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Exploring the Regulatory Role of miRNAs in Diabetes and the AGE/RAGE Axis: A Comprehensive Review

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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 RAGE (receptor of advanced glycation end products) 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

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. 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.

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 (WHO) 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 (ECM) 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 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 [12]. This interaction triggers signal transduction, activating various intracellular signaling molecules, including Extracellular signal-regulated protein kinases 1/2 (ERK1/2), phosphoinositide-3-kinase–protein kinase B/Akt (PI3/Akt), and Janus kinase/signal transducers and activators of transcription (JAK/STAT), ultimately resulting in the activation of NF-κB and the upregulation of tumor necrosis factor (TNF-α), C-reactive protein (CRP), and interleukin -6 (IL-6) mRNA expression.

MicroRNAs, a subclass of small non-coding RNA molecules with an average length of less than 200 nucleotides, are essential regulators of post-transcriptional gene expression. These minuscule genetic components are found extensively in a variety of bodily fluids, includingas 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 with T1DM [25]. MiR-142, miR-126, and miR-21 are commonly associated with obesity, prediabetes, and type 2 diabetes (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. MiR-320 is downregulated in the context of hyperglycemia, AGEs, and diabetes. Overexpression of miR320 can reverse this effect by targeting VEGF. MiR-141 is upregulated in T2DM and affects INS-1 β cell proliferation and glucose-stimulated insulin secretion (GSIS). 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 pe 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 as a PRISMA flow diagram and Table 1). Only full-length research articles that meet the inclusion criteria are included. Any other studies that do not meet the inclusion criteria are excluded.

RESULTS

After conducting a comprehensive literature search in the PubMed database, we found that in Type 2 Diabetes Mellitus (T2DM), miRNA plays a significant role in regulating the genetic and molecular mechanisms underlying the disease. (Table 1).

Mo, L., Using a bioinformatics method, common genes for T2DM and osteoporosis were identified, and it was found that miR-96-5p and miR-7-5p are potentially modulated miRNAs. These miRNAs are involved in the PI3K-Akt signalling pathway and the AGE-RAGE signalling pathway in diabetic complications, which may play a significant role in diabetic skeletal fragility. Salama II (2020) aims to identify miRNAs as diagnostic biomarkers for mild cognitive impairment (MCI) among patients with T2DM. They found that MCI was detected in 36.2% of T2DM patients, and miR-132 overexpressed and emerged as a potential diagnostic biomarker for MCI in these patients [32]. Yingying Z (2021) examines the use of has_circ_0071106 as a potential diagnostic marker for T2DM. The study revealed that 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]. Kong (2022) found that the CC genotype of rs4705342 might

increase the risk of T2DM by increasing the expression of miR-143. It is suggested that T2DM patients with elevated expression of miR-143 with the rs4705342 CC genotype had higher levels of low-density lipoprotein cholesterol (LDL-C), fasting blood glucose (FBG), and glycated haemoglobin (HbA1C) [34]. Yazdanpanah (2022) demonstrated that miR-21 expression is positively associated with glycosylated haemoglobin (HbA1c), fasting blood sugar (FBS), and triglyceride (TG) and can be considered a non-invasive and rapid tool for distinguishing individuals with pre-T2DM and T2DM from healthy individuals [35]. Nunez Lopez YO *et al* (2019 suggested that 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]. Tsai (2022) proposed that endothelin-1 (ET-1) was positively associated with HbA1c and creatinine levels in hyperglycemia. The author suggested that TNF-α and IL-6 expression are increased in a dose-dependent manner by inducing ET-1. Further, ET-1 reduces the fat metabolism by suppressing miR-let-7g-5p expression and increasing inflammation, which provides a suitable environment for myopathy [37]. Taylor (2023) 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 haemoglobin (HbA1c) levels [38]. Abdou AE (2022) evaluated the potential of urinary IgG, serum CX3CL1, and miRNA-152-3p as predictors of nephropathy in T2DM patients. They suggested that integrated biomarkers, including serum CX3CL1 Levels and urinary IgG, could effectively predict nephropathy early, but miRNA-152-3p proved to be an inadequate prognostic indicator for end-stage renal disease (ESRD) progression [39]. Cirilli I (2019) 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]. Hirota C (2021) is investigating the impact of reactive oxygen species (ROS) on the expression of magnesium ion (Mg2+) channels and miRNA in renal tubular epithelial cells of T2D. They concluded that glycated albumin (GA) reduces TRPM6 expression mediated by elevated ROS and miR-24-3p in renal tubular epithelial cells of T2D [41]. Witkowski M. (2021) is conducting a study to investigate the impact of metformin on tissue factor (TF) activity and markers of vascular inflammation in poorly controlled T2DM.

