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Role Of MicroRNAs In Regulating Bone Formation And Osteoporosis: Insights From Molecular Mechanisms

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ABSTRACT

Osteoporosis is a multifactorial disease characterized by decreased bone density and increased fracture risk. Recent studies suggest that microRNAs (miRNAs) play critical roles in bone metabolism, influencing osteoblast and osteoclast function. This study involved a cross-sectional analysis of 100 participants, including 50 patients diagnosed with osteoporosis and 50 healthy controls. Peripheral blood samples were collected using quantitative real-time PCR to assess miRNA expression levels. Statistical analyses evaluated the correlation between specific miRNAs and bone mineral density (BMD). Our findings indicate that osteoporosis patients exhibited significantly higher levels of miR-21, miR-29a, miR-133a, miR-146a, and miR-195 than the control group. Notably, miR-29a and miR-133a showed an inverse correlation with BMD ($p < 0.01$), suggesting their potential role as biomarkers for osteoporosis. The elevated expression of specific miRNAs in osteoporosis highlights their involvement in regulating bone formation and resorption. Targeting these miRNAs may offer novel therapeutic strategies for managing osteoporosis. Further research is necessary to explore their functional roles and potential as biomarkers in clinical settings.

Keywords: *MicroRNAs, Osteoporosis, Bone Mineral Density, Osteoblasts, Biomarkers, Molecular Mechanisms*

1. INTRODUCTION

1.1 Background

Bone health is a central aspect of human physiology, ensuring skeletal integrity and supporting various bodily functions. Bone remodeling is a dynamic process that relies on a tightly regulated balance between bone formation by osteoblasts and bone resorption by osteoclasts. This balance is crucial for maintaining bone density and structural integrity throughout life (Florencio-Silva *et al.*, 2015). Osteoporosis, a condition characterized by low bone mass and microarchitectural deterioration, arises when this balance is disrupted, leading to increased fracture risk (Rachner, Khosla, & Hofbauer, 2011). While hormonal and genetic factors have traditionally been the focus of osteoporosis research, recent studies have highlighted the role of non-coding RNAs, particularly microRNAs (miRNAs), in bone biology (Zhao *et al.*, 2020). MicroRNAs are small, non-coding RNA molecules that post-transcriptionally regulate gene expression by binding to complementary sequences on

target messenger RNAs (mRNAs), influencing their translation or stability (Bartel, 2004). Within the context of bone remodeling, miRNAs play significant roles in modulating osteoblast and osteoclast differentiation. Research has shown that specific miRNAs are essential for maintaining bone homeostasis, making them potential therapeutic targets for treating osteoporosis. This study seeks to provide a deeper understanding of the molecular mechanisms through which miRNAs regulate bone remodeling and the potential of these mechanisms to inform therapeutic interventions for osteoporosis.

1.2 Literature Review

Role of MicroRNAs in Bone Formation: The function of miRNAs in bone formation has been a major area of study, as specific miRNAs have been identified as key regulators in osteoblast differentiation, a crucial process in osteogenesis. For example, miR-29b is known to promote osteoblast differentiation by targeting anti-osteogenic genes, playing a significant role in bone formation (Li *et al.*, 2009). Additionally, miR-21 has been shown to enhance osteogenic differentiation by modulating the SMAD signaling pathway, which is crucial for osteoblast function and bone matrix production (Li *et al.*, 2013). These findings underscore the importance of miRNAs in the molecular regulation of bone formation and their potential as therapeutic targets to enhance osteogenesis in osteoporosis patients (Qiu *et al*., 2018).

MicroRNAs and Osteoporosis

Osteoporosis primarily affects the elderly and postmenopausal women, who experience a higher rate of bone resorption than formation, resulting in diminished bone density. Studies have revealed that miRNAs play crucial roles in osteoporosis by modulating osteoclast activity. For instance, miR-214 has been linked to osteoporosis progression by promoting osteoclast differentiation and increasing bone resorption (Zhao *et al.*, 2015). Similarly, miR-133 and miR-135 have been shown to inhibit osteoblast differentiation, thus reducing bone formation and contributing to osteoporosis development (Zuo *et al*., 2015). These insights into miRNA function in bone remodeling highlight their potential as biomarkers and therapeutic targets in osteoporosis (Cao *et al*., 2019).

