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Investigating the Role of Circular RNAs Circ_0003972 and Circ-PTPN22 in Regulating Cytokine Expression in Postmenopausal Women with Osteoarthritis

Dargham Bayan Mohsen Hammad, Fadyia Mahdi Muslim Al-Ameedy

Department of Pathological Analysis, College of Science, University of Kufa, Najaf, Iraq

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ABSTRACT

Background & Objective: Osteoarthritis (OA) is a common chronic inflammatory condition that gradually damages joints, leading to cartilage and joint tissue degeneration. It is associated with ongoing inflammation and an impaired immune system. Circular RNAs (circRNAs) and cytokines play key roles in regulating inflammation and joint tissue homeostasis in osteoarthritis. This study aims to assess the expression of circular RNAs (circular RNA-0003972 and circular RNA-PTPN22) and cytokines (IL-33, IL-36, IL-38, IL-40) in postmenopausal women with osteoarthritis compared with healthy controls, as potential new biomarkers for osteoarthritis.

Methods: This study has a case-control design. Blood samples from 150 postmenopausal women (75 with newly diagnosed osteoarthritis and 75 healthy control subjects) were analyzed. Circular RNA 0003972, circular RNA-PTPN22, IL-33, IL-36, IL-38, and IL-40 were detected in peripheral blood from both groups using quantitative reverse transcription polymerase chain reaction (RT-qPCR), followed by bioinformatic analysis.

Results: The levels of circular RNA 0003972 ($p < 0.0001$), circular RNA-PTPN22 ($p < 0.001$), and IL-40 ($p < 0.0001$) were significantly higher in the osteoarthritis group, while IL-38 was produced at lower levels in this group ($p < 0.0001$). Further, there was no significant difference in the expression of IL-33 and IL-36 between the cohorts. Of particular interest was the positive association between circular RNA-PTPN22 and IL-40 ($r = 0.4$, $p < 0.001$), suggesting a potential role in modulating the immune response.

Conclusion: Our investigation found that patients with osteoarthritis had altered expression of specific circRNAs and cytokines (circular RNA 0003972, circular RNA-PTPN22, IL-38, and IL-40), which may serve as potential biomarkers and therapeutic targets, particularly in postmenopausal women. However, longitudinal investigations are required to determine whether these molecules can serve as effective biomarkers for diagnosis, prediction, and therapy monitoring.

Corresponding Information: **Dargham Bayan Mohsen Hammad**, Department of Pathological Analysis, College of Science, University of Kufa, Najaf, Iraq Kufa university. Najaf, 50041, IRAQ. E-mail: dhigham.mohsin@uokufa.edu.iq

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Introduction

Osteoarthritis (OA) is a common chronic inflammatory condition that gradually damages joints, leading to cartilage and joint tissue degeneration. Clinical signs include joint pain, stiffness, swelling, and reduced joint mobility. More than 240 million cases of OA have been recorded, and the rate of incidence is expected to increase with aging, obesity, or repetitive joint use, leading to the erosion of cartilage and changes in the joint environment (1–3). Advancements in molecular biology have provided evidence of the critical role of circular RNAs (circRNAs) in gene expression regulation and their involvement in disease. CircRNAs can act as molecular sponges for microRNAs, regulate transcription, and influence protein translation, making them vital regulators in several disorders, including OA (4).

Circular RNA 0003972 (circ0003972) has been identified as potentially involved in OA inflammation. Investigations suggest that it may facilitate the expression of pro-inflammatory cytokines and exhibit a significant response to inflammatory stimuli. This indicates that circ0003972 may contribute to OA pathogenesis by modulating inflammatory responses in joint tissues (5-7).

Circular RNA-PTPN22 (circ-PTPN22) is derived from the PTPN22 gene, which encodes a protein involved in immune regulation. PTPN22 inhibits T-cell

receptor signaling, and mutations in this gene have been associated with autoimmune diseases. The circular form, circ-PTPN22, may modulate cytokine expression and immune cell activity, making it relevant in the inflammatory context of OA (8,9).

