






The milestone – role of miRNAs as predictors of diabetes complications: a literature review

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Abstract

Diabetes mellitus (DM) is one of the biggest health problems of the 21st century. The complications of DM are macrovascular (ischemic diseases of the heart and brain) and microvascular (retinopathy, nephropathy, neuropathy). The aim of this review was to describe the role of micro ribonucleic acids (miRNAs) as markers for the development of distant complications of diabetes. A search was conducted in the PubMed, Scopus, Google Scholar and EMBASE databases for articles published in 2014-2024. Fifty-three original articles, systematic reviews and meta-analyses were included in the review. MiRNAs are involved in metabolic pathways responsible for the onset and development of DM and their altered expression may serve as a non-invasive biomarker for the development of distant DM complications. Among the most significant is miR-21, responsible for normal angiogenesis, whose expression was higher in patients with macroangiopathy and retino-, nephro- and neuropathy. Certain miRNAs may have potential as potential therapeutic targets, e.g. miR-203 (ischemic heart disease), miR-181c (retinopathy) and miR-184-5p (neuropathy). MiRNAs are potential biomarkers for the development of distant complications of diabetes and may serve as therapeutic targets for their reduction.

Keywords: microRNAs · diabetes mellitus · complications · predictors

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Citation

Bigosiński K, Granat M, Salamon K, Góra J, Caliński M, Bednarz H, Dubaj M, Porada D. The milestone – role of miRNAs as predictors of diabetes complications: a literature review. *Eur J Transl Clin Med.* 2025;8(2):58-70.

DOI: [10.31373/ejtc/209126](https://doi.org/10.31373/ejtc/209126)

Introduction

Diabetes mellitus (DM) is a growing global health and economic challenge, with 828 million cases reported in 2022 and projections reaching 1.31 billion by 2050, mainly in low- and middle-income countries [1-3]. Furthermore, in 2021 approximately 11.8% of deaths globally in the working-age population (< 60 years) were estimated to be caused by DM or its complications [1-3].

Chronic complications of DM lead to poor outcomes (increased morbidity, mortality, and healthcare costs) and are traditionally classified as microvascular (retinopathy, nephropathy, neuropathy) and macrovascular (coronary artery disease [CAD], stroke, peripheral artery disease [PAD]) [4-5]. However, Yu et al. suggested a revision of this classification, in accordance with the affected tissues: vascular, parenchymal and hybrid (both vascular and parenchymal) [5].

Microribonucleic acids (miRNAs) are small non-coding RNAs (20-25 nucleotides) that regulate gene expression post-transcriptionally [6]. Circulating miRNAs are stable in body fluids (due to protection in exosomes or protein complexes) and show potential as non-invasive diagnostic and prognostic biomarkers. In DM, miRNAs modulate key pathogenic mechanisms, including beta-cell responses to metabolic, genetic, and inflammatory stimulation [6-7]. Specific miRNAs, such as miR-34 and miR-146, are of particular interest [7]. Moreover, miRNAs offer the potential for the early detection of a particular type of DM and its specific complications [8-9]. Given the urgent need for effective biomarkers of DM, in this article we present a comprehensive review of the available data on the involvement of miRNAs in predicting its complications [10].

Material and methods

A literature search was conducted independently by 3 authors using the PubMed, Scopus, Google Scholar, and EMBASE databases. The results were then compared. The following keywords were used: 'diabetes,' 'complications,' 'miRNAs,' 'miRNAs,' 'markers,' 'retinopathy,' 'neuropathy,' 'nephropathy,' and the 'AND' operator. The articles were

searched sequentially in the given databases, and the results were combined by the same 3 authors. The inclusion criteria were as follows: article published in 2014-2024, article format (original/research article, systematic review and meta-analysis), article about the role of miRNAs in DM, article describing distant complications of DM, study included patients > 18 years of age or animal models. The exclusion criteria were: articles published before 2014, inappropriate format (editorial, letter to the Editor, abstract-only, poster, case report, non-systematic review), articles describing acute complications of DM, and articles on DM in children. The discrepancies between the searches were minor. After analysis, articles that did not meet the inclusion criteria were rejected, and a combined list of articles for the final review was developed. Initially, 476 studies were identified. After excluding duplicate articles and screening the titles and abstracts, 70 articles remained. After a substantive analysis, 53 articles were included in the review.

