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Circulating micro RNA-223 and angiopoietin-like protein 8 as biomarkers of gestational diabetes mellitus

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BSTRACT

Background: Gestational diabetes mellitus (GDM) is a serious health problem associated with both foetal and maternal complications. New biomarkers that can predict or help in the early diagnosis of GDM are needed to minimize the hazards of hyperglycaemia in pregnant women and their offspring. We hypothesised a link between levels of microRNA-223 (miRNA-223) and Angiopoietin-Like Protein 8 (ANGPTL8) and GDM.

Materials and Methods: The study included 109 patients with confirmed early diagnosed GDM and 103 healthy control pregnant women in their second or third trimester. miRNA-223 and ANGPTL8 blood levels were assessed by real-time RT-PCR and sandwich ELISA, respectively, laboratory markers by standard methods.

Results: There was a significant increase in mean [SD] miRNA-223 and ANGPTL8 in GDM (0.31 [0.06] relative units) and (692 [199] pg/ml), respectively, in the GDM women compared to healthy pregnant women (0.17[0.05] relative units) and (261 [127] pg/ml), respectively, $P < 0.001$. miRNA-223 and ANGPTL8 correlated significantly with each other ($r = 0.38$, $P < 0.001$) and with fasting, 1-h and 2-h postprandial blood glucose levels (all $P \leq 0.002$) HbA1 c ($P < 0.025$), total cholesterol ($P < 0.01$), LDL-C and triglycerides (both $P \leq 0.005$). The ROC area under curve (AUC) (95%CI) was 0.94 (0.91–0.97) for ANGPTL8, 0.92 (0.88–0.96) for miRNA-223 and 0.97 (0.95 – 0.99) for their combination.

Conclusions: These findings support the hypothesis of involvement of both miRNA-223 and ANGPTL8 in the pathogenesis of GDM. The difference between levels in GDM patients and in control pregnant women indicates potential use for early diagnosis or prediction of GDM.

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Introduction

Gestational diabetes mellitus (GDM) is a common health hazard affecting around 7% of all pregnant women [1]. It leads to higher risks of poor outcome offspring in addition to its maternal consequences, and the severity of the complications is proportional to the severity of hyperglycaemia and to the insufficient control of the diabetes. GDM is defined as glucose intolerance diagnosed during the second or the third trimester of gestation and no clearly overt diabetes prior to pregnancy [2], the main pathophysiology of this condition is attributed to the insufficient adaptation of β-cells to peripheral insulin resistance [3]. The screening and the diagnosis of GDM are accomplished by a one-step oral glucose tolerance test (OGTT), in which a 75 g of glucose is orally administered at the 24th–28th weeks of pregnancy [2].

Micro RNAs (miRNAs) are non-coding small RNAs that are transcribed by RNA polymerase II. Most miRNAs are named as miR – suffixed by a specified number. They play an essential role in the regulation of multiple biological functions through translational repression or destabilization of mRNA. In addition, miRNAs have been suggested to target one-third of human genes where overexpression of targeted mRNA can occur, and in some cases, DNA can be directly targeted by specific types of miRNAs [4]. Different miRNAs participate in the pathogenesis of diabetes, and there is a link between different miRNAs produced from different insulin sensitive tissues such as white adipose tissue, skeletal muscles, and β-cells of pancreas and diabetes [5,6].

Moreover, several miRNAs are involved in the embryonic development of pancreas, and maternal diabetes is associated with changes in miRNAs in both maternal and foetal tissues [7]. Dysregulation of the expression of some miRNAs like miR-16-5p, miR-17-5p, miR-19a-3p, miR-19b-3p, miR-20a-5p has also been connected to the incidence of GDM and they are reported as potential markers for diagnosis of this disease [8]. These molecules have the potential to be early diagnostic biomarkers due to their high stability in body fluids and their ease of accessibility from the circulation [9]. A recent report described an increased

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expression of miR-223 in the islets of Langerhans of diabetic mice and in humans [10].

Another biochemical marker implicated in the regulation of glucose homoeostasis is angiopoietin-like protein 8 (ANGPTL8), a member of ANGPTL family structurally related to angiopoietins. This protein is expressed in adipose tissue and liver and has a role in the regulation of triglycerides metabolism [11,12]. Moreover, it increases the proliferation and the cell mass of pancreatic β-cells with improving the glucose tolerance in insulin resistance as revealed by a previous experimental study in mice [13]. A similar finding is an increase in its peripheral blood level in type 1 diabetic patients [14]. These findings may indicate that ANGPTL8 is an adipokine hepatokine regulator of blood glucose level [15]. There are recent reports that indicated ANGPTL8 as a significant biomarker for early diagnosis and prediction of GDM [16,17], but few reports of a link with miRNAs in diabetes mellitus during pregnancy.

