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Assessing miR-222-3p and miR-21-5p: Predictive miRNAs for Complications in Gestational Diabetes Mellitus.

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Abstract

Usually identified in the second quarter of being pregnant, pregnant diabetic mellitus (G.D.M) becomes a frequent pregnant problem. Mothering diabetic presents an important medical danger regarding the female as well as the fetus alongside is linked to pregnancies. There is mounting proof showing that pregnant women having presentational diabetic type**1-** mellitus (T**1**.DM) as well as type**2-** diabetes mellitus (T2.DM) experience greater numbers of serious pregnancy-related issues than pregnancies women having pregnancy-related diabetes mellitus (G.D.M). An overview of the current research on miRNAs as diagnostic biomarkers for pregnant as well as pre**-**gestational diabetes is the goal of this research project. Methods: One hundred ladies participated in this research as participants. Between the fifth of September 2024, to the 28th of May 2025, 50 women with pregnancy**-**related diabetes visited the diabetic consulting clinics at the Maternals & Kids**-**Educational**-**Hospital located within Al-Diwaniyah Province. Medically historical events testing in the lab (HbA.1c**-**test), as well as fasting evaluations were used for diagnosing individuals with pregnancy-related diabetes. Results: During the present research, the gene expression of comparative mi.RNA222 as well as the level of expression within the participants in the G.D.M**-**group as well as the presumably controls were quantitatively examined using RT**-**PCR. Additionally, a mathematical RT-PCR examination for comparing miRNA222 expressing themselves was conducted in the present research compared the set of participants GDM as well as the controls, ostensibly. Conclusion: Owing to this research, miR**5-21-**p might be a useful biomarker for G.D.M. Additionally, miR**3-222-**p seems to have a positive correlation between fasting plasma glucose, confirming its function in metabolizing**-**glucose, whereas miR-21 may affect resistant to insulin as well as the absorption of glucose.

1.1. Introduction

One major mother issue occurring as well as is identified when pregnant is gestational-diabetes-mellitus (G.D.M). G.D.M cannot be identified till the very last either even the 3rd trim of pregnant because its pathogenesis is marked with persistent resistant to insulin during the second half of pregnant (1). Comparing to women having later pregnancy-related diabetic (hyperglycemia during 24**-**28 weeks of pregnancy), those having earlier pregnancy**-**related diabetic have poorer pregnancies(2). Globally, pregnancy**-**related diabetic impacts roughly fourteen percent within pregnancy outcomes; distribution varied according to hazards, detection techniques,

as well as diagnostic procedures. (3).This description of G.D.M has remained in usage for a long time, although it has drawbacks, such as the inability to confirm the presence of preexisting hyperglycemia. Whereas G.D.M can occur at any point throughout being pregnant, it is more commonly identified after the 24th week of gestation because women of pregnant age are not eligible for global regular tests for hyperglycemia prior to fertilization or throughout the first semester. (4). G.D.M is linked to the emergence of several immediate and long-term issues for the pregnant woman & the fetus (5), For example, in comparison with babies of moms without diabetes, they are more likely to have congenital abnormalities and a higher body-weight at conception (L.G.A, big during pregnancy period). Furthermore, there is a marked rise in the chances of preterm birth, cesarean sections, and birth traumas (6). The incidence of GDM is rising, which is alarming. New indicators are needed for improved care as well as early identification, especially epigenetic ones. Small non-coding R.N.A molecules are known as mi-RNA. After the discovery of extra-cellular micro-RNAs (mi-RNAs) within bloodstream-circulation during 2008, additional body-fluids came next (7). Current study has shown that micro-RNAs (mi-RNAs), which are among the more common epigenetic-mechanisms, possess a significant role in the patho-physiology of pregnancy-related diseases, like diabetic (8). It is a key mediator in epigenetic alterations (9). Recent research has revealed that altered cytokine and microRNA (miRNA) profiles are linked to pathophysiological processes that occur during pregnancy (10).The primary objective was to look at the possible involvement of miRNA (miR-16-5p, miR-222-3p, & miR-21-5p) in G.D.M & how they relate to clinical characteristics. (11). The purpose of the research was to create a panel of miRNAs by doing a comprehensive examination of mi-RNAs linked to G.D.M. The biological-significance of mi-RNAs is a topic that warrants further investigation.

