Fatty Acid Binding Protein 4 (FABP 4) in Osteoarthritis: Linking Metabolic Inflammation to Joint Degeneration

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Abstract

Background: Osteoarthritis (OA) is a highly prevalent chronic joint disorder and a leading cause of pain, disability, and reduced quality of life. While traditionally viewed as a “wear-and-tear” condition, OA is now recognized as a whole-joint disease driven by biomechanical overload and low-grade inflammation, with a distinct metabolic phenotype in which adipose-derived mediators amplify synovitis, cartilage catabolism, and pain sensitization. Among these mediators, fatty acid–binding protein 4 (FABP4) has emerged as a mechanistically plausible link between systemic metabolic inflammation and structural joint degeneration.

FABP4 is a lipid chaperone highly expressed in adipocytes and macrophages and can also circulate as an adipokine-like molecule. In OA, FABP4 is implicated in the crosstalk between dysfunctional adipose tissue, innate immune activation, and articular tissue breakdown. Experimental evidence suggests that FABP4 can promote macrophage-driven inflammatory responses and activate catabolic signaling pathways in chondrocytes, including nuclear factor kappa B–related cascades, leading to increased production of matrix-degrading enzymes and pro-inflammatory mediators. Clinically, elevated FABP4 levels have been associated with knee OA presence and severity in some cohorts, supporting its potential role as a biomarker of the metabolic-inflammatory OA endotype and as a candidate target for risk stratification.

The aim of this review is to synthesize current evidence on FABP4 in OA across human observational studies and mechanistic models, clarify how FABP4 may connect obesity-related inflammation to cartilage and synovial pathology, and highlight implications for rehabilitation-centered management. We emphasize how FABP4-related pathways intersect with modifiable factors central to rheumatology and rehabilitation practice, including weight reduction, muscle strengthening, physical activity dosing, and management of metabolic comorbidity. In conclusion, FABP4 represents a promising mediator at the intersection of adiposity, inflammation, and joint tissue degeneration in OA. However, key gaps remain regarding causality, longitudinal prediction of progression, tissue-specific sources within the joint, and responsiveness to lifestyle or pharmacologic interventions. Addressing these gaps may enable FABP4-informed phenotyping and more personalized, function-oriented OA care.

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Keywords: *Fatty Acid Binding Protein 4, Osteoarthritis, Joint Degeneration*

Introduction

Osteoarthritis (OA) is the most common chronic joint disease and a leading cause of pain, functional limitation, and disability worldwide. Its prevalence continues to rise in parallel with population aging, increasing obesity rates, and longer life expectancy. Traditionally, OA was described as a purely degenerative “wear-and-tear” disorder of articular cartilage; however, this concept has evolved substantially over the past two decades. OA is now recognized as a complex, multifactorial, whole-joint disease involving cartilage, synovium, subchondral bone, ligaments, periarticular muscles, and the infrapatellar fat pad, with inflammatory and metabolic factors playing central roles in disease initiation and progression [1–3].

A growing body of evidence supports the existence of a distinct **metabolic osteoarthritis phenotype**, in which systemic low-grade inflammation associated with obesity, insulin resistance, and metabolic syndrome contributes to joint degeneration independently of mechanical overload alone [4–6]. Adipose tissue is no longer viewed as an inert energy reservoir but rather as an active endocrine and immune organ that secretes numerous bioactive mediators, collectively termed adipokines. These molecules influence cartilage homeostasis, synovial inflammation, subchondral bone remodeling, and nociceptive pathways, thereby linking excess adiposity to both structural damage and pain in OA [7–9].

Among adipokines, fatty acid–binding protein 4 (FABP4) has recently gained attention because of its dual intracellular and extracellular functions at the intersection of lipid metabolism and inflammation. FABP4 is abundantly expressed in adipocytes and macrophages and can be released into the circulation, where it acts as an adipokine-like signaling molecule. Beyond its established role in metabolic and cardiovascular diseases, emerging data suggest that FABP4 participates in inflammatory joint pathology by promoting macrophage activation, enhancing pro-inflammatory cytokine production, and stimulating catabolic responses in chondrocytes [10–12]. Importantly, FABP4 has been detected in synovial tissue, synovial fluid, and infrapatellar fat pad–derived cells, implicating local joint adipose depots as potential sources of pathogenic signaling in OA [13,14].