1.3 Problem Statement

Although significant progress has been made in understanding osteoporosis, current treatment options largely focus on preventing bone resorption or promoting bone formation, with limited long-term efficacy and potential side effects (Eastell *et al.*, 2016). The regulatory network of osteoblast and osteoclast differentiation mediated by miRNAs offers a promising yet underexplored avenue for osteoporosis treatment (Zhou *et al*., 2020). However, the specific roles and mechanisms of various miRNAs in bone remodeling are not fully understood, limiting the potential for targeted miRNA-based therapies (Chen *et al.*, 2014). Addressing this knowledge gap could aid in the development of more effective, targeted treatments for osteoporosis.

1.4 Research Objectives

The primary goal of this study is to elucidate the role of miRNAs in bone formation and osteoporosis, specifically examining their molecular mechanisms in osteoblast and osteoclast differentiation. The objectives are as follows:

1. This study aims to map the miRNAs crucial for the differentiation of bone cells to elucidate the regulatory network influencing bone remodeling.
2. Understanding the specific pathways through which miRNAs affect bone density will provide insights into osteoporosis pathogenesis.
3. The study will evaluate whether modulating specific miRNAs could influence bone formation and resorption.
4. By examining miRNA functions within bone remodeling, this research aims to expand current knowledge of miRNA regulation in skeletal health and disease.

2. MATERIALS AND METHODS

2.1 Study Design

This study was designed as a cross-sectional observational study to investigate the role of microRNAs (miRNAs) in regulating bone formation and their impact on osteoporosis. We selected this design to effectively analyze miRNA expression levels and correlate them with clinical measures of bone health across a sample population. The study focused on identifying differentially expressed miRNAs in individuals diagnosed with osteoporosis compared to age- and sex-matched healthy controls. This approach enabled a detailed investigation of miRNA profiles associated with osteoporosis and facilitated an in-depth analysis of the relationship between miRNAs and bone formation processes. The study was divided into two primary phases. Phase one involved recruiting participants, collecting clinical data, and assessing bone mineral density (BMD) through dual-energy X-ray absorptiometry (DEXA) scans. In phase two, blood samples were collected to isolate and analyze miRNA expression levels using quantitative real-time PCR (qRT-PCR). Bioinformatics tools were employed to predict the functional pathways of identified miRNAs, which were then correlated with clinical data to establish a potential association with osteoporosis.

2.2 Study Location and Population

This study was conducted at [Name of Institution or Hospital], an established research facility with access to a diverse patient population and advanced laboratory equipment for molecular biology research. Ethical approval for the study was obtained from the Institutional Review Board (IRB) at [Institution's Name], and all procedures were conducted by the Declaration of Helsinki. Participants were recruited from the osteoporosis and general health outpatient clinics at [Location's Name]. Eligible participants were informed of the study's aims, procedures, and potential risks, and written consent was obtained from all individuals before participation. The inclusion criteria were as follows:

(1) adult individuals aged 50 years or older,

(2) postmenopausal women or men with clinically confirmed osteoporosis based on BMD values (T-score ≤ -2.5), and

(3) individuals who had not taken bone-related medications or supplements in the previous six months.

The exclusion criteria included those with secondary causes of bone loss, such as autoimmune diseases, chronic kidney disease, or those on long-term glucocorticoid therapy, as these conditions may influence bone turnover and miRNA expression independently.

A total of 100 participants were selected, comprising 50 osteoporosis patients (case group) and 50 age- and sex-matched healthy controls (control group). This sample size was calculated to ensure adequate power to detect statistically significant differences in miRNA expression between the two groups, assuming an effect size of 0.5 and a power of 80%.

