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Diabetes and associated cardiovascular complications: The role of microRNAs

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Abstract

Diabetes mellitus (DM) refers to a complex cluster of metabolic disorders characterized by hyperglycemia caused by inadequate insulin secretion, insulin resistance, or excessive glucagon secretion. If not correctly treated, the prolonged effects of DM-associated metabolic perturbations lead to systemic vascular complications and cardiovascular disease (CVD), the principal cause of mortality among patients with DM. Given the increase in the global prevalence of diabetes, novel diagnostic and therapeutic procedures are necessary for its effective identification and treatment. Recent findings point to an important role of microRNA (miRNAs) in DM initiation and progression, as well as the occurrence of associated cardiovascular complications. miRNAs are short, highly conserved, single-stranded, non-coding RNAs that contribute to the maintenance of physiological homeostasis through the regulation of crucial processes such as metabolism, cell proliferation, and apoptosis. The increased availability of high-throughput methodologies for identifying and characterizing non-coding RNAs has led to considerable interest in miRNAs as potential biomarkers and therapeutic agents for DM. In this review, we first comprehensively detail the regulatory miRNAs involved in the pathophysiology of DM and diabetic cardiomyopathy (DCMP). Subsequently, we summarize findings regarding the utility of several of these miRNAs as potential prognostic and diagnostic biomarkers for DM and DM-associated CVD. Finally, we evaluate the potential of miRNA-based therapeutic approaches for treating DM and DCMP in the clinical setting.

Keywords: Cardiovascular disease, Diabetes mellitus, Diabetic cardiomyopathy, MiRNA, Therapeutics

INTRODUCTION

Diabetes mellitus (DM) refers to a group of complex metabolic conditions brought about by both environmental and genetic variables. Its pathophysiology is characterized by persistent hyperglycemia and disrupted carbohydrate, lipid, and protein metabolism caused by insulin resistance and/or inadequate insulin production[1]. Ineffective glucose utilization increases reactive oxygen species (ROS) generation and accumulation, mitochondrial dysfunction, and cellular and tissue hypoxia[2]. The long-term effects of the profound metabolic disruptions associated with DM lead to chronic complications, including cardiovascular disease (CVD)[3]. Diabetes is associated with systemic inflammation and endothelial destruction, which contribute to a two-to-four-fold increase in myocardial infarction, stroke, and overall mortality[4].

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The global prevalence of DM is rapidly increasing[1]. Two main types of DM are recognized in clinical settings—type 1 DM (T1DM), caused by insufficient insulin production by pancreatic β cells, and type 2 DM (T2DM)[3], resulting from an ineffective response to insulin. T1DM accounts for approximately 10% of all cases of diabetes worldwide, and its incidence is increasing by 3% annually[5]. The pathogenesis of T1DM is associated with autoimmunity, genetic predisposition, and epigenetic modulation[6]. For instance, T1DM is characterized by the presence of autoantibodies against β-cell autoantigens, such as insulin, tyrosine phosphatases-2 and -2b, glutamic acid, and decarboxylase[5,6]. Furthermore, more than 50 mutations at various genetic loci have been linked to T1DM. Genetic predisposition and obesity are the main risk factors for the development of T2DM, which accounts for most (90%) of the cases of diabetes globally and is characterized by the presence of resistance to insulin in peripheral tissues[3]. The International Diabetes Federation has estimated that the global prevalence of T2DM was 9.3% in 2019 and is expected to rise to 10.9% by 2045, affecting 629 million people[7].

MicroRNA (miRNAs) are highly conserved, small non-coding RNAs with important roles in the regulation of metabolism, cell proliferation, and apoptosis. Rapidly accumulating evidence points to the involvement of miRNAs in the onset and progression of DM, thus making them a promising tool for the diagnosis of DM and the assessment of the risk of vascular complications in patients with this condition. In this review, we address

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the problem of the high global prevalence of DM and associated CVD by providing an up-to-date, systematic summary of the various miRNAs implicated in the pathophysiology of these conditions. We specifically focus on recent advances in the understanding of the roles of miRNAs in DM and diabetic cardiomyopathy (DCMP). We also evaluate the recent findings relating to the potential of miRNAs for diagnostic application and therapeutic interventions in the clinical setting. Finally, we present an overview of the current techniques targeting the expression of miRNAs involved in DM that may be clinically significant for treating these disorders.

SEARCH STRATEGY

PubMed and MEDLINE were searched for English articles and non-English articles with English abstracts published between 2002 and 2023. The search terms were diabetes, miRNA, cardiovascular disease, DCMP, biomarkers, and therapeutic agents. Original peer-reviewed articles focusing on the role of microRNAs in diabetes and associated CVD were retrieved, with an emphasis on findings published in the last 5 years.

GENERAL CHARACTERISTICS OF DM

DM is a metabolic disorder characterized by perturbed carbohydrate metabolism, elevated fasting free fatty acid and triglyceride levels, and impaired tissue uptake of amino acids in response to insulin. The prevalence of DM is rapidly rising and reaching pandemic proportions, with 9.3% of the world's population (463 million people) suffering from the condition, a figure that is expected to reach 10.9% by 2,045 (700 million affected individuals)[7]. The abnormalities in carbohydrate, fat, and protein metabolism in patients with DM result from defects in insulin action in target tissues due to insufficient insulin secretion and/or diminished tissue responses to the hormone. Diabetes can be broadly classified into four main categories—T1DM, T2DM, gestational diabetes, and secondary or other specific types of the disease[5]. Most cases of DM fall into the type 1 and 2 categories, whereas gestational diabetes refers to DM diagnosed during pregnancy. Secondary diabetes comprises a wide spectrum of specific deficiencies, such as genetic defects that impact insulin action, monogenic defects relating to pancreatic β-cell function, or other genetic syndromes associated with diabetes; endocrinopathies; pancreatic diseases such as pancreatitis and hemochromatosis; DM induced by chemicals, surgery, or infections; and immune-mediated diabetes[5].

Multiple pathological processes are involved in DM development, including the autoimmune-mediated destruction of pancreatic β cells, which leads to insulin deficiency, and metabolic abnormalities that result in insulin resistance. Deficiencies in insulin secretion and insulin action may co-occur in patients, and it is not always apparent which abnormality is primarily responsible for the consequent hyperglycemia. Nevertheless, DM-associated metabolic derangements are clinically recognizable when plasma glucose increases to levels that cause glycosuria and polyuria. However, because the onset of hyperglycemia is gradual and progressive, these symptoms may not occur early in patients with T2DM, and they are generally efficiently relieved by nutritional and pharmacological intervention. In contrast, the onset of T1DM is clinically abrupt and requires immediate initiation of insulin therapy. Hyperglycemia leads to complications in both T1DM and T2DM, such as an increased risk of damage to the eyes, kidneys, nerves, heart, and blood vessels. Patients with diabetes have an increased incidence of atherosclerotic cardiovascular, peripheral arterial, and cerebrovascular diseases. In addition, hypertension and lipoprotein metabolism abnormalities are commonly observed in diabetic patients[5]. Diabetes-related complications are associated with high morbidity and mortality and determine the fate of diabetic patients. Meanwhile, in the United States, the total economic costs of diagnosed DM have risen from $245 billion in 2012 to $327 billion in 2017[8].

