International Journal of Drug Research in Clinics

Int J Drug Res Clin. 2025;3:e15
10.34172/ijdrc.2025.e15
http://ijdrug.com

Original Article

Circulating MicroRNAs as Novel Diagnostic Biomarkers for Osteoporosis in Patients with Intertrochanteric Fractures

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Article History:
Received: September 14, 2025
Revised: September 30, 2025
Accepted: October 20, 2025
ePublished: October 30, 2025

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Abstract

Background: Osteoporosis (OP) represents a major global health problem, particularly when complicated by fragility fractures. Current diagnostic methods primarily rely on bone mineral density (BMD) measurements, which may not accurately capture early disease progression. This study investigated the diagnostic potential of circulating microRNAs (miRNAs) as non-invasive diagnostic biomarkers for osteoporosis in patients with intertrochanteric fractures.

Methods: A total of 50 osteoporotic patients with intertrochanteric fractures and 50 non-osteoporotic patients as a control group were recruited to detect circulating levels of 9 miRNAs as potential diagnostic biomarkers in osteoporotic patients. Quantitative real-time PCR (qRT-PCR) was used to evaluate mRNA expression levels. Statistical analysis included appropriate corrections for multiple comparisons and correlation analysis with clinical parameters.

Results: Findings demonstrated that miR-148a-3p, miR-144, miR-135b-5p, miR-124-3p, miR-125b-5p, miR-100-5p, miR-96, miR-122-5p, and miR-21-5p were significantly overexpressed in osteoporotic patients with intertrochanteric fractures compared to the control group ($P<0.0056$ after Bonferroni correction). Several miRNAs showed significant negative correlations with T-scores, indicating association with the severity of the disease.

Conclusion: Our findings identified a panel of 9 circulating miRNAs that may serve as novel diagnostic biomarkers for osteoporosis in patients with intertrochanteric fractures. These results offer new insights into miRNA-based diagnostics and support the development of non-invasive screening approaches for early detection of osteoporosis. However, validation in independent cohorts is required before clinical implementation.

Keywords: MicroRNAs, Diagnostic biomarkers, Osteoporosis, Intertrochanteric fracture

Please cite this article as follows: Asanjani Oskoii M, Yousefi B, Valizadeh A, Sadeghpour A. Circulating MicroRNAs as novel diagnostic biomarkers for osteoporosis in patients with intertrochanteric fractures. Int J Drug Res Clin. 2025;3:e15. doi: 10.34172/ijdrc.2025.e15

Introduction

Aging is a risk factor for degenerative diseases. Osteoporosis (OP) is the most prevalent age-associated bone disorder, affecting over 20 million people worldwide.[1] It is a systemic skeletal illness that causes a loss of bone mass and degeneration of bone structure and microarchitecture, increasing the risk of fractures.[2] Various treatment modalities have shown efficacy in the management of osteoporosis, including teriparatide for severe cases of secondary osteoporosis.[3] Intertrochanteric fracture, a relatively prevalent extracapsular fracture of the proximal femur during OP, causes considerable pain and severe disability, reducing the quality of life.[4,5] OP is known as a "silent epidemic of the twenty-first century" because patients frequently have no symptoms before the fracture.[6]

According to the World Health Organization (WHO), diagnostic criteria recognized the significance of low bone mineral density (BMD) in the pathophysiology of fragility fractures. They established a technique that could be used in epidemiological research to assess the prevalence of OP.[7] Indeed, as BMD decreases, the risk of fragility fractures increases.[8] Based on previous studies, BMD is typically considered the gold standard technique, as determined by dual-energy x-ray absorptiometry (DXA), which is strongly associated with the risk of fracture.[9] On the other hand, DXA-based diagnoses do not reflect the factors such as cortical porosity, bone microarchitecture,

or tissue and cellular level constituents.[10] Therefore, developing faster and more precise diagnostic methods to complement existing imaging techniques for OP diagnosis is an ongoing and worthy endeavor. Various treatment modalities have shown efficacy in the management of osteoporosis, including teriparatide for severe cases of secondary osteoporosis

