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Review Article

Research progress on the regulation of miRNAs in diabetic kidney disease and osteoporosis

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Abstract: Diabetic kidney disease (DKD) stands as one of the most prevalent chronic complications associated with diabetes mellitus. Conversely, osteoporosis (OP) represents another widespread metabolic bone disorder, one that exerts a substantial negative impact on the quality of life among diabetic populations. Together, these two conditions constitute significant threats to patient well-being. MicroRNAs (miRNAs), a class of endogenous non-coding RNA molecules typically around 22 nucleotides in length, exert pivotal regulatory functions across diverse physiological processes. These include critical cellular events such as proliferation, differentiation, apoptosis, and metabolic homeostasis. From the perspective of accumulating evidence, miRNAs have emerged as key regulators in the pathological mechanisms underlying both DKD and OP. Their influence on disease progression is mediated through the intricate modulation of key signaling pathways and target genes. The present review aims to synthesize the current understanding of the regulatory mechanisms, target gene profiles, and pertinent research advancements concerning miRNAs in diabetic nephropathy and osteoporosis. Furthermore, it attempts to consolidate the repertoire of miRNAs exhibiting potential therapeutic implications in both conditions. This work seeks to offer novel insights and actionable strategies for the early diagnosis, therapeutic intervention, and prognostic evaluation of patients suffering from DKD complicated with OP.

Keywords: Diabetic kidney disease, osteoporosis, miRNA, regulation, target

Introduction

Diabetic patients often concurrently suffer from DKD and OP, which influence each other and further aggravate the condition. miRNA, as an important regulatory molecule, may play a bridging role in the pathogenesis of DKD combined with OP. On the one hand, some miRNAs may participate in the occurrence and development of DKD and OP through common signaling pathways or target genes; on the other hand, factors such as hyperglycemia and oxidative stress under diabetic conditions may lead to alterations in miRNA expression profiles, thereby affecting the physiological functions of the kidney and bone and promoting the occurrence of both complications. In-depth research on the mechanism of miRNA in DKD combined with OP can provide new combined intervention targets and strategies for clinical treatment.

MicroRNAs (miRNAs) constitute a category of short non-coding RNA species, generally spanning 20 to 22 nucleotides in length, which exert regulatory effects on gene expression during the post-transcriptional phase. Their primary mechanism of action involves binding to the 3'-untranslated region (3' UTR) of target messenger RNAs (mRNAs), leading to mRNA degradation or translational repression [1]. Currently, the miRBase database contains over 38,000 mature miRNA entries, with new miRNAs continuously being discovered [2]. As critical regulatory molecules, miRNAs participate in a broad spectrum of biological processes and are deeply implicated in the occurrence and development of multiple disease entities. Aberrant expression of these molecules has been demonstrated to correlate with diverse pathological cascades, thereby conferring upon miRNAs promising value as diagnostic biomarkers and

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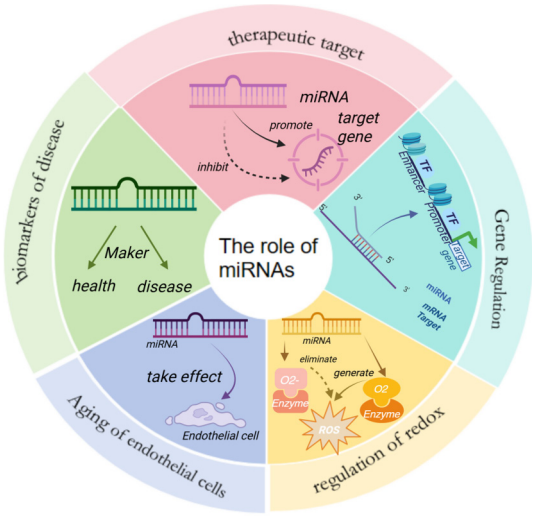

