



## Emerging roles of microRNAs as diagnostics and potential therapeutic interest in type 2 diabetes mellitus

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### Abstract

#### BACKGROUND

Type 2 diabetes mellitus (T2DM) is a metabolic disease of impaired glucose utilization. Uncontrolled high sugar levels lead to advanced glycation end products (AGEs), which affects several metabolic pathways by its receptor of advanced glycation end products (RAGE) and causes diabetic complication. MiRNAs are small RNA molecules which regulate genes linked to diabetes and affect AGEs pathogenesis, and target tissues, influencing health and disease processes.

#### AIM

To explore miRNA roles in T2DM's metabolic pathways for potential therapeutic and diagnostic advancements in diabetes complications.

#### METHODS

We systematically searched the electronic database PubMed using keywords. We included free, full-length research articles that evaluate the role of miRNAs in T2DM and its complications, focusing on genetic and molecular disease mechanisms. After assessing the full-length papers of the shortlisted articles, we included 12 research articles.

#### RESULTS

Several types of miRNAs are linked in metabolic pathways which are affected by AGE/RAGE axis in T2DM and its complications. miR-96-5p, miR-7-5p, miR-132, has\_circ\_0071106, miR-143, miR-21, miR-145-5p, and more are associated with various aspects of T2DM, including disease risk, diagnostic markers, complications, and gene regulation.

#### CONCLUSION

Targeting the AGE/RAGE axis, with a focus on miRNA regulation, holds promise for managing T2DM and its complications. MiRNAs have therapeutic potential as they can influence the metabolic pathways affected by AGEs and RAGE, potentially reducing inflammation, oxidative stress, and vascular complications. Addi-

tionally, miRNAs may serve as early diagnostic biomarkers for T2DM. Further research in this area may lead to innovative therapeutic strategies for diabetes and its associated complications.

**Key Words:** Type 2 diabetes mellitus; MicroRNAs; Advanced glycation end products; Receptor for advanced glycation end products

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**Core Tip:** Type 2 diabetes mellitus (T2DM) is a worldwide problem characterized by uncontrolled hyperglycemia. In T2DM, elevated glucose bound proteins and leading to formation advanced glycation end products. miRNAs play a major role in gene regulation of different proteins which are involved in various metabolic pathways including nuclear factor kappa beta, protein kinase C, and phosphoinositide-3-kinase–protein kinase B/Akt which are responsible for blood glucose and insulin secretion and T2DM. The target of these miRNA changes the regulation of metabolic pathways which can reduce oxidative stress and inflammation. So, the modulate the regulation of these miRNA could be possible approach of the treatment of T2DM.

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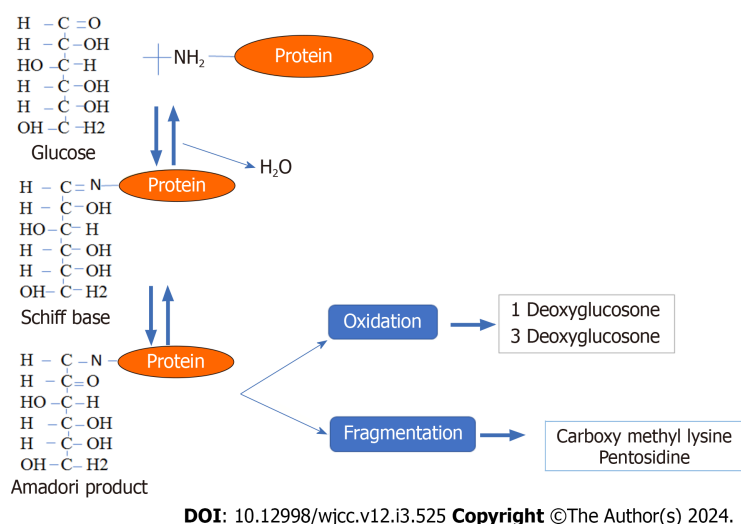
## INTRODUCTION

Type 2 diabetes mellitus (T2DM) characterizes by hyperglycemia which is a metabolic disorder affecting 400 million people worldwide, and projections by the World Health Organization estimate this number will rise to 600 million by 2040[1].

The main cause of diabetes is inadequate insulin production, which results from pancreatic cell dysfunction or reduced responsiveness of glucose receptors[2]. In diabetes, elevated glucose levels are the primary contributors. In diabetic individuals, inadequate management of blood sugar levels is linked to the formation of advanced glycation end products (AGEs) which play an important role in the acceleration of vascular disease[3]. AGEs are the result of a non-enzymatic reaction between the carbonyl group of reducing sugars and the amino groups of proteins and lipids. This process starts with the formation of Schiff bases, followed by Amadori rearrangement and oxidative modification, collectively known as the Maillard reaction (Figure 1)[4]. Under normal physiological conditions, glycation is a spontaneous process contingent upon substrate availability[5]. However, in diabetes, elevated glucose levels accelerate the glycation of various functional and structural proteins.

