World Journal of Orthopedics

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World J Orthop 2026 July 18; 17(7): 120195

DOI: 10.5312/wjo.120195

ISSN 2218-5836 (online)

ORIGINAL ARTICLE

Observational Study

MiR 26a as a stage-dependent biomarker and therapeutic regulator of inflammation in knee osteoarthritis

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Peer review: Externally peer reviewed.
Peer-review model: Single blind
Peer-review report's classification
Scientific quality: Grade A
Novelty: Grade A
Creativity or innovation: Grade A
Scientific significance: Grade A
P-Reviewer: Kostik MM, MD, PhD, Consultant, Professor, Russia
Received: February 24, 2026
Revised: March 8, 2026
Accepted: May 26, 2026
Published online: July 18, 2026
Processing time: 145 Days and 21.5 Hours
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Abstract

BACKGROUND

Osteoarthritis of the knee (KOA) is a prevalent degenerative joint disorder characterised by progressive cartilage breakdown and chronic inflammation. miRNAs have emerged as key regulators of gene expression in cartilage homeostasis and inflammatory signaling. Two of these, miR-26a2 and its isoform miR-26a5, play a role in regulating the NF-κB-mediated catabolic pathway.

AIM
To explore the distinct functions of miR-26a2 and miR-26a5 in the inhibition of inflammatory gene expression in KOA.

METHODS
A cross-sectional study was conducted from June to September 2023, with 100 patients (50 with KOA and 50 healthy controls and 50 KOA patients (grade 1, 2 and 3 according to the Kellgren-Lawrence criteria). Serum samples were analysed for miR-26a2, miR-26a5, and inflammatory genes (*NF-κB*, *COX-2*, *MMP-13*, *NOS2*) using reverse transcriptase quantitative PCR. Data were analysed using *t*-tests, ANOVA and correlation mapping to determine the relationship between miRNA levels and inflammatory gene expression.

RESULTS
MiR-26a2 levels were stable across all groups, indicating a minimal role in KOA. However, miR-26a5 showed a progressive decrease, reaching its lowest in grade-3 patients. Diminished miR-26a5 expression was negatively associated with upregulated NF-κB, COX-2, MMP-13 and NOS2, suggesting a protective effect against inflammation-mediated cartilage destruction. Correlation analyses confirmed significant associations between miRNA expression and upregulation of inflammatory genes, especially in advanced KOA.

CONCLUSION
MiR-26a5 is a stage-specific biomarker and modulator of inflammatory processes in KOA, while miR-26a2 is not. Downregulation of miR-26a5 enhances NF-κB-driven catabolic pathways, driving KOA progression. While the study has limitations in terms of sample size and duration, it highlights the role of miR-26a5 in maintaining cartilage homeostasis and as a potential biomarker for KOA severity.

Key Words: MicroRNA-26a2; MicroRNA-26a5; NF-κB; MMP-13; Osteoarthritis

Core Tip: MiR 26a5, identified as a stage-specific biomarker for osteoarthritis of the knee (KOA), has its levels inversely correlated with the NF-κB, COX 2, MMP 13 and NOS2 expression. In contrast to lowly involved miR 26a2, miR 26a5 protects against inflammation-induced cartilage degradation. Its loss of function speeds up the disease process, highlighting its therapeutic potential and utility in measuring the level of KOA, despite small sample sizes and short-term studies.

Citation: Gunamala V, Hari R, Jeyaraman N, Nallakumarasamy A, Muthu S, Jeyaraman M. MiR 26a as a stage-dependent biomarker and therapeutic regulator of inflammation in knee osteoarthritis. *World J Orthop* 2026; 17(7): 120195
URL: https://www.wjgnet.com/2218-5836/full/v17/i7/120195.htm
DOI: https://dx.doi.org/10.5312/wjo.120195

INTRODUCTION

Osteoarthritis of the knee (KOA) is a prevalent degenerative joint disease, which causes joint pain, stiffness and disability, resulting in significant disability and decreased quality of life[1]. Pathological hallmarks of KOA include damage to articular cartilage, changes to the subchondral bone structure and persistent synovial inflammation that results in joint instability and pain[2]. Articular cartilage is a specialised connective tissue comprising chondrocytes and an extracellular matrix (ECM), and both are critical for cartilage structure and mechanical properties[3]. Type II collagen and aggrecan, which confer tensile and compressive strength to the joint, are the major components of the ECM. In addition to its structural function, the ECM is essential for controlling the extracellular environment; impairment of the highly regulated extracellular milieu leads to cartilage degradation, impaired joint mobility and degeneration in osteoarthritis (OA)[4,5].