STRUCTURAL AND FUNCTIONAL CHANGES IN DIABETIC MYOCARDIUM

It is well-established that DM is a major risk factor for CVD. Patients with DM are at high risk for atherosclerotic cardiovascular events and are placed in a similar risk category as patients with previous ischemic episodes[9]. DM is also associated with an increased risk of heart failure (HF), which can be explained by the presence of hyperglycemia and the accumulation of advanced glycation end-products, accompanied by increased levels of inflammation and oxidative stress (OS), which can also affect myocardial structure and function. Multiple additional factors have been suggested to be responsible for HF in DM patients, including atherosclerosis, sodium and volume retention due to increased expression of sodium-glucose cotransporter-2, mitochondrial dysfunction resulting from insulin resistance, elevated proinflammatory cytokine and ROS contents, impaired vasodilatation and oxygen delivery to skeletal muscle, ischemia, microvascular dysfunction, myocyte hypertrophy, and fibrosis[10,11]. These factors, in combination with comorbidities (e.g., obesity, hypertension, chronic kidney disease) that are frequently present in DM patients, can lead to systolic and diastolic dysfunction, as well as a broad spectrum of conditions ranging from subclinical myocardial dysfunction to clinical HF with preserved or reduced ejection fraction. This syndrome, collectively named DCMP[11], is defined as DM-induced morphological and functional cardiac abnormalities affecting hyperglycemic patients, which results in left ventricular (LV) remodeling, increased LV mass, and impaired systolic and diastolic function[12,13]. DCMP can clinically present

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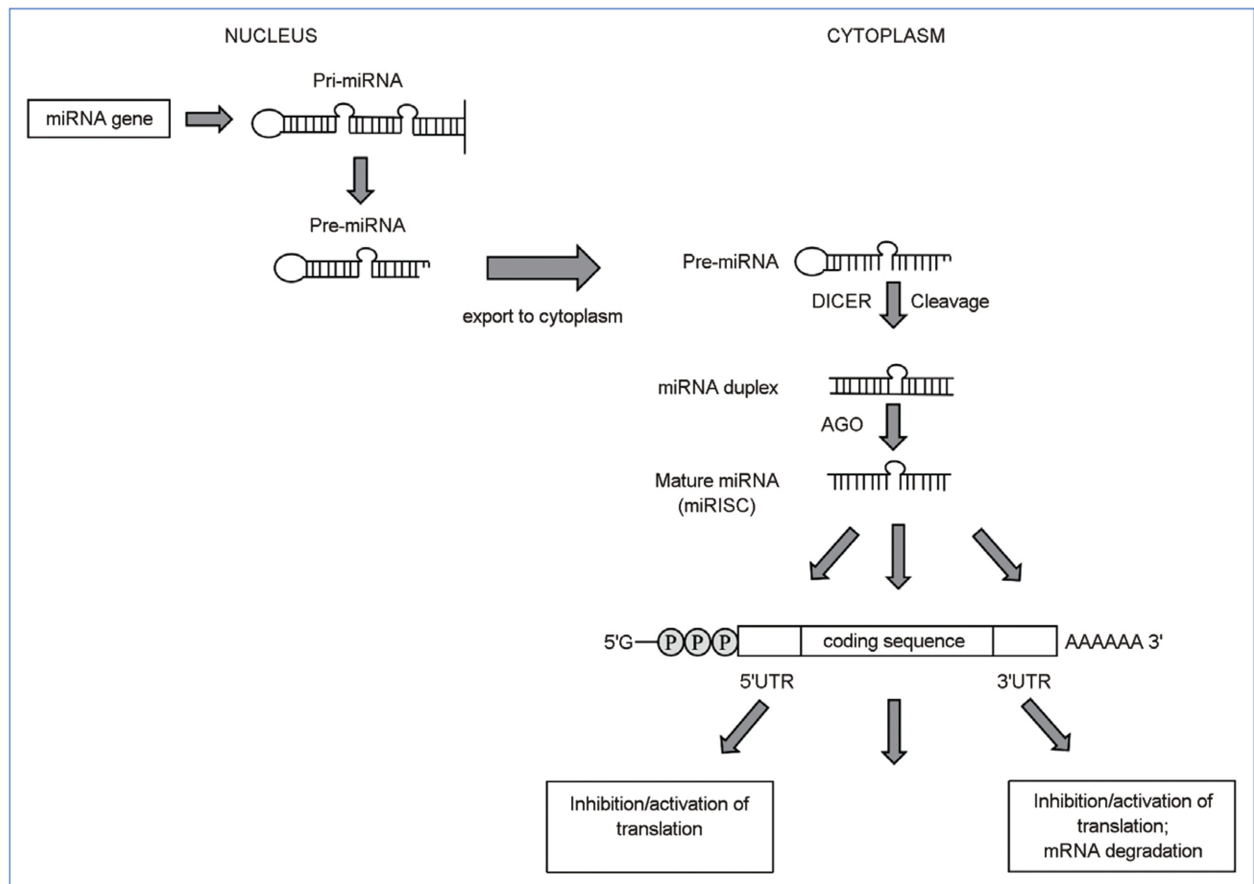

Figure 1. Mechanisms of action of miRNAs.
Parts of the figure were created with BioRender (BioRender.com).
3′UTR: 3′ Untranslated region; 5′UTR: 5′ Untranslated region; AGO: argonaute family of proteins; miRNA: microRNA; miRISC: miRNA-induced silencing complex; pre-miRNA: precursor miRNA; pre-RNA: precursor RNA; pri-miRNA: primary miRNA.

as either a restrictive or dilated form[14]. The restrictive phenotype refers to HF with preserved ejection fraction, whereas the dilated phenotype represents HF with reduced ejection fraction. In both cases, DM increases the risk of hospitalization and fatal outcome[3,14]. DCMP has been associated with poor prognosis and an increased risk for overt HF in patients with DM[15]. The diagnosis of DCMP is based on echocardiography for the detection of structural and functional alterations in the myocardium[14].

MiRNA BIOGENESIS AND FUNCTION

MiRNAs are single-stranded, regulatory RNA molecules that control the expression of target genes post-transcriptionally[16]. They most frequently influence target mRNA stability and turnover by attaching to *cis* elements in their 3′ untranslated regions (3′UTRs). However, they can also interact with coding sections or the 5′UTRs of mRNA[16]. Thousands of miRNAs have been identified to date, and they are thought to influence the expression of up to 30% of all human genes, suggestive of their importance in the preservation of physiological homeostasis[17]. The miRNA-mediated regulation of target gene expression is dependent on the sequence of the mRNA and the prevalent physiological conditions. In principle, one miRNA may interact with more than 100 target mRNAs, and several miRNAs may cooperate to fine-tune the expression of the same mRNA transcript[18]. The miRBase reference repository currently holds information on approximately 2,600 human mature miRNAs[19]. However, despite the rapidly increasing number of non-coding RNAs identified by increasingly available high-throughput methodologies[20,21], only a relatively small number of miRNAs have experimentally confirmed roles in physiological processes.

RNA polymerase II converts miRNAs into primary miRNAs (pri-miRNAs) in the nucleus, and these are then converted into mature miRNA molecules *via* a series of endolytic processes[22] (Figure 1). The DROSHA endoribonuclease or components of the splicing machinery cleave pre-miRNAs before they are exported to the cytoplasm, and these are further processed by DICER, a type III endoribonuclease, generating mature miRNA duplexes. The guide strand of mature miRNA interacts with the chaperones HSC70/HSP90 and, subsequently, with Argonaute (AGO) family proteins, yielding the minimal miRNA-induced silencing complex (miRISC).

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This complex binds to complementary sequences, called miRNA response elements, on target mRNAs, leading either to their cleavage by Argonaute 2 (AGO2) or inhibition of their translation[23].

The activity of miRNAs is determined by their abundance and cellular localization. MiRISCs are present in the nucleus[24] as well as several subcellular compartments[25], and can also be exported to the extracellular milieu *via* exocytosis and transported to other cells *via* extracellular vesicles[26] or protein carriers[27], thereby participating in intercellular communication.