Results and discussion

Macroangiopathy

Vascular disorders are characteristic complications of DM and lead to high risk of death. Morrison et al. demonstrated that patients with vascular complications of DM have elevated levels of HDL-related miRNAs. MiR-181c-5p may underlie proangiogenic processes, with 14-fold higher activity in subjects with PAD ($1454 \pm 1346\%$) than in the healthy group ($100 \pm 121\%$) and patients without PAD ($82 \pm 77\%$). This could also be applied to miRNA-181c-5p in plasma, however the difference was not statistically significant. In contrast, HDL-bound miRNA-27b-3p showed 10-fold higher activity in patients with PAD ($260 \pm 232\%$) than in those without it ($27 \pm 23\%$) [11].

The adverse effect of DM on the prognosis of patients with heart failure (HF) and CAD has been known for a long time. The correlation between miR-1 and miR-21 expression and these conditions was studied by Al-Hayali et al.

in a group of 35 patients with insulin-dependent DM. The results showed significantly (0.22-fold) lower serum levels of miR-1 in patients with HF than in a group with type 2 DM alone, as well as in a group with CAD ($p < 0.001$). Moreover, miR-21 expression was higher in patients with HF (1.7 times) and CAD (1.37 times) than in patients without these conditions. Additionally, they demonstrated positive correlations between miR-21 and NT-proBNP and galactin-3. When miR-21 levels were > 1.695 and NT-proBNP > 4747 pg/mol, the probability of DM and HF co-occurring was 95.2%. In contrast, in cases where miR-21 levels were < 1.695 and NT-proBNP levels were < 4747 pg/mol, the probability of DM alone was 66.7%. In cases where the miR-21 value was > 1.695 and the galactin-3 value was > 9.25 ng/mol, the probability was as high as 74.4% [12].

Other researchers observed decreased miR-130a and miR-130b levels in patients with DM and CAD compared to those with DM alone and in the control group [13]. In their studies of mice, Dai et al. reported an unknown role for miR-21 in alleviating the symptoms and progression of diabetic cardiomyopathy by affecting gelsolin. A notable decrease in miR-21 expression was observed in the hearts with diastolic dysfunction. The supply of exogenous miR-21 effectively protected the heart from the early onset of impaired diastolic function in the reduced emission of reactive oxygen species, increased bioavailability of nitric oxide, and mitigation of cardiomyocyte hypertrophy in diabetic mice [14].

Lopes et al. tested miRNA values from the left ventricle of diabetic rodents to elucidate their role in diabetic cardiomyopathy. They noted decreased expression of rno-miR-877, rno-miR-320 and rno-miR-214 in the study group, together with increased expression of rno-miR-17, rno-miR-187, rno-miR-34a, rno-miR-322, rno-miR-188, rno-miR-532 and rno-miR-21. These results demonstrate the potential usefulness of the aforementioned miRNAs in the early detection of diabetic heart complications [15].

Chen et al. measured miR-30c levels in the myocardium of rodents with diabetic cardiomyopathy and healthy controls. A notable reduction in miR-30c was observed in the myocardium of subjects with cardiomyopathy compared to controls. Moreover, miR-30c overexpression reduced diabetic myocardial dysfunction. In addition, the data showed that overexpression of miR-30c silences the autophagy-initiating protein BECN1, thereby protecting myocardial function in diabetic rodents. However, the reduction of miR-30c expression increased the expression of BECN1 protein and through it, autophagy and progression of pathology within the myocardium [16]. In addition, Chen et al. observed a relationship between decreased levels of miR-133 in cardiac muscle and increased levels of fibrosis biomarkers in a mouse model of diabetic cardiomyopathy. Overexpression of miR-133 can

even reverse DM-induced cardiac remodeling by attenuating these biomarkers [17].

