WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.453
Volume 14, Issue 1, 1309-1324. Review Article ISSN 2277–7105

REVIEW ON OSTEOARTHRITIS

Abhijeet S. Survase[1]*, Sangramsinh D. Bhatekar[2], Vinayak B. Alnure[3], Dr. Santosh Jain[4] and Prof. D. M. Waghmode[5]

[1,2,3]Student, Dr. Babasaheb Ambedkar Technological University, India.

[4]Principal, Dr. Babasaheb Ambedkar Technological University, India.

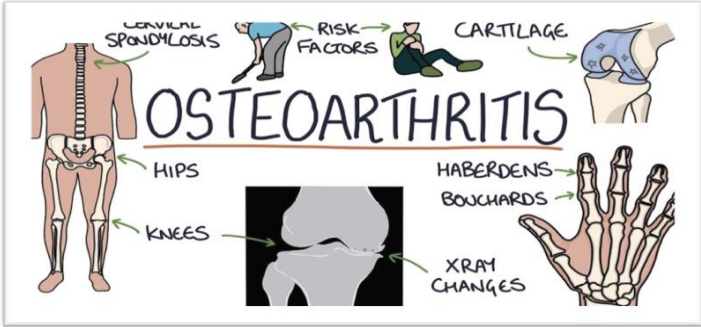
[5]Assistant Professor Dr. Babasaheb Ambedkar Technological University, India.

Article Received on
19 November 2024,

Revised on 10 Dec. 2024,
Accepted on 30 Dec. 2024

DOI: 10.20959/wjpr20251-35082

***Corresponding Author**
Abhijeet S. Survase
Student, Dr. Babasaheb Ambedkar Technological University, India.



1. ABSTRACT

The study analyzed 792 Indian publications on osteoarthritis research included in the Scopus database from 2007 to 2016. The publications exhibited an average annual growth rate of 12% and a citation impact of 10% per year. India contributed 1.80% to the global osteoarthritis research output during this period, increasing from 1.41% in 2007–11 to 2.10% in 2012–16. The share of India's international collaborative publications on osteoarthritis research grew from 13.87% in 2007–11 to 20.27% in 2012–16, with an overall share of 18.06% from 2007–16. The majority of India's osteoarthritis research publications during 2007–16 originated from the medical field (69–95%), followed by pharmacology, toxicology, and pharmaceutics (26–01%), biochemistry, genetics, and molecular biology (18–56%), immunology and microbiology (3–41%).[1]

KEYWORDS: The publications exhibited an average annual growth rate of 12% and a citation impact of 10% per year.

2. INTRODUCTION

Osteoarthritis (OA) is a highly prevalent and debilitating disease that significantly contributes

to disability. It is characterized by various joint issues such as damage to articular cartilage, synovitis, remodeling of subchondral bone, osteophyte formation, and chronic pain. Due to the global rise in obesity and an aging population, the incidence of OA is increasing, presenting a major public health challenge and substantial societal burden. It is estimated that 303 million adults globally suffer from OA, with approximately 61 million affected individuals in China in 2017. Despite the high prevalence, no disease-modifying medications are currently available. The recommended prescription drugs for managing OA primarily alleviate pain symptoms, but their prolonged use is often associated with serious toxicities and side effects.

Osteoarthritis (OA) is a multifaceted disease affecting several joints, such as the knee, hip, lumbar facet joint, and temporomandibular joint (TMJ). Risk factors for knee and hip OA include genetics, aging, being female, race, physical labor, obesity, hypertension, abnormal joint alignment, poor muscle strength, high-intensity exercise, and a history of joint injury.

MicroRNAs (miRNAs) are a widely conserved class of non-coding RNA molecules, typically 22–25 nucleotides in length, which have emerged as key post-transcriptional regulators of gene expression. They influence gene expression by enhancing degradation, suppressing translation, or through other mechanisms. miRNAs are involved in important cellular processes and pathological conditions. Research has suggested that changes in miRNA expression are linked to the regulation of cartilage homeostasis and osteoarthritis (OA). Additionally, certain miRNAs have been identified as responsive to oxidative stress, and specific miRNAs have been shown to modulate oxidative stress. This suggests that one way miRNAs might cause damage to articular cartilage in OA could be through alterations in cellular redox states.[1-2]

2.1 Classification of the osteoarthritis

Osteoarthritis (OA) can be classified based on its severity, the joints it affects, and its underlying causes. Here's a comprehensive explanation.

1. Primary osteoarthritis, also known as idiopathic osteoarthritis, occurs without a known cause and is often associated with aging, affecting multiple joints. In contrast, secondary osteoarthritis has a specific underlying cause, such as an injury, obesity, congenital joint abnormalities, or diseases like rheumatoid arthritis. Typically, secondary osteoarthritis affects a single joint or a specific group of joints that have been exposed to these risk factors.