MiRNAs AS REGULATORS OF INSULIN PRODUCTION AND SECRETION

Adequate insulin secretion from pancreatic β cells is essential for the maintenance of blood glucose homeostasis, and a decline in the secretion of this hormone can lead to hyperglycemia and DM. The regulation of glucose homeostasis by tissue-specific, miRNA-mediated control of insulin production, insulin secretion, and cell proliferation represents an important aspect of DM pathophysiology. The results of studies relating to tissue-specific miRNA expression in cell culture, animal models, and human subjects increasingly support the existence of a connection between miRNAs and DM. Several studies have revealed that some miRNAs, such as miR-7, miR-9, miR-375, and miR-376, are highly abundant in the human pancreas, and participate in pancreas development, β-cell proliferation, and insulin secretion[28,29]. The expression of let-7, miR-148b-3p, miR-27a-3p, miR-7a-5p, miR-7b-5p, miR-26a-5p, and miR-26b-5p was found to be decreased in mice with streptozotocin-induced T1DM, as determined by miRNA microarray profiling and subsequent quantitative reverse transcription-polymerase chain reaction (qRT-PCR) analysis[30]. Meanwhile, the levels of miR-30d, miR-184, miR-203, miR-210, miR-338–3p, and miR-383 were reported to be significantly decreased in pancreatic islets of T2DM mice, whereas those of let-7b, miR-21, miR-34a, miR-132, miR-146, miR-199, and miR-200 were increased[31]. In islets of non-obese Goto-Kakizaki T2DM rats, global expression profiling identified 30 differentially expressed miRNAs[32]. Finally, in pancreatic tissue of T2DM rats, the levels of miR-144, miR-150, miR-29a, miR-192, and miR-320a were upregulated, whereas those of miR-146a, miR-30d, and miR-182 were significantly downregulated[33].

MiRNA profiling in human subjects revealed a distinct subset of miRNAs exhibiting dysregulated expression in human β cells. For instance, in islet tissue of T2DM patients, the expression of miR-124a and miR-187 was increased[34,35], whereas that of miR-127, miR-136, miR-655, miR-656, miR-543, miR-369, miR-411, miR-432, miR-487, miR-495, and miR-589 were significantly downregulated[36]. Additionally, patients with T1DM had higher levels of miR-125a-5p in regulatory T cells derived from pancreatic lymph nodes compared with that seen in healthy controls[37]. However, the most highly expressed miRNA in human pancreatic islets was found to be miR-375, which has a confirmed role in the modulation of insulin secretion[29] (Table 1).

MiR-375 targets the gene encoding myotrophin (MTPN), a protein that promotes the fusion of insulin vesicles with β-cell membranes *via* its role in actin filament depolymerization and, consequently, cytoskeleton remodeling[29] and exocytosis[29,38].

MiR-7, miR-96, and miR-124a also regulate proteins involved in insulin exocytosis and secretion[40] (Table 1). MiR-7 has been implicated in decreasing glucose-induced insulin secretion in β cells through the regulation of the expression of proteins belonging to the

Table 1.

MiRNAs involved in the pathogenesis of diabetes mellitus (↑ and ↓indicate the up- and downregulation, respectively, of miRNA expression)

MiRNA	Expression	Target	Signaling pathway	Pathophysiological mechanism	Experimental model	References
miR-375	↑	*MTPN, PDK1*	PI3K	Cytoskeleton remodeling, endocrine cell exocytosis, expression of the insulin gene	Mice lacking miR-375 (375KO); Goto-Kakizaki (GK) rat	[29,38,39]
miR-124a	↑	*Noc2*	Rab27A	Endocrine cell exocytosis	β-Cell line MIN6B1	[40]
miR-7	↓	Genes encoding SNARE complex proteins	/	Insulin granule exocytosis	Mice lacking miR-7a; transgenic mice overexpressing miR-7a in β cells	[41]
miR-21	↑	*SIRT1*	NF-κB	β-Cell number	INS1 cell line	[42]
miR-204	↑	*GLP1R*	MafA	Insulin secretion	INS1 cell line; islets of *TXNIP*-deficient mice; mouse model of diabetes; primary human islets	[43,44]
miR-96	↓	Granuphilin, *Noc2*	Rab27A	Endocrine cell exocytosis	β-Cell line MIN6B1	[45]

GLP1R: glucagon-like peptide 1 receptor; MafA: MAF bZIP transcription factor A; MTPN: myotrophin; NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells; *Noc2:* nucleolar complex-associated protein 2; PDK1: 3′-Phosphoinositide-dependent protein kinase 1; PI3K: phosphatidylinositol 3-kinase; *SIRT1*: sirtuin 1; SNARE: soluble N-ethylmaleimide-sensitive factor attachment protein receptor; TXNIP: thioredoxin-interacting protein.

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soluble N-ethylmaleimide-sensitive factor attachment protein receptor complex, which mediates the fusion of vesicles with the membranes of their target cellular compartments[41]. MiR-96 was shown to reduce glucose-induced insulin secretion by upregulating the expression of granuphilin, a negative modulator of insulin exocytosis, and inhibiting the expression of nucleolar complex-associated protein 2 (Noc2)[40], which is essential for exocytosis in endocrine cells[46]. Meanwhile, miR-124a has been reported to downregulate Noc2 and Rab27A levels while enhancing those of Rab3A, SNAP25, and synapsin-1A. MiR-124a reportedly suppresses the expression of Rab27A, a GTPase that facilitates the transport of vesicles to the cell membrane, by binding to the 3′UTR of its mRNA[40].

MiR-375, together with other pancreatic miRNAs such as miR-21 and miR-34, regulates β-cell proliferation, survival, and apoptosis. Poy *et al.* reported that miR-375 knockdown in a mouse model of obesity impaired β-cell proliferation and viability, resulting in a severe diabetic state[38]. Additionally, the overexpression of miR-21, whose levels are regulated by the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway, led to a significant decrease in the number of β cells *in vitro*[42] (Table 1). It has also been demonstrated that knocking down miR-34a, which targets SIRT1 and thus leads to p53-mediated apoptosis, increases the net β-cell number[42].

Mir-375 and several other miRNAs are also involved in the regulation of insulin production. MiR-375 downregulates the expression of 3′-phosphoinositide-dependent protein kinase 1 (PDK1), a crucial component of the phosphatidylinositol 3-kinase (PI3K) cascade, which leads to decreased expression of the insulin gene in the presence of glucose stimulation[39]. MiR-204 suppresses glucose-induced insulin secretion by targeting the 3′UTR of glucagon-like peptide 1 receptor (GLP1R) mRNA[43]. Furthermore, it has been demonstrated that the levels of thioredoxin-interacting protein (TXNIP), a regulator of the redox state in β cells, are elevated in T2DM, leading to increased expression of miR-204. In turn, miR-204 curtails insulin secretion by directly targeting MAF bZIP transcription factor A (MafA), a positive regulator of the insulin gene, which enhances MafA degradation[44] (Table 1).

Many studies have shown that distinct miRNAs can directly regulate components of the insulin signaling pathway. MiR-424-5p targets the 3′UTR of insulin receptor (INSR) mRNA, and its overexpression in human hepatocytes *in vitro* results in reduced INSR levels and increased lipid content[47]. MiR-15b[48], miR-96, and miR-195[49] also target human INSR mRNA. The expression of miR-96 and miR-195 was reported to be upregulated in the livers of mice fed a high-fat diet or in HepG2 cells treated with saturated fatty acids, which was accompanied by decreased INSR contents[49]. Other miRNAs, such as miR-122, miR-144, miR-146a, miR-107, and miR-103, can negatively affect insulin signaling by indirectly regulating INSR. In the case of miR-122, miR-144, and miR-146a, this is achieved through the control of the expression of protein tyrosine phosphatases, which enzymatically remove phosphate groups from tyrosine residues present in the cytoplasmic domain of INSR[33,50]. MiR-107 and miR-103 disrupt INSR compartmentalization and signal transduction, mediated by caveolae, specialized microdomains in plasma membranes composed of caveolin proteins. Trajkovski *et al.*[51] reported that miR-107 and miR-103 bind to the 3′UTR of caveolin-1 mRNA and that the silencing of both miRNAs in adipocytes of mice with diet-induced obesity (DIO) resulted in the normalization of the glucose status[51].

