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ORIGINAL ARTICLE

Serum miR-122 levels correlate with diabetic retinopathy

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Abstract
Diabetic retinopathy is the most severe ocular complication of diabetes and may lead to visual disability and blindness. Proliferative diabetic retinopathy (PDR) is characterized by ischemia-induced neovascularization with associated complications. An association was established between the presence of PDR, cardiovascular disease, and mortality among patients with type 1 diabetes mellitus and type 2 diabetes mellitus in epidemiological studies. However, the mechanism underlying increased cardiovascular risk in patients with PDR is still unknown. In recent years, a group of miRNAs has been linked to the pathology of diabetes mellitus. Besides, miRNAs in biofluids such as serum have been suggested as potential minimally invasive biomarkers of diabetes and vascular complications. This was a prospective study that recruited 40 human subjects: 10 healthy subjects, 10 with diabetes but without retinopathy (NDR), 10 with diabetic non-proliferative retinopathy (NPDR), and 10 with proliferative diabetic retinopathy (PDR). To examine whether serum miRNAs show altered levels at different stages of diabetic retinopathy, seven specific miRNA candidates (miR-126-3p, miR-130a-3p, miR-21-1, let-7f-5p, miR-122, miR-30c and miR-451a) were measured by qRT-PCR in RNA isolated from sera of all subjects. miR-122 levels increased in parallel with retinopathy severity: from healthy controls to NDR and from NDR to NPDR. However, when the disease progressed to PDR a marked decrease in miR-122 level was noted. This decrease was significant both compared to NPDR samples ($p=0.016$) and to all non-PDR samples ($p=0.0002$). Additionally, a positive trend was observed comparing miR-122 levels and the number of endothelial progenitor cells in the sera of all subjects. A significant increase in miR-122 was found in patients with diabetic retinopathy that may be related to its role in preventing angiogenesis and proliferation. The dramatic decline in patients with PDR may represent an inhibition or exhaustion of the anti-angiogenic anti-proliferative defense system. Further studies are needed to understand whether miRNA-122 has a role in the pathogenesis of diabetic retinopathy.

Keywords miRNA 122 · Diabetes mellitus · Diabetic reinopathy

Introduction

Type 1 diabetes mellitus (T1DM) occurs predominantly in young people and is generally thought to be precipitated by an immune-associated destruction of insulin-producing pancreatic beta cells, leading to insulin deficiency and an absolute need for exogenous insulin replacement [1]. Type 2 diabetes mellitus (T2DM) is a progressive metabolic disease that is characterized by insulin resistance and failure of pancreatic beta cells [2]. The prevalence of T2DM has been increasing dramatically over the past few decades [3], with projections of an even greater growth over coming decades [4]. Proliferative diabetic retinopathy (PDR) is a devastating complication of DM, developing within 15 years in 50% of patients with T1DM and in 10% of patients with T2DM [5–7]. The Wisconsin Epidemiologic Study of Diabetic Retinopathy has shown a 72% survival rate in older

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onset patients without retinopathy and a 52% in patients with proliferative diabetic retinopathy [PDR] [8]. Patients older than 50 years had a higher rate of ischemic stroke with a strong correlation to the severity of the retinopathy [8, 9]. An association was established between the presence of PDR, cardiovascular disease and mortality among patients with T1DM and T2DM in epidemiological studies [10]. The mechanism underlying increased cardiovascular risk in patients with PDR is still unknown. We previously described a significant increase in levels of adhesion molecules (VCAM-1) and selectins (E-selectin) in parallel with increased severity of diabetic retinopathy, with a significant difference in inflammatory markers between stages of retinopathy [11]. However, we also found that levels of soluble vascular endothelial growth factor (sVEGF), a potent angiogenic factor, was not statistically different among patients with DM at different retinopathy stages (healthy subjects, NDR, and NPDR), but as the disease progressed to PDR, a significant decrease in VEGF was documented [12].

