

Biomarkers in the serum, synovial fluid and articular cartilage show promising utility in patients with femoroacetabular impingement: a systematic review

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ABSTRACT

Importance Biomarkers have promising potential to provide a cost-effective tool to identify patients with femoroacetabular impingement (FAI) who are most at risk and who may benefit most from early joint preservation surgery.

Objective To assess the potential role of biomarkers in the diagnosis and prognosis of FAI.

Evidence review Three databases (PubMed, Ovid (MEDLINE) and Embase) were searched on 20 August 2017 from database inception, and two reviewers independently and in duplicate screened the resulting literature. Methodological quality of all included papers was assessed using the Methodological Index for Non-Randomized Studies criteria. The results are presented in a narrative summary fashion using descriptive statistics including means, proportions and ranges.

Findings Seven studies (one retrospective laboratory series and six controlled laboratory studies) were identified including a total of 227 patients. The mean age of the patients was 41.6 years (range: 13–80), with a mean follow-up period of 29.9 months (SD=3.2). Markers of articular cartilage breakdown, including cartilage oligomeric matrix protein (COMP) and fibronectin–aggrecan complex (FAC), were identified in high concentrations in the serum and synovial fluid of patients with FAI, respectively. Moreover, mRNA expression of catabolic cytokines in the articular cartilage of patients with FAI has been reported.

Conclusions and relevance Although not yet used in clinical settings, several biomarkers of articular cartilage damage have been identified in the serum, synovial fluid and articular cartilage of patients with FAI. These findings provide promising insight into the potential role of biomarkers in guiding clinical practice and assisting with patient selection and preoperative counselling in patients with FAI and should be evaluated further.

Level of evidence IV, systematic review of level III and IV studies.

INTRODUCTION

Femoroacetabular impingement (FAI) is a condition that is characterised by a slow onset of groin pain that can be exacerbated by exercise or prolonged walking.¹ It usually presents in active young adults, specifically those involved in high impact activity that requires hip flexion and internal/external rotation.² FAI can be characterised into ‘pincer type’ (hip motion limited by a functionally excessive acetabular coverage) or ‘cam type’ (hip motion limited by a malshapened and enlarged femoral

What is already known

- The role that proinflammatory cytokines play in osteoarthritis (OA) has been well documented.
- As increasing evidence emerges suggesting that femoroacetabular impingement (FAI) may cause or hasten the onset of OA, it is likely that some of the molecular biomarkers that are present in OA are also present in FAI.
- Should certain biomarkers demonstrate proven efficacy in monitoring disease progression, they would provide a cost-effective tool to identify those patients with FAI who are most at risk and who may benefit most from early joint preservation surgery.

What are the new findings

- Biomarkers of articular cartilage damage such as serum markers cartilage oligomeric matrix protein and C reactive protein, as well as the expression of inflammatory markers such as interleukin-8, a disintegrin and metalloproteinase with thrombospondin motifs-4, aggrecan, chemokine (C-X-C) motif ligand 3, CXCL6, chemokine (C-C) motif ligand 3-like 1 and collagen type II alpha 1 in the articular cartilage have demonstrated promising results in patients with FAI.
- These findings provide insight into the potential role of biomarkers in guiding clinical practice and assisting with patient selection and preoperative counselling in patients with FAI and should be evaluated in further clinical studies.

head–neck junction) variations, or a combination of both.³ Furthermore, the anatomy of FAI is quite prevalent, and FAI may lead to osteoarthritis (OA) in some patients.⁴ Differentiation of those who need treatment from those who do not may be critical in the coming days of precision medicine.

Due to the relatively recent recognition of FAI as a unique hip condition, there continues to be a need to establish more defined standards for assessment. Furthermore, FAI can be difficult to diagnose clinically, as many of the tests that are currently used have a low specificity.⁵ Radiographic analysis is commonly used to help diagnose FAI, and



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although it is a useful tool for clinicians, there are controversies with respect to the ideal radiographic parameters used to diagnose FAI.^{6,7} Thus, the use of molecular biomarkers for FAI diagnosis has emerged as a topic of interest in FAI research.

The role that proinflammatory cytokines play in OA has been well documented.⁸ These secreted inflammatory molecules are one of the critical mediators of the disturbed processes implicated in OA pathophysiology.⁸ As increasing evidence emerges suggesting that FAI may cause or hasten the onset of OA,³ it is likely that some of the molecular biomarkers that are present in OA are also present in FAI.⁹ Several studies have identified the presence of biomarkers signalling early articular cartilage destruction in patients with FAI.^{10–12} These markers of articular cartilage destruction may serve an important role in the future to guide clinical practice and assist with patient selection and preoperative counselling. Another promising area in the use of molecular biomarkers relates to the potential of these markers to indicate disease severity or even prognosis, and further still, those with FAI who may develop premature OA may be identified and treated earlier, with the intent to prevent OA. Therefore, this systematic review was conducted in order to assess the possibility and efficacy of novel diagnostic tools and outcome measures for patients with FAI. The purpose of this systematic review was to assess the potential role of biomarkers in the diagnosis and prognosis of FAI. We hypothesise that inflammatory biomarkers in the serum, synovial fluid and articular cartilage are identified in higher concentrations in patients with FAI.

METHODS

Search strategy

The methodology used in the present study is similar to a previously conducted systematic review by our institution.¹³ Three online databases (Embase, PubMed and Ovid (MEDLINE)) were searched for literature from database inception until 20 August 2017 investigating the use of biomarkers in FAI. The search included the terms ‘femoroacetabular impingement’ ‘biomarker’ and ‘molecular marker’ (online supplementary appendix table 1).

Study screening

The titles, abstracts and full-text articles were screened by two reviewers independently and in duplicate. Disagreements during title and abstract screening moved onto the next stage for more in-depth review. Any disagreements were discussed between reviewers, and a senior author was consulted for any remaining discrepancies. The references of the included studies were subsequently manually screened for additional articles that may have eluded the initial search strategy.