AGEs' pathophysiology can be categorized into two distinct mechanisms. In the first method, AGEs form direct associations with extracellular matrix proteins, including collagen, elastin, laminin, and vitronectin, through trapping, cross-linking, and intramolecular AGE-AGE covalent bonds[6,7]. In the basement membrane, crosslinking of AGEs to collagen IV and elastin increases rigidity and decreases susceptibility to proteolytic digestion, thereby increasing vascular stiffness and causing diastolic dysfunction[8]. Furthermore, AGEs alter the structure of low-density lipoproteins (LDL) through glycation and form glycosylated LDL, which prevent their normal physiological excretion. Glycosylated low-density lipoprotein cholesterol (LDL-C) is absorbed by circulatory monocytes or mast cells and produces foam cells[9]. In the second mechanism, AGEs interact with Receptor for advanced glycation end products (RAGEs), specific cell surface receptors for AGEs[10]. RAGE, a 404-amino acid transmembrane receptor belonging to the immunoglobulin superfamily, plays a central role in mediating cellular dysfunction over an extended period, giving rise to "metabolic memory," characterized by prolonged activation of nuclear factor kappa beta (NF-κB), inflammation, and oxidative stress[11]. This interaction triggers signal transduction, activating various intracellular signaling molecules, including Extracellular signal-regulated protein kinases 1/2, phosphoinositide-3-kinase–protein kinase B/Akt (PI3/Akt), and Janus kinase/signal transducers and activators of transcription, ultimately resulting in the activation of NF-κB and the upregulation of tumor necrosis factor (TNF-α), C-reactive protein, and interleukin -6 (IL-6) mRNA expression[12].

MicroRNAs, a subclass of small non-coding RNA molecules with an average length of less than 200 nucleotides which are essential regulators of post-transcriptional gene expression. These minuscule genetic components are found extensively in a variety of bodily fluids, including as serum, urine, plasma, and saliva. They are also encased in donor cell exosomes and macrovesicles[13]. MiRNA expression significantly influences the regulation of complex genomic, metabolic, and physiological cellular signaling cascades[14]. Altered miRNA expression disrupts the function of various genes, leading to pathophysiological changes and can play a major role in various disease pathogenesis including cancer[15], Alzheimer's disease[16], spinal cord injury[17], epilepsy[18], neurodegenerative diseases[19], cardiac diseases[20], infectious diseases[21], and diabetes[22]. Various miRNAs have been identified in different stages and types of diabetes. For instance, miR-148a-3p is consistently found in all stages of Type 1 diabetes mellitus (T1DM), indicating its potential as an early biomarker specific to T1DM etiology[23,24]. miR-25 exhibits high expression in individuals newly diagnosed



**Figure 1 Advanced glycation end products formation.** Reaction between the carbonyl group of reducing sugar and the amino group of proteins and lipids via a Schiff base reaction cascade, followed by amadori rearrangement and oxidative modification.

with T1DM[25]. MiR-142, miR-126, and miR-21 are commonly associated with obesity, prediabetes, and T2DM[26]. MiR-375 is shared by both prediabetes and T2DM patients, indicating its early involvement in T2DM pathogenesis[27]. MiR-342-3p is shared among individuals with gestational diabetes mellitus (GDM), those at risk of developing T1DM, and T1DM patients, while miR-210 is shared between GDM and long-standing T1DM cases[28]. miR-126 expression in T2DM patients compared to healthy individuals and proposed its potential use as a circulating biomarker for the early detection of T2DM. Additionally, individuals with miR-126 cycle threshold (relative quantification unit) values greater than 35 may develop T2DM over a two-year period[29]. MiR-320 is downregulated in the context of hyperglycemia, AGEs, and diabetes. Overexpression of miR320 can reverse this effect by targeting vascular endothelial growth factor (VEGF). MiR-141 is upregulated in T2DM and affects INS-1  $\beta$  cell proliferation and glucose-stimulated insulin secretion. Silencing miR-141 reduces T2DM-associated damage[30].

In this review, we comprehensively analyze the preclinical and clinical evidence regarding the role of miRNAs in the metabolic pathways activated by the AGE/RAGE axis and explore their potential in therapeutic interventions.

## MATERIALS AND METHODS

The literature search was carried out in the PubMed NCBI database. The search strategy was carried out by combining "MicroRNAs" [Mesh AND "Glycation End Products, Advanced" [Mesh AND "Diabetes Mellitus, Type 2"] with each other using boolean operators. At the start of a literature search, search the NCBI PubMed data base. After applying filters for "free full text, in the last 5 years (2018–2023)" and further limiting it to English language research papers.

At the start of the literature search, the NCBI PubMed database showed 37 articles. After applying filters, limit the search to "full text in the last 5 years (2018–2023)," which gives 12 studies (Figure 2 and Table 1). Only full-length research articles are included.

