

Biomarkers as Diagnostic and Prognostic Indicators in Post-Traumatic Osteoarthritis of Knee- a Narrative Review

Keerthy Rethinam MS¹, Thiagarajan KA², Ramchand CN³, Vinodhini VM⁴, Santhi Silambanan⁵

- 1: PhD scholar of Biochemistry, Sri Ramachandra Institute of Higher Education and Research, Porur, Chennai, India 600116. email: keerthyrethinamm@gmail.com ORCID: 0000-0001-8911-3324
- 2: Professor and Head of Arthroscopy and Sports Medicine, Sri Ramachandra Institute of Higher Education and Research, Porur, Chennai, India 600116. email: drkatn@csstrucoach.in ORCID: 0000-0001-5675-0220
- 3: President and CEO, Saksin Lifesciences Pvt Ltd, Chennai, India 600113, email: ramchand@saksinlife.com; ORCID: 0009-0005-0783-0976
- 4: Professor and Head, Department of Biochemistry, SRM Medical College Hospital and Research Centre, Kattangulathur, Chennai, India 603203, email: vinodhini239@gmail.com; ORCID : 0000-0002-2375-7917
- 5: Professor of Biochemistry, Sri Ramachandra Institute of Higher Education and Research, Chennai, India 600116; email: santhisilambanan@sriramachandra.edu.in ORCID: 0000-0003-0720-6063

Corresponding author: Dr Santhi Silambanan*

Short title: Biomarkers in PTOA

Abstract:

Post-traumatic osteoarthritis (PTOA) is a distinct form of secondary osteoarthritis resulting from joint trauma. It presents significant clinical challenges due to delayed diagnosis. PTOA is diagnosed by Kellgren-Lawrence radiological grading at stage II or later. The identification of reliable biomarkers for detecting early-stage PTOA holds great clinical importance for timely intervention and effective disease management. This review explores the current state of knowledge regarding biochemical, genetic, epigenetic, biomechanical, and imaging biomarkers in PTOA. Inflammatory mediators, including interleukin-1 β (IL-1 β), interleukin-6 (IL-6), and tumor necrosis factor- α (TNF- α), show strong correlations with disease severity and radiographic progression in both plasma and synovial fluid analyses. Cartilage oligomeric matrix protein (COMP) stands out as a consistent structural biomarker of cartilage breakdown and symptoms. Additionally, molecular and proteomic studies reveal distinct patterns over time in cartilage matrix protein degradation and the release of inflammatory factors, offering valuable insights into disease development and progression. Emerging research on single-nucleotide polymorphisms and microRNA profiles suggests promising paths for genetic and epigenetic risk assessment. Overall, these biomarkers- including inflammatory responses, cartilage breakdown products, metabolic pathways, and genetic/epigenetic markers- provide valuable opportunities for early detection, personalized risk evaluation, and targeted treatments for PTOA.

Keywords: biomarkers, epigenetics, genetics, inflammation, osteoarthritis

How to cite this article: Keerthy Rethinam MS¹ Thiagarajan KA² Ramchand CN³ Vinodhini VM⁴ Santhi Silambanan⁵. Biomarkers as Diagnostic and Prognostic Indicators in Post-Traumatic Osteoarthritis of Knee- a Narrative Review. Int J Drug Deliv Technol. 2026;16(83s):840-851. DOI: 10.25258/ijddt.16.83s.95.

Introduction

Osteoarthritis Research Society International (OARSI) has defined osteoarthritis (OA) as a disorder involving movable joints characterized by cell stress and extracellular matrix (ECM) degradation initiated by micro- and macro-injury, which results in maladaptive repair responses, including proinflammatory pathways of innate immunity.¹ The prevalence of knee OA across the globe was 16% by 2020.² In India, the prevalence was 22 - 39% between 2016 and 2019.³ Total Disability-Adjusted Life Years (DALYs) have increased by 2.69-fold, from 0.79 million in 1990 to 2.12 million in 2019.⁴ Various causes- obesity, old age, joint injuries, genetics, female gender, and metabolic diseases- lead to OA. The condition may be either primary or secondary, which results from trauma to the knee or autoimmune factors.⁴

Post-traumatic osteoarthritis (PTOA) is the OA that starts after an injury to the joint. Over time, the

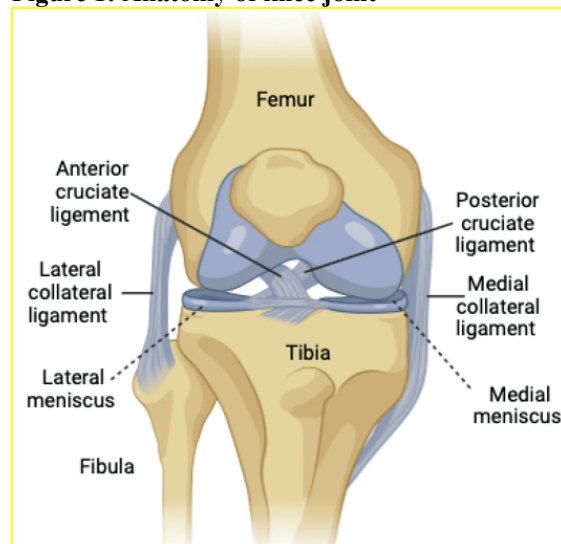
injured joint may develop pain, swelling, stiffness, and a reduction in joint movement. This disrupts the normal functions of the knee and accelerates cartilage degeneration. Factors such as the magnitude of the injury, the type of initial treatment, and the rehabilitation processes influence the development and progression of PTOA. Hence, unlike primary OA, where the cause is unknown, PTOA has a clear causative event and can occur at any age.⁵ PTOA of the knee represents 12% of all cases of symptomatic OA. Individuals who experience a knee injury are 4.2 times more likely to develop OA than those who have never had a knee injury.⁶ Although OA has been linked to mechanical overloading and aging, "wear and tear" is not the sole reason; inflammation is recognized as a key factor in its development and progression of OA.⁷ This review article aimed to provide an understanding of the various biomarkers that have

the potential role in the diagnosis and prognosis of knee PTOA.

1. Anatomy of the joint and its biomechanics

The knee is a complex joint bordered by a fibrous capsule. It is among the primary joints in the body, which involves sagittal body motion involving flexion and extension. It comprises bones, such as the femur, tibia, and patella, and cartilage, such as articular cartilage and medial and lateral menisci. Menisci help in shock absorption, joint stability, and load distribution, thus facilitating free movement of the knee joint. The joint has many intra-articular and extra-capsular ligaments.⁴ The anatomy of the knee joint is given in Fig. 1.

