https://doi.org/10.48047/AFJBS.7.2.2025.524-556

African Journal of Biological Sciences

Journal homepage: http://www.afjbs.com

Research Paper Open Access

# KNEE OSTEOARTHRITIS: PATHOGENESIS, RISK FACTORS, AND DIAGNOSTIC APPROACHES

**Anushya Vardhini V [1], Evelyn Sharon S*, Tamil Azhagan S R[2], Abdul Sameer S[3], Sakthi R[4] Uma Maheshwari G[5], Komala[6], Akalya K[7], Gomathi[8] and Sujitha R[9]**

[1,2,3,4,5,6,7,8,9]M. Pharmacy, Department of Pharmacology, Faculty of Pharmacy, Dr.M.G. R Educational and Research Institute.

***Corresponding author**, Associate Professor, Department of Pharmacology, Dr.M.G. R Educational and Research Institute,

**E mail :** evelyan.pharm@drmgrdu.ac.in

Volume 7, Issue 2, Feb 2025

Received: 05 Jan 2025

Accepted: 29 Jan 2025

Published: 09 Feb 2025

doi:10.48047/AFJBS.7.2.2025.524-556

ABSTRACT :

Osteoarthritis is a complicated and mixed condition that affects the whole joints including the bones , cartilage and soft tissues. The incidence of Osteoarthritis increases with advancing age , obesity and joint injuries being the major causes. The most outstanding sign of Osteoarthritis is chronic pain that does not let people function effectively daily. Though the pathogenesis of OA has not been fully elucidated, it is often considered to be an imbalance between catabolic and anabolic processes in articular cartilage. The risk factors that could lead to OA are ageing, genetic predisposition, body mass index, sex race, trauma and co-morbidities such as diabetes and cardiovascular diseases. Diagnosis of OA is confirmed using imaging modalities like MRI, ultrasound and X-rays. This review will focus on the pathogenesis, risk factors and various diagnostic approaches.

Key Word: Osteoarthritis, Pathogenesis, Risk factors, Imaging modalities, Chronic pain.

## INTRODUCTION:

Osteoarthritis (OA), is mainly defined by the gradual loss of articular cartilage in synovial joints as well as pathological alterations in other joint components such as synovitis, osteophyte formation, and subchondral bone change *(de Sousa Gomes et al., 2021; Zhu et al., 2022)* that is affected by the metabolism of the cartilage matrix and cell stress*(Z. Lin et al., 2021)*. It is estimated that over 67 million

individuals will develop OA by 2030, and the annual treatment expenditures will surpass $3 billion*(B. W. Wang et al., 2019)*. Osteoarthritis can occur in any synovial joint in the body, but it most commonly affects the joints of the hands, knees, hips, and spine. On the other hand, clinically, OA of the knee is the most prevalent *(Chang et al., 2021; Whittaker et al., 2021)*

In knee joint tissue, including cartilage, menisci, synovial membrane, infrapatellar fat pads, and subchondral bone, is affected by osteoarthritis (OA), a disease of the entire joint that results from the interaction of local and systemic susceptibility factors (Abramoff & Caldera, 2020) Etiology-based classifications of OA often separate it into primary (idiopathic) and secondary groups*(Li et al., 2020)*. The main causes of OA in the knee are namely, ageing, genetic predisposition, sex, trauma,obesity metabolic syndrome, trauma, race, joint stress, and activation of the inflammatory pathways occurs in cartilage (Georgiev & Angelov, 2019; Mora et al., 2018a; Palazzo et al., 2016; Silman & Symmons, 1995; B. W. Wang et al., 2019). The balance between the cartilage is mainly affected by the pro-inflammatory mediators.The increased production of inflammatory mediators such as IL-1β, IL-6, and TNF have the ability to modify the development and function of chondrocytes, stimulate the production and activation of aggrecanases and Matrix Metalloproteinases (MMPs), which are cartilage-degrading enzymes that are believed to be the subsequently effectors of osteoarthritis (KOA) pathogenesis *(Szala et al., 2024)*

Knee Osteoarthritis (KOA) pathogenesis is characterized by increased apoptosis, increased catabolism, and reduced anabolism. Osteophyte production, subchondral bone remodeling, cartilage degradation, and alterations to the synovium and joint capsule are frequent structural features of osteoarthritis*(Yao et al., 2023)*. Pro-inflammatory cytokines, mainly interleukin (IL-6) and tumor necrosis factor alpha (TNF-α), proteolytic enzymes, osteoclast differentiation, and activation of various synovial cells, such as leukocytes and synovial fibroblasts, are produced by macrophages and play fundamental roles in the development of pain and inflammation(Brophy & Fillingham, 2022; Zhang et al., 2022)The usual clinical symptoms of osteoarthritis patients include severe joint pain, stiffness, severely restricted mobility and joint cracking (crepitus)(15).

The goal of an knee osteoarthritis review article is to present an in-depth overview of the state of understanding and recent advances with Knee osteoarthritis (KOA). A typical article of this type covers the various approaches used today to diagnose knee osteoarthritis (KOA), including imaging

modalities, clinical criteria, and biomarkers, and evaluates their usefulness and accuracy. It also provides evidence-based advice for clinicians managing KOA, such as the best possible treatment and choices.

**PATHOGENESIS:**

The knee, which is the biggest synovial joint in humans, is made up of ligaments, cartilage , osseous components, and a synovial membrane. The synovium produces synovial fluid, which lubricates and nourishes a vascular cartilage, it is the responsibility of the latter*(Geng et al., 2023; Kohn et al., 2016)*. Cartilage is a highly specialized connective tissue, composed of water (>70%) and organic extracellular matrix components, mainly type II collagen, aggrecan, or other proteoglycans . The only cartilage cells, called chondrocytes, are in charge of the creation and degradation of the matrix, which is controlled by growth hormones and cytokines (Brophy & Fillingham, 2022). However, because of its high stress level and regular use,this equilibrium may be upset*(Mora et al., 2018b)*. The pathogenesis of knee osteoarthritis is in figure 1.

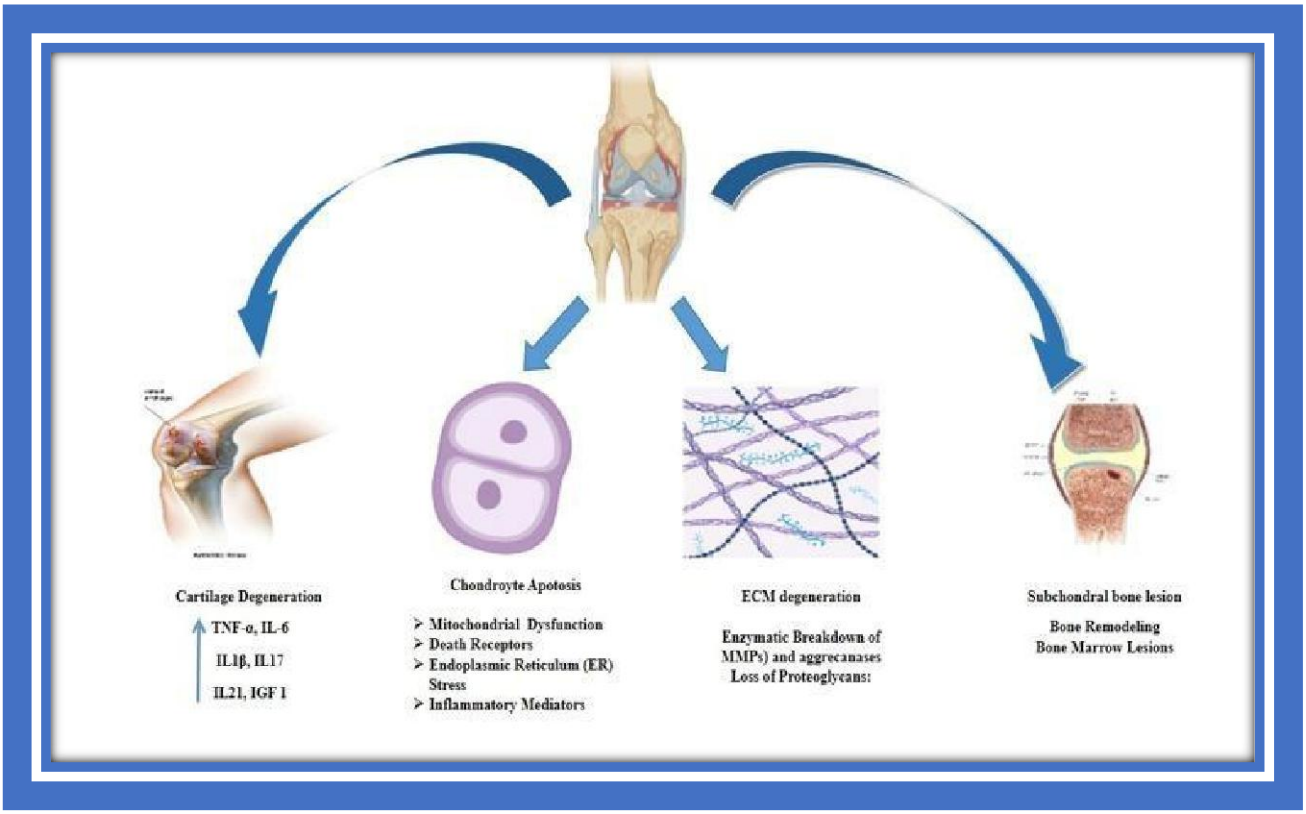


Figure 1: Pathogenesis of Knee Osteoarthritis

**Cartilage Degeneration**

The equilibrium between cartilage production and breakdown throughout KOA development is mainly influenced by Prostaglandins (PGE2), leukotrienes (LKB4), pro-inflammatory cytokines such as Tumor necrosis factor-α (TNF-α) and interleukins such as IL1β, IL6, IL15, IL17, IL18, IL21, growth factors (TGFβ, FGFs, VEGF, NGF, free radicals and complement being potent inducers of the breakdown of the extracellular matrix (ECM) in cartilage (*Iannone2003,* n.d.).

Each of these compounds possesses the ability to selectively activate hydrolytic enzymes, including Matrix Metalloproteinases (MMP), Cyclooxygenase II, and PGE2. This could cause collagen and proteoglycan to break down, which would cause cartilage to disintegrate (Georgiev & Angelov, 2019; *Iannone2003*, n.d.; Palazzo et al., 2016; Szala et al., 2024).Chemokines such as CCL2, CCL3, CCL4, and CCL5, which support the production of pro-inflammatory cytokines, by triggering chondrocytes production of MMP3, which in turn causes the decomposition of cartilage matrix components and anti-inflammatory cytokines like IL-4 and IL-10. Moreover, increased mast cell counts in OA synovial tissues are linked to a higher degree of synovitis and structural damage in the synovial joints *(Szala et al., 2024)*.