## RESULTS

After conducting a comprehensive literature search in the PubMed database, we found that in T2DM, miRNA plays a significant role in regulating the genetic and molecular mechanisms underlying the disease (Table 1).

miR-96-5p and miR-7-5p are potentially modulated gene and plays a major role in T2DM and osteoporosis, These miRNAs are involved in the phosphoinositide 3-kinase (PI3K)-Akt signalling pathway and the AGE-RAGE signalling pathway in diabetic complications, which may play a significant role in diabetic skeletal fragility[31]. Over expression of miR-132 was identified in mild cognitive impairment (MCI) among patients with T2DM and emerged as a potential diagnostic biomarker for MCI in these patients[32]. has\_circ\_0071106 increases the risk of T2DM by effecting protein binding and gene transcription, may be involved in the pathway of hsa-miR-29a-5p regulating diabetes, and could potentially serve as a diagnostic marker[33]. The upregulated expression of miR-143 in the presence of the CC genotype of rs4705342 increases the risk of T2DM and potentially associated with higher levels of LDL-C, fasting blood glucose, and glycated haemoglobin[34]. miR-21 expression is positively associated with glycosylated haemoglobin (HbA1c), fasting blood sugar, and triglyceride and can be considered a non-invasive and rapid tool for distinguishing individuals with pre-T2DM and T2DM from healthy individuals[35]. miR-145-5p and miR-483-3p/5p control TP53-mediated apoptosis in T2DM. They also observed a significant fold change in miR-138-5p, miR-192-5p, miR-195-5p, miR-320b, and let-7a-5p in T2DM, all of which are involved in beta cell dysfunction[36]. miR-let-7g-5p expression is suppressed by ET-1 (endothelin-

Table 1 MiRNAs involved in type 2 diabetes clinical and pre-clinical evidence

No.	Micro RNA	Status	Disease	Model	Publish year	Ref.
1	miR-96-5p and miR-7-5p		T2DM	Bioinformatic	2022	[31]
2	miR-132	Upregulated	T2DM	Human	2020	[32]
3	hsa-miR-29a-5p	Upregulated	T2DM	Human	2021	[33]
4	miR-143	Upregulated	T2DM	Human	2022	[34]
5	mir-21 and miR-126	Upregulated	T2DM	Human	2022	[35]
6	miR-145-5p, miR-483-3p/5p, miR-138-5p, miR-192-5p, miR-195-5p, miR-320b, and let-7a-5p		T2DM	Human	2019	[36]
7	miR-let-7g-5p	Downregulated	T2DM	Human	2022	[37]
8	miR-187-3p, miR-21-5p, miR-668, miR-199b-5p, mir-216a, miR-25 miR-30a-3p miR-30a-5p		T2DM	Human	2023	[38]
9	miRNA-152-3p	Upregulated	T2DM	Human	2022	[39]
10	Microrna-146a and microrna-130a	Upregulated	T2DM	Human	2019	[40]
11	miR-24-3p	Upregulated	T2DM	Human	2021	[41]
12	miR-126-3p/u6sno	Upregulated	T2DM	Human	2021	[42]

T2DM: Type 2 diabetes mellitus.

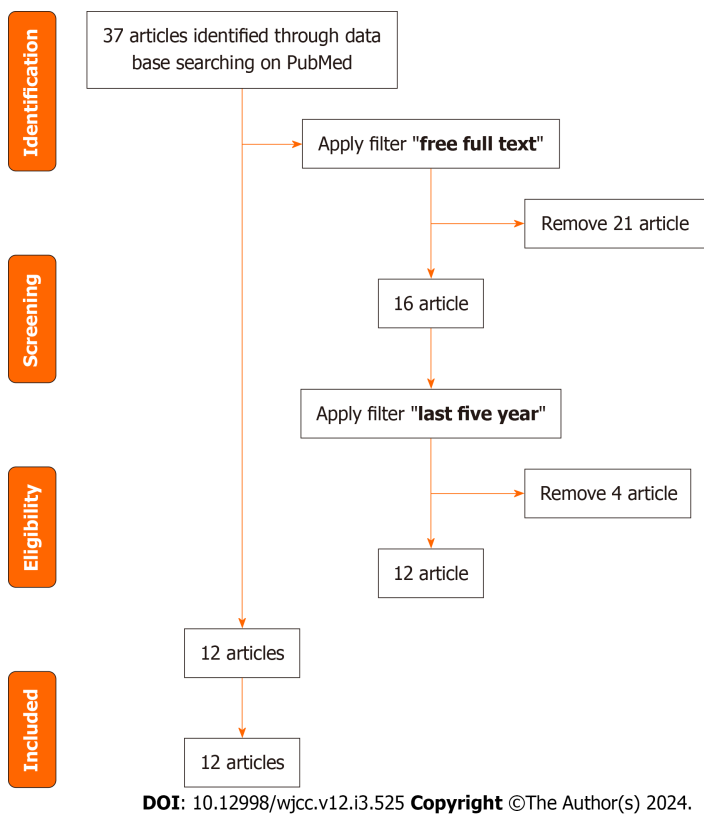


Figure 2 PRISMA flow diagram of study selection process for preclinical and clinical evidence.