MicroRNAs (miRNAs) are small (~22 nt) single-stranded endogenous RNAs which post-transcriptionally regulate or suppress translation and stability of mRNA through imperfect base pairing in the 3′ untranslated region of its mRNA targets, contributing to alterations in gene expression observed in many pathologies [13]. There are over 2500 human miRNAs according to the latest release of miRBase (available online: www.mirbase.org).

In recent years, a group of miRNAs was linked to the pathology of both T1D and T2D. Additionally, profiling miRNAs in biofluids (such as serum) revealed their potential to serve as minimally invasive biomarkers of various diseases including DM [14–17]. These miRNAs are encapsulated in extracellular vesicles, in exosomes, or bind to ribonucleoproteins or lipoprotein complexes. Impaired glucose tolerance was found to be associated with increased levels of miR-122, miR-99, and decreased levels of let-7d, miR-18a, miR-18b, miR-23a, miR-27a, miR-28, and miR-30d. A unique microRNA profile may thus be helpful in predicting DM development [18].

Our hypothesis was that different stages of diabetic retinopathy are associated with different levels of miRNAs that may accompany the progressive vascular complications observed in patients with DM [19]. Our aim was to find a specific miRNA that could be used as a biomarker of diabetic retinopathy progression.

Methods

Study subjects

This prospective study was approved by the Institutional Review Board of the Baruch Padeh Poria Medical Center. All subjects were recruited from the ophthalmology outpatient clinic and underwent a detailed assessment of cardiovascular risk after signing an informed consent document.

We have recruited 40 subjects divided into four different groups (half were women in each group): 10 healthy controls, 10 T2DM patients with no retinopathy (NDR), 10 T2DM patients with non-proliferative diabetic retinopathy (NPDR), and 10 T2DM patients with proliferative diabetic retinopathy (PDR) who were not treated with anti VEGF injections. None of the subjects had renal impairment or cardiovascular disease, coronary artery disease, or heart failure from any etiology. The ophthalmologic examination defined NDR when there were no signs of retinopathy, and NPDR was diagnosed by observing macular edema and/or microaneurisms and microhemorrhages, and/or intra-retinal neovascular vessels (severe NPDR). PDR was diagnosed as neovascularization of retinal vessels that protrude into the vitreous.

All patients had mild-to-moderate hypercholesterolemia and were treated with HMG-CoA reductase inhibitors (statins), and in oder to prevent diabetic nephropathy with albuminuria, they were treated with angiotensin-converting enzyme inhibitors (ACE inhibitors). Subjects were excluded from the study if they had known or symptomatic cardiovascular disease or had any chronic condition such as cancer, acute of chronic infection, autoimmune or inflammatory conditions.

Patients' clinical characteristics are presented in Table 1.

Samples processing

The investigator who performed the laboratory experiments was blinded to the patients' clinical data. Venous blood samples were drawn from an antecubital vein into ethylenediaminetetraaceticacid-containing tubes. All blood samples were centrifuged at 1200×*g* for 10 min at 25 °C, and serum was aliquoted and stored at − 80 °C. Total RNA was isolated using the QIAGEN miRNeasy Serum/Plasma kit (Cat. 217184), with an elution volume of 14 µl. After elution, RNA samples were stored at − 80 °C.

qRT-PCR

To examine whether serum miRNAs show altered levels at different stages of diabetic retinopathy, seven specific miRNA candidates (miR-126-3p, miR-130a-3p, miR-21-1, let-7f-5p, miR-122, miR-30c, and miR-451a) were measured by qRT-PCR. Reverse transcription, primer design, and quantitative PCR for endogenous miRNAs were performed using SYBR Green chemistry and DNA primers as previously described (13,14); primers were designed using the miRPrimer software (14) and are listed in Table 2. qPCR was performed in quadruplicates on an Applied Biosystems

Table 1 Clinical characteristics

	Controls		NDR		NPDR		PDR
No.	10		10		10		10
Age (years)	43 ± 11.6		62.8 ± 10.8		62.9 ± 10.8		59.2 ± 10.3
p value		0.001		NS		NS	
Men	5		5		5		5
BMI	25 ± 4		30 ± 6		29 ± 4		30 ± 5
p value		0.05		NS		NS	
DM duration (years)			9 ± 6		17 ± 9		19 ± 6
p value				0.001		NS	
HgAlC%			7.1 ± 2.7		8.5 ± 1.5		8.5 ± 1.6
p value				0.02		NS	

