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Overview of joint tissue alterations in femoroacetabular impingement: What we know through laboratory analyses

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Summary. Hip osteoarthritis (HOA) is the most common hip joint disorder, accounting for approximately 27.9% of all cases of osteoarthritis (OA), often leading to total hip replacement (THR).

In the last decades, femoroacetabular impingement (FAI) has been addressed as a significant etiological factor in the development of early-onset HOA, especially in young adults with non-dysplastic hips.

FAI has been found to cause damage to all joint tissues, cartilage, labrum, and subchondral bone, thus underlining the importance of an early diagnosis and intervention to prevent progression to end-stage disease.

This review aims to provide a comprehensive overview of the biochemical, morphological, and cellular alterations occurring in hip joint tissues in the presence of FAI. Understanding the early pathological changes is of crucial importance as they often precede radiographic signs of disease and may serve as valuable biomarkers for early detection and management of FAI and peri-arthritic conditions to delay or prevent the need for THR in younger populations.

Key words: Hip joint, Femoroacetabular impingement, Acetabular labrum, Cartilage, Bone, Intra-articular tissues, Laboratory techniques

Introduction

Hip osteoarthritis (HOA) is the most common hip disorder and represents 27.9% of osteoarthritis (OA) cases (Berto et al., 2021), thus affecting a significant component of the adult population. Unfortunately, HOA is one of the most important causes of disability, leading to total hip replacement (THR) as a solution for treating patients with severe HOA (Ganz et al., 2003).

In the last decade, femoroacetabular impingement (FAI) has been discovered to play a prominent etiological role in the development of early HOA, especially in the non-dysplastic hip in young adults, where FAI represents the most common mechanism that leads to the development of early cartilage and labral damage (Vail, 1999; Ganz et al., 2003; Griffin et al., 2016).

The treatment of the early stages of the disease and the pre-arthritic condition in adolescents and young adults is crucial to reduce the incidence of end-stage HOA and the need for THR.

To this aim, understanding the biochemical and morphological alterations occurring in FAI is pivotal to better elucidate the pathological mechanisms leading to the progression towards HOA onset.

Our review aims to provide a comprehensive overview of the biochemical, morphological, and cellular alterations in the hip joint tissues in the presence of FAI.

This is extremely useful as these alterations often precede the radiographic evidence of the disease and, for this reason, they could be considered potential biomarkers of FAI and peri-arthritic conditions (Hashimoto et al., 2013).

Femoroacetabular impingement (FAI) syndrome

FAI was originally described by Myers et al. in 1999 (Myers et al., 1999), and it is defined as a pathological mechanical process caused by morphologic alterations of the acetabulum or femur, leading to hip pain and limited hip range of motion (Ganz et al., 2003; Leunig et al., 2004; Philippon et al., 2007; Wang et al., 2011; Kuhns et al., 2015).

The abnormal biomechanics between the femoral head and acetabulum cause impaired joint functionality,

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which in turn leads to the mechanical impingement of the hip joint. Consequently, degenerative effects of the hip joint may occur, resulting in HOA onset, with acetabular labrum injury, cartilage damage, and all joint tissue components affected by the degenerative process (Samaan et al., 2017).

Two types of FAI can be described, as illustrated in Figure 1: one caused by an abnormality in acetabular shape or orientation, the pincer type, and the other caused by a shape abnormality in the proximal femur, that is, the cam type. Frequently, a combined impingement (mixed type) occurs when both the pincer and cam types are present.

In pincer impingement, the abnormal contact between the femoral neck and the over-covered acetabular rim is thought to cause an impactful type of impingement, which compresses the labrum and could subsequently lead to labral tear and circumferential cartilage damage. The cam type of FAI is caused by extra bone formation at the anterolateral head-neck junction, which results in a non-spherical, cam-shaped abnormality. The cam is forced into the acetabulum during flexion and internal rotation of the hip, and this mechanical alteration can cause inclusion-type damage to the acetabular labrum and articular cartilage, which is typically accompanied by detachment of the acetabular cartilage from the subchondral bone (Agricola et al., 2013).

Consequently, in both pincer and cam types of FAI, the abnormal contact between the femoral head-neck junction and the acetabular rim may result in progressive damage to the acetabular labrum, chondrolabral junction, and articular cartilage, thus affecting all components of the joint compartment (Gómez-Verdejo et al., 2024).

Concerning risk factors, the most relevant and impactful is cumulative and repetitive mechanical overloads at the hip joint, as evidenced by the high prevalence of FAI in high-level athletes. Similarly, occupations requiring high-intensity and high-impact physical activities, as well as those requiring repetitive hip loading, are more exposed to FAI onset (Safran et al., 2022; Gómez-Verdejo et al., 2024).

To date, management strategies can range from conservative approaches to surgical intervention, depending on patient-specific factors, such as age, functional status, symptom severity, and tissue integrity Gómez-Verdejo et al., 2024).

In general, non-surgical management includes physical therapy (i.e., stretching, strengthening exercises, and manual therapy), which is well accepted by patients, but the results are variable, and the literature data are not exhaustive (Terrell et al., 2021). When this conservative treatment fails, surgical management is often required, and open or arthroscopic techniques are applied. Among open surgical techniques, procedures such as surgical femoral head dislocation, periacetabular osteotomy, and femoral derotational osteotomy can be performed. In contrast, arthroscopic approaches, being minimally invasive, are associated with faster recovery and a lower incidence of complications (Mansell et al., 2018; Aoyama et al., 2019; Qiao et al., 2020; Hassan et al., 2023).

Notably, in the last 10-15 years, the focus has been shifted to the importance of preserving the acetabular labrum during hip arthroscopic surgery for FAI, as it plays a crucial role in maintaining both joint stability and overall hip function (Al Mana et al., 2019). Since the turn of the century, significant advances have occurred in the management of the acetabular labrum during hip arthroscopy. Although early studies pointed to

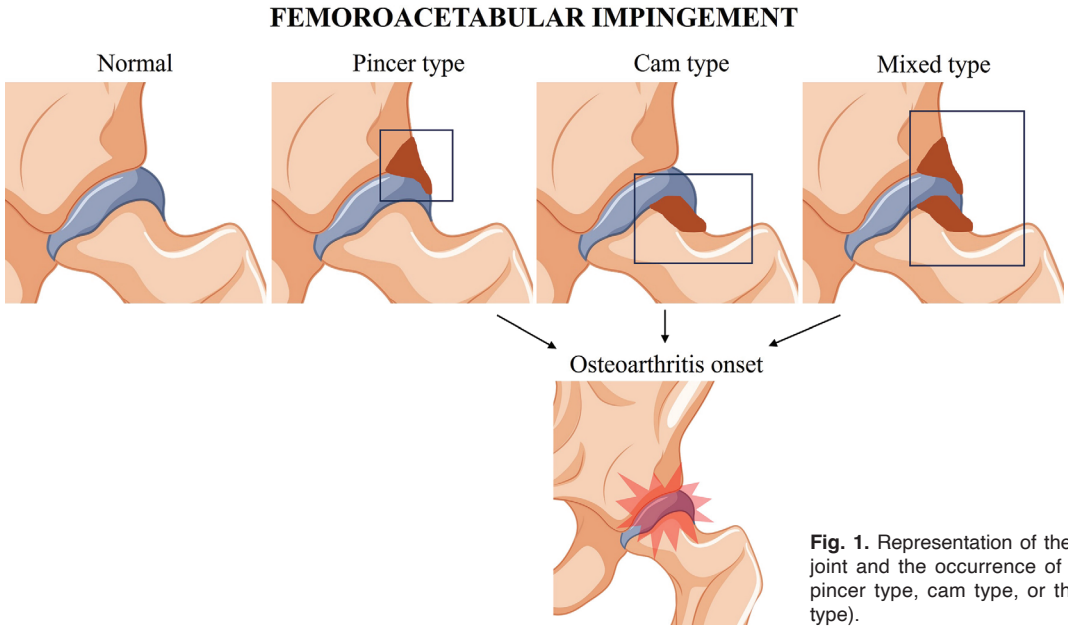

Fig. 1. Representation of the normal morphology of the hip joint and the occurrence of FAI, which can be defined as pincer type, cam type, or the combination of both (mixed type).