2. By Affected Joint: One of the most prevalent types of osteoarthritis, knee osteoarthritis

affects the knee joints. Hip osteoarthritis is another common type that affects the hip joints. The joints in the fingers and the base of the thumb are usually affected by hand osteoarthritis.[3]

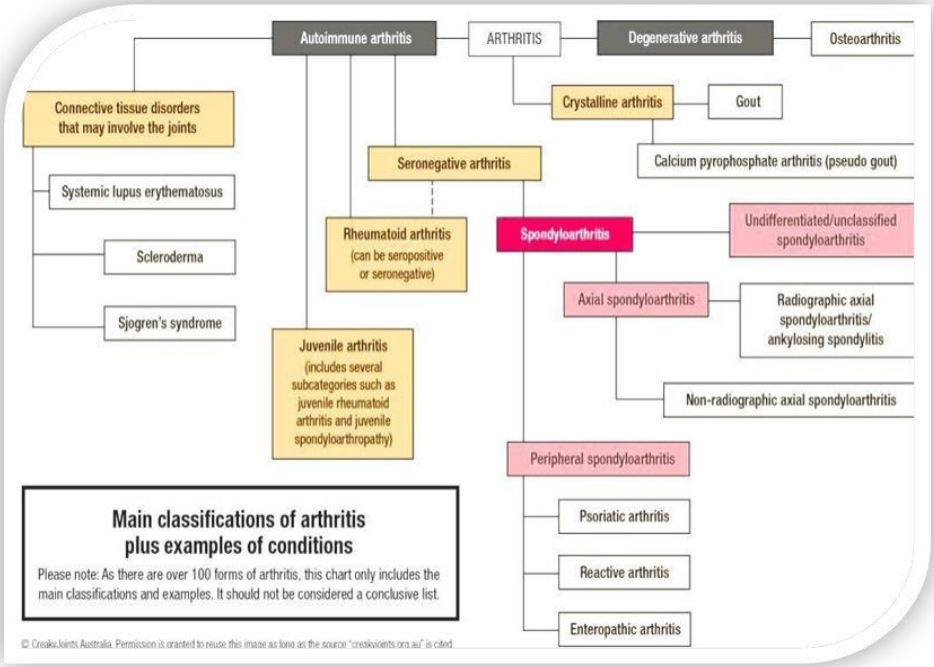


Figure 1: Classification.

3. Pathophysiology: biomechanics and inflammation

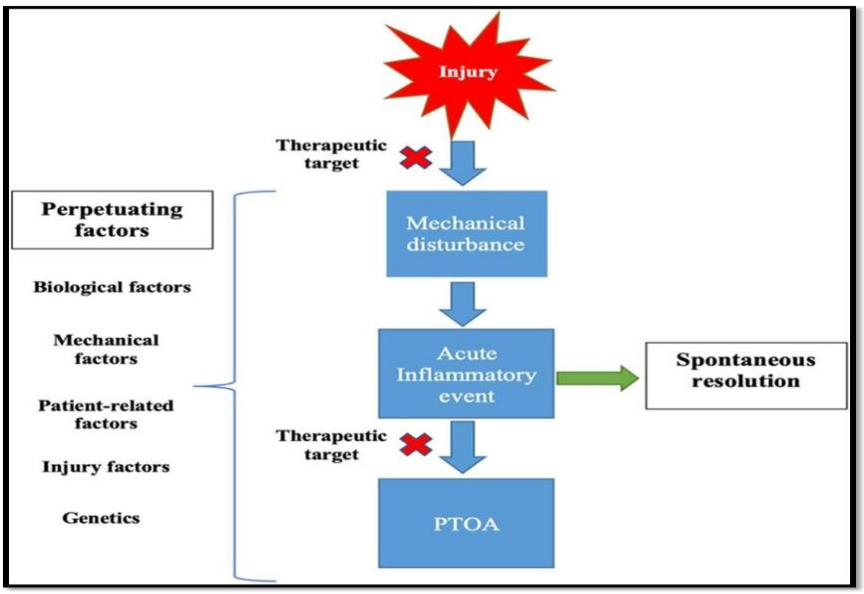


Figure 2: Pathophysiology.

4. Difference between the Osteoarthritis and Rheumatoid Arthritis

OSTEOARTHRITIS	RHEUMATOID ARTHRITIS
Osteoarthritis is a degenerative, wear & tear type disorder	Rheumatoid arthritis is an autoimmune condition
Unusually affects people over 40	Incidence is higher among individuals around the age of 20
Can be caused by long-term pressure on large Joints	Etiology is not very clear
Typically affects one particular area or joint	Affect multiple joints all over the body
Does not cause extra-articular manifestation	extra-articular manifestation such as fatigue and fever
ESR, CPR, anti-CCP may be elevated	No change in ESR, CPR, and anti-CCP
Immune suppressant are not required	Has to be treated Specifically with Immune- Suppressant

5. Joint tissue interaction

In the last decade, it has become increasingly evident that osteoarthritis (OA) impacts not only the entire joint but potentially the entire body. The different tissues within the joint interact in numerous ways, contributing to the degenerative processes. Advancements in methodological approaches, such as omics technologies and deep learning-based techniques, have enhanced our understanding of these complex tissue interactions and provided valuable new insights.[3]

