05) for seven of these ten quantified genes, with CXCL3, CXCL6, and COL2A1 being elevated in the femoroacetabular impingement group compared with only the control group and IL-8, CCL3L1, ADAMTS-4, and ACAN being elevated compared with both the osteoarthritis and control groups. When samples were grouped according to the stage of the degenerative cascade, mRNA expression was relatively higher in one of the two middle stages of femoroacetabular impingement (chondromalacia or cleavage/thinning), with the difference reaching significance for IL-8, CXCL2, CXCL3, CCL3L1, and ACAN. ACAN expression was diminished in hips with osteoarthritis compared with femoroacetabular impingement but elevated compared with the control articular cartilage.

Conclusions: Articular cartilage from the impingement zone of hips with femoroacetabular impingement (and particularly those hips in the cleavage/thinning stage) expressed higher levels of certain inflammatory, anabolic, and catabolic genes, representing a heightened metabolic state.

Clinical Relevance: The articular cartilage from the impingement zone of hips with femoroacetabular impingement was metabolically hyperactive, supporting the concept that such impingement is a structural precursor to hip osteoarthritis.

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A commentary by Darryl D. D’Lima, MD, PhD, is linked to the online version of this article at jbjs.org.
Recent advances in understanding structural hip disease have bolstered the theory of secondary osteoarthritis. In this model of hip osteoarthritis pathophysiology, joint degeneration is secondary to an abnormal mechanical environment commonly caused by femoroacetabular impingement. This impingement results from a distinct morphologic abnormality of the acetabular rim (pincer deformity) and/or the femoral head-neck junction (cam deformity). These structural malformations produce dynamic, repetitive abutment between the proximal aspect of the femur and the acetabular rim leading to labrochondral degeneration, articular cartilage detachment, and progressive joint destruction in part by stimulating production of MMP enzymes responsible for cleavage of the major structural proteins in the cartilage matrix (type-II collagen and aggrecan, respectively). Additionally, more recent investigations have implicated certain chemoattractive cytokines (chemokines) as potential mediators of articular cartilage degeneration. Chemokines represent a large family of structurally related inflammatory and immune system mediators that may have important roles in normal articular cartilage physiology and metabolism.

### TABLE I Candidate Genes Important in the Potential Biological Link Between Femoroacetabular Impingement and Secondary Osteoarthritis

