

## Circulating microRNAs as biomarkers for diabetic neuropathy: A novel approach

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### Abstract

Oxidative stress stemming from tissue exposure to constant hyperglycemia is one of the major pathogenetic pathways of diabetic macro- and microvascular complications. Diabetic polyneuropathy, commonly manifesting as distal, symmetrical sensorimotor polyneuropathy, is characterized by progressive severity of symptoms, with rates analogous to the quality of glycemic control achieved by the patients and physicians. Palliative care with analgesics and aggressive glycemic control often improve quality of life in the absence of causative treatment. Currently, there is a growing body of evidence indicating the role of microRNAs in the pathogenesis of diabetic complications, with emphasis on diabetic nephropathy and neuropathy. Therefore, in this review, we aim to explore the role of microRNAs and their polymorphisms in the pathophysiology of diabetic polyneuropathy, as well as, the possibility of novel diagnostic and therapeutic applications by epigenetic profiling and manipulation.

**Key words:** Diabetic neuropathy; Type 2 diabetes mellitus; Type 1 diabetes mellitus; Epigenetic; MicroRNAs

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**Core tip:** In this review, we aim to create a concise overview of the epigenetics underlining the pathogenesis of diabetic neuropathy with emphasis on the altered microRNA expression patterns identified on both animal and human subjects, while, exploring the manner by which they could be manipulated and utilized as novel therapeutic targets.

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## INTRODUCTION

Diabetic neuropathy (DN), a common microvascular complication in type 1 (T1DM) and type 2 diabetes mellitus (T2DM) and is defined as the presence of signs and/or symptoms of peripheral nerve dysfunction in patients with diabetes after the exclusion of other causes<sup>[1,2]</sup>. Population and clinical-based studies suggest DN prevalence rates of 20% in T1DM following 20 years of disease duration and approximately 10%-15% at T2DM diagnosis increasing to as high as 50% at 10 years of disease<sup>[3]</sup>. Despite the research conducted on the topic, the pathophysiology underlying the process has not been clearly defined, on account of both the numerous intertwining causative mechanisms and the difficulty in establishing a definite diagnosis<sup>[4]</sup>. Specifically, the diagnostic approach of DN is complicated rather than standardized, commonly comprising of a combination of various qualitative and quantitative methods in order to increase the sensitivity and specificity of the results.

Additionally, effective screening for early abnormalities preceding the appearance of overt clinical manifestations, patients with asymptomatic disease course, or identification of candidates for the development of DN has not been achieved, to a satisfactory degree, by use of current methods<sup>[5]</sup>. In correlation to the lack of a highly reliable diagnostic method for DN, there is a similar degree of complexity concerning the treatment regimens currently in use. In the absence of causative treatment for the development of DN, current therapeutic approach is often comprised of a combination of glycemic control and pain management<sup>[3]</sup>. Both the need for development of a high repeatability, non-invasive, diagnostic method and the identification of a possible causative therapeutic approach for DN, allow for consideration the possible use of microRNAs (miRNAs), molecules that have been utilized as biomarkers and focus points of targeted therapy in numerous pathophysiological processes<sup>[6]</sup>.

Therefore, in the present review, we attempt to summarize the existing literature data on the role of miRNAs and their polymorphisms in the pathophysiology of DN, as well as the possibility of utilizing the aforementioned research for novel diagnostic and therapeutic applications by means of epigenetic profiling and manipulation.

## CIRCULATING MIRNAs AS BIOMARKERS AND THERAPEUTIC TARGETS

MiRNAs are small, non-coding RNA sequences with a regulatory role in post-transcriptional modification of gene products. Structurally, they comprise of 18-24 nucleotides in length that are organized in a partially complementary manner to cellular mRNA molecules. MiRNAs bind to mRNAs *via* base pairing and induce various changes to the latter, ranging from destabilization to cleavage of the molecule. Alternatively, the mRNA-ribosome complex formation is disrupted by miRNA interference, resulting into similar deregulation of the normal protein formation sequence<sup>[7]</sup>. Various cellular and tissue types have been shown to express miRNAs as part of their metabolic, developmental and homeostatic processes<sup>[8]</sup>.

It has long been established that the prospect of utilizing circulating miRNAs as diagnostic and therapeutic tools could provide substantial insight into the mechanisms underlining numerous disease processes, as well as become the substrate for therapeutic advances in multifactorial disease states<sup>[6]</sup>. Currently, novel prospects are being explored concerning the utility of miRNA measurement in the clinical setting, such as assessing response to treatment or disease activity<sup>[7]</sup>.

Researchers have isolated stable miRNA molecules from various tissue types including human plasma, indicating the ability for genetic profiling by use of blood samples, a process far more accessible and easily conducted on both in- and outpatient setting than tissue biopsy<sup>[9]</sup>. The possible value of miRNA profiling in DN is supported by the fact that mapping of aberrant miRNA expression has been performed in both nervous system and metabolic disorders, along with the observation that most of the currently discovered miRNAs are located in the brain and peripheral neural tissue<sup>[9]</sup>.