1), subsequently leading to increased TNF- $\alpha$  and IL-6 expression in a dose-dependent manner. This suppression of miR-let-7g-5p contributes to reduced fat metabolism and increases inflammation, promoting myopathy[37]. Taylor *et al*[38] identified 84 heritable miRNAs and 5 miRNA-expression (miR-216a, miR-25, miR-30a-3p, and miR-30a-5p) quantitative trait loci associated with blood glucose and glycated HbA1c levels. miRNA-152-3p expression, despite initial consideration ineffectiveness as a prognostic indicator for the progression to end-stage renal disease, unlike serum CX3CL1 levels and urinary IgG, which showed promising efficacy in early prediction of nephropathy[39]. Cirilli *et al*[40] assessed

the correlation between the amount of daily exercise recorded with a wearable gravitometer and selected biochemical and clinical parameters in sedentary T2D patients. The authors suggested that in the high-exercise group, miRNA-146a decreased, reducing inflammation and regulating systolic blood pressure, while the upregulation of microRNA-130a decreased HbA1c levels. Furthermore, the authors concluded that these miRNAs can serve as potential biomarkers for further investigation in T2DM[40]. miR-24-3p expression, in conjunction with elevated reactive oxygen species (ROS) levels due to glycated albumin, contributes to the reduction in TRPM6 expression within renal tubular epithelial cells of type 2 diabetes (T2D)[41]. Witkowski *et al*[42] suggested that supplementation with metformin increases tissue factor expression by reducing lipopolysaccharide, indicating its potential for vascular protective properties and can regulate microRNA synthesis.

## DISCUSSION

MiRNAs are crucial in regulating diabetic complications, especially in the context of AGE and RAGE-related processes. They play a key role in controlling important signaling pathways like NF- $\kappa$ B, protein kinase C (PKC), PI3K, and nitric oxide, which are essential in diabetic complication development (Table 2)[43].

### Role of miRNA in AGE/RAGE targeted metabolic signaling pathways

The AGEs/RAGE axis initiates a complex signaling cascade involving various signaling molecules and transcription factors, and the synthesis of these factors is under the influence of miRNAs. The involvement of miRNAs in the AGEs/RAGE targeted metabolic pathways is discussed below.

**Regulation of the NF- $\kappa$ B Pathway by miRNA:** NF- $\kappa$ B, is a heterodimeric transcription factor that can efficiently bind to the target gene's regulatory region (promoter or/and enhancer)[44]. The AGEs/RAGE axis, as well as the generation of oxidative stress, activate the NF- $\kappa$ B pathway and increase the pro-inflammatory response in diabetes[45]. NF- $\kappa$ B activation is required for cellular proliferation and migration under physiological conditions. NF- $\kappa$ B significant release of cytokines including IL-1, IL-6, CD36, TNF- $\alpha$ , and Monocyte Chemoattractant Protein-1 as well as chemokines, tumor growth factor (TGF), and vesicular cell adhesion molecules, eventually leading to vascular damage[46]. NF- $\kappa$ B dependent miR124, controls cytokine signaling in hyperglycemic conditions. The overexpression of miR124 downregulates exocytosis and decreases glucose-mediated insulin release[47]. The relationship between microRNAs and NF- $\kappa$ B across various health conditions, miR-21 showed an up-regulation in cases of Metabolic syndrome and obesity[48]. miR-124 down-regulation in diabetic condition[49]. miR-471-3p exhibited an up-regulation in instances of diabetic cardiomyopathy[50], and miR-46a displayed an up-regulation in cases of Hyperlipidemia[51]. Conversely, both miR-200b and miR-200c were down-regulated in relation to NF- $\kappa$ B[52] (Figure 3).

**Regulation of PKC pathway by miRNA:** The interaction between AGEs/RAGE triggers the PKC (protein kinase C) pathway, promoting fibrosis and inflammation. Elevated glucose levels in diabetes result in increased diacylglycerol (DAG) synthesis through a de novo method, which upregulates the PKC pathway. MiRNAs have been found to regulate the PKC pathway in various diabetic complications[53]. miR-210 downregulation plays a protective role in T2DM by regulating endothelial function. MiR-210 also mitigates AGE-mediated activation of JNK (c-Jun N-terminal kinase) and PKC, reversing pathological conditions in cardiomyocytes[54]. MiR-25 regulates the AGE/RAGE-activated PKC pathway in diabetic nephropathy, inhibiting PKC phosphorylation and reducing oxidative stress[55]. Furthermore, miR-21-3p upregulation in diabetic atherosclerosis inhibits ROS generation and promotes RAGE/NADPH (nicotinamide adenine dinucleotide phosphate hydrogen) oxidase signaling[56]. Exposure to AGEs on diabetic endothelial cells increases the expression of miR-92a, which causes endothelium dysfunction and decreases the expression of heme oxygenase-1 and increases oxidative stress. Inhibition of miR-92a up-regulates the expression of heme oxygenase-1 and reverses endothelium dysfunction[57] (Figure 4).

**Regulation of the nitric oxide pathway by miRNA:** Diabetes leads to endothelial dysfunction, partly due to reduced nitric oxide (NO) production. The AGEs/RAGE interaction lowers eNOS (endothelial Nitric Oxide Synthase) and NO levels, leading to endothelial dysfunction and an increased risk of cardiovascular diseases. MiRNAs also have a role in the regulation of NO pathway[58]. In diabetic mice, miR-185 downregulation increases ROS generation and decreases NO levels. Treatment with Huayu Tongmai Granules can reverse these effects[59]. MiR-195 and miR-582 upregulation in deep vein thrombosis affects NOS3 (nitric oxide synthase 3) expression and NO levels, contributing to the pathogenesis [60] (Figure 5).