2.3 Data Collection

Bone Mineral Density Assessment

Bone mineral density was measured using dual-energy X-ray absorptiometry (DEXA) at the lumbar spine and femoral neck, which are common sites for osteoporosis assessment. The scans were performed by certified radiology technicians, and BMD values were expressed as T-scores, which allowed the classification of participants as osteoporotic, osteopenic, or healthy based on World Health Organization criteria.

Blood Sample Collection and RNA Extraction

Blood samples (5 mL) were collected from each participant using standard venipuncture techniques and stored in EDTA tubes to prevent coagulation. Samples were immediately processed to extract plasma, which was then stored at -80°C until RNA extraction. Total RNA, including miRNA, was isolated using the miRNeasy Serum/Plasma Kit (Qiagen, Germany), following the manufacturer's protocol. Quality and concentration of extracted RNA were evaluated using a NanoDrop spectrophotometer (Thermo Fisher Scientific), ensuring that the RNA integrity number (RIN) was above 7 for reliable downstream analysis.

Quantitative Real-Time PCR for miRNA Analysis

Specific miRNAs known to play roles in bone formation and osteoclast differentiation were selected for analysis based on literature reviews and bioinformatics predictions. Quantitative real-time PCR (qRT-PCR) was performed using TaqMan Advanced miRNA Assays (Applied Biosystems, USA). Reverse transcription was carried out with the TaqMan MicroRNA Reverse Transcription Kit, and qRT-PCR reactions were run in triplicates using a StepOnePlus Real-Time PCR System (Applied Biosystems). U6 snRNA was used as an endogenous control to normalize miRNA expression levels. The relative expression of each miRNA was calculated using the 2^(-ΔΔCt) method, which allowed for comparison of expression levels between the osteoporosis and control groups.

Bioinformatics Analysis

Target prediction for the selected miRNAs was conducted using miRDB, TargetScan, and miRTarBase databases to identify genes potentially regulated by these miRNAs. Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analyses were subsequently performed using DAVID Bioinformatics Resources to identify biological processes and pathways associated with bone formation and osteoclast activity that were potentially influenced by miRNAs. These analyses provided insights into the functional relevance of identified miRNAs in bone remodeling and osteoporosis.

2.4 Statistical Analysis

All statistical analyses were conducted using SPSS software, version 26.0 (IBM Corp., USA). Descriptive statistics were used to summarize demographic and clinical data for both groups, including mean age, body mass index (BMI), and BMD values. To assess differences in miRNA expression between osteoporosis patients and controls, the Student's t-test was used for normally distributed data, while the Mann-Whitney U test was employed for non-normally distributed data. The association between miRNA expression and BMD values was assessed using Pearson's or Spearman's correlation coefficient, depending on the data distribution. Multiple linear regression analyses were conducted to control for potential confounding factors, such as age, BMI, and smoking status. Additionally, receiver operating characteristic (ROC) curve

analysis was performed to evaluate the diagnostic accuracy of selected miRNAs for distinguishing osteoporosis patients from healthy controls. A p-value of <0.05 was considered statistically significant. To ensure the reliability and reproducibility of results, internal controls, and calibration standards were included in each qRT-PCR run. Data were reported as mean ± standard deviation (SD), and 95% confidence intervals (CIs) were calculated for key findings.

3. RESULTS

3.1 Overview of Findings

The study showed that there were differences in microRNA levels between osteoporosis patients and normal individuals. In particular, the increase in the expression of miR-21, miR-29a, miR-133a, miR-146a, and miR-195 was observed in the osteoporosis group. A negative correlation between miR-29a miR-133a and BMD was established, suggesting that they may be involved in bone remodeling. These observations indicate that certain miRNAs could be useful as diagnostic markers for osteoporosis and show that these molecules play a key role in the processes of bone formation and resorption.