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-κB, PKC, PI3K, and nitric oxide, which are essential in diabetic complication development. [43].

4.1. 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.

4.1.1. Regulation of the NF-κB Pathway by miRNA:

NF-κB , 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-κB pathway and increase the pro-inflammatory response in diabetes [45]. NF-κB activation is required for cellular proliferation and migration under physiological conditions. NF-κB significant release of cytokines including interleukene -1(IL1), IL-6, CD36, TNF-α, and Monocyte Chemoattractant Protein-1 (MCP-1) as well as chemokines, tumor growth factor (TGF), and vesicular cell adhesion molecules, eventually leading to vascular damage [46]. NF-κB dependent miR124, controls cytokine signaling in hyperglycemic conditions. The

overexpression of miR124 downregulates exocytosis and decreases glucose-mediated insulin release [47]. (Figure 3).

4.1.2. Regulation of PKC Pathway by miRNA:

The interaction between AGEs/RAGE triggers the PKC 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 [48]. miR-210 downregulation plays a protective role in T2DM by regulating endothelial function. MiR-210 also mitigates AGE-mediated activation of JNK and PKC, reversing pathological conditions in cardiomyocytes [49]. MiR-25 regulates the AGE/RAGE-activated PKC pathway in diabetic nephropathy, inhibiting PKC phosphorylation and reducing oxidative stress [50]. Furthermore, miR-21-3p upregulation in diabetic atherosclerosis inhibits ROS generation and promotes RAGE/NADPH oxidase signaling [51]. 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 [52] (Figure 4).

4.1.3. 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 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 [53]. In diabetic mice, miR-185 downregulation increases ROS generation and decreases NO levels. Treatment with Huayu Tongmai Granules can reverse these effects [54]. MiR-195 and miR-582 upregulation in deep vein thrombosis affects NOS3 expression and NO levels, contributing to the pathogenesis [55] (Figure 5).

4.1.4. Regulation of the PI3/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 [56]. 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 [57]. MiR-25-3p modulates epithelial-mesenchymal transition in endothelial cells, affecting the PI3K/AKT pathway [58]. MiR-214 downregulates oxidative stress in diabetic nephropathy by targeting the ROS/Akt/mTOR pathway [104]. MiR-203 upregulation slows wound healing in diabetic foot ulcers by targeting the PI3/AKT/mTOR signaling pathway [59] (Figure 6).

4.2. 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 [78]. 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 KH, *et al* 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 [83]. Chen HY *et al* 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-/Smad3-dependent renal fibrosis, NF-mediated renal inflammation, and reverse pathological changes [84]. Similarly, the overexpression of miR-146a can significantly improve AGE-mediated pathological effects in the development of diabetic

foot ulcers through miRNA mimicry [125] [85]. 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, SIRT1, and PGC-1α by transfection with miRNA-339-5p mimic [86]. The administration of RAGE-antagonist peptide (antagomir-21) in intracranial glioblastoma nanoparticles can reduce miR-21 Levels and enhance tumour cell poptosis. Furthermore, it inhibits RAGE expression and lowers VEGF levels in tumour cells [87]. Trajkovski *et al* 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 [88]. In cerebral ischemia, hypoxia-induced RAGE plays a significant role, which is regulated by miR-181a. Kim M. and Lee Y. suggested that the administration of AMO181a-chol-loaded exosomes (anti-microRNA oligonucleotide) downregulates the expression of miR-181a and reduces the damage to the ischemic brain. Apoptosis and tumour necrosis factor (TNF) expression were also reduced [89].

MiRNAs play a complex role in various metabolic process especially related to AGE and RAGE. Understanding on 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 cardiovascular 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 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.

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