Liu et al. were the first to report the role of miR-222 in the protective effect of physical exercise on the cardiovascular system. Mice exposed to swimming showed higher expression of miR-222 in cardiomyocytes, which stimulated cell proliferation and growth. In contrast, miR-222 inhibition led to apoptosis of cardiomyocytes, indicating its potential therapeutic relevance [18]. Other researchers have found that increased levels of circulating miR-1 and miR-133 are correlated with a higher probability of CAD in patients with type 2 DM [19]. Similar conclusions were published in a study of miR-126, the expression of which was significantly reduced in the type 2 DM and CAD groups compared to the reference group [20]. Jansen et al. noted that DM alters vascular endothelial miRNA expression in circulating endothelial microvesicles. MiR-126 and miR-26a expression levels were lower in the DM group than in the controls. The group with reduced expression of the molecules mentioned above was more likely to have concomitant CAD [21]. Xubin et al. noted that increased expression of miR-203 could act as a cardio-protective factor in diabetic cardiomyopathy by inhibiting the PI3K/Akt path [22]. Deng et al. investigated that the level of circulating miR-24 was significantly reduced in the peripheral blood of patients with type 2 DM and CAD compared to controls [23]. The summary is presented in Table 1.

Retinopathy

Hyperglycemia causes vascular wall dysfunction and that is why diabetic retinopathy (DR) is one of the most common complications of DM and the most common cause of vision loss. One study showed that miR-21 expression was increased in patients with non-proliferative DR ($n = 73$) compared to controls ($n = 115$) and increased in patients with proliferative DR ($n = 51$) than in those with non-proliferative DR. Increased miR-21 levels were associated with the development of DR and can be used as an indicator of its severity [24]. Moreover, Qing et al. proved that the merger of miR-21, miR-181c and miR-1179 is useful in distinguishing the proliferative DR from the non-proliferative form. They noted that miR-21 was strongly correlated with angiogenesis in hyperglycemia. Simultaneously, miR-181c expression was higher in endothelial cells in a DM-like environment, indicating that it is related to vascular proliferation at high glucose concentrations [25]. McAuley et al. noted that the A allele of the miR-126 polymorphism is associated with sight-threatening DR compared to those without DR or early-stage disease. It acts as a vascular endothelial growth factor (VEGF) and boosts the probability of progression of the DR, thus it could become a potential therapeutic target [26]. Other scholars have identified

Table 1. Role of miRNAs as potential biomarkers in diabetic macroangiopathy [11-23]

Authors	Study group (n)*	Study material	miRNA	Change in expression	Targets
Morrison et al. 2019 [11]	27	Plasma endothelial cell cultures	miR-181c-5p	↑	FOXO1 COX-2 BCL2 LIF HIF1A
Al-Hayali et al. 2019 [12]	135	plasma	miR-1	↓	XPO6 Irx5 HAND2 KLF4
			miR-21	↑	Spry1, PTEN
Yuan et al. 2019 [13]	201	plasma	miR-130	↓	PPAR-γ
Dai et al. 2018 [14]	-	mice cell lines	miR-21	↓	gelsolin
Lopes et al. 2017 [15]	-	rats	rno-miR-877 rno-miR-320 rno-miR-214	↓	Pla2g2a
			rno-miR-17, rno-miR-187, rno-miR-34a, rno-miR-322, rno-miR-188, rno-miR-532 rno-miR-21	↑	Hk2
Chen et al. 2017 [16]	91	mice plasma	miR-30c	↓	BECN1
Chen et al. 2014 [17]	-	mice	miR-133a	↓	TGFB1 COL4A1 FN1 ERK1/2 SMAD-2
Liu et al. 2015 [18]	28	mice plasma	miR-222	↑	HIPK1 HMBOX1
Al-Muhtaresh et al. 2019 [19]	60	whole blood	miR-1	↑	HDAC4
			miR-133	↑	SRF
Al-Kafaji et al. 2017 [20]	135	plasma	miR-126	↓	SPRED1 VEGF PIK3R2
Jansen et al. 2016 [21]	135	plasma	miR-26a miR-126	↓	TRPC6 BMP/SMAD1 CXCL12
Yang et al. 2019 [22]	-	mice	miR-203	↑	PI3K/Akt
Deng et al. 2017 [23]	94	plasma	miR-24	↑	YKL-40

