Circulating Micro-RNAs in Diabetic Patients: What Meaning? Short Review

Carella AM*, Marinelli T, Melfitano A, Di Pumpo M, Modola G and Benvenuto A

Department of Internal Medicine, "T. Masselli-Mascia" Hospital, San Severo, Italy

*Corresponding author: Angelo Michele Carella, Department of Internal Medicine, "T. Masselli-Mascia" Hospital, San Severo, Foggia, Italy, Tel: +39 0882200478/479; E-mail: mic.carella@virgilio.it

Abstract

microRNAs (miRNAs) are short noncoding RNA sequences, approximately 20-22 nucleotides, synthesized in the cell nucleus, through a complex multi-step biosynthetic process, starting from RNA polymerase II. miRNAs regulate a wide range of biological processes as cell differentiation, proliferation and development, cell-to-cell communication, cell metabolism and apoptosis. There is evidence that miRNAs may have a role in molecular mechanisms linked to cellular pathways of certain diseases, as viral infections, cancer, diabetes and cardiovascular disease.

miRNAs expression was investigated in diabetes mellitus: a lot of altered circulating levels of different miRNAs were found to be linked to type 1 and type 2 diabetes, both at onset and in advanced disease. At least 12 circulating miRNAs were found consistently dysregulated in type 1 diabetes mellitus and, more or less, 40 circulating miRNAs in type 2 diabetic patients. miR-126 seems to be miRNA most linked to pathways and development of type 1 and type 2 diabetes and their complications.

Dysregulation of several miRNAs involves different aspects of diabetic disease: glycemic control, residual beta cell function, insulin secretion and sensitivity, micro- and macro-vascular complications, particularly endothelial dysfunction, renal disease and retinopathy. The analysis of circulating miRNAs might be a good source of diagnostic and prognostic biomarkers in diabetic patients. Large and long-term clinical studies should be conducted to evaluate the value of these nucleotides as biomarkers for predicting progression of diabetes, though the high detection costs might be the main limitations on their use in daily clinical practice.

Keywords: Circulating microRNA; Diabetes Mellitus

Introduction

microRNAs (miRNAs) are a large family of short noncoding RNA sequences [1] which modulate gene expression and regulate a wide range of biological cell processes, including cell growth and proliferation, differentiation, organogenesis, metabolism, stress response, and tissue remodeling [2]. It has been estimated that the human genome contains more than 2500 mature miRNAs [1,2] and they could regulate 74-92% of all

protein-encoding mRNAs in a tissue- and or cell-specific manner [3].

There is evidence that miRNAs may have a role in molecular mechanisms linked to cellular pathways of certain diseases, as viral infections, cancer, Alzheimer's, diabetes and cardiovascular disease [2,4-7].

miRNAs are detectable in plasma, urine, cerebrospinal and other extracellular fluids, where they are carried within small membrane vesicles, exosomes, in the form of high-density lipoprotein complexes, or complexed to carrier proteins, known as argonaute-2 proteins [8-10]. The presence of circulating endogenous miRNAs makes sure that they may be identified, measured and used as potential disease biomarkers [6]. Several techniques are available for quantifying circulating miRNAs, such as quantitative real-time Polimerase Chain Reaction (qRT-PCR) [11], Northern blotting [12], bead-based flow Cytometry [13], Microarray [14] or Deep sequencing [15].

In several studies the potential role of different miRNAs in cardiovascular diseases has been widely proved [16-20] and other studies have investigated a possible role of circulating miRNAs as biomarkers for atherosclerotic disease [21-23]; in the past few years, a potential link between miRNAs expression and diabetes mellitus was also recognized by means in vitro, in vivo and in clinical studies [24].

Detection of miRNAs expression can be implicated in physiological or pathological changes and it can even be useful for the prognosis or diagnosis of the onset and progression of diseases.

Aim of the Study

The purpose of the present review was to examine the latest evidences on potential links between circulating miRNAs and diabetic disease, as well as to evaluate whether the detection of these nucleotides in the bloodstream can play a role in daily clinical practice.