Therefore, we hypothesised that blood levels of miRNA-223 and ANGPTL8 are altered in GDM and are related to clinical features and laboratory markers.

Materials and methods

We tested our hypothesis in a cross-sectional case-control study of 109 pregnant women with a recently diagnosed GDM at the 24th-28th weeks of gestation. OGTT was used to diagnose GDM with three blood samples to determine the blood glucose levels before and after ingestion of 75 g of oral glucose load (fasting, 1- and 2-h postprandial blood glucose) and their glucose levels were ≥5.1 mmol/L, ≥10 mmol/L and/or ≥8.5 mmol/L, respectively [2]. In addition, 103 healthy pregnant control women who showed normal OGTT with matched age, BMI and gestational age were enrolled as controls. All women were recruited from the Gynaecology and obstetrics outpatient's clinic of Mansoura University hospitals from January 2019 till December 2019. Each participant was subjected to full history taking and complete medical examination. Height and weight were measured to calculate body mass index (BMI).

Exclusion criteria were age <18 years, patients with GDM who already started oral hypoglycaemic drugs, prehypertensive (SBP 120–139 mmHg and/or DBP 80–89 mmHg) and hypertensive patients, overweight and obese patients (BMI ≥25), history of associated chronic comorbidities such as chronic liver or renal disorders, malignancies or autoimmune disorders and/or patients with history of pre-existing type 1 or 2 DM. The study protocol was approved by Mansoura ethical committee and a signed informed consent was obtained from each participant and the study was performed according to Helsinki standards.

Ten millilitres of overnight fasting venous blood samples was obtained from each subject for full laboratory investigations. Routine blood markers were measured by standard techniques: fasting blood glucose (FBG) by the colorimetric glucose oxidase method (Randox laboratories, Antrim, UK), total cholesterol, low-density lipoprotein (LDL-C), high-density lipoprotein (HDL-C), triglycerides (TGs) by standard techniques (Crystal Chem, Zaandam. the Netherlands), glycated haemoglobin (HbA1c) by micro-column (Bio-Rad, Hercules, CA, USA) and ANGPTL8 by ELISA (ELabscience, Houston, TX, USA). Another two blood samples were obtained from all participants at 1 and 2 h after ingesting of the glucose load (75 g) to determine the 1 h (1 h-PPBG) and 2 h postprandial blood glucose (2 h-PPBG) levels, respectively.

ANGPTL8 was measured using Sandwich-ELISA kits. The plates are coated with specific antibodies to human ANGPTL8. Method was performed according to manufacturer's instructions. Optical density (OD) was assessed by spectrophotometer at a wavelength of 450 nanometer. The OD values were proportional to the levels of human ANGPTL8. The ANGPTL8 concentrations in the samples were calculated by comparing the OD values of the samples to the standard curve.

RNA was isolated from 200 µL of serum using miRVana PARIS kits (Life Technologies, Grand Island, NY, USA), according to the included manufacturer's instructions. Synthetic spiked–in *Caenorhabditis elegans* miR-39 was used as internal control, it was added to the samples of serum before the procedures of RNA extraction. miRNA-223 expression was examined in the RNA extracts of all samples using TaqMan quantitative RT-PCR. All reagents, primers, and probes were purchased from Life Technologies (Thermo scientific, Waltham, MA, USA) (TaqMan Gene Expression Master Mix 4369016, TaqMan MicroRNA Reverse Transcription Kit 4366596, miR-223-3p primer Assay ID–002295). Real-time PCR was done using an ABI 7500 Sequence Detection System (Life Technologies), and $2^{-\Delta\Delta Ct}$ method was used to calculate fold changes in gene expression [18].

Data were analysed using SPSS 26 (IBM Corp., Armonk, NY, USA). Comparison between groups was done using unpaired T-test. Data were summarized using mean and standard deviation. Correlations between quantitative variables were done using Pearson correlation coefficient. Linear regression analysis was done to detect the predictor parameters of miRNA-223 and ANGPTL8. Logistic regression was done to detect independent predictors of GDM. Receiver operative curve (ROC) was plotted for miRNA-223 and ANGPTL8 to show the connection between clinical sensitivity and specificity for every possible cut-off value. P-values less than 0.05 were considered as statistically significant.

Table 1. Comparison between the demographic data and biochemical parameters of the gestational diabetic patients and normal pregnant controls.