* Not all articles mentioned the exact number of people and animals participating in the described study.

miR-1281 as a sensitive biomarker for the early detection of DR. It had the most elevated expression in patients with non-proliferative DR compared to healthy controls, and its expression was increased in retinal cell cultures in high-glucose environments [27]. The authors observed an overexpression of miR-423-5p in DR with enhanced hyperglycemia-induced apoptosis in retinal pigment epithelial cells [28]. Moreover, Santovito et al. found that DR was correlated with higher circulating miR-25-3p and miR-320b and lower miR-495-3p levels compared to the subjects without DR and healthy controls [29]. Blum et al. showed a reduced expression of miR-423 in a group with DR compared to controls [30]. Moreover, García de la Torre et al. observed that the level of miR-126 did not differ between the groups with and without DR, whereas the level of miRNA-221 was increased [31]. Gomaa et al. noticed that miR-200b expression was approximately 5 times higher in vitreous body samples collected from patients with proliferative DR [32]. In another study, miR-15a, miR-320a, miR-320b, miR-93, miR-29a, and miR-423-5p were significantly elevated in patients with proliferative DR [33]. Li et al. investigated the role of miR-200b in the evolution of DR. They found that its increased expression could reduce the expression of VEGFA, mitigating DR progression [34]. According to Liang et al., miR-28-3p, miR-151a-5p, and miR-148a-3p were correlated with the progression of DR and can serve as non-invasive diagnostic markers [35]. Liu et al. discovered that miR-211 may also serve as a new marker with high sensitivity and specificity for DR by affecting Sirtuin 1 [36]. Murray et al. showed overexpression of miR-200b in Akita mice retinas (experimental benchmark of insulin-dependent DM). This miRNA reduces expression of Oxr1. These results suggest that downregulating miRNA-200b expression while enabling Oxr1 expression may have a protective role against DR progression [37]. Rezk et al. found that the group with DR had a lower miR-126 level compared to the group without it [38]. Zampetaki et al., in a group of patients with type 1 DM (n = 300), identified high expression of miR-320a and miR-27b as potential biomarkers of DR progression [39]. Moreover, Zou et al. identified increased

miR-93 as a new promising diagnostic biomarker of DR progression [40]. Pastukh et al. showed that miR-122 expression increased in subjects with severe DR compared to healthy controls. However, when the illness progressed to proliferative DR, miR-122 expression decreased [41]. Moreover, Huihui et al. identified elevated expression of both miR-3197 and miR-2116-5p as potential diagnostic biomarkers for DR [42]. The above data are summarized in Table 2. The role of miRNAs as diagnostic and prognostic markers in DR is shown in Figure 1.