Figure 1: Anatomy of knee joint



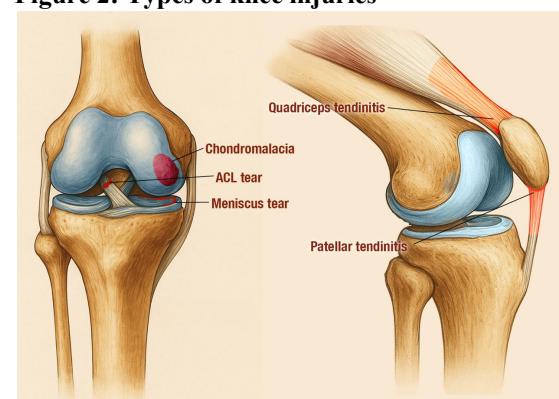
The stability of the knee is due to ligaments, menisci, muscles, and the capsule. The biomechanics involve the complex interactions between the patellofemoral and tibiofemoral joints, enabling them to withstand mechanical loads and function effectively. The knee is a modified hinge joint that allows translational and rotational movements due to the imperfect fit between the bone surfaces.⁹ The motions are guided by sliding the joint surfaces of the tibia and femur and positioning the primary ligaments of the knee. During daily activities, the knee is vital in supporting body weight, absorbing the impact from heel strikes, and aiding in swinging the lower limbs. External knee joint movements are categorized into knee adduction movement (KAM), knee flexion movement (KFM), and knee rotation movement (KRM).¹⁰

2. Types of knee injuries

Injury to the anatomical structures inside the joint may lead to loss of stabilization. Common causes include acute trauma, overuse, and biomechanical imbalances. Acute injuries lead to ligament tears, such as the anterior cruciate ligament (ACL) or medial collateral ligament (MCL) injuries. The epidemiological analysis revealed knee injuries as a significant portion (36.6%) of sports injuries, which

may occur during basketball, weightlifting, or boxing, particularly among athletes aged 18 - 22 years. The injuries may be meniscal, ligament, and joint capsule tears, joint dislocation, and fractures within the joints. (Fig. 2) In patients with isolated ACL injuries, the prevalence of PTOA is around 39%, while the prevalence is higher among those with combined ACL and meniscal injuries, ranging from 21 - 100%.⁶ A systematic review reported a PTOA prevalence of 37.9% in patients with surgically treated ACL injuries after an average follow-up of 14.6 years, compared to 40.5% in non-surgically treated patients with an average follow-up of 15 years.¹¹ A follow-up study for 36 years found that joint injury increased the risk by 5.1% compared to those without injury.¹²

Figure 2: Types of knee injuries



3. Pathogenesis of PTOA

PTOA predominantly affects young and active individuals engaged in various sports activities. Individuals with ACL reconstruction have a higher likelihood of developing OA, with an odds ratio of 3.37, 25 years after sustaining a knee injury.¹³ Joint injuries in young adults significantly elevate the risk of PTOA by 20-50%, leading to chondrocyte death, inflammation, and cartilage damage if untreated.¹⁴ PTOA evolves due to joint injuries, such as dislocations, ligament tears, meniscal tears, fractures, or cartilage damage. It occurs months to years after the initial trauma, with joint cartilage, subchondral bone, synovium, and ligaments. Initial trauma disrupts the standard mechanics of the joint, which can further damage cartilage directly or alter the biomechanics, leading to joint instability or misalignment. The mechanical forces from the injury result in chondrocyte apoptosis or necrosis. Chondrocytes are crucial for maintaining cartilage integrity, and their damage compromises cartilage repair. The pathogenesis of PTOA involves complex biological, structural, mechanical, and molecular changes that interact to influence chondrocyte viability and disease progression.¹⁵ The disease is usually diagnosed later unless the patient becomes symptomatic. However, the pathological mechanisms start immediately after the trauma. The development of OA involves cartilage degeneration that is preceded by low-grade chronic

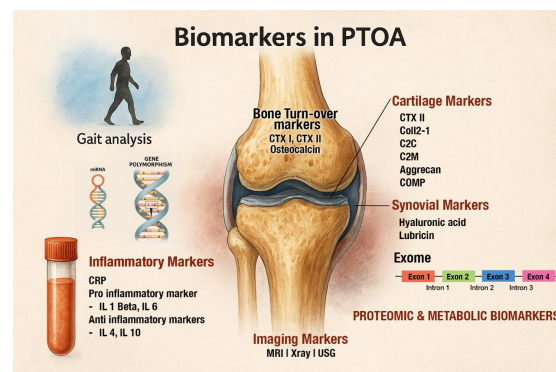
inflammation, immune responses, and subchondral bone lesions, ultimately leading to joint damage and pain.¹⁶ Changes in joint structures result from mechanical injury and active cell-driven processes influenced by complex signaling pathways and genetic factors.¹⁷ It includes damage to the ECM, chondrocyte responses to injury, and failure to regenerate cartilage, which cause progressive tissue loss and structural alterations in the joint components. The progression occurs in three stages: immediate, acute, and chronic. The immediate phase consists of various mechanical events. The acute phase, lasting a few months, involves cell death, apoptosis, and inflammatory responses. The chronic phase, which can exist from months to years, features synovitis, joint pain, and dysfunction.¹⁸ Initial trauma places excessive mechanical stress on the ECM and chondrocytes, leading to cell necrosis and the release of ECM debris as well as intracellular molecules called damage-associated molecular patterns (DAMPs). The DAMPs activate intracellular signaling pathways through pattern recognition receptors (PRRs), including toll-like receptors (TLR) and receptors for advanced glycation end products (RAGE), initiating a cascade of inflammatory and catabolic responses. DAMPs are recognized by the immune system as signals of tissue injury, prompting an inflammatory response even without infection. The rapid release of DAMPs such as fibronectin and alarmins triggers processes related to OA, including oxidative stress, increased production of catabolic enzymes, and inflammation of the synovium.¹⁴ (Fig. 3)

Figure 3: Pathogenesis of post-traumatic osteoarthritis

Intraarticular fractures lead to mitochondrial dysfunction, releasing reactive oxygen species (ROS) and proinflammatory cytokines, which act via mitogen-activated protein kinase (MAPK).⁵ Nitric oxide (NO) and ROS are involved in the breakdown of ECM, suppression of collagen formation, and cell death. Trauma may trigger the complement system, which accelerates the course of OA by increasing complement activation and controlling chondrocyte mortality. Hence, the disease is caused by various factors, including an imbalance between the anabolic and catabolic elements that support the overall health of the knee joint.

There are various classifications for the biomarkers involved in the disease depending upon the anatomical, physiological, and biochemical origin.⁴¹ (Fig. 4)

Figure 4: Role of Biomarkers in PTOA



4. Cartilage biomarkers

The hyaline cartilage seen in the knee is ECM with chondrocytes and non-collagenous components. The collagen contains types I, II, IV, V, VI, IX, and XI. A significant contribution is made by collagen type II. The proteoglycans in the cartilage include aggrecan, decorin, fibromodulin, and biglycan. It produces osmotic properties to withstand compression.²⁰ Cartilage biomarkers include CTX-II, Coll2-1, C2C, C2M, aggrecan fragments, and cartilage oligomeric matrix protein (COMP).²¹ All the biomarkers are measured in synovial fluid, urine, and serum.