Figure 1. Mechanisms of miRNA action. Therapeutic targets: By inhibiting overexpressed pathogenic miRNAs or supplementing underexpressed protective miRNAs, normal cellular protein expression levels can be restored to treat diseases. Gene regulation: miRNAs bind to the 3' UTR of mRNAs via base complementarity, preventing protein synthesis or accelerating mRNA degradation. Regulation of redox: miRNAs regulate the stability or translation of mRNAs encoding antioxidant enzymes or oxidases. Endothelial Cell Senescence: Abnormal miRNA expression can accelerate the functional decline of endothelial cells. Biomarkers of disease: The differences in miRNA expression profiles between healthy and disease states provide potential biomarkers for disease diagnosis.

candidate therapeutic targets (**Figure 1** and **Table 1**).

Overview of DKD and OP

Diabetic kidney disease (DKD) is a major microvascular complication of diabetes mellitus (DM) and a leading cause of end-stage renal disease and mortality in diabetic patients. Its pathogenesis stems from metabolic disturbances induced by hyperglycemia, which subsequently trigger hemodynamic abnormalities, inflammatory responses, oxidative stress, and fibrotic processes, collectively leading to renal impairment [3]. With the progression of diabetic kidney disease (DKD), glomerular and tubular functions undergo progressive impairment. These renal structures are integral to the maintenance of systemic calcium and phosphate homeostasis. The severity of DKD exhibits a positive correlation with the incidence of osteoporosis (OP) and subsequent fracture events, a relationship that not only diminishes patients' quality of life but also elevates the overall risk of mortality.

Osteoporosis represents a systemic metabolic skeletal disorder hallmarked by diminished bone mineral density, disrupted bone microarchitectural integrity, and elevated susceptibility to fragility fractures. The pathogenesis of this condition stems from an imbalance between osteoclastic bone resorption and osteoblastic bone formation, a process modulated by a spectrum of genetic predispositions and environmental determinants. Advanced age, female sex, Caucasian ethnicity, early menopause or oophorectomy, prolonged immobilization, and long-term glucocorticoid use are significant risk factors for OP and related fractures [4]. Due to its strong association with increased fracture risk, OP imposes a substantial burden on both patient health and healthcare systems [5].

miRNA and DKD

In the absence of timely and effective therapeutic interventions, diabetic kidney disease (DKD) can advance to end-stage renal disease, a clinical outcome that ultimately requires renal dialysis or kidney transplantation. Therefore, early detection and therapeutic intervention are critical for DKD patients [6]. Functional studies show that miRNA not only has the ability to regulate target gene expression but also has potential for treating DKD. miRNAs are present in plasma, serum, and urine [7], for example, within the KEGG pathway visualization associated with miR-4534, the SIRT1/FOXO signaling pathway [8] exhibits the closest association with DKD. Research on the pathogenesis of DKD is increasingly focusing on inflammatory responses [9], and FOXO is one of the most well-known pathways. TTGF-β1 demonstrates a profound association with the inflammatory cascades and fibrogenic processes implicated in DKD [10], and as miRNA-615-3p increases, plasma TGF-β1 expression levels also increase [11]. Studies show that the CUL4B/miR-194-5p/ITGA9 axis is an important regulator of monocyte infiltration in DKD [12]. MiR-223-3p seems to function as a pivotal regulator within the core regulatory network involving long non-coding RNAs and messenger RNAs in DKD [13], and miR-223-3p is associated with IL6ST mRNA and slows DKD progression by inhibiting downstream STAT3 activation, suggesting the miR-223-3p/IL6T/STAT3 axis is sig-

Table 1. Roles of miRNA

Roles of miRNA	References
Potential therapeutic targets	[86]
Key role in post-transcriptional gene regulation	[87]
Involvement in redox regulation, acting on ROS-generating enzymes and antioxidant enzymes	[88]
Important role in endothelial cell senescence	[89]
miRNA expression profiles are altered between health and disease, therefore they can be considered as disease biomarkers	[90]

nificant in DKD pathogenesis [14]. Increased expression of miR-663a reduces CXCR4 and HSPG2 expression; the expression of miR-663a in urinary exosomes may reflect differences in the underlying mechanisms of renal involvement in proteinuric DKD (PDKD) and non-proteinuric DKD (NPDKD) [15].