Assessment of study eligibility

The research question and study eligibility criteria were established a priori. The inclusion criteria were English language studies, studies investigating living humans, studies with level of evidence I–V and those studying the use of biomarkers in patients with FAI. Exclusion criteria were animal studies, cadaveric reports, commentaries, book chapters, review articles and technical studies.

Data abstraction

Data were collected by two reviewers and recorded them in a Microsoft Excel spreadsheet (V.2007). Abstracted data included the authors, year of publication, study design, sample sizes, sex ratio, mean age, biomarker type, biomarker source, sample

collection and storage, assay type, assay analysis and follow-up time whenever reported.

Quality assessment

The methodological quality of the included studies was assessed using the Methodological Index for Non-Randomized Studies (MINORS) instrument. This tool was designed to assess the methodological quality of comparative and non-comparative, non-randomised surgical studies.¹⁴ Using the MINORS checklist, non-comparative studies are assigned a maximum score of 16, and comparative studies can achieve a maximum score of 24.

Assessment of agreement

In order to assess the inter-reviewer agreement, a kappa (κ) statistic was calculated for the title, abstract and full-text screening stages. An intraclass correlation coefficient (ICC) was calculated for the quality assessment using the MINORS criteria. Agreement was categorised a priori as follows: κ /ICC of 0.61 or greater was considered substantial agreement; κ /ICC of 0.21–0.60, moderate agreement; and κ /ICC of 0.20 or less indicating slight agreement.¹⁵

Statistical analysis

Given the non-uniform nature of the studies included in this systematic review in terms of techniques and outcome reporting, the results are presented in a narrative summary fashion. Descriptive statistics including means, proportions, SD and 95% CIs were calculated using Minitab statistical software (V.17, Minitab, State College, Pennsylvania, USA).

RESULTS

Search strategy

The initial search of the online databases resulted in 4056 total studies. Six hundred and fifty-five duplicate studies were removed. A systematic screening and assessment of eligibility identified seven full-text articles that satisfied the inclusion and exclusion criteria (figure 1). The reviewers reached substantial agreement at the title ($\kappa=0.853$; 95% CI 0.812 to 0.894), abstract ($\kappa=0.882$; 95% CI 0.804 to 0.960) and full-text ($\kappa=0.942$; 95% CI 0.821 to 1.00) screening stages.

Study quality and characteristics

Of the six included studies, one retrospective laboratory series and five controlled laboratory studies were identified, which were of level IV and III evidence, respectively. The MINORS score of the single non-comparative study was 9 out of 16, whereas the median MINORS score for the five comparative studies was 13 out of 24 (ranging from 11 to 14). The overall inter-rater agreement for the MINORS score was substantial, with an ICC of 0.823 (95% CI 0.712 to 0.934). In total, 194 patients with a mean age of 41.6 years (ranging from 13 to 80) were included in this systematic review. Overall, 43.8% of the included patients were female. Mean follow-up time, only reported in one study, was 29.9 months (SD=3.2) (table 1).

Diagnosis

All seven studies, including 227 patients, reported on biomarker characterisation and their utility in diagnoses. Of these studies, one study investigated biomarkers within the plasma, two studies investigated biomarkers within articular cartilage, two studies investigated biomarkers within the labrum and four studies investigated biomarkers within the synovium and synovial fluid. Details of the biomarkers evaluated, and the method