4.1. C-terminal telopeptide fragment of type II collagen (CTX-II)

Urinary CTX-II (uCTX-II) has emerged as a significant biomarker for OA, particularly in assessing disease severity and progression. Studies indicate that uCTX-II levels are notably higher in patients with knee OA compared to healthy controls, suggesting its potential for early diagnosis and monitoring treatment efficacy.²¹ uCTX-II levels show association with radiographic severity (Kellgren-Lawrence grades), suggesting its role in monitoring the disease progression.²⁸ Innovative detection strategies, such as antibody-conjugated gold nanoparticles, enhance sensitivity and specificity for uCTX-II measurement.²² Weight-bearing joint pain is linked to uCTX-II levels, which further connect it to the clinical manifestations of OA. However, the age and gender-related variations in the levels remain challenging, necessitating further research to standardize their clinical application.²²

4.2. ColII-1 peptide of collagen type II

ColII-1 is formed from the breakdown of type II collagen, which is crucial for cartilage integrity. Its nitrated form, ColII-1NO₂, is an essential biomarker in OA. Elevated levels of ColII-1NO₂ correlate with inflammatory and cartilage degradation in OA patients, particularly in pre-and post-menopausal women.²² Furthermore, ColII-1 and ColII-1NO₂ levels are associated with magnetic resonance imaging (MRI) features of knee OA, suggesting their potential in predicting disease progression and worsening symptoms. ColII-1NO₂ levels are significantly high in OA patients, indicating their role in monitoring disease severity.

Elevated levels are linked to specific knee OA features, such as periarticular cysts, enhancing its utility in clinical assessments.²² The sensitivity of the marker as a prognostic biomarker suggests it could guide therapeutic strategies in OA management. Studies have demonstrated that intra-articular administration of collagen type II solutions can mitigate symptoms and cartilage damage in PTOA models.²²

4.3. Type II Collagen Cleavage (C2C)

C2C is generated by the breakdown of type II collagen in cartilage and indicates the structural deterioration of the joint. It is recognized as a valuable marker for assessing the progression and severity of OA, especially in PTOA. Studies show that higher C2C levels are associated with increased OA scores and more tissue damage. Torga et al. found that C2C expression in tissue samples positively correlated with OA severity, as assessed by the OARSI histopathology grading system, highlighting its usefulness for evaluating OA progression.²³ Furthermore, among patients with total knee arthroplasty (TKA), elevated urinary C2C levels could predict better pain relief and functional improvements post-surgery, thus linking C2C measurements with clinical outcomes.²³ In animal models of ACL-induced OA, combining serum C2C and CTX-II detection offered greater predictive accuracy for OA progression than using each marker individually, suggesting that C2C could be valuable for early-stage OA diagnosis.²³

4.4. C-terminal neopeptide of type II collagen (C2M)

The collagenase-generated C2M is a notable biomarker in OA, especially relevant to assessing cartilage degradation in PTOA. C2M is also a by-product of type II collagen breakdown. Luo et al. demonstrated that C2M levels, along with other collagen biomarkers, offer insight into cartilage degradation dynamics, suggesting that the presence of C2M may be linked to the rate of cartilage loss and OA progression.²⁴

4.5. Aggrecan

Aggrecan, a crucial part of the ECM, plays a key role in maintaining cartilage health. In PTOA, aggrecan breakdown is an early sign of joint damage, often triggered by aggrecanases and other enzymes after traumatic injury. Initially, aggrecan levels rise in the synovial fluid as a response to injury, but ongoing degradation over time leads to cartilage thinning and the progression of OA. Tourville et al. found that high levels of aggrecanase-generated fragments (ARGS) in synovial fluid are linked to inflammatory responses after ACL injuries. Aggrecan breakdown is closely tied to cytokine activity in early PTOA stages.²⁵ Additionally, recent studies highlight the role of synovial mesenchymal progenitor cells in secreting aggrecan, which supports cartilage repair and maintains homeostasis. Krawetz et al. showed that these progenitor cells build up aggrecan in

PTOA joints, and therapies that aim to increase aggrecan levels show promise in slowing cartilage degeneration and promoting repair.²⁶

4.6. Cartilage oligomeric matrix protein (COMP)

COMP is among the key biomarkers in OA. High levels in serum and synovial fluid reflect cartilage degradation and disease activity. Higher COMP levels are typically associated with knee OA severity. OA patients exhibit elevated serum COMP compared to healthy controls.²⁷ COMP is increasingly recognized as a significant biomarker in understanding knee PTOA, where its levels indicate tissue response to joint damage. COMP plays a dual role in reflecting joint degeneration and inflammation. Elevated levels are linked to the chronic phase of PTOA and correlate with structural changes observable through imaging.²⁷ COMP levels in serum and synovial fluid are indicative of cartilage breakdown and inflammatory response, aligning with degeneration patterns observed in the meniscus and articular cartilage.²⁷ This protein is a valuable early-stage marker, as its fluctuations precede visible damage, making it useful in pre-emptive diagnostics and disease-modifying interventions.

5. Bone turnover markers

Bone turnover markers include bone alkaline phosphatase, osteocalcin, procollagen I N-propeptide, and N and C telopeptides of type I collagen.²⁸

5.1. Osteocalcin (OC)

OC, a non-collagenous protein secreted by osteoblasts, has garnered attention for its involvement in OA due to its dual forms, carboxylated (cOC) and undercarboxylated (ucOC)-which exhibit distinct biological activities. While cOC is primarily associated with bone mineralization, ucOC has shown protective effects in OA by inhibiting chondrocyte hypertrophy, thus preventing cartilage degradation. OC levels are higher in early OA compared to advanced stages, indicating intense bone remodeling that decreases as the disease progresses.²⁸

6. Inflammatory markers

6.1. Cytokines

Cytokines are small, soluble proteins essential for cell signaling in immune and inflammatory responses. These molecules, including interleukin (IL), interferons (IFN), and tumor necrosis factor-alpha (TNF- α), are synthesized and secreted by various cells in response to immune stimuli and function in autocrine, paracrine, and endocrine manners.²⁹ Inflammatory cytokines, such as IL-1 β , IL-6, and TNF- α , are central to the development of PTOA. They drive inflammatory cascades that degrade cartilage and worsen joint pathology. After traumatic injuries, cytokines increase in synovial fluid, triggering matrix metalloproteinases (MMPs) and aggrecanases, which degrade cartilage ECM

components.³⁰ Blocking IL-1 and TNF- α with biologics like Anakinra and Infliximab may reduce inflammation and cartilage breakdown in PTOA, although their effects on long-term structural outcomes remain limited.³¹ Pro-inflammatory cytokines remain elevated in PTOA-prone joints after injuries, with concurrent increases in anti-inflammatory cytokines like IL-10, indicating a compensatory yet insufficient anti-inflammatory response.³⁰ Mechanistic studies utilizing in vitro models of injured human knee cartilage and bone suggest that the sustained cytokine-driven inflammation promotes metabolic and structural alterations in joint tissues, accelerating PTOA progression.³⁰

Anti-inflammatory cytokines, such as IL-1 receptor antagonist (IL-1RA) and IL-10, play an essential role in regulating inflammation in PTOA by opposing IL-1 β and TNF- α , which are upregulated after joint injuries. IL-10 and IL-1RA reduce inflammation and cartilage degradation by inhibiting cytokine-induced matrix degradation enzymes, potentially slowing PTOA progression.³⁰ Targeted therapies using biologics like Anakinra, an IL-1RA, have shown efficacy in reducing pro-inflammatory responses and decreasing degradation markers in synovial fluid following intra-articular fractures. Moreover, dynamic loading interventions, which help increase IL-10 levels in joint tissues, show complementary strategies for maintaining an anti-inflammatory environment post-injury.³²