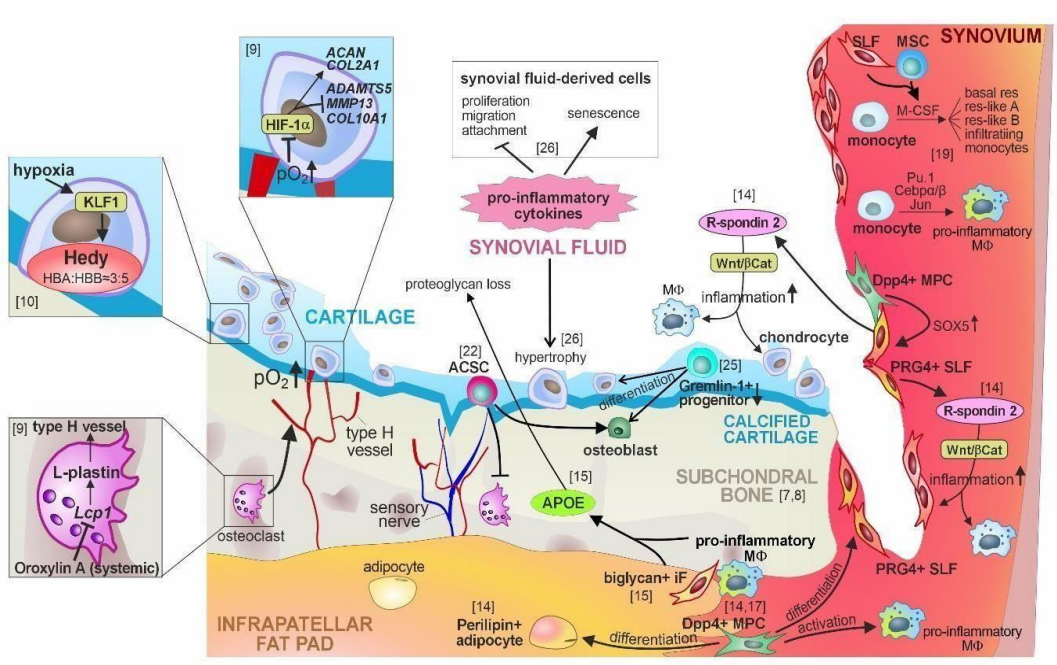


Figure 3: Overview of the manifold interactions between different joint tissue osteoarthritis.

5.1 Meniscus

Knee trauma is known to elevate the risk of future osteoarthritis (OA), suggesting that damage to one tissue can lead to the degeneration of another. A recent scoping review extensively detailed how changes in meniscus integrity cause subchondral bone alterations in rats and mice. Gao and colleagues used deep learning-based segmentation to analyze a large dataset from the Osteoarthritis Initiative, involving 4790 participants. They identified distinctive shape features of the medial and lateral meniscus associated with changes in cartilage thickness over eight years, leading to OA onset. Their research indicates that variations in the meniscus's length–width ratios, horn lengths, root attachment angles, and concavity may increase the risk of OA.[10]

5.2 Cartilage

Due to its avascular nature and the limited activity of chondrocytes, cartilage has a poor intrinsic ability to repair itself after injury or in the presence of disease. Despite the identification of stem/progenitor cells residing in cartilage over ten years ago, there is still limited knowledge about their origins and roles.

A study conducted by Li et al. showed that articular cartilage stem cells can release tumor necrosis factor alpha-induced protein 3 (TNFAIP3). This protein plays a role in inhibiting osteoclasts, which are cells responsible for bone resorption, and it also promotes subchondral bone remodeling in experimental models of knee osteoarthritis. Despite these findings, it seems that the stem/progenitor cells found in cartilage are not sufficient to prevent cartilage degradation or facilitate complete cartilage regeneration during osteoarthritis. Therefore, while they contribute to the process of subchondral bone remodeling, these cells alone cannot fully counteract the progression of cartilage damage in OA.[14]

5.3 Subchondral bone

As previously stated, subchondral bone changes as osteoarthritis (OA) progresses and is now seen as a regulator of the disease. Recently, Koria et al. demonstrated, for the first time, an overall increase in bone volume fraction and trabecular thickness in the human ankle using μCT. This finding supports earlier research showing similar alterations in the bone microarchitecture of the human knee and hip joints. Delsmann et al. conducted a multiscale analysis of the femoral heads of patients with primary OA. They found that several subchondral bone parameters were positively correlated with cartilage degeneration in OA. Their comprehensive analysis of bone turnover, matrix quality, biomechanical characteristics,

and the osteocyte lacunocanalicular network in various subchondral compartments revealed that greater matrix mineralization heterogeneity, more osteocyte canaliculi, and a higher number of osteoblasts, along with a similar number of osteoclasts, were associated with the thickening of the subchondral bone.