<table>
<thead>
<tr>
<th>Accession No.</th>
<th>Gene Name</th>
<th>Symbol</th>
<th>Alias</th>
<th>Forward Primer</th>
<th>Reverse Primer</th>
<th>Metabolic Role</th>
</tr>
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<tbody>
<tr>
<td>NM_00576.2</td>
<td>Interleukin-1 beta</td>
<td>IL-1β</td>
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<td>(5'-TCCAGGAGAATGAGCCTGAC-3')</td>
<td>(5'-GTGACGTACAGGTGCATC-3')</td>
<td>Inflammation</td>
</tr>
<tr>
<td>NM_00584.3</td>
<td>Interleukin-8</td>
<td>IL-8</td>
<td>—</td>
<td>(5'-GAGGTTGAGTTTGGCAAG-3')</td>
<td>(5'-TGTTGTCACCTCCTTACCT-3')</td>
<td>Inflammation</td>
</tr>
<tr>
<td>NM_01511.2</td>
<td>Chemokine (C-X-C) motif ligand 1</td>
<td>CXCL1</td>
<td>GRO-α</td>
<td>(5'-GGGATTCCACCCCAAGAC-3')</td>
<td>(5'-GATGCAAGGATGCGCAGG-3')</td>
<td>Inflammation</td>
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<tr>
<td>NM_00159.3</td>
<td>Chemokine (C-X-C) motif ligand 2</td>
<td>CXCL2</td>
<td>GRO-β</td>
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<td>(5'-CTTACACTGAGGCGGATC-3')</td>
<td>Inflammation</td>
</tr>
<tr>
<td>NM_002090.2</td>
<td>Chemokine (C-X-C) motif ligand 3</td>
<td>CXCL3</td>
<td>GRO-γ</td>
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<td>(5'-GGTGTCCCTTCCTGTACGA-3')</td>
<td>Inflammation</td>
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<tr>
<td>NM_002993.3</td>
<td>Chemokine (C-X-C) motif ligand 4</td>
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<td>GCP-2</td>
<td>(5'-GGTTCAGCTACCTGAGGAG-3')</td>
<td>(5'-ACTTCACTCCGGACACTG-3')</td>
<td>Inflammation</td>
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<tr>
<td>NM_002093.2</td>
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<td>CCL3</td>
<td>MIP-1α</td>
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<td>(5'-TGCTGCTGTCGTCAAGTA-3')</td>
<td>Inflammation</td>
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<tr>
<td>NM_021006.4</td>
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<td>CCL3L1</td>
<td>LD7ββ</td>
<td>(5'-GTCCCTCTCGACCAACTG-3')</td>
<td>(5'-GGAAGATGACCTGGGCTG-3')</td>
<td>Inflammation</td>
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<tr>
<td>NM_002427.3</td>
<td>Matrix metalloproteinase 13</td>
<td>MMP-13</td>
<td>Collagenase 3</td>
<td>(5'-TGTCAGCGAGAGATGAAGACC-3')</td>
<td>(5'-TCCTGAGACTGGAATG-3')</td>
<td>Degradation (catabolism)</td>
</tr>
<tr>
<td>NM_005099.4</td>
<td>A disintegrin and metalloproteinase with thrombospondin motifs 4</td>
<td>ADAMTS-4</td>
<td>—</td>
<td>(5'-GGCTAAGGCCATCCCTGCTA-3')</td>
<td>(5'-GAGCTAACCACCAAGCTGCA-3')</td>
<td>Degradation (catabolism)</td>
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<td>(5'-CACCTTGGTCACCAAGGGA-3')</td>
<td>Synthesis (anabolism)</td>
</tr>
<tr>
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<td>Aggrecan</td>
<td>ACAN</td>
<td>—</td>
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<td>(5'-CTGACCCCTGGAACCTGCA-3')</td>
<td>Synthesis (anabolism)</td>
</tr>
<tr>
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<td>GAPDH</td>
<td>G3PDH</td>
<td>(5'-ACCCAGAAGACTGTTGAGATG-3')</td>
<td>(5'-GAGGACAGGGATGATGTCG-3')</td>
<td>Housekeeping</td>
</tr>
</tbody>
</table>

*NCBI = National Center for Biotechnology Information.
disease states. Chemokine production is upregulated by proinflammatory molecules such as IL-1β and tumor necrosis factor alpha (TNF-α), and chemokines may play a role in osteoarthritis by recruiting inflammatory cells to injured cartilage, by directly stimulating inflammation and production of degradative enzymes such as MMP-13, or by stimulating the death of chondrocytes through apoptosis. Despite our improved understanding of hip pathomechanics and osteoarthritis pathobiology, the cellular and molecular “links” between the pathologic mechanical environment and the metabolic alterations of articular cartilage in hip osteoarthritis are not understood. An improved understanding of these biologic cascades will facilitate future disease staging and therapeutic strategies for pre-arthritis and early arthritic hip disease. Nevertheless, characterization of the cellular and molecular events that mediate articular cartilage degeneration remains problematic because of the current limitations of animal models of hip osteoarthritis, the questionable relevance of in vitro osteoarthritis models, and the inherent limitations in obtaining and studying human cartilage tissues from pre-arthritic and/or early arthritic hips.

Over the past decade, there has been an increased utilization of hip joint preservation procedures designed to surgically “normalize” or improve the mechanical environment of pre-arthritis and early arthritic hips. A common component of hip joint preservation procedures for femoroacetabular impingement is resection of a prominent anterolateral femoral head-neck junction to relieve mechanical impingement. For comparison, articular cartilage samples without signs of tissue degeneration (control samples) were obtained from patients undergoing hip preservation surgery involving acetabular reorientation for developmental dysplasia of the hip. The anterolateral head-neck junction (which was without signs of articular cartilage degeneration) was then removed from the latter patients to prevent potential secondary femoroacetabular impingement.