labrum debridement as the first option in labrum lesion treatments (Byrd and Jones, 2009), soon thereafter, labrum repair/refixation became the new strategy to preserve labrum anatomy (Krych et al., 2013; Haddad et al., 2014; Wu et al., 2020). However, in recent years, a paradigm shift has emerged toward labral augmentation and reconstruction to treat hypoplastic and irreparable labra, respectively (White and Herzog, 2015; Chandrasekaran et al., 2017; Philippon et al., 2018; Domb et al., 2019). Early results have been promising, as labrum reconstruction with tendon allografts or autografts (Atzmon et al., 2019; Lodhia et al., 2021) is considered the treatment of choice in hip arthroscopy reviews (White et al., 2016), particularly as surgeons seek a solution for patients who are in pain after labrum debridement (Byrd and Jones, 2009; Krych et al., 2013; Haddad et al., 2014; White and Herzog, 2015; White et al., 2016; Chandrasekaran et al., 2017; Philippon et al., 2018; Al Mana et al., 2019; Atzmon et al., 2019; Domb et al., 2019; Wu et al., 2020; Lodhia et al., 2021).

Joint tissue degeneration: characterization of tissue alterations and morphological changes

Acetabular labrum

The acetabular labrum is the fibrocartilaginous ring of tissue attached to the edge of the acetabulum of the hip joint, merging with the acetabular hyaline cartilage on the articular site, and with the bony acetabulum on the capsular site (Bsat et al., 2016). It is composed of fibrochondrocytes and type I collagen fibers, responsible for resistance to shear stress, maintenance of uniformly distributed joint pressure, and protection of the articular surface. Thanks to its characteristic of increasing the contact surface area with the femoral head, the acetabular labrum provides a fluid seal, guaranteeing joint stability and improving the lubrication of the joint (Cashin et al., 2008; Hill et al., 2008; Grant et al., 2012; Tey-Pons et al., 2021).

Histological and scanning electron microscopy analysis revealed the presence of three distinct layers in the labrum: firstly, the articular surface, covered by a meshwork of thin collagen fibrils; secondly, an intermediate layer of lamella-like collagen fibrils; and thirdly, an inner layer in which most collagen fibrils are oriented circumferentially. The internal zone of the labrum is avascular, with blood vessels distributed in a non-homogeneous manner only in the peripheral one-third of the labrum (Petersen et al., 2003; Kelly et al., 2005).

In case of damage, the labrum is responsible for intense pain; Haversath et al. found pain-associated free nerve endings at the base of the labrum (less in the periphery), with the highest concentration in the anterolateral (middle third), close to the labral-acetabular attachment (Haversath et al., 2013).

In the presence of FAI, the labrum is initially impinged and subsequently injured, with consequent loss of function (Grant et al., 2012) (see Figure 2 for a summary of the observed alterations in acetabular labrum tissue).

The degeneration of the labrum leads to the formation of labral tears, which decrease the ability of the joint to maintain normal synovial fluid (SF) pressure, thus resulting in abnormal loading. However, regarding acetabular labrum regeneration, Audenaert et al. observed that the labrum responded well to regenerative stimuli in 6 patients diagnosed with FAI and labral tears who underwent an arthroscopic procedure, including labral repair. Histological analysis of biopsy specimens of labral tissue retrieved during total hip arthroplasty after clinical failure revealed tissue integrity with the absence of tears or fibrovascular scar tissue. In addition,

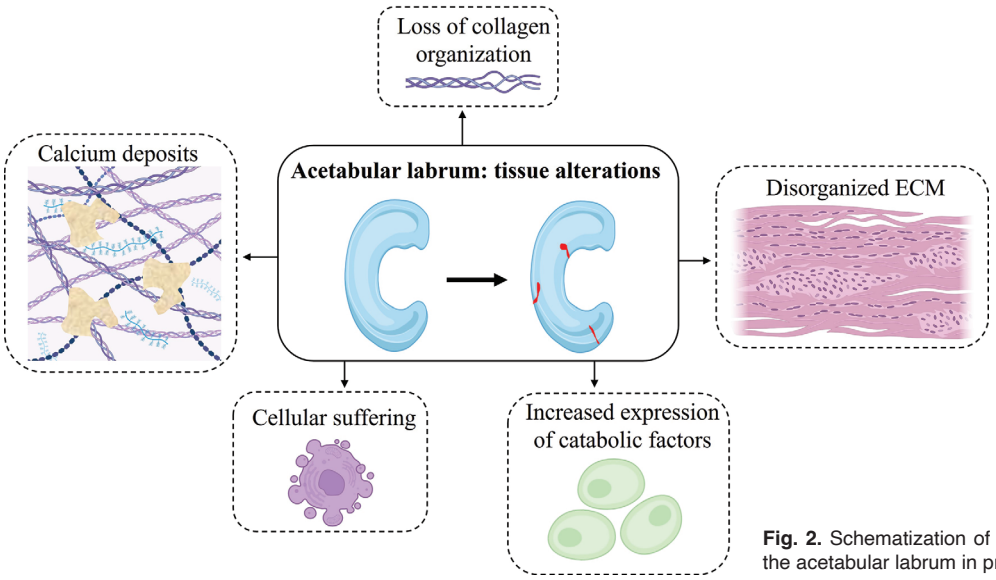

Fig. 2. Schematization of the main tissue alterations occurring in the acetabular labrum in presence of FAI.

3 patients showed neovascularization near the sutures (with no evidence of giant cells), indicating a favorable healing response of the labrum tear (Audenaert et al., 2012).

Concerning the histomorphological changes of the labrum during FAI and OA onset and progression, a disorganized, weaker, hyperplastic matrix, with disorganized cystic matrices, was observed by Ito et al. using histological examination with light microscopy and electron microscopy (Ito et al., 2004). Similarly, Battistelli et al. conducted a comparative histological and transmission electron microscopy (TEM) study of labral tissue obtained from healthy donors, patients with FAI, and patients with OA undergoing THR. The extracellular matrix (ECM) of healthy donors showed a homogenous distribution and orientation of collagen fibers, with a regular pattern and distribution, and periodic collagen organization in the inner zone (Battistelli et al., 2023). On the other hand, patients with FAI showed a structural disorganization of collagen fibers in the superficial layers, with heterogeneous diameters and loss of the typical periodic structure, probably due to the presence of many immature fibers. Similarly, in patients with OA, collagen fibers appeared disorganized, accompanied by a marked increase in proteoglycans content, which structurally replaced the collagen network. Moreover, large calcium deposits were observed in the FAI labral matrix, especially correlating with older age, resembling the extensive calcified areas in patients with OA. Also, Trisolino et al. found calcium deposits in labral tissue, which also showed a pattern of degeneration in 67% of patients undergoing hip arthroscopy for FAI (n=21 patients enrolled) (Trisolino et al., 2020).