MiRNAs can also regulate insulin receptor substrates (IRSs) as well as insulin-like growth factor-1 (IGF-1) and its receptor, IGF-1R, thus modulating insulin signaling. Distinct miRNA subsets regulate the expression of IRS1 and IRS2 in different target tissues. For instance, it has been noted that miR-96, miR-126, and miR-145 regulate the expression of IRS1[52,53], whereas miR-33a/b targets IRS2[54]. It has also been reported that in skeletal muscle, miR-29a, miR-29c, and miR-128a regulate the expression of IRS1[49,55,56], while IRS2 expression is regulated by miR-135a[57]. In adipocytes, meanwhile, IGF-1 expression and insulin sensitivity are regulated by miR-320[58], whereas in cardiac and skeletal muscles, the levels of IGF-1 and IGF-1R are under the control of miR-1[59]. Insulin signaling can also be modulated by a single miRNA interacting with multiple targets, such as happens with let-7, which binds to the 3′UTRs of INSR, IRS2, and IGF-1R[60].

THE ROLE OF MiRNAs IN THE INSULIN SIGNALING PATHWAY

It has been established that miRNAs are involved in almost every step of insulin signaling, including the regulation of INSR, insulins (INSs), and IGF-1R expression, as well as glucose transporter 4 (GLUT4) translocation and glucose uptake. For instance, miR-383 regulates the expression of IGF-1R[61], whereas miR-320 similarly regulates insulin pathway signaling by modulating the expression of both IGF-1 and IGF-1R, resulting in enhanced insulin resistance in endothelial cells (ECs) and adipose tissue[58]. The upregulation of miR-96, miR-126, and miR-144 leads to decreased IRS1 expression and perturbed insulin signaling[52,53], whereas the increased expression of another miRNA, miR-135, significantly reduces the expression of both IRS2 and INSR[52] and diminishes glucose uptake *in vitro*[62].

MiR-128 is upregulated in visceral adipose tissue of humans with obesity, accompanied by decreased INSR expression in adipocytes[63]. It was reported that members of the miR-128 family downregulate INSR and IRS1, proteins that are involved in insulin signaling cascades[55]. Furthermore, the levels of miR-128-3p were found to be increased in the myocardium of mice with

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cardiac dysfunction, accompanied by insulin resistance and IRS1 degradation. In contrast, the inhibition of this microRNA reportedly ameliorated cardiac insulin resistance[64]. MiR-128a/b, along with several other miRNAs (e.g., miR-320, miR-29), also modulates PI3K activity by controlling the expression of PI3K p85 subunit beta in skeletal muscle and adipose tissue[55,58,65]. MiR-126 also regulates the expression of this subunit, whereas miR-384-5p regulates the levels of the PI3K catalytic subunit p110 delta[66]. In ECs under shear stress, PI3K is regulated by miR-19a[67].

Insulin-stimulated protein kinase B (AKT) activation can be additionally modulated by miR-143, which exhibits increased expression in mouse models of obesity and is associated with perturbed glucose homeostasis[68]. In the 3T3-L1 adipose tissue cell line, miR-29 overexpression mitigates AKT activation and glucose uptake[69]. In skeletal muscle cells, miR-449a promotes insulin-mediated PI3K/AKT signaling[70]. MiR-33a/b, together with miR-205-5p, miR-338-3p, and miR-499-5p, has been implicated in the regulation of AKT phosphorylation and insulin signaling pathways in the liver[54,71–73],. Zhuo *et al*.[74] found that the expression of miR-451 was upregulated in the livers of diabetic mice and that this was associated with the negative regulation of AKT-dependent hepatic gluconeogenesis and the amelioration of hyperglycemia[74]. Finally, in human umbilical vein ECs, it was shown that miR-199a-3p overexpression leads to the activation of the PI3K/AKT signaling pathway, resulting in increased proliferation. This is an important finding given that the levels of miR-199a-3p were reported to be reduced in peripheral blood from T2DM patients, which was associated with vascular EC injury[75].

MiR-133 can influence insulin-stimulated glucose uptake by modulating GLUT4 translocation in adipose tissue and skeletal muscle[76]. Moreover, it has been demonstrated that the overexpression of miR-106b, miR-27a, miR-30d, and miR-29a decreases glucose uptake and consumption and reduces the expression of GLUT4 and PI3K p85 subunit beta[77,78]. Latouche *et al*.[79] observed that miR-194 knockdown in skeletal muscle cells increases basal and insulin-stimulated glucose uptake as well as glycogen synthesis *via* an increase in insulin-induced AKT phosphorylation[79]. GLUT4 protein expression is targeted by miR-143 in adipocytes[80], whereas, in cardiomyocytes, GLUT4 is regulated by miR-200a-5p, which augments glucose uptake[81].

THE INVOLVEMENT OF MiRNAs IN ENDOTHELIAL AND VASCULAR SMOOTH MUSCLE CELL FUNCTION AND LIPID METABOLISM IN DM

The role of miRNAs in endothelial and vascular smooth muscle cell function in DM

The vascular endothelium is regarded as an endocrine organ that secretes vasoactive molecules with autocrine, paracrine, and/or endocrine functions and is involved in the regulation of vascular homeostasis. It also connects vascular function with metabolic demands[82]. The secretion of vasoactive molecules modulates crucial physiological functions such as vascular tone, vessel diameter, leukocyte and platelet activation, and vascular smooth muscle cell (VSMC) proliferation[82]. Endothelial dysfunction is commonly associated with T2DM and results in multiple macro- and microvascular complications, which increase the risk of adverse cardiovascular events. Endothelial function in T2DM patients is compromised due to complex metabolic perturbations such as hyperinsulinemia, insulin resistance, ROS accumulation, and excessive release of free fatty acids[82]. These disturbances initiate a cascade of proatherogenic and inflammatory events, which further increase the risk of macro- and microvascular complications, including CVD. ECs and VSMCs are the main cell types in the vasculature[82]. ECs form the inner, thin layer that lines the entire circulatory system. The major functions of these cells include vascular tone regulation and hemostasis, fluid filtration, hormone trafficking, and neutrophil recruitment[83]. VSMCs regulate the caliber of blood vessels and can contract in response to a wide range of stimuli, thereby controlling blood redistribution within the body[83].

Increasing evidence supports that miRNAs play an important role in regulating EC functions, such as migration, proliferation, angiogenesis, and oxidative and inflammatory responses[84], and also maintain endothelial homeostasis in DM[84]. The central role in regulating angiogenesis is assigned to the EC-specific miRNA, miR-126, which is involved in angiogenic growth factor signaling responsible for EC growth and adhesion[84]. MiR-126 modulates vascular development and homeostasis by targeting vascular cell adhesion molecule 1, a key mediator of leukocyte adhesion and inflammation, and phosphoinositide 3-kinase regulatory subunit 2 (PIK3R2)[85]. MiR-126 is abundantly expressed in ECs, endothelial progenitor cells, and platelets and serves as a marker for EC detection and purification[86]. It has also been implicated in the endothelial dysfunction associated with the pathogenesis of diabetes and its complications[87]. Plasma miR-126 levels can be modulated by a variety of stimuli, leading to differential outcomes in a cell-type-dependent manner. For instance, the expression of miR-126 is increased in plasma of patients with diabetes and HF, as well as in patients with acute myocardial infarction and angina[88]. In contrast, the concentrations of miR-126 are reduced in plasma of patients with diabetic retinopathy[89]; additionally, by targeting polo-like kinase 4, miR-126 overexpression reduces diabetic retinopathy by suppressing proliferation and migration in human retinal capillary ECs and male streptozotocin-induced diabetic rats[89]. It has been suggested that circulating miR-126, released by ECs, functions as an intercellular messenger that is internalized by monocytes

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and VSMCs, thereby protecting against endothelial dysfunction[84].