Material and Methods

A review of recent literature has been carried out via Pub Med database, using these search term: circulating microRNA and diabetes mellitus. Search was not limited by language or human subjects. All the found items, published in the last three years, from January 2015 to December 2017, were analysed. Additional articles were selected from the bibliographies of the quoted references.

Results

60 items were obtained and article types were determined using filters available on Pub Med database; 2 items were editorials and 58 journal articles, including 8 reviews (2 systematic reviews), 3 clinical studies/trials (1 randomized controlled trial), 1 comparative study, 1 meta-analysis, 3 comments; 14 items were related to animal models. Guidelines were not found, neither consensus nor observational studies nor case report; the remaining items were prevalently other journal articles or other publication types. Other data were deduced from retrospective analysis and by careful assessment of the obtained items and their references. Most of the data are provided by laboratory research rather than by clinical data; our research has provided only four clinical studies enrolling a small number of patients.

The analysis of obtained data showed that a lot of altered circulating levels of different miRNAs were found to be linked to type 1 and type 2 diabetes, both at onset and in advanced disease. Dysregulation of several miRNAs involves different aspects of diabetic disease: glycemic control, residual beta cell function, insulin secretion and sensitivity, micro- and macro-vascular complications, particularly endothelial dysfunction, renal disease and retinopathy.

At least 12 circulating miRNAs were found consistently dysregulated in type 1 diabetes mellitus: miR-21-5p, miR-24-3p, miR-100-5p, miR-126, miR-146a-5p, miR-148a-3p, miR-150-5p, miR-181a-5p, miR-210-5p, miR-342-3p, miR-375 and miR-1275; these miRNAs were involved in pathways related to immune system and adaptive immune response, cell survival, cell proliferation and insulin biosynthesis and secretion.

On the other hand, more or less 40 circulating miRNAs emerge significantly dysregulated in type 2 diabetes; particularly miR-7, miR-14q32, miR-21, miR-29a, miR-92a, miR-122, miR-126, miR-130b, miR-155 and miR-192 are potential circulating biomarkers of type 2 diabetes.

miR-126 seems to be miRNA most linked to pathways and development of type 1 and type 2 diabetes and their complications.

Discussion

Increasing evidence suggests a potential relevant role of circulating miRNAs as novel diagnostic and prognostic biomarkers for diabetes, assuming their implications in the pathogenesis of this disease, so much that miRNAs might contribute to a better understanding of the

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mechanisms involved in diabetes and its complications. In this regard, we have found several evidence for both type 1 and type 2 diabetes.

miRNAs in Type 1 Diabetic Patients

There is evidence that the levels of several miRNAs were found deregulated in plasma and urine from patients with diagnosed type 1 diabetes compared to age-matched controls [25]. miR-21, miR-126, and miR-210 resulted significantly deregulated in a cohort study carried out among clinical pediatric type 1 diabetic patients with duration of disease longer than 1 year. More in detail, urinary miR-126 levels in diabetics were significantly lower than in age- and gender-matched controls and there was a significant correlation between patients' glycated hemoglobin mean and urinary miR-126 concentration, whereas no significant difference for miR-126 plasma levels was found between diabetics and control group; moreover, in diabetic patients, a significant correlation between inflammatory C-reactive protein values and urinary miR-21 concentration was found. A significant increase of miR-21 and miR-210 was also observed both in the plasma and urine of diabetic patients [26].

Since miR-126 was found to be expressed in glomerular and peritubular endothelial cells [27], and decreased levels of miR-126 are associated with reduced response to vascular endothelial growth factor and endothelial dysfunction [28,29], deregulation of miR-126 could indicate a potential local endothelial dysfunction in the kidney of type 1 diabetic children. In the EURODIAB Prospective Complications Study, miR-126 levels emerged significantly lower in type 1 diabetic patients and were associated with proliferative retinopathy [30].

miR-21 is known to induce fibrosis in many organs including heart [31] and kidney [32] and promotes Transforming growth factor-β-mediated effects on endothelial dysfunction [33], therefore miR-21 levels in plasma and urine of young type 1 diabetic patients might serve as a potential noninvasive biomarker to identify patients with a high risk for ongoing endothelial dysfunction or future kidney and cardiovascular injuries. There is evidence that miR-210 is modulated by hypoxia and high glucose in cardiomyocytes and endothelial cells cultured in vitro [34]; it is not surprising that upregulation of this miRNA leads to mitochondrial dysfunction and oxidative stress, potential determinants of ischemic heart failure [35]. In conclusion, these findings, that need to be validated in future large-cohort prospective studies, show that a dysregulation of circulating miR-21, miR-126, and miR-210 might indicate an early onset of diabetes-related cardiovascular diseases.