1.2. Methodology and Approaches

Generally, Case-control research was conducted within Al-Diwaniyah-Governorate, & the subjects enrolled in this study consisted of 100 women. Fifty women were suffering from gestational diabetes whose ages ranged from 2042- years, & a healthy-control group of 50 individuals with ages ranged from 17 to 35 years' old who attended the diabetes consultation clinic at the Maternity and Children's Teaching Hospital in Al-Diwaniyah-Governorate from September 5, 2024, to May 28, 2025, under medical supervision. Patients with gestational-diabetes were diagnosed according to medical history and laboratory examination (HbA.1c test) & (fasting test). Five-milliliters of venous blood-stream have been drowned using a disposable syringe regarding sterile methods. 2 ml of blood-stream have been placed inside an EDTA tube to perform the HbA.1c test. 3 ml of blood-stream were placed in an It was placed in a gel-tube & centrifuged to obtain the serum for RNA-extraction.

1.2.1. Ethical approval

The current research has been managed according to the recommendation guide gained from the Medicine-College / University of Al-Qadisiyah. This work did not include forbidden biological materials or genetically modified organisms. All patients were informed about the research and permitted to obtain a questionnaire and draw blood from them (100 subjects were accepted).

1.2.2 Molecular study

The qPCR-Primers for miRNA 2223-p (MIMAT.0000279) miR-21-p5 (MIMAT.000007), were created for this work utilizing the miRNA Primer-Designing Tool and the Sanger Center miRNA information registration to choose the miRNA sequence. In contrast, the NCBI-Database and Primer3 Plus design online were used to create the q.PCR Housekeeping gene (G-A-P.DH) (NM001256799.3-) for this investigation.

1.2.3 statistical analysis

Microsoft-Office-Excel 2010 & the statistical-package for social-sciences (S.P.SS) version 26 were used to gather, compile, analyze, & display the data. Following the Kolmogorov-Smirnov normality test & the determination of whether the variability was naturally or non-normally distributed, the numerical values have been displayed as the average & the standard-deviation.

1.3. Results and Conclusions

Baseline Characteristics of Subjects

A total of 100 blood-specimens of pregnant-women enrolled volunteers was collected & divided into 2 groups, 50 pregnant women with Gestational-diabetes-mellitus (G.D.M) and 50 pregnant individual controls who are apparently healthy. All of these are categorized according to age, weight, biochemical-markers (fasting-blood-sugar (F.B.S), glycated hemoglobin (HbA.1c). The age range in both patient and healthy groups was 17 to 42 years.

According to age, the mean age of GDM patients was 29.16 ± 5.88 years old, and that of normal pregnant woman was 27.24 ± 6.80 years old and there was non-significant difference among infected-individuals & control-subjects within mean-age (P= 0.135). Regarding age group, in overall, 7 (7.0%) less than 20 years, 51 (51.0%) between 20-29 years, 42 (42.0%) more than 30 years were included, G.D.M patients included 2 (4.0%) less than 20 years, 25 (50.0%) between 20-29 years, and 23 (46.0%) more than 30 years, while normal pregnant woman included 5 (10.0%) less than 20 years, 26 (52.0%) between 20-29 years, & 19 (38.0%) more than 30

years and there was non-significant difference in the frequency distribution of patients and control subjects according to age groups (P = 0.430) as shown in (Table 1).

Table (1) Comparison between patients and control groups in Age group.

Study groups		Age group			Mean ±SD
		< 20 years	20-29 years	≥ 30 years	
Groups	GDM Patients	2 (4.0%)	25 (50.0%)	23 (46.0%)	29.16 ± 5.88
	Control	5 (10.0%)	26 (52.0%)	19 (38.0%)	27.24 ± 6.80
Total		7 (7.0%)	51 (51.0%)	42 (42.0%)	
p-value		0.430 ¥ NS			0.135 † NS

n: number of cases.: **SD**. standard deviation.: †: Independent T test.: ¥: Chi-square test: **S**: significant at $P < 0.05$.