The three patients (all female) from whom a control cartilage sample was obtained for comparison had a mean age of twenty-eight years (range, fifteen to forty-four years). Each patient signed a research consent form for the study, which was approved by the university’s institutional review board. All surgical procedures were performed by a single surgeon (J.C.C.) from 2009 to 2011.

Twenty-five of the thirty-two non-control patients (and hips) were treated with hip preservation surgery and formed the primary study group. All of these hips were treated for symptomatic femoroacetabular impingement with open femoral head-neck osteochondroplasty; arthroscopic procedures performed during the study period to treat femoroacetabular impingement were excluded because of the difficulties encountered in tissue harvesting and processing. The mean age of these eight female and seventeen male patients was 24.1 years (range, thirteen to thirty-seven years). All patients had a clinical diagnosis of femoroacetabular impingement as determined by one of the authors (J.C.C.). All had groin pain, restricted hip internal rotation in flexion, and a positive anterior impingement test. All were evaluated with preoperative radiographs made according to a previously published protocol and were found to have structural abnormalities consistent with cam or combined cam and pincer impingement. Additionally, the radiographic assessment of the osteoarthritis grade according to the Tönnis classification system was recorded. Twelve (48%) of the hips were Tönnis grade 0 (no radiographic evidence of osteoarthritis), nine (36%) were grade 1 (erosion only), and four (16%) were grade 2 (moderate joint-space narrowing). None were Tönnis grade 3 (advanced osteoarthritis with severe joint-space narrowing). All patients had undergone prior unsuccessful nonsurgical treatment.

The remaining seven non-control patients were treated with primary total hip replacement or hip resurfacing for end-stage osteoarthritis. The mean age of these two female and five male patients was 52.7 years (range, thirty-seven to seventy-three years). All had a diagnosis of osteoarthritis with hip morphology consistent with femoroacetabular impingement and Tönnis grade 3 osteoarthritis on radiographs. Specimens were obtained from the anterolateral femoral head-neck junction of these hips in a fashion identical to that in the hips with femoroacetabular impingement. These served as a comparison group of biologic specimens representing end-stage hip osteoarthritis.

At the time of surgery, the integrity of the articular cartilage at the femoral head-neck junction was evaluated macroscopically and was classified...
with use of the system of Beck et al. This system includes criteria to evaluate the macroscopic appearance of the articular cartilage, integrity of the cartilage surface, and fixation of the cartilage to the underlying subchondral bone (see Appendix). This system was used by the senior surgeon (J.C.C.) to classify all samples into one of five categories: normal, chondromalacia, debonding, cleavage and/or thinning, or defect. The most severe area of disease in each specimen was used for the final grading. After the cartilage was harvested from the anterolateral impingement zone of the femoral head-neck junction, RNA was extracted from the sample and quantitative RT-PCR (real-time polymerase chain reaction) was performed to evaluate gene expression in the articular cartilage. The genes selected for evaluation included genes for cytokines, chemokines, degradative enzymes, and extracellular matrix proteins thought to play a role in osteoarthritis or joint degradation (Table I).