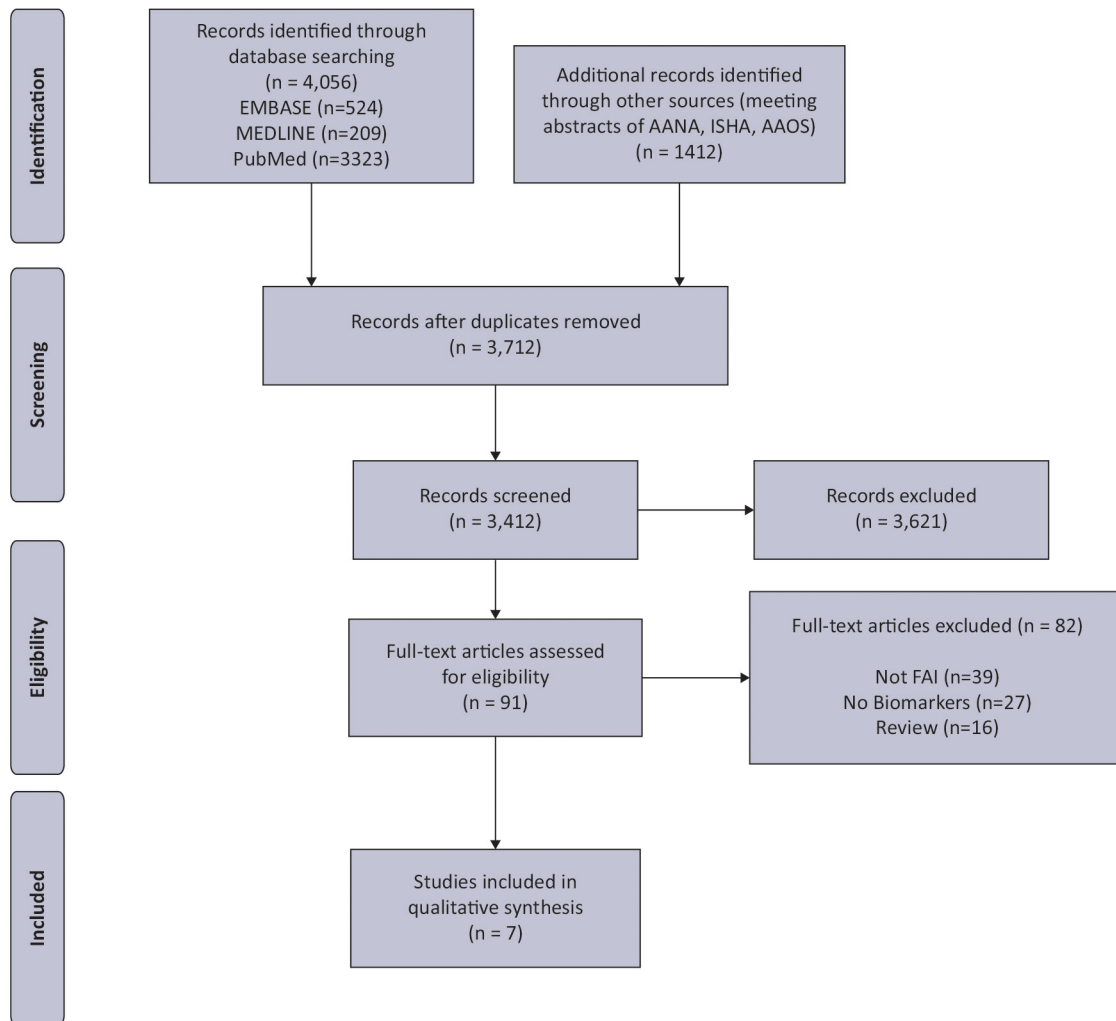


Figure 1 PRISMA flow diagram demonstrating the systematic review of the literature for the use of biomarkers in the diagnosis and prognosis of FAI. FAI, femoroacetabular impingement; AANA, Arthroscopy Association of North America; ISHA, International Society for Hip Arthroscopy; AAOS, American Academy of Orthopaedic Surgeons.

of assessment are available in [table 2](#). The diagnosis of FAI in each of the studies was made based on a history of hip pain, clinical examination findings consistent with FAI including flexion,

adduction and internal rotation and impingement tests, as well as radiographic (plain radiographs and, when needed, MRI) findings consistent with cam or pincer lesions.^{10–12 16–18} OA was

Table 1 Characteristics of included studies and patients

Author (year)	Study design (level of evidence)	MINORS score (mean)	Sample size (patients/hips)	Per cent female	Age, years, (range) or SD	Follow-up time, months, (range) or SD
Abrams <i>et al</i> (2014) ¹⁶	Controlled laboratory study (III)	12	FAI+OA	17/17	47.1	59.2±11.9
			FAI+non-OA	17/17	70.6	38.3±11.1
Bedi <i>et al</i> (2013) ¹⁰	Controlled laboratory study (III)	14	FAI	10/NR	0	23.1±6.4
			Non-FAI	19/NR	0	22.3±3.4
Chinzei <i>et al</i> (2016) ¹¹	Controlled laboratory study (III)	11	FAI	30/30	40	42 (14–60)
			OA	30/30	93.3	69 (50–80)
Elias-Jones <i>et al</i> (2015) ¹⁸	Controlled laboratory study (III)	13	FAI	10/NR	NR	36 (20–54)
			OA	10/NR	NR	39 (32–49)
Fukushima <i>et al</i> (2017) ¹⁹	Prospective controlled study (II)	14	FAI	33/34	70	41.8±2.5
Hashimoto <i>et al</i> (2013) ¹²	Controlled laboratory study (III)	13	FAI	25/25	32	24.1 (13–37)
			OA+FAI	7/7	28.6	52.7 (37–73)
			Control	3/3	100	28 (15–44)
Shapiro <i>et al</i> (2016) ¹⁷	Retrospective laboratory series (IV)	9		16/16	75	38.9±11.2
						29.9±3.2

FAI, femoroacetabular impingement; MINOR, Methodological Index for Non-Randomised Studies; NR, not reported; OA, osteoarthritis.

Table 2 Biomarkers investigated and laboratory assay protocols

Author (year)	Biomarker type	Biomarker source	Sample collection and storage	Assay type	Assay analysis
Abrams <i>et al</i> (2014) ¹⁶	Proteins: FAC (OD), IL-1 β , IL-1RA, IL-6, Eotaxin, IFN- γ , IP-10, MCP-1, MIP-1 β , PDGF-BB, RANTES, TNF α , VEGF	Synovial fluid	Collection of synovial fluid done at time of hip arthroscopy or arthroplasty by injecting 10 mL of sterile normal saline intra-articularly and aspirating back the fluid. Lavasate placed into 2 mL tubes containing 130 μ L of protease inhibitor (Roche Diagnostics, Indianapolis, Indiana, USA) dissolved in phosphate-buffered saline solution (0.045 tablet/mL sample) at pH 7.4 and stored at -80°C.	ELISA	Human multiplex inflammatory cytokine panel and the BioPlex 200 System (Bio-Rad Laboratories, Hercules, California, USA) used to determine biomarker concentration in a 96-well plate.
Bedi <i>et al</i> (2013) ¹⁰	Proteins: COMP, CRP	Plasma	~3 mL of blood was collected from an antecubital vein into a K2-EDTA tube, spun down at 1000 g for 10 mins and plasma was removed and stored at -80°C.	ELISA	Plasma analysed in duplicates using ELISA for COMP and ultrasensitive CRP in a SpectraMax plate reader.
Chinzei <i>et al</i> (2016) ¹¹	mRNA: IL-1 β , IL-8, MMP-3, COL1A1, COL2A1, ACAN, ADAMTS-4, MMP-13	Tissue: synovium, labrum, articular cartilage	Tissue samples collected from anterolateral femoral head-neck junction.	Transcript analysis	Total RNA extracted from all tissue samples using TRIzol Reagent (Invitrogen (ThermoFisher Scientific)) and RNeasy spin columns (Qiagen, Valencia, California, USA). cDNA was then synthesised using SuperScript II reverse transcriptase (Invitrogen). Finally, qPCR was performed using 20 mL of reaction mixture containing SYBR Green PCR Master Mix (Applied Biosystems (ThermoFisher Scientific)) and primers on the ABI PRISM 7700 Sequence Detection System (Applied Biosystems). Gene expression levels were compared between FAI and OA groups using the comparative C _t cycle method.
Elias-Jones <i>et al</i> (2015) ¹⁸	Proteins: CD68, CD3, CD4, CD34, VEGF, CD206, IL-13, mast cell tryptase	Tissue: labrum	Labrum samples obtained at time of arthroscopy or arthroplasty. Tissue samples immediately fixed in 10% (vol/vol) formalin for 4–6 hours and then embedded in paraffin. Sections were cut to 5 mm thickness using a Leica-LM microtome (Leica Microsystems) and placed onto Superfrost Ultra Plus glass slides (Gerhard Menzel).	Immunohistological analysis	After the removal of paraffin from the slides, the sections were stained with H&E and toluidine blue. Then, the sections were stained with primary monoclonal antibodies directed against the biomarkers of interest. Next, endogenous peroxidase activity was quenched, and non-specific antibody binding was blocked. Afterwards, antigen retrieval was performed, and the sections were incubated with the primary antibody. After two washes, the slides were incubated with an ImmPRESS Reagent kit (Vector Laboratories Ltd) per manufacturer instructions. The slides were washed and incubated with Vector ImmPACT DAB chromagen solution. Finally, the sections were counterstained with haematoxylin and dehydrated again before mounting. Positive control with human tonsil tissue and negative control specimens were assessed as well. Only structures that morphologically appeared as vascular and stained with either immunomarker (CD34/VEGF) were taken into account when determining the vessel count.
Fukushima (2017) ¹⁹	mRNA: TNF α , IL-1 β , IL-6, ADAMTS-4, MMP1, MMP3	Tissue: synovial membrane	Total RNA was extracted from harvested synovial samples using TRIzol (Invitrogen, Carlsbad, California, USA) according to the manufacturer's instructions and was used as a template for first-strand cDNA synthesis using SuperScript III RT (Invitrogen).	Transcript analysis	The PCR reaction mixture consisted of 2 μ L cDNA, the specific primer set (0.2 μ M final concentration) and 12.5 μ L SYBR Premix Ex Taq (Takara, Kyoto, Japan) in a final volume of 25 μ L. Quantitative PCR was performed using a real-time PCR detection system (CFX-96; Bio-Rad Laboratories). The PCR cycle parameters consisted of an initial denaturation at 95°C for 1 min, followed by 40 cycles of 95°C for 5 s and 60°C for 30 s. mRNA expression was normalised to the level of GAPDH mRNA.