The present treatment of OA primarily focuses on pain and inflammation reduction and does not address the molecular pathways involved in cartilage breakdown[6]. Therefore, it is essential to comprehend the regulatory processes underlying cartilage matrix metabolism and inflammatory communication in creating disease-modifying treatment. miRNAs, 17 to 23-nucleotide-long non-coding RNA molecules, are in this way becoming important epigenetic regulators of gene expression due to post-transcriptional repression. A number of miRNAs are dysregulated in joint tissues and circulation and are involved in cartilage homeostasis, inflammatory regulation, and OA progression[7,8].

MiRNA-26a has two genomic locations, miR-26a-1 and miR-26a-2, that produce the mature strand miRNA-26a5[9]. It has been proposed that miRNA-26a5 is a protective factor in articular cartilage, by regulating the signaling pathways involved in inflammation, ECM remodeling, and chondrocyte survival[10]. Alterations in miRNA-26a5, which is derived from miRNA-26a2, have been shown to lead to amplified inflammatory responses and up-regulation of cartilage matrix-degrading enzymes, and thus contribute to the disease process in OA[11].

The NF-κB pathway is a key regulator of inflammatory and catabolic processes in OA, which, when chronically activated in chondrocytes and synovial cells, leads to disease progression. Emerging evidence indicates that NF-κB signaling directly influences the expression of the *miRNA-26a* gene cluster, including miRNA-26a2 and miRNA-26a5, leading to their downregulation under inflammatory conditions. Suppression of miRNA-26a2 and miRNA-26a5 has been

associated with the de-repression of key NF-κB-responsive target genes, *MMP-13*, *COX2*, and *NOS2*, which are major mediators of cartilage ECM degradation, nitric oxide (NO) production, and prostaglandin-driven inflammation. Loss of miRNA-26a mediated post-transcriptional control therefore amplifies NF-κB-dependent inflammatory signalling, accelerates collagen type II breakdown, and promotes chondrocyte dysfunction, establishing the NF-κB-miR-26a2/miR-26a5–MMP13/COX2/NOS2 regulatory axis as a critical contributor to OA pathogenesis[10,12].

Despite growing evidence supporting the involvement of miRNA-26a2 and miRNA-26a5 in OA, most studies have been conducted in East Asian and European populations. Consequently, there remains a significant gap in understanding the expression dynamics and regulatory role of miRNA-26a in KOA across diverse ethnic groups[13]. Addressing this gap, the present study investigates the grade-wise expression patterns of miRNA-26a2 and miRNA-26a5 and their association with key inflammatory and cartilage-degrading genes, including *NF-κB*, *COX2*, *MMP-13*, and *NOS2*, in KOA patients from South India. This research will map these protein interactions during the various stages of KOA to characterise stage-specific regulatory networks and to discover potential markers and targets for the inflammation-induced cartilage degradation.

MATERIALS AND METHODS

A cross-sectional observational study was done in the Department of Orthopaedics, Faculty of Medicine-Sri Lalithambigai Medical College and Hospital, Chennai, between June and September 2023. A total of 100 adults (66 women and 34 men) from the community were enrolled in the study. Participants were categorised into two cohorts: 50 healthy individuals and 50 patients with KOA, graded as 1, 2, or 3 according to the Kellgren-Lawrence classification system. Individuals with concomitant joint pathologies, autoimmune disorders, or post-malignancy conditions were excluded. Recruitment was performed using convenience sampling. Ethical approval for the study protocol was obtained from the Institutional Ethics Committee, and written informed consent was secured from all participants prior to enrollment.

Demographic patient data, clinical history, and clinical stage were collected from individuals classified as grade 1, 2, and 3. Blood samples were collected from the study participants using the venipuncture method. Blood samples were centrifuged for 10 minutes at 1500 RPM, and the supernatant serum was subsequently frozen at -80 ^{o}C for future use. miRNA-26a2, miRNA-26a5 and RNA were extracted from 100 serum samples using the Aura pure miRNA and RNA extraction kit, respectively. Complementary DNA (cDNA) synthesis was conducted using the Aura Pure cDNA Synthesis Kit for reverse transcriptase quantitative PCR. Primer sequences (Table 1) were prepared for miRNA-26a2 (MIMAT0004681), miRNA-26a5 (MIMAT0000082) and OA inflammatory genes such as *NF-κB* (NM_001382628.1), *COX2* (AY462100.1), *MMP13* (NM_002427.4), *NOS2* (NM_000625.4), beta actin (M10277.1) and U6 small nuclear RNA (reference gene for normalisation). Detection of miRNA-26a2 and miRNA-26a5 and OA inflammatory gene expression in the samples of cases and controls was done using RT PCR.