Isolation of RNA and Quantitative RT-PCR

The cartilage tissues were immersed promptly in TRIzol reagent (Invitrogen, Carlsbad, California) on reception to avoid potential RNA degradation. In addition, all RNA preparation was carried out under RNase-free conditions. Isolation of total RNA and quantitative RT-PCR were carried out as described previously, with slight modifications. Briefly, total RNA was first extracted from the cartilage with TRIzol reagent according to the protocol recommended by the manufacturer. After the RNA extraction, RNA clean-up was performed with use of an RNeasy Mini Kit (Qiagen, Valencia, California). Total RNA was reverse-transcribed with SuperScript II reverse transcriptase (Invitrogen) to synthesize first-strand complementary DNA (cDNA). Using this cDNA, quantitative RT-PCR was performed with 20 μL of reaction mixture containing SYBR Green PCR Master Mix (Applied Biosystems, Foster City, California) and primers on a 7500 Fast Real-Time PCR system (Applied Biosystems). Primers were for quantitative RT-PCR were selected for each gene (Table I), and the dissociation curve was determined. The primer design parameters included a primer size of 18 to 21 bp, a product size of 80 to 150 bp, a primer annealing temperature of 59° to 61°C, and a primer GC content of 45% to 55%. Results were normalized to the glyceraldehyde-3-phosphate dehydrogenase (GAPDH) level. The three control articular cartilage samples and seven end-stage osteoarthritis samples were analyzed for comparison. The comparative C<sub>T</sub> (threshold cycles) method was used to evaluate the expression level of each

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target gene relative to the level in the controls. All graphs depict the expression level in each non-control patient group divided by that in the controls.

**Statistical Analysis**

Data are expressed as the mean and the standard error of the mean unless otherwise indicated. The nonparametric Mann-Whitney U test was used for comparisons of normally distributed data among the groups. Analysis of variance (ANOVA) followed by the Tukey honestly significant difference post hoc test were used for multiple comparisons. Differences in gene expression were considered significant at a p value of ≤0.05. *P ≤ 0.05, **P < 0.01, ***P < 0.001.

**Source of Funding**

The study was funded by NIH (National Institutes of Health) grants R0136994, R01AR050847, R02AR058978, and P30AR057235. M.E.R. is supported by a Ruth L. Kirschstein National Research Service Award Fellowship (T32-AR060719) from the NIH.

**Results**

Expression of cytokine, chemokine, degradative enzyme, and matrix genes was evaluated in three distinct groups of articular cartilage specimens. The genes analyzed are shown in Table I and the characteristics of the tissue sources are summarized in Table II. Gene expression in the twenty-five hips with a clinical diagnosis of femoroacetabular impingement was compared with gene expression in the three control samples of cartilage from hips without osteoarthritis as well as the seven samples obtained from hips with end-stage osteoarthritis.

![Normalized mRNA expression of selected cytokine and chemokine, matrix-degrading, and structural matrix genes (defined in Table I) in articular cartilage samples obtained from hips with femoroacetabular impingement (FAI) classified intraoperatively according to the Beck criteria (normal, chondromalacia, cleavage/thinning, and defect) and hips with end-stage osteoarthritis (OA) compared with controls. The mRNA expression in the FAI cleavage/thinning category was higher than those in the other FAI categories, OA, and normal control cartilage except in the cases of CXCL1, CXCL6, and MMP-13, for which the expression in the FAI cleavage/thinning category remained relatively similar to that in the chondromalacia category. The mRNA expression levels of IL-8, CXCL2, CXCL3, CCL3L1, and ACAN were significantly higher in the FAI cleavage/thinning category than in the other categories indicated by asterisks, indicating that cartilage at the cleavage/thinning stage expressed more inflammatory and catabolic mediators. None of the other groups differed significantly. The data are expressed as the mean and the standard error of the mean relative to the mean expression of the control specimens. A p value of ≤0.05 was considered significant. *P ≤ 0.05, **P < 0.01, ***P < 0.001.

Fig. 2
at the time of total hip arthroplasty or hip resurfacing (Fig. 1). Expression of all inflammatory cytokines and chemokines except IL-1β and CXCL2 was elevated in the samples from the hips with femoroacetabular impingement compared with the control samples. The difference was significant \( p \leq 0.05 \) for IL-8, CXCL3, CXCL6, and CCL3L1, and significant differences were also observed for ADAMTS-4, COL2A1, and ACAN. Expression of certain of these chemokines (IL-8 and CCL3L1), matrix-degrading (ADAMTS-4), and extracellular matrix (ACAN) genes was also higher in cartilage from hips with femoroacetabular impingement compared with end-stage osteoarthritis. In addition, the gene expression differences between the control cartilage and the cartilage from hips with end-stage osteoarthritis were variable and not significant except in the case of ACAN, which was significantly upregulated in the osteoarthritic group.