**Excessive Chondrocyte Apoptosis:**

A limited degree of apoptosis is present in healthy cartilage (*Iannone2003*, n.d.). Inflammatory mediators change the cells phenotypically to become hypertrophic chondrocytes, which mimic cells seen on the growth plate's hypertrophic zones(Gs & Mologhianu G, n.d.). After then, the articular cartilage is completely destroyed by apoptosis of the articular chondrocytes ,these are primarily regulated by the mitochondrial, death receptor and endo- plasmic reticulum stress response pathways (*Iannone2003*, n.d.).

**Subchondral Bone Lesion :**

Proinflammatory cytokines also upset cartilage matrix homeostasis, and repeated mechanical abrasions cause degenerative changes in the meniscus, including the loss of type I and type II collagen *(Mora et al., 2018a)***.** The presence, incidence, and progression of bone marrow lesions have been linked to progression and worsening of cartilage loss, including in locations adjacent to the lesions. Degenerative bone marrow lesions include inflammation, trabecular abnormalities, fluid retention, and bone marrow necrosis. They are a marker for increased metabolic activity, and their persistence is associated with local cartilage damage (Gs & Mologhianu G, n.d.).Subchondral bone exhibits the typical morphologic alterations including sclerosis, thickening of trabecules, and the development of osteophytes, which signal increased bone tissue synthetic activity is known as bone remodeling. Type I collagen synthesis rises and is most likely caused by a local rise in growth factors that promote osteoblast metabolism, such as IGF-1, IGF-2, and TGF-β. It used to be believed that these bone abnormalities were "reactive" to cartilage injury, but it is now believed that they happen early and concurrently with cartilage involvement *(Kuyinu et al., 2016; Li et al., 2020)*

Mechanical stress has been linked to the cartilage fibrosis, thickening of the synovium and joint capsule, subchondral bone marrow lesions that show up on magnetic resonance imaging (MRI) and have been linked to discomfort *(Mora et al., 2018a)*.Because of its strong innervation, the remodeling

of the subchondral bone may be the source of pain. In this condition, pain can also result from degenerated articular surfaces that include cartilage fragments cause the synovium membrane to become inflamed (synovitis). Furthermore, the pain associated with osteoarthritis may be influenced by peripheral neuronal sensitization and central sensitization, which may offer targets for medication treatment (8).

**Synovial Inflammation**

There are two layers in a common synovium. The inner layer, also known as the lining layer, which is crucial for preserving joint homeostasis. The outer layer of the synovium that assist various joint functions *(Zhao et al., 2023)*.In the KOA joint, synovitis is due to structural changes of enlargement of the lining layer, vascular expansion, and infiltration of inflammatory cells (Scanzello & Goldring, 2012; Wenham & Conaghan, 2010).The integrity of the articular cartilage surfaces is preserved and protected by two vital chemicals produced by synovial lining cells: lubricin and hyaluronic acid (HA).Pro-inflammatory and catabolic products, including as aggrecanases and metalloproteinases, are also found in the synovial membrane and aid in the breakdown of the articular matrix. As a result, changes in the synovial membrane may lead to lower levels of lubricin and hyaluronic acid components that protect cartilage and higher levels of substances that promote articular matrix deterioration (Scanzello & Goldring, 2012).

Wear debris and soluble cartilage-specific neo-antigens formed by the proteolytic breakdown products of the cartilage matrix. These materials are discharged into the synovial fluid, the macrophages phagocytose them. This leads to the synthesis of mediators, which permeate cartilage itself through the fluid inside the synovial sac and feed the vicious cycle of elevated swelling and increased degeneration of cartilage (21).

**Molecular & Cellular Mechanism**

In KOA, cytokines, chemokines, and other inflammatory mediators cause the degradation of cartilage.Chondrocytes produce a variety of inflammatory mediators, including reactive oxygen species like nitric oxide, superoxide, hydrogen peroxide, and peroxynitrite; cytokines and chemokines like IL1, IL-6, IL-7, IL8, IL-17, IL-18, MCP-1, LIF, GRO, and oncostatin M; and prostaglandins and leukotrienes. These mediators work in an autocrine and paracrine manner to induce the production of proteolytic enzymes by the chondrocyte, such as matrix metalloproteinases and aggrecanases, which aid in the breakdown of the cartilage matrix *(Geng et al., 2023; Loeser, 2008; Szala et al., 2024)*.

Apoptotic pathways, such as caspase 3 and poly (ADP-ribose) polymerase (PARP), are also triggered. Changes in processes that preserve cellular balance, such as autophagy, are also observed, along with a decrease in the expression of genes involved in the synthesis of ECM components, such as COL2A1 and ACAN *(Geng et al., 2023)*.The pharmacological activation of the TGF-b pathway can

maintain the integrity of the articular cartilage during knee osteoarthritis, as loss of TGF-b signaling in cartilage causes chondrocyte enlargement, which ultimately results in cartilage degradation *(B. Xia et al., 2014)*.

Articular cartilage homeostasis is greatly affected by the MMP family. While stromelysin (MMP-3) and aggrecanase (ADAMT-4) play important roles in the degradation of extracellular matrix (ECM), the collagenases (MMP-1, MMP-13) are in charge for breaking down the collagenous structure it play a major role in the advancement of Knee osteoarthritis (KOA). IL-1 and TNF-α, two inflammatory cytokines produced by KOA chondrocytes, that enhanced MMP expression, and reduce the formation of extracellular matrix *(Yunus et al., 2020)*.

The HIF-1α regulation system is primarily responsible for maintaining the tissue's homeostasis. Chondrocyte enlargement in response to the hypoxic environment was caused by abnormalities in HIF1α. A significant part of the joint development is attributed to the Wnt signaling pathways. Articular cartilage degrades when the pathway that regulates Wnt is activated in subchondral bone. This reaffirms the possibility that the pathway of Wnt signaling contributes to the KOA pathophysiology. After inflammation, a neurotrophin called nerve growth factor (NGF) relays pain signals. Smad 2/3 complex and activin receptor-like kinase 5 (ALK5) cause the increased production of NGF. To sum up, NGF may play a significant role as a mediator in the KOA occurrence *(Yunus et al., 2020)*.

**EPIDEMIOLOGY**

Knee Osteoarthritis is primarily an age-related condition; it is less frequent before the age of 40 but becomes more common as people age, aged 70 or older have radiographic evidence of the condition in certain joints *(de Sousa Gomes et al., 2021)*.The age- and sex-adjusted prevalence of knee osteoarthritis was higher in rural areas (6.25 [95%CI 5.92–6.60]%) than in urban areas (4.01 [3.74–4.29]%), according to a Maharashtra population-based study *(Geng et al., 2023)*.The meta-analysis focusing on the evaluation of the prevalence of symptomatic knee OA in China,21 studies (74,908 people) ,this shows a prevalence was found to be 14.6%. In previous research, the overall prevalence of symptomatic knee OA was found to be 15.4% in southern Swede, while it was 10.5% in Canada *(Giorgino et al., 2023)*.Research conducted between 2012 and 2016 revealed that the total prevalence of OA when compared to men, women had a greater prevalence of knee OA (19.1% vs. 10.9%, respectively). Data from the Chingford Study in the United Kingdom revealed that over a 5-year period, women between the ages of 45 and 64 had an incidence of radiographic knee OA of 17.6%*(Kohn et al., 2016)*.

## RISK FACTORS

### Age

Since aging is defined by a progressive decline in cell and organ functioning over time, it is the single highest risk factor for KOA. According to the Framingham Osteoarthritis Study, the prevalence of KOA evidence increases with age, starting at 12.9% in those between the ages of 30 and 40 and reaching 43.7% in those over 80 (He et al., 2020; Silman & Symmons, 1995).

### Genetics

KOA is influenced by family history. Femoral, tibial, patellar, and total cartilage volumes were predicted to have high heritability frequencies in a prior study. Anomalies in the COL2A1 gene, linked to type II collagen production, are also connected to KOA (Georgiev & Angelov, 2019; Grässel & Muschter, 2020; Silman & Symmons, 1995).

### Obesity / Over weight

Metabolic syndrome (Georgiev & Angelov, 2019; Kuyinu et al., 2016; Silman & Symmons, 1995) and Obese patients *(Zhao et al., 2023)* causes an excessive mechanical loading on their knee joints, which wears and tears articular cartilage and ruins ligaments, ultimately leading to a form of KOA (Blagojevic et al., 2010; Carman et al., n.d.; Coppola et al., 2024; Georgiev & Angelov, 2019; Silman & Symmons, 1995; Zeng et al., 2021)

### Sex

The prevalence levels of KOA range by gender.Women were more likely than males to have KOA in rural Tianjin (14.1% vs. 6.5%). Although the exact causes of the sex-based variations in KOA incidence are unknown, estrogen levels may be involved (Silman & Symmons, 1995; Szilagyi et al., 2023).

### Race

The study was conducted among the elderly same-age group population in an urban area of Chinese women and American women in the United States. The prevalence rates of radiological and clinical KOA were significantly higher than those in American women which were 34.8 and 11.6%, respectively *(Palazzo et al., 2016)*.

### Trauma

Trauma includes fractures to the articular surface, joint dislocations and articular injuries such as the meniscus and ligament injury. The probabilities of developing KOA following Anterior Cruciate Ligament (ACL) surgery and injury are around seven- and eight-fold higher (Georgiev & Angelov, 2019; Silman & Symmons, 1995).

**Comorbidity**

- Diabetics: Persistent hyperglycemia stimulates the production of oxidants, which in turn increases the osteoarthritic cartilage's matrix catabolism (Coppola et al., 2024; Georgiev & Angelov, 2019).
- Depression: The cause-and-effect link between the depressed symptoms and pain in KOA patients is still unclear, there is a significant correlation between the two. KOA patients are more likely to experience depressive symptoms compared with healthy people (Blagojevic et al., 2010; S. T. Wang & Ni, 2022).
- Cardiovascular disease(CVD): Hall Aj et al discovered that the prevalence of heart failure and ischaemic heart disease is much higher in those with KOA *(B. Xia et al., 2014)*.The development and progression of symptomatic OA are linked to the risk factors of CVD *(Kadam et al., 2011)*.

Additional risk factors, including living in humid, chilly, and dark conditions, joint stress, physical activity, occupational factors and professional sports training, and the effects of food, smoking, and exercise, are disputed and need to be further investigated *(McWilliams et al., 2011)*.

## DIAGNOSIS

### Clinical evaluation

A visual evaluation should be done before beginning a physical examination of the knee. While the patient is upright, check for periarticular erythema and edema, flexion or valgus movement deformities, and thigh muscle atrophy. Examine the surrounding skin for the presence and position of any scars from prior surgical procedures, underlying evidence of trauma, or soft tissue lesions. Testing for range of motion (ROM) is a crucial component of the knee exam .Exam findings associated with Knee osteoarthritis (KOA) typically include crepitus, bone enlargement, non-inflammatory effusions, and restricted range of motion. There could be pain with passive motion and tenderness at the joint lines *(Eijkenboom et al., 2019)*.