The Gestational Diabetes Mellitus (GDM) diagnosis was based on results of metabolic factors (F.B.S & HbA.1c) within the patients and the healthy controls and the results were demonstrated in table. The Fasting blood sugar diagnosis were measured in the blood-serum with concentrations between 70 mg/dL to & 100 mg/dL considered as normal (negatively-results) & ≥ 100 mg/dL were considered as positive. Mean levels of fasting blood sugar (F.B.S) were 126.62 ± 11.96 & 94.30 ± 10.7, in G.D.M patients and healthy women respectively; the level was higher in G.D.M patients in comparison with healthy women and the difference was highly significant ($P < 0.001$). Regarding to qualitative results: 46 (92.0%) of patients with G.D.M were positive F.B.S, while 10 (20.0%) healthy control was positive for FBS & the difference was significant ($p < 0.05$). Glycated-Hemoglobin (HbA1c%) with concentrations ≥6.0% were considered as positive and with concentrations < 6.0% were considered as negative. Also the mean of HbA1c% were 7.98 ± 1.09, and 4.05 ± 0.56 in GDM patients and healthy women respectively; the level was higher in GDM patients in comparison with healthy women and the difference was highly significant (P < 0.001). Regarding to qualitative results: 49 (98.0%) of patients with G.D.M were positive Hb.A1c%, while all healthy control was negative and the difference was significant (p <0.05), figure (1,2).