6.2. C-Reactive protein (CRP)

CRP is an acute-phase biomarker for inflammation. It is correlated to the severity and progression of OA. Monomeric CRP (mCRP) is found at the inflammation site, and it is responsible for cartilage degradation by promoting inflammatory responses in chondrocytes through the activation of pathways such as NF- κ B, leading to the release of matrix-degrading enzymes.³³ High CRP concentrations are also associated with increased IL-1 β and IL-6, aggravating the inflammatory profile. In a study done on temporomandibular joint OA, CRP-knockout models showed reduced inflammation and lower cytokine levels, indicating that targeting CRP could modulate OA-related inflammation.³³

7. Synovial biomarkers:

7.1. Hyaluronic acid (HA)

HA is crucial in managing OA, particularly knee OA. It provides pain relief and improves joint function. Its therapeutic mechanisms include lubrication, shock absorption, and anti-inflammatory effects, contributing to enhanced mobility and reduced patient discomfort. Clinical studies indicate that intra-articular HA injections can significantly reduce pain and improve functional outcomes in patients with knee OA. HA has the potential to slow joint degeneration and provide long-term relief with minimal side effects. It also exhibits anti-inflammatory properties and promotes

cartilage repair by influencing proteoglycan synthesis.³⁴ Platelet-rich plasma (PRP)-treated patients reported better results and longer-lasting benefits than those receiving HA injections.

In preclinical studies, intra-articular injections of HA alone or combined with other agents, such as corticosteroids or dexamethasone, have shown potential to alleviate PTOA symptoms. A study utilizing a cross-linked HA-dexamethasone (cHA-Dex) hydrogel demonstrated significant reductions in chondrocyte apoptosis and inflammation markers like IL-1 β and MMP-13, highlighting the effectiveness of sustained drug release in early PTOA management.³⁵ Additionally, HA conjugated with alendronate (ALN) in PTOA animal models resulted in improved cartilage integrity and reduced pain by suppressing inflammatory and catabolic processes.³⁵ This combination suggests that modifying HA with other therapeutic compounds can enhance its efficacy in addressing joint degeneration and inflammation.

7.2. Lubricin

Lubricin is also known as proteoglycan 4 (PRG-4). It is a mucinous glycoprotein critical in joint lubrication and cartilage health. It acts as a boundary lubricant, protecting articular surfaces from wear and tear and reducing friction during joint movement. In OA, altered expression and glycosylation patterns of lubricin have been observed, contributing to compromised joint lubrication and increased cartilage degradation.³⁶ Reduced lubricin levels in OA synovial fluid correlate with increased cartilage wear, underscoring its protective function.³⁷ Such approaches aim to reduce oxidative stress, enhance autophagy, and improve mitochondrial function, contributing to overall chondroprotection and slowing OA progression. Furthermore, in vitro models show that lubricin-based treatments can resist enzymatic degradation and maintain joint lubrication, presenting the potential for therapeutic applications in OA management.³⁸

8. Imaging biomarkers

OA is diagnosed with a traditional method- a knee joint X-ray. X-ray helps us to diagnose the formation of osteophytes on the joint margin or the tibial spines, periarticular ossicles, narrowing of joint cartilage associated with sclerosis of subchondral bone, small pseudo cystic areas with sclerotic walls situated usually in the subchondral bone, and an altered shape of the bone ends. The diagnosis is done according to the Kellgren-Lawrence grading system.³⁹ MRI shows changes in subchondral bone composition, bone marrow lesions, and subchondral cyst lesions, contributing to disease progression.⁴⁰

9. Genetic and epigenetic biomarkers

9.1. Genetic markers

OA is influenced by various genetic factors contributing to its onset and progression. Recent studies have identified genetic polymorphisms and

mutations linked to OA susceptibility and severity. Table 1 gives a list of a few genes that are affected in the disease.

Table 1: Gene variations in knee osteoarthritis

Gene involved	Significance	Reference
<i>COL2A1</i>	Encodes type II collagen, critical for cartilage structure; associated with OA susceptibility	41
<i>GDF5</i>	Involved in joint development and repair; linked to OA severity	42
<i>ACAN</i>	Polymorphisms associated with knee OA in Volga-Ural women	43
<i>DVWA</i>	Genetic variations associated with increased risk of knee OA in Volga-Ural women	43
<i>IL-6</i>	Polymorphism linked to increased OA risk in Pakistani population; influences inflammation	43
<i>TGF-β1</i>	Genetic variation correlated with OA risk; important in tissue repair	43
<i>CALM1</i>	Polymorphism associated with OA susceptibility in Pakistanis	43
<i>ALKBH1</i>	N6-methyladenosine - RNA methylation regulator, potential early diagnostic and prognostic marker for OA	44
<i>IGF2BP3</i>	N6-methyladenosine - RNA methylation regulator, may serve as an early diagnostic marker for OA	44
<i>TRPM5</i>	Ion channel gene identified as a potential diagnostic marker for OA	45
<i>KCNJ2</i>	An ion channel gene that may inform targeted OA therapies	45
<i>ITGAM</i>	Associated with symptomatic knee OA	46
<i>IL-1β</i>	Gene polymorphism correlates with synovial cytokine	47

	levels and influences PTOA risk	
<i>TNF-α</i>	Gene variant affects inflammation and increases risk of developing OA	47

Note: ACAN: Aggrecan, ALKBH 1: AlkB Homolog 1, CALM1: Calmodulin I, COL2A1: Collagen type II alpha 1 chain, DVWA: double von Willebrand factor domain A, GDF5: Growth differentiation factor 5, IGF2BP3: Insulin-like growth factor 2 binding protein 3, IL-1β: interleukin- 1 beta, IL-6: Interleukin-6, KCNJ2: Potassium inwardly rectifying channel subfamily J member 2, TGF-β1: Transforming growth factor-beta1, TNF-α: Tumour necrosis factor -alpha, TRPM5: Transient receptor potential cation channel subfamily M member 5.

Single-nucleotide polymorphisms (SNPs) are common genomic DNA variations within a population. SNPs significantly influence the genetic predisposition to OA, influencing its onset, progression, and severity. SNPs such as those in the *GDF5* gene (rs143383) are associated with OA risk, especially in populations of Asian and Caucasian descent. The *GDF5* SNP impacts cartilage development and joint maintenance, linking to knee and hand OA.⁴² Similarly, *ADAMTS14* SNPs, such as rs4747096, are associated with OA susceptibility by affecting the breakdown of ECM, which is crucial for joint integrity.⁴⁸ A broader genetic analysis reveals that SNPs influencing DNA methylation, such as rs34195470 in *WWP2*, can modulate gene expression via epigenetic changes, underscoring the complexity of genetic regulation in OA.⁴⁹ *COLGALT2* rs1046934 affects the expression of *COLGALT2*, a gene involved in collagen glycosylation, through its influence on enhancer methylation. It contributes to OA risk by impacting collagen stability and cartilage resilience.⁵⁰

9.2. Epigenetic biomarkers

Epigenetic mechanisms include DNA methylation, histone modifications, and non-coding RNA regulation. It significantly influences OA pathogenesis by modulating gene expression without altering the DNA sequence. A systematic review highlights the role of these mechanisms in regulating key genes associated with cartilage homeostasis and inflammatory pathways in knee OA.⁵¹ Aberrant DNA methylation patterns are linked to changes in gene expression that exacerbate cartilage degradation and inflammation, contributing to OA progression.⁵² Histone acetylation and methylation also affect chromatin structure and can either promote or inhibit the transcription of OA-associated genes.⁵³ Non-coding RNAs, including microRNAs (miRNAs), circular RNAs (circRNAs), and long non-coding RNAs

(lncRNAs), play regulatory roles by targeting mRNA for degradation or inhibiting translation, impacting genes involved in cartilage integrity and inflammatory responses. Some of the altered expression of microRNAs in osteoarthritis are given in Table 2.