Nephropathy

Diabetic nephropathy (DN) manifests in approximately one-third of diabetic patients and is associated with multiple complications and premature mortality. The disease progresses as the number of podocytes is reduced, the mesangial matrix expands, the glomerular basement membrane thickens, and the glomeruli undergo sclerosis. Initially, DN is often asymptomatic and the patient can be unaware of its progression. Zang et al. reported significantly higher urinary miR-21-5p (2.13-fold) and lower miR-30b-5p (0.82-fold) in DN patients versus subjects without kidney injury, supporting their use in early detection [43]. Beltrami et al. examined the profile of 754 miRNAs and noted increases in miR-126 (2.8-fold), miR-155 (1.8-fold), and miR-29b (4.6-fold) levels in urine from a group with confirmed DN (n = 20) compared to controls (n = 20). Concurrently, comparing patients without DN and the control group was statistically significant for miR-126 (3.1-fold increase) and miR-155 (1.6-fold increase), with a trend toward increased miR-29b (4.1-fold increase). Histopathological analysis revealed that the detection of miRNA-126 and miR-29b was significantly higher in podocyte cells and endothelial cells from glomeruli, while miR-155 was higher in proximal tubule epithelial cells, which could also be used as a valuable biomarker of DN progression [44]. Moreover, An et al. proved that increased urinary miRNA-196a expression is correlated with the level of kidney injury and may constitute a valuable biomarker of progressive fibrotic lesions in DN. Urinary miR-196a levels correlated positively with proteinuria ($\rho = 0.385$), duration of DM ($\rho = 0.255$) and systolic blood pressure ($\rho = 0.267$). Additionally, miR-196a was associated with glomerular sclerosis and renal interstitial fibrosis in patients with DN [45]. Zhao et al. discovered that miR-142-3p is weakly expressed in renal tubular epithelial cells stimulated by hyperglycemia. Increasing its expression can attenuate apoptosis and oxidative stress in chronic hyper-

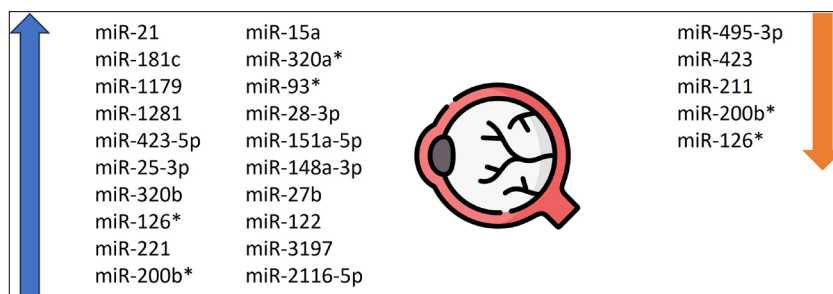


Figure 1. The role of miRNAs as diagnostic and prognostic markers in diabetic retinopathy

* molecules appearing in 2 or more articles

Table 2. Role of miRNAs as potential biomarkers in diabetic retinopathy [24-42]

Authors	Study group (n)*	Study material	miRNA	Change in expression	Targets
Jiang et al. 2017 [24]	189	plasma	miR-21	↑	TMEM49
Qing et al. 2014 [25]	200	serum	miR-21 miR-181c miR-1179	↑	PTEN Akt Erk1/2 VEGF
McAuley et al. 2015 [26]	531	plasma and urine	miR-126	SNP rs4636297-A	VEGF EGFL7
Greco et al. 2016 [27]	60	serum	miR-1281	↑	VEGFA HIF1AN
Xiao et al. 2017 [28]	30	plasma	miR-423-5p	↑	TFF1 NF-κB NFE2
Santovito et al. 2019 [29]	30	plasma	miR-25-3p miR-320b	↑	CDH1 PTEN NOTCH1
			miR-495-3p	↓	
Blum et al. 2019 [30]	69	serum	miR-423	↓	VEGF
García de la Torre et al. 2015 [31]	114	serum	miR-126 miR-221	↑	Spred-1 PI3K/Akt/ eNOS Ras/ERK/VEGF MEK/ERK PAK1
Gomaa et al. 2017 [32]	59	vitreous	miR-200b	↑	Ets1 VEGFR2
Hirota et al. 2015 [33]	8	human vitreous and human whole blood	hsa-miR-15a hsa-miR320a hsa-miR-320b hsa-miR-93 hsa-miR-29a hsa-miR-423-5p	↑	-
Li et al. 2017 [34]	508	human plasma	miR-200b	↓	VEGFA PEDF
	70	rat retinal cells			
Liang et al. 2018 [35]	129	serum	miR-28-3p miR-151a-5p miR-148a-3p	↑	TGF-β MAPK
Liu et al. 2018 [36]	-	human vitreous cell lines	miR-211	↓	Sirt1
Murray et al. 2014 [37]	-	Mice cell lines	miR-200b	↑	Oxr1
Rezk et al. 2016 [38]	286	serum	miR-126	↓	VEGF EGFL7
Zampetaki et al. 2016 [39]	300	serum	miR-27b miR-320a	↑	TSP-1
Zou et al. 2017 [40]	267	plasma	miR-93	↑	TNF-α VEGF
Pastukh et al. 2019 [41]	40	serum	miR-122	↑	TIMP3
Huihui et al. 2020 [42]	90	serum cell lines	miR-3197 miR-2116-5p	↑	NOTCH2