Several members of the interleukin (IL) family, particularly IL-33, IL-36, IL-38, and IL-40, play significant roles. IL-33 is released by stressed or injured joint cells (e.g., chondrocytes and synovial cells). It acts as an "alarm," activating other immune cells, such as T-helper cells and mast cells, thereby intensifying the inflammatory response (10). Moreover, IL-36, including IL-36α, IL-36β, and IL-36γ, activates its receptor (IL-36R), leading to the production of pro-inflammatory cytokines and recruitment of immune cells. It is associated with severe OA symptoms and cartilage degradation (11,12). IL-38 may help regulate the immune response and influence the severity and duration of inflammation (13). Lastly, IL-40 has recently been identified as a potential modulator of immune responses in OA. Although less studied, it appears to affect T-cell function and cytokine production, maintaining chronic inflammation (14-15).

When acting together, these cytokines create a complex inflammatory network that drives OA progression. Their elevated levels in synovial fluid and joint tissues of patients with OA highlight their role in disease maintenance and joint degradation.

This study evaluates circ0003972, circ-PTPN22, and the cytokines IL-33, IL-36, IL-38, and IL-40 as potential biomarkers for OA diagnosis and treatment. Their expression profiles could serve as indicators of disease severity and response to therapy, offering a step toward personalized medicine for patients with OA.

Materials and Methods

Study Participants

The study design is a case–control study; blood specimens were collected from 75 newly diagnosed patients with symptomatic knee osteoarthritis, defined by the American College of Rheumatology (ACR) criteria, aged ≥50 years, following the 2019 ACR/Arthritis Foundation Guideline (16). Inclusion criteria were adults ≥50 years with a new clinical and radiographic diagnosis (Kellgren–Lawrence grade II–IV) who provided written informed consent. Exclusion criteria included other inflammatory arthropathies, prior knee arthroplasty, intra-articular corticosteroid or hyaluronic acid injections within six months, and major systemic comorbidities (uncontrolled diabetes, chronic renal impairment, or active malignancy). Participants unable or unwilling to consent were also excluded. The study protocol was approved by the Ethics Committee of Kufa University (KU/239502).

Participants were matched for age and sex, body mass index (BMI), and major comorbidities. This approach helps control for health-related confounding factors, create more homogeneous groups, minimize bias, and ensure therapeutic relevance, particularly in studies of joint inflammatory diseases.

Sample collection occurred from January 3 to June 30, 2025. Moreover, blood samples were accurately labeled and stored at −80 °C in the laboratory until analysis, which included checking for circ0003972, circ-PTPN22, IL-33, IL-36, IL-38, and IL-40 using reverse transcription–quantitative polymerase chain reaction (RT-qPCR).

Analyzing Human Sample Participants

Diagnosis of human subjects involved performing qPCR using primers listed in Table 1, which were obtained from NCBI, designed by us, and optimized according to the protocol. This technique aimed to amplify human RNA genes to detect IL-33, IL-36, IL-38, IL-40, circ0003972, and circ-PTPN22 using the RNA kit (Cat. No. E2075, EcoPURE, Turkiye). The PCR mixture was prepared to a final volume of 20 µL, comprising nuclease-free H2O (1 µL), 2× Add RT-PCR SYBR Master Mix (10 µL), forward primer (10 µM, 2 µL), reverse primer (10 µM, 2 µL), and RNA template (5 µL). cDNA synthesis was conducted using RT-PCR SYBR Master cDNA (Cat. No. K1691, Thermo Scientific, Waltham, MA, USA).

The PCR conditions included pre-denaturation at 95 °C for 2 minutes (one cycle), denaturation at 95 °C for 30 seconds, annealing at 57.2 °C for 30 seconds, extension at 72 °C for 50 seconds (for 40 cycles), final extension at 72 °C for 5 minutes (one cycle), and holding at 4 °C. (17). All samples from patients with OA and the control group yielded consistent and dependable Ct values for circular RNAs, cytokines, and GAPDH. During the examination, no duplicates with a concentration of 40 cycles were observed (Fig. 1).