## IMAGING TECHNIQUES :

Radiographic imaging is necessary in addition to a comprehensive history and physical examination *(Cushnaghan et al., 1990)*.

### X-Rays / Radiographs

These are frequently used to diagnose and evaluate knee OA. The radiographic manifestation of osteoarthritis includes the development of osteophytes, or bone spurs, on the joint borders and a narrowing or reduction in the space between the joint's bones where cartilage has worn away. The

following standard X-ray views can be used to image each joint: An AP (anteroposterior, or front-toback) view, An external, lateral view, One or two 45-degree angled perspectives (Braun & Gold, 2012).

**Advantages**:

- Because of their speed, cost-effectiveness, safety, and wide accessibility, they have remained the gold standard for knee OA screening *(Kean ¤ et al., 2004; Ruan et al., 2019; H. Xu et al., 2019)*.

**Limitations:**

- Radiographic results may not be seen early in the course of the illness and are not correlated with its severity *(Eijkenboom et al., 2019)*.

**MRI:**

When it comes to early clinical diagnosis, management, and therapy, the high sensitivity of MRI imaging is important in identifying early KOA cartilage lesions and demonstrating early cartilage degradation. Additionally, variations in bone marrow edema can be identified using the cartilage sequence imaging approach (Ahmed & Mstafa, 2022; Kean ¤ et al., 2004; Ruan et al., 2019; H. Xu et al., 2019)

**Advantages:**

- KOA can be identified earlier with it than with standard radiographs.
- good sensitivity and excellent specificity *(Menashe et al., 2012)*.

**Limitations:**

- Contrast agents come with rare adverse effects such as nephrogenic fibrosis, and require intravenous access.
- Very low risks of sensitivity reactions *(Wenham et al., 2014)*

**CT scans**:

When compared to XR's conventional 2D imaging, CT can provide 3D imaging of a joint. When compared to MRI or XR, calcified cartilage, the subchondral bone plate, and trabecular subchondral bone may provide better visualization of subchondral bone cysts and osteophytes *(Wenham et al., 2014)*

**Advantages:**

- CT is more affordable, more accessible, and has significantly faster scan acquisition times than MRI and it does require ionizing radiation *(Wenham et al., 2014)*

**Limitations:**

- CT's incapacity to identify abnormalities in soft tissues *(Roemer, 2021)*

**High-Frequency Color Ultrasound Examination:**

Ultrasonography is used to detect synovial inflammation, effusions, and any osteophyte developments linked to Knee osteoarthritis can aid in the diagnosis. It provides excellent specificity and accuracy for the liquid anechoic zones and soft tissue (Ahmed & Mstafa, 2022).

**Advantages**:

- It is quick, inexpensive, non-invasive imaging method.

**Limitations:**

- The Ultrasound beam's incapacity to enter the bone cortex*(Möller et al., 2008)*

**LABORATORY TEST**

- **Cartilage Degradation Markers:**

The C-telopeptide of cross-linked type II collagen (CTX-II), 45-mer peptide (C2C), shown during degradation from the triple helical region of type II collagen (Coll2-1) are among the various degradation products of type II collagen that have been identified. The detection of these degradative type II collagen fragments by immunoassays has become a potential approach in the hunt for KOA molecular biomarkers.

Serum biomarkers of cartilage metabolism, such as cartilage oligomeric matrix protein (sCOMP) and procollagen type II C-terminal propeptide (sPIICP), implicated in pathophysiology of KOA *(Papaneophytou et al., 2022)*.Urinary C-terminal type I collagen telopeptides (CTX I) was an accurate predictor of the development of osteoarthritis, predicting both cartilage loss and osteophyte (FunckBrentano & Cohen-Solal, 2015; Henrotin, 2022).

- **Inflammatory-driven phenotype:**

**C-Reactive protein metabolite**(CRPM) : The primary source of CRP is the liver, which also releases it in reaction to infection and damage. Proteases like matrix metalloproteinases (MMPs) can break down CRP and release its metabolites, it shows an inflammation markers.

**Cytokine Oncostatin M** (OSM): belongs to the IL-6 family and has been found in synovial fluid from knee OA patients. The cytokine was found to have greater levels of other inflammatory cytokines, such as TNF-α, IL-1α, and interferon gamma (IFN-γ), which suggests a more inflammatory condition *(Henrotin, 2022)*.Patients with knee OA had plasma that has higher amounts of IL-1β, IL-5, IL-6, IL-10, IL-13, and TNF-α than samples that show the same values *(Bernotiene et al., 2020a)*.

OA environment may be linked to elevated blood levels of erythrocyte sedimentation rate (ESR) and C-creative protein (CRP) due to its inflammatory character *(Munjal et al., 2019)*

- **Collagen degradation markers**:

Collagen degradation markers (such as type II collagen cleavage product [C2C] and carboxyterminal telepeptides of type II collagen [CTx-II]) and collagen synthesis markers (such as N-propeptide IIA and IIB of type II collagen [PIIANP, PIIBNP, and CPII]) are investigated because abnormalities in these markers can signal the onset or progression of OA (*(Burland et al., 2023)*.

- **ECM-derived markers and noncollagenous proteins:**

Serum COMP has been investigated thoroughly in KOA populations and is a viable candidate as a KOA diagnostic and prognostic biomarker .Patients with OA have been found to have significantly higher serum HA levels, which have been linked to both radiographic progression and other factors *(Burland et al., 2023)*. ECM synthesis—PIIANP, PIIBNP, CPII, CS846, and several others; ECM degradation—CTX-II, Coll2-1, C2C, C2M, Coll2-1NO2, cartilage oligomeric matrix protein (COMP), aggrecan epitopes (ARGS, TEGE, FFGV), fibulin-3 epitopes, etc *(Bernotiene et al., 2020b)*

**EMERGING DIAGNOSTIC TOOLS**

- **Machine Learning and Artificial Intelligence:** s

A promising method for computer-aided diagnosis of osteoarthritis in the knee is deep learning from 2D to 3D. The use of 3D CNN is still in its early stages, we believe that the creation of 3DCNN techniques based on MR images will improve our knowledge of how the KOA illness progresses, particularly about early identification of OA in the knee joint. This is where the role of artificial intelligence becomes relevant. In summary, deep learning has great potential for creating clinical decision support for osteoarthritis *(Yeoh et al., 2021)*.

- **Genetic and Molecular Testing :**

One of the most active fields of study for KOA biomarkers is miRNA-based diagnostics. Non-coding RNA molecules called miRNAs target the 3' UTR of mRNA to control gene expression by either causing mRNA degradation or preventing translation .Serum and synovial fluid were found to contain OA-specific miRNAs in multiple investigations.They discovered that OA affected both men and women differently in terms of miRNA signature expression. *(Yeoh et al., 2021)*.

- **Advanced Imaging Techniques :**
    - MRI-based biomarkers that have been validated for the purpose of forecasting KOA outcomes, including as incidence, progression, and risk of TKA. Many MRI-based biomarkers with excellent predictive performance Semi-quantitative evaluation of bone marrow lesions for risk of TKA; quantitative measurements of cartilage and meniscus for KOA incidence; quantitative assessments of osteophyte scores and quantitative

infrapatellar fat pad texture analysis-based features for KOA progression*(Nevalainen et al., 2023)*.

- US is a cost-effective and easily accessible imaging technique that offers a compelling means of evaluating the inflammatory and structural alterations in osteoarthritic joints. The literature suggests that in the clinical setting for KOA diagnoses, US can be genuinely viewed as an additional tool to CR *(Nevalainen et al., 2023)*.

- **Smart Devices :**

Consumer electronics could support this tailored strategy by helping to determine each patient's ideal amount of physical activity before it causes an exacerbation of pain.This creates the possibility of individualized (digital) coaching, in which patients might be directed to engage in physical activity at a level suitable for them, promoting activity levels that are up to but not more than those that worsen their pain *(Vivekanantham et al., 2023)*.

## MANAGEMENT AND TREATMENT STRATEGIES

## PHARMACOLOGICAL APPROACH

### Analagesic

Clinical research also indicates that certain KOA patients may benefit from acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), and opioids, which are necessary medications for individuals with moderate to severe pain *(T. Chen et al., 2021)*.

### Acetaminophen

Acetaminophen is very potent analgesic that is frequently used to treat a variety of painful disorders as a first-line analgesic. Acetaminophen should only be used for short-term rescue analgesia when paired with long-term glucosamine or chondroitin sulfate, according to the 2019 policies from the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis, and Musculoskeletal Diseases (ESCEO). No recommendation for or against the use of acetaminophen could be made by the American Academy of Orthopaedic Surgeons (AAOS) *(Primorac et al., 2021)*.

### Non-Steroidal anti-inflammatory drugs (NSAIDs)

**Drugs** : Etoricoxib and Diclofenac are probably more beneficial *(Primorac et al., 2021)*.

Most recommendations for the first-line treatment of pain for KOA point to acetaminophen and nonsteroidal anti-inflammatory medications (NSAIDs) *(Primorac et al., 2021)*. NSAIDs reduce prostanoids, such as prostaglandins, and their anti-inflammatory and analgesic effects by reversibly inhibiting the activity of the cyclooxygenase isoenzymes COX-1 and COX-2 *(Yu et al., 2022)* .

**Side effects** : Liver toxicity, Gastrointestinal disorders, and Cardiovascular difficulties, safety should be a top consideration when selecting them *(T. Chen et al., 2021)*.

**Opioids**

**Drugs**: oxycodone, morphine, and tramadol.

These are not frequently given for the treatment of osteoarthritis. Opioids are agonists of the opioid receptors in the central nervous system (CNS), which cause depression in the CNS when they are activated *(Intra-Articular Therapy in Osteoarthritis, n.d.)*.As a second-line therapy for arthritic conditions the Asian guidelines recommend the use of opioids when NSAIDs are deemed insufficient or ineffective.Opioids are useful in reducing pain and enhancing function; however, there is a higher frequency of adverse events. When considering basic analgesics or nonsteroidal anti-inflammatory drugs (NSAIDs), opioids are quite costly *(Primorac et al., 2021)*

**Side effects:** Sedation, Dizziness, Nausea, Vomiting, Constipation, Physical Dependence, Tolerance, And Respiratory Depression(68).

**TOPICAL AGENTS**

**Drugs** :Daclofenac, ketoprofen, and ibuprofen .

These are commonly used NSAIDs that are used topically as a very easy and well-liked approach of treating osteoarthritis *(Intra-Articular Therapy in Osteoarthritis, n.d.)*.Topical NSAIDs are quite effective in relieving pain in the musculoskeletal system when compared to oral NSAIDs *(Primorac et al., 2021)*.Their primary benefit over oral NSAIDs is their significantly lower side-effect profile, with just a 5–15% serum concentration when compared to oral treatment .

**Side effects**: Systemic gastrointestinal 49and cardiovascular side effects ,skin reactions (dermatitis, pruritus, and rash )at the application site *(Iannitti et al., n.d.; Intra-Articular Therapy in Osteoarthritis, n.d.)*.