Statistical analysis

Data are expressed as mean ± SD. The differences between pairs of groups were analyzed statistically with a *t*-test in GraphPad Prism 10.4.1 (627) (GraphPad Software Inc., San Diego, CA, United States). Statistical analysis included assessing the normality of data using the ANOVA, followed by the Bonferroni multiple comparison test. Data analysis was performed using the SPSS program (version 25.0, IBM Corp, Chicago, IL, United States). $P < 0.05$ was considered statistically significant.

RESULTS

The study was conducted with 100 individuals comprising four groups who were designated control persons of 50 numbers. Their average age was 39.67 ± 7.4 years, consisting of 22 males (44%) and 28 females (56%). The other 50 individuals are categorised under KOA patients based on the Kellgren-Lawrence grading system and were further classified into grade 1, 2, and 3 with $n = 16$, $n = 22$, and $n = 12$, respectively. The mean age group observed in KOA patients was 65.3 ± 10.2 years, with 76% ($n = 38$) female population and 24% ($n = 12$) male population. Among the study population of KOA patients, 8 individuals had comorbidities such as hypertension and diabetes mellitus, 11 patients had only hypertension, and 5 patients had diabetes mellitus (Table 2).

Expression of serum miRNA-26a2 in KOA patients

The expression pattern of miRNA26a2 across the study population is shown in Figure 1A. The expression of miRNA26a-2 did not show any variation between all the groups, such as control subjects, grade 1, 2, and 3 KOA patients, with no statistically significant differences observed between any groups, indicating its lesser contribution in the development of KOA.

Expression of serum miRNA-26a5 in KOA patients

The distinct expression pattern of miRNA-26a5 in the different study groups was depicted in Figure 1B. In the current investigation, the miRNA-26a5 expression was high in the control group. There was a stage-dependent decrease in the expression of miRNA26a5 in grade 1 and 2 patients, showing a moderate decrease. In contrast, in the grade 3 patients, there was a sharp decline in the level of expression of miRNA26a5, which indicates a positive protective role in the early

Table 1 Primer sequences used

Name	Sequence 5'→ 3'	Sequence 3'→ 5'
miRNA-26a2-3p SL	ACAAAGCAGCATAGGTCACGCTTATGGAGC CTGGGACGTGACCTATGCTG	GTCGTATCCAGTGCAGGGTCCGAGGTATTC GCACTGGATACGACGAAACA
miRNA-26a-2-3p F	CTTTGTTCATTAGTTCTTATCC	CCTATTCTTGATTACTTGTTTC
miRNA-26a-5p SL	GTCGTATCCAGTGCAGGGTCCGAGGTATTC GCACTGGATACGACAGCCTA	ATCCGACAGCATAGGTCACGCTTATGGAGC CTGGGACGTGACCTATGCTG
miRNA-26a-5p F	TTCAAGTAATCCAGGATAGGCT	TCGGATAGGACCTAATGAACTT
U6 SL	GTCGTATCCAGTGCAGGGTCCGAGGTATTCG CACTGGATACGACAAAAATATG	GTATAAAAACAGCATAGGTCACGCTTATGGA GCCTGGGACGTGACCTATGCTG
U6 F	GCGCGTCGTGAAGCGTTC	CTTGCGAAGTGCTGCGCG
URP	GTGCAGGGTCCGAGGT	TGGAGCCTGGGACGTG
NF-κB F	GAGACATCCTTCCGCAAACT	TCAAACGCCTTCCTACAGAG
NF-κB R	GGTCCTTCCTGCCCATAATC	CTAATACCCGTCCTTCCTGG
COX2 F	ATTGACAGTCCACCAACTTACA	ACATTCAACCACCTGACAGTTA
COX2 R	CAGGAGGAAGGGCTCTAGTAT	TATGATCTCGGGAAGGAGGAC
MMP13 F	GTTTGGTCCGATGTAACTCCTC	CTCCTCAATGTAGCCTGGTTTG
MMP13 R	GAAGTCGCCATGCTCCTTAAT	TAATTCCTCGTACCGCTGAAG
NOS2 F	CTCAGCCTCATTCCTGCTTTA	ATTTCGTCCTTACTCCGACTC
NOS2 R	GACCTGTGCCTTGAGAACTT	TTCAAGAGTTCCGTGTCCAG
Beta Actin F	GGATCAGCAAGCAGGAGTATG	GTATGAGGACGAACGACTAGG
Beta Actin R	AGAAAGGGTGTAACGCAACTAA	AATCAACGCAATGTGGGAAAGA

Table 2 Demographic characteristics of study population

Category	Control group (*n* = 50)	KOA patients (*n* = 50)
Mean age (years)	39.67 ± 7.4	65.3 ± 10.2
Gender distribution	22 males (44%)	12 males (24%)
	28 females (56%)	38 females (76%)
KOA grade (Kellgren-Lawrence)	-	Grade 1 16
		Grade 2 22
		Grade 3 12
Comorbidities	–	Hypertension + diabetes: 8
		Hypertension only: 11
		Diabetes only: 5

KOA: Osteoarthritis of the knee.

disease status.