Continued

Table 2 Continued

Author (year)	Biomarker type	Biomarker source	Sample collection and storage	Assay type	Assay analysis
Hashimoto <i>et al</i> (2013) ¹²	mRNA: IL-1 β , IL-8, CXCL1, CXCL2, CXCL3, CXCL6, CCL3, CCL3L1, MMP-13, ADAMTS-4, COL2A1, ACAN	Tissue: articular cartilage	Cartilage sample obtained from anterolateral femoral head-neck junction at site of mechanical impingement. Sample immersed promptly in TRIzol reagent (Invitrogen) to avoid RNA degradation.	Transcript analysis	RNA clean-up using RNeasyMini Kit (Qiagen). Reverse-transcription performed with SuperScript II reverse transcriptase (Invitrogen) to synthesise first-strand cDNA. qPCR performed using cDNA with 20 mL of reaction mixture containing SYBR Green PCR MasterMix (Applied Biosystems, Foster City, California, USA) and primers on a 7500 Fast Real-Time PCR system (Applied Biosystems). Results normalised to GAPDH levels. Comparative C _t method used to evaluate the expression level of each target gene relative to control.
Shapiro <i>et al</i> (2016) ¹⁷	Proteins: FAC (OD), IFN- γ , IL-6, IL-1RA, IL-1 β , MCP-1, Eotaxin, MIP-1 β , IP-10, PDGF-BB, RANTES, TNF α , VEGF	Synovial fluid	Collection of synovial fluid done at time of hip arthroscopy by injecting 10 mL of sterile normal saline intra-articularly and aspirating back the fluid. Lavasate placed in 2 mL tubes with 130 μ L of protease inhibitor (Roche Diagnostics), dissolved in phosphate-buffered saline solution (0.045 tablet/mL sample) at pH 7.4 and frozen at -80°C.	ELISA	Human multiplex inflammatory cytokine panel and the BioPlex 200 System (Bio-Rad Laboratories) used to determine biomarker concentration. The assay was performed through the use of antibody linked polystyrene beads with various fluorophore levels (validated against standard ELISA). Heterogeneous sandwich ELISA used to determine FAC concentration, reported as OD.

ACAN, aggrecan; ADAMTS-4, a disintegrin and metalloproteinase with thrombospondin motifs-4; CCL3, chemokine (C-C) motif ligand 3; CCL3L1, chemokine (C-C) motif ligand 3-like 1; COL1A1, collagen type I alpha 1; cDNA, complementary DNA; COL2A1, collagen type II alpha 1; COMP, cartilage oligomeric matrix protein; CRP, C reactive protein; C_t, threshold cycle; CXCL1, chemokine (C-X-C) motif ligand 1; CXCL2, chemokine (C-X-C) motif ligand 2; CXCL3, chemokine (C-X-C) motif ligand 3; CXCL6, chemokine (C-X-C) motif ligand 6; FAD, fibronectin-aggrecan complex; FAC, femoroacetabular impingement; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; IFN, interferon; IL-1 β , interleukin-1 beta; IL-8, interleukin-8; IP-10, interferon-inducible protein 10; MCP, monocyte chemoattractant protein; MMP-3, matrix metalloproteinase-3; MMP-13, matrix metalloproteinase-13; OA, osteoarthritis; OD, optical density; PDGF-BB, platelet-derived growth factor-BB; qPCR, quantitative PCR; RANTES, regulated on activation normal T cell expressed and presumably secreted; TNF, tumour necrosis factor; VEGF, vascular endothelial growth factor.

diagnosed based on the Tonnis grade assessed using plain radiographs.^{11 12 18}

One study investigating biomarkers within the plasma found that cartilage oligomeric matrix protein (COMP) and C reactive protein (CRP) levels were 24% (238 µg/L vs 192 µg/L, $P=0.04$) and 276% greater (3.15 mg/L vs 0.83 mg/L, $P<0.001$),¹⁰ respectively, in patients with FAI compared with patients with radiographically normal hips (absence of FAI) (table 3).