**Regulation of the PI3K/AKT pathway by miRNAs:** The PI3K/AKT pathway is essential for glucose and lipid metabolism, insulin secretion, and cellular glucose uptake. In diabetes, AGEs disrupt this pathway, leading to insulin resistance[61]. Various miRNAs are involved in the regulation of the PI3K/AKT pathway. MiR-29b-3p, miR-29c-3p, miR-93-5p, miR-150-5p, miR-199a-5p, miR-345-3p, and miR-532-3p are all implicated in the downregulation of the slc2a4 gene and GLUT-4 expression, affecting glucose metabolism[62]. MiR-25-3p modulates epithelial-mesenchymal transition in endothelial cells, affecting the PI3K/AKT pathway[63]. MiR-214 downregulates oxidative stress in diabetic nephropathy by targeting the ROS/Akt/mTOR pathway[64]. MiR-203 upregulation slows wound healing in diabetic foot ulcers by targeting the PI3/AKT/mTOR signaling pathway[65]. Similarly, down-regulation of miR-129-5p and miR-146b-3p while showed an up-regulation of miR-191 and miR-29b-3p regulate the PI3K/AKT pathway[66-69] (Figure 6).



**Table 2** Role of miRNA in various metabolic pathways

No.	miRNA	Target pathway	Model	Disease	Effect	Ref.
1	miR-21	NF- $\kappa$ B	db/db mice	Metabolic syndrome and obesity	Up-regulated	[48]
2	miR-124	NF- $\kappa$ B	Primary rat retinal microglial cells		Down-regulated	[49]
3	miR-471-3p	NF- $\kappa$ B	Raw264.7 cells and db/db mice	Diabetic cardiomyopathy	Up-regulated	[50]
4	miR-46a	NF- $\kappa$ B	Human blood	Hyperlipidemia	Up-regulated	[51]
5	miR-200b	NF- $\kappa$ B	Huvec line		Down-regulated	[52]
6	miR-200c	NF- $\kappa$ B	Huvec line		Down-regulated	[52]
7	miR-210	PKC			Down-regulated	[54]
8	miR-25	PKC	Adult male balb/c mice and diabetic db/db mice	Diabetic peripheral neuropathy	Down-regulated	[55]
9	miR-21-3p	PKC	Human aortic vsmcs (C-12511, promocell, and human vets	Diabetic atherosclerosis	Down-regulated	[56]
10	miR-92a	PKC	db/db mice	Diabetes mellitus	Up-regulated	[57]
11	miR-185	NO	Three-month-old male sprague-dawley rats	Diabetes mellitus	Down-regulated	[59]
12	miR-195	NO	Mvec cell lines	Deep vein thrombosis	Down-regulated	[60]
13	miR-582	NO	Mvec cell lines	Deep vein thrombosis	Down-regulated	[60]
14	miR-191	PI3K/AKT	Male C57bl/6j mice		Up-regulated	[62]
15	miR-29b-3p	PI3K/AKT	Human serum and Hek-293t cells	Diabetic retinopathy	Up-regulated	[62]
16	miR-29c-3p	PI3K/AKT	Rat	Diabetes mellitus	Up-regulated	[62]
17	miR-199a-5p	PI3K/AKT	Rat	Diabetes mellitus	Down-regulated	[62]
18	miR-532-3p	PI3K/AKT	Rat	Diabetes mellitus	Down-regulated	[62]
19	miR-93-5p	PI3K/AKT	Rat	Diabetes mellitus	Down-regulated	[62]
20	miR-150-5p	PI3K/AKT	Rat	Diabetes mellitus	Down-regulated	[63]
21	miR-345-3p	PI3K/AKT	Rat	Diabetes mellitus	Down-regulated	[64]
22	miR-25-3p	PI3K/AKT	Human blood	Diabetic retinopathy	Down-regulated	[65]
23	miR-214	PI3K/AKT	Male sprague dawley rats	Diabetic nephropathys	Down-regulated	[66]
24	miR-203	PI3K/AKT	Rat	Diabetic foot ulcer	Up-regulated	[67]
25	miR-129-5p	PI3K/AKT	Sprague dawley rats	Intracerebral Haemorrhage	Down-regulated	[68]
26	miR-146b-3p	PI3K/AKT	Human blood		Down-regulated	[69]

PI3K: Phosphoinositide 3-kinase; NF- $\kappa$ B: Nuclear factor kappa B subunit 1.

### MiRNA as therapeutics in diabetes mellitus

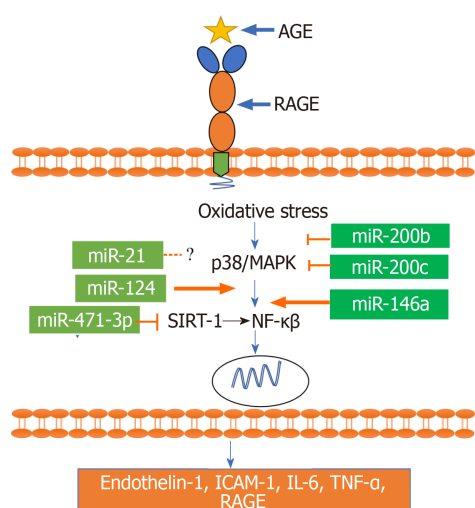
MiRNAs are thought to have a role in regulating various biological processes. This regulation can involve the direct targeting of specific tissues or cell types, potentially regulate both physiological and pathological processes[70]. Due to this, researchers looking into alternative therapeutic approaches based on miRNA alteration have started to gain greater attention. Numerous techniques and strategies have recently been created to correct the dysregulated expression (overexpression or under expression) of miRNAs.