From a rheumatology and rehabilitation perspective, understanding FABP4 biology is particularly relevant. FABP4-associated pathways overlap with modifiable risk factors central to OA management, including obesity, physical inactivity, muscle weakness, and metabolic comorbidities. Interventions such as weight loss, exercise therapy, and lifestyle modification not only improve pain and function but may also attenuate systemic and local inflammatory mediators, potentially influencing FABP4-related mechanisms [15–17].

The **aim of this review** is to comprehensively examine the role of FABP4 in osteoarthritis by integrating current knowledge on OA pathophysiology, adipokine biology, and experimental and clinical evidence linking FABP4 to joint degeneration. We also aim to highlight key research gaps, particularly regarding causality, biomarker validity, and therapeutic responsiveness, and to discuss the implications of FABP4-driven metabolic inflammation for rehabilitation-oriented, personalized OA management.

Osteoarthritis as a Metabolic–Inflammatory Joint Disease

Osteoarthritis is increasingly conceptualized as a heterogeneous disease comprising multiple clinical and biological phenotypes rather than a single uniform entity. While mechanical overload and joint injury remain key contributors, accumulating evidence indicates that metabolic and inflammatory factors substantially influence OA onset, symptom severity, and structural progression. This paradigm shift is particularly evident in patients with obesity, metabolic syndrome, or type 2 diabetes, in whom OA may develop even in non–weight-bearing joints, underscoring mechanisms beyond simple biomechanical stress [18,19].

Low-grade systemic inflammation represents a hallmark of the metabolic OA phenotype. Adipose tissue expansion is associated with increased infiltration of macrophages and other immune cells, leading to enhanced secretion of pro-inflammatory mediators such as tumor necrosis factor–α, interleukin (IL)-1β, and IL-6. These cytokines are detectable not only in the circulation but also within synovial fluid, synovial membrane, subchondral bone, and cartilage of patients with OA, where they promote catabolic processes, inhibit extracellular matrix synthesis, and sensitize nociceptive pathways [20–22].

Adipokines serve as critical molecular intermediates linking systemic metabolic dysfunction to local joint pathology. Molecules such as leptin, adiponectin, resistin, and visfatin have been shown to modulate chondrocyte metabolism, synovial inflammation, angiogenesis, and bone remodeling. Importantly, adipokines can exert both endocrine and paracrine effects, acting locally within the joint microenvironment as well as systemically. Their expression patterns differ by sex, age, adiposity, and disease stage, contributing to clinical heterogeneity in OA presentation and progression [23–25].

Within the joint, several tissues participate in metabolic-inflammatory signaling. The synovium acts as an immunologically active tissue capable of producing cytokines and chemokines, while the subchondral bone undergoes dynamic remodeling that influences cartilage integrity through biomechanical and biochemical coupling. The infrapatellar fat pad has emerged as a particularly relevant structure in knee OA, functioning as a local adipose depot that secretes adipokines and inflammatory mediators in close proximity to cartilage and synovium. Alterations in infrapatellar fat pad volume, fibrosis, and inflammatory profile have been associated with pain, synovitis, and structural damage [26–28].

Recognition of OA as a metabolic-inflammatory disease has important implications for both research and clinical care. It provides a biological rationale for stratifying patients according to metabolic risk factors, inflammatory burden, and adipokine profiles, and it highlights potential targets for intervention beyond symptom control. In this context, fatty acid–binding protein 4 has gained attention as a candidate mediator that integrates lipid metabolism, macrophage-driven inflammation, and joint tissue degeneration, positioning it as a key molecule of interest within the metabolic OA framework [29–31].

FABP4 in Osteoarthritis: Evidence from Human Studies

Clinical and translational studies have begun to clarify the association between fatty acid–binding protein 4 and osteoarthritis in humans, particularly within the context of obesity-related and metabolic phenotypes. Several observational investigations have reported elevated circulating FABP4 levels in patients with knee osteoarthritis compared with age-matched controls, with higher concentrations correlating with body mass index, insulin resistance, and radiographic disease severity. These findings support the concept that FABP4 reflects systemic metabolic inflammation rather than mechanical joint damage alone [32,33].

Importantly, FABP4 has been detected not only in serum but also within the joint microenvironment. Studies analyzing synovial fluid and synovial tissue samples from patients with knee OA have demonstrated measurable FABP4 expression, suggesting local production or accumulation within inflamed joints. The infrapatellar fat pad, a metabolically active adipose structure adjacent to the knee joint, has been proposed as a major local source of FABP4. Given its proximity to cartilage and synovium, infrapatellar fat pad–derived FABP4 may exert paracrine effects that amplify synovial inflammation and cartilage catabolism [34].