With respect to biomarkers identified in the articular cartilage, one study found that levels of interleukin (IL)-8, a disintegrin and metalloproteinase with thrombospondin motifs-4 (ADAMTS-4), aggrecan (ACAN), chemokine (C-X-C) motif ligand 3 (CXCL3), CXCL6, chemokine (C-C) motif ligand 3-like 1 (CCL3L1) and collagen type II alpha 1 (COL2A1) were greater within FAI specimens compared with control specimens without FAI or signs of degeneration ($P<0.05$).¹² Furthermore, another study investigating biomarkers within articular cartilage found that levels of interleukin-1 beta (IL-1β), interleukin-8 (IL-8), matrix metalloproteinase-13, ADAMTS-4 and CCL3L1 were greater within FAI specimens compared with OA specimens with no signs of FAI ($P<0.05$).¹¹ However, the study found that levels of collagen type I alpha 1 (COL1A1) were greater in cartilage from OA specimens without FAI compared with FAI specimens ($P<0.01$).¹¹ Regarding the ACAN biomarker, one study found that levels were greater in FAI specimens,¹² while another study found that levels were greater in OA specimens with no FAI ($P<0.05$).¹¹

Of the two studies investigating biomarkers within the acetabular labrum,^{11 18} one study found that levels of IL-1β, IL-8, MMP-3 and COL1A1 were greater in OA specimens compared with FAI specimens ($P<0.05$).¹¹ The other study found that levels of IL-13, CD34, vascular endothelial growth factor (VEGF), M2 macrophages and mast cells were greater in labrum samples from FAI specimens compared with OA specimens with no signs of FAI ($P<0.05$).¹⁸

Additionally, of the four studies investigating biomarkers within the synovium and synovial fluid,^{11 16 17 19} three studies reported significant findings. One study found that levels of IL-1β, IL-8¹¹ and matrix metalloproteinase-3 (MMP-3) were greater in the synovial fluid from OA specimens compared with FAI specimens ($P<0.05$). Another study reported that fibronectin-aggrecan complex (FAC) levels were higher in patients with FAI and no radiographic signs of OA compared with patients with radiographic evidence of OA ($P<0.05$).¹⁶ Additionally, in those patients with FAI and no radiographic signs of OA (Tonnis grade 0) undergoing microfracture (and thus, greater area of loss of articular cartilage), FAC levels were higher compared with those with lesser chondral pathology ($P<0.05$).¹⁶ Finally, this study found that age was not a predictor for FAC concentration in synovial fluid ($P>0.05$). Fukushima *et al* reported significantly higher concentrations of the cytokines IL-1β, tumour necrosis factor alpha (TNFα) and IL-6 in patients with diffuse synovitis in comparison with those with focal disease.¹⁹ Another study reported the concentrations of various biomarkers found within the synovial fluid of patients with FAI,¹⁷ including FAC, interferon (IFN)-γ, IL-6, IL-1RA, IL-1β, monocyte chemoattractant protein 1 (MCP-1), Eotaxin, macrophage inflammatory prote (MIP)-1β, interferon-inducible protein 10 (IP-10), platelet-derived growth factor-BB (PDGF-BB), regulated on activation normal T cell expressed and presumably secreted (RANTES), TNFα and VEGF; however, there was no control group used to provide context to these values.

One study compared biomarker concentrations between cartilage,¹¹ labrum and synovium samples from patients with FAI and found that IL-1β and IL-8 were greater within the cartilage

compared with the labrum and synovium ($P<0.01$). Additionally, this study found that levels of IL-8 in cartilage were greater in patients over 30 years of age compared with patients less than 30 years of age ($P<0.05$). Furthermore, patients with alpha angles less than 60° expressed higher levels of COL1A1 in labral tissue compared with patients with alpha angles greater than 60°. These patients with alpha angles greater than 60° also expressed higher levels of ADAMTS-4 and ACAN in cartilage samples compared with patients with alpha angles less than 60° ($P<0.05$). (table 3).

Prognosis

Overall, three studies^{16 17 19} ($n=83$ patients combined) reported biomarker findings and attempted to find a utility in predicting patient prognoses. Two studies collected synovial fluid for biomarker sampling and found no significant correlation between biomarker values and preoperative and 2-year postoperative outcome scores, including the modified Harris Hip Score (mHHS), Western Ontario and McMaster Universities Arthritis Index and International Hip Outcomes Tool. Collectively, a range of biomarkers were tested within the two studies, including FAC, IFN-γ, IL-6, IL-1RA, IL-1β, MCP-1, Eotaxin, MIP-1β, IP-10, PDGF-BB, RANTES, TNFα and VEGF.^{16 17} Another study found a significant correlation between increased pain/loss of function and synovial membrane cytokine levels. The study found a significant positive correlation between VAS scores and TNFα ($r=0.465$, $P=0.0056$) as well as ADAMTS4 ($r=0.508$, $P=0.0022$). Furthermore, mHHS pain score showed a significant negative correlation with TNFα ($r=-0.472$, $P=0.0049$), IL-6 ($r=-0.455$, $P=0.0068$) and ADAMTS4 ($r=-0.349$, $P=0.043$).¹⁹

Two studies investigated the correlation between staging of articular cartilage damage in patients with FAI and biomarker expression levels.^{12 19} Levels of IL-8, ACAN, CXCL3, CCL3L1 and chemokine (C-X-C) motif ligand 2 were greatest in FAI specimens in the cleavage and/or thinning stage of articular cartilage damage as per the Beck criteria compared with specimens at other stages within the Beck criteria, including normal bone, chondromalacia, debonding and full-thickness defects ($P<0.05$).²⁰ Table 4 presents a summary of the important biomarkers identified in the included studies.

DISCUSSION

The most significant finding in this systematic review is that several biomarkers have been investigated with regards to their role in patients with FAI. Markers of articular cartilage destruction such as COMP and FAC were identified in high concentrations in the serum and synovial fluid of patients with FAI, respectively.^{10 16} Moreover, two studies identified increased mRNA expression of catabolic cytokines in the articular cartilage of patients with FAI.^{11 12} With respect to biomarkers within the labrum, one study reported increased expression of anabolic inflammatory macrophages such as the M2 phenotype of IL-13.¹⁸ Although no biomarkers are currently being used in clinical settings, these findings provide promising data regarding potential roles in the future to guide clinical practice and assist with patient selection and preoperative counselling or as predictive factors for postoperative recovery in patients with FAI.