Concerning the calcification process within the labrum, Byrd et al. analyzed the tissue of 2 patients with pincer FAI and labral ossification (LO) and observed that LO was present as a bony extension from the acetabular rim and, at the same time, as endochondral ossification of the labrum, generating a gradual transition of the ossification from the acetabular rim outward (Byrd et al., 2016).

Similarly, Corten et al. observed that osseous apposition can replace part of the labrum in patients with FAI, with subperiosteal bone apposition pushing away the labrum from its native location and causing a thinner labrum on the bone apposition (Corten et al., 2011). Moreover, Domzalski et al. observed calcifications within the fibrocartilage of the labrum, as well as a heterogeneous matrix and vascular formation, as a hypothetical response to degenerative changes (Domzalski et al., 2017).

The mechanical stress caused by labral impingement can trigger cellular damage processes in patients FAI, showing features similar to those observed in OA. Indeed, Battistelli et al. also observed small autophagic vacuoles in FAI patients, with older patients also exhibiting more condensed nuclear chromatin, and "chondroptosis" (i.e., "chromatin margination and condensation with a specific pattern", termed by Roach et al. (2004), and patients with traumatic injury exhibiting abundant vacuoles, sparse cytoplasmic organelles, swollen and emptied mitochondria, empty areas of matrix, and autophagic vacuoles in the cytoplasm (Battistelli et al., 2023). A similar pattern of cellular degeneration was observed in patients with OA.

Elias-Jones et al., using immunohistochemistry, deeply analyzed the inflammatory reaction and neovascularization in 10 patients with FAI, compared with 10 patients with OA (Elias-Jones et al., 2015). Authors observed greater macrophage, mast cell, and vascular endothelium expression in the labra from patients with FAI compared to those from OA patients, with a significant correlation between mast cell and CD34 expression in FAI. Interestingly, macrophage phenotype M2 was observed in FAI, suggesting a regenerative process instead of a degenerative one. These findings may suggest a role for innate immune pathways in the events that mediate hip impingement.

Chinzei et al. observed, by quantitative real-time polymerase chain reaction (PCR), that the mRNA expression of inflammatory cytokines, such as interleukin-1 beta (IL-1β) and IL-8, matrix metalloproteinase-3 (MMP-3), and type I collagen (COL1), was higher in OA samples than in FAI ones (30 hips with FAI and 30 hips with OA), underlining a susceptibility and progressive increase from FAI to OA (Chinzei et al., 2016). Similarly, Schon et al. evaluated the expression profile of seven MMPs and three tissue inhibitors of metalloproteinases (TIMPs) by extracting proteins from tissue samples and performing immunohistochemistry in 4 patients with FAI and 3 normal hips of deceased donors (Schon et al., 2020). Authors found that the expression of MMP-1 and MMP-2 was increased in FAI, while TIMP-1 was reduced compared with control patients, underlining the pathogenic role and the progression of FAI towards OA.

In the frame of inflammatory characterization, Juchtmans et al. compared cells from OA labra to those from healthy labra cultured in a three-dimensional (3D) alginate bead system, by using a microarray analysis (Juchtmans et al., 2015). Authors observed increased cytokine and chemokine signaling in OA labral cells, reduced ECM interactions, and transforming growth factor (TGF)-β signaling. These results highlighted that labral fibrochondrocytes are metabolically active cells, subjected to OA-associated changes, like those occurring in cartilage during OA. However, other authors did not observe suggestions of inflammatory arthropathy in patients with cam/pincer/mixed type FAI (Kohl et al., 2011).

In general, in acetabular labra affected by FAI, the primary morphological alterations involve the ECM, which becomes heterogeneous, disorganized, and structurally compromised, with marked disruption of collagen fiber architecture. In some cases, these degenerative changes are accompanied by inflammatory response, neovascularization, and presence of calcium

deposits or calcifications within the fibrocartilaginous tissue.

Articular cartilage

The hip articular cartilage plays a pivotal role in absorbing mechanical loads and protecting joint surfaces by distributing weight across the joint. It also facilitates joint function by fluid movement, which maintains a low frictional coefficient with the underlying bone.

Cartilage tissue is avascular, aneural, and alymphatic, and its homeostasis depends mainly on oxygen and nutrient diffusion from SF and basal subchondral bone, thus justifying its very poor regenerative potential by itself (Fox et al., 2009; Carballo et al., 2017; Ng et al., 2017).

The articular cartilage is mainly composed of chondrocytes embedded within the ECM, which consists mainly of type II collagen, negatively charged proteoglycans, and water, with smaller amounts of glycoproteins and non-collagenous proteins. The ECM is highly organized in four different zones, i.e., the superficial zone, the transitional zone, the deep zone, and the calcified zone, each zone having a specific architecture, proper functions, and mechanical properties (with the chondrocytes responding differently based on their zonal location) (He et al., 2014; Ng et al., 2017).

Due to the presence of FAI and the resulting damage to the acetabular labrum, secondary degenerative effects on the articular cartilage can occur (see Figure 3 for a summary of the observed alterations in articular cartilage). Indeed, damage to the acetabular labrum has been associated with articular cartilage degeneration in multiple cadaveric and clinical studies (Dorrell and Catterall, 1986; Ferguson et al., 2000a, 2003; McCarthy et al., 2001, 2003).

In the case of damaged acetabular labrum, increased fluid efflux from the articular cartilage is observed under loading conditions. As a result, a greater portion of the mechanical load is consequently supported by the cartilage matrix itself, with increased friction between the femoral and acetabular cartilage layers, leading to elevated stress within the matrix (Ferguson et al., 2000a).

Therefore, damage to the articular cartilage resulting from altered contact has been proposed as a potential initiating factor in OA. Patients with FAI exhibited specific cartilage injury patterns, as shown by intraoperative arthroscopic findings, i.e. delamination, when compared with other diseases, such as dysplasia (Cho et al., 2022). Moreover, Song et al., through mechanical testing of cadaveric specimens, demonstrated that damage to the acetabular labrum can impair joint sealing and progressively increase joint friction (Song et al., 2006, 2012).

Indeed, in a recent review, Li et al. observed that more than 80% of patients with FAI also possess acetabular cartilage lesions at the time of surgery, especially partial-thickness in the anterosuperior region of the acetabulum, while lesions of the femoral head cartilage are quite rare (Li et al., 2024). The correlation with older age was observed, as well as with sex (male), and body mass index (BMI) (higher). Unfortunately, the presence of cartilage lesions has a worse clinical outcome (Li et al., 2024). Jannelli et al. found that cam ($p<0.01$) and pincer morphologies ($p<0.05$) were significantly associated with acetabular delamination on magnetic resonance imaging (MRI), predominantly localized at the acetabular chondrolabral junction, especially in the anterosuperior quadrant. Histological analysis of the acetabular delamination revealed hypocellularity and an increase presence of eosinophils