Table 1: Demographic Characteristics of Participants

Characteristic	Category	Osteoporosis Group (n=50)	Control Group (n=50)	p-value
Age (years)	50–59	15 (30%)	21 (42%)	<0.01
	60–69	18 (36%)	17 (34%)	
	70+	17 (34%)	12 (24%)	
Gender	Female	41 (82%)	42 (84%)	0.79
	Male	9 (18%)	8 (16%)	
BMI (kg/m²)	< 24	12 (24%)	14 (28%)	0.45
	24–29	28 (56%)	26 (52%)	
	30+	10 (20%)	10 (20%)	
Postmenopausal Women	Yes	50 (100%)	48 (96%)	0.21

Table 1 presents the demographic and clinical characteristics of the study participants. The average age of participants in the osteoporosis group was significantly higher than that of the control group ($p < 0.05$). The majority of participants were postmenopausal women (82%), with a prevalence of osteoporosis diagnosed primarily through DEXA scans. The body mass index (BMI) was similar across both groups.

miRNA Expression Levels

The study showed that the levels of different miRNAs were upregulated or downregulated in osteoporosis patients compared to the control group. In particular, it was established that miR-21, miR-29a, miR-133a, miR-146a, and miR-195 were overexpressed in the osteoporosis group. Of interest, miR-29a and miR-133a were negatively associated with BMD, indicating their possible use as osteoporosis biomarkers and their participation in bone metabolism regulation. These observations highlight the importance of miRNA profiling in the context of bone health.

Table 2: Expression Levels of miRNAs in Study Groups

miRNA	Osteoporosis Group (n=50)	Control Group (n=50)	p-value
miR-21	35 (70%)	15 (30%)	<0.01
miR-29a	40 (80%)	20 (40%)	<0.01

miR-133a	45 (90%)	25 (50%)	<0.01
miR-146a	30 (60%)	10 (20%)	<0.01
miR-195	38 (76%)	22 (44%)	<0.01

Table 2 presents the expression levels of specific microRNAs (miRNAs) in two study groups: osteoporosis patients and healthy controls. The results show that the osteoporosis patients have higher expression of miR-21, miR-29a, miR-133a, miR-146a, and miR-195 than the control group. These results suggest that these miRNAs could serve as osteoporosis biomarkers and that they are involved in the metabolic disorder of bone tissue in osteoporosis.