The authors suggest that targeting signaling pathways within the osteoblast lineage could serve as a promising therapeutic approach, even though the precise mechanism of communication between bone and cartilage remains unknown. To explore the potential role of increased osteoclastogenesis in subchondral bone, Zhang and colleagues utilized a mouse model lacking lymphocyte cytosolic protein (Lcp1) to study osteoarthritis (OA) progression following anterior cruciate ligament transection. The absence of this protein results in the suppression of subchondral osteoclast activity. It was found that cartilage degeneration is driven by oxygen originating from the subchondral bone. Intriguingly, Zhang and his team have recently undertaken a study focusing on this area.[11]

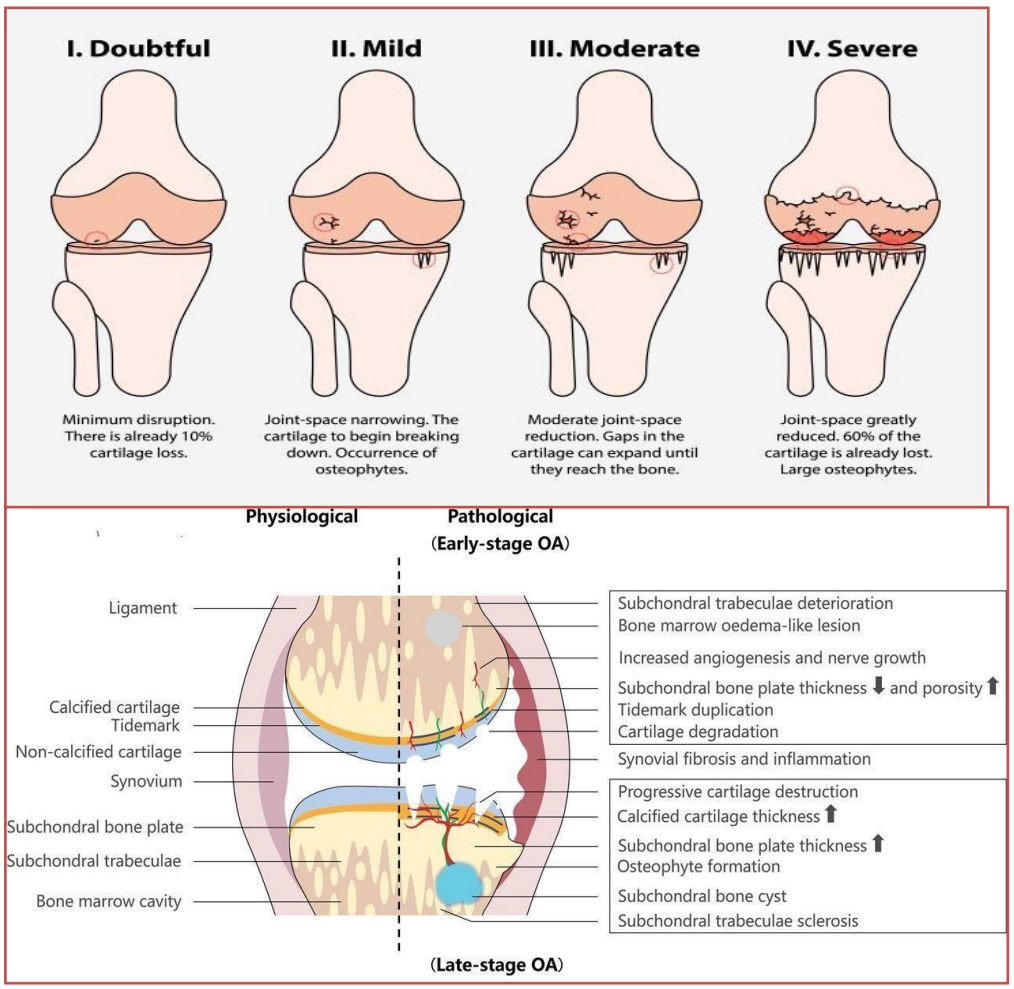


Figure 4: Subchondral bone (Late Stage).

5.4 Adipose Tissue/Synovium

Osteoarthritis (OA) involves at least two types of adipose tissue within the joint: intraarticular adipose tissue and bone marrow adipose tissue. The infrapatellar fat pad (IFP), a specific intraarticular adipose tissue, often forms a functional unit with the synovium, contributing to OA pain, synovial inflammation, and fibrosis. In contrast, bone marrow adipose tissue plays a crucial role in regulating the bone microenvironment.

Recent studies have utilized single-cell sequencing to create an atlas of the various cell types present in a synovial joint. This advanced technique has revealed significant cellular heterogeneity and identified changes in joint tissues under pathological conditions like rheumatoid arthritis (RA) and OA. Li et al. employed single-cell sequencing to investigate the synovium and IFP in human and mouse knee joints, confirming the functional connection between these tissues. They discovered that these tissues share a similar population of mesenchymal progenitors.

Histological analysis and the use of various reporter mouse lines further demonstrated that, during OA progression, Dpp4-positive mesenchymal progenitor cells in the synovial sublining layer differentiate into distinct cell types. These include PRG4-positive fibroblasts in the thickening synovial tissue and perilipin-positive adipocytes in the IFP. While PRG4-positive synovial lining fibroblasts have been shown to secrete the canonical Wnt agonist R-spondin-2, driving pathological changes, the precise role of perilipin-positive adipocytes remains unclear.