Accumulating evidence has indicated that targeting the miR-144-3p/NRF2 signaling pathway may serve as a promising therapeutic strategy to attenuate the progression of chronic kidney disease induced by hypertension and diabetes. Downregulating the expression of TGF-β1 and miR-144-3p, together with upregulating NRF2 and its downstream target genes in renal tissues, could effectively alleviate renal injury in diabetic hypertensive rats [16]. Renal tubular cell death is an important feature of experimental and human DKD, leading to renal cell loss and tubular atrophy [17-19]. miR-23a-3p, whose target Kruppel-like factor 3 (KLF3) inhibits the STAT3 signaling pathway in high glucose (HG)-induced HK-2 cells, is crucial for the renoprotective properties of Mesenchymal Stromal Cell-derived small extracellular vesicles (MSC-sEVs) [20]; one is activated in a high glucose environment and triggers oxidative stress by inhibiting the expression of the antioxidant gene SIRT1, while miR-4449 is an upstream regulator of HIC1, highlighting the important role of miR-4449 in DKD pathogenesis [21]. miR-7a-5p can specifically target the 3'UTR of P311 mRNA and inhibit P311 expression in SV40-MES-13 cells [22], van Roeyen et al. demonstrated that GAS1 protein inhibits mesangial cell proliferation [23], while downregulation of miR-34a alleviates mesangial proliferation in vitro and glomerular hypertrophy in early diabetic nephropathy mice by targeting GAS1 [24]. Urinary exosomal miR-145-5p from DKD patients induces Podocyte apoptosis by inhibiting Srgap2 and activating the RhoA/ROCK pathway, indicating that urinary exosomal miR-145-5p is involved in the pathological process of DKD and may serve as a non-invasive diagnostic biomarker for DKD [25]. Studies show that UC-MSC-derived miR-146a-5p promotes M2 macrophage polarization by targeting TRAF6, having the potential to restore renal function in DN rats. This paves the way for the application of miRNA-modified cell therapy in the treatment of kidney disease [26]. Findings indicate a novel mechanism where miR-214 and Dnm3os act as negative and positive regulators of fibrosis, respectively, through the RAGE-DIAPH1 axis [27]. Mechanistically, mir-802 activates both non-canonical and canonical NF-κB pathways by targeting its negative regulator TRAF3. Subsequently, NF-κB regulates the expression of chemokines and SREBP1, leading to strong macrophage recruitment and M1-like polarization [28]. ChREBP expression has been reported to increase in the kidneys of STZ-induced diabetic rats [29], Studies show that miR-1225-3p promotes fibrosis and oxidative stress by mediating ARHGAP5/SMURF2-mediated ubiquitination of ChREBP [30]. miR-26a alleviates tubulointerstitial fibrosis (TIF) in a DKD model by directly targeting PAR4, which may provide a new molecular strategy for DKD treatment [31]. Data suggest that miR-504-3p regulates HG-induced podocyte injury by sponging HNF1B, providing a new direction for DKD treatment [32]. As a member of the HECT family, Smurf1 functions as a critical E3 ubiquitin ligase that governs substrate specificity during the ubiquitin modification process. This ligase is capable of recognizing target protein substrates and selectively mediating the ubiquitination and subsequent degradation of Smad effector molecules [33, 34]. Studies show that miR-154-5p regulates the TGFβ1/Smads pathway via Smurf1 ubiquitination and promotes the fibrotic process in DKD [35]. miR-302a-3p may play a protective role by targeting ZEB1 in