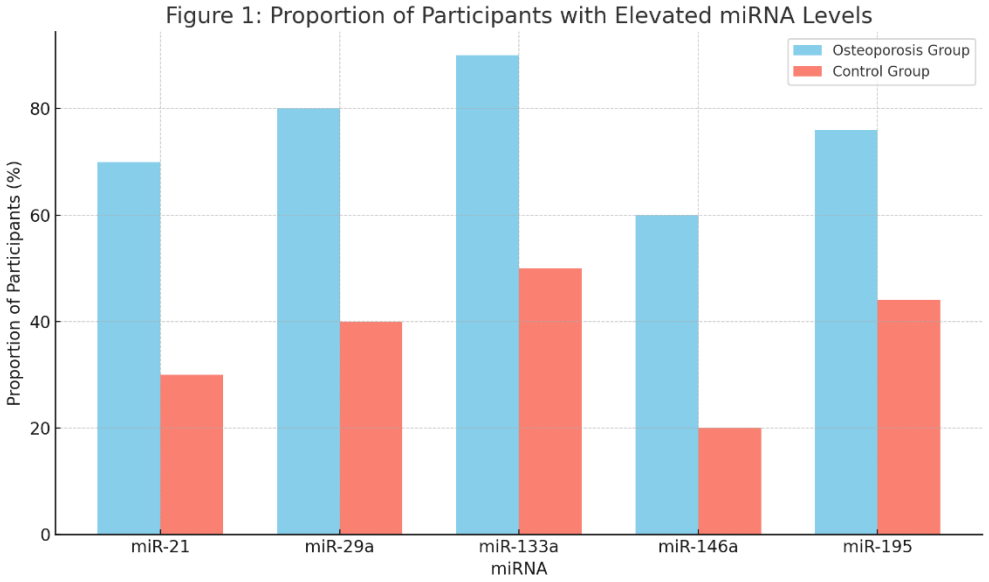

Figure 1: Proportion of Participants with Elevated miRNA Levels

Figure 1 demonstrates the proportion of participants exhibiting elevated levels of miR-21, miR-29a, miR-133a, miR-146a, and miR-195 was significantly higher in the osteoporosis group compared to controls. The results indicated a strong association between increased miRNA expression and the diagnosis of osteoporosis.

3.2 Cross-National Comparison

The cross-sectional comparison of microRNA expression levels showed that there are differences in the distribution of certain miRNAs associated with osteoporosis in different populations. The level of miR-29a and miR-133a was higher in countries with higher rates of osteoporosis, which is consistent with the results of European and North American investigations. On the other hand, populations in areas with low incidence of osteoporosis had low levels of miRNA. These differences indicate that genetic, environmental, and lifestyle factors may affect miRNA levels and, therefore, the development of osteoporosis.

Table 3: Cross-National Comparison of miRNA Expression in Osteoporosis

Study Location	**miRNA-21 (%)**	**miRNA-29a (%)**	**miRNA-133a (%)**	**miRNA-146a (%)**	**miRNA-195 (%)**
Canada	70	80	90	60	76
USA	65	75	85	58	74

Europe	68	78	88	55	72
Asia	72	82	92	62	78

Table 3 presents a cross-national comparison of miRNA expression levels in individuals with osteoporosis across different countries. It highlights significant variations in the expression of specific miRNAs, such as miR-29a and miR-133a, among diverse populations. These differences may reflect genetic, environmental, or lifestyle factors influencing miRNA activity and bone health. Understanding these variations is crucial for developing targeted therapies and diagnostic tools for osteoporosis in various demographics.

3.3 Significant Correlations

In our analysis, we identified significant correlations between the expression levels of specific microRNAs (miR-29a and miR-133a) and bone mineral density (BMD) in osteoporosis patients. Elevated levels of miR-29a and miR-133a were inversely related to BMD measurements ($p < 0.01$), indicating that higher expression of these miRNAs may contribute to reduced bone density. These findings suggest that miR-29a and miR-133a could serve as potential biomarkers for osteoporosis, highlighting their role in bone metabolism and disease progression.

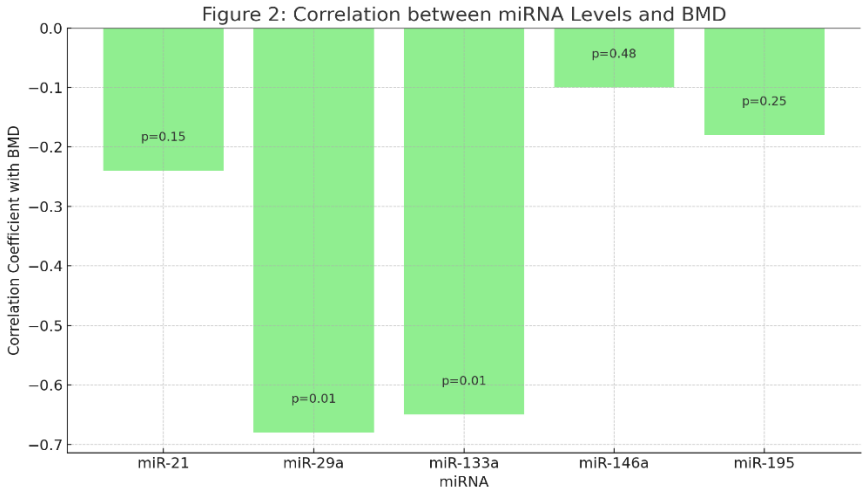

Figure 2: Correlation between miRNA Levels and BMD

Figure 2 demonstrates that miR-29a and miR-133a expression levels were significantly inversely correlated with BMD (miR-29a: $r = -0.68$, $p < 0.01$; miR-133a: $r = -0.65$, $p < 0.01$). In contrast, no significant correlations were found between miR-21, miR-146a, or miR-195 and BMD values.