Table 2: Altered Expressions of MicroRNAs in Osteoarthritis

MicroRNA	Significance	Reference
miR-146a-5p	↑ chondrocyte apoptosis, ↓ autophagy; ↑ OA progression; ↓ cell growth, ↑ apoptosis and inflammation in OA cartilage damage by regulating thioredoxin-interacting protein. In an animal study, ↓ miR-146a-5p counteracts IL-1β-induced inflammatory responses and catabolic effects in vitro. Silencing miR-146a in chondrocytes improves articular cartilage integrity. ↓ OA-related pain in an injury-induced murine OA model.	54-56
miR-140	↓ ADAMTS-5 to maintain cartilage integrity; essential for chondrocyte proliferation and cartilage stability.	57
miR-214	↓ inflammation; supports anabolic activities in response to mechanical loading; protective in PTOA recovery.	58
miR-146a	↑ expression in untreated OA cartilage is associated with inflammation and tissue degeneration severity.	59
miR-150	↑ in untreated OA cartilage; involved in cartilage	59

	inflammation and degeneration.	
miR-409	↑ in untreated OA cartilage; linked to inflammation and tissue degeneration.	59
miR-125a-3p	↑ chondrocyte apoptosis & inhibits autophagy; causes OA progression; regulates Thioredoxin-interacting protein.	60
miR-200c	↓ expression after MSC treatment associated with tissue damage and therapeutic potential.	60
miR-499-5p	↓ expression following MSC treatment; candidate for therapeutic strategies in PTOA.	60
miR-144	Involved in regulation of chondrocyte differentiation & apoptosis in PTOA	61
miR-219-3p	Chondrocyte differentiation and apoptosis in PTOA	61
miR-199a-3p	Regulates chondrocyte differentiation & apoptosis in PTOA	61
miR-34a-5p	↑ Expression in synovial fluid of patients with late-stage OA	62
miR-140-3p	↑ survival & migration of inflammatory chondrocytes; ↑ chondrogenic differentiation & ↓ apoptosis under hypoxia	63
miR-140-5p	↓ chondrocyte pyroptosis & alleviates cartilage injury by targeting cathepsin B & ↓ NLRP3 inflammasome.	64

The potential of targeting these epigenetic pathways for OA therapy has been suggested, with specific miRNAs being proposed as biomarkers and therapeutic agents due to their ability to modulate catabolic and anabolic processes in joint tissues.⁵³

Emerging research emphasizes that the epigenetic landscape evolves through different life stages, potentially unmasking genetic susceptibilities as individuals age, thus impacting OA onset and severity.⁵³ This highlights the importance of integrating genetic and epigenetic data for comprehensive OA risk assessment and developing targeted treatments.

10. Proteomic and metabolomic biomarkers

Proteomic and metabolomic profiling in OA has illuminated potential biomarkers and pathways central to understanding and managing the disease. Synovial fluid and serum analyses have identified proteins such as complement components, serine protease inhibitors, and apolipoproteins that play roles in the pathogenesis of OA. These proteomic markers potentially aid in early diagnosis.⁶⁵ Furthermore, serum metabolomics has revealed significant changes in amino acid, lipid, glucose, and energy metabolism between OA patients and healthy controls, indicating metabolic pathway disruptions that could be leveraged for diagnostic or therapeutic purposes.⁶⁵ Integrating proteomic and metabolomic data helps delineate OA subtypes and progression. Alterations in metabolic pathways related to UDP-glucuronic acid synthesis and amino sugar metabolism, impacting hyaluronic acid and ECM production, are key components in maintaining joint health. Proteomic research utilizing 2D gel electrophoresis and mass spectrometry has emphasized differential protein expression in OA, pointing to potential therapeutic targets and biomarkers.⁶⁵

11. Mechanical biomarkers

11.1. Gait analysis

After ACL injuries, gait analysis is important for understanding biomechanical changes in PTOA. Patients with PTOA demonstrate abnormal gait patterns, which include changes in the knee joint's mechanics with varying degrees of muscle activity during different phases, especially during the load acceptance phase of walking.⁶⁷ Unlike non-traumatic OA, PTOA is associated with greater degeneration of cartilage because of abnormal knee adduction and rotation moments during PTOA progression, coupled with reduced muscle activation. Patients with PTOA have different muscle activation patterns, including reduced activation of the gastrocnemius muscle, which governs the knee, changing its angle, which increases the tendency to lose control of the disease.⁶⁷

11.2. Joint kinematics

In PTOA, lower limb joint kinematics are markedly different, significantly affecting function and accelerating the disease. Research shows that subchondral bone changes and cartilage deterioration occur alongside ACL injury, where lower flexion angles of the knee are associated with

greater bone porosity.⁶⁸ It is important to highlight that in some cases, PTOA development can happen without considerable external joint load.⁶⁸ Assessment of movement in PTOA patients demonstrates sustained alterations in knee and hip high-level coordination, which include lower postoperative hip moments and greater inhibition than expected.⁶⁹ This underlines the importance of joint movement parameters, including their speed and muscle contraction, during the progression of PTOA.

12. Exome derived Biomarkers

Exome-derived biomarkers have become valuable tools in OA research, offering insights into disease mechanisms and identifying potential therapeutic targets. Identifying gene variants through exome sequencing has enabled the detection of differentially expressed genes (DEGs) and pathways that play critical roles in OA progression. Notably, COL3A1, COL5A1, and COL6A2 have been highlighted as potential biomarkers due to their increased expression in OA subchondral bone, implicating them in ECM remodeling and joint tissue integrity.⁷⁰ These findings were supported by protein-protein interaction analyses and immunohistochemical studies, which demonstrate higher expression levels in OA tissues. Additionally, the integration of multi-omics approaches, which includes genomic, transcriptomic, and proteomic data, has allowed the establishment of comprehensive databases like OAomics. These resources compile OA-related gene markers and omics features, facilitating targeted research into specific genes associated with the disease.⁷⁰ Research on senescence-derived protein biomarkers further underscores their relevance in OA, where exosome proteins and senescence-associated secretory phenotypes (SASP) contribute to joint degradation and inflammation.⁷¹ The application of exome sequencing has also revealed immune-related gene markers such as HLA-DMB and FCER1G, identified through Mendelian randomization and transcriptome analyses, suggesting their involvement in OA's immune microenvironment.⁷²

13. Conclusion

After the joint has undergone trauma, it may lead to arthritis of the joint. Hence, the measures to prevent, diagnose, and prognosticate the disease are crucially important. The disease is a multifaceted illness with many factors deteriorating the joint. Effective prevention and early intervention techniques are limited, despite improvements in the knowledge of the pathophysiology and risk factors for PTOA. To improve outcomes for patients with PTOA, future research is required to investigate novel biomarkers, regenerative treatments, and customized therapy techniques. To improve patient treatment and lessen the burden of this crippling illness, a multidisciplinary strategy combining biomechanics, molecular biology, and clinical insights will be

crucial to improving our capacity to slow the development and progression of PTOA.