Table 2. miRNAs associated with diabetic nephropathy

miRNA Sequence	Mechanism	References
miR-4534	Affects FoxO signaling pathway by targeting BNIP3	[91]
miR-615-3p	Increases plasma TGF-β1 expression levels	[11]
miR-194-5p	CUL4B is upregulated in macrophages under high glucose. Increased levels of Integrin α9 (ITGA9) promote migration and adhesion	[12]
miR-223-3p	Inhibits downstream STAT3 activation, targets IL6ST/STAT3 pathway	[14]
miR-663a	Increased expression reduces CXCR4 and HSPG2 expression	[15]
miR-144-3p	TGF-β1-induced NRF2 inhibition and elevated ROS	[16]
miR-23a-3p	Target Kruppel-like factor 3 (KLF3) inhibits STAT3 signaling pathway in high glucose (HG)-induced HK-2 cells	[20]
miR-4449	Inhibits HIC1 (functional target) expression and causes oxidative stress by inhibiting antioxidant gene SIRT1 expression	[21]
miR-7a-5p	Targets the 3' UTR of P311 mRNA and inhibits P311 (an RNA-binding protein) expression in SV40-MES-13 cells (high glucose-induced)	[22]
miR-34a	miR-34a Regulates early mesangial proliferation and glomerular hypertrophy in DN by targeting growth arrest-specific protein 1 (GAS1)	[24]
miR-145-5p	Promotes podocyte apoptosis by inhibiting Srgap2 and subsequently activating the RhoA/ROCK signaling pathway	[25]
miR-146a-5p	Promotes M2 macrophage polarization by targeting TRAF6	[26]
miR-214	Targets Receptor for Advanced Glycation Endproducts (RAGE) signaling mediator protein Diaphanous homolog 1 (DIAPH1)	[27]
miR-802	Activates canonical and non-canonical NF-κB pathways by targeting its negative regulator TRAF3, leading to macrophage recruitment	[28]
miR-1225-3p	Promotes fibrosis and oxidative stress by mediating ARHGAP5/SMURF2-mediated ubiquitination of ChREBP	[30]
miR-26a	Alleviates TIF in DKD by directly targeting PAR4	[31]
miR-504-3p	Regulates HG-induced podocyte injury by sponging HNF1B	[32]
miR-154-5p	Regulates TGFβ1/Smads pathway via Smurf1 ubiquitination and promotes the fibrotic process in diabetic kidney disease	[35]
miR-302a-3p	May play a protective role by targeting ZEB1 in renal EMT in DKD	[36]
miR-29b	Plays a crucial role in mitochondrial dysfunction by targeting PGC-1α, leading to podocyte damage and DKD progression	[37]

renal EMT in DKD. Given these findings, miR-302a-3p may serve as a potential novel target for improving renal fibrosis in the pre-EMT state in DKD [36]. MicroRNA-29b plays a key role in podocyte injury and glomerular disease by inducing mitochondrial dysfunction [37]. These suggest their potential as biomarkers for DKD (**Table 2**).

miRNAs related to OP

OP is a metabolic disease caused by oxidative stress or inflammation resulting from kidney disease. miRNAs have recently been recognized as being involved in OP [38]. miRNAs play a key regulatory role in the occurrence and development of OP, participating in bone metabolism by affecting the function of osteoblasts, osteoclasts, and bone marrow mesenchymal stem cells (BMSCs).

miRNAs that inhibit the progression of osteoporosis by regulating substances related to osteoblast and osteoclast differentiation

miR-96 can specifically bind to the 3'-untranslated region of HB-EGF mRNA, thereby suppressing the post-transcriptional expression of HB-EGF. In MC3T3-E1 cells, the reduction in HB-EGF mediated by miR-96 further inhibits the phosphorylation of epidermal growth factor receptor (EGFR) and its downstream signaling kinases, including extracellular signal-regulated kinase 1 (ERK1) and AKT. Collectively, these findings suggest that miR-96 facilitates osteoblast differentiation via repressing HB-EGF and