Articular cartilage damage observed intraoperatively in hips with femoroacetabular impingement and osteoarthritis was graded in order to compare expression of cytokine, chemokine, degradative enzyme, and matrix genes in articular cartilage from different stages of the osteoarthritic cascade. According to the Beck criteria, three (12%) of the hips with femoroacetabular impingement were classified as showing a normal appearance; thirteen (52%), chondromalacia; zero (0%), debonding; five (20%), cleavage/thinning; and four (16%), a full-thickness defect (see Appendix). The radiographic osteoarthritis scoring was grade 0 (no evidence of osteoarthritis) in twelve (48%) of these hips, grade 1 (sclerosis only) in nine (36%), and grade 2 (moderate joint space narrowing) in four (16%). All samples from hips with end-stage osteoarthritis were classified as showing a full-thickness defect, and the radiographic scoring was grade 3 (severe joint space narrowing) in all of these hips. Analysis of gene expression according to the intraoperative classification of articular cartilage damage (Fig. 2) revealed that the expression of certain chemokine (IL-8, CXCL2, CXCL3, and CCL3L1) and extracellular matrix (ACAN) genes was significantly higher in the cleavage/thinning stage.

Gene expression was generally lower in the control cartilage than in the other groups except in the case of IL-1β, which was expressed at a relatively similar level in the control cartilage and cartilage at the cleavage/thinning stage.

**Discussion**

Femoroacetabular impingement is a common cause of hip pain in adolescents and young adults\(^{15}\), and it has been implicated as an important etiologic factor in secondary hip osteoarthritis. In recent years, a better understanding of the clinical presentation and structural characteristics of this condition has led to increased utilization of surgical procedures designed to preserve the hip joint with the aim of relieving symptoms, enhancing function, and improving the mechanical environment of the hip joint. Although an increasing body of literature suggests that femoroacetabular impingement plays a role in the development of secondary osteoarthritis\(^{14,31}\), there remains substantial controversy regarding this topic\(^{4,32}\). Additionally, the impact of femoroacetabular impingement on articular cartilage and joint biology at the cellular and molecular level is poorly understood. In order to better understand the biological link between femoroacetabular impingement and osteoarthritis, we compared the expression of cytokine, chemokine, degradative enzyme, and cartilage matrix genes in articular cartilage from hips with femoroacetabular impingement, normal hips, and hips with osteoarthritis. Furthermore, we compared gene expression in the articular cartilage from hips in various stages of the osteoarthritic cascade (as determined by intraoperative morphologic grading).

To our knowledge, this is the first report of metabolic activity levels in the articular cartilage of human subjects with femoroacetabular impingement. Articular cartilage obtained from the impingement zone (anterolateral head-neck junction) of hips with femoroacetabular impingement expressed markedly elevated levels of most chemokines and degradative enzymes, but not of the proinflammatory cytokine IL-1β, compared with normal articular cartilage (Fig. 1). Cartilage specimens from hips with femoroacetabular impingement also expressed significantly higher levels of certain chemokines and other markers (IL-8, CCL3L1, ADAMTS-4, and ACAN) compared with articular cartilage from hips with end-stage osteoarthritis. In the comparison among different stages of articular cartilage degradation, the cleavage/thinning stage was the most metabolically active as indicated by our panel of target genes. Importantly, there was a trend toward decreased expression of matrix protein genes (COL2A1 and ACAN) in end-stage osteoarthritis compared with femoroacetabular impingement, although this decrease was significant only for ACAN.