Another miRNA, for which a potential link with type 1 diabetes has been hypothesized, is miR-375; in vitro studies have shown that this miRNA is involved in pancreatic islet cell development [36], inhibits insulin gene expression in response to glucose [37], and regulates voltage-gated Na^+ channels and the exocytotic machinery [38]. As miR-375 is highly expressed in the endocrine pancreas, it has been postulated that its circulating level might reflect beta cell alterations and might be altered in the blood of type 1 diabetics recently diagnosed. Serum levels of miR-375 were found lower in type 1 diabetic children versus age-matched controls, without any correlations with glycated hemoglobin, glycemia, and number of autoantibodies [39]. Circulating levels of this miRNA might be proposed as a biomarker to detect pancreatic beta cell death, maintenance of normal insulin synthesis and secretion and to predict the development of type 1 diabetes mellitus.

An association with improved glycemic control and better residual beta cell function has also been found for miR-25, suggesting that circulating levels of this miRNA could be used during early and intensive management of newly diagnosed diabetes, to improve blood glucose control and reduce microvascular complications [40]. In a cohort of 123 children with new-onset type 1 diabetes mellitus, the miRNA hsa-miR-197-3p was found as strong predictor of residual beta cell function, 1 year after diagnosis in type 1 diabetic children [41].

Lastly, it has been postulated that several miRNAs, as miR-14q32, miR-24-3p, miR-100-5p, miR-146a-5p, miR-148a-3p, miR-150-5p, miR-181a-5p, miR-342-3p, miR-375 and miR-1275, have a recognized role in the immune system and significantly modulate several miRNAs expression of the major type 1 diabetes autoantigens, suggesting that these miRNAs may be involved in the development of autoimmunity and inflammation in diabetic patients [25,42,43].

miRNAs in Type 2 Diabetic Patients

Circulating miRNAs expression was also investigated in type 2 diabetes mellitus. miR-126 was found to be one of miRNAs most linked to the development of diabetes and its complications. In susceptible individuals, decreased levels of miR-126 in peripheral blood were found already before the clinical manifestation of type 2 diabetes [44], whereby miR-126 has been proposed as a predictor of type 2 diabetes onset [45]. Moreover, because reduced levels of miR-126 were found in type 2 diabetics and in patients with coronary artery disease [46], miR-126 might also serve as a biomarker for predicting diabetic myocardial ischemia. The endothelial cell–derived miR-126 is also one of the identified downregulated miRNAs in

atherosclerotic disease and it was found most consistently associated with type 2 diabetes [47]; actually, since miR-126 has been shown to play an important role in maintaining endothelial cell homeostasis and vascular integrity [28,29], it has been suggested that this unique plasma miRNA might become a valuable tool to predict micro- and macro-vascular complications of diabetes. In truth, apart from miR-126, other miRNAs as miR-92a, miR-145, miR-155 and miR-17, are also abundantly expressed in the vessel wall, in endothelial cells, in vascular smooth muscle cells and in inflammatory cells of patients with atherosclerotic disease [21]. Other findings have shown that miR-126, but also miR-92a, miR-155, miR-14q32 and others, might play a determinant role in several processes involving regulation of lipid biosynthesis, lipoprotein metabolism, immune responses, and vascular remodeling including maladaptive processes of atherosclerosis, vascular restenosis and aneurysm formation [22,23]. At last but not least, there is evidence that miR-126 exhibits also antithrombotic properties via regulating post-transcriptional tissue factor expression. In a recent study, low miR-126 levels were found to be associated with markedly increased vascular inflammation, as evident from the levels of vascular adhesion molecule-1 and fibrinogen as well as leukocyte counts. With optimization of the anti-diabetic treatment miR-126 levels increased and thrombogenicity was reduced [48]; therefore the detection of circulating miR-126 might be also useful for follow-up, to evaluate therapeutic response and glycemic control.