The tissues even share a similar population of mesenchymal progenitors. Histological analysis and the use of various reporter mouse lines revealed that during OA progression, Dpp4-positive mesenchymal progenitor cells in the synovial sublining layer differentiate into distinct cell types, including PRG4-positive fibroblasts in thickening synovial tissue and perilipin-positive adipocytes in the IFP. While PRG4-positive synovial lining fibroblasts have been shown to secrete the canonical Wnt agonist R-spondin-2, driving pathological changes, the precise function of perilipin-positive adipocytes remains unclear.[12]

5.5 synovial fluid

The study found that proliferation and attachment were suppressed, and synovial fluid from OA patients induced cellular senescence. This fluid also caused healthy chondrocytes to lose their differentiated state and become hypertrophic. The authors suggested that the high levels

of pro-inflammatory cytokines in OA synovial fluid likely prevent chondrocytes and synovial fluid-derived cells from contributing to tissue regeneration.

In a preclinical OA model induced by monosodium iodoacetate, the researchers developed an immunomodulatory cell treatment that restored joint homeostasis. This treatment utilized cartilage-activated proregenerative T cells, adipose tissue-derived mesenchymal stem cells, and mononuclear cells from blood or spleen. Their findings led to the development of a clinical compassionate study to further test their approach.[21]

The study found that proliferation and attachment were inhibited, and synovial fluid from OA patients induced cellular senescence. Additionally, this fluid caused healthy chondrocytes to lose their differentiated state and become hypertrophic. The authors suggested that the high levels of pro-inflammatory cytokines in OA synovial fluid likely prevent chondrocytes and synovial fluid-derived cells from contributing to tissue regeneration.[22]

In a preclinical OA model induced by monosodium iodoacetate, the researchers developed an immunomodulatory cell treatment that restored joint homeostasis. This treatment utilized cartilage-activated proregenerative T cells, adipose tissue-derived mesenchymal stem cells, and mononuclear cells from blood or spleen. The findings led to a clinical compassionate study to test their approach further.

6. Risk of Osteoarthritis

- **Age:** is a key risk factor for OA. The likelihood increases with age as the cumulative damage to joints over time can result in cartilage deterioration.
- **Gender:** Women are more prone to developing OA than men, especially after age 50. Hormonal influences may contribute to this higher risk.
- **Obesity:** Excess weight places additional strain on weight-bearing joints like the knees and hips, speeding up cartilage wear and tear.
- **Joint Injuries:** Past injuries to joints can raise the risk of OA in the affected area. This includes injuries from sports, accidents, or repetitive stress.
- **Genetics:** A family history of OA can heighten an individual's risk, indicating a genetic link to the disease.[15]

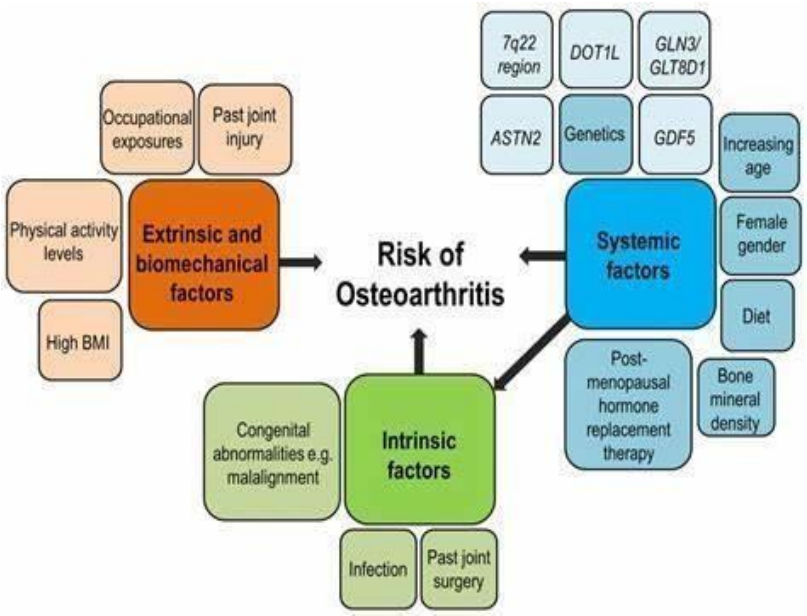


Figure 5 Risk Of Osteoathritis.

7. METHOD

7.1 Current Treatment Strategies

Osteoarthritis (OA) can be managed through three main treatment approaches: nonpharmacological interventions, pharmaceutical interventions, and surgical interventions. Current consensus guidelines recommend a combination of pharmacological, nonpharmacological, and, when necessary, surgical interventions to manage OA effectively. Most OA patients can benefit from a mix of pharmacological and nonpharmacological treatments. Surgical methods should be considered in later stages to restore function by replacing the joint or repairing cartilage lesions.[18-19]

The primary nonpharmacological interventions include physical therapy and lifestyle changes. For obese patients, managing body weight can alleviate symptoms and reduce the likelihood of OA symptoms manifesting. Exercise helps keep the muscles around the joints strong and stable. Various physical therapy techniques, such as the use of pulsed electromagnetic fields (Yang et al. 2018a), extracorporeal shock wave therapy (ESWT) (2017), and acupuncture (Tu et al. 2021), have been shown to improve mobility and relieve symptoms. Additionally, dietary supplements like glucosamine and chondroitin sulfate have been used to support joint health.[22]

Pharmacological interventions typically involve nonsteroidal anti-inflammatory drugs (NSAIDs) to reduce inflammation and pain, along with analgesics for pain relief. In some

cases, corticosteroid injections may be administered to provide temporary relief from severe symptoms. Hyaluronic acid injections might also be considered to enhance joint lubrication and function.