Simultaneously to new details for miRNA aberrant expression patterns in disease constantly being unveiled, current methods for epigenetic manipulation of target genes are being ameliorated. The two main approaches to miRNA centered therapy are substitution of under-expressed or otherwise modified miRNAs with functional copies designed *ex vivo*, termed miRNA mimics, or delivery of small molecules, *in vivo*, that disrupt the pathophysiological cellular pathways in which the target genes participate. Both miRNA mimics and inhibitors have been delivered at the target tissues by use of numerous conjugate molecules in the experimental setting<sup>[9]</sup>. The

main delivery platforms are subdivided into two categories, non-viral and viral, with the latter harboring many safety concerns. Some of the non-viral molecules are cationic polymers, various conjugates and liposomes, with neutral lipid particles having a more balanced organ-wide distribution than cationic complexes, resulting in less unwanted accumulation in certain tissues. Exosomes and bacteriophages, while being efficient delivery platforms, have the possibility of triggering adverse events such as immune dysregulation and are, therefore, not the vectors of choice<sup>[10]</sup>.

The integration of miRNA-centered treatments in real-world conditions is progressing rapidly, with several clinical trials currently underway<sup>[11]</sup>.

## MIRNAS IN DIABETES MELLITUS AND METABOLIC DYSREGULATION

Aberrant expression of miRNAs in tissue and plasma samples has been linked to the pathogenesis of several metabolic diseases, mainly because of their role in the development and homeostasis of metabolically active tissues.

Ample evidence has suggested the involvement of disrupted miRNA expression patterns in metabolic dysregulation. While the spectrum of metabolic disease is wide and includes many, often overlapping, syndromes and pathological states, some prime examples of aberrant tissue miRNA expression include those of miRNA-15b in non-alcoholic fatty liver disease, miRNA-744 in non-alcoholic steatohepatitis, miRNA-132-3p in obesity and miRNAs -30b, -455, -491 and -365-3p in pathological adipose tissue differentiation<sup>[12]</sup>.

MiRNAs from many tissue types involved in diabetes have been linked to many components of the disease state. Several pancreatic, cardiac, liver, kidney, skeletal, endothelial and adipose tissue miRNAs interact directly or indirectly with  $\beta$ -cell pathophysiology, inducing or suppressing pathways involved in lipid metabolism and adipocyte differentiation (miRNA-181d, -27a/b, -103, -107, -143), insulin resistance, glucose-mediated insulin secretion and exocytosis (miRNA-29a/b/c, -375, -9, -124a, -96, -34a, -30d, -223, -320, -21),  $\beta$ -cell development, apoptosis and function (miRNA-375, -9, -195, -126, -296, -34a, -146b, -21) cardiomyocyte apoptosis and cardiac arrhythmogenesis (miRNA-206, -1, -133a), endothelial dysfunction and angiogenesis (miRNA-93, -320, -125a/b) and glomerular activity (miRNA-192, -216a, -217)<sup>[13]</sup>.

Further, disease-specific research on diabetics and more specifically, profiling of circulating miRNAs as predictors for T2DM or prediabetes in healthy subjects indicated the existence of a link between higher plasma levels of miRNA-150 and miRNA-30a-5p, and lower levels of miRNA-375 and miRNA-15a at baseline and disease development after a median follow-up of 60 mo<sup>[14]</sup>.

Similarly, to miRNA-15a, the expression of several other circulating molecules has been found to be down- or upregulated in plasma samples of T2DM subjects. La Sala *et al*<sup>[15]</sup> note that miRNAs -20b, -21, -24, -126, -191, -197, -223, -320 and -486 in T2DM plasma samples are present in lower concentrations when compared to healthy controls, while miRNA-28-3p is upregulated. Among the aforementioned miRNAs, -15a, -28-3p, -126, -223 and -320 have been proposed for possible use as biomarkers of T2DM.

Additionally, recent data acquired from analysis of various expression patterns of quantitative trait loci in mouse inbred strains with varying susceptibility to metabolic dysregulation and T2DM development has indicated an upregulation of miRNA-31 in adipose tissue of obese and type 2 diabetic subjects. MiRNA-31 interacts with genes of the insulin signaling pathway and adipose tissue proliferation<sup>[12]</sup>.

## MIRNAS AS BIOMARKERS IN DIABETIC NEUROPATHY: WHY, WHICH AND WHEN?

The most important problem posed when discussing a novel treatment possibility in the clinical setting is the clarification of the circumstances under which a new interventional approach should be applied, or, in simpler terms, the evaluation of the cost-effectiveness of the method. In the setting of DN, the two pivotal arguments in favor of epigenetic modification are the lack of causative treatment for a major complication of a chronic disease with a high prevalence and the enormous impact of DN on the patients' quality of life, an indisputable fact that has been repeatedly documented<sup>[3,16]</sup>.