miRNAs' expression in metabolic disease and reported therapeutic approaches are given in Table 3. Lin *et al*[54] suggested the therapeutic role of miR-210 in AGEs-exposed cardiomyocytes by using a miR-210 mimic and hypothesised that downregulation of miR-210 in AGEs-induced cardiomyocytes would reduce PKC-enhanced JNK-dependent mitochondrial damage. Chen *et al*[71] suggested that downregulation of miR-29b plays a role in the development of diabetic nephropathy. MiR-29b therapy using an ultrasound-microbubble-mediated gene transfer technique can improve TGF- $\beta$ /Smad3-dependent renal fibrosis, NF-mediated renal inflammation, and reverse pathological changes. Similarly, the overexpression of miR-146a can significantly improve AGE-mediated pathological effects in the development of diabetic foot ulcers through miRNA mimicry[72]. Another study shows that the overexpression of miRNA-339-5p ameliorates the AGEs-induced complications in vascular endothelial progenitor cells in patients with PCOS by targeting PI3K, AKT,

**Table 3 miRNAs expression in metabolic disease and reported therapeutic approaches**

No.	miRNA	Model	Method	Disease	Target	Ref.
1	miR-210	H9c2 cells (rat embryonic cardiac myoblast; ATCC)	miR-210 mimic and inhibitor	Diabetic cardiomyopathy	c-Jun N-terminal kinase (JNK)	[54]
2	miR-29b	db/db mice	Ultrasound-microbubble-mediated gene transfer technique was used to deliver doxycycline (Dox)-inducible pre-miR-29b	Diabetic nephropathy	TGF- $\beta$ /Smad3	[71]
3	miR-146a	HaCaT cells	Mimic and inhibitor miR-146a deliver <i>via</i> lipofecter liposomal transfection	Diabetic foot ulcer	AKAP12, Wnt3a and $\beta$ -catenin	[72]
4	miRNA-339	Endothelial progenitor cell of humans	Transfection with miRNA-339-5p mimic or miRNA-339-5p inhibitor	Polycystic ovary syndrome	PI3K, AKT and SIRT1 PGC-1 $\alpha$	[73]
5	miR-21	C6 glioblastoma cells	Antagomir-21/RAP nanoparticles	Intracranial glioblastoma	PTEN and PDCD4	[74]
6	miR-107 and miR-103	C57BL/6J	Antagomir of miR-103 and miR-107 delivered by liver-targeting lipid nanoparticle	Diabetes	Caveolin-1	[75]
7	miR-181a	Mouse neuroblastoma cells (Neuro2A) and HEK293T cells and male sprague dawley rats	AMO181a-cholesterol loaded exosomes	Cerebral ischemia	Hypoxia-induced RAGE and Bcl2	[76]

RAGE: Receptor of advanced glycation end products; TGF: Tumor growth factor.