Declarations:

Ethical Approval: Ethics Committee was not required since this was a review article

Use of AI: AI was not used in any stage of preparation of the manuscript

Competing Interests: The authors declare they have no competing interests.

Financial Disclosure: No financial support has been received for this study.

Author Contributions: KRMS: Concept, Data Collection and/or Processing, Writing original draft; TKA: Concept, Analysis and/or Interpretation, Writing original draft; RCN: Concept, Analysis and/or Interpretation, Writing original draft; VVM: Concept, Analysis and/or Interpretation, Writing original draft; SS: Concept, Data Collection and/or Processing, Analysis and/or Interpretation, Writing original draft. All the authors have verified the final draft of the article.

Acknowledgement: Nil

References:

- Kraus VB, Blanco FJ, Englund M, Karsdal MA, Lohmander LS. Call for standardized definitions of osteoarthritis and risk stratification for clinical trials and clinical use. *Osteoarthr. Cartil.* 2015;23:1233-41. doi: 10.1016/j.joca.2015.03.036
- Cui A, Li H, Wang D, Zhong J, Chen Y, Lu H. Global, regional prevalence, incidence and risk factors of knee osteoarthritis in population-based studies. *EClinicalMedicine.* 2020;29-30:100587. doi: 10.1016/j.eclinm.2020.100587
- Pal CP, Singh P, Chaturvedi S, Pruthi KK, Vij A. Epidemiology of knee osteoarthritis in India and related factors. *Indian J Orthop.* 2016;50:518-522. doi: 10.4103/0019-5413.189608
- Singh A, Das S, Chopra A, Danda D, Paul BJ, March L, et al. Burden of osteoarthritis in India and its states, 1990-2019: findings from the Global Burden of disease study 2019. *Osteoarthr. Cartil.* 2022;30:1070-1078. doi: 10.1016/j.joca.2022.05.004
- Dilley JE, Bello MA, Roman N, McKinley T, Sankar U. Post-traumatic osteoarthritis: A review of pathogenic mechanisms and novel targets for mitigation. *Bone Rep.* 2023;18:101658. doi: 10.1016/j.bonr.2023.101658
- Thomas AC, Hubbard-Turner T, Wikstrom EA, Palmieri-Smith RM. Epidemiology of Posttraumatic Osteoarthritis. *J Athl Train.* 2017;52:491-496. doi: 10.4085/1062-6050-51.5.08
- Loeser RF, Collins JA, Diekmann BO. Ageing and the pathogenesis of osteoarthritis. *Nat Rev Rheumatol.* 2016;12:412-420. doi: 10.1038/nrrheum.2016.65
- Gupton M, Imonugo O, Black AC, Launico MV, Terreberry RR. Anatomy, Bony Pelvis and Lower Limb, Knee. 2023 Nov 5. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2026 Jan-. PMID: 29763193.
- Vaienti E, Scita G, Ceccarelli F, Pogliacomi F. Understanding the human knee and its relationship to total knee replacement. *Acta Biomed.* 2017;88:6-16. doi: 10.23750/abm.v88i2-S.6507
- Chang AH, Moisio KC, Chmiel JS, Eckstein F, Guermazi A, Prasad PV, et al. External knee adduction and flexion moments during gait and medial tibiofemoral disease progression in knee osteoarthritis. *Osteoarthr. Cartil.* 2015;23(7):1099-1106. doi: 10.1016/j.joca.2015.02.005
- Liukkonen R, Vaajala M, Mattila VM, Reito A. Prevalence of post-traumatic osteoarthritis after anterior cruciate ligament injury remains high despite advances in surgical techniques. *Bone Joint J.* 2023;105-B:1140-1148. doi: 10.1302/0301-620X.105B11.BJJ-2023-0058.R1
- Gelber AC, Hochberg MC, Mead LA, Wang NY, Wigley FM, Klag MJ. Joint injury in young adults and risk for subsequent knee and hip osteoarthritis. *Ann Intern Med.* 2000;133(5):321-328. doi: 10.7326/0003-4819-133-5-200009050-00007
- Seon JK, Song EK, Park SJ. Osteoarthritis after anterior cruciate ligament reconstruction using a patellar tendon autograft. *Int Orthop.* 2006;30:94-98. doi: 10.1007/s00264-005-0036-0
- Lidder S, Chubinskay S. Post-Traumatic Osteoarthritis: Biologic Approaches to Treatment [Internet]. Principles of Osteoarthritis- Its Definition, Character, Derivation and Modality-Related Recognition. *InTech*; 2012. doi: 10.5772/26454
- Godoy-Santos AL, de Cesar C, Santini S, Herrera-Pérez M, Valderrabano V, Rammelt S. Pathophysiology of Posttraumatic Ankle Osteoarthritis: a Multicenter Perspective. *Acta Ortop Bras.* 2024;32:e282286. doi: 10.1590/1413-785220243203e282286
- Coaccioli S, Sarzi-Puttini P, Zis P, Rinonapoli G, Varrassi G. Osteoarthritis: New Insight on Its Pathophysiology. *J Clin Med.* 2022;11(20):6013. doi: 10.3390/jcm11206013
- Goldring MB, Goldring SR. Osteoarthritis. *J Cell Physiol.* 2007;213:626-34. doi: 10.1002/jcp.21258
- Punzi L, Galozzi P, Luisetto R, Favero M, Ramonda R, Oliviero F, et al. Post-traumatic arthritis: overview on pathogenic mechanisms and role of inflammation. *RMD Open.* 2016;2:e000279. doi: 10.1136/rmdopen-2016-000279