* Not all articles mentioned the exact number of people and animals participating in the described study.

glycemia [46]. Moreover, miR-31 expression was reduced in the group with type 2 DM and coexisting DN was reduced relative to that in the group without complications. Interestingly, this difference was more prominent in the group with macroalbuminuria than in that with microalbuminuria [47]. Assmann et al. showed increased expression of miR-21-3p and miR-378-3p in a group with DN. In contrast, miR-16-5p and miR-29a-3p showed decreased expression compared with a group of patients with type 1 DM and moderate DN [48]. Furthermore, Delić et al. concluded that urinary miR-320c levels were elevated in DN patients compared to diabetic patients without complications and healthy controls [49]. Huang et al. found that increased level of miR-155 and miR-146a in subjects with DM and animal models leads to inflammation-induced glomerular endothelial damage, inducing the progression of DN [50]. Other researchers have observed that miR-155 deficiency attenuates DN during chronic exposure to hyperglycemia [51]. Liu et al. noted that miR-25 is downregulated in patients and animals with DN and the administration of miR-25 to mice inhibited the progression of renal damage [52]. Zanchi et al. concluded in their DN rat model with tubulointerstitial fibrosis, there was an 18-fold higher ex-

pression of miR-184 than in controls [53]. Another molecule with decreased expression in advanced DN was miR-98, and its overexpression inhibits the disease progression [54]. The data on DN are presented in Table 3. The role of miRNAs as diagnostic and prognostic markers in DN is shown in Figure 2.

Neuropathy

Diabetic neuropathy is a significant complication of DM and it occurs due to chronic exposure to elevated blood glucose levels. Recent studies and observations have shown that miRNAs are crucial for the onset of neuropathic pain. The contribution of miR-190a-5p to the overall pathomechanism is therefore significant. In an experiment on mice with induced DM and neuropathy, significantly reduced miR-190a-5p expression was identified after sampling the dorsal horns of the lumbar spine. Regarding the positive effects of expression-enhancing therapy and even the regression of some neuropathic lesions, this offers great hope for a novel treatment strategy for this disease [55]. Moreover, a study by Wang et al. provided reliable evidence for the role of miR-146a in the initiation of apoptosis of dorsal root ganglion neurons in an environment of chronic hyperglycemia and they found that DM reduced miR-146a expression in the mice model [56]. Another study identified miR-184-5p and miR-190a-5p as valuable therapeutic targets for patients with diabetic neuropathy [57]. Ciccacci et al. demonstrated increased levels of miR-128a in patients with diabetic polyneuropathy, whereas miR-155 and miR-499a levels were decreased in the patient group [58]. The same authors in another study noted that the T allele SNP in miR-128a was associated with a higher risk, while the C allele SNP in miR-146a had a lower risk of developing diabetic polyneuropathy. Moreover, the SNP in miR-27a was correlated with the probability of initial cardiovascular autonomic neuropathy, while the SNP in miR-146a proved to have a risk-reducing role [59]. The same group demonstrated that miR-499a may be involved in the development of diabetic neuropathy, specifically showing a higher risk of developing severe cardiovascular autonomic neuropathy [60]. Furthermore, Feng et al. noted decreased miR-146a