Variable	GDM (n = 109)	Control (n = 103)	*P* value
ANGLP8 (pg/mL)	692 [199]	261 [127]	<0.001
miRNA-223 (relative units)	0.31 [0.06]	0.17 [0.05]	<0.001
Age (years)	29.9 [6.28]	29.7 [5.85]	0.76
BMI (kg/m^2)	23.5 [1.03]	23.4 [1.02]	0.52
FBG (mmol/L)	7.94 [1.09]	4.58 [0.58]	<0.001
1 h-PPBG (mmol/L)	11.8 [1.59]	8.61 [0.83]	<0.001
2 h-PPBG (mmol/L)	10.1 [1.14]	6.99 [0.74]	<0.001
HbA1 c (%)	8.29 [0.92]	4.29 [1.02]	<0.001
Total cholesterol (mmol/L)	5.46 [1.21]	4.86 [1.13]	<0.001
LDL-C (mmol/L)	3.32 [0.41]	2.46 [0.28]	<0.001
HDL-C (mmol/L)	1.13 [0.18]	1.17 [0.14]	0.04
Triglycerides (mmol/L)	2.56 [0.55]	1.76 [0.37]	<0.001

Data mean [SD]. BMI = body mass index, FBG = fasting blood glucose, PPBG = post-prandial blood glucose, LDL-c = low density lipoprotein cholesterol, HDL-C – high density lipoprotein cholesterol.

Table 2. Pearson correlation between ANGPTL8 and miRNA-223 and the other biochemical parameters in GDM patients.

		miRNA-223 (n = 109)	ANGPTL8 (n = 109)
FBG	*r*	0.32	0.62
	p	0.001	<0.001
1 h-PPBG	*r*	0.31	0.56
	p	0.001	<0.001
2 h-PPBG	*p*	0.30	0.52
	p	0.002	<0.001
HbA1 c	*r*	0.24	0.22
	p	0.011	0.022
Total cholesterol	*r*	0.6	0.25
	p	<0.001	0.009
LDL-C	*r*	0.27	0.7
	p	0.005	<0.001
HDL-C	*r*	−0.08	−0.02
	p	0.415	0.082
Triglycerides	*r*	0.27	0.63
	p	0.005	<0.001

Abbreviations and units as Table 1.

Results

Both ANGLP8 and miR-223 were higher in GDM than in the controls (Table1, Figure 1(a,b)). Table 1 also shows clinical, demographic and routine biochemical variables. There was a significant positive correlation between ANGPTL8 and miRNA-223 (r = 0.38, p < 0.001) and with many laboratory indices of GDM patients, except for HDL-C (Table 2).

Multivariate linear regression analysis was performed to detect independent predictors of miR-223 serum levels, these being FBG (β = 0.02, *P* < 0.001), total cholesterol (β = 0.014, *P* < 0.001) and 2 h-PPBG (β = 0.015, *P* = 0.004). The regression equation for prediction of miR-233 level was: miR-233 = −0.085 + 0.02*FBG (mmol/L) + 0.014*Total cholesterol (mmol/L) + 0.015*2 h-PPBG (mmol/L). Similarly, independent predictors of serum ANGPTL8 were FBG (β = 55.8, *P* < 0.001), LDL (β = 168, *P* < 0.001) and 2 h-PPBG (β = 26.2, *P* = 0.033). The regression equation for prediction of ANGPTL8 level was: ANGPTL8 (pg/mL) = −580 + 55.8*FBG (mmol/L) + 168*LDL (mmol/L) + 26.2*2 h-PPBG (mmol/L). Multivariate logistic regression was performed to assess the probability of the combination of ANGPTL8 and miRNA-223 to diagnose GDM. Both of ANGPTL8 and miRNA-223 were found to act as independent predictors of GDM with OR (95%CI) of ANGPTL8 = 1.010 (1.006–1.013).

Area under curve (AUC) (95%CI) was 0.94 (0.91–0.97) for ANGPTL8, 0.92 (0.88–0.96) for miRNA-223 and 0.97 (0.95–0.99) for their combination (Figure 2). The optimal cut-off value for detection of GDM using ANGPTL8 was 385 pg/mL with 93.6% sensitivity and 89.3% specificity. The optimal cut-off value for detection of GDM using miRNA-223 was 0.245 fold change in gene expression with 93.6% sensitivity and 90.3% specificity.