MiR-34a is also reported to be an important mediator of DM-associated vascular pathologies. Le *et al*.[90] reported that miR-34a is upregulated in the endothelium of diabetic patients *via* an oxidative-dependent mechanism. The presence of hyperglycemia and high levels of free fatty acids leads to the recruitment of the OS-related protein p66Shc, resulting in increased miR-34a expression, which promotes endothelial dysfunction *via* the targeting of SIRT1[90]. These findings highlight the importance of miRNAs in endothelial function, providing novel means for the development of potential therapies to prevent or ameliorate DM-associated endothelial dysfunction.

MicroRNAs and lipid metabolism in DM

It has been established that perturbed lipid metabolism in pancreatic islets contributes to β-cell dysfunction and apoptosis, resulting in the progressive reduction of insulin secretion and the onset of T2DM. Several miRNAs are affected by metabolic alterations in β cells and islets, and some of the gene networks targeted by these miRNAs have been identified, offering the possibility for the development of novel therapeutic interventions that can protect against β-cell dysfunction as well as prevent or delay the onset of T2DM. For instance, miR-33 and sterol regulatory element-binding protein (SREBP) genes, which together control lipid metabolism and cholesterol homeostasis, were suggested to be potential therapeutic targets for cardiometabolic diseases[91]. Additionally, the expression of many miRNAs is modulated by exposure to metabolic alterations, which affects the expression of a variety of genes involved in β-cell function. The upregulation of miR-34a, which is associated with changes in lipid metabolism in DM, has been strongly linked to β-cell lipotoxicity resulting from exposure to saturated fatty acids. This effect of miR-34a is exerted *via* the targeting of the gene encoding SIRT1, an nicotinamide adenine dinucleotide (NAD^+)-dependent deacetylase, leading to the activation of the expression of NF-κB, STAT3, and the forkhead box class O family member protein (FOXO) family of transcription factors[92]. MiR-34a also targets peroxisome proliferator activator receptor alpha (PPARα) in liver cells, which can affect fatty acid utilization[93].

The expression of several other miRNAs, such as miR-375[94], miR-182-5p[95], and miR-146a[45], is altered in β cells exposed to saturated fatty acids. MiR-375, which has an established role in diabetes, inhibits high-fat diet-induced insulin resistance and obesity in C57BL/6 mice by inducing the hepatic expression of genes involved in responses to insulin, thus exerting a protective influence against the effects of a fat-rich diet[96]. MiR-182-5p was shown to decrease the expression of interleukin-6 (IL-6) and tumor necrosis factor-alpha in the liver in the presence of oleic acid[97] as well as prevent cholesterol and triglyceride accumulation in macrophages by targeting Toll-like receptor 4[98]. MiR-182-5p targets thrombospondin-1 in β cells[95], which was shown to regulate lipid metabolism in hepatic cells by inhibiting the proteolytic cleavage of SREBP-1, thereby decreasing lipogenesis and triglyceride accumulation[99]. The miRNA-146 family (miR-146a/b) targets genes involved in the host immune response and inflammation. In human islets, the level of miR-146 decreases after exposure to high concentrations of glucose, increases in the presence of proinflammatory cytokines, and remains unaltered upon exposure to palmitate[100].

MiR-33a, encoded in an intronic region of the *SREBF2* gene, is one of the most extensively studied miRNAs involved in lipid metabolism[101]. The knockout of miR-33a in mice promotes cholesterol efflux via ATP-binding cassette sub-family A member 1 (ABCA1) and ATP-binding cassette sub-family G member 1 (ABCG1), thereby increasing circulating high-density lipoprotein (HDL) levels and the excretion of hepatic cholesterol in bile[102]. It has also been observed that HDL increases the export of miR-375-3p, which is inversely correlated with insulin secretion *in vitro*[103], while treatment with cholesterol upregulates miR-24a and reduces insulin secretion[104]. MiR-24, a critical regulator of β-cell function, is also overexpressed in obesity[105] and has been implicated in the regulation of lipid metabolism in different tissues by controlling cholesterol uptake *via* targeting scavenger receptor class B member 1 (SR-B1). It was reported that miR-24 promotes atherosclerosis by reducing lipid uptake from HDL cholesterol *via* the repression of SR-B1[106]. In addition, miR-24 inhibition prevents lipid accumulation and hyperlipidemia[107], suggesting that it may have a role in regulating lipid metabolism in pancreatic islets and β cells.

THE ROLE OF MiRNAs IN DIABETES-ASSOCIATED CARDIOVASCULAR COMPLICATIONS

It is increasingly clear that miRNAs are involved in DM-related cardiovascular pathological processes, including cardiac hypertrophy, myocardial fibrosis, OS, mitochondrial dysfunction, apoptosis, and cardiac electrical remodeling[108]. DCMP is a leading cause of morbidity and mortality in DM patients globally and manifests as cardiac interstitial fibrosis, cardiomyocyte hypertrophy, and apoptosis. HF may eventually result from these conditions. Hyperglycemia, hyperinsulinemia, and dyslipidemia contribute to the pathogenesis of CVD, including DCMP, alongside the formation and accumulation of glycation end-products, mitochondrial dysfunction, disturbed Ca^{2+} homeostasis, endoplasmic reticulum stress, altered gene regulation, activation of the renin–angiotensin system, microvascular myocardial rarefaction, and cardiomyocyte apoptosis[109] (Figure 2).

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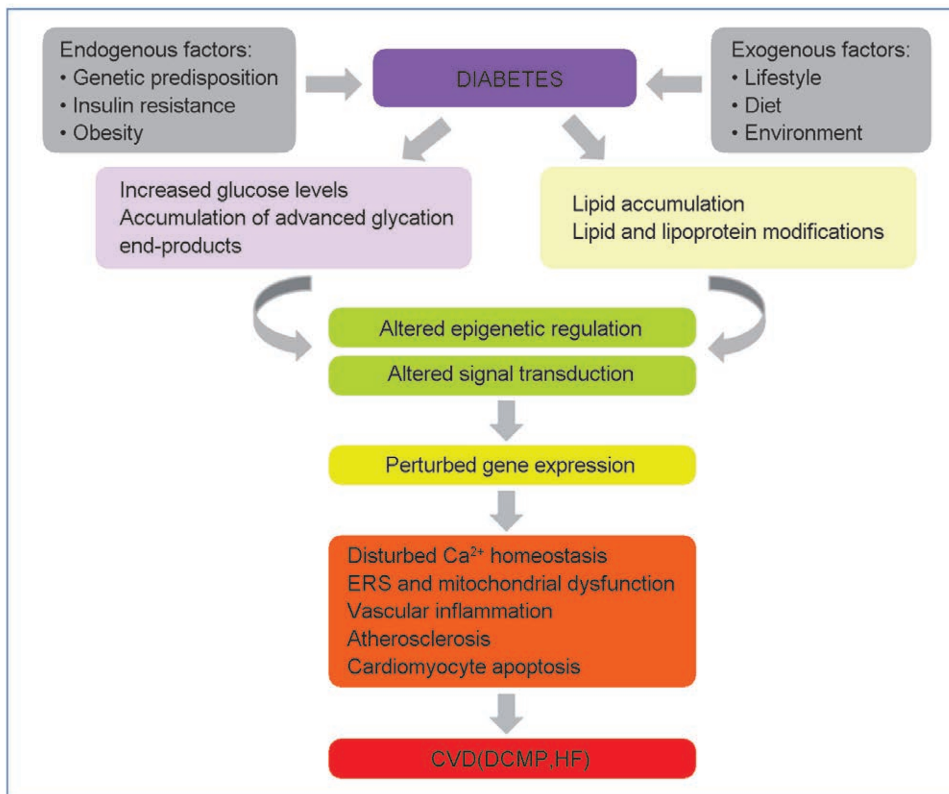

Figure 2. The connection between diabetes mellitus and its associated CVD.
CVD: cardiovascular disease; DCMP: diabetic cardiomyopathy; DM: diabetes mellitus; ERS: endoplasmic reticulum stress; HF: heart failure.