Target genes influenced by miRNA-26a2 and 26a5

The expression of genes such as *NF-κB*, *MMP13*, *COX2* and *NOS2* is under the control of miRNA-26a2 and 26a5. The downstream products of these genes are responsible for the ECM and cartilage degradation, leading to OA. Being an inflammatory cytokine, NF-κB induces the MMP13, the matrix-degrading proteolytic enzyme, and the COX2, which causes the pain and inflammation observed in the KOA patients. In the present investigation (Figure 2), an increased expression of NF-κB was observed in the Grade 3 KOA patients when compared ($P < 0.01$ and $P < 0.001$) to control persons. This increase coincided with the elevated expression of MMP13 and COX2 in the grade 3 patients, suggesting the row of interrelated molecular events occurring in the OA patients. However, in grade 1 KOA patients, these three gene expressions were not significant when comparable to control persons. In fact, the *MMP13* gene expression was almost

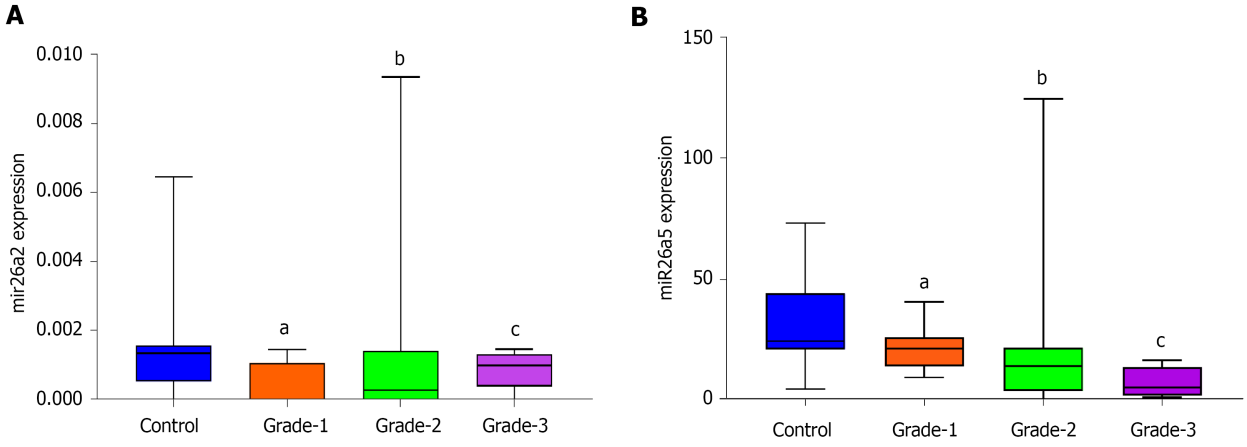


Figure 1 Comparison of serum between study groups. A: Comparison of serum miRNA-26a-2-3p fold change levels between study groups. Control (n = 50); grade 1 (n = 16); grade 2 (n = 22); and grade 3 (n = 12) (t test was insignificant at $P > 0.05$); B: Comparison of serum miRNA-26a5 fold change levels between study groups. Control (n = 50); grade 1 (n = 16); grade 2 (n = 22) and grade 3 (n = 12). t test was significant at $^{a}P \leq 0.05$, $^{b}P < 0.01$ and $^{c}P < 0.001$.

similar between the control and the grade 1 patients, suggesting the less severity of the disease in the early stages. NOS2 is also involved in the inflammation of chondrocytes. In alignment with the COX2, the level of expression NOS2 was also elevated in the grade 3 KOA patients, comparable to control persons ($P < 0.001$), showing the high inflammatory status of the individuals.

Correlation analysis

The coefficients of correlation heat map existing between the miRNA-26a and 26a5 *vs* its target genes *NF-κB*, *COX*, *MMP13* and *NOS* were explained in Figure 3. A strong positive correlation (r = 0.45) is seen between the NF-κB and miRNA-26a2 in grade 2 KOA patients. The exact positive correlation (r = 0.34) is seen for miRNA-26a5 in the case of grade 3 patients.