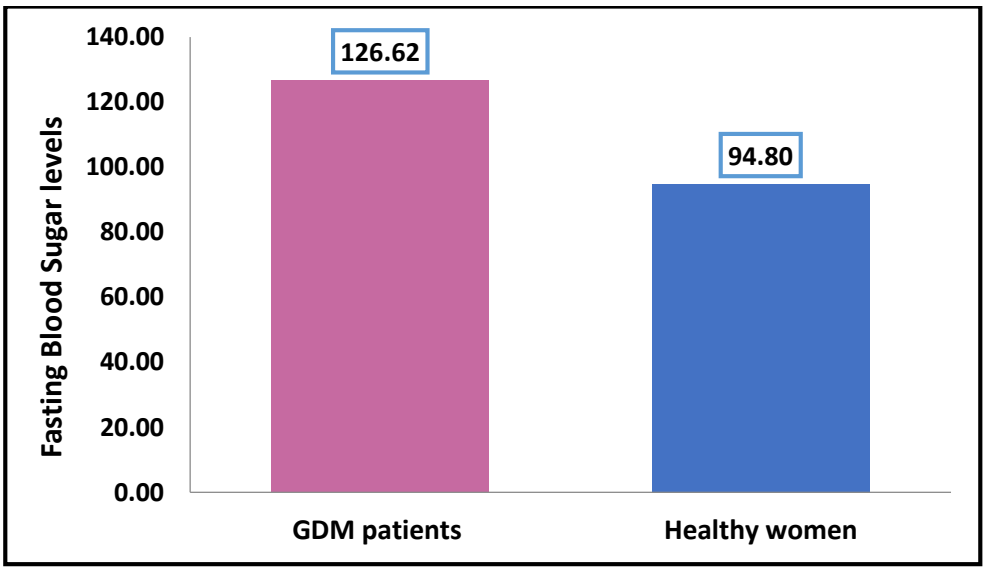

Figure (1): The means level of RBS in patients and control groups

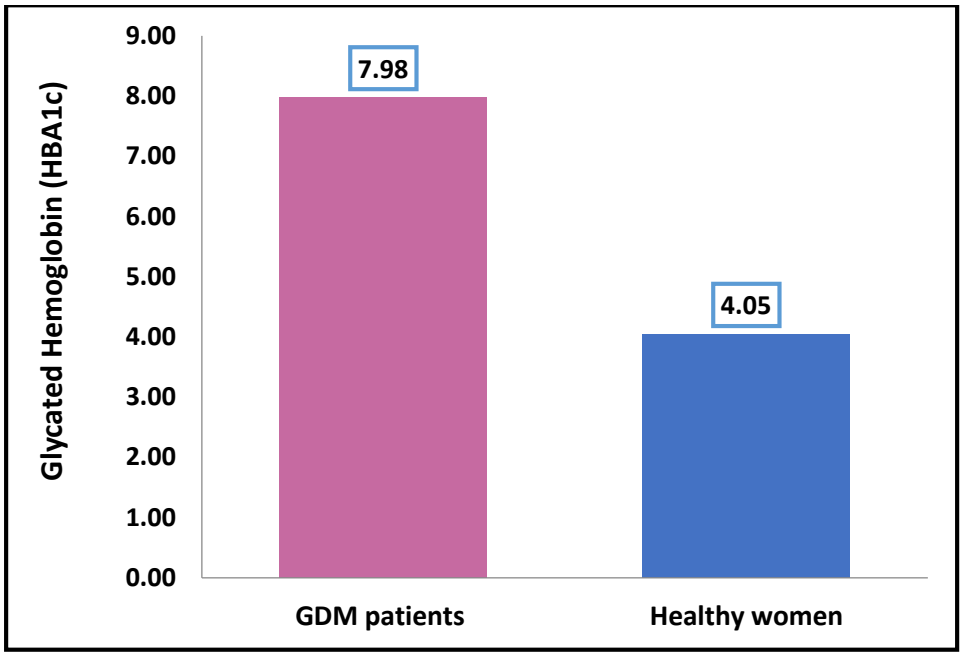

Figure (2): The means level of HbA1c % in patients and control groups

Gene Expression Profile Study by Quantitative Reverse Transcriptase Real Time PCR

The purity of total R.N.A specimen's ranged from 1.65 to1.92 ng/µl during this research groups with a mean ± SD of 1.84±0.12 ng/µl. The RNA purity of the study groups as well Proper sterilization methods need to be followed in order to obtain a satisfactory output containing a substantial amount of total RNA. The utilizing of TRIzol in the extracting of total RNA from blood-specimens is well-established.). The most effective outcomes can be achieved by using working aids such as RNase-free devices, such as tips & microfuge tubes, and nuclease-free water. The working field can also be decontaminated utilizing surprise & U.V-radiation. A high RNA content was linked to nill DNA.

Real time PCR Quantification of *miRNA222 Expression*

For every specimen, an additional replication of every single quantitative PCR reaction was conducted. Every experiment included non-template as well as non-primer control in additional to the G.D.M along with control specimens. This was necessary to specify the calibrator and to perform the statistical calculations for each group. Each run's plots, comprising separation lines as well as amplification plots, were documented. The amplification plots and dissociation curves for mi-RNA-222 are displayed in Figure (3).

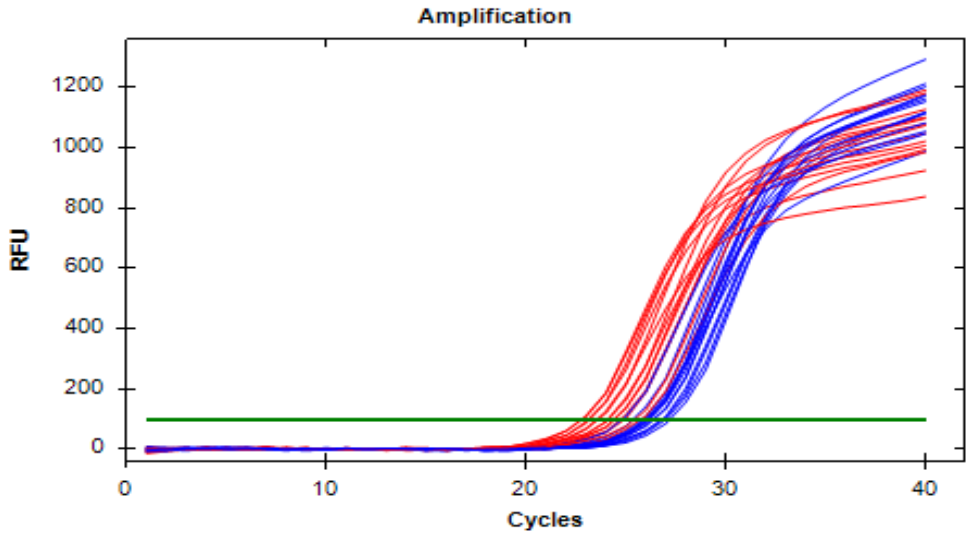

Figure (3) The real time PCR amplification plots of *miRNA 222-3p* in patient and control blood samples.