When nonpharmacological treatments are insufficient, particularly in advanced stages of OA, surgical options such as joint replacement or arthroscopy may be explored. These procedures aim to restore joint function and alleviate pain, significantly improving the patient's quality of life.[17]

7.2 Study Design

To gain a deeper understanding of the OA pain experience and its changes over time, a secondary analysis of focus groups and one-on-one interviews from a 2006 OMERACT/OARSI initiative was conducted for this qualitative study. The analysis used qualitative description methodology to provide detailed information. This approach aims to offer a comprehensive account of experiences, staying close to the original data with minimal interpretation. It is particularly relevant for health sciences research that seeks to gather data from individuals experiencing the phenomenon under study. According to its philosophical foundations, qualitative description is an inductive process that develops, understands, and describes phenomena. Researchers maintain an interpretivist stance and actively participate in the research process. Written informed consent was obtained from each participant, and the Women's College Hospital research ethics board approved the study (REB 2022-0098-E). The study adhered to the Consolidated Criteria for Reporting Qualitative Studies (COREQ) standards for reporting qualitative research.[14]

7.3 Sampling and Data Collection

Transcripts from 17 focus groups and three one-on-one interviews with 91 individuals experiencing symptomatic knee OA were analyzed. Individuals with hip OA as the primary joint were excluded from these sessions. The focus groups and interviews took place in five different locations: Sydney, Australia; Toronto and Vancouver, Canada; Bristol, UK; and Houston, USA. Participants were categorized based on their pain intensity using a 10-point numerical rating scale, divided into "mild to moderate" and "moderate to severe" pain groups. Recruitment of participants was achieved through advertisements, the researchers' clinical practices, and research cohorts.[4]

8. Analysis

Our study drew on Braun and Clarke's thematic analysis approach, employing an inductive method to delve deeply into our data. Two researchers, LK and MG, led the process, holding several meetings to discuss their data interpretations after becoming familiar with it. The first author then developed an initial coding framework inductively, which became the foundation for our analysis.

Our analytical team was diverse and comprehensive, consisting of six researchers (LK, EW, AM, IS, VH, MG), two physical therapists, two research assistants with open access research experience, one summer research student, and a rheumatologist skilled in qualitative research. This diversity brought a wide range of expertise and perspectives, enriching the depth and precision of our analysis.[21]

Each team member independently coded four transcripts line by line. This method guaranteed that each transcript was thoroughly examined from multiple viewpoints. Following the individual coding process, the team convened to compare codes, discuss discrepancies, and propose new codes. These discussions were essential in refining our coding framework, ensuring it accurately captured the nuances and themes within the data.

This collaborative approach highlighted the importance of diverse perspectives in qualitative research, as it allowed us to comprehensively understand the data. The varied backgrounds of the team members ensured that no aspect of the transcripts was overlooked, leading to a more robust and detailed analysis.

By incorporating different viewpoints, we could identify subtle themes and patterns that might have been missed with a less diverse team. The process of discussing and resolving discrepancies further ensured that the final coding framework was well-rounded and reflective of the data's complexity.[23]

9. Treatment

Recent Progress in Biological Interventions

9.1 DNA- or Gene-Based Therapy

DNA is a long, double-stranded polymer composed of four deoxynucleotides (Minchin and Lodge, 2019). Genes, which are segments of DNA, carry genetic information. Numerous genes have been associated with the onset and progression of osteoarthritis (OA) by

increasing susceptibility, enhancing the degradation of the cartilaginous matrix, preventing cartilage repair, increasing the expression of inflammatory factors, or promoting fibroblast transformation.[15]

9.2 Aoncoding RNA-Based Therapy

Numerous studies have focused on the epigenetic regulation of OA's pathogenesis and potential therapeutic targets, particularly noncoding RNAs (ncRNAs). Only about 2% of the human genome is comprised of protein-coding RNA, while the vast majority consists of ncRNAs. These ncRNAs, which include circular RNA (circRNA), long noncoding RNA (lncRNA), and microRNA (miRNA), play a role in the pathological development of OA and can be used as markers for prognosis. Recent preclinical data (Duan et al., 2020) indicates that many ncRNAs can directly influence the expression of key OA genes. This finding holds significant translational potential for the treatment of OA, as targeting ncRNAs may offer new therapeutic strategies.[6]

- **MiRNA**

Among the various ncRNAs, miRNAs—small molecules about 22 nucleotides in length—are key players in RNA silencing and the posttranscriptional regulation of gene expression. In recent years, they have attracted significant attention. Studies have shown that numerous miRNAs play crucial roles in maintaining the homeostasis of bone and cartilage (Shen et al., 2019), by regulating signaling pathways involved in chondrocyte apoptosis or hypotrophy, synovial inflammation, and extracellular matrix (ECM) degradation.

- **CircRNA**

CircRNA molecules, which contain exon sequences and are covalently closed, are spliced at the canonical splicing site (Tam et al., 2019). These molecules function as competing endogenous RNAs or miRNA sponges, naturally sequestering and inhibiting miRNA activity. CircRNAs also play a role in the development of osteoarthritis (OA) by regulating inflammation, extracellular matrix (ECM) degradation, and chondrocyte proliferation and apoptosis (Yang et al., 2020).