A moderate positive correlation (r = 0.21) and a strong positive correlation (r = 0.37) were observed between COX and miRNA-26a2 in grade 2 and 3 KOA patients. However, no significant correlation was observed for the same *COX* gene *vs miRNA-26a5*. In the current study, a strong positive correlation exists between the MMP13(r = 0.53) and miRNA-26a2 in the grade 1 KOA patients, as well as a slightly positive (r = 0.19) correlation exists between them in the case of grade 3 KOA patients. A similar type of correlation was seen between the miRNA-26a5 and MMP13, with "r" values of 0.18 and 0.23, respectively, in grade 1 and 3 KOA patients. When we consider NOS expression, a positive correlation (r = 0.24, r = 36) was seen for miRNA-26a2 in grade 2 and 3 patients. The exact positive correlation (r = 0.17, r = 0.27) was observed between NOS and miRNA-26a5 in grade 2 and 3 patients. In some instances, the control individuals had a positive correlation between miRNA and the genes. COX and MMP13, the control patients had a positive correlation with miRNA-26a2 and NOS with miRNA-26a5. This indicates that there is a strong interplay among these inflammatory molecules, which can even affect the miRNA expression patterns responsible for the complicated pathophysiology observed in the progression of KOA.

DISCUSSION

KOA is a progressive type of knee joint degenerative disorder with chronicity, which is considered the leading cause of disability due to pain and discomfort, mainly in the population of elders. The pathophysiology underlying this disease is the synovial inflammation and sclerosis in the subchondral bone, formation of osteophytes, and sequential loss of articular cartilage, including peri-articular tissues[1]. KOA presents with joint stiffness and pain, resulting in limited joint movement and function, with an impact on the quality of life. The factors of obesity, growing life expectancy and inactivity are major contributors to the increased prevalence of KOA around the world, which is a global health challenge [14]. Susceptibility factors (local and systemic) play a role in the deregulation of key signaling pathways and cascades that regulate nociception and chondrocytes. The study is summarised in Figure 4.

While the exact mechanisms of disease development in KOA have yet to be fully understood, joint pain and degeneration associated with the disease are largely attributed to pathological changes in the cartilage. Epigenetic processes have emerged as a potential mechanism for the heritable factors of KOA that are unexplained by genetic factors. These involve stable but reversible regulatory mechanisms such as histone modifications, DNA methylation and miRNA-mediated gene expression, which regulate gene expression but do not change the DNA sequence[15]. Recent years have seen miRNAs gain increasing attention as potential therapeutic targets and diagnostic and prognostic markers. Growing evidence suggests that the expression of miRNAs is significantly altered in OA; such changes are believed to play a critical role in the initiation and progression of OA by regulating inflammatory cascades, ECM degradation and chondrocyte physiology.