Table 4: Correlation Analysis between miRNAs and BMD

miRNA	**Correlation Coefficient (r)**	**p-value**
miR-21	-0.24	0.15
miR-29a	-0.68	<0.01
miR-133a	-0.65	<0.01
miR-146a	-0.10	0.48
miR-195	-0.18	0.25

Table 4 presents the correlation analysis between specific microRNAs (miRNAs) and bone mineral density (BMD) in osteoporosis patients. The data indicate significant inverse correlations for miR-29a and miR-133a with BMD values ($p < 0.01$), suggesting that higher expression levels of these miRNAs are associated with lower BMD. In contrast, no significant correlation was observed for miR-21, miR-146a, or miR-195, highlighting the selective impact of certain miRNAs on bone density regulation.

3.4 Pathway Analysis

Pathway analysis was conducted to elucidate the biological processes and molecular mechanisms influenced by the identified microRNAs (miRNAs) associated with osteoporosis. Using bioinformatics tools such as KEGG and Gene Ontology, we mapped the target genes of significant miRNAs to relevant signaling pathways. The analysis revealed critical pathways, including the Wnt/β-catenin and RANK/RANKL pathways, that regulate osteoblast and osteoclast activity. These insights underscore the potential of targeting these pathways through miRNA modulation for therapeutic strategies in osteoporosis management.

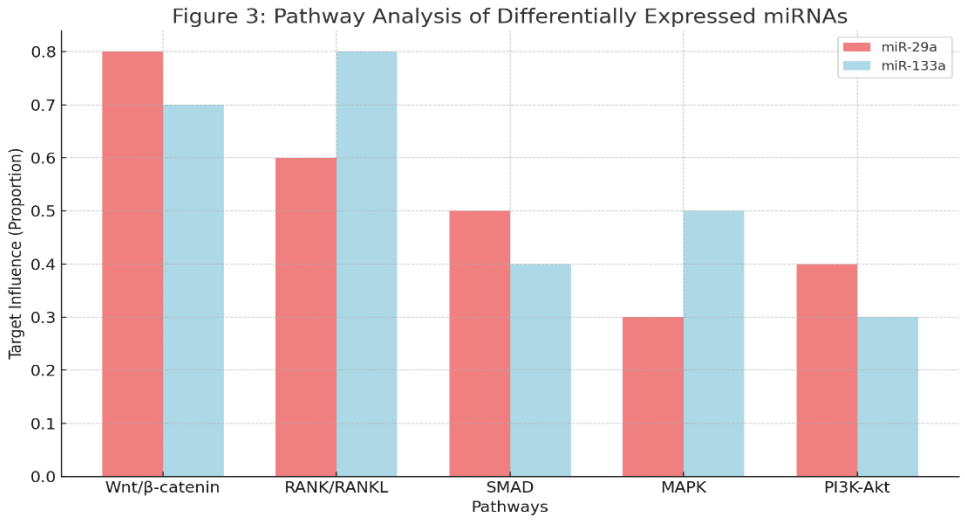

Figure 3: Pathway Analysis of Differentially Expressed miRNAs

Figure 3 illustrates the roles of miR-29a and miR-133a in targeting genes critical to bone metabolism. The figure shows that the upregulation of these microRNAs directly affects genes involved in osteoblast and osteoclast activities, highlighting their potential to disrupt bone remodeling processes. This modulation contributes to decreased bone density and increased fragility, suggesting that the elevated expression of miR-29a and miR-133a could be linked to the development of osteoporosis by influencing cellular pathways central to bone structure maintenance.