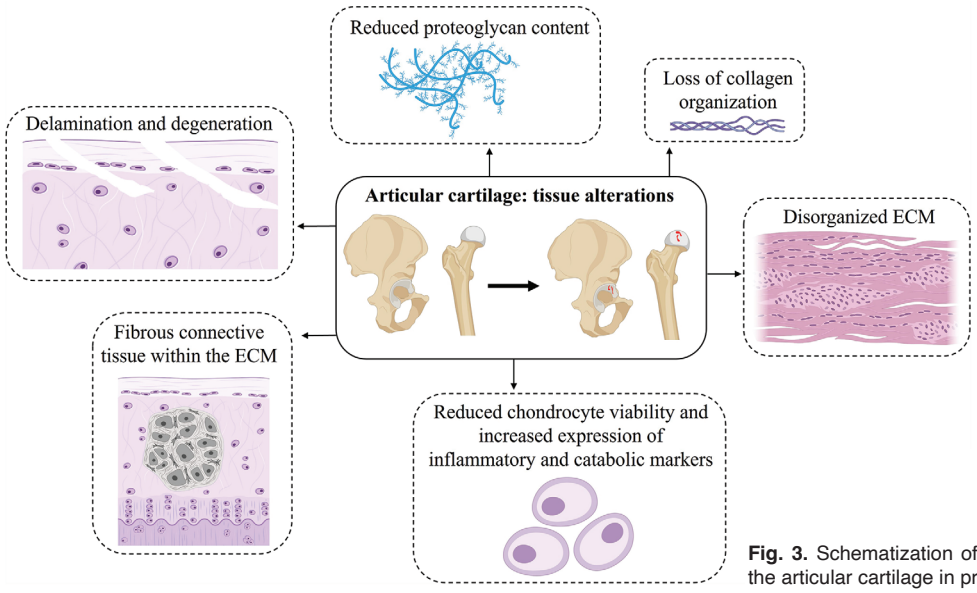

Fig. 3. Schematization of the main tissue alterations occurring in the articular cartilage in presence of FAI.

in the matrix (Jannelli et al., 2019).

Cartilage appears to be the joint compartment most affected by FAI. Speirs et al. analyzed cartilage tissue of osteochondral specimens from 13 patients with cam-type FAI and 10 age-matched cadaveric controls using histological analysis and nanoindentation tests (Speirs et al., 2017). They found that cartilage from patients with FAI exhibited approximately 70% lower compressive stiffness and threefold higher permeability compared with control samples, along with reduced or absent proteoglycan content, highlighting that cartilage showed severe degeneration in mechanical properties in presence of FAI. In addition, alterations in ECM composition were also found, with Safranin O staining intensity (reflecting proteoglycan content) positively correlated with cartilage stiffness (proteoglycan content found depleted in FAI).

These observations underlie the high incidence of alterations in cartilage functionality in the presence of FAI.

Chinzei et al. and Hashimoto et al. observed that articular cartilage from the impingement zone of FAI hips possesses higher levels of inflammatory, anabolic, and catabolic genes compared with OA patients and healthy controls, due to changes in cartilage contact patterns following labral damage (Hashimoto et al., 2013; Chinzei et al., 2016). Specifically, authors found significant differences in the mRNA expression of chemokines (IL-8, chemokine (C-X-C motif) ligand (CXCL) 3, CXCL6, and chemokine (C-C motif) ligand 3-like 1 (CCL3L1)), a disintegrin and metalloproteinase with thrombospondin motifs 4 (ADAMTS-4), and structural matrix genes (ACAN), being higher in cartilage from patients with FAI compared with OA and healthy controls.

Chinzei et al. reported significantly higher MMP-13 mRNA expression in FAI compared with OA, whereas Hashimoto et al. did not observe significant differences among FAI, OA, and control specimens. Additionally, Hashimoto et al. found increased collagen type II alpha 1 (COL2A1) expression in FAI compared with control, while Chinzei et al. noted COL2A1 significantly upregulated in OA compared with FAI (Hashimoto et al., 2013; Chinzei et al., 2016).

Kuhns et al., using whole-genome RNA sequencing in 10 gender-matched patients per group, found increased anabolic signaling in FAI compared with catabolic signaling in the OA group, with higher *MMP-13* and *ADAMTS-4* catabolic gene expression in OA than in FAI (Kuhns et al., 2023).

Collectively, these findings support the hypothesis that FAI is associated with a metabolically hyperactive cartilage state, a pathological condition contributing to the development of OA.

When comparing early and late stages of FAI, Haneda et al. found similar level of inflammation and catabolic activity in both acetabular and femoral head-neck cartilage, as assessed by immunostaining (Haneda et al., 2020a).

Haneda et al. performed histological analysis of head-neck cartilage samples from 15 patients with cam-type FAI (early FAI), 15 patients with advanced OA secondary to cam-type FAI (late FAI), 15 patients with advanced OA secondary to developmental dysplasia of the hip (DDH OA) with no impingement, and 7 healthy young adult donors served as controls (Haneda et al., 2020b). In general, early FAI and late FAI showed more degenerative changes (osteoarthritic phenotype) than DDH OA, while control cartilage samples showed normal hyaline cartilage with minimal expression of inflammatory signs. Authors found more abundant osteoarthritic changes in the cartilage of early FAI and late FAI groups compared with DDH OA and control groups, in terms of higher expression of inflammatory molecules-IL-1β, MMP-13, ADAMTS-4, and type II collagen (COL2). In detail, inflammatory markers were found expressed in all cartilage zones of early and late FAI, while in DDH OA only in the superficial zone.

Liang et al. compared full-thickness cartilage specimens from patients with FAI (29 symptomatic patients underwent hip arthroscopic cam resection, mean age 37.2 years) to healthy donors (4 cadavers with no evidence of FAI, to be considered as control group) (Liang et al., 2021). The authors found that the gene expression of the transcription factor *Sox9*, *COL2*, and *ACAN* was lower in FAI compared with the control group, while *MMP-13*, *ADAMTS-4*, and *IL-1β* were higher in the FAI group. The expression of cyclin-dependent kinase inhibitor 1A (p21), B-cell lymphoma 2 (Bcl-2), and Fas ligand (FasL), markers of cellular senescence, was higher in FAI compared with controls. Concerning histological analysis, Safranin O (SO) staining was positive in FAI samples only in the pericellular area, compared with controls that presented uniformly positive staining in most of the ECM. However, some cases were completely negative for SO (SO-), while others were weakly positive (SO+). At the same time, the immunostaining analysis of COL2 was densely positive in control ECM, while it was weakly expressed in FAI; in some cases, faintly close to the surface, and quite absent in deep zones. In FAI cases with absent SO, ACAN expression was seen in the deep zone near the bone and in some cells within the superficial zone, together with MMP-3, while FAI cases exhibiting pericellular SO+ demonstrated more extensive staining of ACAN, although still lower than the control group, along with MMP-3 in the superficial layer. Regarding cell proliferation, immunohistochemical staining for proliferating cell nuclear antigen (PCNA) was found positive throughout the entire sample of both control and SO-FAI cases, whereas in SO+ cases, almost no cells exhibited positive PCNA staining.

Chondrocytes in FAI likely exhibit pronounced senescence, reduced cell survival and proliferation but resistance to apoptosis, along with increased expression of inflammatory mediators and decreased metabolic activity, as the authors suggest occurs in the cell Senescence Associated Secretory Phenotype (SASP)

(Liang et al., 2021).

These observations underline the higher inflammation and ECM degeneration in articular cartilage of patients with FAI, supporting the concept that FAI may be a trigger for joint degeneration.

Regarding ECM morphological status, Ho et al. analyzed 22 damaged and 22 healthy-appearing articular cartilage samples from patients with FAI who underwent arthroscopic treatment. The authors found a loss of matrix organization, lower parallel-oriented and more randomly oriented collagen fibers in the damaged articular cartilage (Ho et al., 2016). Moreover, the histological analysis of punch biopsies collected from patients with FAI showed that the hyaline cartilage at the acetabular rim was transformed into fibrous connective tissue with abundant blood vessels and cartilage degeneration in the medial part of pincer lesions. On the contrary, in the deeper layers, microfractures and tears were found, with necrotic and apoptotic cells and sometimes absent nuclei, along with some calcifications in the reparative zone. In the case of cam-type impingement, fibrocartilage with cluster cells, tangential tears, and separation of cartilage from bone matrix were noticed (Kohl et al., 2011).