Table 3. MiRNAs that inhibit osteoporosis progression

miRNA Sequence	Mechanism	References
miR-96	Promotes osteogenic differentiation by inhibiting heparin-binding EGF-like growth factor (HB-EGF)-EGF receptor signaling in bone cells	[39]
miR-194	Regulates osteoblast differentiation by modulating signal transducer and activator of transcription 1 (STAT1)-mediated Runx2 nuclear translocation	[40]
miR-216a	Restores osteogenesis and enhances osteoblast differentiation and bone formation by regulating the c-Cbl-mediated phosphatidylinositol 3-kinase (PI3K)/protein kinase B/serine-threonine protein kinase (AKT) pathway	[43]
miR-17/20a	Targets RANKL and inhibits glucocorticoid-induced osteoclast differentiation in osteoblasts	[44]
miR-155	Mediates its inhibitory effect on osteoclast differentiation by targeting transforming growth factor β1 (TGFβ1)/Smad4 signaling pathway	[46]
miR-26a	(1) Positively regulates osteogenic differentiation of adipose tissue-derived stem cells (ADSCs) into osteoblasts by targeting SMAD1 transcription factor; (2) Inhibits osteoclastogenesis by targeting connective tissue growth factor (CTGF)	[49-92]
miR-142-3p	Promotes osteoblast differentiation by targeting APC to activate Wnt signaling	[50]
miR-1224-5p	Regulates osteogenesis by coordinating osteoblast/osteoclast differentiation via targeting ADCY2 through the Rap1 signaling pathway	[52]

blocking the HB-EGF-EGFR signaling cascade [39]. Data indicate that miR-194 regulates osteoblast differentiation by modulating STAT1-mediated Runx2 nuclear translocation [40]. It has been reported that elimination of the c-Cbl-PI3K interaction increases bone formation and osteoblast proliferation [41, 42]. miR-216a promotes osteoblast differentiation and enhances bone formation by regulating the c-Cbl-mediated PI3K/AKT pathway; miR-216a may serve as a novel therapeutic agent for preventing and treating OP and other bone metabolism-related diseases [43]. MicroRNA-17/20a inhibits glucocorticoid-induced osteoclast [44]. SOCS1 and MITF have been reported as potential targets of miR-155 [45], Transforming growth factor β1/Smad4 signaling exerts a regulatory effect on osteoclastogenesis through the modulation of miR-155 expression. This finding underscores the significant potential of miR-155 as a therapeutic target for the treatment of osteoclast-related disorders [46]. Northern blot showed that inhibition of miR-26a leads to upregulation of SMAD1 protein without affecting Smad-1 mRNA levels, supporting the postulated post-transcriptional mechanism of miRNA-regulated gene expression [47, 48]. Osteogenic differentiation of human adipose tissue-derived stem cells is regulated by the targeting of the SMAD1 transcription factor by miR-26a [49]. miR-142-3p promotes osteoblast differentiation by targeting APC to activate Wnt signaling [50]. In past decades, osteoclasts were considered end-stage cells [51]. In vitro, overexpression of miR-1224-5p slows RANKL-induced osteoclast differentiation by targeting ADCY2 and promotes osteoblast differentiation via the Rap1 signaling pathway. Additionally, in vivo overexpression of miR-1224-5p significantly promotes fracture healing and improves the progression of OP caused by estrogen deficiency or aging [52] (**Table 3** and **Figure 2**).

miRNAs that make osteoporosis healing (referring to symptom relief and increased BMD) difficult by inhibiting osteoblast or promoting osteoclast differentiation related substances

miR-15b regulates KDM6B expression by targeting USP7, inhibiting osteoblast differentiation and autophagy, thereby aggravating OP [38].