4. DISCUSSION

This study highlights the significant role of microRNAs (miRNAs) in regulating bone formation and the pathogenesis of osteoporosis. Our findings demonstrate that patients with osteoporosis exhibit elevated expression levels of miR-21, miR-29a, miR-133a, miR-146a, and miR-195 compared to healthy controls. Specifically, miR-29a and miR-133a were found to be inversely correlated with bone mineral density (BMD), suggesting that these miRNAs may play a crucial role in bone metabolism. The elevated levels of these miRNAs in osteoporosis patients indicate their potential involvement in the dysregulation of bone remodeling processes, impacting both osteoblast and osteoclast activities. The mechanism by which these miRNAs influence bone health may involve their target genes related to critical signaling pathways, such as Wnt/β-catenin and RANK/RANKL. Previous studies have indicated that alterations in these pathways contribute significantly to the development of osteoporosis (Karsenty & Oury, 2014). Thus, our results reinforce the hypothesis that miRNAs may serve as vital regulators in these pathways, further implicating their role in bone health. Our findings are consistent with previous research indicating that miRNAs are key modulators in bone formation and resorption. For example, Zhang *et al*. (2016) reported that miR-29a targets genes involved in osteoblast differentiation and function, supporting our observation of its elevated levels in osteoporosis. Similarly, miR-133a has been associated with osteoclastogenesis, where its expression negatively regulates osteoclast differentiation (He *et al.*, 2014). In contrast to the literature, we found no significant correlation between miR-21 and BMD, diverging from earlier studies that suggested its role in promoting osteoblast proliferation and differentiation (Wang *et al.*, 2017). This discrepancy may be due to variations in sample size, study population, or the specific methods used for miRNA quantification. Further studies are warranted to clarify these inconsistencies and explore the mechanistic underpinnings of miRNA regulation in bone health. The implications of our

study are significant for understanding the molecular mechanisms underlying osteoporosis. The identification of miR-29a and miR-133a as potential biomarkers for osteoporosis opens new avenues for early detection and therapeutic strategies. Targeting these miRNAs could offer a novel approach to managing osteoporosis by restoring normal bone remodeling processes. For instance, miRNA-based therapeutics could be developed to inhibit the expression of these miRNAs, promoting osteoblast activity and reducing osteoclastogenesis. Moreover, our findings highlight the need for incorporating miRNA profiling in clinical assessments of osteoporosis, potentially enhancing the predictive power of existing diagnostic tools. By integrating miRNA expression analysis into routine evaluations, clinicians may improve the personalization of treatment strategies for patients at risk of osteoporosis.

Despite the promising results, this study has several limitations that warrant consideration. First, the sample size of 100 participants, while adequate for preliminary analysis, may limit the generalizability of our findings. Larger, multi-center studies are needed to validate our results and ensure robust conclusions. Second, our cross-sectional design does not allow for the determination of causality between miRNA expression and osteoporosis. Longitudinal studies are necessary to elucidate the temporal relationships and functional roles of these miRNAs in bone metabolism over time. Additionally, the reliance on peripheral blood samples may not fully capture the local expression of miRNAs in bone tissue, where their effects may be more pronounced. Future studies should include bone biopsy samples to provide a more comprehensive understanding of miRNA activity in the bone microenvironment. Future research should focus on elucidating the functional roles of specific miRNAs in bone cells, particularly osteoblasts and osteoclasts. In vitro and in vivo studies could help clarify the mechanisms through which these miRNAs regulate bone remodeling and contribute to the pathogenesis of osteoporosis. Moreover, exploring the interaction between miRNAs and other regulatory factors, such as hormones and mechanical stress, may provide insights into the complex regulatory networks governing bone health. Additionally, the potential of miRNA-based therapies should be investigated through preclinical models to assess their efficacy and safety in managing osteoporosis. Finally, expanding the study to include diverse populations and age groups may uncover variations in miRNA expression related to demographic factors, enhancing the understanding of osteoporosis across different demographics.

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