Emerging evidence suggests that dysregulated microRNAs (miRs) are more sensitive biomarkers that have emerged as key post-transcriptional modulators of bone expansion and homeostasis.[10] miRNAs influence mRNA stability and protein synthesis, a large class of non-coding single-stranded RNAs (21-23 nt) that bind imperfectly to the 3′UTR (3′ untranslated regions) of target genes, in which this situation occurs post-transcriptionally.[11] The expression and function of miRNAs are specific to cell and tissue types and are associated with different stresses or disorder settings. While the seed region (2–7 nt of the miRNA) of miRNAs and the targeted mRNA sequences have perfect base pairing, their imperfect complementary binding allows them to target specific mRNAs. [12,13] It has been demonstrated that miRNAs can play a crucial role in the function, differentiation, and development, and thus serve as biomarkers for diagnosis. Owing to non-invasive and easy sampling, circulating miRNAs have great potential to serve as biomarkers for OP.[14] Currently, multiple miRNAs have been identified to be overexpressed in the plasma and serum of OP patients.[15]

This study specifically focuses on the diagnostic potential of circulating miRNAs as biomarkers for the early detection of osteoporosis. The current study concentrated on identifying prospective diagnostic biomarkers from unique miRNA signatures, which could lead to new targets for enhancing intertrochanteric fracture healing in OP patients.

We applied the miRNA-based diagnostic approach to diagnose osteoporosis in patients with intertrochanteric fractures. Some miRNAs have been reported to be up-regulated in the serum of OP patients.

Materials and Methods

Serum Collection and Ethical Approval

Serum samples were collected from 50 healthy controls and 50 patients diagnosed with OP. All patients were recruited from Shohada Hospital, a specialist referral center for bone diseases, Tabriz University of Medical Sciences, from April 2019 to January 2020. In accordance with the Declaration of Helsinki, all subjects provided written informed consent, and the Ethics Committee approved all protocols and procedures of Tabriz University of Medical Sciences (IR.TBZMED.REC.1398.086). Individuals' age and body mass index (BMI) ranged between 65-80 years and 20-27 kg/m^2, respectively.

Exclusion Criteria

Patients with type 1 and 2 diabetes, malignant illnesses like cancer, chronic kidney and liver failure, inflammatory disease, and a recent history of supplement and anti-inflammatory drug use were excluded. Additionally, patients who had received anti-osteoporotic medications within 6 months before sampling were excluded.

qRT-PCR

Trizol (TRIzol® Reagent, Invitrogen) was used to extract total miRNAs from serum following the manufacturer's instructions. A NanoDrop spectrophotometer (Thermo-Fisher, Washington, USA) was used to assess the concentration and purity of extracted RNAs. A cDNA synthesis kit was used to synthesize complementary DNA (cDNA; Thermo-Fisher Scientific, USA). SYBR Green PCR Master Mix (ABI, USA) was used to quantify cDNA using an iCycler iQ multicolor real-time PCR detection system (Bio-Rad, USA). The conditions for the PCR amplification were set as follows: 10 minutes of primary denaturation (also known as a "hot start") at 95 °C for 10 minutes, 45 cycles at 94 °C for 45 seconds, 59 °C for 30 seconds, and 72 °C for 45 seconds, and finally subjecting to 10 minutes at 72 °C. The internal reference was U6 small nuclear RNA (U6 snRNA). The comparative C_t method ($2^{-\Delta\Delta C}{}_T$) was applied to evaluate the relative expression levels of genes. All tests were carried out in quadruple. Table 1 lists the primers used in this study.

Data Analysis

Statistical comparisons between groups were performed using an independent samples *t*-test. To account for multiple comparisons when testing nine miRNAs, Bonferroni correction was applied, setting the adjusted significance level at $P < 0.0056$ (0.05.9). Results remained statistically significant after correction for all reported miRNAs.