PDR proliferative diabetic retinopathy, *NPDR* non-proliferative diabetic retinopathy, *NDR* no retinopathy, *DM* diabetes mellitus

Table 2 QPCR primers used

Gene	Forward primer	Reverse primer
miR-30d	AGTGTAAACATCCCCGACT	TCCAGTTTTTTTTTTTTTTTCTTCCA
miR-21-1	GCAGTAGCTTATCAGACTGATG	GGTCCAGTTTTTTTTTTTTTTTCAAC
miR-122	AGTGGAGTGTGACAATGGT	CCAGTTTTTTTTTTTTTTTCAAACACC
miR-451a	CAGAAACCGTTACCATTACTGA	GGTCCAGTTTTTTTTTTTTTTTTAACTC
miR-126-3p	GCAGTCGTACCGTGAGT	TCCAGTTTTTTTTTTTTTTTCGCA
let-7f-5p	CGCAGTGAGGTAGTAGATTG	GGTCCAGTTTTTTTTTTTTTTTTAACTATAC
miR-130a-3p	CAGCAGTGCAATGTTAAAAGG	GGTCCAGTTTTTTTTTTTTTTTATGC

ABI-7900HT Sequence Detection System equipped with a 384-well block, using iTaq SYBR Green (BioRad). Results were analyzed with SDS 2.3 (Applied Biosystems) and Microsoft Excel. Normalization was performed using the average of all measured miRNA levels per sample.

Statistical analysis

Data are expressed as mean ± SD. A one-way ANOVA with Tukey's HSD test or Student's *t* test was performed to compare miRNA levels between groups of patients.

Results

Clinical characteristics

No difference in age was found between NDR (62.8 ± 10.8 years), NPDR (61.9 ± 9.4 years), and PDR (59.2 ± 10.3 years) (p = NS); however, the control group was younger (44.3 ± 11.6 years) (p = 0.001) (Table 1).

Half of the patients were women in each group. BMI was not different between the groups of patients—NDR (30 ± 6), NPDR (29 ± 4), PDR (30 ± 5) (p = NS), but the healthy volunteers had a lower BMI (25 ± 4)(p = 0.05). The duration of DM was much longer in patients with PDR (19 ± 6 years) and with NPDR (17 ± 9 years) (p = NS). However, in patients with NDR, it was shorter (9 ± 6 years) (p = 0.001). Hemoglobin A1C % was 8.5 ± 1.6% in PDR, 8.5 ± 1.5% in NPDR (p = NS), and 7.1 ± 2.7% in NDR (p = 0.02) (Table 1).

Serum miR-122 levels correlate positively with T2DM progression, but are significantly lower in subjects with proliferative diabetic retinopathy (PDR)

To identify specific miRNAs that could be used as biomarkers of diabetic retinopathy progression, we quantified the levels of seven candidate miRNAs in the sera of four groups of subjects representing T2DM without retinopathy, T2DM with NPDR, T2DM with PDR, and healthy controls. The candidate miRNAs were selected based on our and others' previous studies: let-7f-5p, miR-21, miR-30d, miR-122, miR-126-3p, miR-130a-3p, and miR-451a. Of these, miR-122 levels showed a trend of increase from healthy controls to T2DM and from T2DM to NPDR, but a marked decrease from NPDR to PDR samples (Fig. 1). This decrease was significant both compared to NPDR samples (p = 0.016) and to all non-PDR samples (p = 0.0002). let-7f-5p levels showed the opposite trend, of decrease in NPDR and increase in PDR, but the differences between groups were not statistically significant. Other miRNAs, such as miR-30d (shown),