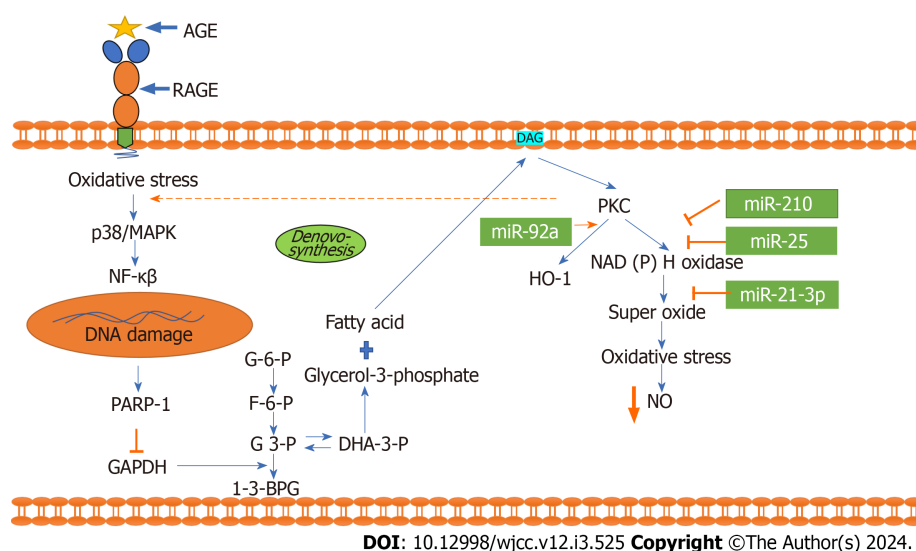


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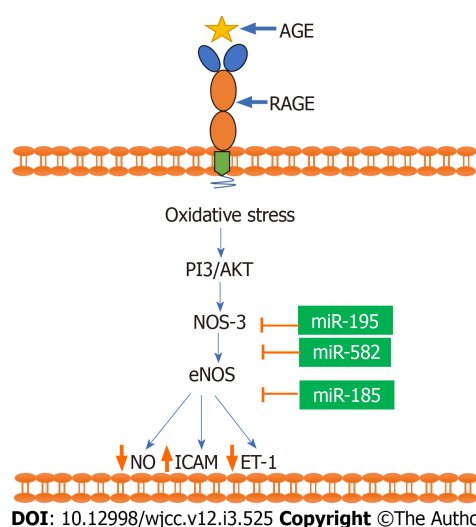
**Figure 3 MiRNA regulation in the advanced glycation end product/receptor of advanced glycation end products activated nuclear factor pathway.** Advanced glycation end product - receptor of advanced glycation end product interaction activates the nuclear factor pathway, which is inhibited by miR-200b, miR-200c, and miR-471-3p and upregulated by miR-124 and miR-146a. AGE: Advanced glycation end product; RAGE: Receptor of advanced glycation end product; MAPK: Mitogen-activated protein kinases; NF-κB: Nuclear factor kappa beta; TNF-α: Tumor necrosis factor.

SIRT1, and PGC-1 $\alpha$  by transfection with miRNA-339-5p mimic[73]. The administration of RAGE-antagonist peptide (antagomir-21) in intracranial glioblastoma nanoparticles can reduce miR-21 Levels and enhance tumour cell apoptosis. Furthermore, it inhibits RAGE expression and lowers VEGF levels in tumour cells[74]. Trajkovski *et al*[75] modified anti-miRNA oligonucleotides were administered to ob/ob mice and HFD-C57BL/6J by tail-vein injection to suppress both miR-107 and miR-103 in adipose tissue and liver, and they suggested that inhibition of miR-107 and miR-103 can improve insulin sensitivity in the liver and adipose tissues. In cerebral ischemia, hypoxia-induced RAGE plays a significant role, which is regulated by miR-181a. Kim *et al*[76] suggested that the administration of AMO181a-cholesterol-loaded exosomes (anti-microRNA oligonucleotide) downregulates the expression of miR-181a and reduces the damage to the ischemic brain. Apoptosis and TNF expression were also reduced.

MiRNAs play a complex role in various metabolic processes especially related to AGE and RAGE. Understanding the role of miRNAs in regulation of pathways like NF-κB, PKC, Nitric Oxide, and PI3/AKT highlights their crucial importance in diabetes. However, beyond delineating these pathways, comprehending the broader implications of these findings is crucial for advancing therapeutic interventions in diabetes. These revelations open avenues for targeted therapeutic interventions that might potentially alleviate these complications, thereby mitigating the burden of diabetic-related car-



**Figure 4 Interaction of advanced glycation end product and receptor of advanced glycation end product activates the protein kinase C pathway: The interaction of advanced glycation end product and advanced glycation end product activates the nuclear factor pathway and damages DNA, causing PARP-1 to be released and GAPDH to be inhibited.** The inhibition of GAPDH affects the glycolysis pathway and increases fatty acid synthesis. This increased synthesis of fatty acids activates diacyl glycerol in the cell membrane, which is a potent activator of protein kinase C (PKC). Increased PKC promotes synthesis of NADPH oxidase, super oxide and oxidative stress and ultimately decreases cellular nitric oxide. In this pathway, miRNA 210, miR-25, and miR-21-3p inhibit NADPH oxidase and oxidative stress. Apart from that, miR 92a promotes the expression of the antioxidant HO-1. AGE: Advanced glycation end product; RAGE: Receptor of advanced glycation end product; NF-κB: Nuclear factor kappa beta.



**Figure 5 Regulation of miRNA in the nitric oxide pathway: The interaction of advanced glycation end product and receptor of advanced glycation end product affects the availability of Nitric Oxide via inhibition of eNOS.** miR-195, miR-582, and miR-182 all inhibit AGE/RAGE-mediated eNOS alterations and nitric oxide production. AGE: Advanced glycation end product; RAGE: Receptor of advanced glycation end product; NF-κB: Nuclear factor kappa beta; NO: Nitric oxide.

diovascular disease.

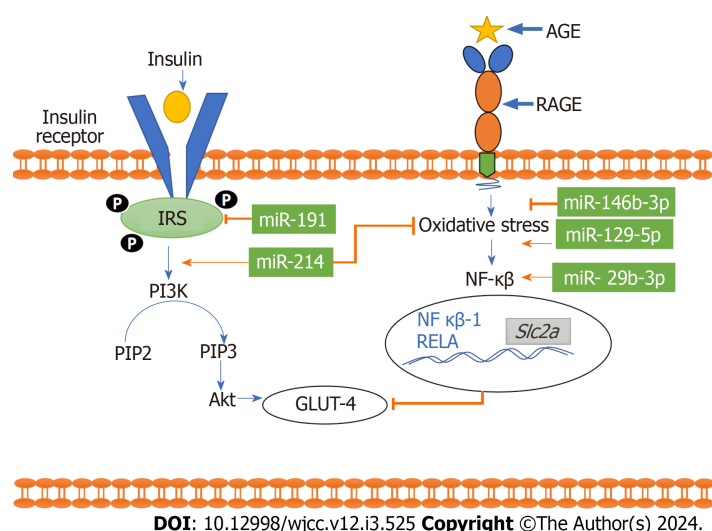
### Clinical implications and translation

Exploring the therapeutic potential of targeting specific miRNAs to modulate these pathways could revolutionize diabetes management. While current studies show promise in animal models and *in vitro* experiments. For miRNA-based therapies to be validated and effectively used as a therapeutic intervention for diabetes complications, more preclinical and clinical research is needed.