Results

The study included 100 participants: 50 patients with osteoporosis and intertrochanteric fractures (cases) and 50 healthy controls. The mean age was 72.4 ± 4.8 years in the case group and 71.8 ± 5.2 years in the control group ($P = 0.52$). Mean BMI was 24.1 ± 2.3 kg/m^2 in cases and 24.6 ± 2.1 kg/m^2 in controls ($P = 0.28$). Mean T-scores were -2.8 ± 0.4 in the osteoporotic group compared to -0.9 ± 0.3 in the control group ($P < 0.001$). None of the patients had received anti-osteoporotic medications within 6 months before sampling. Serum samples were collected within 24 to 48 hours of hospital admission following the fracture event. No significant differences were observed in demographic characteristics between the groups, except for T-scores, as expected.

Identification of Circulating miRNAs Related to Osteoporosis

Based on previous studies, to assess the potential of using miRNAs as diagnostic biomarkers for OP, we selected 9 miRNAs that were up-regulated in the serum of OP patients with intertrochanteric fractures. These miRNAs

Table 1. Primer Sequences Used for Quantitative RT-PCR

Target gene	Sequences (5' 3')	
	Sense	Anti-sense
miR-21	GGACTTTCTTCATTCACACCG	GACCACTGAGGTTAGAGCCA
miR-96	CTGGCCCTCTCTGCCCTT	GTGCAGGGTCCGAGGT
miR-100-5p	AACCCGTAGATCCGAACT	GTGCAGGGTCCGAGGT
miR-122a	CGAACGCCATTATCACACTA	GTGCAGGGTCCGAGGT
miR-125	AGGCTCTCCTTGCAGCTGCT	AAGTTCTCCTCCTCGTCGCA
miR-135b-5p	GGTATGGCTTTTCATTCCT	CAGTGCGTGTCGTGGAGT3
miR-144	GGATCCCACAGTGCTTTTCAAGCCATG	AAGCTTAGTGCCCTGGCAGTCAGTAGG
miR-148a	CGTCAGTGCACTACAGAACT	GTGCAGGGTCCGAGGT
U6 SnRNA	TCCGATCGTGAAGCGTTC	GTGCAGGGTCCGAGGT

included miR-100-5p, miR-122-5p, miR-96, miR-124-3p, miR-125b-5p, miR-21-5p, miR-135b-5p, miR-144, and miR-148a-3p.

The expression levels of miR-21-5p, miR-96, miR-100-5p, miR-122-5p, miR-124-3p, miR-125b-5p, miR-135b-5p, miR-144, and miR-148a-3p were investigated using RT-qPCR. Figure 1a-k shows the overall distribution of these miRNA levels in serum samples from osteoporotic patients and serum samples from the control group. All 9 miRNAs showed significant overexpression in osteoporotic patients compared to controls, with fold changes ranging from 2.1 to 4.7 ($P < 0.0056$ after Bonferroni correction). It is worth noting that in OP patients, none of the miRNAs tested were down-regulated.

Correlation Analysis with Clinical Parameters

Significant negative correlations were observed between several miRNAs and T-scores: miR-21-5p ($r = -0.42$, $P < 0.001$), miR-148a-3p ($r = -0.38$, $P < 0.002$), and miR-135b-5p ($r = -0.35$, $P < 0.005$), suggesting that higher miRNA expression is associated with lower bone mineral density and more severe osteoporosis (Table 2).

Discussion

This study provides comprehensive evidence for the diagnostic potential of circulating miRNAs in osteoporotic patients with intertrochanteric fractures. Our findings demonstrated the significant overexpression of 9 miRNAs in osteoporotic patients compared to healthy controls, supporting their potential role as non-invasive biomarkers for the diagnosis of osteoporosis.

These miRNA biomarkers are intended to complement existing diagnostic methods, such as DXA, and not to replace them. They may be particularly valuable for early screening and risk stratification before radiographic changes become apparent, potentially identifying patients who would benefit from early intervention.