Associations between FABP4 levels and clinical manifestations of OA have also been explored. Higher FABP4 concentrations have been linked to increased pain intensity and reduced physical function in some cohorts, even after adjustment for body mass index. This observation suggests that FABP4 may contribute to symptom generation through inflammatory sensitization pathways rather than acting solely as a surrogate marker of adiposity. However, heterogeneity in study design, OA definitions, and outcome measures has limited the consistency of these findings across populations [32,35].

Sex-related differences represent another important consideration in human FABP4–OA research. Women generally exhibit higher circulating FABP4 levels than men, paralleling known sex differences in adipose tissue distribution, adipokine profiles, and OA prevalence. These differences raise the possibility that FABP4-mediated mechanisms may contribute to the greater burden of pain and disability observed in women with OA, particularly after menopause. Nevertheless, few studies have been sufficiently powered to examine sex-specific effects, highlighting a key gap in the current literature [33].

Despite growing interest, existing human studies are largely cross-sectional, limiting conclusions about causality or predictive value. Longitudinal data examining whether FABP4 levels predict OA incidence, structural progression, or response to intervention remain scarce. Standardization of assay methods, adjustment for metabolic comorbidities, and integration with imaging and functional outcomes will be essential to determine whether FABP4 can be translated from an associative marker into a clinically meaningful biomarker in osteoarthritis care [32–35].

Mechanistic Role of FABP4 in Joint Degeneration and Inflammation

Experimental studies have provided important mechanistic insights into how fatty acid–binding protein 4 may actively contribute to osteoarthritis pathogenesis rather than serving merely as a metabolic bystander. A central mechanism involves macrophage-driven inflammation within the joint microenvironment. FABP4 is highly expressed in pro-inflammatory (M1) macrophages, where it amplifies inflammatory signaling and promotes the release of cytokines such as interleukin-1β and interleukin-6. These mediators are well known to disrupt cartilage homeostasis by enhancing catabolic pathways and suppressing anabolic matrix synthesis in chondrocytes [36,37]. Chondrocytes appear to be direct targets of FABP4-mediated signaling. In vitro and in vivo models have demonstrated that FABP4 can activate intracellular inflammatory cascades within chondrocytes, most notably the nuclear factor kappa B (NF-κB) pathway. Activation of this pathway leads to upregulation of matrix metalloproteinases, cyclooxygenase-2, and prostaglandin E2, all of which contribute to extracellular matrix degradation and cartilage breakdown. Suppression or genetic deletion of FABP4 has been shown to attenuate these catabolic responses, supporting a causal role in cartilage degeneration [38].

The infrapatellar fat pad represents a key anatomical and functional interface for FABP4 activity in knee osteoarthritis. This local adipose tissue depot is rich in adipocytes and macrophages and is capable of producing FABP4 in response to inflammatory and metabolic stimuli. Paracrine diffusion of FABP4 from the infrapatellar fat pad to adjacent synovium and cartilage may amplify local inflammation, synovitis, and pain sensitization. This mechanism is particularly relevant in obese individuals, in whom adipose tissue dysfunction further enhances inflammatory mediator release [34,38]. FABP4 may also influence subchondral bone remodeling, an increasingly recognized component of OA pathophysiology. Inflammatory mediators downstream of FABP4 signaling can alter osteoblast and osteoclast activity, contributing to abnormal bone turnover, sclerosis, and altered mechanical support for overlying cartilage. Although direct evidence in OA remains limited, data from metabolic and inflammatory bone models suggest that FABP4-related pathways could participate in the cartilage–bone crosstalk that characterizes disease progression [39].

Collectively, these mechanistic findings position FABP4 as an active participant in osteoarthritis pathogenesis, integrating lipid metabolism, innate immune activation, and joint tissue catabolism. By linking systemic metabolic inflammation to local structural damage, FABP4 provides a biologically plausible explanation for the strong association between obesity and OA severity and highlights a potential target for phenotype-specific intervention strategies [39].

Clinical and Rehabilitation Implications of FABP4 in Osteoarthritis

Recognition of FABP4 as a mediator linking metabolic inflammation to joint degeneration has important clinical implications, particularly from a rheumatology and rehabilitation perspective. OA management increasingly emphasizes patient stratification and personalized care, and FABP4 may contribute to identifying a metabolic-inflammatory OA phenotype characterized by obesity, heightened inflammatory burden, and disproportionate pain relative to structural damage. Such phenotyping could help explain interindividual variability in symptoms and treatment response commonly observed in clinical practice [40].

