The miRNA Expression in Knee Osteoarthritis

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ABSTRACT

Background and Aim: Osteoarthritis (OA) is a degenerative condition of the joints that affects the surrounding tissues. MicroRNAs (miRNAs) have emerged as critical regulators in OA pathophysiology, including inflammatory processes and proliferation. This study aims to investigate the link involving miRNAs and OA. **Methods:** A systematic search was performed employing databases such as PubMed, Scopus, EBSCO, EMBASE, and Cochrane. This research emphasizes randomized controlled trials (RCTs) and quasi-randomized controlled investigations. Data were examined using established parameters, and the integrity of research was rated using National Institutes of Health (NIH) guidelines. **Results:** Three RCT publications were selected for miRNA expression patterns from the 677 publications examined. This research focused on miR-140 and miR- 146, which play substantial functions in cartilage health and OA development. **Conclusion:** miR-140 and miR-146 have the potential to be used as a biomarker for OA.

INTRODUCTION

Osteoarthritis (OA) is a degenerative joint disorder distinguished by increasing articular cartilage disintegration, subchondral reconstruction of bones, chondrocyte enlargement, and synovial inflammation.[1] OA is a widespread and persistent joint circumstance that continues to rise in prevalence as people age and gain weight. It is triggered by articular cartilage degradation, which results in persistent discomfort, incapacity, worse quality of life, and financial obligations. The global incidence of OA is estimated at 20%, but regional differences exist. The susceptibility to OA is influenced by genetic and environmental factors, and studying its epidemiology in different populations can help understand the global burden and underlying mechanisms.[2-3]

Recent studies have demonstrated that microRNAs (miRNAs) serve an important role in the pathophysiology of OA, such as apoptosis, inflammatory processes, and proliferation, and may possess a protective or progressive function. miRNA, or MicroRNA, is a tiny category of non-coding RNA molecules that regulate gene expression after transcription.[1] miRNAs can be used as biomarkers for OA since their levels vary in the circulatory system and synovial fluid in OA. However, further research must be performed to determine how reliable they are as biomarkers. Therefore, this research investigated the link between miRNAs and OA.

MATERIALS AND METHODS

Search Strategy and Selection Criteria

The electronic databases (PubMed, Scopus, EBSCO, EMBASE, and Cochrane) and Cochrane Handbook of Systematic Reviews 2.0 search strategy were used in this study. We used the keywords “miRNA OR micro-RNA AND osteoarthritis OR arthritis and used all randomized controlled studies (RCTs) or quasi-randomized controlled studies (qRCTs) about the relationship between mRNAs and OA. Patients with osteoarthritis at any age regardless of the stage of severity were eligible participants, excluding recent trauma.

Data Analysis

Possible studies (2000-2024) were extracted for the full texts, and each was assessed for inclusion eligibility. Two authors assessed the risk of bias for every included study based on the Cochrane Handbook for Systematic Reviews of Intervention. Any arising conflicts were resolved through discussion. We used the National Institutes of Health (NIH) standard, which consisted of selection, comparability, and outcome to assess each study's quality. Obtained studies can be classified as good if there are 3 or 4 stars in the selection domain, 1 star in the comparability domain, and 2 or 3 stars in the outcome domain.

RESULTS

The search retrieved 677 articles, including 537 from PMC, 73 from PubMed, 33 from MedRvix, and 34 from the Cochrane Central Database. After eliminating duplication and getting rid of irrelevant scientific papers depending on the article title, 51 articles underwent assessment for full-text availability and data relevant to the study's goal. Following a full-text review, three papers have been selected for further analysis (Figure 1). Each primary research study was categorized into data on patient characteristics were noted and described in Table 1.[4-6]

Table 1. List of the studies included in this review

Title	Authors	Publication Year	Study design	Subject number	Age	Sex	
						Male (%)	Female (%)
RNA-Seq Reveals the mRNAs, miRNAs, and lncRNAs Expression Profile of Knee Joint Synovial Tissue in Osteoarthritis Patients	Qiao et al.[4]	2023	Randomised Control Trial	10	62-75	4 (40%)	6 (60%)
Can balneotherapy modify microRNA expression levels in osteoarthritis? A	Giannitti et al.[5]	2017	Randomised Control Trial	32	69-80	-	32 (100%)

comparative study in patients with knee osteoarthritis							
Curcumin as an effective suppressor of miRNA expression in patients with	Atabaki et al.[6]	2021	Randomised Control Trial	30	40-55	N/A	N/A
knee osteoarthritis							

Risk of Bias Analysis

The risk of bias study of clinical trials was performed using the National Institute of Health's (NIH) assessment of quality instruments (Table 2).