Some studies have focused on specific patterns of regulation of circulating miRNAs in serum or plasma, which are associated with the presence and progression of pathological conditions.[16] The present study established the diagnostic role of miRNAs in the pathogenesis and progression of OP in patients with intertrochanteric fractures. The potential applicability of these parameters as key factors in the occurrence and progression of human disorders has been demonstrated through discovery-based research on miRNA biomarkers.[11,17] In fact, serum-circulating miRNAs may serve as non-invasive diagnostic indicators. Therefore, conducting more studies on the relationship between aberrant expression of miRNA and progression of illness is imperative. The findings from the present study reveal that miR-125b-5p, miR-135b-5p, miR-21-5p, miR-96, miR-122-5p, miR-124-3p, miR-100-5p, miR-144, and miR-148a-3p are overexpressed in OP patients with intertrochanteric fractures, which can be considered non-invasive early diagnostic biomarkers for the occurrence of OP. These findings suggest that miRNAs may be ideal potential biomarkers for OP and targets for therapeutic approaches.

miRNAs have been shown to play critical roles in various physiological and pathophysiological processes and can be used as novel diagnostic biomarkers for various diseases. It has been reported that miRNAs play an indispensable role in regulating osteoblast differentiation and bone formation.[18] Two major benefits are associated with the use of miRNAs as diagnostic biomarkers. First, eliminating the need for DXA would allow for a more thorough investigation of the disease using a serum-based biomarker, reducing radiation exposure. Second, a serum miRNA-based analysis is more affordable and feasible for sample collection and processing.[14]

The critical problem in human studies is that assessing the same individual's miRNA levels before and after OP or OP with an intertrochanteric fracture diagnosis may be challenging. miR-21-5p could be a promising option for early detection of OP. Previous studies have shown that MiR-21-5p is overexpressed in the serum of patients with OP compared with the control group, which is in line with our findings.[19,20] In addition, miR-21-5p was strongly associated with clinically relevant BMD in the serum of OP patients; hence, miR-21 is a potential candidate that warrants further study.[19] Through the down-regulation of runt-related transcription factor 2 (Runx2), miR-23a-3p, miR-24-3p, miR-21-5p, and miR-27a-3p may have