**INTRA ARTICULAR INJECTIONS:**

When medication is no longer helpful, for patients who prefer to postpone or avoid surgery, or for those who do not tolerate pharmacological oral therapy, intra-articular injection of the knee may be a good option. A 22-gauge needle with a length of between 1.5 and 3.5 inches is the suggested needle size. The most often reported side effects at the area of injection are pain and bleeding *(Iannitti et al., n.d.)*

**Corticosteroids(CS)**: Injectable corticosteroids are used to treat specific conditions, such as osteoarthritic joint pain or tendinitis-related inflammation and pain. For a little while, CS injections seem to reduce osteoarthritis patients' pain levels *(Samuels et al., 2021)*.These stress hormones function by interfering with the inflammatory and immunological cascade on several levels. They bind to the glucocorticoid receptor*(Intra-Articular Therapy in Osteoarthritis, n.d.)* and produce antagonistic action

(interleukin-1); reduced production of immunoglobulins; impairment of leukotriene and prostaglandin synthesis; inhibition of neutrophil superoxide production *(Intra-Articular Therapy in Osteoarthritis, n.d.; Testa et al., 2021)*.

**Glucocorticoid (GC):** Injections have been demonstrated to reduce pain, increase mobility, and enhance quality of life in individuals with KOA*(Q. Wang et al., 2022)*. When it comes to lowering pain at our primary end goal of four weeks trial , an IA injection may have a greater effect than an intramuscular glucocorticoid injection *(Oo et al., 2018)*. Table 1:List of corticosteroids and glucocorticoids drugs are mentioned in the table 1.

| DRUGS | DOSAGE | REFERENCES |
|---|---|---|
| Triamcinolone acetonide,<br>Prednisolone acetate,<br>Dexamethasone Acetate<br>Methyl prednisolone acetate<br>Triamcinolone hexacetonide<br>Dexamethasone sodium<br>Hydrocortisone acetate<br>Betamethasone sodium phosphate and acetate | 10–20 mg<br>40mg<br>8 mg<br>20–80 mg<br>10–20 mg<br>8 mg<br>10–25 mg<br>0.25–2 mL | *(Geng et al., 2023; Robinson et al., 2016)* |

TABLE 1:LIST OF CORTICOSTEROIDS AND GLUCOCORTICOIDS DRUGS

**REGENERATIVE THERAPIES WITH STEM CELLS**

Regenerative medicine may be a promising treatment for OA in the future, as evidenced by the 144 clinical trials that have been reported to far at www.clinicaltrials.gov examining the therapeutic influence of stem cells on OA and on cartilage injuries*(K. Xia et al., 2024)*. It has been observed that the less intrusive method of introducing autologous Mesenchymal Stem Cells (MSCs) into the joint through intra-articular injection in SCID mice is both practical and safe. Direct engrafting of MSCs into the wounded location has been proposed as a way to prevent systemic distribution and toxicity while also extending the cells' lifespan (Chow & Chin, 2020).In the cartilage of a rabbit arthritis model, MSCs were found to restrict the breakdown of proteoglycan by reducing the production of TNF-α and MMP-1. Also, by releasing growth factors (like TGF-beta and IL-6), antioxidant compounds, and growth factors, MSCs greatly reduced apoptosis and fibrosis *(Antebi et al., 2014; Wu et al., 2019)*.Adult stem cells, induced pluripotent stem cells (iPSCs), and embryonic stem cells (ESCs) are now the three types of stem cells that are most frequently explored in relation to stem cell treatment *(Wandel et al., 2010)*.

**Hyaluronic Acid (HA)**

In 1934, Karl Meyer proposed the term "hyaluronic acid" (which is a combination of the Latin phrases "hyaloid" [opaque] and "uronic acid") to describe the glycosaminoglycan that he could not identify that he discovered from the humor of the vitreous of a cow's eye (81). HA is a huge viscous glycosaminoglycan molecule that occurs naturally in cartilage and synovial fluid. It is often referred to as hyaluronate or hyaluronan. Its properties include shock absorption, traumatic energy dissipation, protective coating of the articular cartilage surface, and lubrication *(Raeissadat et al., 2013)*.Visco supplementation was first authorized by the Food and Drug Administration in 1997 as a conservative method for managing osteoarthritis (OA). In 2000, the American College of Rheumatology (ACR) published a recommendation introducing viscosupplementation as a treatment option Control of pain for osteoarthritis *(Iannitti et al., n.d.)*.When administered early in the course of the disease, HA not only reduces the symptoms of KOA but also alters the structure of the affected joint and slows the disease's progression (Trigkilidas & Anand, 2013).

**Platelet-Rich Plasma (PRP)**

PRP, an autologous whole blood derivative, has been demonstrated to have an agonistic effect on mesenchymal stem cell proliferation as shown in vitro by the findings of Huang et al. *(Huang et al., 2009)*. and Kilian et al *(EUROPEAN JOURNAL OF MEDICAL RESEARCH, n.d.)* and chondrogenesis due to its high concentration of growth factors. Additionally, PRP has been shown to have antinociceptive and anti-inflammatory features *(Majeed et al., 2018)*.According to findings from randomized clinical trials,

PRP is preferable to other IA and HA injections, for improving pain scales throughout the short- and medium-term (6–12 months) *(K. Y. Lin et al., 2019)*. PRP has been used to rejuvenate tissues and utilized to treat soft tissue lesions, including fasciitis, tendinopathies, and the healing of persistent ulcers. Prominent dental treatments that it is used for include bone regeneration in grafts, fracture healing, and periodontal regeneration in dental implants *(Gato-Calvo et al., 2019; Karsdal et al., 2016)*.

**Disease Modifying Agents**

Anticipate an improvement in osteoarthritis symptoms with disease-modifying osteoarthritis medications (DMOADs). DMOADs logically target many targets, including subchondral bone remodeling, cartilage breakdown, and synovial inflammatory mediators.The examples of DMOADS are listed in the table 2.

| S.NO | DRUG CLASS /COMPOUND | DESCRIPTION | RESULT | REFERENCE |
|---|---|---|---|---|
| 1. | **Wnt pathway inhibition**<br><br>Loricivint (LOR)( SM04690) | Blocking bispecific tyrosine phosphorylation kinase 1 a (DYRK 1A) and CDC-like kinase 2 (CLK 2), two componentsof the Wnt signaling pathway | Shielding impact on chondrocytes and preventing the cartilage break down factors . | *(X. R. Chen et al., 2024)* |
| | **Inhibition of inflammatory response**<br><br>Tofacitinib (Tofa) and TPCA-1 | Inhibitors of Janus kinases (Jak)and κB kinase (Ikk) | Decreased proteoglycan loss and safeguarding the extracellular matrix of cartilage. | |
| 2 | **Bispecific antibodies**<br><br>Canakinumab | Human IgGκ monoclonal antibody. | 300mg (S.C.)Blocks the interaction between IL-1β and its receptors. | *(X. R. Chen et al., 2024)* |
| | **Fibroblast growth factor family(FGF)**<br><br>FGF-18 or sprifermin) | Recombinant human fibroblast growth factor 18 (rhFGF18) | 30 µg i.a in anabolic effects on joint cartilage | |

| | | | | |
|---|---|---|---|---|
| 3 | **Inhibition of extracellular matrix degradation**<br><br>CL82198<br><br>Doxycycline | Specific MMP-13 inhibitor.<br><br>Strong antibiotic, inhibits MMPs. | Significant relief from OA progression.<br><br>Slow down the rate of joint space narrowing knee joint | *(Jiang et 2024)*<br><br>(Rannou Poiraudeau, 2010; Saraev et al., 2020) |
| 4 | **Bisphosphonate**s (alendronate, risedronate, zoledronic acid | anti-resorptive drugs | Reducing subchondral bone lesions and its symptoms | *(Brito et al., 2023; Perlman et al., 2012)* |

**TABLE 2 : EXAMPLES OF (DMOADS )DISEASE-MODIFYING OSTEOARTHRITIS MEDICATIONS**

**Oral/dietary supplement**

**Curcumin, vitamin D, and ginger:** alleviate KOA patients' pain-related symptoms and improve in physical function.

**Chondroitin sulfate** :It has been demonstrated that chondroitin sulfate reduces p38MAPK, erk1/2 phosphorylation, and NF-κB nuclear translocation caused by IL-1β, improving the patient's quality of life by easing the severe symptoms of the illness .When glucosamine is used with chondroitin, either alone or in combination, it is statistically more efficient over a six-month duration and more effective than a placebo at reducing pain in KOA patients (Ghouri & Conaghan, 2019)

**NON PHARMACOLOGICAL APPROACH**

Non-pharmacological therapies, including education and self-management, physical activity, weight control, and walking aids, are now universally acknowledged as being essential to the care of individuals with KOA.

**Exercise and neuromuscular training**

These programs, which focus on balance, agility, and coordination, may reduces the pain and enhance performance-based function, muscles surrounding the joints are strengthened with exercise treatment and walking speed in the treatment of osteoarthritis in the knee *(Mathieu et al., 2022; Yabuki et al., 2019)*.Diet therapy, particularly reduced diets that lead to weight loss, appears to be a successful therapy for osteoarthritis (OA) of the knee joint. Losing weight is useful in relieving symptoms and preventing the development of structural damage *(Bellamy, 1997)*.

**Braces and canes**

It could help patients with osteoarthritis in their knees feel better in terms of pain and function *(T. Chen et al., 2021)*

**Massage**

According to recent study, massage can help promote muscle fiber regeneration by eliminating inflammatory chemicals created throughout the process and removing neutrophils from severely wounded muscle tissue *(Liu et al., 2021)*. Because of its great safety record, low cost, and ease of use, KOA patients often use it as an adjunctive and alternative therapy to manage their pain *(J. Xu et al., 2022)*.

**Acupuncture**

Electroacupuncture therapy can block inflammatory responses and lower the expression of inflammatory cytokines in knee joints to provide beneficial properties *(Ezzo et al., 2001; Wei et al., 2022)*.Fire needle done by fairly puncturing certain bodily parts with a red-hot needle *(Duan, 2023)*. It relieves patients with their clinical symptoms, reduces inflammation and joint degeneration, and enhances local blood circulation.Warm needles reduce MMP-3 and TNF-α inflammatory responses and improve clinical symptoms by inhibiting the breakdown of subchondral bone. and reduces bone resorption in subchondral bone in KOA patients *(Ezzo et al., 2001)*.

**Transcutaneous electrical nerve stimulation (TENS)**

TENS primarily uses electrical stimulation to decrease nociceptive neurons' activity in the spinal cord and inhibit nociceptive fibers' ability to transmit pain signals. Simultaneously, it causes the release of endogenous opioids by the central nervous system to manage pain (McLarnon & Heron, 2021).

**SURGERY INTERVENTION**

When both pharmacological and non-pharmacological treatments are inefficient at producing the desired results surgery is carried out (106).