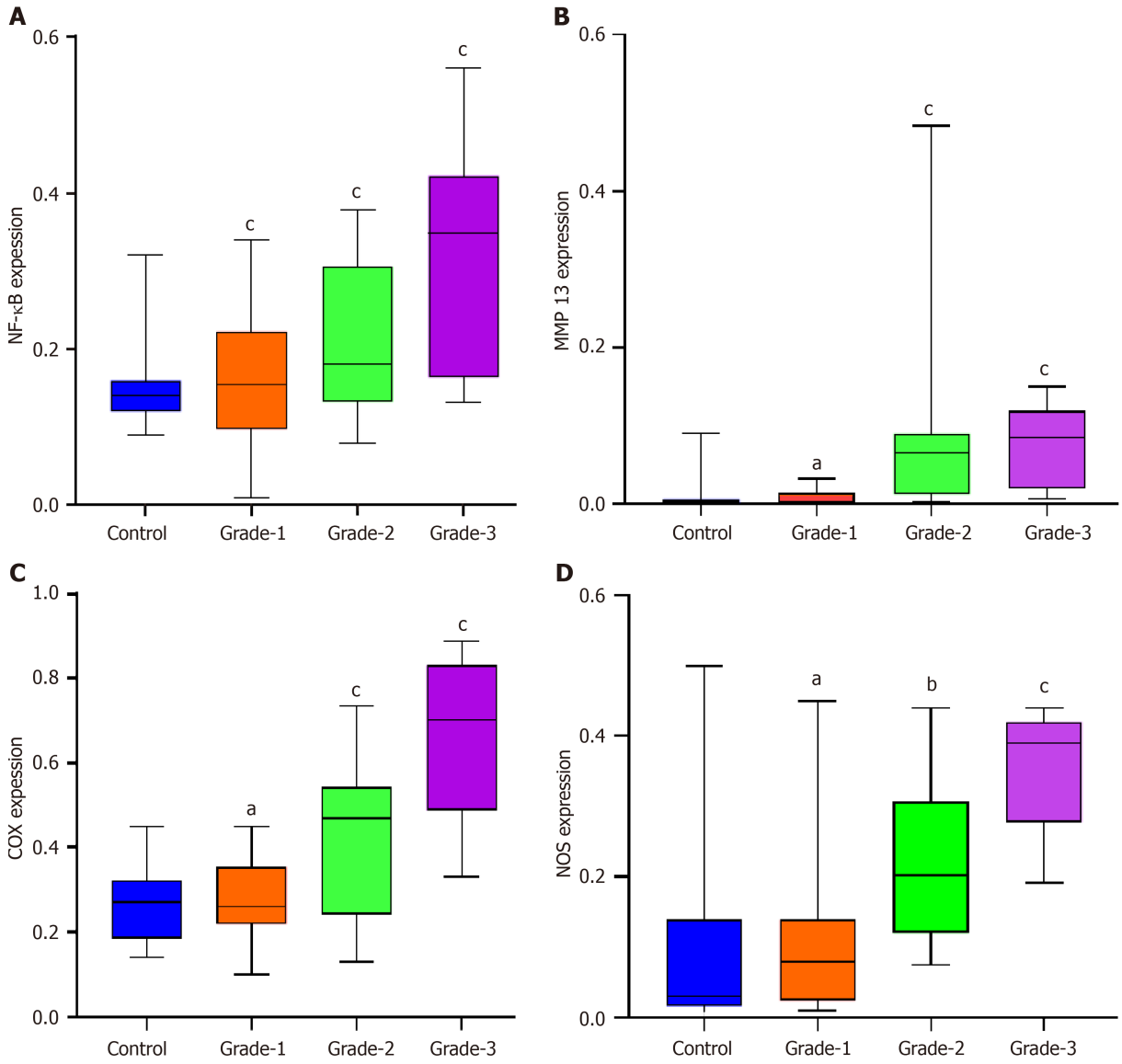


Figure 2 MiRNA-26a2 and 26a5 influencing the osteoarthritis genes in study groups. A: NF-κB expression; B: MMP 13 expression; C: COX expression; D: NOS expression. Control (n = 50); grade 1 (n = 16); grade 2 (n = 22); and grade 3 (n = 12) t test was significant at $^{a}P \leq 0.05$, $^{b}P < 0.01$ and $^{c}P < 0.001$.

Approximately 50% of the human transcriptome is under the control of miRNAs, and the human genome contains more than forty-five thousand miRNA target sites[16]. As a result of their ability to exert control over target genes, miRNAs are recognized as mediators of the effects of the primary risk factors for KOA, which include inflammation and ageing[17]. Yin *et al*[18], have shown the critical role of miRNA-26a5 in the homeostasis of the cartilage cells by controlling the signaling pathways involved in the chondrocytes' survival, inflammatory reactions occurring in them and the metabolism of the matrix of extracellular region in the chondrocytes. The significant role of dysregulated miRNA-26a2/miRNA-26a5 expression was shown in the pathogenesis of OA and in the altered higher levels of inflammatory molecules, cartilage-degrading enzymes and signaling cascades associated with pain[19]. In our current study, though miR-26a2 expression was almost similar in normal and all grades of KOA patients, there was a differential expression of miR-26a5 noted between the control and different grades of KOA patients, suggesting its putative role in protecting the chondrocytes from the degenerative effects of proteolytic enzymes and inflammatory molecules. The genomic loci miRNA-26a-1 and miRNA-26a-2 on chromosome 12 encode for miRNA-26a, which produces the functional strand miRNA-26a5, and so logically miRNA-26a-2 was considered as the precursor gene to produce the matured miRNA-26a5 [20]. So, in our study, although significant variation in the expression of miRNA-26a2 was not observed, its functional isoform miRNA-26a5 could show variation in the expression pattern among the different groups, suggesting their active role in protecting the knee joints from degenerative reactions.

OA holds a complex aetiology where several factors contribute towards its progression and chronicity. The joints are composed of highly specialised structures, namely articular cartilage made up of chondrocytes and the ground substance, namely ECM. The proteoglycan ECM is supportive and shock absorptive in nature and contains the protein component named as collagen type 2 and the carbohydrate component aggrecan[21,22]. Due to the limited nature of cartilage's intrinsic repair mechanisms, the preservation of cartilage well-being is crucial. Moreover, the entire cartilage homeostasis in terms of its structural and functional integrity depends on the synthesis and degradation of ECM, which is under the