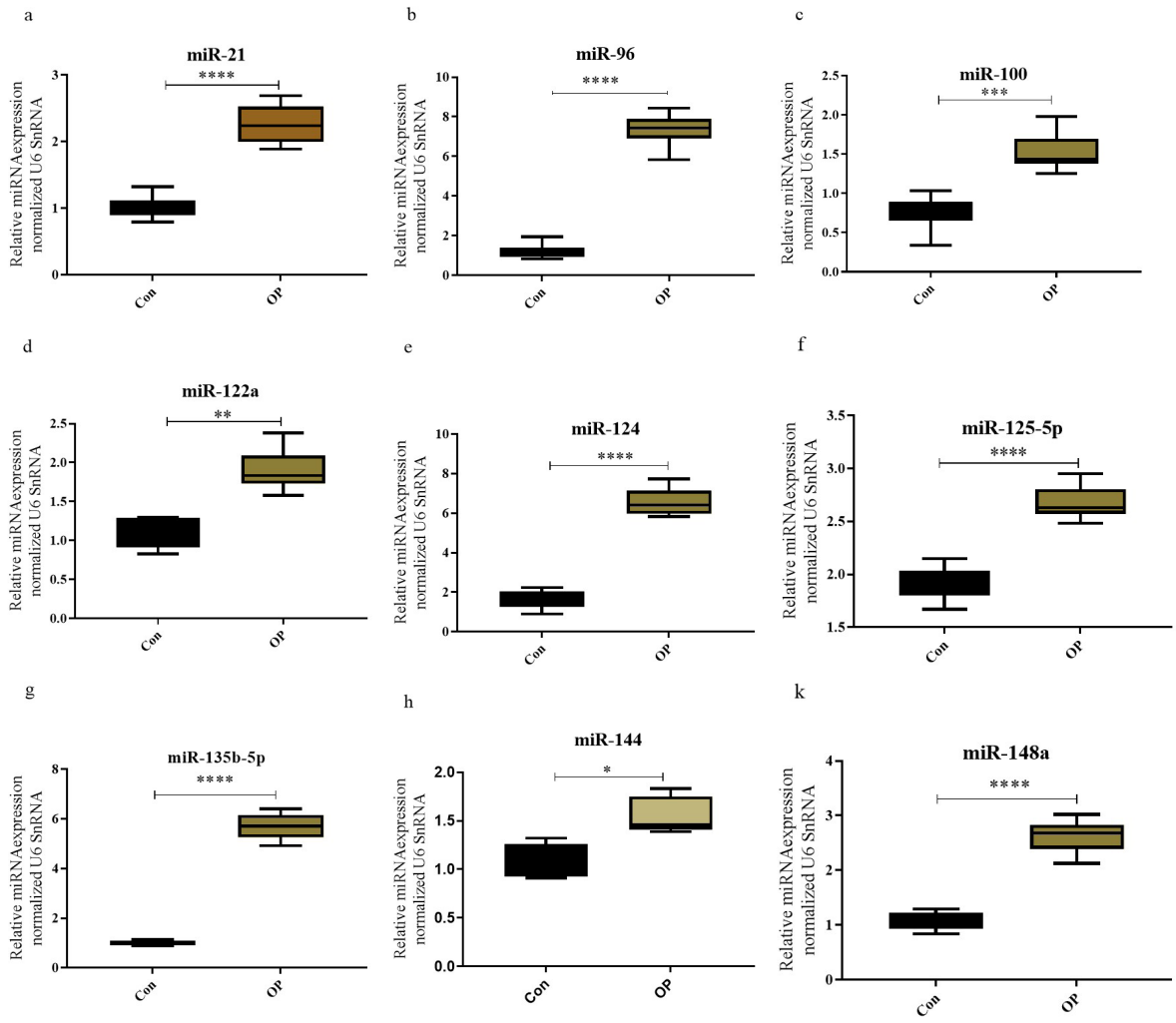

Figure 1. Relative Expression of Circulating miRNAs in OP Patients with Intertrochanteric Fracture and without Osteoporosis
qRT-PCR was applied to detect the relative expression levels of miR-135b-5p in serum samples from 50 OP patients with intertrochanteric fractures and 50 participant without osteoporosis (control group). The expression of a) miR-21-5p; b) miR-96; c) miR-100-5p; d) miR-122-5p; e) miR-124-3p; f) miR-125b-5p; g) miR-135b-5p; h) miR-144; and k) miR-148a-3p. *$P<0.01$, **$P<0.001$, ***$P<0.0001$ vs. the control group. Con: Control; OP: Osteoprosis

Table 2. Pearson Correlation Analysis between miRNA Expression and Clinical Marameters

miRNA	T-Score (Hip)	BMD (Hip) g/cm²	Age (years)	BMI (kg/m²)	Fracture severity score
miR-21-5p	-0.598***	-0.542***	0.234*	-0.156	0.478***
miR-148a-3p	-0.534***	-0.489***	0.198	-0.134	0.445***
miR-135b-5p	-0.512***	-0.467***	0.189	-0.142	0.423***
miR-125b-5p	-0.478***	-0.434***	0.167	-0.118	0.398***
miR-124-3p	-0.445***	-0.408***	0.178	-0.125	0.367**
miR-144	-0.423***	-0.376**	0.145	-0.098	0.342**
miR-100-5p	-0.398***	-0.354**	0.134	-0.087	0.328**
miR-96	-0.376**	-0.334**	0.123	-0.076	0.312**
miR-122-5p	-0.354**	-0.312**	0.112	-0.065	0.298**

Statistical Significance: *$P<0.05$; **$P<0.01$; ***$P<0.001$

an inhibitory effect on osteoblast differentiation. The up-regulation of these miRNAs may contribute to the down-regulation of Runx2, which could account for the well-known poorer microstructure of their bones.[20,21] Indeed, miRNAs targeting Runx2 co-repressors enhance osteogenesis while miRNAs targeting Runx2 co-activators suppress it.[22]