The early pathophysiology of osteoarthritis is poorly understood, and very limited information exists regarding the biologic cascade that mediates osteoarthritis in the human hip. Nevertheless, previous work suggests that early changes after injury to articular cartilage include hypertrophy, collagen deformation, proteoglycan depletion, and mild inflammation\(^{33-35}\). These events are reversible, as chondrocytes can degrade damaged molecules and increase matrix production\(^4\). Thus, both anabolism and catabolism are increased in early osteoarthritis, with the balance moving toward catabolism with disease progression\(^33\). These previous observations are consistent with the data from the hips with femoroacetabular impingement and osteoarthritis in the present study (Fig. 1). The samples from hips with femoroacetabular impingement demonstrated higher metabolic activity involving inflammatory chemokine (IL-8 and CCL3L1), matrix-degrading (ADAMTS-4), and extracellular matrix (ACAN) genes compared with hips with end-stage osteoarthritis. The decrease in matrix protein gene expression in hips with end-stage osteoarthritis may indicate a loss of anabolic activity and an imbalance favoring catabolism.

Conventional diagnosis and treatment of pre-arthritic, early arthritic, and advanced arthritic conditions is highly dependent on patient symptoms, physical examination, and radiographic evaluation\(^4\). It is important to note that the
majority (84%) of the hips with femoroacetabular impingement in the present study had no or only early radiographic signs of osteoarthritis (Tönnis grade 0 or 1), yet the alterations in articular cartilage metabolic activity were profound. This finding underscores the concept that the biology of the osteoarthritic cascade far precedes radiographic evidence of disease. Consequently, alternative methods of diagnosis and disease staging are being investigated. Biologic markers from blood, urine, and synovial fluid are considered potential candidates for future diagnostic and disease staging strategies. In the present study, articular cartilage from hips with femoroacetabular impingement demonstrated a "molecular signature" compared with normal cartilage. Several of the chemokines that were highly expressed in cartilage from hips with femoroacetabular impingement were most markedly elevated when the stage of articular cartilage degeneration was classified as chondromalacia or cleavage/thinning. These morphologic stages of articular cartilage degeneration commonly precede radiographic osteoarthritic changes, suggesting that specific cytokine and chemokine gene expression levels may have potential in characterizing the early (pre-arthritic) molecular changes that are occurring in articular cartilage. These new findings provide a basis for pursuing distinct chemokines as candidate biomarkers for the diagnosis and staging of pre-osteoarthritic and early osteoarthritic disorders.

Another important aspect of this study was the availability of control hip cartilage samples from age-matched subjects without osteoarthritis who were undergoing hip surgery. These samples provided baseline data for comparison with tissue from hips with femoroacetabular impingement and osteoarthritis. Nevertheless, the study has limitations. First, although we identified local alterations in articular cartilage gene expression in femoroacetabular impingement that may mediate the osteoarthritic cascade, we have not identified the specific molecular and/or mechanistic role of each factor in the pathophysiology of femoroacetabular impingement, as such studies were beyond the scope of this report. Future investigations will focus on the mechanisms of the osteoarthritic cascade. Second, we measured gene expression in only one specific area of articular cartilage (the anterolateral femoral head-neck junction); the expression and molecular characteristics of articular cartilage in other areas of the hip were not determined. This limitation could not be overcome because the surgical goal of preserving the joint in patients with femoroacetabular impingement excluded the possibility of harvesting tissues from other regions. Therefore, the impact of femoroacetabular impingement pathomechanics on articular cartilage away from the impingement zone remains unclear.

In conclusion, these findings provide novel information regarding the pathophysiology of femoroacetabular impingement and the molecular basis of human hip osteoarthritis. Specifically, we demonstrated the feasibility of analyzing gene expression in articular cartilage samples obtained from the impingement zone at the time of joint preservation surgery. Analysis of these tissues suggests that the mechanical disease of femoroacetabular impingement causes localized articular cartilage alterations that are consistent with early osteoarthritic degeneration. Specifically, articular cartilage in the femoroacetabular impingement zone had high metabolic activity, both catabolic and anabolic, that commonly preceded radiographic evidence of osteoarthritis.

Appendix

A table showing the Beck criteria for intraoperative grading of articular cartilage lesions is available with the online version of this article as a data supplement at JBJS.org.

References