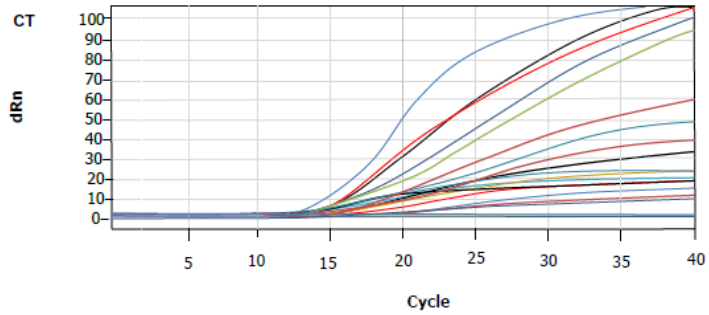

Fig. 1. RT-qPCR for the identification of Circ-PTPN22, Circ_0003972, and GAPDH in cohorts

Table 1. Primer sequences used for quantitative reverse transcription polymerase chain reaction (RT-qPCR) analysis of IL-33, IL-36, IL-38, IL-40, circ0003972, circPTPN22, and GAPDH. Forward (F) and reverse (R) primer sequences, expected product sizes (bp), and corresponding Gene IDs are presented.

type	Gene name sequences	Size products	Gene ID
IL33	F5′-GCCTGTCAACAGCAGTCTACTG-3′ R5′-TGTGCTTAGAGAAGCAAGATACTC-3′	150bp	90865
IL-36	F5′-TGGGACTTTGCAGGAAGGAG-3′ R5′-CCTTCAGGGAAGCAGCAGAA-3′	110bp	56300
IL38	F5′-AGGCTGGAAGAGGAGGAAGA-3′ R5′-TGGTGGTGATGGTGGAAGAG-3′	120bp	84639
IL40	F5′-CAAAGGAGCCTGAGGAGAGA-3′ R5′-GGTGGTCTGTCTGGTGGTTC-3′	130bp	100141515
circ0003972	F5'-AGGCTTCTCGTCTCGTCTCA-3' R5'-TCCACAGGAGAGTGCAGAGT-3	120bp	23196
circPTPN22	F5'-CTGGTGAGGTTGGAAGAGGA-3' R5'-TCTGGCTCTGAGTCCACTGA-3'	130bp	26191
GAPDH-F **GAPDH-R**	F5'-ACGACCACTTTGTCAAGCTC-3' R5'-ACGACCACTTTGTCAAGCTC-3'	138bp	2597

Primer specificity was confirmed by melt-curve analysis, which demonstrated a single sharp peak for each primer pair, indicating specific amplification without primer-dimer formation.

Equations for ΔCt Analysis of RT-qPCR Outcomes

To analyze the results of RT-qPCR, the threshold cycle (Ct) value was determined using the following formulas:

The formula is ΔCt value (control) (ΔCtC) =

average Ct value of the test gene in the control group minus the average Ct value of the housekeeping gene in the control group.

The experimental Ct value (ΔCtE) is equal to the average Ct value of the experimental group (test gene) minus the average Ct value of the experimental group (housekeeping gene).

ΔCtE − ΔCtC = delta-delta Ct value (ΔΔCt).

The relative expression of the target genes was determined by comparing gene expression levels between the control and experimental groups using these equations.

Analytical Statistics

The Shapiro–Wilk test was used to evaluate the normality of the data distribution. The assessments showed that the Ct values in the cohort distributions were not normally distributed; therefore, all groups were analyzed using the Mann–Whitney U test to determine significant differences between subjects. 95% confidence intervals were also estimated to provide a more comprehensive evaluation of group differences. The interquartile range and median were used to display data from both groups.