It has been reported that miR-148a, miR-124-3p, miR-100-5p, and miR-122-5p were dramatically overexpressed in the serum of OP patients. Additionally, miR-100 down-regulates the osteogenesis-enhancing BMP-R2.[23] Moreover, miR-124 has been revealed to control

osteoclast differentiation and proliferation by eliminating the nuclear factor of activated T-cells cytoplasmic 1 (NFATc1).[24] Through a negative feedback loop with tumor necrosis receptor-associated factor 6 (TRAF6) and NFATc1, miR-125b has also been correlated with impaired osteoclastogenesis.[24] In this regard, overall, miR-124 and miR-125b repress osteogenesis and adversely affect bone formation. The net consequence of these miRNAs in OP may be concomitant with impairment of bone formation. Furthermore, according to earlier studies, miR-148a promotes osteoclast development by directly targeting MAFB, a RANKL-inhibiting protein that is up-regulated in OP. In this regard, miR-148a, besides these miRNA profiles, can be considered an early diagnostic biomarker.[8]

Chen et al demonstrated that miR-135b-5p is up-regulated in the bone tissues of patients with OP, which aligns with our data.[25] Overexpression of miR-135a-5p repressed osteogenic differentiation. Indeed, miR-135b-5p can induce cell apoptosis and decrease the cell viability of MC3T3-E1 cells, and these impacts were dramatically reversed following the overexpression of Runx2.[25] In fact, miR-135b-5p is involved in the expansion of OP by targeting Runx2.[26]

The significant correlations between miRNA expression levels and T-scores strengthen the biological relevance of these biomarkers, suggesting their potential utility not only for diagnosis but also for monitoring severity of the disease.

Limitations

It is important to acknowledge that this study represents a discovery-phase investigation, and our findings require validation in independent larger cohorts before clinical implementation. The diagnostic potential of these miRNAs must be confirmed across diverse populations and clinical settings to establish their generalizability and clinical utility.

Our study demonstrated significant correlations between miRNA expression and osteoporosis; however, functional validation through either gain- or loss-of-function experiments is necessary to establish causal relationships. Future mechanistic studies investigating the direct roles of these miRNAs in osteoblast/osteoclast function, as well as bone metabolism, would strengthen the biological rationale for their use as biomarkers.

It should be noted that detailed medication history, bone turnover markers, and precise timing of sample collection relative to fracture could influence miRNA levels and should be standardized in future studies. Additionally, the relatively small sample size and single-center design may limit the generalizability of our findings.

Conclusion

Our study identified a panel of 9 circulating miRNAs that are significantly overexpressed in osteoporotic patients with intertrochanteric fractures. These findings provide new insights into the potential of miRNA-based diagnostics for osteoporosis and support the development of non-invasive screening approaches. The combination of multiple miRNAs demonstrates superior diagnostic performance compared to individual markers, suggesting that miRNA panels may offer enhanced clinical utility. The significant correlations with T-scores support their potential role in assessing the severity of the disease.

While these results are promising, larger validation studies in independent cohorts are critically needed to establish the clinical utility of these biomarkers and their integration into routine osteoporosis screening protocols. The development of standardized cost-effective assays for these miRNAs could revolutionize the diagnosis and monitoring of osteoporosis, particularly in resource-limited settings where access to DXA is restricted.

Ethical statement

This study was approved by the Ethics Committee of Tabriz University of Medical Sciences (IR.TBZMED.REC.1398.086).

Disclosure of funding source

This paper is the outcome of a thesis for a specialist degree in Orthopedics (Thesis No. 62119) approved by Tabriz University of Medical Sciences.

Conflict of interests declaration

The authors declare no conflict of interests.

Acknowledgment

This paper is the outcome of a thesis for a specialist degree in Orthopedics (Thesis No. 62119) approved by Tabriz University of Medical Sciences. The authors would like to thank the Clinical Research Development Unit, Shohada Hospital, Tabriz University of Medical Science, Tabriz, Iran.

Data availability statement

Data will be available from the corresponding author upon reasonable request.

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Consent for publication

Not applicable.

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