Kuhns et al. applied whole-genome RNA sequencing to cartilage samples from FAI and HOA secondary to FAI (OA-FAI) (10 gender-matched patients in each group) and observed distinct transcriptomic profiles, with increased anabolic signaling in the FAI group compared with catabolic signaling in the OA-FAI group (Kuhns et al., 2023). Indeed, chondroprotective *fibroblast growth factor 18* (*FGF18*) and *WNT16* gene expression was found to be higher in FAI with low histologic OARSI grades compared with higher degradation.

At the same time, immunohistochemical positivity for FGF18 in articular cartilage was stronger in patients with low-grade cartilage degeneration than in those with FAI exhibiting high-grade cartilage lesions.

Consistent with the findings of Kuhns et al. (2023), Kamenaga et al. observed reduced catabolic activity in cartilage samples from patients with early-stage FAI compared with those with advanced OA secondary to cam FAI (late-FAI-OA) (consistently higher when compared with healthy individuals) (Kamenaga et al., 2023). Indeed, authors observed DNA methyltransferase 3B (DNMT3B) underexpression and 4-aminobutyrate aminotransferase promoter (ABAT) overexpression throughout disease progression.

Concerning histological evaluation, early-stage FAI and late-FAI-OA groups showed a similar degenerative cartilage process (i.e., presence of clefts, cell cloning, and reduced Safranin O staining), compared with normal hyaline cartilage of healthy individuals.

Wright et al. found that full-thickness, delaminated acetabular chondral flaps obtained from 10 patients (8 male and 2 female, average age 36±11years) undergoing arthroscopic hip surgery for FAI contained approximately 87-90% viable cells, as determined by live/dead assay and confocal microscopy image quantification. No correlation was found between cell viability and patient age, sex, or BMI (Wright et al., 2018).

On the other hand, Rodriguez-Fontan et al. evaluated the viability and tissue quality of chondral flaps from patients with FAI at the time of arthroscopy to determine whether chondral flap reattachment could be a potential preservation technique or whether if the tissue was too degenerated, containing few viable cells (Rodriguez-Fontan et al., 2017). To this aim, 10 patients with cam-type FAI were enrolled, and chondral flaps (study group) and a cartilage sample from the perifoveal area (control) were harvested for the histological evaluation.

Authors observed that the chondral flaps of patients with FAI possess loss of viability and tissue degeneration despite a normal appearance at the macroscopic level. Interestingly, the control samples also showed signs of cartilage damage and degeneration. These findings highlight the need for careful consideration when attempting chondral flap reattachment.

Levinson et al. histologically evaluated 7-10 acetabular chondral flaps from patients with FAI (9 male and 1 female) and 3 non-delaminated control cartilage samples (obtained from patients underwent either arthrodesis or THR for avascular necrosis with laterally adherent cartilage), in order to assess the rationale for clinically performed refixation of delaminated chondral flaps (Levinson et al., 2020). They characterized chondrocyte viability and ECM composition, and the chondrogenic potential of resident cells to migrate towards fibrin sealant and regenerate cartilage following refixation. Authors found decreased chondrocyte viability in delaminated flaps compared with non-delaminated controls, without any correlation between viability and the patients' age. Concerning ECM status, hematoxylin and eosin staining highlighted the presence of fibrillated ECM either throughout the sample or located at the surface of the cartilage towards the delaminated edge of the flap, indicating a gradient of degeneration. The loss of the glycosaminoglycan gradient emerged in all flap samples, but not the loss of collagen.

Interestingly, minced flap cartilage were encapsulated in fibrin gel and chondrocytes showed to be able to migrate and proliferate along the fibrin gel, leading to extended coverage of the gel with cells, probably thanks to the degraded state of the ECM that permits cell spreading.

Pascual-Garrido et al. extensively investigated the role of peroxisome proliferator-activated receptor gamma (PPARγ) signaling in cartilage from patients across the spectrum of OA progression, ranging from early-stage cam-FAI (9 patients) to advanced OA secondary to cam-FAI (13 patients, late-stage) (Pascual-Garrido et al., 2022). In cartilage samples from the anterolateral head-neck junction (impingement zone) of 9 early-stage FAI and 13 late-stage FAI, PPARγ, and

DNA methylation enzyme DNMT3B were found to be gradually suppressed along with disease progression. Conversely, disease progression induced the expression of DNA methylation enzymes DNMT1 and 3A. Thus, it can be stated that the potential preservation of endogenous PPARγ may have a role as a therapeutic for delaying or preventing HOA progression.

Pascual-Garrido et al. observed that PPARγ seems to play a critical role in OA progression, concerning cartilage homeostasis, inflammation, and catabolic regulation. Via the mammalian target of rapamycin (mTOR) signaling pathway, PPARγ regulates autophagy and inflammation, and its hypermethylation, especially by the DNMT family, in the promoter region, is connected to OA progression, where DNMT3A has been addressed as pivotal in gene silencing during disease progression (Pascual-Garrido et al., 2023).

Overall, articular cartilage in FAI undergoes significant morphological, mechanical, and molecular alterations, especially in the anterosuperior region of the acetabulum, whereas the femoral head cartilage is comparatively less affected. Damage to the acetabular labrum causes fluid efflux and increases the mechanical stress on the cartilage, promoting delamination and degeneration.

Histological and biochemical analyses consistently demonstrate ECM disorganization, reduced proteoglycan content, and disrupted collagen architecture, sometimes with fibrous connective tissue, particularly at the anterosuperior acetabular region. Consequently, the mechanical integrity of the cartilage is compromised, with reduced compressive stiffness and increased permeability.

Additional tissue alterations include reduced chondrocyte viability, increased expression of inflammatory and catabolic markers (e.g., IL-1β, MMP-13, ADAMTS-4), reduced expression of Sox9, COL2, and ACAN, and upregulation of senescence-associated genes, compared with OA. No significant differences were found in early and late FAI, showing similar levels of inflammation and catabolic stimuli.

Interestingly, the abovementioned studies highlight a distinct transcriptomic profile between FAI and OA, where increased anabolic signaling in early stages shifts towards a catabolic, OA-like phenotype in advanced disease stages.

Emerging evidence highlights DNA methylation and suppression of PPARγ signaling as key contributors to disease progression, suggesting potential therapeutic targets for early intervention.

Subchondral bone

Subchondral bone has a pivotal role in joint health, providing structural support to the attached cartilage and impacting the mechanical and biological features of the joint.

Subchondral bone is formed by two mineralized layers, combined in a single unit, separating the articular cartilage from the bone marrow. It is composed of the subchondral bone plate and the subarticular spongiosa, and it is rich in arterial and venous vessels and nerves, which form branches into the calcified cartilage. Subchondral bone thickness varies both within and between joints; based on the distribution of the stress acting on the articular surface, its mechanical and structural properties vary, in terms of density, thickness, and vascularization (Madry et al., 2010). Recently, nanopores have been found to be responsible for solute transport and biochemical signaling at the osteochondral interface, thus maintaining joint homeostasis (Pouran et al., 2021). Thus, morphological and biochemical alterations in subchondral bone can influence the mechanical integrity of the osteochondral unit, compromising joint functionality (Höger et al., 2025).

For a summary of the observed alterations in subchondral bone in presence of FAI, see Figure 4.