DCMP, which occurs in approximately 12% of DM patients[110], is characterized by disrupted Ca^{2+} signaling, altered metabolism, and abnormalities in the structure of the myocardium[109], including cardiac fibrosis, which is facilitated by increased collagen deposition and changes in extracellular matrix (ECM) structure[111]. Cardiomyocytes with impaired metabolism are more likely to uptake and oxidize free fatty acids, which can promote lipotoxicity and, consequently, cardiomyocyte mortality[109]. Lipid accumulation in ECs can also slow nitric oxide bioavailability, which aggravates endothelial dysfunction and accelerates atherosclerosis[14]. Augmented ROS generation resulting from increased intracellular fatty acid concentrations and mitochondrial dysfunction further enhances OS and ERS while limiting autophagy[112]. Combined, these alterations lead to ECM remodeling, fibrosis, inflammation, and cardiac enlargement, ultimately resulting in decreased cardiac relaxation and diastolic dysfunction[112].

MiRNA dysregulation is an important epigenetic mechanism in DCMP pathophysiology[109,113]. The fact that the expression of more than 300 miRNAs is disrupted in DCMP provides evidence for the involvement of miRNA regulatory networks in DM-associated pathophysiological processes in the myocardium[113]. For instance, the expression of 317 miRNAs was found to be dysregulated in the hearts of mice with streptozotocin-induced diabetes, with miR-1 downregulation and miR-19b, miR-27a, miR-125b, miR-34a, miR-155, miR-146 miR-210, and miR-221 upregulation representing the most significant changes[108]. Subsequent bioinformatic analysis revealed that the differentially expressed miRNAs were involved in signaling networks associated with OS, apoptosis, autophagy, fibrosis, hypertrophic growth, and HF. For instance, miR-34a, which was upregulated in the diabetic myocardium, was associated with cardiac senescence in DM, whereas miR-221, which was also overexpressed, was suggested to have an important role in the progression of diabetic myocardial damage[108]. MiR-1, which targets junctin, a component of the ryanodine receptor-Ca^{2+} release channel complex, was downregulated in the diabetic heart and was associated with arrhythmias, myocardial hypertrophy, and myocardial infarction[108,114,115] (Table 2).

Decreased levels of miR-1 in high-glucose conditions lead to increased junctin expression, which alters Ca^{2+} release, resulting in arrhythmia and cardiac hypertrophy[116,117] (Table 2).

MiRNAs can modulate the survival of cardiomyocytes by regulating their response to inflammation and OS[132,133]. Meanwhile, the pathogenesis of DCMP depends on multiple processes mediated by mitogen-activated protein kinase (MAPK) signaling pathways, such as inflammation, OS, and extracellular fibrosis. Evidence suggests that the expression of p38 MAPK, which is activated during apoptosis, inflammation, and OS, as well as following metabolic perturbations[134], is altered in the diabetic myocardium, and that p38

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Table 2.

MiRNAs involved in the pathogenesis of DCMP (↑ and ↓ indicate the up- and downregulation, respectively, of miRNA expression)

MiRNA	Expression	Target	Signaling pathway	Pathophysiological mechanism	Experimental model	References
miR-1	↓	Junctin	Ryanodine receptor-calcium release channels	OS	STZ-induced mouse and rat models of diabetes	[108,114–117]
miR-373	↓	*MEF2C*	P38 MAPK	Cardiomyocyte hypertrophy	Neonatal rat myocytes; STZ-induced mouse model of diabetes	[118–120]
miR-30c	↓	*PGC-1β*, *Cdc42*, *PAK1*	PPARα, p53-p21	OS, cardiomyocyte hypertrophy	Neonatal rat cardiomyocytes; STZ-induced mouse model of diabetes	[121,122]
miR-21	↑	*LAZ3*, *PDCD4*	PPARα, Nrf2, NF-κB	OS, inflammation, apoptosis	Neonatal rat cardiomyocytes; STZ-induced mouse model of diabetes	[123–125]
miR-503	↑	*Nrf2*	Nrf	OS, apoptosis	Rat primary cardiomyocytes; STZ-induced Wistar rat model of diabetes	[126]
miR-22	↓	*SIRT1*	SIRT1	OS, apoptosis	STZ-induced mouse model of diabetes; embryonic cardiac myoblast cell line (H9c2 cells)	[127]
miR-203	↓	*PIK3CA*	PI3KT/AKT	OS, fibrosis, hypertrophy, apoptosis	STZ-induced mouse model of diabetes	[128]
miR-150-5p	↑	*Smad7*	NF-κB, TGF-β1	Inflammation, fibrosis	Rat cardiac fibroblasts; HG-induced diabetes model	[129–131]

Cdc42: cell division control protein 42 homolog; DCMP: diabetic cardiomyopathy; HG: high glucose; *LAZ3*: lymphoma-associated zinc finger 3; *MEF2C*: myocyte enhancer factor 2C; NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells; Nrf2: nuclear factor erythroid 2-related factor 2; OS: oxidative stress; *PAK1*: P21-activated kinase 1; *PDCD4*: programmed cell death 4; *PGC-1β*: peroxisome proliferator-activated receptor-gamma coactivator 1 beta; PI3KT/AKT: phosphatidylinositol 3-kinase/protein kinase B; *PIK3CA*: phosphatidylinositol 4,5-bisphosphate 3-kinase catalytic subunit alpha; PPARα: peroxisome proliferator-activated receptor alpha; *SIRT1*: sirtuin 1; *Smad7*: mothers against decapentaplegic homolog 7; STZ, streptozotocin; TGF-β1: transforming growth factor-beta 1.

MAPK inhibition using atorvastatin prevents DCMP development in a transgenic animal model[118,119]. *In vitro*, inhibiting p38 MAPK downregulates the expression of miR-373, whereas cardiomyocytes transfected with miR-373 and cultivated under high-glucose conditions show hypertrophy, accompanied by decreased levels of the transcription factor myocyte enhancer factor 2C (MEF2C), the target of miR-373[120] (Table 2). Excessive ROS accumulation in DM results in increased activation of the transcription factor nuclear factor erythroid 2-related factor 2 (Nrf2), a key regulator of OS-related gene[135]. Additionally, Nrf2 and PPARα have been reported to act synergistically, whereby the activation of the PPARα pathway results in Nrf2 activation[136–138]. Meanwhile, miR-30c was proposed to play a protective role in DCMP *via* the PPARα pathway[121]. In a mouse model of T2DM, miR-30c levels were found to be decreased, which was associated with increased expression of its target, peroxisome proliferator-activated receptor-gamma coactivator 1 beta (PGC-1β), leading to metabolic alterations, cardiac lipotoxicity, and elevated ROS accumulation[121]. MiR-30c overexpression attenuated myocardial lipid accumulation and ROS production both *in vitro* and in db/db mice, resulting in reduced cardiomyocyte apoptosis and improved cardiac function[121]. In rat cardiomyocytes exposed to high concentrations of glucose, the overexpression of miR-30c also downregulated the expression of the pro-hypertrophic genes *Pak1* and *Cdc42*, thereby decreasing cardiomyocyte hypertrophy[122] (Table 2). Furthermore, compared with healthy controls, the overexpression of miR-30c in db/db mice resulted in decreased LV mass and a higher LV ejection fraction[139]. These results imply that miR-30c has potential as a therapeutic target in the management of DCMP[121].