From a diagnostic standpoint, FABP4 holds potential as a circulating biomarker that reflects both systemic metabolic dysfunction and local joint inflammation. Unlike traditional radiographic markers that primarily capture late structural changes, FABP4 may provide complementary information related to disease activity, symptom severity, and inflammatory status. However, its strong association with adiposity necessitates careful interpretation, as elevated levels may reflect general metabolic risk rather than OA-specific pathology. Integration with clinical features, imaging findings, and other biomarkers would be essential to improve specificity and clinical utility [38].

Rehabilitation interventions are particularly relevant in the context of FABP4 biology. Weight reduction, aerobic exercise, and resistance training are cornerstone therapies for knee and hip osteoarthritis and are known to reduce systemic inflammation and improve metabolic health. These interventions may indirectly modulate FABP4 levels by decreasing adipose tissue mass, altering macrophage polarization, and improving insulin sensitivity. Exercise-induced anti-inflammatory effects, including reductions in pro-inflammatory cytokines, provide a plausible mechanism through which rehabilitation strategies could attenuate FABP4-driven pathways and improve both pain and function [38].

Muscle strengthening and neuromuscular training may further counteract FABP4-related joint stress by improving joint stability, shock absorption, and movement efficiency. Given that FABP4-associated inflammation may sensitize nociceptive pathways, reducing mechanical overload through optimized movement patterns could have synergistic effects on pain modulation. Importantly, these benefits can be achieved without the systemic adverse effects associated with long-term pharmacologic anti-inflammatory therapies, aligning with current guideline recommendations for first-line OA management [38].

Overall, incorporation of FABP4 into a broader metabolic-inflammatory framework reinforces the role of comprehensive, non-pharmacological management in osteoarthritis. While FABP4 measurement is not yet ready for routine clinical use, understanding its biological relevance supports a more integrated approach that targets metabolic health, physical function, and inflammation simultaneously. This perspective underscores the value of rehabilitation-centered strategies in modifying disease expression and optimizing outcomes for patients with osteoarthritis [39].

Limitations of Current Evidence and Future Research Directions

Despite growing interest in fatty acid–binding protein 4 as a mediator in osteoarthritis, several limitations constrain the interpretation and translation of current evidence. Most human studies examining FABP4 in OA are cross-sectional in design, which precludes conclusions regarding causality or temporal relationships between FABP4 elevation and disease onset or progression. It remains unclear whether FABP4 actively drives joint degeneration, represents a marker of metabolic inflammation, or reflects a downstream consequence of established disease [32].

Another important limitation relates to heterogeneity in patient populations and outcome measures. OA is a clinically diverse condition influenced by age, sex, joint site, mechanical loading, and metabolic comorbidities. FABP4 levels are strongly affected by adiposity, insulin resistance, and sex-specific fat distribution, complicating efforts to isolate OA-specific effects. Many studies lack adequate adjustment for these confounders or stratification by OA phenotype, limiting comparability across cohorts and reducing biomarker specificity [33].

At the tissue level, the relative contribution of systemic versus local FABP4 production remains insufficiently defined. While the infrapatellar fat pad, synovium, and macrophage populations are plausible intra-articular sources, the extent to which circulating FABP4 penetrates joint tissues and exerts biological effects is not fully understood. Advanced approaches combining tissue-specific sampling, imaging, and molecular profiling are needed to clarify FABP4's spatial and temporal role within the osteoarthritic joint [34].

From a therapeutic perspective, direct FABP4-targeted interventions have not yet been evaluated in osteoarthritis. Although FABP4 inhibition has shown beneficial effects in metabolic and inflammatory disease models, safety, feasibility, and efficacy in OA populations remain unknown. Future studies should explore whether established OA interventions—such as weight loss, structured exercise, and metabolic risk modification—can meaningfully reduce FABP4 levels and whether such reductions correlate with improvements in pain, function, or structural outcomes [40].

In summary, future research should prioritize longitudinal cohort studies, standardized FABP4 measurement protocols, and integration of molecular biomarkers with imaging and functional assessments. Clarifying FABP4's mechanistic and clinical relevance may enable its use in OA phenotyping and support more personalized, metabolism-informed rehabilitation strategies aimed at slowing disease progression and optimizing patient-centered outcomes.

Conclusion

In conclusion, FABP4 represents a promising link between metabolic inflammation and joint degeneration in osteoarthritis. Further longitudinal and interventional research is needed to clarify causality, validate clinical utility, and explore FABP4-targeted or FABP4-informed therapeutic approaches. Advancing this line of investigation may contribute to more precise, mechanism-based management strategies that improve long-term outcomes for patients with osteoarthritis.

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