Several studies included in this review detected the presence of biomarkers signalling articular cartilage destruction in patients with FAI. These findings were detectable in both patients' sera as well as the synovial fluid and provide important potential insight due to their known relationship with OA. COMP is a glycoprotein

Table 3 Key findings, biomarker characterisation and functional outcome scores of included studies

Author (year)	Key findings	Biomarker characterisation	Functional outcome scores
Abrams <i>et al</i> (2014) ¹⁶	FAC higher in non-OA group compared with those with OA ($P<0.001$). In non-OA group, FAC higher in those undergoing microfracture versus those with lesser chondral pathology ($P<0.05$). Age was not a predictor of FAC concentration ($P>0.05$) and accounted for <1% of the variance in FAC values. FAC concentration of 2.18 $\mu\text{g}/\text{mL}$ was 75% sensitive and 84% specific in predicting microfracture in non-OA group (area under ROC curve=0.87).	Mean FAC OA: 0.08 $\mu\text{g}/\text{mL}\pm 0.4$ Mean FAC non-OA: 1.15 $\mu\text{g}/\text{mL}\pm 0.35$ Mean FAC non-OA microfracture: 2.40 $\mu\text{g}/\text{mL}\pm 0.8$ Mean FAC non-OA non-microfracture: 0.77 $\mu\text{g}/\text{mL}\pm 0.3$	No significant correlation between biomarkers and preoperative functional assessment scores (mHHS, WOMAC, iHOT-33).
Bedi <i>et al</i> (2013) ¹⁰	24% higher serum COMP ($P=0.04$) in FAI group. 276% higher serum CRP ($P<0.001$) in FAI group.	Mean COMP FAI: 238 $\mu\text{g}/\text{L}$ Mean COMP non-FAI: 192 $\mu\text{g}/\text{L}$ Mean CRP FAI: 3.15 mg/L Mean CRP non-FAI: 0.83 mg/L	SF-12 PCS: 22% reduction in FAI group ($P<0.001$). SF-12 MCS: No difference between FAI and non-FAI group ($P=0.11$). HOOS: 21% reduction ($P<0.001$) in pain subscale score in FAI group 30% reduction ($P<0.001$) in symptoms score in FAI group. 17% decrease ($P<0.001$) in activities of daily living scores in FAI group. 39% decrease ($P<0.001$) in sport and recreation scores in FAI group. 40% reduction ($P<0.001$) in hip-related quality of life scores in FAI group.
Chinzei <i>et al</i> (2016) ¹¹	Labrum: mRNA expression of inflammatory cytokines (IL-1 β and IL-8), catabolic genes (MMP-3) and anabolic genes (COL1A1) higher in OA hips compared with FAI hips ($P<0.05$). Synovium: mRNA expression of inflammatory cytokines (IL-1 β and IL-8) and catabolic genes (MMP-3) higher in OA hips compared with FAI hips ($P<0.05$). Cartilage: mRNA expression of inflammatory cytokines (IL-1 β and IL-8) and catabolic genes (ADAMTS-4 and MMP-13) higher in FAI hips compared with OA hips ($P<0.01$). mRNA expression of anabolic genes (COL2A1 and ACAN) higher in OA hips compared with FAI hips ($P<0.01$). FAI analysis: mRNA expression of inflammatory cytokines (IL-1 β and IL-8) highest in cartilage compared with synovium and labrum ($P<0.01$). OA analysis: No significant differences in mRNA expression of cytokines among the OA tissue samples. FAI and age: mRNA expression of inflammatory cytokines (IL-8) higher in patients >30 years old compared with patients <29 years old. FAI and alpha angle: mRNA expression of anabolic genes (COL1A1) higher in labrum of patients with alpha angles <59° ($P<0.05$). mRNA expression of anabolic genes (ACAN) and catabolic genes (ADAMTS-4) higher in cartilage of patients with alpha angles >60° ($P<0.01$).	NR	NR

Continued

Table 3 Continued

Author (year)	Key findings	Biomarker characterisation	Functional outcome scores
Elias-Jones <i>et al</i> (2015) ¹⁸	<p>Histology: Fewer features of degenerative changes (including thickening and mucoid changes) in FAI specimens compared with OA specimens. More well-defined areas of hypercellular fibroblasts in FAI specimens compared with OA specimens. Inflammation: Greater macrophage and mast cell expression in FAI samples compared with OA samples. Macrophages of M2 phenotype present in FAI samples – involved in regenerative process as opposed to degenerative process. Higher levels of IL-13 in FAI samples compared with OA samples, supporting shift toward a proresolving type 2 macrophage environment. Neovascularisation: Greater CD34- and VEGF positive vessels in FAI samples compared with OA samples. Correlation between mast cells and CD34 expression ($r=0.4$, $P<0.01$) in FAI samples.</p>	NR	NR
Fukushima (2017) ¹⁹	<p>Existence of labral instability was not statistically correlated with any cytokine level. In patients with chondral injury classified as Outerbridge grade 4, the levels of TNFα were significantly increased. In patients with grade 3 cases of synovitis, the levels of TNFα, IL-1β, IL-6 and MMP-1 were significantly increased compared with those in cases of grade 2 synovitis ($P<0.05$).</p>	NR	<p>VAS score during rest showed significant positive correlation with IL-6 ($r=0.453$, $P=0.0071$), while VAS score on walking showed a significant positive correlation with TNFα ($r=0.465$, $P=0.0056$) and ADAMTS-4 ($r=0.508$, $P=0.0022$). mHHS pain score showed a significant negative correlation with TNFα ($r=-0.472$, $P=0.0049$), IL-6 ($r=-0.455$, $P=0.0068$) and ADAMTS-4 ($r=-0.349$, $P=0.043$).</p>
Hashimoto <i>et al</i> (2013) ¹²	<p>mRNA expression of IL-8, CXCL3, CXCL6, CCL3L1, ADAMTS-4, COL2A1 and ACAN greater in FAI samples compared with control samples ($P<0.05$). mRNA expression of IL-8, CCL3L1, ADAMTS-4, and ACAN higher in cartilage from FAI samples compared with OA samples ($P<0.05$). mRNA expression of ACAN higher in OA samples than control samples ($P<0.05$). mRNA expression of chemokines (IL-8, CXCL2, CXCL3 and CCL3L1) and extracellular matrix (ACAN) higher in FAI samples in the cleavage/thinning stage of articular cartilage damage as per the Beck criteria ($P<0.05$).</p>	NR	NR
Shapiro <i>et al</i> (2016) ¹⁷	<p>No significant correlation between cytokine values versus preoperative and 2-year postoperative outcome scores (mHHS, WOMAC and iHOT-33).</p>	<p>Biomarker=mean (SEM) FAC (OD)=1.052 (0.361) IFN-γ (pg/mL)=29.047 (14.155) IL-6=37.853 (20.534) IL-1RA=879.174 (512.799) IL-1β=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)</p>	<p>Preoperative to postoperative: mHHS: 61.9–82.5 ($P<0.0001$) WOMAC: 42.7–16.4 ($P<0.0001$) iHOT-33: 44.6–83.4 ($P<0.0001$)</p>