Kohl et al. observed substantial histological differences between pincer and cam-type FAI lesions in subchondral bone. In pincer-type lesions, the

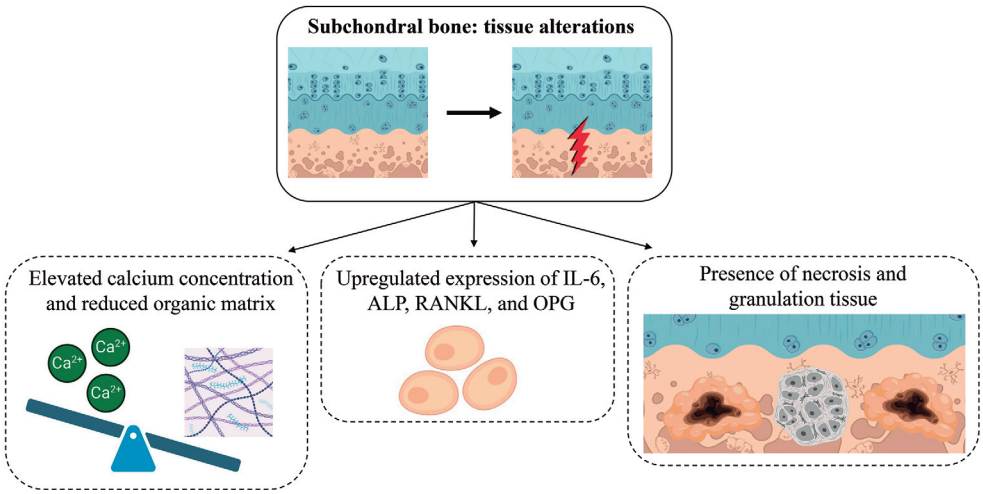

Fig. 4. Schematization of the main tissue alterations occurring in subchondral bone in presence of FAI.

subchondral bone exhibited necrosis, accompanied with granulation tissue, osseous callus, and several mucoid-filled cysts, whereas in cam-type lesions, the subchondral bone was mostly normal, with only minor evidence of remodeling (Kohl et al., 2011).

Haider et al. compared the subchondral bone from patients with cam-type FAI to normal subchondral bone from control specimens, using a combination of mechanical testing, micro-CT, and finite element analysis. They found that subchondral bone in patients with FAI was hypermineralized and exhibited approximately twice the stiffness of normal controls, while no differences were observed in architectural parameters (Haider et al., 2016). These findings indicate that cam-type deformity may originate from a developmental abnormality rather than from a degenerative process or remodeling secondary to FAI, with the malformed, mineralized epiphyseal growth plate leading to cam deformity.

Regarding mineralization, Hohmann et al. reported that bone tissue from the osteochondral unit of patients with FAI (21 biopsies from 18 patients) exhibited a higher calcium concentration and a decreased organic content compared with healthy tissue areas, as assessed by laser-induced breakdown spectroscopy (Hohmann et al., 2025). The increase of mineral content was likely due to calcium hydroxyapatite deposition at the osteochondral junction. Raman spectroscopy revealed higher levels of amide I, indicative of bone damage, a common consequence of FAI, whereas the reduced hydroxypyroline suggested the generation of new bone.

Concerning calcification areas, Jager et al. observed osteoblasts localized in the capsule near calcifications, and in some cases, in direct contact with the bony structures. Immunohistochemical analysis of perilesional capsule tissue revealed the presence of mesenchymal progenitor cells in the absence of bone or calcifications (Jäger et al., 2004). These findings could indicate that osteoprogenitor cells can be locally recruited and, under the stimulus of mechanical forces, may be responsible for secondary calcifications and the formation of osseous bump deformity. Comparing early-stage cam-type FAI and controls, Gao et al found significantly higher expression of IL-6, alkaline phosphatase (ALP), receptor activator of nuclear factor-kB ligand (RANKL), and osteoprotegerin (OPG) in FAI patients, whereas IL-8 expression did not differ between groups, (control bone tissue samples were collected from 6 patients who underwent THR following femoral neck fracture) (Gao et al., 2021).

Taken together, these data indicate that morphological and biochemical alterations in subchondral bone during FAI compromise the mechanical integrity of the osteochondral unit, impairing joint function.

Pincer-type lesions are typically associated to necrosis and cystic formations, whereas cam-type lesions exhibit hypermineralization and increased stiffness without significant architectural remodeling. In early-stage cam-type FAI, upregulated expression of IL-6, ALP, RANKL, and OPG suggest enhanced inflammatory and remodeling activity.

Overall, elevated calcium concentration and reduced organic matrix were observed, suggesting potential bone damage.

Synovial membrane and synovial fluid

The synovium, or synovial membrane, is a vascular connective structure found in the inner lining of diarthrodial joints, essential for maintaining normal joint function, especially through the production of SF.

Structurally, the synovium consists of the intima, which contains specialized cells, and the subintima, which contains blood vessels, lymphatics, fat pads, unmyelinated nerves, and isolated cells, such as mast cells. The two predominant cell types are synoviocytes: type A, monocyte-derived phagocytic cells responsible for debris removal, and type B, secretory cells synthesizing hyaluronate and other SF components. Key functions of the synovial membrane include: (i) secretion of hyaluronate into the SF (B synoviocytes), (ii) phagocytosis of waste material derived from other districts of the joint (A synoviocytes), and (iii) homeostasis of solutes, electrolytes, and proteins within the SF (Smith, 2011).

In presence of FAI, the synovium may exhibit metabolic hyperactivity (Haneda et al., 2020a), but appears to maintain its regenerative potential (see Figure 5 for a summary of the observed alterations in synovial membrane). Indeed, Murata and colleagues evaluate the regenerative properties of mesenchymal stem cells (MSCs) derived from FAI synovium (Murata et al., 2020). Comparing synovial MSCs from 21 patients with FAI and 14 patients with OA, they found that FAI-derived MSCs exhibited higher chondrogenic potential, viability, and proliferative potential, but lower colony-forming ability and reduced osteogenic and adipogenic potential compared with OA-derived MSCs.

Further investigations on the different zones of the synovium, i.e., paralabral and cotyloid fossa, showed that MSCs from the cotyloid fossa possess a higher number of colonies and higher differentiation capacity toward adipose, bone, and cartilage than MSCs from the paralabral synovium (analyses performed on 18 patients, 7 male and 11 females, with mean age 41.8±16.2 years, undergoing arthroscopic hip surgery) (Murata et al., 2018). These findings suggest that not all synovial regions in FAI patients are equally compromised in terms of tissue and potential regenerative properties, with cotyloid fossa MSCs representing a more robust source for potential stem cell therapies.

Similarly, Hunziker et al. reported that the synovium of young adults with FAI retains chondrogenic potential comparable to healthy individuals, consistent with observations in older adults with osteoarthritic knee degeneration (Hunziker et al., 2023). In addition, synovial membrane explants from healthy, FAI and OA

patients were cultured *in vitro* under the stimuli of bone morphogenetic protein-2 (BMP-2), TGF-β1, or a combination of both. Histological and gene expression analysis revealed the formation of adult articular-like cartilage under the combined BMP-2/TGF-β1 stimulation in all three groups, with adequate gene expression of the anabolic chondrogenic markers and low levels of the catabolic markers.