Furthermore, Spearman's test was used to assess the correlation between circRNA expression and cytokine gene expression. All graphs were produced using GraphPad Prism 10.

Results

Demographic characteristics of participants with osteoarthritis and matched healthy controls. Whole-blood samples were obtained from 150 participants between 55 and 72 years of age. The osteoarthritis (OA) group (n = 75) presented a mean age of 63.5 years (SD = 5.0), whereas the control group (n = 75) had a mean age of 63.0 years (SD = 4.7) (Table 2).

Moreover, the study included body mass index (BMI) and major comorbidities for all participants. The two groups exhibited comparable BMI and comorbidity profiles, thereby minimizing potential confounding effects on the study outcomes.

Comparison of BMI and comorbidity profiles revealed no statistically significant differences between osteoarthritis (OA) patients and controls (all $p > 0.05$). These findings indicate that the groups were well matched, thereby reducing the likelihood of confounding bias (Table 2).

Table 2. Demographic characteristics of study participants

Variable	OA Patients (n = 75)	Controls (n = 75)	*P* value
Age (years), mean ± SD	63.5 ± 5.0	63.0 ± 4.7	(P > 0.05)
Sex (F/M)	75 /0	75 / 0	(P > 0.05)
BMI (kg/m²), mean ± SD	26.6 ± 2.4	25.4 ± 3.2	(P > 0.05)
BMI category, n (%)			
• Normal weight (18.5–24.9)	23 (30.6%)	27 (36.0%)	(P > 0.05)
• Overweight (25–29.9)	40 (53.3%)	35 (46.6%)	(P > 0.05)
• Obese (≥30)	12 (16.0%)	13 (1.0%)	(P > 0.05)
Hypertension, n (%)	18 (24.0%)	15 (20%)	(P > 0.05)
Type 2 diabetes mellitus, n (%)	13 (17.3%)	12 (16%)	(P > 0.05)
Cardiovascular disease, n (%)	5 (6.6%)	3 (4%)	(P > 0.05)
Current smokers, n (%)	13 (17.3%)	12 (22.6%)	(P > 0.05)

Data are presented as mean ± SD or number (%). Groups were matched for age and sex, Body mass index and major comorbidities to reduce potential confounding effects.

Expression Level of Circ-PTPN22 and Circ_0003972 in the Blood

RT-qPCR was used to estimate the expression levels of Circ-PTPN22 and Circ_0003972 in blood samples obtained from OA patients and healthy control subjects. GAPDH, which operates as a control for circRNA qPCR, was compared at these levels. All samples from OA patients and the control group yielded consistent and dependable Ct values for Circ-PTPN22, Circ_0003972, and GAPDH. During the examination, no duplicates with a Ct value higher than 40 were observed.

Patients with OA had significantly higher levels of PTPN22 ($p < 0.001$) and Circ-0003972 ($p < 0.0001$) than healthy controls, as determined by our analysis. The median fold change in Circ-PTPN22 was 1.65 in OA patients and 1 in healthy participants, whereas the median fold change in Circ_0003972 was 1.9 in OA patients and 0.82 in healthy individuals (Fig. 2).

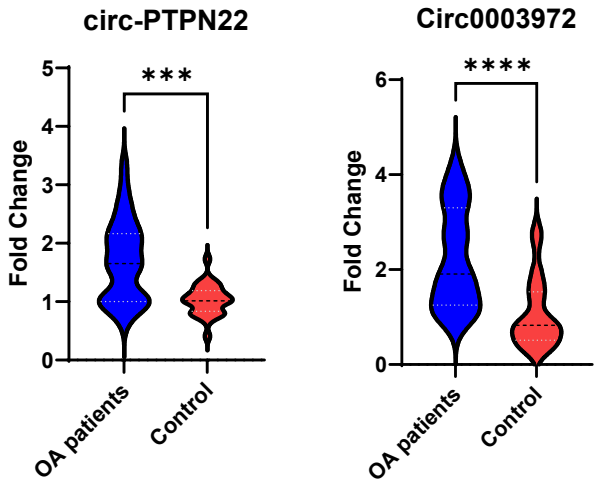

Fig. 2. Level of expression of Circ-PTPN22 and Circ_0003972 in blood.