19. Evers BJ, Bosch MHJVD, Blom AB, van der Kraan PM, Koëter S, Thurlings RM. Post-traumatic knee osteoarthritis; the role of inflammation and hemarthrosis on disease progression. *Front Med (Lausanne)*. 2022;9:973870. doi: 10.3389/fmed.2022.973870
20. Fox AJS, Bedi A, Rodeo SA. The basic science of articular cartilage: structure, composition, and function. *Sports Health*. 2009;1(6):461-468. doi: 10.1177/1941738109350438
21. Oliviero F, Ramonda R. Cartilage-derived biomarkers in osteoarthritis. *Indian J Med Res*. 2021;153(4):413-5. doi: 10.4103/ijmr.IJMR_436_20
22. Bay-Jensen AC, Mobasheri A, Thudium CS, Kraus VB, Karsdal MA. Blood and urine biomarkers in osteoarthritis - an update on cartilage associated type II collagen and aggrecan markers. *Curr Opin Rheumatol*. 2022;34(1):54-60. doi: 10.1097/BOR.0000000000000845
23. Torga T, Suutre S, Kisand K, Aunapuu M, Arend A. Cartilage Collagen Neopeptide C2C Expression in the Articular Cartilage and Its Relation to Joint Tissue Damage in Patients with Knee Osteoarthritis. *Biomedicines*. 2024;12:1063. doi: 10.3390/biomedicines12051063
24. Luo Y, He Y, Reker D, Gudmann NS, Henriksen K, Simonsen O, et al. A Novel High Sensitivity Type II Collagen Blood-Based Biomarker, PRO-C2, for Assessment of Cartilage Formation. *Int J Mol Sci*. 2018;19:3485. doi: 10.3390/ijms19113485
25. Tourville TW, Poynter ME, DeSarno MJ, Struglics A, Beynnon BD. Relationship between SF ARGS-aggrecan fragments, cytokines, MMPs, and TIMPs following acute ACL injury: A cross-sectional study. *J Orthop Res*. 2015;33:1796-803. doi: 10.1002/jor.22961
26. Krawetz RJ, Wu YE, Bertram KL, Shonak A, Masson AO, Ren G, et al. Synovial mesenchymal progenitor-derived aggrecan regulates cartilage homeostasis and endogenous repair capacity. *Cell Death Dis*. 2022;13:470. doi: 10.1038/s41419-022-04919-1
27. Nakhjavani MRJ, Ghorbanihaghjo A, Asadollahipour OD, Azar SA, Pourlak T, Mahdavi AM. Correlation Between Serum Cartilage Oligomeric Matrix Protein (COMP), 25-Hydroxy Vitamin D, and Disease Activity in Patients with Knee Osteoarthritis. *IRCMJ*. 2024; 21(5):1-7. doi: 10.5812/ircmj.91113
28. Schini M, Vilaca T, Gossiel F, Salam S, Eastell R. Bone Turnover Markers: Basic Biology to Clinical Applications. *Endocr Rev*. 2023;44(3):417-473. doi: 10.1210/edrev/bnac031
29. Silva RC, Travassos LH, Dutra FF. The dichotomic role of single cytokines: Fine-tuning immune responses. *Cytokine*. 2024;173:156408. doi: 10.1016/j.cyto.2023.156408
30. Pham TM, Erichsen JL, Kowal JM, Overgaard S, Schmal H. Elevation of Pro-Inflammatory Cytokine Levels Following Intra-Articular Fractures-A Systematic Review. *Cells*. 2021;10(4):902. doi: 10.3390/cells10040902
31. Valerio MS, Edwards JB, Dolan CP, Motherwell JM, Potter BK, Dearth CL, et al. Effect of Targeted Cytokine Inhibition on Progression of Post-Traumatic Osteoarthritis Following Intra-Articular Fracture. *Int J Mol Sci*. 2023;24:13606. doi: 10.3390/ijms241713606
32. Hazbun L, Martinez JA, Best TM, Kaplan L, Huang CY. Anti-inflammatory effects of tibial axial loading on knee articular cartilage post-traumatic injury. *J Biomech*. 2021;128:110736. doi: 10.1016/j.jbiomech.2021.110736
33. Grzech-Leśniak Z, Matuszewska A, Fiegler-Rudol J, El Mobadder M, Wiench R, Więckiewicz M. The Role of Proinflammatory Cytokines in Temporomandibular Disorders: A Systematic Review. *Int. J. Mol. Sci*. 2026; 27(8):3677. doi: 10.3390/ijms27083677
34. Setiady J, Mustari MN, Latief J, Hamid F, Laiding SR, Faruk M. The effect of intra-articular hyaluronic acid injection on clinical function among knee osteoarthritis patients over one year. *Chirurgia* 2024;37:236-242. doi: 10.23736/S0394-9508.23.05663-2
35. Zhang ZW, Zhao JY, Feng Y, Yin K, Li PC, Wei XC. [Study on the mechanism of cross-linked hyaluronic acid-dexamethasone hydrogelin post-traumatic osteoarthritis]. *Zhonghua Yi Xue Za Zhi*. 2024;104(9):695-703. Chinese. doi: 10.3760/cma.j.cn112137-20231008-00672.
36. Afshari AR, Thomsson KA, Höglund J, Ryberg H, Gidwani K, Pettersson K, et al. A Novel Fluorescent Immuno-Lectin Assay to Identify Osteoarthritis Associated Glycoforms of Lubricin. *medRxiv*. 2024:2024-2001. doi: 10.1101/2024.01.02.23300279
37. Roggio F, Petrigna L, Trovato B, Di Rosa M, Musumeci G. The Role of Lubricin, Irisin and Exercise in the Prevention and Treatment of Osteoarthritis. *Int J Mol Sci*. 2023;24:5126. doi: 10.3390/ijms24065126
38. Gong C, Cui L, Xiong D, Ding Y. In vitro drug release and cartilage interface lubrication properties of biomimetic polymers. *J Mech Behav Biomed Mater*. 2024;152:106439. doi: 10.1016/j.jmbbm.2024.106439
39. KELLGREN JH, LAWRENCE JS. Radiological assessment of osteo-arthritis. *Ann*