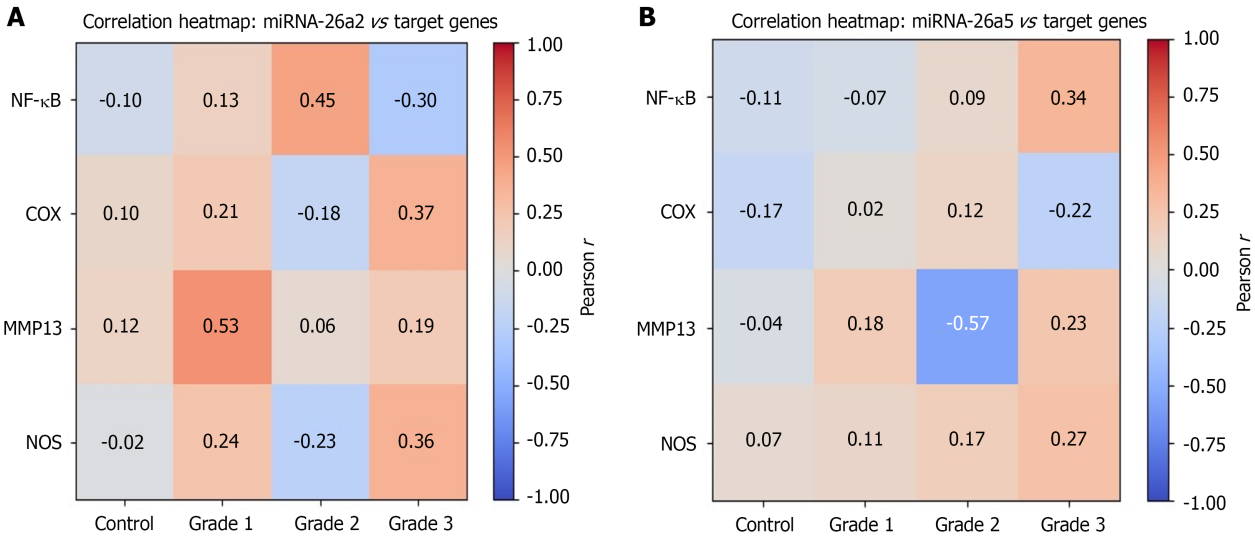


Figure 3 Correlation heat map of 26a2 and 26a5 *vs* target genes. A: 26a2; B: 26a5. Heat map depicting the Pearson correlation coefficients between miRNA-26a2 and 26a5 and their target genes (NF-κB, Cox, MMP13, and NOS) among different grades of osteoarthritis individuals: The scale on the right-hand side indicates the correlation coefficient values. Values closer to ± 1 show stronger correlations, while values near 0 imply a weak or non-linear relationship. Red shades denote positive correlations. Blue shades denote negative correlations.

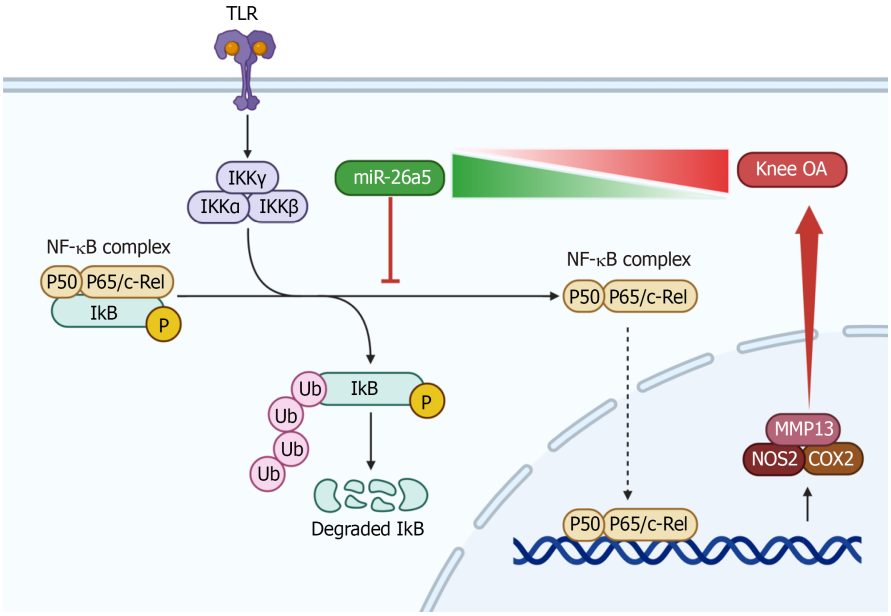


Figure 4 Schematic representation of miR-26a5 in knee osteoarthritis. OA: Osteoarthritis.

control of chondrocytes. When the balance between the catabolism of chondrocytes and their anabolism is disturbed, with the chondrocyte catabolism overtaking the anabolism, the integrity of the matrix substance in the chondrocytes is damaged[23]. These catabolic reactions taking place in the chondrocytes are triggered by the proinflammatory cytokines such as IL-6, TNF-α, and IL-1β, leading to their damage not only through autocrine and paracrine reactions but also triggering the NF-κB pathway[24].