NR, not reported; ACAN, aggrecan; ADAMTS-4, a disintegrin and metalloproteinase with thrombospondin motifs-4; CCL3, chemokine (C-C) motif ligand 3; CCL3L1, chemokine (C-C) motif ligand 3-like 1; cDNA, complementary DNA; COL1A1, collagen type I alpha 1; COL2A1, collagen type II alpha 1; COMP, cartilage oligomeric matrix protein; CRP, C reactive protein; Ct, threshold cycle; CXCL1, chemokine (C-X-C) motif ligand 1; CXCL2, chemokine (C-X-C) motif ligand 2; CXCL3, chemokine (C-X-C) motif ligand 3; CXCL6, chemokine (C-X-C) motif ligand 6; FAC, fibronectin-aggrecan complex; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; IFN, interferon; iHOT-33, International Hip Outcomes Tool; IL-1 β , interleukin-1 beta; IL-8, interleukin-8; IP-10, interferon-inducible protein 10; MCP, monocyte chemoattractant protein; mHHS, modified Harris Hip Score; MIP, macrophage inflammatory protein; MMP-3, matrix metalloproteinase-3; MMP-13, matrix metalloproteinase-13; OD, optical density; PDGF-BB, platelet-derived growth factor-BB; qPCR, quantitative PCR; RANTES, regulated on activation normal T cell expressed and presumably secreted; TNF, tumour necrosis factor; VEGF, vascular endothelial growth factor; WOMAC, Western Ontario and McMaster Universities Arthritis Index.

Table 4 Summary of key biomarkers

Biomarker	Source	Study reported	Key findings
COMP	Plasma	Bedi <i>et al</i> ¹⁰	24% higher COMP (P=0.04) in FAI group compared with control
CRP	Plasma	Bedi <i>et al</i> ¹⁰	276% higher CRP (P<0.001) in FAI group compared with control
IL-1 β	Articular cartilage	Chinzei <i>et al</i> ¹¹ Fukushima ¹⁹	mRNA expression higher in FAI hips compared with OA hips (P<0.01) mRNA expression higher in greater stages of synovitis (P<0.05) mRNA highest in cartilage compared with synovium and labrum (P<0.01)
IL-8	Articular cartilage	Chinzei <i>et al</i> ¹¹ Hashimoto <i>et al.</i> ¹²	mRNA expression higher in FAI hips compared with OA hips (P<0.01) mRNA expression higher in FAI hips compared with controls (P<0.05) mRNA highest in cartilage compared with synovium and labrum (P<0.01)
ADAMTS-4	Articular cartilage	Chinzei <i>et al</i> ¹¹ Hashimoto <i>et al</i> ¹² Fukushima ¹⁹	mRNA expression higher in FAI hips compared with OA hips (P<0.01) mRNA expression higher in FAI hips compared with controls (P<0.05) mRNA expression significant positive correlation with VAS pain score and significant negative correlation with mHHS score
MMP-13	Articular cartilage	Chinzei <i>et al</i> ¹¹	mRNA expression higher in FAI hips compared with OA hips (P<0.01)
COL2A1	Articular cartilage	Chinzei <i>et al</i> ¹¹ Hashimoto <i>et al</i> ¹²	mRNA expression higher in OA hips compared with FAI hips (P<0.01) mRNA expression higher in FAI hips compared with controls (P<0.05)
ACAN	Articular cartilage	Chinzei <i>et al</i> ¹¹ Hashimoto <i>et al</i> ¹²	Conflicting results: 1. mRNA expression higher in OA hips compared with FAI hips (P<0.01) 2. mRNA expression higher in FAI hips compared with controls, OA hips (P<0.05)
CXCL3	Articular cartilage	Hashimoto <i>et al</i> ¹²	mRNA expression higher in FAI hips compared with controls (P<0.05)
CXCL6	Articular cartilage	Hashimoto <i>et al</i> ¹²	mRNA expression higher in FAI hips compared with controls (P<0.05)
CCL3L1	Articular cartilage	Hashimoto <i>et al</i> ¹²	mRNA expression higher in FAI hips compared with controls (P<0.05) mRNA expression of higher in FAI hips compared with OA hips (P<0.05)
FAC	Synovial fluid	Abrams <i>et al</i> ¹⁶	FAC higher in FAI, non-OA group compared with those with FAI and OA (P<0.001)