- **LncRNA**

Long noncoding RNAs (lncRNAs) are a type of noncoding RNA (ncRNA) that exceed 200 nucleotides in length (Zhang et al., 2021b). These lncRNAs interact with RNA and are often referred to as silent miRNA sponges. This designation stems from their ability to regulate the

translation and degradation of messenger RNA (mRNA).

The regulatory roles of lncRNAs in cellular processes are significant, and recent research has highlighted their involvement in various biological functions, particularly in the context of cartilage formation and osteoarthritis (OA). Unlike miRNAs, which typically have about 22 nucleotides and are well-known for their role in RNA silencing and post-transcriptional regulation of gene expression, lncRNAs perform a broader range of functions.

LncRNAs can influence gene expression at multiple levels, including chromatin modification, transcription, and post-transcriptional processing. By acting as molecular sponges, lncRNAs can sequester miRNAs, thereby preventing these miRNAs from binding to their target mRNAs. This interaction modulates the availability of miRNAs to interact with their targets, ultimately affecting the stability and translation of mRNAs.

In the context of cartilage formation, lncRNAs play a critical role. They modulate the expression of genes involved in chondrocyte differentiation, proliferation, and extracellular matrix (ECM) synthesis. Chondrocytes are the primary cell type in cartilage, and their function is crucial for maintaining cartilage health.

10. CONCLUSION

Osteoarthritis (OA) involves cartilage breakdown, causing joint pain and stiffness. Though common, new insights into OA's causes and treatments offer hope. Promising strategies include improving joint tissue interactions and exploring gene and protein therapies. Lifestyle changes like exercise and weight management are key in preventing and managing OA. Ongoing research aims to develop effective treatments to improve patients' lives. Despite challenges, advancements in science and medicine are expected to greatly improve OA management in the future.

11. REFERENCE

1. Liping Tong, Huan Yu, Xingyun Huang, Jie Shen, Guozhi Xiao, Lin Chen, Huaiyu Wang, Lianping Xing & Di chen, Current understanding of osteoarthritis pathogenesis and relevant new approaches, 2022 Sep 20.(Bone research)
2. Ashok Kumar, Sapna Goel, Raju Gupta And B.M. Gupta A Scientometric Assessment of publication output during, 2007-16. (Microsoft Edge)
3. L.K. King, A. Mahmoudian, E.J. Waugh, I. Stanaitis, M. Gomes, V. Hung, C. MacKay,

J.W. Liew, Q. Wang, A. Turkiewicz, I.K. Haugen, C.T. Appleton, S. Lohmander, M. Englund, J. Runhaar, T. Neogi, G.A. Hawker Osteoarthritis and Cartilage Open Published on June 2024 (G.A. Hawker, L. Stewart, M.R. French, et al., Understanding the pain experience in hip and knee osteoarthritis–an OARSI/OMERACT initiative, Osteoarthritis Cartilage).

4. Zsuzsa Jenei-Lanzl and Frank Zaucke, Osteoarthritis year in review 2024: biology, Osteoarthritis and Cartilage, (2024) doi:https://doi.org/10.1016/j.joca.2024.10.008
5. Jinxia Deng[1], Zhixian Zong[1], Zhanpeng Su[1], Haicong Chen[1], Jianping Huang 2,3, Yanru Niu[1], Huan Zhong[1]*, Bo Wei[1], Pharmacological Pharmacological Intervention of Osteoarthritis: A Biological 2021 OCT 4.
6. Ai D., Yu F. (2019). LncRNA DNM3OS Promotes Proliferation and Inhibits Apoptosis through Modulating IGF1 Expression by Sponging MiR-126 in CHON- 001 Cells. Diagn. Pathol, 14: 106. 10.1186/s13000-019- 0877-2 [DOI] [PMC free article] [PubMed] [Google Scholar] Apostu D., Lucaciu O., Mester A., Oltean-Dan D., Baciut M., Baciut G., et al. (2019). Systemic Drugs with Impact on Osteoarthritis. Drug Metab. Rev, 51: 498–523. 10.1080/03602532.2019.1687511 [DOI] [PubMed] [Google Scholar]
7. Bai J., Zhang Y., Zheng X., Huang M., Cheng W., Shan H., et al. (2020). LncRNA MM2P-Induced, Exosome-Mediated Transfer of Sox9 from Monocyte-Derived Cells Modulates Primary Chondrocytes. Cell Death Dis, 11: 763. 10.1038/s41419-020-02945-5 [DOI] [PMC free article] [PubMed] [Google Scholar]
8. Berenbaum F., Blanco F. J., Guermazi A., Miki K., Yamabe T., Viktrup L., et al. (2020). Subcutaneous Tanezumab for Osteoarthritis of the Hip or Knee: Efficacy and Safety Results from a 24-week Randomised Phase III Study with a 24-week Follow-Up Period. Ann. Rheum. Dis, 79: 800–810. 10.1136/annrheumdis-2019-216296 [DOI] [PMC free article] [PubMed] [Google Scholar]
9. Beretti F., Zavatti M., Casciaro F., Comitini G., Franchi F., Barbieri V., et al. (2018). Amniotic Fluid Stem Cell Exosomes: Therapeutic Perspective. Biofactors, 44: 158–167. 10.1002/biof.1407 [DOI] [PubMed] [Google Scholar] Cao L., Wang Y., Wang Q., Huang J. (2018). LncRNA FOXD2-AS1 Regulates Chondrocyte Proliferation in Osteoarthritis by Acting as a Sponge of miR-206 to Modulate CCND1 Expression. Biomed. Pharmacother, 106: 1220–1226. 10.1016/j.biopha.2018.07.048 [DOI] [PubMed] [Google Scholar]
10. Celik E., Bayram C., Denkbaş E. B. (2019). Chondrogenesis of Human Mesenchymal Stem Cells by microRNA Loaded Triple Polysaccharide Nanoparticle System. Mater. Sci. Eng. C Mater. Biol. Appl, 102: 756–763. 10.1016/j.msec.2019.05.006 [DOI] [PubMed]