Collectively, the abovementioned studies provide encouraging evidence for regenerative approaches in FAI, particularly when inflammation and mechanical tissue compromise are less severe than in OA. Indeed, Haneda et al. found minimal signs of synovitis (low-grade or no synovitis) in early-stage FAI compared with late-stage, where greater synovitis was detected (15 patients with early-stage cam-type FAI, 15 patients with advanced/late-stage OA secondary to cam-type FAI, and 7 healthy young adult donors as controls) (Haneda et al., 2020a). Similarly, Chinzei et al. observed higher mRNA levels of IL-1 β, IL-8, and MMP-3 in OA hips compared to FAI samples (Chinzei et al., 2016).

Recent work by Anderson et al. provided insights into the earliest changes in HOA pathogenesis. Authors examined synovial histopathology across patients with FAI, FAI with early HOA, and advanced HOA. They demonstrated the presence of synovitis with mature, inactive microvasculature and other OA-associated changes in all groups investigated. The histopathological similarities between FAI and HOA synovium suggest that synovial disorganization arises early in FAI and may contribute to progression toward HOA, emphasizing the importance of early intervention and further mechanistic studies (Anderson et al., 2025).

Furthermore, Trisolino et al. identified synovial mononuclear cell infiltration in 25% of patients undergoing hip arthroscopy for FAI (n=21 patients), with increased CD68-positive cells correlating with poorer postoperative outcomes (Trisolino et al., 2020).

Abrams et al. detected the presence of synovial inflammation in patients with FAI (12 patients with cam and mixed-type FAI), with high CD68 positivity in patients with cam-type FAI and cartilage damage (Abrams et al., 2017). This study, published in 2017, improved the knowledge about the assessment of inflammation in that musculoskeletal disease, which is considered non-inflammatory. These findings highlight that baseline inflammation in FAI may reflect the innate immune system response to damage-associated molecular patterns (DAMPs), driving the recruitment of inflammatory cells and production of inflammatory mediators. Interestingly, CD45+/CD68+ cells, indicative of mononuclear cells differentiating into macrophages, were observed in the synovial lining of the joint, near the articular space, suggesting that innate immune cell recruitment to extracellular matrix (ECM) damage plays a key role in FAI-associated inflammation.

In light of the above, it can be stated that although synovial tissue in FAI exhibits features of metabolic hyperactivity, it appears to retain considerable regenerative potential. MSCs derived from FAI-affected synovium demonstrate higher chondrogenic potential and viability than those isolated from OA-affected synovium, with site-specific differences; MSCs obtained from the cotyloid fossa display superior multipotency compared with those from the paralabral synovium.

Synovial cellular elements are a major source of SF components that contribute to the unique lubricating and mechanobiological properties of articular surfaces and modulate chondrocyte activity. Among these, lubricin and hyaluronic acid (HA), produced by synovial lining cells, play central roles in protecting and maintaining the integrity of articular cartilage in diarthrodial joints (Hui et al., 2012).

Under physiological conditions, joint loading is

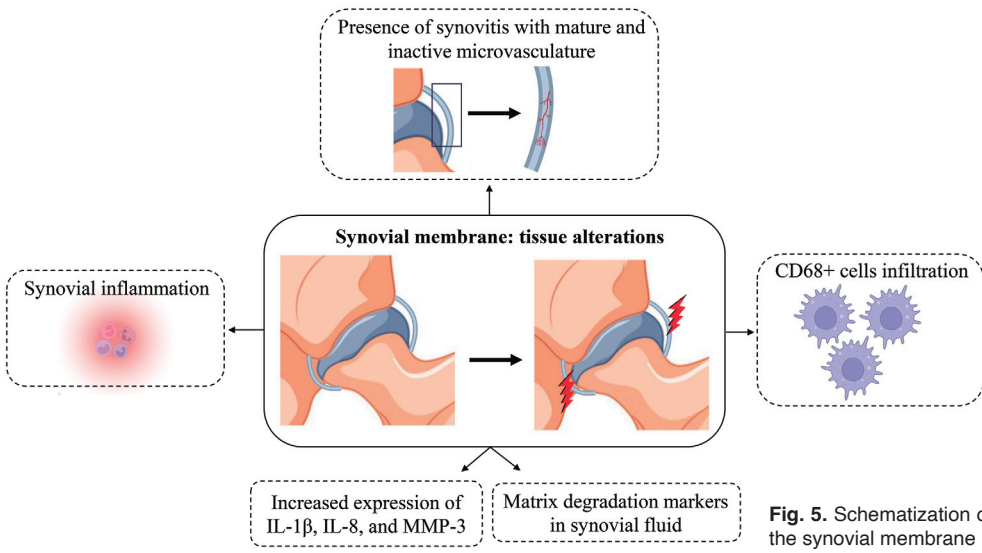

Fig. 5. Schematization of the main tissue alterations occurring in the synovial membrane in presence of FAI.

supported mainly by the fluid phase of the articular cartilage. However, when the acetabular labrum and its sealing function are compromised in FAI, the efflux of SF from the joint is enhanced during mechanical loading (Ferguson et al., 2000b, 2003; Cadet et al., 2012; Philippon et al., 2014). As a result, an increased fluid exudation from the joint can occur, thus worsening the biomechanics of the joint (Kim et al., 2019).

Tassinari et al. recently investigated the presence of inflammatory biomarkers in the SFs of FAI patients undergoing arthroscopy, including cytokines IL-6, IL-1β, TGF-α, and chemokines (IL-8, CCL2/MCP-1, CCL5/RANTES, CCL19/MIP-3β, and CCL21/6kine), typically involved in OA pathology (Tassinari et al., 2025).

Among these mediators, elevated IL-8 synovial concentration correlated with poorer preoperative status, as assessed by the hip disability and osteoarthritis outcome score (HOOS). A similar inverse correlation was observed between the monocyte chemoattractant protein-1 (CCL2/MCP-1) and the quality of daily life activities. Interestingly, chemokines such as IL-8 and CCL2/MCP-1 can recruit additional inflammatory cells, thereby amplifying the intra-articular inflammation (Tassinari et al., 2025). The authors also confirmed the presence of matrix degradation markers, including C-telopeptide fragments of type II collagen (CTX-II) in SFs of patients with FAI, which are known to be elevated in patients with advanced OA and correlate with radiographic severity.

Regarding the inflammatory profile of FAI, synovitis is generally low-grade or absent, though increased expression of IL-1β, IL-8, and MMP-3, along with infiltration of CD68+ macrophages have been reported. These findings are clinically relevant, as synovial inflammation is associated with poorer postoperative outcomes, underscoring its relevance in the clinical management of FAI.

Conversely, as FAI progresses to secondary OA, inflammatory activity becomes more pronounced, likely driven by innate immune activation through DAMPs, thereby potentially accelerating disease progression.

Tendon and other tissues

In cam-type FAI, abnormal contact between the femoral head-neck junction and the acetabular rim alters hip biomechanics. This can lead to abnormal hip kinematics and may place an excessive load on tendons, thus leading to a higher prevalence of proximal hamstring tendon injuries in individuals with FAI compared with the general population (Talathi et al., 2017; Kraeutler et al., 2019; Fortier et al., 2022).

Talathi et al. analyzed magnetic resonance imaging and magnetic resonance arthrography of the hamstring tendons of 40 FAI patients and 45 age-matched controls, observing a higher occurrence of hamstring tendon pathology in the FAI cohort (Talathi et al., 2017).

Similarly, Kraeutler et al. considered 120 hips in 97 patients (mean age: 45 years) affected by symptomatic proximal hamstring tendon pathology (acute and chronic) and found that 70.8% of hips had a diagnosis of FAI (pincer-type 9.2%, cam-type 40.8%, mixed-type 20.8%), which corresponds to an approximate 2- to 7-fold increased prevalence compared with the general population (Kraeutler et al., 2019).