miR-21 has been identified as a characteristic miRNA signature during RANKL-induced osteoclastogenesis. Mechanistically, miR-21 exerts a suppressive effect on the protein levels of programmed cell death 4 (PDCD4). The consequent reduction in PDCD4 alleviates its-mediated inhibition of c-Fos, which serves as a key transcription factor essential for osteoclastogenesis and also regulates the expression of osteoclast-specific target genes. Additionally, RANKL stimulation induces the upregulation of c-Fos, which in turn transcriptionally activates the expression of the miR-21 gene [53]. RUNX2

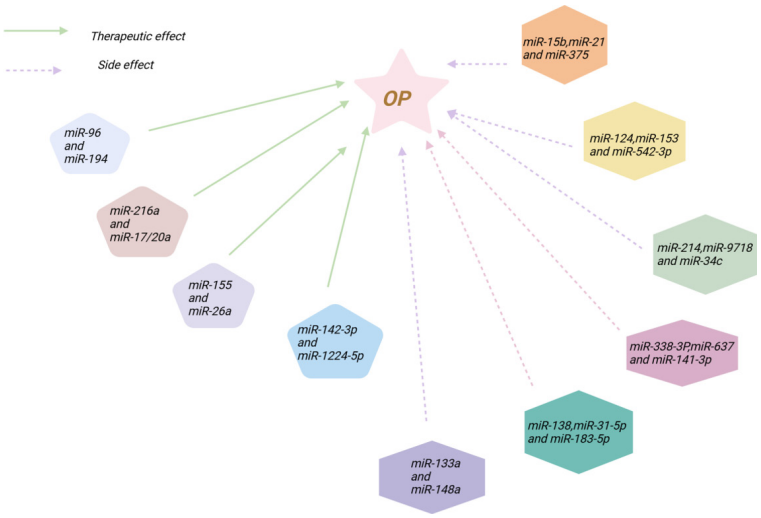

Figure 2. miR-96, miR-194, miR-216a, miR-17/20a, miR-155, miR-26a, miR-142-3p, miR-1224-5p; these miRNA combinations exert a predominantly therapeutic effect for osteoporosis. While, miR-15b, miR-21, miR-375, miR-124, miR-153, miR-542-3p, miR-214, miR-9718, miR-34c, miR-338-3p, miR-637, miR-141-3p, miR-138, miR-31-5p, miR-183-5p, miR-133a, miR-148a; these miRNA combinations exhibit predominant side effects for osteoporosis.