- Rheum Dis.* 1957;16(4):494-502. doi: 10.1136/ard.16.4.494
40. Kaspiris A, Hadjimichael AC, Lianou I, Iliopoulos ID, Ntourantonis D, Melissaridou D, et al. Subchondral Bone Cyst Development in Osteoarthritis: From Pathophysiology to Bone Microarchitecture Changes and Clinical Implementations. *J. Clin. Med.* 2023;12(3):815. doi: 10.3390/jcm12030815
41. Li P, Wang A, Li J, Li X, Sun W, Liu Q. COL2A1 Mutation (c.611G>C) Leads to Early-Onset Osteoarthritis in a Chinese Family. *Int J Gen Med.* 2021;14:2569-2574. doi: 10.2147/IJGM.S310050
42. Kania K, Colella F, Riemen AHK, Wang H, Howard KA, Aigner T, et al. Regulation of Gdf5 expression in joint remodelling, repair, and osteoarthritis. *Sci Rep.* 2020;10:157. doi: 10.1038/s41598-019-57011-8
43. Tyurin A, Akhiirova K, Minniakhmetov I, Mokrysheva N, Khusainova R. The Genetic Markers of Knee Osteoarthritis in Women from Russia. *Biomedicines.* 2024;12:782. doi: 10.3390/biomedicines12040782
44. Zhang D, Zhang D, Yang X, Li Q, Zhang R, Xiong Y. Expression of m⁶A Methylation Regulator in Osteoarthritis and Its Prognostic Markers. *Cartilage.* 2023;14:321-328. doi: 10.1177/19476035221137722
45. Yongming L, Yizhe X, Zhikai Q, Yupeng W, Xiang W, Mengyuan Y, et al. Identification of ion channel-related genes as diagnostic markers and potential therapeutic targets for osteoarthritis through bioinformatics and machine learning-based approaches. *Biomarkers.* 2024;29:285-297. doi: 10.1080/1354750X.2024.2358316
46. Intharanut K, Suttanon P, Nathalang O. Integrin Subunit Alpha M, ITGAM Nonsynonymous SNP Is Associated with Knee Osteoarthritis among Thais: A Case-Control Study. *Curr Issues Mol Biol.* 2023;45:4168-1680. doi: 10.3390/cimb45050265
47. Vnukov VV, Krolevets IV, Panina SB, Milutina NP, Ananyan AA, Sagakyants AB, et al. Gene polymorphism and levels of pro-inflammatory cytokines in plasma and SF of patients with posttraumatic knee osteoarthritis. *Adv Gerontol.* 2016;6:198-203. doi: 10.1134/S2079057016030152
48. Li B, Li X, Zhang L, Mou L. Correlation investigation between a single nucleotide polymorphism in ADAMTS14 (rs4747096) and osteoarthritis: a meta-analysis. *J Orthop Surg Res.* 2023;18:575. doi: 10.1186/s13018-023-04056-1
49. Roberts JB, Aubourg G, Deehan DJ, Rice SJ, Loughlin J. Molecular Genetic and Epigenetic analysis identifies WWP2 as an effector gene of the OA association marked by SNP rs34195470. *Osteoarthr. Cartil.* 2022;30:S344. doi: 10.1016/j.joca.2022.02.463
50. Kehayova YS, Wilkinson JM, Rice SJ, Loughlin J. Allelic Heterogeneity in COLGALT2 expression contributes to osteoarthritis risk through decreased DNA methylation at multiple enhancers. *Osteoarthr. Cartil.* 2022;30:S341. doi: 10.1002/art.42427
51. Caldo D, Massarini E, Rucci M, Deaglio S, Ferracini R. Epigenetics in Knee Osteoarthritis: A 2020-2023 Update Systematic Review. *Life (Basel).* 2024;14(2):269. doi: 10.3390/life14020269
52. Kielbowski K, Herian M, Bakinowska E, Banach B, Sroczynski T, Pawlik A. The Role of Genetics and Epigenetic Regulation in the Pathogenesis of Osteoarthritis. *Int J Mol Sci.* 2023;24:11655. doi: 10.3390/ijms241411655
53. Núñez-Carro C, Blanco-Blanco M, Villagrán-Andrade KM, Blanco FJ, de Andrés MC. Epigenetics as a Therapeutic Target in Osteoarthritis. *Pharmaceuticals (Basel).* 2023;16:156. doi: 10.3390/ph16020156
54. Zhang H, Zheng W, Li D, Zheng J. miR-146a-5p Promotes Chondrocyte Apoptosis and Inhibits Autophagy of Osteoarthritis by Targeting NUMB. *Cartilage.* 2021;13:1467S-1477S. doi: 10.1177/194760352111023550
55. Zhao G, Gu W. Effects of miR-146a-5p on chondrocyte interleukin-1 β -induced inflammation and apoptosis involving thioredoxin interacting protein regulation. *J Int Med Res.* 2020;48:300060520969550. doi: 10.1177/0300060520969550
56. Qin H, Wang C, He Y, Lu A, Li T, Zhang B, et al. Silencing miR-146a-5p Protects against Injury-Induced Osteoarthritis in Mice. *Biomolecules.* 2023;13:123. doi: 10.3390/biom13010123
57. Miyaki S, Sato T, Inoue A, Otsuki S, Ito Y, Yokoyama S, et al. MicroRNA-140 plays dual roles in both cartilage development and homeostasis. *Genes Dev.* 2010;24:1173-1185. doi: 10.1101/gad.1915510
58. Cao H, Zhou X, Li H, Wang M, Wu W, Zou J. Study on the Role of MicroRNA-214 in the Rehabilitation of Cartilage in Mice with Exercise-Induced Traumatic Osteoarthritis. *Curr Issues Mol Biol.* 2022;44:4100-4117. doi: 10.3390/cimb44090281
59. Kung LH, Ravi V, Rowley L, Bell KM, Little CB, Bateman JF. Comprehensive expression analysis of microRNAs and mRNAs in synovial tissue from a mouse model of early post-traumatic osteoarthritis. *Sci. Rep.* 2017;7:17701. doi: 10.1038/s41598-017-17545-1
60. Andersen C, Walters M, Bundgaard L, Berg LC, Vonk LA, Lundgren-Åkerlund E, et al. Intraarticular treatment with integrin α 10 β 1-

- selected mesenchymal stem cells affects microRNA expression in experimental post-traumatic osteoarthritis in horses. *Front Vet Sci.* 2024;11:1374681. doi: 10.3389/fvets.2024.1374681
61. Connard SS, Gaesser AM, Clarke EJ, Linardi RL, Even KM, Engiles JB, et al. Plasma and synovial fluid extracellular vesicles display altered microRNA profiles in horses with naturally occurring post-traumatic osteoarthritis: an exploratory study. *J Am Vet Med Assoc.* 2024;262(Suppl. 1):S83-S96. doi: 10.2460/javma.24.02.0102
62. Endisha H, Datta P, Sharma A, Nakamura S, Rossomacha E, Younan C, et al. MicroRNA-34a-5p Promotes Joint Destruction During Osteoarthritis. *Arthritis Rheumatol.* 2021;73(3):426-439. doi: 10.1002/art.41552
63. Hu Y, Liu HX, Xu D, Xue X, Xu X. The Anti-Inflammatory Effect of miR-140-3p in BMSCs-Exosomes on Osteoarthritis. *Acta Chir Orthop Traumatol Cech.* 2023;90:267-276. doi: 10.55095/achot2023/032
64. Zhang L, Qiu J, Shi J, Liu S, Zou H. MicroRNA-140-5p represses chondrocyte pyroptosis and relieves cartilage injury in osteoarthritis by inhibiting cathepsin B/Nod-like receptor protein 3. *Bioengineered.* 2021;12:9949-9964. doi: 10.1080/21655979.2021.1985342
65. Chandra V, Ashraf T, Yadav P, Raghuvanshi V. Synovial fluid proteomics and serum metabolomics reveal molecular and metabolic changes in osteoarthritis. *MOJPH.* 2023;12(3):155-160. doi: 10.15406/mojph.2023.12.00426
66. Dewig DR, Mills HR, Evans-Pickett A, Pietrosimone BG, Troy Blackburn J. Aberrant gait biomechanics in individuals with ACL reconstruction are magnified during treadmill walking. *J Biomech.* 2022;134:110989. doi: 10.1016/j.jbiomech.2022.110989
67. Robbins SM, Pelletier JP, Abram F, Boily M, Antoniou J, Martineau PA, et al. Gait risk factors for disease progression differ between non-traumatic and post-traumatic knee osteoarthritis. *Osteoarthr. Cartil.* 2021;29(11):1487-1497. doi: 10.1016/j.joca.2021.07.014
68. White MS, Brancati RJ, Lepley LK. Relationship between altered knee kinematics and subchondral bone remodeling in a clinically translational model of ACL injury. *J Orthop Res.* 2022;40(1):74-86. doi: 10.1002/jor.24943
69. Piet J, Esrafilian A, Elahi SA, Mielke F, Van Nuffel M, Orozco G, et al. Joint and tissue mechanics in post-traumatic osteoarthritis: insights from the rat model. *bioRxiv.* 2024:2024-06. doi: 10.1101/2024.06.27.601039
70. Wang X, Chen J, Xu H, Wu J, Xie S. Identification of a novel diagnostic biomarker for osteoarthritis associated with chromatin regulators based on bioinformatics and experiments. *J Orthop Surg Res.* 2025;20(1):1047. doi: 10.1186/s13018-025-06493-6
71. Schilling B, Patel S, Rose J, Campisi J, Bons J, King C, et al. Senescence-Derived Protein Biomarkers During Aging and Osteoarthritis. *Innov Aging.* 2022;6(Suppl 1):196. doi: 10.1093/geroni/igac059.782
72. Pang WW, Cai YS, Cao C, Zhang FR, Zeng Q, Liu DY, et al. Mendelian randomization and transcriptome analysis identified immune-related biomarkers for osteoarthritis. *Front Immunol.* 2024;15:1334479. doi: 10.3389/fimmu.2024.1334479