Table 2. NIH critical appraisal for clinical trial

Major Composition	Qiao et al.[4]	Giannitti et al.[5]	Atabaki et al.[6]
1. Was the study question or objective clearly stated	Yes	Yes	Yes
2. Was the population clearly and fully described, including case definition	Yes	Yes	Yes
3. Were the case consecutive	Yes	Yes	Yes
4. Were the subjects comparable	Yes	Yes	Yes
5. Were the intervention clearly described	Yes	Yes	Yes

6. Were the outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants	Yes	Yes	Yes
7. Was the length of follow-up adequate?	Yes	Yes	Yes
8. Were statistical methods well described	Yes	Yes	Yes
9. Were the results well described	Yes	Yes	Yes
Quality Rating	Good	Good	Good

DISCUSSION

The Role of miRNA in Diagnosis and Therapy

MicroRNAs are very small non-coding RNA molecules that regulate the activity of genes by limiting protein translation and boosting mRNA cleavage. miRNAs, also known as MiRtrons, have expression patterns that correspond with the host gene depending on whether they are located in introns or splice site junctions.[1] Figure 2 depicts how miRNAs begin as primary transcripts (pri-miRNA) produced in the nucleus by RNA polymerase II. The Drosha/DGCR8 associations then transform these pri-miRNAs into pre-miRNA precursors, that are then transported to the plasma membrane by exportin. Dicer and TRB in the plasma membrane transform pre-miRNAs into miRNA duplexes. miRNAs are capable of entering the bloodstream in three ways: via extracellular vesicles (exosomes), as shown by green arrows, or by other RNA-binding proteins such as Ago (red arrows) or NPM1 (blue arrows).[7]

MicroRNAs have been discovered to facilitate cell-to-cell communication through circulating miRNA. Circulating miRNAs are microRNAs that migrate outside of cells and into body fluids. Approximately 90% of these circulating miRNAs develop interactions with proteins such as Ago2, NPM1 (nucleophosmin 1), and high-density lipoprotein, whereas the other 10% are released in exosomes. This packing in exosomes is critical for protecting miRNAs from destruction by RNases in physiological fluids.[8] Furthermore, circulating microRNAs may serve as prognostic indicators for cancer, reflecting the effectiveness of treatment and the possibility of disease recurrence. MiR-125b levels in breast cancer may predict response to treatment, but miR-21 levels in prostate cancer are associated with medication resistance.[7]

The Role of miRNA in Osteoarthritis

Figure 3 depicts the normal knee joint, which includes the femur, tibia, articular cartilage, and synovial lining. A thin layer of calcified cartilage lies beneath the articular cartilage, and the subchondral bone beneath it is made up of cortical and trabecular bone that is porous and actively functioning. This fresh investigation has contributed to a new understanding of OA as a complex joint disease including inflammatory and metabolism variables.[9]

Figure 4 demonstrates the beginning and late phases of osteoarthritis. In the advancement of OA, the osteochondral unit experiences sequential improvements. Early osteoarthritis includes enhanced repair done to the subchondral bone plates. As the condition advances, the depletion of cartilage matrix parts and degradation of the collagen network cause extensive cracks and delamination of the cartilage, exposing the underneath sections of calcified cartilage and subchondral bones. In late-stage OA, chondrocytes frequently become clustered, and apoptosis is perceived.[9]