Levels of expression of blood Circ-PTPN22 and Circ_0003972 were detected in 75 Expression levels of blood Circ-PTPN22 and Circ_0003972 were detected in 75 patients with OA and 75 healthy control participants. Blood samples were used to extract total RNA, which was then reverse-transcribed into complementary DNA (cDNA) using primers specific to circular RNA. Using reverse transcription–quantitative polymerase chain reaction, the expression levels of blood circ-PTPN22, circ_0003972, and GAPDH were measured. The results were displayed as fold change. Data are shown as box-and-whisker plots, with the upper and lower borders reflecting the 25th and 75th percentiles (upper and lower quartiles). The middle horizontal line represents the median, while the upper and lower whiskers display the maximum and

minimum values of non-outliers. The blue violin plot in the graphical representation shows patients with OA, whereas the red one represents the healthy control subjects. The Mann–Whitney nonparametric test was used to evaluate statistical significance between groups, with ***p < 0.01 and ****p < 0.0001.

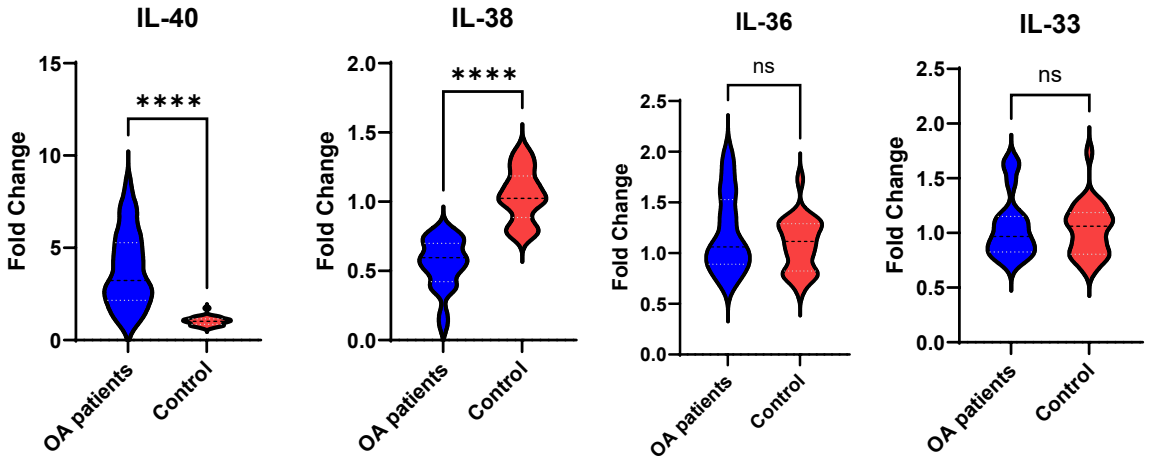

Fig. 3. Level of expression of IL-40,IL-38,IL-36 and IL-33 in blood.

Cytokine Expression Levels in Osteoarthritis

Compared with healthy controls, OA patients showed a significantly higher median fold change in IL-40 expression (3.22 vs 0.56; p < 0.0001). In contrast, patients with OA showed a substantially lower fold change in IL-38 expression compared with healthy controls (median fold change, 0.6 vs 1; p < 0.0001) (Fig. 3). Moreover, IL-33 and IL-36 levels were not significantly different between OA patients and healthy participants.

Seventy-five patients with OA and seventy-five healthy individuals were found to have a fold change in the gene expression of four cytokines (IL-40, IL-38, IL-36, and IL-33). Violin plots graphically represent the expression of each cytokine. For both groups, the data were displayed as medians with interquartile ranges. Further, "ns" denoted no significant difference, and ****p < 0.0001 indicated statistically significant differences.