Additionally, given its role in PPARα and Nrf2 signaling, the modulation of miR-21 levels has been suggested as a viable therapeutic strategy for the treatment of DCMP[123]. Both miR-21 and the lymphoma-associated zinc finger 3 (*LAZ3*) gene, which encodes a transcriptional repressor that inhibits NF-κB signaling and thus plays a role in the regulation of inflammation, are under the control of PPARα and Nrf2[123]. In the hearts of diabetic mice, LAZ3 was reported to be downregulated[123], and its silencing boosted the production of miR-21, which targets PPARα. This led to the downregulation of the PPARα and Nrf2 signaling pathways, resulting in an ineffective OS response. Studies have also shown that increased miR-21 expression *via* programmed cell death 4 (PDCD4) protects cardiac myocytes from ROS-induced injury, whereas decreased miR-21 expression reduces aberrant heart remodeling in cardiac fibroblasts[124,125]

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(Table 2). These findings suggest that the roles of miR-21 may differ in a cell-type- and condition-dependent manner and further studies on human subjects are required to explain the above-mentioned contradictory findings.

MiR-503 and miR-22 dysregulation impairs the ability of Nrf2 to mitigate the adverse effects of excessive ROS generation in DM. Nrf2 activation upregulates the expression of miR-503, an effect that can be further enhanced using protective effect of phase II enzyme inducer (CPDT), an inducer of Phase II antioxidant enzymes[126]. MiR-503 was reported to be downregulated in diabetic rats treated with CPDT, which was accompanied by elevated Nrf2 levels and the attenuation of cardiomyopathy[126] (Table 2). Meanwhile, miR-22, which targets the 3′UTR of *Sirt1* and increases its expression, was found to be downregulated in the myocardium of mice with streptozotocin-induced diabetes[127]. The overexpression of miR-22 in diabetic mice was accompanied by reduced ROS levels, increased superoxide dismutase activity, and improved blood glucose levels, LV end-diastolic pressure, and LV ejection fraction (Table 2)[127]. Several miRNAs, such as miR-203 and miR-150-5p, have been associated with the PI3K/AKT signaling pathway, which plays a critical role in insulin resistance and DCMP pathogenesis[128]. PI3K/AKT signaling regulates the activity of NF-κB, a transcription factor connected with the immune response and inflammation[140]. This pathway also mediates platelet activation and transforming growth factor-beta 1 (TGF-β1) release associated with atrial fibrosis in cell culture and ventricular fibrosis in an experimental mouse model[141]. Increased miR-203 expression reduces myocardial apoptosis, fibrosis, cardiac hypertrophy, and ROS levels in myocardial tissue of diabetic mice through the inhibition of PI3K/AKT pathway activation *via* its target the phosphatidylinositol 4,5-bisphosphate 3-kinase catalytic subunit alpha (*PIK3CA*) gene[128] (Table 2). MiR-150-5p expression was upregulated in cardiac fibroblasts under high-glucose conditions, concomitant with a significant increase in NF-κB activity and IL-1β production. MiR-150-5p downregulates the expression of mothers against decapentaplegic homolog 7 (*Smad7*)[129], which suppresses TGF-β1 signaling[130]. Furthermore, miR-150-5p is associated with inflammatory cytokine production, vascular remodeling, and fibrosis[131] (Table 2), and its knockdown was shown to reverse cardiac remodeling[113,129]. These observations indicate that miR-150-5p attenuates both inflammation mediated by the NF-κB and TGF-β1/Smad pathways and cardiomyocyte fibrosis, suggesting that it also has potential as a target for DCMP treatment.

CIRCULATING PLASMA MiRNAs AS DM BIOMARKERS

Extracellular circulating miRNAs are emerging as promising biomarkers for several pathophysiological conditions[142,143] given their presence in almost every biological fluid, including serum[144], plasma[145], cerebrospinal fluid[146], saliva[147], urine, and tears[148], as well as their high stability, even after prolonged storage. Although miRNAs are present in body fluids at femtomolar concentrations[149], they can nevertheless be detected in samples using qRT-PCR, microarrays, and RNA sequencing (RNA-seq)[148]. Their remarkable stability and ability to avoid degradation are due to their presence in exosomal vesicles[147] or their association with HDLs[150] or AGO2 proteins[145,151].

Several circulating miRNAs have been consistently reported as being differentially abundant in DM patients compared with healthy controls. For instance, 11 circulating miRNAs (miR-100-5p, miR-21-5p, miR-150-5p, miR-24-3p, miR-146a-5p, miR-148a-3p, miR-181a-5p, miR-210-5p, miR-342-3p, miR-1275, and miR-375) involved in pathways mediating cell survival, proliferation, immune system function, and insulin synthesis were reported to be dysregulated in patients with T1DM[152] (Table 3).

Investigation of the serum miRNA expression profile of children with new-onset T1DM identified 12 upregulated miRNAs—miR-24, miR-26a, miR-27b, miR-27a, miR-29a, miR-25, miR-152, miR-30a-5p, miR-200, miR-148a, miR-181a, and miR-210—some of which are associated with establishing glycemic control and restoring the function of pancreatic β cells (Table 3). Other circulating miRNAs, including miR-30d, miR-29a, miR-21, miR-24, miR-34a, miR-148a, miR-126, miR-146, miR-210, and miR-181a, have also been reported as being upregulated in patients with T1DM[153,159,160].

In T2DM patients, global miRNA profiling in blood samples identified approximately 70 upregulated and 100 downregulated miRNAs[33]. Further analysis suggested that plasma levels of miR-103, miR-29a, miR-107, miR-34a, miR-142–3p, miR-132, miR-375, and miR-144 have potential to serve as T2DM biomarkers[161] (Table 3). Several studies have reported that miR-126a is the most significantly downregulated circulating miRNA in T2DM patients[156,162–165], whereas several other serum miRNAs have been associated with the pathogenesis of T2DM[163,166–174]. A comparative analysis of miRNA profiles between T2DM patients and healthy individuals with normal glucose tolerance showed that the levels of miR-9, miR-34a, miR-27a, miR-15b, miR-29a, miR-124a, miR-30d, miR-192, miR-150, miR-375, miR-146b, miR-320a, miR-571, miR-486, miR-661, miR-1303, miR-770, and miR-892b were significantly increased in patients[169–172], whereas those of miR-486, miR-96, miR-23a, miR-191, miR-186, miR-192, and let-7g were decreased[168].

Circulating miR-17-5p, miR-15a-5p, miR-221, and let-7g have a well-established connection with β-cell apoptosis, central obesity, and insulin resistance[154,155] and were suggested to be reliable predictive biomarkers of metabolic syndrome (MetS)[158] (Table 3). In contrast, plasma levels of miR-192 and miR-194 were proposed

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Table 3.

Circulating miRNAs as potential biomarkers of DM and metabolic syndrome

Circulating miRNA	Condition	Function	References
miR-21	T1DM	Cell survival, proliferation, immune system function, glycemic control, β-cell function, islet inflammation, insulin synthesis	[152,153]
miR-24	Same as above	Same as above	[152,153]
miR-25	Same as above	Same as above	[152,153]
miR-26a	Same as above	Same as above	[152,153]
miR-27a	Same as above	Same as above	[152,153]
miR-27b	Same as above	Same as above	[152,153]
miR-29a	Same as above	Same as above	[152,153]
miR-30a-5p	Same as above	Same as above	[152,153]
miR-100-5p	Same as above	Same as above	[152,153]
miR-126	Same as above	Same as above	[152,153]
miR-146a-5p	Same as above	Same as above	[152,153]
miR-148a-3p	Same as above	Same as above	[152,153]
miR-150-5p	Same as above	Same as above	[152,153]
miR-152	Same as above	Same as above	[152,153]
miR-181a-5p	Same as above	Same as above	[152,153]
miR-200	Same as above	Same as above	[152,153]
miR-210	Same as above	Same as above	[152,153]
miR-342-3p	Same as above	Same as above	[152,153]
miR-375	Same as above	Same as above	[152,153]
miR-1275	Same as above	Same as above	[152,153]
miR-9	T2DM	Glucose metabolism, β-cell proliferation, insulin sensitivity, insulin secretion	[154–157]
miR-28-3p	Same as above	Same as above	[154–157]
miR-29a	Same as above	Same as above	[154–157]
miR-30a-5p	Same as above	Same as above	[154–157]
miR-34a	Same as above	Same as above	[154–157]
miR-103	Same as above	Same as above	[154–157]
miR-107	Same as above	Same as above	[154–157]
miR-126a	Same as above	Same as above	[154–157]
miR-132	Same as above	Same as above	[154–157]
miR-142–3p	Same as above	Same as above	[154–157]
miR-144	Same as above	Same as above	[154–157]
miR-150	Same as above	Same as above	[154–157]
miR-375	Same as above	Same as above	[154–157]
miR-15a-5p	MetS	Obesity, β-cell apoptosis, insulin resistance	[154,155,158]
miR-17-5p	Same as above	Same as above	[154,155,158]
miR-221	Same as above	Same as above	[154,155,158]
let-7g	Same as above	Same as above	[154,155,158]