### Limitations and future prospects

Despite the strides made in understanding miRNA-mediated mechanisms, several limitations persist. Comprehensive research is necessary to identify more miRNA-target interactions due to the intricate control of miRNA and the dynamic nature of cellular responses. Additionally, the translation of these findings from bench to bedside necessitates meticulous





**Figure 6 Functional role of miRNA in the advanced glycation end product/receptor of advanced glycation end products activated phosphoinositide 3-kinase pathway.** The advanced glycation end product/receptor of advanced glycation end products-activated nuclear factor (NF) pathway inhibits GLUT-4 release from the cellular membrane. miR-129-5p, miR-29b-3p upregulate the pathway. However, miR-191, miR-146b-3p and miR-191 show an inhibitory effect. Furthermore, miR 214 increases GLUT-4 expression by simultaneously upregulating the PI3k/AKT pathway and inhibiting the NF- pathway. AGE: Advanced glycation end product; RAGE: Receptor of advanced glycation end product; NF-κB: Nuclear factor kappa beta.

attention to the safety, efficacy, and delivery strategies of miRNA-based therapeutics.

Future research endeavours should focus on comprehensively elucidating the regulatory networks involving miRNAs in diabetic complications. Addressing the specific roles of understudied or newly discovered miRNAs in different diabetic complications could provide a more holistic understanding. Moreover, exploring innovative delivery systems and improving bioavailability could enhance the feasibility of miRNA-based therapeutics in clinical settings.

## CONCLUSION

Targeting the AGE/RAGE axis, with a focus on miRNA regulation, holds promise for managing T2DM and its complications. MiRNAs have therapeutic potential as they can influence the metabolic pathways affected by AGEs and RAGE, potentially reducing inflammation, oxidative stress, and vascular complications. Additionally, miRNAs may serve as early diagnostic biomarkers for T2DM. Further research in this area may lead to innovative therapeutic strategies for diabetes and its associated complications.

## ARTICLE HIGHLIGHTS

### Research background

Type 2 diabetes mellitus (T2DM) as a metabolic disorder due to impaired glucose utilization. Uncontrolled high sugar levels generate advanced glycation end products (AGEs) *via* receptor of advanced glycation end products (RAGE) receptor, causing complications. MiRNAs regulate genes linked to diabetes, impacting AGEs pathogenesis and influencing T2DM aspects—risk, diagnostics, complications, and therapeutic potential in managing metabolic pathways, inflammation, oxidative stress, and vascular complications. MiRNAs also hold promise as early diagnostic biomarkers, paving the way for innovative diabetes therapies.

### Research motivation

Understanding miRNA roles in T2DM's metabolic pathways and their influence on AGEs/RAGE axis presents therapeutic prospects for managing diabetes complications. Identifying miRNAs as diagnostic markers could revolutionize early intervention strategies. Exploring their impact on gene regulation offers insights for innovative therapeutic targets, potentially mitigating diabetes-related complexities.

### Research objectives

To investigate the regulatory role of specific miRNAs in T2DM's metabolic pathways affected by AGEs/RAGE axis, exploring their potential as diagnostic markers and therapeutic targets for managing diabetes complications.

## Research methods

The study systematically searched PubMed using specific keywords to identify free, full-length research articles evaluating miRNA involvement in T2DM and its complications. Twelve articles were selected after assessing relevance to genetic and molecular disease mechanisms. The investigation focused on miRNA impact on AGEs/RAGE axis and their associations with T2DM aspects.

## Research results

Multiple miRNAs, including miR-96-5p, miR-7-5p, miR-132, has\_circ\_0071106, miR-143, miR-21, miR-145-5p, exhibit links to diverse facets of T2DM—risk, diagnostics, complications, and gene regulation. These miRNAs are intricately associated with metabolic pathways affected by the AGEs/RAGE axis, illuminating potential roles as diagnostic markers and therapeutic targets for managing T2DM complexities.

## Research conclusions

Targeting the AGEs/RAGE axis *via* miRNA regulation holds promise for managing T2DM complexities. MiRNAs offer therapeutic potential by influencing affected metabolic pathways, potentially mitigating inflammation, oxidative stress, and vascular complications. Moreover, their role as early diagnostic biomarkers suggests innovative strategies for addressing diabetes and its associated complications.

## Research perspectives

Further exploration of miRNA-mediated regulation in the context of the AGEs/RAGE axis holds significant promise for advancing T2DM management. Investigating specific miRNAs' functional roles could unveil novel therapeutic avenues, potentially targeting metabolic pathways to alleviate complications. Additionally, validating miRNAs as reliable early diagnostic markers might revolutionize diabetes intervention strategies.

## FOOTNOTES

**Author contributions:** Shrivastav D and Singh DD design and written the manuscript and all data were generated in-house and that no paper mill was used.

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