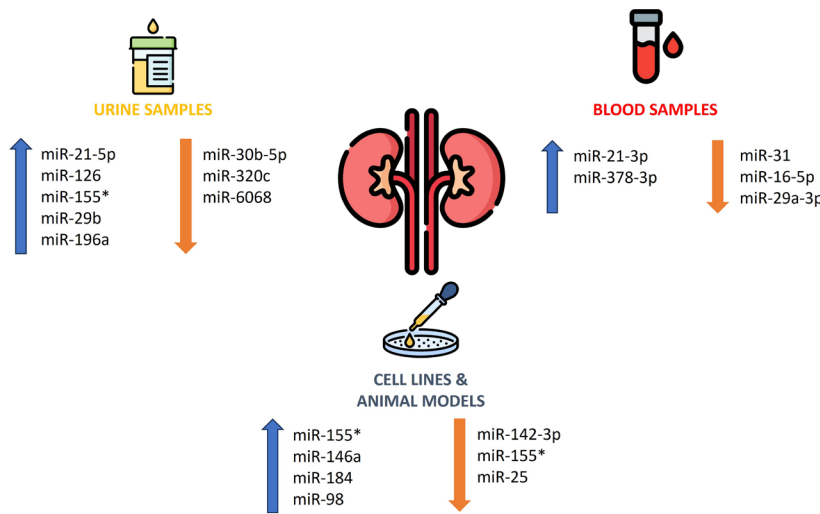


Figure 2. The role of miRNAs as diagnostic and prognostic markers in diabetic nephropathy
* molecules appearing in 2 or more articles

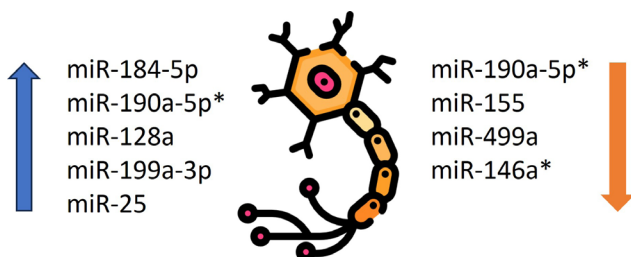


Figure 3. The role of miRNAs as diagnostic and prognostic markers in diabetic neuropathy
* molecules appearing in 2 or more articles

of dorsal root ganglion neurons in an environment of chronic hyperglycemia and they found that DM reduced miR-146a expression in the mice model [56]. Another study identified miR-184-5p and miR-190a-5p as valuable therapeutic targets for patients with diabetic neuropathy [57]. Ciccacci et al. demonstrated increased levels of miR-128a in patients with diabetic polyneuropathy, whereas miR-155 and miR-499a levels were decreased in the patient group [58]. The same authors in another study noted that the T allele SNP in miR-128a was associated with a higher risk, while the C allele SNP in miR-146a had a lower risk of developing diabetic polyneuropathy. Moreover, the SNP in miR-27a was correlated with the probability of initial cardiovascular autonomic neuropathy, while the SNP in miR-146a proved to have a risk-reducing role [59]. The same group demonstrated that miR-499a may be involved in the development of diabetic neuropathy, specifically showing a higher risk of developing severe cardiovascular autonomic neuropathy [60]. Furthermore, Feng et al. noted decreased miR-146a

Table 3. Role of miRNAs as potential biomarkers in diabetic nephropathy [43-54]