In this study, a quantitative analytical of RT-PCR analyzed Expressing of comparison *mi.RNA-222* & of its expression between, apparently control group, the group G.D.M group Figure (4). The change in gene expression was calculated using a relative quantitative measurement (12). This is based on the normalization of the Ct values for calculating $^{\Delta}$Ct & represents the difference between the average Ct values of *the mi-RNA-2224* cDNA amplification replica for each case and case of G.A.P.D.H. The comparison of *mi.RNA-222* gene expression between G.D.M patients and healthy women subjects has been carried out and the results were demonstrated in table (2). Mean of *miRNA-222 gene expression* were 11.39 ± 3.22, & 1.38 ± 0.42 in G.D.M patients and healthy control respectively; the mean levels was higher in G.D.M patients in compared to healthy control and the difference was highly significant ($P < 0.001$).

Table (2): Comparison of mean of *miRNA222 gene expression* between GDM patients and healthy controls

Groups	Mean	SD	SE	p-value
GDM patients	11.39	3.22	0.93	0.001**
Control	1.38	0.42	0.13	

SD: standard deviation; SE: standard error; †: one-way ANOVA; ******: significant at $P< 0.05$

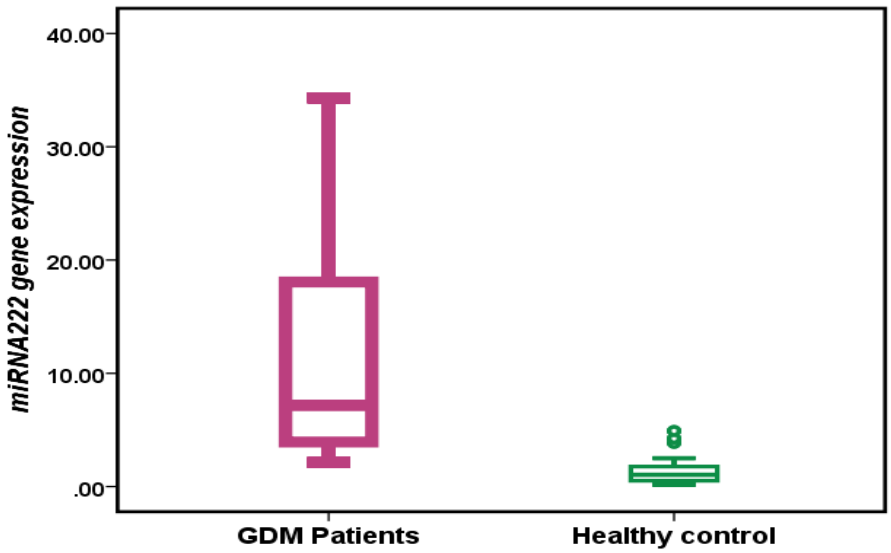

Figure (4): The means *miRNA222 gene expression* in patients and control groups

Real time PCR Quantification of *miRNA21 Expression*

The mean C.t value of *mi.RNA-21 c.DNA amplification* was (26.78) in the G.D.M patients. While Ct values in control were mean (23.97), the mean Ct values in control group were lower than those of G.D.M patients. "This is important in reflecting the original *mi.RNA-21* present in the samples. It is evident from the results that patients group is associated with the highest copy number of *mi.RNA21* reflecting its lower expression. Each quantificative P.C.R reactions was run in duplicate for each sample. In each run, samples from G.D.M and control were run in addition to non-template and non- primer controls." This was necessary for selecting the measuring instrument and to perform the mathematical computations for each group. Each run's plots, comprising the separation lines as well as amplified graphs, were documented. The amplification plots and dissociation curves for mi.RNA21 are displayed in Figure. (5).