Researchers on the field of epigenetics have provided insight on some miRNA molecules that could be evaluated as possible biomarkers or therapeutic targets in

diabetes-induced neuropathy. A study including 60 diabetic subjects revealed a correlation between miRNA-199a-3p and reduced expression of extracellular serine protease inhibitor E2 resulting in DN manifestation and accelerated progression<sup>[17]</sup>. A similar pathway has been described, involving miRNA-190a-5p downregulation and resultant impaired solute carrier family 17 member 6 gene inhibition in painful DN<sup>[18]</sup>. Conversely, medically induced downregulation of miRNA-25 exacerbated the development of DN *via* an increase of advanced end glycation products and their receptors in peripheral neural tissue, indicating the neuroprotective attributes of miRNA-25 molecules<sup>[19]</sup>. In an experimental model on diabetic rodents, miRNA-9 and its interaction with calcium homeostasis modulator 1 were suggested to be involved in the pathophysiological pathway of painful DN<sup>[20]</sup>. MiRNA-146 located in circulating mononuclear cells modulates inflammatory response in diabetic peripheral neuropathy<sup>[21,22]</sup>. DN painful manifestation and inflammatory response are also affected by miRNA-23a *via* chemokine CXC receptor 4-related signaling<sup>[23]</sup>. Recent data indicate that a certain genotype termed “GG” in miRNA499A has been linked to cardiovascular autonomic neuropathy as well as diabetic polyneuropathy<sup>[24]</sup>. Finally, substantial upregulation of miRNA-29c and subsequent protein kinase C  $\alpha$  gene under-expression have been associated with distal neural damage in a model of diabetic rodents<sup>[25]</sup>. A brief comparison of all relevant to DN miRNAs discussed above is presented in Table 1. Circulating molecules can be used more readily as biomarkers when compared to tissue-derived molecules.

Even with the existence of an abundance of possible biomarkers and therapeutic targets, as indicated by the research described above, the timeframe in which predisposition for DN development can be detected or DN can be treated is yet to be defined. While it is expected that miRNA aberrant expression patterns precede the clinical manifestation of DN, the elucidation of the exact timeline describing when these changes occur and can be detected in the research setting in advance is of uttermost importance in the design of effective intervention algorithms for complication prevention. When miRNA manipulation is examined in the scope of neuropathy treatment, it should be studied whether miRNA expression normalization can reverse damage already done to the neural tissue or impede the progression of sensory and motor deterioration. Furthermore, the particular points in disease progression appropriate for treatment initiation or termination can be defined, based on treatment efficacy at different stages and forms of disease.

## CONCLUSION

MiRNA-based diagnosis and therapy are highly likely to be the future of treatment and prevention, especially in multifactorial disease processes. The transition from theory to practice, while an ongoing process, is rapidly progressing, with several molecules being used in clinical trials and many more currently on the preclinical-stage. While DN is the result of several complex pathophysiological processes, several miRNA molecules involved and their role have been described, setting the stage for the practical application of the aforementioned information. A next step in the development of miRNA-based diagnosis, staging and therapy is examining the miRNAs so far associated with neuropathy and diabetes in a prospective cohort study including diabetic subjects free of complications, with the goal of evaluating miRNA epigenetic changes accumulating over time in correlation with the appearance and severity of DN. Current available research data indicate that miRNAs -199a-3p, -146 and -499a can be used as circulating biomarkers, while the aforementioned along with miRNAs -190a-50, -25, -9, -23a and -29c have potential as therapeutic targets in DN.

**Table 1** Possible biomarkers and therapeutic targets in diabetic neuropathy

MiRNA molecule	Mechanism	Expression in DN	Circulating	Citation
miRNA-199a-3p	Inhibition of SerpinE2 expression - coagulation in peripheral circulation	Upregulated	Yes	[17]
miRNA-190a-5p	Inhibition of SLC17A6 gene	Downregulated	No	[18]
miRNA-25	Inhibition of oxidative stress, decreases AGEs and RAGE production	Downregulated	No	[19]
miRNA-9	Interacts with CALHM1 in neuron-glial signalling	Upregulated	No	[20]
miRNA-146	Interacts with NFκB and inflammatory cytokines production	Downregulated	Yes	[21,22]
miRNA-23a	Targets CXCR4 - regulates neuropathic pain	Downregulated	No	[23]
miRNA499A	Prevents cardiomyocyte apoptosis and mitochondrial fission (impaired in cardiac autonomic neuropathy); regulates insulin resistance	Upregulated (GG genotype with rs3746444)	Yes	[24]
miRNA-29c	Inhibits neural axonal growth <i>via</i> inhibiting PRKCI gene expression	Upregulated	No	[25]

MiRNAs: microRNAs; CALHM1: Calcium homeostasis modulator 1; AGEs: Advanced end glycation products; RAGE: Receptor of advanced end glycation product; SerpinE2: Serine protease inhibitor E2; SLC17A6: Solute carrier family 17 member 6; PRKCI: Protein kinase C iota.

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