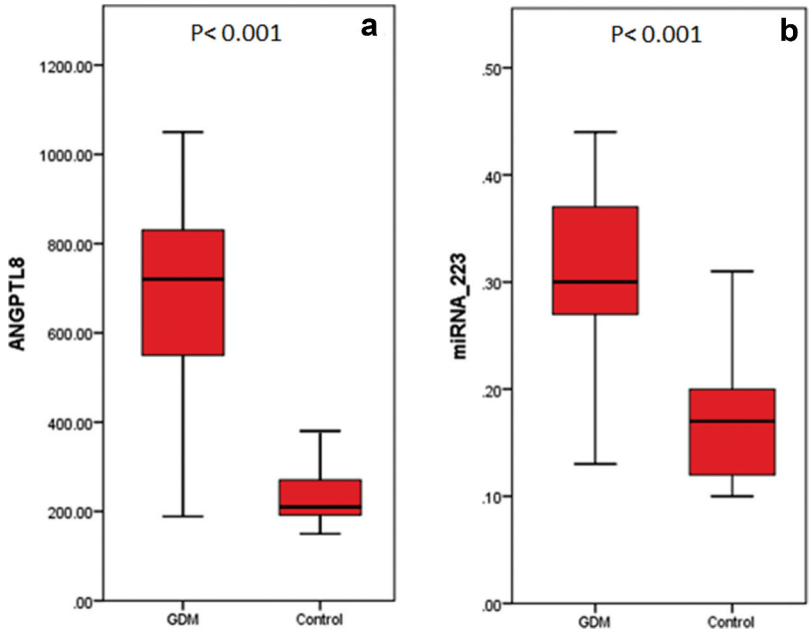

Figure 1. (a, b): Comparison between the two studied groups (GDM and Control) showing the median and interquartile range of ANGPTL8 (a), miRNA-223 (b).

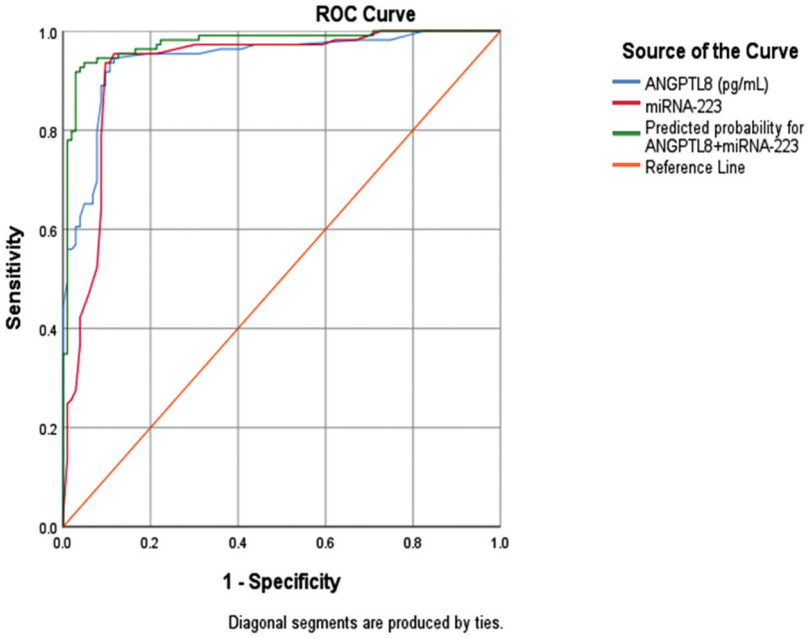

Figure 2. Receiver operating characteristic (ROC) curve for prediction of GDM using ANGPTL8 and miRNA-223 each alone and their combination. Area under curve (AUC) (95%CI) was 0.94 (0.91–0.97) for ANGPTL8, 0.92 (0.88–0.96) for miRNA-223 and 0.97 (0.95–0.99) for their combination.

The specificity of the combination of miR-223 and ANGPLT8 was increased to be 95.1%.

Discussion

Several studies have demonstrated a link between miR-223 and glucose uptake by tissues in addition to maintaining β- cells function [10,19], and is reported to be a potential marker of type 2 diabetes [20]. However, there are few studies of miR-223 in GDM although some have shown a link between ANGPTL8 and GDM, and almost all of them have concluded that ANGPTL8 is an emerging potential biomarker for diagnosis and/or prediction of GDM [16,17,21–23]. ANGPTL8 expression was reported to be regulated by different types of miRNAs including miRNA-103, miRNA-133a, miRNA-143-3p in hepatocytes, and by miRNA-221-3p in human adipose tissue [8,24,25]. Our data add to the literature in showing a link between ANGPTL8 and miRNA-223 in GDM, and with laboratory markers.