Given the high prevalence of FAI in patients with symptomatic proximal hamstring tendon pathology, future studies are warranted to clarify whether, and to what extent, FAI predisposes individuals to tendon injury and degeneration.

In addition to tendon involvement, Kuhns et al. examined pulvinar tissues within the acetabular fossa in patients with FAI and secondary OA due to FAI (FAI-OA). Authors observed greater histologic synovitis in FAI-OA, although inflammatory gene expression for *PPARγ*, *TGF-β*, *IL-1β* and *MMP13* was similar between groups (Kuhns et al., 2025). Interestingly, PPARγ, TGF-β, and IL-1β were found to be more expressed in pulvinar tissues with a lower synovitis score, suggesting that these molecular changes may precede overt synovial degeneration. The evaluation of pulvinar tissue seems to play an important role in the degenerative process leading to OA, as other authors observed the correlation between pulvinar tissue and OA (Sampatchalit et al., 2009).

Overall, FAI, in particular cam-type, alters hip biomechanics, contributing to increased stress on tendons, which is connected to a higher prevalence of proximal hamstring injuries.

Emerging evidence also indicates that pulvinar tissue may play a role in FAI-related OA, highlighting its potential involvement in early degenerative changes.

Correlation between FAI and HOA

FAI causes abnormal biomechanics between the femoral head and acetabulum, leading to mechanical impingement of the hip joint and degenerative changes of the tissues of the entire joint compartment.

Consequently, FAI is recognized as a risk factor for HOA, causing pain and, in some cases, requiring THR, even in young adults (Ganz et al., 2003). Indeed, FAI has been identified as a potential cause of secondary OA in up to 50% of HOA cases (Haneda et al., 2020a). However, the specific factors that increase the risk of OA in FAI patients remain poorly understood (Melugin et al., 2020).

To date, it remains unclear whether modifiable patient lifestyle habits, such as smoking status or increased BMI, can be possible risk factors for HOA progression in patients with FAI, even if increased BMI is a well-known risk factor in the general population (Melugin et al., 2020).

A study conducted by Melugin et al. (Melugin et al., 2020) evaluated 952 patients with FAI with a mean age of 27.6 ± 8.7 years at the time of presentation, where most of whom had mixed-type FAI (785 patients;

71.1%), 211 (19.1%) had pincer-type FAI, and 108 (9.8%) had cam-type FAI. After a mean follow-up of 24.7 years, 14% of hips developed symptomatic OA and 4% underwent THR. These rates are higher compared with the prevalence of symptomatic HOA reported in the general population (Kim et al., 2014; Allen and Golightly, 2015). Such studies are extremely useful because provide baseline data for monitoring HOA progression in young patients with hip pain and the proportion of patients undergoing surgery. The authors also identified male sex, increased age, and BMI >29 as risk factors for HOA, but further studies are needed to identify non-radiographic risk factors for OA, such as BMI, sex, and lifestyle habits, specifically in patients with FAI, rather than only in the general population.

Although a clinical relationship between FAI and OA appears to exist, the concept of FAI as a direct cause of OA remains debated (Chinzei et al., 2016).

Inflammation resulting from mechanical impingement may play a pivotal role, as it is associated with both cartilage loss and the onset and persistence of symptoms, including pain (Sellam and Berenbaum, 2010; Goldring and Otero, 2011). Considering that OA arises from an imbalance between anabolic and catabolic regulatory mechanisms, heightened inflammation may exacerbate catabolic stimuli, worsening the integrity of tissue components.

Despite these insights, further studies are required to better elucidate the mechanisms linking FAI with joint degeneration. In this context, the present review aims to summarize current knowledge concerning the histological and molecular alterations observed in FAI, with the goal of determining whether a distinct biological phenotype can be identified as a precursor stage of secondary OA.

Tissue engineering as a future perspective for regenerative purposes

Current reconstructive solutions, such as autografts and allografts, are limited by donor tissue availability, inconsistent integration, and risk of immunogenic responses (Domb et al., 2016). In contrast, the next-generation synthetic graft fabricated by means of 3D-printing and electrospinning technologies will focus on the use of advanced synthetic materials (including silk fibroin, polycaprolactone, and human platelet lysate-derived methacrylate proteins) to achieve tunable, reproducible, and biomimetic properties (Rockwood et al., 2011). These grafts aim to closely recapitulate the native acetabular labrum, representing more than an incremental improvement over current reconstructive techniques, and introducing the possibility of a customizable, off-the-shelf biomimetic implant with defined mechanical properties. The application of these technologies and biomaterials could lead to scalable production of functional labral grafts capable of restoring joint sealing and fluid pressurization, and preventing cartilage overload, functions lost in FAI-related labral pathology (Ferguson et al., 2000a). The long-term goal is to integrate the synthetic graft into minimally invasive hip preservation strategies (Domb et al., 2016).

Biodegradable scaffolds with embedded signaling molecules (e.g., TGF-β or BMPs) may further enhance host integration and tissue remodeling, extending the application of this platform to other fibrocartilaginous tissues, such as the glenoid labrum or knee meniscus (Rockwood et al., 2011; Liu et al., 2013).

The unique clinical study mentioned in the literature is from Tey-Pons et al., who presented their initial experience using a synthetic polyurethane scaffold (normally used for meniscus transplantation) for augmentation and reconstruction of segmental labral tissue loss or irreparable labral damage (Tey-Pons et al., 2021). The authors showed an improvement in hip joint function in 3 patients at four years after implantation, with pain reduction and scaffold preservation on follow-up imaging. The main limitation of the present study was the small sample size. Moreover, the augmentation was limited to the frayed or manipulated labrum for pincer resection but not extended to the complete hypoplastic labrum.

A synthetic graft represents more than an incremental improvement over current reconstructive techniques, introducing the possibility of overcoming all those limitations with a customizable, off-the-shelf biomimetic implant with defined mechanical properties. Therefore, there is a need to find new biomaterials that cover the reconstruction of most lesions.

Conclusion

The degenerative processes associated with FAI are primarily linked to cartilage degeneration and enhanced catabolism, characterized by high-grade inflammation that is exacerbated by mechanical impingement.

However, other tissues are also affected by the degenerative progression of the disease. Indeed, in the early stage of FAI, inflammation is already occurring in the acetabular labrum and synovial membrane, where the expression of inflammatory molecules, such as IL-1β, MMP-13, and ADAMTS-4, was found in both early- and late-stage OA, suggesting that chronic inflammation and degeneration at the impingement zone are also partially present in the early stage of the disease.

During the progression of OA, transcriptome analysis revealed 50 differentially expressed genes between early-stage FAI and advanced OA, suggesting that an intervention at the early stage is of great importance in stopping the progression. Interestingly, the hip synovial membrane appears to retain notable regenerative potential despite the presence of FAI.

Understanding the evolution of FAI toward OA is crucial to identifying specific hallmarks of disease progression, preventing the transition from focal impingement to global joint destruction.

In particular, a deeper understanding of molecular

differences among the FAI phenotypes, as well as variations across disease stages, and correlating these findings with patient sex and age, represents a promising direction for future research. In these studies, the standardization of collected clinical and pathological data, such as consistent disease staging and patient conditions, will be essential.

In conclusion, all the joint tissue alterations and morphological changes described in patients with FAI may be helpful in identifying individuals at high risk for OA progression, advancing the diagnosis, treatment, and prevention of HOA.

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