is a member of the RUNX family of transcription factors with a runt DNA-binding domain. RUNX2 has been identified as a key transcription factor regulating osteogenesis and chondrogenesis [54]. miR-375 can inhibit osteogenic differentiation by regulating RUNX2 expression [55]. miR-124 negatively regulates osteogenic differentiation of mesenchymal stem cells and bone formation in vivo [56]. Results show that miR-153 is a mechanosensitive miRNA that regulates osteoblast differentiation by directly targeting BMPR2, and therapeutic inhibition of miR-153 may be an effective strategy for skeletal diseases caused by pathological mechanical loading [57]. One target of miR-542-3p is survivin, a member of the inhibitor of apoptosis protein family that inhibits apoptosis through the caspase enzyme system [58]. miR-542-3p inhibits osteoblast proliferation and differentiation, targets BMP-7 signaling, and inhibits bone formation [59]. In bone tissue, miR-214 has been found to target ATF4 in osteoblasts [60]. miR-214 promotes osteoclastogenesis by targeting the Pten/PI3k/Akt pathway, which would provide a potential therapeutic target for OP [61]. Studies show that miR-9718 plays an important role in osteoclast differentiation both in vitro and in vivo by targeting PIAS3 [62]. Research shows miR-34c promotes osteoclast differentiation by targeting LGR4, providing new insights into understanding the molecular mechanisms of osteoclast differentiation [63]. Data indicate miR-338-3p plays an important role in BMSC osteoblast differentiation and acts as a potential osteoporosis regulator through its effects on osteoblasts [64]. As a downstream gene of Runx2, Osterix (Osx) is essential for the differentiation of pre-osteoblasts into mature osteoblasts [65]. In Osx-deficient embryos, cartilage forms normally but bone formation is completely absent [66]. miR-637 maintains the balance between adipocytes and osteoblasts by directly targeting Osterix; data suggest that miR-637 expression is crucial for maintaining the balance between adipocytes and osteoblasts. Disruption of the miR-637 expression pattern leads to irreversible damage to the differentiation balance in the bone marrow [67]. miR-141-3p acts as a negative regulator of hMSC proliferation and osteoblast differentiation. Targeting miR-141-3p could serve as an anabolic therapy for low bone mass diseases such as osteoporosis [68]. miR-138 inhibits bone formation in vivo at least partially by inhibiting focal adhesion kinase signaling pathway. The findings suggest that pharmacological inhibition of miR-138 by antisense miR-138 may represent a therapeutic strategy to enhance bone formation in vivo [69]. miR-31-5p is a positive regulator of osteoclast formation and bone resorption by targeting RhoA [70]. miR-183-5p is a positive regulator of osteoclast differentiation by inhibiting HO-1 expression [70]. RANKL stimulation triggers recruitment of tumor necrosis factor receptor-associated factor 6 (TRAF6), thereby activating downstream transcription factors including c-Fos and NFATc1, leading to increased TRAP expression [71]. Then, many osteoclastogenesis-related marker genes are activated, such as TRAP, MMP-9, and cathepsin K [72]. NFATc1-deficient embryonic stem cells fail to differentiate into osteoclasts, while ectopic expression of NFATc1 enables precursor cells to differentiate efficiently without RANKL stimulation [73]. Mice lacking c-Fos develop OP due to a complete absence of osteoclast formation [74]. miR-133a plays an

Table 4. MiRNAs that hinder osteoporosis recovery

miRNA Sequence	Mechanism	References
miR-15b	Regulates KDM6B expression by targeting USP7	[38]
miR-21	Involves a positive feedback loop of c-Fos/miR-21/PDCD4 (programmed cell death 4)	[53]
miR-375	Targeted Runx2 inhibits osteogenic differentiation, leading to decreased activity of several key osteoblast markers such as alkaline phosphatase (ALP), osteocalcin, and IBSP	[55]
miR-124	Inhibits osteogenic differentiation and bone formation by targeting Dlx transcription factors, including Dlx5, Dlx3, and Dlx2 genes	[56]
miR-153	Inhibits osteogenic differentiation, targets bone morphogenetic protein receptor type II (BMPR2)	[57]
miR-542-3p	Inhibits osteoblast differentiation and proliferation, targets bone morphogenetic protein-7 (BMP-7) signaling, thereby inhibiting bone formation	[59]
miR-214	Overexpression promotes osteoclastogenesis via the PI3K/Akt pathway, with phosphatase and tensin homolog (Pten) as a potential target	[61]
miR-9718	Enhances osteoclast differentiation and inhibits protein inhibitor of activated STAT3 (PIAS3) at the post-transcriptional level	[62]
miR-34c	Significantly promotes osteoclast differentiation by targeting the 3'-untranslated region of leucine-rich repeat-containing G-protein coupled receptor 4 (LGR4)	[63]
miR-338-3P	Inhibited the expression level of the osteoblast differentiation transcription factor Osterix in BMSCs by targeting Runx2 and Fgfr2	[64]
miR-637	Also shows inhibitory effects on osteoblasts by targeting Osterix	[67]
miR-141-3p	Inhibits osteoblast differentiation by targeting cell division cycle 25A in hBMSCs, reducing ALP and collagen	[68]
miR-138	Inhibits osteoblast differentiation by targeting focal adhesion kinase (FAK)	[69]
miR-31-5p	Is a positive regulator of osteoclast formation and bone resorption by targeting RhoA	[70]
miR-183-5p	Is a positive regulator of osteoclast differentiation by inhibiting HO-1 expression	[70-75]
miR-133a	Participates in the regulation of postmenopausal osteoporosis by promoting osteoclast differentiation	[75]
miR-148a	Promotes osteoclast differentiation by directly targeting MAFB (a protein that inhibits RANKL)	[76]