The epigenetic regulatory mechanisms of some miRNAs such as miR-29a, miR-132, miR-222, miR-508-3p, miR-33a, miR-27a, and miR-137 are common pathophysiological features of type 2 diabetes mellitus and GDM [26,27], indicating that these miRNAs could be potential indicators or even predictors of developing insulin resistance and incidence of diabetes. In the present study, there was a significant increase in circulating miRNA-223 in GDM patients as compared to control pregnant women, results consistent with previous studies that reported significant differences in miRNA expression in the endothelial cells of umbilical vein and placenta at the time of delivery of GDM pregnant women compared to controls [20,21]. There are few reports that had determined second-trimester circulating miRNA levels in women with GDM compared to controls [26,28], especially miRNA-223 which was reported to have elevated expression in patients with GDM [29].

Regarding ANGPTL8, there was a significant increase in its levels in pregnant patients as compared to healthy pregnant women. Our data support and extend other studies where the higher levels of ANGPTL8 in early weeks of gestation were associated with increased incidence of subsequent GDM in the third trimester; therefore, it can be used as an early predictor of GDM [16,17]. The exact pathophysiological mechanisms connecting between ANGPTL8 and GDM are not fully elucidated. Circulating levels of ANGPTL8 in healthy pregnant women are significantly higher than in non-pregnant women and levels fall dramatically after delivery [30]. Furthermore, levels of ANGPTL8 were higher in umbilical cord blood than maternal circulation [31], indicating that ANGPTL8 might play a role in maintaining pregnancy and in foetal development and growth, and it may provide us with a new insight about the physiology of pregnancy and the pathogenesis of GDM [30].

We also report that ANGPTL8 is significantly correlated with dyslipidemia and with hyperglycaemia which can be explained by inhibiting the activity of lipoprotein lipase enzyme by ANGPTL8. *ANGPTL8* gene contains a carbohydrate responsive element which is activated by high glucose and lipid levels [31–33].

Normally, there are mild forms of hyperlipidaemia that are common during pregnancy [34]. In the present study, there was a significant increase in total cholesterol, LDL, and triglycerides with a significant reduction in HDL levels in pregnant patients compared to healthy pregnant women.

Hyperglycaemia, insulin resistance and hypertriglyceridaemia are important risk factors of atherosclerosis in type 2 DM [35]. In adults, a previous study reported a significant association between lipids in patients with type 2 DM and atherosclerosis with an evidence of a strong connection between subclinical atherosclerosis and ANGPTL8 [35,36]. The impact of dysregulation of maternal lipid metabolism can go beyond maternal morbidity to affect foetal programming and increasing susceptibility of offspring to atherosclerosis [37]. Accordingly, a recent study has suggested that ANGPTL8 inhibition might offer a new line of treatment of dyslipidemia and its associated cardiovascular risks [38]. *ANGPTL8* is targeted by other miRNAs including miRNA-143-3p and miRNA-223-p [24,25]. The regulatory actions of miRNAs on protein expression may be explained by several mechanisms including regulation of the stability of mRNA in nucleoli, alternative splicing, and direct regulation of gene expression at the transcriptional level [39].

ROC curve revealed a higher discrimination and higher sensitivity and specificity for the use of miRNA-223 and ANGPTL8 as compared to previous studies. A previous study used three different microRNAs (miRNA-29a, miRNA-132, and miRNA-222) that were downregulated in the serum of women with GDM versus control subjects. However, the ROC curves did not achieve high sensitivity and specificity (combined microRNAs: sensitivity = 66.7% and specificity = 63.3%) to clearly distinguish between GDM and controls [26]. This may be explained by the hypothesis that miRNA-223 is more associated with regulation of glucose metabolism as it increases gene expression of insulin-dependent glucose transporter GLUT4 protein which is a key player in glucose homoeostasis [20], in addition to the role miR-223 in regulation of β- cell functions [10].

Further prospective study is still needed to assess the blood levels of miRNA-223 and ANGPTL8 during the first trimester of pregnancy to determine whether their levels are increased prior to the 24th week of gestation and to be correlated with the future development of GDM to investigate the ability of these two biomarkers to predict GDM.

This work represents an advance in biomedical science because it shows an association between the increased circulating levels of both miRNA-223 and ANGPTL8 and GDM, so they could be potential combined diagnostic biomarkers in future for early diagnosis or even prediction of this disease with high specificity and sensitivity.

Summary table

What is known about this subject:
- Gestational diabetes mellitus (GDM) is a serious health problem associated with both fetal and maternal complications.
- The oral glucose tolerance cannot early diagnose or predict the susceptibility of the patient to GDM.

What this paper adds
- miRNA-223 and angiopoietin-like protein 8 (ANGPTL8) are increased in patients with GDM and co-correlate modestly.
- Both molecules correlate strongly with some lipid markers and with fasting blood glucose, weakly with HbA1c, but not with HDL-cholesterol.

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Disclosure statement

The authors declare no conflict of interest.

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