There is evidence that circulating miR-122 is associated with prevalent insulin resistance, obesity, metabolic syndrome, type 2 diabetes, and an adverse lipid profile. Circulating miR-122 levels are elevated in people with prevalent metabolic syndrome or type 2 diabetes; moreover elevated serum levels of miR-122 antedate the manifestation of metabolic syndrome and type 2 diabetes, so that miR-122 might be associated with future development of metabolic syndrome and type 2 diabetes in the general population [49].

Plasma levels of miR-7 were found significantly elevated in type 2 diabetics and significantly associated with microvascular complications [50], whereas serum miR-130b levels were found significantly decreased in type 2 diabetic patients and further decreased in diabetics with nephropathy [51]; circulating miR-130b might be proposed as new biomarker for early diagnosis of diabetic nephropathy. miR-130b may possibly be involved in the pathological mechanism of diabetic nephropathy, such as lipid metabolic disorders, oxidative stress, extracellular matrix deposition and renal fibrosis.

The results of a recent Taiwanese study, carried out in type 2 diabetic patients, have shown that miR-21 level is more significantly increased in patients with overt proteinuria and microalbuminuria than in patients without diabetic nephropathy; whereas miR-29a level is up-regulated in subjects with more progressive diabetic nephropathy compared with normoalbuminuric patients. Moreover, although no significant difference was observed in circulating levels of miR-192 between diabetics with and without diabetic nephropathy, circulating levels of miR-192 were different between microalbuminuria and overt proteinuria groups, suggesting that miR-192 levels might be a potential marker for late diabetic nephropathy progression [52].

Current Limits and Future Perspectives

Analysis and detection of circulating miRNAs might be a good source of diagnostic and prognostic biomarkers in diabetic patients, as well as potential interesting therapeutic targets for the development of novel treatments, due to their regulatory role on gene networks controlling different crucial aspects of metabolism, including lipid and glucose homeostasis [53].

Circulating miRNAs might be ideal biomarkers because they are stable and resistant to degradation by ribonucleases and may be easily detected in the bloodstream by highly sensitive and specific quantitative assay [6]. Several techniques are available for quantifying circulating miRNAs, such as quantitative real-time Polymerase Chain Reaction (qRT-PCR) [11], Northern blotting [12], bead-based flow Cytometry [13], Microarray [14] or Deep sequencing [15]; of these assays, qRT-PCR seems superior because of its high sensitivity, specificity and reproducibility. Unfortunately, the current methods used for miRNAs detection usually require high costs and this aspect exerts limits on their use in daily clinical practice; in this way, research should try to overcome this limiting factor by developing less expensive detection techniques whereas spending review and cost-containment measures in health care represent a significant management problem.

Another limit on use of miRNAs in daily clinical practice might be the lack of availability of long-term and comparative clinical trials; larger longitudinal clinical studies with large sample size and with standardized system for the analysis of miRNAs should be conducted to confirm the clinical value of these nucleotides as biomarkers of diabetic disease.

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Conclusion

The potential role of circulating miRNAs as stable blood-based biomarkers for early detection, follow-up and treatment of diabetes and its complications is promising. There are currently no circulating miRNAs that are validated as biomarkers of diabetic disease for use in routine clinical practice; the lack of evidence from significant clinical studies in both type 1 and type 2 diabetic patients as well as high detection costs are the main limitations to the use of these nucleotides in daily clinical practice. In the next future, larger and long-term randomized controlled trials must be undertaken; comparative clinical studies, between circulating miRNAs and biomarkers commonly employed for management of diabetics in daily clinical practice, are also desirable. Particularly, new low-cost and wide availability assays to detect specific biomarkers with high sensitivity and specificity need to improve early diagnosis and follow-up as well as to predict disease progression, complications and therapeutic response in diabetic patients.

Conflict of Interest Statement: The authors declare no conflict of interests.

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