ACAN, aggrecan; ADAMTS-4, a disintegrin and metalloproteinase with thrombospondin motifs-4; CCL3L1, chemokine (C-C) motif ligand 3-like 1; COL2A1, collagen type II alpha 1; COMP, cartilage oligomeric matrix protein; CRP, C reactive protein; CXCL3, chemokine (C-X-C) motif ligand 3; CXCL6, chemokine (C-X-C) motif ligand 6; FAC, fibronectin-aggrecan complex; FAI, femoroacetabular impingement; IL-1 β , interleukin-1 beta; IL-8, interleukin-8; mHHS, modified Harris Hip Score; MMP-3, matrix metalloproteinase-3; MMP-13, matrix metalloproteinase-13; OA, osteoarthritis; VAS, visual analogue scale.

located in articular cartilage, and it is released in the circulation during the cartilage degeneration process of OA.²¹ Several studies have identified increased levels of COMP with increased burden of disease.^{22–24} Therefore, the identification of increased COMP in the serum of athletes with FAI in comparison with matched controls lends support to the notion that FAI predisposes individuals to OA of the hip.¹⁰ Another study identified elevated concentrations of FAC in the synovial fluid of patients with FAI. FAC is a cartilage breakdown product, which has also been identified in high concentrations in the synovial fluid of patients with intra-articular knee pathology.²⁵ Interestingly, the synovial fluid of patients with OA had low concentrations of FAC. It is thought that FAC is cleared rapidly from the synovial fluid, and therefore its level is indicative of the total amount of cartilage being destroyed acutely. As patients with OA have little articular cartilage remaining in the severely arthritic hip, the clearance of FAC likely exceeds its breakdown, and therefore the concentration of FAC in the synovial fluid would be expected to be low.¹⁶ These markers of articular cartilage destruction may serve an important role in the future to guide clinical practice and assist with patient selection and preoperative counselling.

The concept of articular cartilage destruction is further supported by the two studies in this review that evaluated the expression of inflammatory markers in the articular cartilage of patients with FAI in the absence of OA.^{11, 12} Molecularly, chondrocytes can become activated with inflammatory markers that are catabolic or anabolic in nature.²⁶ Typically, these processes are balanced. However, a predominantly anabolic state becomes increasingly catabolic as OA progresses in the joint.²⁷ The studies in this review identified increased mRNA expression of catabolic cytokines in the articular cartilage of patients with FAI.^{11, 12} Such findings are important as currently the diagnosis and treatment of patients with advanced stages of OA are dependent on clinical

and radiographic examinations.²⁸ These findings suggest that because the metabolic activity of the OA cascade significantly precedes the clinical and radiographic progression of the disease, biomarkers in the serum, synovial fluid, or articular cartilage could play an important role in future diagnostic strategies by making the diagnosis much earlier than current technology allows.

It is known that the mechanisms of FAI (Cam and Pincer) cause damage to both the labrum as well as the articular cartilage.^{1, 20} Interestingly, the recent study by Chinzei *et al* found a high expression of inflammatory cytokines in the articular cartilage samples, whereas samples taken from the labrum or synovium demonstrated lower levels of expression of these inflammatory markers.¹¹ These findings may suggest that articular cartilage, rather than the labrum, is the primary area of inflammation and degradation in patients with FAI. However, Elias-Jones *et al* identified a significant proportion of macrophages expressing CD206 in the labrum of patients with FAI.¹⁸ While these macrophages play a critical role in the inflammatory process, there are several possible explanations to this apparent discrepancy. First, the study by Elias-Jones *et al*¹⁸ histologically evaluated only tissue samples from the labrum, and therefore it is unclear whether these markers would be found in higher concentrations in samples from the articular cartilage. Furthermore, the macrophages of M2 phenotype present in the FAI samples in this study are involved in the regenerative process rather than a degenerative process.¹⁸

A promising area in the use of molecular biomarkers relates to the potential of these markers to indicate disease severity or even prognosis. Should certain biomarkers demonstrate proven efficacy in monitoring disease progression, they would provide a useful tool to identify those patients with FAI who are most at risk and who may benefit most from early joint preservation surgery. However,

Shapiro *et al* found no association between synovial cytokine concentration intraoperatively and outcome scores of patients after hip arthroscopy for the management of FAI.¹⁷ While intraoperative cytokine levels may not have utility in predicting postoperative outcome scores, the study by Fukushima *et al* did find a significant association between the expression of synovial cytokines and the severity of clinical symptoms.¹⁹ Future studies should investigate whether biomarkers predict clinical severity in order to assess for utility in guiding clinical management and preoperative planning. Based on current evidence, there have been promising results evaluating the inflammatory serum markers COMP and CRP, as well as the expression of inflammatory markers such as IL-8, ADAMTS-4, ACAN, CXCL3, CXCL6, CCL3L1 and COL2A1 in the articular cartilage of patients with FAI.

Limitations

Several limitations exist within the present systematic review. The study designs were case control/retrospective, therefore no causative inferences can be made with respect to the presence of biomarkers and the incidence or severity of FAI nor the rate of progression or prognosis. Specifically, serum biomarkers may be elevated due to systemic pathologies or pathological processes in other joints. Moreover, these biomarkers are subject to daily variation and can change depending on recent activity level. Furthermore, the overall sample size of the patients included in this review was relatively small, and therefore, does not yet warrant widespread application based on the current results alone. Additionally, while many studies reported an elevation of various biomarkers, no study has reported definitive quantitative values that could be used in practice. Due to the difference in pathogenesis between these mechanisms, the biomarkers generated from tissue changes may be different across these subtypes of impingement.²⁰ Furthermore, there were significant differences across the included studies with respect to the specific biomarkers evaluated, as well as the location of the tissue samples for analysis, which precluded the pooling of data.

CONCLUSION

Although not yet used in clinical settings, several biomarkers of articular cartilage damage such as serum markers COMP and CRP, as well as the expression of inflammatory markers such as IL-8, ADAMTS-4, ACAN, CXCL3, CXCL6, CCL3L1 and COL2A1 in the articular cartilage have demonstrated promising results in patients with FAI. These findings provide insight into the potential role of biomarkers in guiding clinical practice and assisting with patient selection and preoperative counselling in patients with FAI. However, the use of biomarkers as they relate to outcomes following FAI has not yet been demonstrated and warrants further evaluation.

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