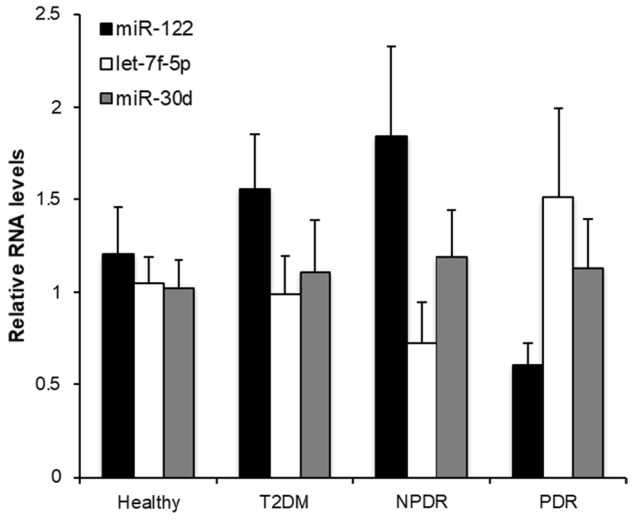

Fig. 1 Relative MiRNA levels in different groups of T2DM patients designated by DR progress. Bars: SE

exhibited no such pattern. The microRNA levels measured in the cohort showed a normal distribution.

Serum miR-122 levels correlate positively with colony forming units

We previously reported that the numbers of colony forming units—endothelial progenitor cells (CFU-EPCs) show a progressive decrease in the serum of diabetic retinopathy patients, so that in PDR CFU-EPCs were almost undetectable [20]. To check for any associations between serum miRNA levels and the prevalence of CFU-EPCs, we compared individual CFU-EPCs numbers for all subjects (regardless of disease status) with their respective serum miRNA measurements. MiR-122 levels showed a tentative association with CFU-EPCs numbers. Although this association was not statistically significant due to high variation, it could be observed both at the level of individual values (Fig. 2a) and when the subjects were divided into 2 bins based on CFU-EPCs numbers (Fig. 2b) (p value = 0.13, t test).

Discussion

Our study demonstrated that miR-122 levels were significantly increased in association with the severity of diabetic retinopathy. However, when patients progressed to develop PDR, miR-122 levels were significantly decreased. In the population-based Bruneck Study, circulating miR-122 levels were associated with insulin resistance, obesity, metabolic syndrome, T2DM, and an adverse lipid profile [21–25]. In the Anglo-Scandinavian Cardiac Outcomes Trial (ACOT), 12 months' treatment with atorvastatin reduced circulating miR-122 [26–28]. Both studies have demonstrated that circulating miR-122 was strongly associated with the risk of developing metabolic syndrome and T2DM [29]. MiR-122-5p/133b ratio was found to be a prognostic biomarker for a higher risk of developing major adverse events in patients with acute myocardial infarction undergoing primary percutaneous coronary intervention [30]. Plasma levels of miR-122 and miR-370 were significantly elevated in patients with hyperlipidemia, and levels of miR-122 and miR-370 were positively correlated with total cholesterol, triglyceride, and low-density cholesterol levels, both in patients with hyperlipidemia and in controls. Increased levels of miR-122 and miR-370 were associated with coronary artery disease and were positively correlated with the severity of the coronary artery disease [31]. On the other hand, we recently reported an increase in serum miR-122 levels in bariatric surgery patients, which correlated with improved endothelial function [32]. In vitro data further provided a direct link