**Arthroscopy**

Knee joint arthroscopy for the analysis of the endoscopic interventions' timeliness in patients with OA of the knee joint. Currently, the most common surgical treatments include total and partial knee arthroplasty, and correcting periarticular osteotomies. Because of its well-proven technology and effectiveness, which offer 90–95% pain relief with a 1-2% chance of complications *(Karsdal et al., 2016; Nguyen et al., 2017)*.

**Joint Lavage**

Joint lavage is the process of clearing the joint space of any loose tissue or debris. It entails temporally placing tiny tubes into one or more knee entrance sites. At three months, joint lavage provides a somewhat better level of pain alleviation than control, with a 0.3-cm decrease in discomfort and a 0.2-cm increase in function on a 10-cm visual analogue scale *(Steinhaus et al., 2017)*.

**Total Joint Replacement**

It is the only treatment that can effectively treat osteoarthritis in the knee and offers good overall results in terms of cost-effectiveness, functional results, and reoperation. The last option for treating KOA is thought to be total joint replacement. Numerous studies shown that following joint replacement surgery, pain and function significantly improved *(Liddle et al., 2013)(Chand et al., 2020; Gawai et al., 2023)*.

**CONCLUSION:**

Knee osteoarthritis (OA) is a complex and multifactorial disease characterized by the progressive degeneration of joint cartilage, subchondral bone changes, and synovial inflammation. The pathogenesis of knee OA involves a combination of mechanical stress, metabolic alterations, and inflammatory processes, influenced by both genetic and environmental factors. Key risk factors such as aging, obesity, joint injury, and biomechanical abnormalities significantly contribute to its development and progression. Early diagnosis of knee OA is critical for managing symptoms and preventing further joint damage. Current diagnostic approaches include clinical evaluation, imaging techniques such as radiography and MRI, and the assessment of biochemical markers, all of which can provide a more comprehensive understanding of disease severity and progression.Continued research into the molecular mechanisms underlying OA and the development of novel diagnostic tools may enhance our ability to detect and treat the condition at earlier stages, ultimately improving patient outcomes. Given the growing burden of knee OA globally, a multidisciplinary approach encompassing lifestyle modifications, pharmacotherapy, and potentially regenerative medicine will be essential in managing this debilitating condition.

**DISCUSSION:**

Knee osteoarthritis (OA) is still one of the most common and disabling joint disorders afflicting older adults more than any other age groups. The disease process of knee OA is complex and involves various biomechanical and biochemical mechanisms, such as cartilage loss, remodeling of subchondral bone, and inflammation of the synovium. In recent work, researchers have shown that pro-inflammatory cytokines, matrix metalloproteinases (MMPs), and oxidative stress are drivers of the destruction of tissues in the joints. This knowledge is essential in the formulation of drugs for treatments.

There are a number of known knee osteoarthritis (OA) risks, and it is age and obesity that bears the highest weight. Even though it is highly adaptive for children and young adults, aging causes the degeneration of this capability ideal for regenerative repair or restoration limiting such functions for degenerative changes of such a joint only. Obesity on the other hand, elevates mechanical stresses on the knees but also promotes the lowering of the threshold for the onset of inflammation development thus aggravating OA. Other factors include previous damage to the joints, frequent trauma-causing activities, and hereditary tendencies. These aspects indicate that environmental and physical predispositions work together in the aetiology of osteoarthritis, which in turn, calls for interventions that are tailored to individual risks.

Currently, the available diagnostic techniques of knee OA mostly depend upon clinical findings and imaging studies. X-ray has been traditionally the preferred modality to assess the narrowing of joint space and formation of osteophytes, it is however not capable of detecting minute changes involving cartilage at an early stage of the condition. While MRI has sensitivity advantages, it is expensive, and imaging at the initial stages of the disease is not the practice. Currently developing imaging analyses are differentiating techniques with the potential to help in arthritis intervention and monitoring.

**DECLARATION OF INTEREST:**

**Acknowledgements:**

The authors are thankful to Prof. Dr Hari Krishnan for their continuous support and encouragement to carry out this research as a part of the student's post-graduation project.

**conflicts of interest :**

No conflicts of interest

**Authors' contributions:**

Authors Anushya Vardhini, Tamil Azhagan, Abdul Sameer, Sakthi, Uma Maheshwari G, Komala, Akalya K, Gomathi and Sujitha R. prepared the complete manuscript. Author Evelyn Sharon guided and monitored the research and contributed to the final drafting of the manuscript. All authors have read and approved the manuscript.

**Availability of data and material:**

The data generated and analyzed during this research work are included in this article; if any excess data are required, it will be available from the corresponding author on reasonable request.

**Ethics approval and consent to participate:**

Not applicable

**Consent to participate:**

Not applicable

**Consent to publish:**

Not applicable

**ABBREVIATION:**

| | |
|---|---|
| OA | Osteoarthritis |
| KOA | Knee Osteoarthritis |
| RA | Rheumatoid Arthritis |
| IL | Interleukin |
| TNF-A | Tumor Necrosis Factor |
| MMP | Matrix Metalloproteinases |
| HA | Hyaluronic Acid |
| IGF | Insulin-Like Growth Factor-1 |
| COMP | Cartilage Oligeometric Matrix Protein |
| PGE | Prostaglandin |
| LKB | Lyman-Kutcher-Burman |
| FGF | Fibrinogen B Beta |
| VEGF | Vascular Endothelial Growth Factor |
| NGF | Nerve Growth Factor |
| ECM | Extracellular Matrix |
| CCL | Chemokine Ligand |
| BCL | B-Cell Lymphoma |
| ICE | Immune Effector Cell Encephalopathy |
| GRO | Cytokines |
| ADP- RIBOSE | Adenosine Diphosphate–Ribose |
| PARP | Poly Adenosine Diphosphate-Ribose Polymerase |
| COL2 A1 | Collagen Type 2 Alpha 1 Chain |
| ACAN | Aggrecan |
| ADAMT-4 | A Disintegrin-Like And Metalloprotease Domain |
| HIF-1A | Hypoxia-Inducible Factor-1α |
| WNT – SIGNALLING | Wingless-Type MMTV Integration Site Family |
| ALK 5 | Activin Receptor-Like Kinase-5 |
| CVD | Cardiovascular Disease |
| ROM | Range Of Motion |

| | |
|---|---|
| ROM | Range Of Motion |
| MRI | Magnetic Resonance Imaging |
| CT | Computed Tomography |
| CTX 11 | Cerebrotendinous Xanthomatosis |
| C2C | Mmp-Degraded Type II Collagen |
| SCOMP | Cartilage Oligomeric Matrix Protein |
| CRPM | C-Reactive Protein Metabolite |
| OSM | Oncostatin M |
| P11AMP | Type Iia Collagen N-Propeptide |
| ARGS | Antibiotic Resistance Genes |
| CNN | Convolutional Neural Network |
| TKA | Total Knee Arthroplasty |
| CR | Computed Radiography |
| NSAIDS | Nonsteroidal Anti-Inflammatory Drugs |
| COX | Cyclooxygenase |
| CS | Corticosteroids |
| SCID MICE | Severe Combined Immunodeficiency Disease - Mice |
| MSC | Mesenchymal Stem Cells |
| IPSC | Induced Pluripotent Stem Cells |
| PRP | Platelet-Rich Plasma |
| DMOADS | Disease-Modifying Osteoarthritis Medications |
| TENS | Transcutaneous Electrical Nerve Stimulation |

**REFERENCES:**

Abramoff, B., & Caldera, F. E. (2020). Osteoarthritis: Pathology, Diagnosis, and Treatment Options. In *Medical Clinics of North America* (Vol. 104, Issue 2, pp. 293–311). W.B. Saunders. https://doi.org/10.1016/j.mcna.2019.10.007

Ahmed, S. M., & Mstafa, R. J. (2022). Identifying Severity Grading of Knee Osteoarthritis from X-ray Images Using an Efficient Mixture of Deep Learning and Machine Learning Models. *Diagnostics*, *12*(12). https://doi.org/10.3390/diagnostics12122939

Antebi, B., Pelled, G., & Gazit, D. (2014). Stem cell therapy for osteoporosis. In *Current Osteoporosis Reports* (Vol. 12, Issue 1, pp. 41–47). Current Science, Inc. https://doi.org/10.1007/s11914-0130184-x

Bellamy, Nicholas. (1997). *Osteoarthritis*. Bailliere Tindall.

Bernotiene, E., Bagdonas, E., Kirdaite, G., Bernotas, P., Kalvaityte, U., Uzieliene, I., Thudium, C. S., Hannula, H., Lorite, G. S., Dvir-Ginzberg, M., Guermazi, A., & Mobasheri, A. (2020a). Emerging Technologies and Platforms for the Immunodetection of Multiple Biochemical Markers in Osteoarthritis Research and Therapy. In *Frontiers in Medicine* (Vol. 7). Frontiers Media S.A. https://doi.org/10.3389/fmed.2020.572977

Bernotiene, E., Bagdonas, E., Kirdaite, G., Bernotas, P., Kalvaityte, U., Uzieliene, I., Thudium, C. S., Hannula, H., Lorite, G. S., Dvir-Ginzberg, M., Guermazi, A., & Mobasheri, A. (2020b). Emerging Technologies and Platforms for the Immunodetection of Multiple Biochemical Markers in Osteoarthritis Research and Therapy. In *Frontiers in Medicine* (Vol. 7). Frontiers Media S.A. https://doi.org/10.3389/fmed.2020.572977

Blagojevic, M., Jinks, C., Jeffery, A., & Jordan, K. P. (2010). Risk factors for onset of osteoarthritis of the knee in older adults: a systematic review and meta-analysis. *Osteoarthritis and Cartilage*, *18*(1), 24–33. https://doi.org/10.1016/j.joca.2009.08.010

Braun, H. J., & Gold, G. E. (2012). Diagnosis of osteoarthritis: Imaging. *Bone*, *51*(2), 278–288. https://doi.org/10.1016/j.bone.2011.11.019

Brito, R., Costa, D., Dias, C., Cruz, P., & Barros, P. (2023). Chondroitin Sulfate Supplements for Osteoarthritis: A Critical Review. *Cureus*. https://doi.org/10.7759/cureus.40192

Brophy, R. H., & Fillingham, Y. A. (2022). AAOS Clinical Practice Guideline Summary: Management of Osteoarthritis of the Knee (Nonarthroplasty), Third Edition. In *Journal of the American Academy of Orthopaedic Surgeons* (Vol. 30, Issue 9, pp. E721–E729). Lippincott Williams and Wilkins. https://doi.org/10.5435/JAAOS-D-21-01233

Burland, J. P., Hunt, E. R., & Lattermann, C. (2023). Serum biomarkers in healthy, injured, and osteoarthritic knees: a critical review. In *Journal of Cartilage and Joint Preservation* (Vol. 3, Issue 2). Elsevier B.V. https://doi.org/10.1016/j.jcjp.2022.100091

Carman, W. J., Sowers, M., Hawthorne, V. M., & Weissfeld, L. A. (n.d.). *American Journal of EPIDEMIOLOGY Obesity as a Risk Factor for Osteoarthritis of the Hand and Wrist: A Prospective Study* (Vol. 139).