Followed by the activation of NF-κB pathway directly or indirectly the activation of matrix degrading enzymes as well as other OA causing factors are triggered leading to the execution of cartilage catabolic reactions. The molecular events that follows due to the activation of NF-κB is it triggers the NF-κB elements present in the promoter regions of *MMP13* gene as well as promoting the key proinflammatory molecules such as *COX2*, and *iNOS2*[25]. The sustained inflammatory stimuli and pain perception in OA patients is maintained by the NF-κB-mediated upregulation of COX2[26]. Elevated COX-2 expression in chondrocytes and synoviocytes leads to increased PGE_2 production, which not only amplifies local inflammation but also promotes matrix degradation by enhancing the expression of matrix-degrading enzymes, including MMP-13, and by suppressing ECM synthesis. Importantly, COX-2-derived prostaglandins can further activate NF-κB signaling in a positive feedback loop, thereby perpetuating chronic inflammation and cartilage destruction [27].

Elevated iNOS2 expression results in sustained production of NO, a reactive nitrogen species that contributes to cartilage degeneration in OA. Excessive NO suppresses ECM synthesis by inhibiting collagen type II and aggrecan production, while simultaneously promoting chondrocyte apoptosis and enhancing the expression of matrix-degrading enzymes such as MMP-13[28]. Importantly, NO can further potentiate inflammatory signaling by enhancing NF-κB activation through redox-dependent mechanisms, thereby establishing a self-amplifying NF-κB-iNOS2-NO feedback loop that sustains chronic inflammation and accelerates joint tissue destruction.

The continuous activation of NF-κB signaling represses the miR-26a2 and miR-26a5 expression leading to the activation of the transcription factors responsible for the chain of degenerative events leading to the progression of the KOA condition. Increased levels of NO due to the overexpression of NO synthase enzyme and elevated levels of prostaglandin synthesis due to the higher cyclooxygenase enzyme levels, both are essential downstream products of NF-κB signaling, mediate and amplify the immunological events significantly, by the enhanced production of the matrix-degrading collagenase type of enzyme, the MMP13 leading to the loss of the ECM and cartilage damage through apoptosis.

CONCLUSION

The involvement of miR-26a2 and miRNA-26a5 in KOA highlights their significance in regulating inflammation and cartilage destruction. Acting endogenously at the transcriptional level, these miRNAs suppress the NF-κB-iNOS/COX-2-MMP-13 axis, thereby maintaining homeostasis in healthy individuals. In KOA patients, altered expression disrupts this posttranscriptional control, resulting in sustained inflammation that accelerates chondrocyte degradation and progression of OA. Furthermore, the inverse relationship between miR-146a and key inflammatory as well as matrix-degrading molecules highlights its potential utility as both a biomarker and therapeutic target. Although limitations such as small sample size and short study duration exist, these findings provide valuable insights into the molecular mechanisms driving KOA and emphasise the therapeutic promise of miR-26a2 and miRNA-26a5 in preserving cartilage integrity.

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FOOTNOTES

Specialty type: Orthopedics

Country of origin: India

Author contributions: Gunamala V, Hari R, and Jeyaraman N contributed to conceptualization, acquiring clinical data and performing the data analysis; Nallakumarasamy A and Muthu S contributed to manuscript writing; Muthu S and Jeyaraman M helped in manuscript revision; Muthu S contributed to image acquisition; Jeyaraman M contributed to proofreading; Jeyaraman M contributed to administration; and all authors have agreed to the final version to be published and agree to be accountable for all aspects of the work.

AI contribution statement: No artificial intelligence tools were used to write the manuscript. Grammary is a built-in software in our system used to correct grammar errors.

Institutional review board statement: This study was reviewed and approved by the Ethics Committee of Lalithambigai Medical College and Hospital, No. ERI/SLMCH/2023/003.

Informed consent statement: Ethical approval for the study protocol was obtained from the Institutional Ethics Committee, and written informed consent was secured from all participants prior to enrollment.

Conflict-of-interest statement: All authors declare no conflict of interest in publishing the manuscript.

Data sharing statement: All data is contained within the manuscript.

STROBE statement: The authors have read the STROBE Statement-checklist of items, and the manuscript was prepared and revised according to the STROBE Statement-checklist of items.

S-Editor: Qu XL
L-Editor: A
P-Editor: Liu JH

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