CircRNAs and Cytokine Levels Correlation in OA Disease Patients

Our analysis examined the correlation between experimentally measured cytokine levels in OA patients and the blood levels of Circ-PTPN22 and Circ_0003972. Circ-PTPN22 and IL-40 levels exhibited a statistically significant positive correlation (r = 0.4, p < 0.001), as determined via the Spearman correlation test (Fig. 4).

Blood levels of IL-40 and Circ-PTPN22 were compared in patients with osteoarthritic disease. A scatter plot curve revealed a strong positive correlation between IL-40 and Circ-PTPN22 (r = 0.4, P < 0.001). The Spearman correlation test was used for statistical analysis, and a 95% confidence level (P < 0.05) was set as the threshold for statistical significance. P < 0.05 displayed significant data.

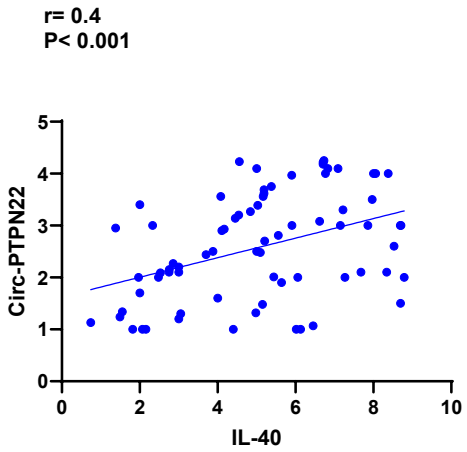

Fig. 4. The correlation between Circ-PTPN22 and IL-40

Discussion

These results reveal a new molecular interaction underlying osteoarthritis, based on distinct changes in circRNAs and interleukins that shape inflammation and immunity in the disease. Changes in the expression levels of circ-PTPN22 and circ_0003972 in blood may indicate a control mechanism that regulates immune cells and inflammation in osteoarthritis synovial tissue.

The considerable elevation in circ_0003972 expression observed in OA patients indicates that it may be an immediate regulator of inflammatory signaling pathways. The most plausible mechanism at play here is that circ_0003972 acts as a competing endogenous RNA, thereby sequestering microRNAs such as miR-326 or miR-149-5p, which repress the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway (18). As a molecular sponge, circ_0003972 may take away the inhibitory function of these microRNAs, thus leading to the activation of NF-κB (18). This transcriptional activation cascade could increase the release of proinflammatory mediators, such as IL-33, IL-36, and matrix metalloproteinases (MMPs), leading to cartilage destruction and synovial inflammation (18). Furthermore, the enhanced stability and abundance of circRNAs increase the potency of circ_0003972 as a key player and potential biomarker for early OA detection in this location (18, 19).

In OA patients, circ-PTPN22 also appears to impact immune cell activity, as suggested by its elevated levels. circ-PTPN22 stems from the PTPN22 gene, which encodes lymphoid-specific tyrosine phosphatase (LYP), a potent negative regulator of T-cell receptor signaling (20-23). With circ-PTPN22 overexpression, there is the possibility of enhanced transcription or stability of the precursor mRNA, leading to increased LYP activity (20-23). A lowered T-cell activation threshold would facilitate the proliferation of autoreactive or proinflammatory T-cell subsets, such as Th1 and Th17 (20-23). Such an immune imbalance may foster persistent low-grade inflammation, which is often chronic in joints (20). Evidence supports the rationale for OA not only being viewed as a result of aging and mechanical damage, but rather as “wear and tear” intertwined with immune system disturbances, in part driven by circular RNAs.

Among the cytokines analyzed, IL-40 was found to be most considerably overexpressed in OA patients (14). IL-40 is a recently discovered cytokine expressed only on activated B and T lymphocytes and is associated with the regulation of adaptive immune responses (23). Its increased presence may result from increased T-cell activity or continuous antigenic stimulation in the joints of OA (14). IL-40 can even act as a trigger of local inflammation by increasing B-cell survival and initiating the production of other cytokines, thereby creating a self-reinforcing inflammatory loop (14).