Chand, S., Raj C, B. K., P, N. U., Mohammed R, H. A., & Babu, N. (2020). Study on prescription pattern for osteoarthritis in a tertiary care teaching hospital: A retrospective study. In *biomedicineonline.org Biomedicine* (Vol. 40, Issue 3). www.biomedicineonline.org

Chang, L. hua, Chen, C. H., Wu, S. C., Chang, J. ken, & Ho, M. L. (2021). Cyclooxygenase-2 regulates PTHrP transcription in human articular chondrocytes and is involved in the pathophysiology of osteoarthritis in rats. *Journal of Orthopaedic Translation*, *30*, 16–30. https://doi.org/10.1016/j.jot.2021.06.003

Chen, T., Weng, W., Liu, Y., Aspera-Werz, R. H., Nüssler, A. K., & Xu, J. (2021). Update on Novel NonOperative Treatment for Osteoarthritis: Current Status and Future Trends. In *Frontiers in Pharmacology* (Vol. 12). Frontiers Media S.A. https://doi.org/10.3389/fphar.2021.755230

Chen, X. R., Song, J., Sun, J. L., Zhang, J. Q., Chen, X. J., Zeng, C. W., Hu, J. X., Chang, X. T., Jin, F. Q., Luo, S. Y., Chen, Z., & Luo, Y. (2024). Hepatitis B infection is associated with periodontitis: the

national health and nutrition examination survey (2009–2014). *BMC Oral Health*, *24*(1). https://doi.org/10.1186/s12903-024-04489-y

Chow, Y. Y., & Chin, K. Y. (2020). The Role of Inflammation in the Pathogenesis of Osteoarthritis. In *Mediators of Inflammation* (Vol. 2020). Hindawi Limited. https://doi.org/10.1155/2020/8293921

Coppola, C., Greco, M., Munir, A., Musarò, D., Quarta, S., Massaro, M., Lionetto, M. G., & Maffia, M. (2024). Osteoarthritis: Insights into Diagnosis, Pathophysiology, Therapeutic Avenues, and the Potential of Natural Extracts. In *Current Issues in Molecular Biology* (Vol. 46, Issue 5, pp. 4063–4105). Multidisciplinary Digital Publishing Institute (MDPI). https://doi.org/10.3390/cimb46050251

Cushnaghan, J., Cooper, C., Dieppe, P., Kirwan, J., Mcalindon, T., Mccrae, F., Cushnaghan, J., Cooper, C., Dieppe, P., Kirwan, J., Mcalindon, T., Mccrae, F., & Cushnaghan, M. (1990). Clinical assessment of osteoarthritis of the knee. In *Annals ofthe Rheumatic Diseases* (Vol. 49). http://ard.bmj.com/

de Sousa Gomes, L. M. R., Czeczko, N. G., Araújo, R. L. T. M., de Sousa Cartagenes, M. do S., Neto, J. O. B., & Garcia, J. B. S. (2021). Effect of intra-articular dexmedetomidine on experimental osteoarthritis in rats. *PLoS ONE*, *16*(1 January). https://doi.org/10.1371/journal.pone.0245194

Duan, W. (2023). Treatment of Knee Osteoarthritis with Transcutaneous Electrical Nerve Stimulation. In *Highlights in Science, Engineering and Technology MISBP* (Vol. 2022).

Eijkenboom, J. F. A., Timmer, E. R., Van Heijden, R. A. D., De Kanter, J. M. L., Oei, E. H. G., BiermaZeinstra, S. M. A., & Van Middelkoop, M. (2019). Association between self-reported measures, physical examination, and early magnetic resonance imaging signs of osteoarthritis in patients with patellofemoral pain. *Journal of Orthopaedic and Sports Physical Therapy*, *49*(9), 634–639. https://doi.org/10.2519/jospt.2019.8889

*EUROPEAN JOURNAL OF MEDICAL RESEARCH*. (n.d.).

Ezzo, J., Hadhazy, V., Birch, S., Lao, L., Kaplan, G., Hochberg, M., & Berman, B. (2001). Acupuncture for Osteoarthritis of the Knee A Systematic Review. In *ARTHRITIS & RHEUMATISM* (Vol. 44, Issue 4).

Funck-Brentano, T., & Cohen-Solal, M. (2015). Subchondral bone and osteoarthritis. In *Current Opinion in Rheumatology* (Vol. 27, Issue 4, pp. 420–426). Lippincott Williams and Wilkins. https://doi.org/10.1097/BOR.0000000000000181

Gato-Calvo, L., Magalhaes, J., Ruiz-Romero, C., Blanco, F. J., & Burguera, E. F. (2019). Platelet-rich plasma in osteoarthritis treatment: Review of current evidence. In *Therapeutic Advances in Chronic Disease* (Vol. 10, pp. 1–18). SAGE Publications Ltd. https://doi.org/10.1177/2040622319825567

Gawai, S. H., Dhoble, N. N., Padole, N., Dhapke, P., & Baheti, J. R. B. (2023). Review: Therapetic Approach in the Management of Osteoarthritis. *Asian Journal of Pharmaceutical Research and Development*, *11*(1), 52–59. https://doi.org/10.22270/ajprd.v11i1.1220

Geng, R., Li, J., Yu, C., Zhang, C., Chen, F., Chen, J., Ni, H., Wang, J., Kang, K., Wei, Z., Xu, Y., & Jin, T. (2023). Knee osteoarthritis: Current status and research progress in treatment (Review). *Experimental and Therapeutic Medicine*, *26*(4). https://doi.org/10.3892/etm.2023.12180

Georgiev, T., & Angelov, A. K. (2019). Modifiable risk factors in knee osteoarthritis: treatment implications. In *Rheumatology International* (Vol. 39, Issue 7, pp. 1145–1157). Springer Science and Business Media Deutschland GmbH. https://doi.org/10.1007/s00296-019-04290-z

Ghouri, A., & Conaghan, P. G. (2019). Update on novel pharmacological therapies for osteoarthritis. In *Therapeutic Advances in Musculoskeletal Disease* (Vol. 11). SAGE Publications Ltd. https://doi.org/10.1177/1759720X19864492

Giorgino, R., Albano, D., Fusco, S., Peretti, G. M., Mangiavini, L., & Messina, C. (2023). Knee Osteoarthritis: Epidemiology, Pathogenesis, and Mesenchymal Stem Cells: What Else Is New? An Update. In *International Journal of Molecular Sciences* (Vol. 24, Issue 7). Multidisciplinary Digital Publishing Institute (MDPI). https://doi.org/10.3390/ijms24076405

Grässel, S., & Muschter, D. (2020). Recent advances in the treatment of osteoarthritis. In *F1000Research* (Vol. 9). F1000 Research Ltd. https://doi.org/10.12688/f1000research.22115.1

Gs, M., & Mologhianu G. (n.d.). Osteoarthritis pathogenesis-a complex process that involves the entire joint. In *Journal of Medicine and Life* (Vol. 7).

He, Y., Li, Z., Alexander, P. G., Ocasio-Nieves, B. D., Yocum, L., Lin, H., & Tuan, R. S. (2020). Pathogenesis of osteoarthritis: Risk factors, regulatory pathways in chondrocytes, and experimental models. In *Biology* (Vol. 9, Issue 8, pp. 1–32). MDPI AG. https://doi.org/10.3390/biology9080194

Henrotin, Y. (2022). Osteoarthritis in year 2021: biochemical markers. In *Osteoarthritis and Cartilage* (Vol. 30, Issue 2, pp. 237–248). W.B. Saunders Ltd. https://doi.org/10.1016/j.joca.2021.11.001

Huang, Q., Wang, Y. D., Wu, T., Jiang, S., Hu, Y. L., & Pei, G. X. (2009). Preliminary separation of the growth factors in platelet-rich plasma: Effects on the proliferation of human marrow-derived mesenchymal stem cells. *Chinese Medical Journal*, *122*(1), 83–87. https://doi.org/10.3760/cma.j.issn.0366-6999.2009.01.015

Iannitti, T., Lodi, D., & Palmieri, B. (n.d.). *Intra-Articular Injections for the Treatment of Osteoarthritis Focus on the Clinical Use of Hyaluronic Acid*.

*iannone2003*. (n.d.).

*Intra-articular therapy in osteoarthritis*. (n.d.). www.postgradmedj.com

Jiang, P., Hu, K., Jin, L., & Luo, Z. (2024). A brief review of current treatment options for osteoarthritis including disease-modifying osteoarthritis drugs (DMOADs) and novel therapeutics. *Annals of Medicine & Surgery*, *86*(7), 4042–4048. https://doi.org/10.1097/MS9.0000000000002214

Kadam, U. T., Holmberg, A., Blagojevic, M., Nilsson, P., & Åkesson, K. (2011). Risk factors for cardiovascular disease and future osteoarthritis-related arthroplasty: A population-based cohort study in men and women from Malmö, Sweden. *Scandinavian Journal of Rheumatology*, *40*(6), 478–485. https://doi.org/10.3109/03009742.2011.585619

Karsdal, M. A., Michaelis, M., Ladel, C., Siebuhr, A. S., Bihlet, A. R., Andersen, J. R., Guehring, H., Christiansen, C., Bay-Jensen, A. C., & Kraus, V. B. (2016). Disease-modifying treatments for osteoarthritis (DMOADs) of the knee and hip: lessons learned from failures and opportunities for the future. In *Osteoarthritis and Cartilage* (Vol. 24, Issue 12, pp. 2013–2021). W.B. Saunders Ltd. https://doi.org/10.1016/j.joca.2016.07.017

Kean ¤, W. F., Kean, R., & Buchanan, W. W. (2004). Osteoarthritis: symptoms, signs and source of pain. In *Inn ammopharmacology* (Vol. 12, Issue 1).