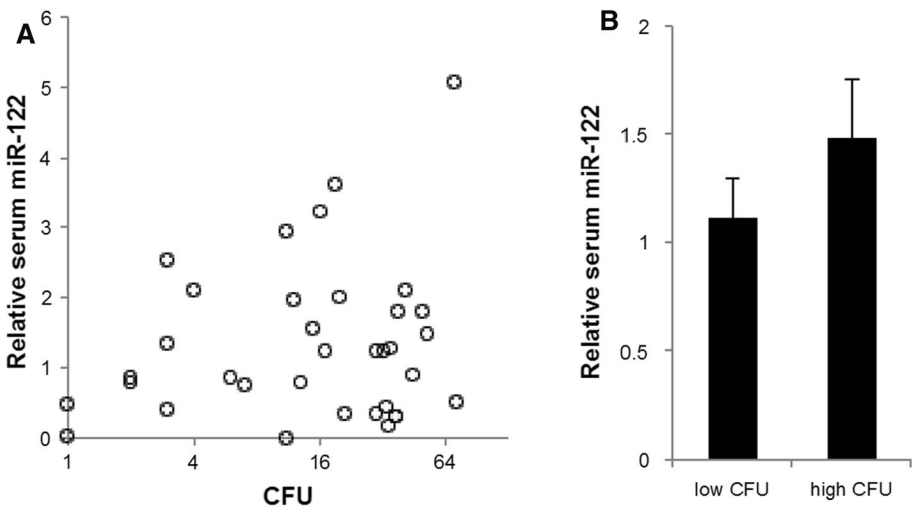

Fig. 2 Individual (**a**) and aggregate (**b**) associations between CFU-EPCs and serum miR-122 levels in all subjects. **a** CFU numbers are displayed on a log scale; samples with 0 CFU were omitted from the plot. **b** Bars: SE

between induction of miR-122-controlled genes and impairment of mitochondrial metabolism. It appears that miR-122 is involved in the regulation of mitochondrial metabolism and that its loss may be detrimental to sustaining critical liver function and contribute to morbidity and mortality of liver cancer patients [33]. The effects of miR-122 on myocardial hypoxia injury and its possible underlying mechanisms were also explored. Thus, knockdown of miR-122 enhanced PTEN/PI3K/AKT activation and cell autophagy and protected H9c2 cells from hypoxia-induced apoptosis and enhanced cell viability [34].

Our study demonstrated an increase in miR-122 level associated with increased severity of diabetic vascular micro-vessel complications (diabetic retinopathy). MiR-122 could serve as a biomarker of severity of T2DM and its complications, or it could represent a mechanistic pathway of induced hypoxia-dependent vascular proliferation and apoptosis. However, in PDR, the documented downregulation of miR-122 could represent an inhibition of apoptosis with activation of cell autophagy—even though it seems to be too late at this stage.

Of note, let-7f-5p levels were elevated in patients with PDR. Let-7f-5p is a pro-angiogenic miRNA, whose expression is inhibited in human umbilical vein endothelial cells after exposure to cigarette smoke extracts. In a mouse hindlimb ischemia, intramuscular injection of let-7f-5p restored neovascularization with improved capillary density and capillary blood flow [35]. ALK5 (TGF-βR1), an important modulator of angiogenesis, is a target of let-7f. ALK5 level was increased in endothelial cells that were exposed to cigarette smoke extracts, with downstream activation of the anti-angiogenic factors SMAD2/3 and PAI-1. Treatment with let-7f mimic reduced the expression of ALK5, SMAD2/3, and PAI-1 in vitro and in vivo experiments [35]. This could represent a "salvage" mechanistic pathway trying to preserve EPC proliferation through upregulation of let-7f, which could lead to the chaotic vascular proliferation in the retina of diabetic patients.

Study strengths and limitations

This was a prospective study that recruited human subjects at different stages of diabetic retinopathy. Seven different miRNAs were examined. To our knowledge, no previous study had examined miRNAs levels in the serum of T2DM patients subdivided by retinopathy stages. The main limitation of the study is the relatively small sample size and the a priori defined set of miRNAs measured. A hypothesis-free study involving a larger sample size could identify more significant differences between the levels of specific miRNA that could be involved in the process of diabetic vasculopathy.

Summary

We have observed an increase in miR-122 levels with each stage of diabetic retinopathy, with a significant decline in the stage of PDR. We also noted a trend toward higher let-7f-5p levels in patients with PDR. Both phenomena could represent mechanisms that compensate for the diminishing endothelial stem cell population observed in DM, but eventually both may contribute to chaotic proliferation of retinal blood vessels and blindness. Periodic measurements of miR-122 level in patients with T2DM could aid the staging and establish the progression of diabetic retinopathy. Elucidating miRNA-regulated mechanisms could enable their therapeutic targeting, to slow the progression of microvascular complications in patients with DM.

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests

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