Authors	Study group (n)*	Study material	miRNA	Change in expression	Targets
Zang et al. 2020 [43]	84	urine	miR-21-5p	↑	PTEN TGF-β EMT
			miR-30b-5p	↓	
Beltrami et al. 2018 [44]	192	urine	miR-126 miR-155 miR-29b	↑	TNF-α TGF-β
An et al. 2020 [45]	209	urine	miR-196a	↑	TGF-β Bram1
Zhao et al. 2021 [46]	-	HG-stimulated HK-2 cells	miR-142-3p	↓	BOD1
Rovira-Llopis et al. 2018 [47]	31	serum	miR-31	↓	Satb2 MAPK2
Assmann et al. 2019 [48]	58	serum	miR-21-3p miR-378-3p	↑	TGF-β1 Pi3K/Akt AGE-RAGE
			miR-16-5p miR-29a-3p	↓	
Delić et al. 2016 [49]	24	urine	miR-320c miR-6068	↓	TGF-β TSP-1
Huang et al. 2014 [50]	6	renal tissue cell lines	miR-155 miR-146a	↑	TGF-β1 TNF-α NF-κB
Lin et al. 2015 [51]	-	mice	miR-155	↓	WT-1 IL17A SOCS1
Liu et al. 2017 [52]	-	mice serum	miR-25	↓	CDC42
Zanchi et al. 2017 [53]	-	rats	miR-184	↑	LPP3 NF-κB
Zhu et al. 2019 [54]	-	Mouse mesangial cells and HEK-293T cells	miR-98	↓	HMGA2 Nedd4L TGF-β/ Smad2/3

* Not all articles mentioned the exact number of people and animals participating in the described study.

Table 4. Role of miRNAs as potential biomarkers in diabetic neuropathy [55-63]

Authors	Study group (n)*	Study material	miRNA	Change in expression	Targets
Yang et al. 2017 [55]	-	mice	miR-190a-5p	↓	SLC17A6
Wang et al. 2014 [56]	-	mice	miR-146a	↓	IRAK1 TRAF6
Gong et al. 2015 [57]	-	mice	miR-184-5p miR-190a-5p	↑	-
Ciccacci et al. 2020 [58]	49	serum	miR-128a	↑	PTEN
			miR-155 miR-499a	↓	
Ciccacci et al. 2014 [59]	260	serum	miR-128a miR-146a miR-27a	SNP	-
Ciccacci et al. 2018 [60]	150	serum	miR-499a	SNP	-
Feng et al. 2018 [61]	-	rats	miR-146a	↓	TNF- α IL-1 β NF- κ B
Li et al. 2017 [62]	110	plasma skin tissue	miR-199a-3p	↑	SerpinE2
Zhang et al. 2018 [63]	-	mice	miR-25	↑	AGE-RAGE Nox4

* Not all articles mentioned the exact number of people and animals participating in the described study.
SNP – single nucleotide polymorphism

expression in rats with diabetic neuropathy compared to those without it [61]. Li et al. proved that expression of miR-199a-3p was higher in the diabetic neuropathy group compared to patients without this complication [62]. Other researchers have pointed out that miR-25 plays a protective role against diabetic neuropathy, while the use of drugs that inhibit miR-25 may contribute to the development of this complication [63]. The data are presented in Table 4. The role of miRNAs as diagnostic and prognostic markers in diabetic neuropathy is shown in Figure 3.

Limitations of the study

We used a narrative rather than a systematic review method. No quality or risk of bias assessment was conducted. Due to the relatively small number of studies in human groups, data from both human groups and animal models were included in our review.

Conclusions

MiRNAs play an essential function in metabolic pathways and the pathogenesis of DM. MiRNAs are potential biomarkers for the evolution of distant consequences of DM and may serve as their therapeutic targets. Randomized trials on large groups of human populations are still lacking. More research is needed to understand the role and potential future diagnostic use of miRNAs.

Conflict of interest

None.

Funding

None.

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