important role in RANKL-induced differentiation of RAW264.7 and THP-1 cells into osteoclasts [75]. Research results show that miR-148a promotes osteoclast differentiation by directly targeting MAFB (a protein that inhibits RANKL), providing new insights into the role of miRNAs in osteoclastogenesis and opening new avenues for the treatment of OP [76] (**Figure 2** and **Table 4**).

Potential role of miRNA in DKD combined with OP

miRNAs associated with DKD combined with OP

Current research has evidenced that the serum expression levels of miR-338-3p and miR-150-3p in DKD patients display a remarkable correlation with bone metabolic biomarkers. This finding indicates that these two miRNAs are potentially involved in the initiation and progression of diabetic nephropathy (DN). Mechanistically, miR-338-3p serves as a crucial regulatory factor in bone tissue homeostasis. It modulates osteoclast formation through targeted regulation of the IKKβ gene. Additionally, this miRNA governs the osteogenic differentiation of murine bone marrow mesenchymal stem cells by targeting Runx2 and Fgfr2. Notably, miR-338-3p exerts an inhibitory effect on osteoclast differentiation via targeting MafB, thereby contributing to the therapeutic intervention of osteoporosis [77]. Furthermore, the serum levels of these two miRNAs and bone metabolism markers differ among DKD patients at different stages, and their expression is significantly correlated with bone metabolism markers. Combined detection of them could

provide new ideas for the clinical treatment of DKD combined with OP and is also of great significance for finding potential therapeutic targets for this condition. miR-154-5p is the mature serum sequence of miR-154 [78], regulating osteogenesis and differentiation of mesenchymal stem cells from adipose tissue [79, 80], and it may be related to renal fibrosis [81]. Collectively, these findings implicate a potential mechanistic link between miR-154-5p and the pathological processes underlying impaired osteogenic differentiation and elevated proteinuria in chronic kidney disease (CKD). Furthermore, the dysregulated expression profile - characterized by elevated serum levels of miR-154-5p concomitant with reduced osteocalcin (OC) concentrations - may collectively modulate osteogenic activity and proteinuria pathogenesis in type 2 diabetes mellitus (T2DM). This observation not only highlights the clinical utility of miR-154-5p but also suggests its potential as a novel diagnostic biomarker and therapeutic target for the intervention of diabetic kidney disease (DKD) complicated with osteoporosis [82-84]. Through experiments, WGCNA successfully identified 63 miRNAs related to DNOP (DKD-OP). Notably, miR-574 was observed to be markedly upregulated in both DN and OP specimens, a finding that underscores its potential significance in the pathological interplay underlying DKD complicated by osteoporosis [85].

Conclusion

This review has summarized the regulatory roles and related molecular mechanisms of miRNAs in Diabetic Kidney Disease (DKD) and Osteoporosis (OP). Current research has clearly established that miRNAs play significant roles in the pathogenesis of both DKD and OP, with some miRNAs even participating in the pathological processes of both diseases, suggesting they may serve as molecular bridges connecting the two conditions. Notwithstanding the growing understanding of miRNA-mediated regulation, inherent challenges nonetheless persist in this field of inquiry. Primarily, the majority of investigative efforts have centered on individual miRNAs or isolated disease entities. Consequently, our comprehension of the intricate synergistic regulatory networks that bridge miRNA signaling pathways in both DKD and OP remains notably fragmented. Moreover, the prospective translation of miRNAs into clinical practice - either as robust diagnostic biomarkers or actionable therapeutic targets - confronts substantive hurdles pertaining to their clinical specificity, targeted delivery modalities, and overall safety profiles.

Disclosure of conflict of interest

None.

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