MicroRNAs (miRs) play a critical role in OA by influencing the degree of stability and translations of target mRNAs involved in pathological events including inflammatory processes, apoptosis, matrix emergence, and chondrogenesis (Table 3). MiRs additionally tend to impact extracellular matrix deposition and may delay or accelerate chondrocyte mortality.[10-11] When there's an abnormal expression of miRs, it can lead to an imbalance between factors promoting cartilage breakdown and those supporting cartilage health, resulting in cartilage degradation when its normal balance is disrupted.[12]

Table 3. The MiRNA and the corresponding pathways to induce apoptosis

Apoptosis	**Induced Effect**	**Signaling Pathway**
miR-195-5p	mRNA and protein levels of IL-1β, IL-6, and TNF-α were considerably elevated	In ATDC5 cells, mir-195-5p inhibited the Wnt/β-catenin signaling pathway and increased the NF-κB signaling pathway after LPS stimulation
miR-335-5p	significantly reduces the expression of inflammatory factors (IL-1β, IL-6, and TNF-α)	substantially raised the expression levels of autophagy-related genes encoding the autophagy-related proteins Beclin-1, ATG5, and ATG7
miR-9	reduces the IL-1β mediated production of TNF-α and reduces basal and IL-1β-induced MMP13 protein release	PXR/RXR activation, G-protein coupled receptor (GPCR) signaling and Wnt/b-catenin signaling
miR-145	miR-145 up-regulation reduces LPS-induced inflammatory damage in ATDC5 cells via SAL	functioned in LPS-induced injury by blocking NF-κB and p38MAPK signaling pathways
miR-337-3p	-	miR-337-3p in OA enhanced PTEN expression, hence the PI3K/AKT signaling pathway was inhibited by PTEN
miR-27b-3p	Knocking down miR-27b-3p in C28/I2 cells treated with IL-1β dramatically increased TNF-α and IL-6 levels, which were previously suppressed by PVT1 silencing	miR-27b-3p decreased cell viability that was promoted by the silencing of PVT1 in IL-1β-treated C28/I2 cells, miR- 27b-3p abrogated the promoting effect of PVT1 knockdown on

		autophagy in C28/I2 cells challenged by IL-1β
miR-125b	-	miR-125b noticeably alleviated the LPS+pc-THRIL- induced JAK1/STAT3 and NF-κB pathways activation
miR-107	-	miR-107 inhibited the activation of AKT/mTOR and NF- κB pathway
miR-218-5p	-	The expression of PIK3C2A, Akt, mTOR, and S6 was downregulated, whereas 24 4EBP1 was increased
miR-140-5p	miR-140-5p decreased the expression of HMGB1 protein, p-AKT (Ser473), and p-PI3K in IL-1β-induced chondrocytes	Inhibited the PI3K/AKT signaling pathway and reduced the development of OA via targeting HMGB1
miR-1236	-	Overexpression of miR-1236 causes OA by reducing chondrocyte growth and inducing apoptosis, which is largely mediated by PIK3R3 regulation
miR-93-5p	Overexpression of miR-93-5p effectively inhibited IL-1β-induced chondrocyte death. In overall, IL-1β increases the production of matrix-degrading enzymes (MMP3 and MMP13), which breakdown the ECM	miR-93-5p exerted its actions in chondrocytes partially through suppression of TCF4 expression
miR-675-3p	Overexpression of miR-675-3p reduced IL-6 and IL-8 expression after IL-1b stimulation	miR-675-3p mimic significantly reduced the rise in GNG5 expression levels

miR-455-3p	miR-455-3p significantly inhibited the viability of CHON-001 cells IL-1β-induced apoptosis of CHON-001 was significantly increased by up-regulation of miR-455-3p	miR-455-3p directly regulated COL2A1 expression through binding its 3′UTR sequence
miR-142-5p	Overexpressing miR-142-5p lowered IL-1β and TNF-α levels while increasing IL-10 levels	miR-142-5p overexpression decreased CXCR4 expression

miRNA Specific for OA

The expression of different microRNAs (miRNAs) in osteoarthritic cartilage and subchondral bone has been identified (Figure 3). Researchers have discovered particular miRNAs in the plasma, such as miR-16 and miR-132, which might distinguish OA patients from healthy controls. Furthermore, miR-16, miR-146a, miR-155, and miR-223 levels in synovial fluid were shown to be considerably lower in OA patients than in rheumatoid arthritis.[13] Furthermore, overexpressed miRNAs in OA patients' plasma was found, including miR-16, miR-20b, miR-29c, miR-30b, miR-93, miR-126, miR-146a, miR-184, miR-186, miR-195, miR-345, and miR-885-5p.[14] The bulk of these investigations look at the expression of miRNAs targeting genes considered to be associated with OA. Figure 5 illustrates miRNA 140 and 146 and their targeted genes.