Kohn, M. D., Sassoon, A. A., & Fernando, N. D. (2016). Classifications in Brief: Kellgren-Lawrence Classification of Osteoarthritis. *Clinical Orthopaedics and Related Research*, *474*(8), 1886–1893. https://doi.org/10.1007/s11999-016-4732-4

Kuyinu, E. L., Narayanan, G., Nair, L. S., & Laurencin, C. T. (2016). Animal models of osteoarthritis: Classification, update, and measurement of outcomes. In *Journal of Orthopaedic Surgery and Research* (Vol. 11, Issue 1). BioMed Central Ltd. https://doi.org/10.1186/s13018-016-0346-5

Li, D., Li, S., Chen, Q., & Xie, X. (2020). The Prevalence of Symptomatic Knee Osteoarthritis in Relation to Age, Sex, Area, Region, and Body Mass Index in China: A Systematic Review and MetaAnalysis. *Frontiers in Medicine*, *7*. https://doi.org/10.3389/fmed.2020.00304

Liddle, A. D., Pegg, E. C., & Pandit, H. (2013). Knee replacement for osteoarthritis. In *Maturitas* (Vol. 75, Issue 2, pp. 131–136). https://doi.org/10.1016/j.maturitas.2013.03.005

Lin, K. Y., Yang, C. C., Hsu, C. J., Yeh, M. L., & Renn, J. H. (2019). Intra-articular Injection of Platelet-Rich Plasma Is Superior to Hyaluronic Acid or Saline Solution in the Treatment of Mild to Moderate Knee Osteoarthritis: A Randomized, Double-Blind, Triple-Parallel, Placebo-Controlled Clinical Trial. *Arthroscopy - Journal of Arthroscopic and Related Surgery*, *35*(1), 106–117. https://doi.org/10.1016/j.arthro.2018.06.035

Lin, Z., Miao, J., Zhang, T., He, M., Wang, Z., Feng, X., & Bai, L. (2021). JUNB-FBXO21-ERK axis promotes cartilage degeneration in osteoarthritis by inhibiting autophagy. *Aging Cell*, *20*(2). https://doi.org/10.1111/acel.13306

Liu, W., Fan, Y., Wu, Y., Hou, X., Xue, B., Li, P., Zhang, S., & Yue, Q. (2021). Efficacy of acupuncturerelated therapy in the treatment of knee osteoarthritis: A network meta-analysis of randomized controlled trials. In *Journal of Pain Research* (Vol. 14, pp. 2209–2228). Dove Medical Press Ltd. https://doi.org/10.2147/JPR.S315956

Loeser, R. F. (2008). Molecular mechanisms of cartilage destruction in osteoarthritis. In *Article in Journal of Musculoskeletal & Neuronal Interactions*. https://www.researchgate.net/publication/23791892

Majeed, M. H., Sherazi, S. A. A., Bacon, D., & Bajwa, Z. H. (2018). Pharmacological Treatment of Pain in Osteoarthritis: A Descriptive Review. In *Current Rheumatology Reports* (Vol. 20, Issue 12). Current Medicine Group LLC 1. https://doi.org/10.1007/s11926-018-0794-5

Mathieu, S., Soubrier, M., Peirs, C., Monfoulet, L. E., Boirie, Y., & Tournadre, A. (2022). A MetaAnalysis of the Impact of Nutritional Supplementation on Osteoarthritis Symptoms. In *Nutrients* (Vol. 14, Issue 8). MDPI. https://doi.org/10.3390/nu14081607

McLarnon, M., & Heron, N. (2021). Intra-articular platelet-rich plasma injections versus intra-articular corticosteroid injections for symptomatic management of knee osteoarthritis: systematic review and meta-analysis. *BMC Musculoskeletal Disorders*, *22*(1). https://doi.org/10.1186/s12891-021-04308-3

McWilliams, D. F., Leeb, B. F., Muthuri, S. G., Doherty, M., & Zhang, W. (2011). Occupational risk factors for osteoarthritis of the knee: A meta-analysis. *Osteoarthritis and Cartilage*, *19*(7), 829–839. https://doi.org/10.1016/j.joca.2011.02.016

Menashe, L., Hirko, K., Losina, E., Kloppenburg, M., Zhang, W., Li, L., & Hunter, D. J. (2012). The diagnostic performance of MRI in osteoarthritis: A systematic review and meta-analysis. *Osteoarthritis and Cartilage*, *20*(1), 13–21. https://doi.org/10.1016/j.joca.2011.10.003

Möller, I., Bong, D., Naredo, E., Filippucci, E., Carrasco, I., Moragues, C., & Iagnocco, A. (2008). Ultrasound in the study and monitoring of osteoarthritis. *Osteoarthritis and Cartilage*, *16*(SUPPL. 3), S4. https://doi.org/10.1016/j.joca.2008.06.005

Mora, J. C., Przkora, R., & Cruz-Almeida, Y. (2018a). Knee osteoarthritis: Pathophysiology and current treatment modalities. In *Journal of Pain Research* (Vol. 11, pp. 2189–2196). Dove Medical Press Ltd. https://doi.org/10.2147/JPR.S154002

Mora, J. C., Przkora, R., & Cruz-Almeida, Y. (2018b). Knee osteoarthritis: Pathophysiology and current treatment modalities. In *Journal of Pain Research* (Vol. 11, pp. 2189–2196). Dove Medical Press Ltd. https://doi.org/10.2147/JPR.S154002

Munjal, A., Bapat, S., Hubbard, D., Hunter, M., Kolhe, R., & Fulzele, S. (2019). Advances in Molecular biomarker for early diagnosis of Osteoarthritis. *Biomolecular Concepts*, *10*(1), 111–119. https://doi.org/10.1515/bmc-2019-0014

Nevalainen, M. T., Uusimaa, A. P., & Saarakkala, S. (2023). The ultrasound assessment of osteoarthritis: the current status. In *Skeletal Radiology* (Vol. 52, Issue 11, pp. 2271–2282). Springer Science and Business Media Deutschland GmbH. https://doi.org/10.1007/s00256-02304342-3

Nguyen, L. T., Sharma, A. R., Chakraborty, C., Saibaba, B., Ahn, M. E., & Lee, S. S. (2017). Review of prospects of biological fluid biomarkers in osteoarthritis. In *International Journal of Molecular Sciences* (Vol. 18, Issue 3). MDPI AG. https://doi.org/10.3390/ijms18030601

Oo, W. M., Yu, S. P. C., Daniel, M. S., & Hunter, D. J. (2018). Disease-modifying drugs in osteoarthritis: current understanding and future therapeutics. In *Expert Opinion on Emerging Drugs* (Vol. 23, Issue 4, pp. 331–347). Taylor and Francis Ltd. https://doi.org/10.1080/14728214.2018.1547706

Palazzo, C., Nguyen, C., Lefevre-Colau, M. M., Rannou, F., & Poiraudeau, S. (2016). Risk factors and burden of osteoarthritis. In *Annals of Physical and Rehabilitation Medicine* (Vol. 59, Issue 3, pp. 134–138). Elsevier Masson SAS. https://doi.org/10.1016/j.rehab.2016.01.006

Papaneophytou, C., Alabajos-Cea, A., Viosca-Herrero, E., Calvis, C., Costa, M., Christodoulides, A. E., Kroushovski, A., Lapithis, A., Lapithi, V. M., Papayiannis, I., Christou, A., Messeguer, R., Giannaki, C., & Felekkis, K. (2022). Associations between serum biomarkers of cartilage metabolism and serum hyaluronic acid, with risk factors, pain categories, and disease severity in knee osteoarthritis: a pilot study. *BMC Musculoskeletal Disorders*, *23*(1). https://doi.org/10.1186/s12891-022-05133-y

Perlman, A. I., Ali, A., Njike, V. Y., Hom, D., Davidi, A., Gould-Fogerite, S., Milak, C., & Katz, D. L. (2012). Massage therapy for osteoarthritis of the knee: A randomized dose-finding trial. *PLoS ONE*, *7*(2). https://doi.org/10.1371/journal.pone.0030248

Primorac, D., Molnar, V., Matiši, V., Hudetz, D., Jeleč, Ž., Rod, E., Cukelj, F., Vidovi, D., Vrdoljak, T., Dobriči, B., Antičevi, D., Smoli, M., Miškulin, M., & Bori, I. (2021). pharmaceuticals Comprehensive Review of Knee Osteoarthritis Pharmacological Treatment and the Latest Professional Societies' Guidelines. *Pharmaceuticals*, *14*, 205. https://doi.org/10.3390/ph

Raeissadat, S. A., Rayegani, S. M., Babaee, M., & Ghorbani, E. (2013). The effect of platelet-rich plasma on pain, function, and quality of life of patients with knee osteoarthritis. *Pain Research and Treatment*, *2013*. https://doi.org/10.1155/2013/165967

Rannou, F., & Poiraudeau, S. (2010). Non-pharmacological approaches for the treatment of osteoarthritis. In *Best Practice and Research: Clinical Rheumatology* (Vol. 24, Issue 1, pp. 93–106). https://doi.org/10.1016/j.berh.2009.08.013

Robinson, W. H., Lepus, C. M., Wang, Q., Raghu, H., Mao, R., Lindstrom, T. M., & Sokolove, J. (2016). Low-grade inflammation as a key mediator of the pathogenesis of osteoarthritis. In *Nature Reviews Rheumatology* (Vol. 12, Issue 10, pp. 580–592). Nature Publishing Group. https://doi.org/10.1038/nrrheum.2016.136

Roemer, F. W. (2021). Weight-bearing CT for knee osteoarthritis assessment: A story unfolds. In *Radiology* (Vol. 299, Issue 3, pp. 660–661). Radiological Society of North America Inc. https://doi.org/10.1148/radiol.2021210357

Ruan, G., Xu, J., Wang, K., Zheng, S., Wu, J., Bian, F., Chang, B., Zhang, Y., Meng, T., Zhu, Z., Han, W., & Ding, C. (2019). Associations between serum IL-8 and knee symptoms, joint structures, and cartilage or bone biomarkers in patients with knee osteoarthritis. *Clinical Rheumatology*, *38*(12), 3609–3617. https://doi.org/10.1007/s10067-019-04718-8

Samuels, J., Pillinger, M. H., Jevsevar, D., Felson, D., & Simon, L. S. (2021). Critical appraisal of intraarticular glucocorticoid injections for symptomatic osteoarthritis of the knee. In *Osteoarthritis and Cartilage* (Vol. 29, Issue 1, pp. 8–16). W.B. Saunders Ltd. https://doi.org/10.1016/j.joca.2020.09.001

Saraev, A. V., Kulyaba, T. A., Rasulov, M. Sh., & Kornilov, N. N. (2020). Arthroscopy for Knee Osteoarthritis in the XXI Century: a Systematic Review of Current High Quality Researches and Guidelines of Professional Societies. *Traumatology and Orthopedics of Russia*, *26*(4), 150–162. https://doi.org/10.21823/2311-2905-2020-26-4-150-162

Scanzello, C. R., & Goldring, S. R. (2012). The role of synovitis in osteoarthritis pathogenesis. In *Bone* (Vol. 51, Issue 2, pp. 249–257). https://doi.org/10.1016/j.bone.2012.02.012

Silman, A. J., & Symmons, D. P. M. (1995). *Classification and assessment of rheumatic diseases. Pt. 1*. Baillière Tindall.