[Google Scholar]

11. Chang Y. H., Wu K. C., Harn H. J., Lin S. Z., Ding D. C. (2018). Exosomes and Stem Cells in Degenerative Disease Diagnosis and Therapy. Cel Transpl, 27: 349–363. 10.1177/0963689717723636 [DOI] [PMC free article] [PubMed] [Google Scholar]
12. Cheleschi S., Tenti S., Mondanelli N., Corallo C., Barbarino M., Giannotti S., et al. (2019). MicroRNA-34a and MicroRNA-181a Mediate Visfatin-Induced Apoptosis and Oxidative Stress via NF-Kb Pathway in Human Osteoarthritic.
13. Chen C., Yin P., Hu S., Sun X., Li B. (2020). Circular RNA-9119 Protects IL- 1βtreated Chondrocytes from Apoptosis in an Osteoarthritis Cell Model by Intercepting the microRNA-26a/PTEN axis. Life Sci, 256: 117924. 10.1016/j.lfs.2020.117924 [DOI] [PubMed] [Google Scholar]
14. Chen G., Liu T., Yu B., Wang B., Peng Q. (2020). CircRNA-UBE2G1 Regulates LPS-Induced Osteoarthritis through miR-373/HIF-1a axis. Cell Cycle, 19: 1696– 1705. 10.1080/15384101.2020.1772545 [DOI] [PMC free article] [PubMed]
15. Chen K., Zhu H., Zheng M. Q., Dong Q. R. (2019). LncRNA MEG3 Inhibits the Degradation of the Extracellular Matrix of Chondrocytes in Osteoarthritis via Targeting miR-93/TGFBR2 Axis. Cartilage, 1947603519855759. [DOI] [PMC free article] [PubMed] [Google Scholar]
16. Chu P., Wang Q., Wang Z., Gao C. (2019). Long Non-coding RNA Highly Up- Regulated in Liver Cancer Protects Tumor Necrosis Factor-Alpha-Induced Inflammatory Injury by Down-Regulation of microRNA-101 in ATDC5 Cells. Int. Immunopharmacol, 72: 148–158. 10.1016/j.intimp.2019.04.004 [DOI] [PubMed] [Google Scholar]
17. Cong L., Zhu Y., Tu G. (2017). A Bioinformatic Analysis of microRNAs Role in Osteoarthritis. Osteoarthritis Cartilage, 25: 1362–1371. 10.1016/j.joca.2017.03.012 [DOI] [PubMed] [Google Scholar]
18. D'Adamo S., Cetrullo S., Guidotti S., Borzì R. M., Flamigni F. (2017). Hydroxytyrosol Modulates the Levels of microRNA-9 and its Target Sirtuin-1 Thereby Counteracting Oxidative Stress-Induced Chondrocyte Death. Osteoarthritis Cartilage, 25: 600–610. 10.1016/j.joca.2016.11.014 [DOI] [PubMed] [Google Scholar]
19. Lackland DT, Roccella EJ, Deutsch AF, Fornage M, George MG, Howard G, Kissela BM, Kittner SJ, Lichtman JH, Lisabeth LD, et al. Factors influencing the decline in stroke mortality: a statement from the American heart association/American stroke association. *Stroke*, 2014; 45(1): 315–353.
20. Kronenberg HM. Developmental regulation of the growth plate. Nature, 2003; 423:

332–336. doi:10.1038/nature01657. - DOI - PubMed

21. Hiroshi K. Endochondral ossification signals in cartilage degradation during osteoarthritis progression in experimental mouse models. Mol. Cells, 2008; 25: 1–6. - PubMed
22. Bijlsma JWJ, Berenbaum F, Lafeber FPJG. Osteoarthritis: an update with relevance for clinical practice. Lancet, 2011; 377: 2115–2126. doi: 10.1016/S0140-6736(11)60243-2. - DOI - PubMed
23. Altman, R. D., Schemitsch, E. & Bedi, A. Assessment of clinical practice guideline methodology for the treatment of knee osteoarthritis with intra-articular hyaluronic acid. Semin. Arthritis Rheum. 10.1016/j.semarthrit.2015.04.013 (2015). - PubMed