miR-140 in OA

miR-140 has been one of the most frequently researched miRNAs in osteoarthritis. The level of miR-140 expression in chondrocytes rises, implying a regulatory function in the differentiation of cells. In osteoarthritic cartilage, miR-140 expression is lower than in healthy cartilage. Targeting genes include ADAMTS5, MMP13, IGFBP5, and RALA, which are involved in cartilage degradation. The cytokines IL-1β and TGF-β suppress miR-140 expression in chondrocytes, resulting in a higher expression of the target genes and cartilage matrix breakdown.[15]

miR-146 in OA

miR-146 is an additional miRNA whose expression rises in early OA and falls as the illness develops. IL-1β upregulates MiR-146, which targets MMP13 and functions as an adverse feedback regulator. It reduces IL-1β-induced MMP13 and ADAMTS5 synthesis, suppresses collagen type II and aggrecan, and elevates TNF-α levels in OA cartilage. MiR-146 inhibits SMAD4, leading to decreased reactivity to TGF-β and chondrocyte death. It also influences pain-related circuits by controlling pain modulators. Downregulation of miR-146 in the neural system contributes to osteoarthritis pain.[15]

miR-26a and miR-26b in OA

MiR-26a and miR-26b have been reduced in cartilage from osteoarthritic joints. Downregulation of miR-26a and miR-26b causes overexpression of KPNA3 and NF-κB, resulting in joint inflammation and cartilage breakdown. Activation of the NF-κB pathway inhibits miR-26a, suggesting a reciprocal restriction. MiR-26a also targets NOS2, which is implicated in NO excessive production, chondrocyte death, and cartilage destruction in OA. IL-1β downregulates miR-26a in OA chondrocytes via NF-κB activation, leading to cartilage degradation.[13]

The Therapeutic Role of miRNA in the Management of Osteoarthritis

The present therapy for OA includes nonsteroidal anti-inflammatory drugs (NSAIDs) and complete joint arthroplasty. This technique has the benefit of being isolated in synovial joints, making intra-articular delivery of miRNAs less likely to cause systemic effects.[1] Targeting miR-34a has recently been investigated for OA therapy. Raised miR-34a levels in osteoarthritic chondrocytes block SIRT1, resulting in enhanced cell death. Using antisense oligonucleotides to silence miR-34a inhibited chondrocyte death in IL-1β-treated rat cells.[13] MiR-140, one of the most thoroughly researched miRNAs in OA, exhibits protective properties. Transfecting miR-140 into IL-1β-treated articular chondrocyte and mesenchymal stem cell cultures improved the formation of cartilage matrix substances while decreasing the generation of cartilage breakdown enzymes. In a rat OA model, exosomes high in miR-140 were administered into osteoarthritic joints, lowering articular cartilage destruction relative to the untreated group.[1]

CONCLUSION

miRNAs possess the potential to be used as biomarkers for OA, providing understanding of disease causes and development. Moreover, addressing miRNAs may offer new treatment methods for OA. Further studies are needed to investigate their therapeutic potential in clinical circumstances.

CONFLICTS OF INTEREST

The authors declare that they have no relevant financial or non-financial interests to report.

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This research did not receive any specific funding.

DATA AVAILABILITY

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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Figure legends

Figure 1. Flowchart of study

Figure 2. Extracellular export and biogenesis of miRNA

Figure 3. Composition of normal knee joint

Figure 4. The changes occurring in the progression of osteoarthritis

Figure 5. Schematic diagram of the target genes of each