MetS: metabolic syndrome; T1DM: type 1 diabetes mellitus; T2DM: type 2 diabetes mellitus.

as potential biomarkers for DM risk assessment[175]. It was also proposed that circulating miR-29a, miR-9, miR-28-3p, miR-30a-5p, miR-103, and miR-150 can serve to distinguish between T2DM and non-T2DM patients[157]. Interestingly, it was reported that this set of miRNAs is associated with cell proliferation, insulin sensitivity, and insulin secretion and that changes in their levels can be detected up to three years before the onset of T2DM[157]. Nevertheless, studies on larger patient cohorts are needed to establish the potential of proposed miRNAs as reliable and useful biomarkers for T1DM, T2DM, and their associated cardiovascular complications.

MiRNA-BASED THERAPEUTIC STRATEGIES FOR THE TREATMENT OF DM AND DCMP

RNA-based therapies have many advantages over other treatments, including the simultaneous targeting of several genes, the targeting of genes inaccessible to traditional medicines, and the circumvention of drug resistance. MiRNA levels can be modulated *in vivo* either by limiting miRNA function using miRNA-targeting antisense oligonucleotides (ASOs) or by restoring downregulated miRNA levels using miRNA mimics, which are synthetic double-stranded miRNAs or viral vectors that express miRNAs with the same sequence as endogenous ones. Using these methods, numerous mRNAs can be simultaneously targeted[176]. ASOs complementary to an endogenous miRNA are called anti-miRs and they prevent interaction between miRNAs and their target mRNAs. AntagomiRs are anti-miRs that are coupled to cholesterol for improved intracellular delivery[177]. Many chemical modifications that increase

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the pharmacokinetics and pharmacodynamics of RNA therapies have been undertaken aiming to overcome the instability of RNA and its inability to cross cell membranes owing to its negative charge[178].

First-generation modifications increased the stability of RNA therapeutics by replacing phosphodiester with phosphorothioate (PT) backbone linkages. Second-generation modifications improved bioavailability and decreased immunostimulation and toxicity by replacing the 2′-O-alkyl group of the sugar moieties with 2′-O-Me, 2′-MOE, or 2′-Fluoro. For the creation of peptide nucleic acids, locked nucleic acids (LNAs), and phosphorodiamidate morpholino oligomers, which represent third-generation modifications, changes were introduced in the RNA furanose ring. RNA therapies currently approved for clinical research have second- or third-generation chemical modifications[178].

Regarding the potential treatment of T2DM and insulin resistance, LNA anti-miR-122 treatment has been tested in mice and non-human primates, where it decreased blood cholesterol levels and improved liver steatosis with no indications of hepatic toxicity[179]. ASOs were used to inhibit miR-103 and miR-107 in the liver and adipose tissue of obese mice, resulting in improved insulin sensitivity and glucose homeostasis[51]. Modified GalNAc-conjugated oligonucleotides targeting miR-103/miR-107RG-125 (AZD4076) were developed by Regulus Therapeutics (Inc. La Jolla, USA) and assessed in phase I and IIa clinical trials for their effect on insulin sensitivity and liver fat content in patients with T2DM and nonalcoholic steatohepatitis[180]. Regulus Therapeutics also developed another antagomir for treating metabolic diseases—2′-fluoro/methoxyethyl (2′F/MOE) modified, PT backbone modified anti-miR-33, which was shown to reduce atherosclerotic plaque in T2DM mice[181]. miRagen therapeutics developed an LNA-modified ASO targeting miR-208A (MGN-9103)[182], which improved insulin sensitivity and systemic glucose tolerance in MetS[183]. MiR-21 suppression with LNA-modified anti-miR-21 in adipose tissue of db/db mice resulted in a substantial body weight decrease[184], while ASO-mediated miR-181 downregulation in DIO mice ameliorated insulin sensitivity and glucose homeostasis[185].

In the context of DCMP, several anti-miRs have been tested in animal models. For instance, antagomiR-155 decreased cardiac infiltration of inflammatory mediators, thus improving myocardial damage and overall cardiac function. Additionally, the aggravation of inflammation induced by estrogen deficiency in the hearts of diabetic mice, characterized by excessive infiltration by proinflammatory M1 macrophages, was mitigated by the administration of gold nanoparticle-conjugated antagomiR-155[186], resulting in improved heart function. These results suggest that a therapeutic strategy based on miR-155 inhibition shows promise in ameliorating cardiac function in patients with DCMP[186]. Meanwhile, a preclinical study in pigs showed that an intracoronary injection of antagomiR-92 encapsulated in poly(lactic-co-glycolic acid) in the post-infarcted heart stimulated angiogenesis and ameliorated myocardial function[187].

Gene editing with Clustered Regularly Interspaced Short Palindromic Repeats/CRISPR-associated protein-9 (CRISPR/Cas9) can be used for whole-genome editing and has been used to target the expression of miRNAs implicated in several pathophysiological conditions[188]. CRISPR/Cas9 was recently used for the development of a candidate antidiabetic therapeutic by ViaCyt and CRISPR Therapeutics. A CRISPR/Cas9-edited stem cell-derived therapy VCTX210, which replaces β cells lost in DM, was developed for treating T1DM and T2DM and has been approved for a clinical trial in Canada. Importantly, however, any future applications of gene editing for therapeutic purposes will require improved delivery of the components of the editing system to specific target tissues and strict control of off-target Cas9 activity[189].

CONCLUSIONS AND PROSPECTIVES

Many animal and human studies have established the role of miRNAs in the pathogenesis of diabetes and its associated cardiovascular complications, such as DCMP. Specific miRNAs have been reported to regulate the expression of genes involved in glucose homeostasis, fat metabolism, and immune system balance. When dysregulated, these processes can lead to the physiological alterations associated with DM and DCMP. Mounting evidence suggests that miRNAs can be used as potential prognostic and diagnostic T1DM and T2DM biomarkers and therapeutic tools in DM patients. Future research should further clarify the roles of the identified miRNAs and examine their utility for predicting vascular risk and end-organ vascular damage. Additionally, research efforts should concentrate on the design and development of highly specific miRNA-based therapeutics to facilitate their translation to clinical settings. With further advancements in high-throughput methodologies, such as whole-genome and transcriptome profiling and associated metabolomic and proteomic analyses, a deeper link between various miRNAs and the pathophysiology of DM and associated cardiovascular complications is expected to be more firmly established.

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AUTHOR CONTRIBUTIONS

MTM wrote the article and ERI wrote and critically reviewed the article. Both authors approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

Esma R. Isenovic is currently an Editorial Board member of *Cardiology Plus*. The article was subject to the journal's standard procedures, with peer review handled independently of the Editorial Board members and their research groups.

DATA SHARING STATEMENT

All data generated or analyzed during this study are included in this published article.

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