The positive correlation between circ-PTPN22 and IL-40 expression observed is indicative of a possible mechanistic association. circ-PTPN22 may indirectly enhance IL-40 expression by competing with miRNAs that drive IL-40 downregulation, thereby neutralizing their suppressive effect on IL-40 (24). Furthermore, circ-PTPN22 can modulate the function of its host gene, PTPN22, which is involved in T-cell receptor signaling; thereby, it can increase T-cell activation and, consequently, cytokine release, including IL-40 (25-27). Additionally, the circular RNA circ-PTPN22 can interact with proteins with RNA-binding activity to facilitate the processing of IL-40 mRNA (28, 29). This, in turn, leads to more prolonged periods of expression. In concert, these pathways reveal circ-PTPN22 as a potential intervention target that can potentiate immune effectors and perpetuate OA pathophysiology. Although this correlation may reflect possible causal mechanisms, the current study is observational, and causal relationships cannot be established. Future functional studies are needed to explore whether circular RNA-PTPN22 directly influences IL-40 expression or other immune pathways, which may contribute to osteoarthritis pathophysiology.

Reduced IL-38 expression in osteoarthritis (OA) patients suggests an issue in resolving inflammation (30). IL-38 has immunomodulatory effects, including the suppression of inflammatory mediators by regulating dendritic cell and macrophage function. Lower IL-38 may hinder macrophage polarization toward an anti-inflammatory state, sustaining inflammation (31). Additionally, IL-38 regulates Th17 cell differentiation, which is pertinent to chronic joint issues (32). Thus, IL-38 is a key factor in maintaining immune balance, and its deficiency may cause persistent inflammation and joint damage in OA.

This molecular insight sheds light on the complexity of OA as an inflammatory joint disease and provides new evidence of the involvement of circular RNAs in immune responses. Given their stability, detectability, and efficacy, circ_0003972 and circ-PTPN22 represent compelling candidates for noninvasive biomarkers. At the same time, cytokines such as IL-40 and IL-38 could be manipulated to alter the inflammatory microenvironment in OA.

This study has limitations due to the absence of disease severity evaluation, female-only inclusion, and its small sample size. Peripheral blood does not fully represent joint tissue activity. More extensive, diversified, and long-term investigations are needed.

Conclusion

Our study demonstrates the vital role of circular RNAs in OA pathogenesis, highlighting their interactions with cytokines. High expression of circ_0003972 and circ-PTPN22 may regulate both inflammatory and immune responses by binding to miRNAs and modulating cytokine expression, including IL-40 and IL-38. These results suggest that circRNAs may be new potential noninvasive biomarkers and treatment targets for OA. These will

need to be validated in joint tissues and larger patient cohorts.

Acknowledgments

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Authors' Contributors

DH; conceptualization, methodology, software, validation, formal analysis, investigation, resources, data curation, writing – original draft, writing – review and editing, visualization, project administration, and funding acquisition. FA; methodology, software, validation, formal analysis, investigation, resources, writing – original draft, writing – review and editing, supervision, and funding acquisition. All authors read and approved the final manuscript.

Data Availability

The data supporting the results of this study are available upon request from the corresponding author.

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This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Ethics Approval

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki. The study protocol was reviewed and approved by the Ethics Committee of Kufa University, Najaf, Iraq (approval number: KU/239502). The manuscript already states that the study included human blood samples from postmenopausal women with osteoarthritis and healthy controls, and that ethical approval was obtained from Kufa University.

Consent to Participate:

Written informed consent was obtained from all participants before enrollment in the study and before blood sample collection. Participants who were unable or unwilling to provide consent were excluded from the study. This is consistent with the Methods section, which states that eligible participants provided written informed consent and that inability or unwillingness to consent was an exclusion criterion.

Conflict of Interest

The authors declared no conflict of interest.

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