Steinhaus, M. E., Christ, A. B., & Cross, M. B. (2017). Total Knee Arthroplasty for Knee Osteoarthritis: Support for a Foregone Conclusion? In *HSS Journal* (Vol. 13, Issue 2, pp. 207–210). Springer New York LLC. https://doi.org/10.1007/s11420-017-9558-4

Szala, D., Kopańska, M., Trojniak, J., Jabłoński, J., Hanf-Osetek, D., Snela, S., & Zawlik, I. (2024). The Role of MicroRNAs in the Pathophysiology of Osteoarthritis. *International Journal of Molecular Sciences*, *25*(12), 6352. https://doi.org/10.3390/ijms25126352

Szilagyi, I. A., Waarsing, J. H., Van Meurs, J. B. J., Bierma-Zeinstra, S. M. A., & Schiphof, D. (2023). A systematic review of the sex differences in risk factors for knee osteoarthritis. In *Rheumatology (United Kingdom)* (Vol. 62, Issue 6, pp. 2037–2047). Oxford University Press. https://doi.org/10.1093/rheumatology/keac688

Testa, G., Giardina, S. M. C., Culmone, A., Vescio, A., Turchetta, M., Cannavò, S., & Pavone, V. (2021). Intra-articular injections in knee osteoarthritis: A review of literature. In *Journal of Functional Morphology and Kinesiology* (Vol. 6, Issue 1). MDPI AG. https://doi.org/10.3390/jfmk6010015

Trigkilidas, D., & Anand, A. (2013). The effectiveness of hyaluronic acid intra-articular injections in managing osteoarthritic knee pain. *Annals of The Royal College of Surgeons of England*, *95*(8), 545–551. https://doi.org/10.1308/003588413x13629960049432

Vivekanantham, A., Selby, D., Lunt, M., Sergeant, J. C., Parkes, M. J., O'Neill, T. W., & Dixon, W. (2023). Day-to-day variability of knee pain and the relationship with physical activity in people with knee osteoarthritis: An observational, feasibility study using consumer smartwatches. *BMJ Open*, *13*(3). https://doi.org/10.1136/bmjopen-2022-062801

Wandel, S., Jüni, P., Tendal, B., Nüesch, E., Villiger, P. M., Welton, N. J., Reichenbach, S., & Trelle, S. (2010). Effects of glucosamine, chondroitin, or placebo in patients with osteoarthritis of hip or knee: Network meta-analysis. *BMJ (Online)*, *341*(7775), 711. https://doi.org/10.1136/bmj.c4675

Wang, B. W., Jiang, Y., Yao, Z. L., Chen, P. S., Yu, B., & Wang, S. N. (2019). Aucubin protects chondrocytes against IL-1β-induced apoptosis in vitro and inhibits osteoarthritis in mice model. *Drug Design, Development and Therapy*, *13*, 3529–3538. https://doi.org/10.2147/DDDT.S210220

Wang, Q., Mol, M. F., Bos, P. K., Dorleijn, D. M. J., Vis, M., Gussekloo, J., Bindels, P. J. E., Runhaar, J., & Bierma-Zeinstra, S. M. A. (2022). Effect of Intramuscular vs Intra-articular Glucocorticoid Injection on Pain among Adults with Knee Osteoarthritis: The KIS Randomized Clinical Trial. *JAMA Network Open*, E224852. https://doi.org/10.1001/jamanetworkopen.2022.4852

Wang, S. T., & Ni, G. X. (2022). Depression in Osteoarthritis: Current Understanding. In *Neuropsychiatric Disease and Treatment* (Vol. 18, pp. 375–389). Dove Medical Press Ltd. https://doi.org/10.2147/NDT.S346183

Wei, J., Liu, L., Li, Z., Lyu, T., Zhao, L., Xu, X., Song, Y., Dai, Y., & Li, B. (2022). Fire Needling Acupuncture Suppresses Cartilage Damage by Mediating Macrophage Polarization in Mice with Knee Osteoarthritis. *Journal of Pain Research*, *15*, 1071–1082. https://doi.org/10.2147/JPR.S360555

Wenham, C. Y. J., & Conaghan, P. G. (2010). The role of synovitis in osteoarthritis. In *Therapeutic Advances in Musculoskeletal Disease* (Vol. 2, Issue 6, pp. 349–359). https://doi.org/10.1177/1759720X10378373

Wenham, C. Y. J., Grainger, A. J., & Conaghan, P. G. (2014). The role of imaging modalities in the diagnosis, differential diagnosis and clinical assessment of peripheral joint osteoarthritis. In *Osteoarthritis and Cartilage* (Vol. 22, Issue 10, pp. 1692–1702). W.B. Saunders Ltd. https://doi.org/10.1016/j.joca.2014.06.005

Whittaker, J. L., Runhaar, J., Bierma-Zeinstra, S., & Roos, E. M. (2021). A lifespan approach to osteoarthritis prevention. *Osteoarthritis and Cartilage*, *29*(12), 1638–1653. https://doi.org/10.1016/j.joca.2021.06.015

Wu, D., Zhu, X., Kang, X., Huang, H., Yu, J., Pan, J., & Zhang, X. (2019). The protective effect of sophocarpine in osteoarthritis: An in vitro and in vivo study. *International Immunopharmacology*, *67*, 145–151. https://doi.org/10.1016/j.intimp.2018.11.046

Xia, B., Di Chen, Zhang, J., Hu, S., Jin, H., & Tong, P. (2014). Osteoarthritis Pathogenesis: A Review of Molecular Mechanisms. In *Calcified Tissue International* (Vol. 95, Issue 6, pp. 495–505). Springer Science and Business Media, LLC. https://doi.org/10.1007/s00223-014-9917-9

Xia, K., Min, L., Xie, W., Yang, G., Yon, D. K., Lee, S. W., Koyanagi, A., Jacob, L., Smith, L., Shin, J. Il, Rahmati, M., Xiao, W., & Li, Y. (2024). Is unicompartmental knee arthroplasty a better choice than total knee arthroplasty for unicompartmental osteoarthritis? A systematic review and meta-analysis of randomized controlled trials. *Chinese Medical Journal*. https://doi.org/10.1097/CM9.0000000000003193

Xu, H., Zhao, G., Xia, F., Liu, X., Gong, L., & Wen, X. (2019). The diagnosis and treatment of knee osteoarthritis: a literature review. In *Int J Clin Exp Med* (Vol. 12, Issue 5). www.ijcem.com/

Xu, J., Wu, B., Xie, S., Wu, G., Zhang, H., Fu, Y., & Guo, G. (2022). Effectiveness and safety of massage for chronic pain in patients with knee osteoarthritis: A protocol for systematic review and metaanalysis. In *Medicine (United States)* (Vol. 101, Issue 3, p. E28533). Lippincott Williams and Wilkins. https://doi.org/10.1097/MD.0000000000028533

Yabuki, S., Ushida, T., Sun, W.-Z., & Williamson, O. (2019). Evidence-Based Recommendations on the Pharmacological Management of Osteoarthritis and Chronic Low Back Pain: An Asian Consensus. *Article in Asian Journal of Anesthesiology*. https://doi.org/10.6859/aja.201908/PP.0002

Yao, Q., Wu, X., Tao, C., Gong, W., Chen, M., Qu, M., Zhong, Y., He, T., Chen, S., & Xiao, G. (2023). Osteoarthritis: pathogenic signaling pathways and therapeutic targets. In *Signal Transduction and Targeted Therapy* (Vol. 8, Issue 1). Springer Nature. https://doi.org/10.1038/s41392-02301330-w

Yeoh, P. S. Q., Lai, K. W., Goh, S. L., Hasikin, K., Hum, Y. C., Tee, Y. K., & Dhanalakshmi, S. (2021). Emergence of Deep Learning in Knee Osteoarthritis Diagnosis. In *Computational Intelligence and Neuroscience* (Vol. 2021). Hindawi Limited. https://doi.org/10.1155/2021/4931437

Yu, H., Huang, T., Lu, W. W., Tong, L., & Chen, D. (2022). Osteoarthritis Pain. *International Journal of Molecular Sciences*, *23*(9). https://doi.org/10.3390/ijms23094642

Yunus, M. H. M., Nordin, A., & Kamal, H. (2020). Pathophysiological perspective of osteoarthritis. In *Medicina (Lithuania)* (Vol. 56, Issue 11, pp. 1–13). MDPI AG. https://doi.org/10.3390/medicina56110614

Zeng, C. Y., Zhang, Z. R., Tang, Z. M., & Hua, F. Z. (2021). Benefits and Mechanisms of Exercise Training for Knee Osteoarthritis. In *Frontiers in Physiology* (Vol. 12). Frontiers Media S.A. https://doi.org/10.3389/fphys.2021.794062

Zhang, W., Zhang, L., Yang, S., Wen, B., Chen, J., & Chang, J. (2022). Electroacupuncture ameliorates knee osteoarthritis in rats via inhibiting NLRP3 inflammasome and reducing pyroptosis. *Molecular Pain*, *18*. https://doi.org/10.1177/17448069221147792

Zhao, K., Ruan, J., Nie, L., Ye, X., & Li, J. (2023). Effects of synovial macrophages in osteoarthritis. In *Frontiers in Immunology* (Vol. 14). Frontiers Media SA. https://doi.org/10.3389/fimmu.2023.1164137

Zhu, J., Yang, S., Qi, Y., Gong, Z., Zhang, H., Liang, K., Shen, P., Huang, Y.-Y., Zhang, Z., Ye, W., Yue, L., Fan, S., Shen, S., Mikos, A. G., Wang, X., & Fang, X. (2022). H E A L T H A N D M E D I C I N E Stem cell-homing hydrogel-based miR-29b-5p delivery promotes cartilage regeneration by suppressing senescence in an osteoarthritis rat model. In *Sci. Adv* (Vol. 8). https://www.science.org

COVER LETTER 25th Dec 2024

From

Anushya Vardhini .V,

Faculty of Pharmacy, Dr.MGR Educational and Research Institute,

Velapanchavadi, Chennai-77. anushyavenkat92@gmail.com

To

The Editor,

Journal of Chemical Health Risks.

Dear Editor,

I am writing to submit our manuscript titled " **Knee Osteoarthritis: Pathogenesis, Risk Factors And Diagnostic Approaches** "for your consideration for publication in Journal of Chemical Health Risk. This work investigates knee osteoarthritis and its pathogenesis , risk factor and recent advancements in diagnostic methods and tools.By integrating these insights, we aim to enhance understanding and contribute to the development of more effective diagnostic and management strategies for KOA.

In this comprehensive review, we explore the multifaceted nature of knee osteoarthritis, focusing on its underlying pathogenesis, a wide range of risk factors, and current diagnostic methodologies. Given the increasing prevalence of osteoarthritis and its significant impact on patient quality of life, our findings provide valuable insights into the development of novel diagnostic tools may enhance our ability to detect and treat the condition at earlier stages, ultimately improving patient outcomes.

We believe this manuscript will be of great interest to the readers of in Journal of Chemical Health Risk as it not only synthesizes existing literature but also identifies gaps in current research and potential directions for future studies.

This manuscript is original, has not been published previously, and is not under consideration by any other journal. All authors have reviewed and approved the final version of the manuscript, and we declare no conflicts of interest.

Thank you for considering our work. We look forward to your feedback.

Sincerely,

Anushya vardhini. V

Dr. M.G.R. educational and research institute.