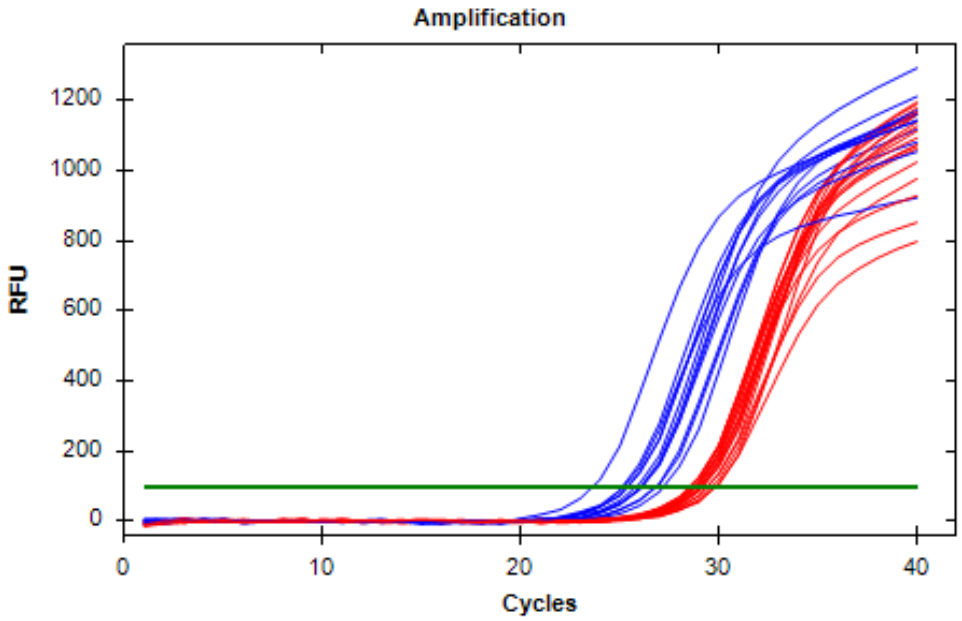

Figure (5): The real. time PCR amplification plots of *miRNA. 21-5p* in patient and control blood samples. The red q.PCR plots (patient samples) & the blue q.PCR plots (control samples)

A statistical evaluation of RT-PCR was conducted in this work. Self-expression of comparative miRNA-21 and the way it is expressed difference between the GDM group and the group that appears to be the control group. A relative quantitative measurement was used to determine the change in gene expression. (13). his is the variation within the mean Ct values of the mi.RNA21 cDNA amplification replica for each case and case of G.A.P.D.H, and is based on the normalization of the Ct values for calculating ΔCt. The 2-ΔCt findings were used to calculate the relative expression of the miRNA.21 gene in each study group. One of the samples of the controls with high expression of miRNA.21 was utilized as a calibrator. The control group's mean 2-ΔCt value was 2.22, while the G.D.M patients' was 0.39. Calculations showed that the group of GDM patients had considerably higher gene expression than the control group. The G.D.M group's fold number was 0.409.

1.4. Discussion

GDM, which is regarding the rise, can cause major, long-term problems for the mom and the kid. The prospective roles of miRNAs as tissue crosstalk mediation, biologic procedure regulatory bodies, and G.D.M biomarkers are of great interest. Numerous mechanisms linked to pregnancy & G.D.M involve mi.RNAs. (14). Pregnant issues have been associated with dysregulated mi.RNAs, indicating that these molecules may be used as prognostic markers for G.D.M disease. Additionally, earlier studies have demonstrated that GDM patients and controls had different levels of miRNA expression. (15). Although MiR-21 plays a significant role in many illnesses, it may additionally be employed for the treatment of individuals with type-2 diabetes as well as pancreatic tumors as a genetic detection biomarker. (15). *miR-21-5p*, a chromosomal structure (15) along with has a significant amount of gene similarities between species. NF-κB raised the levels of miR-21 in the pancreas-cells of mice with a model of type 1 diabetes, but miR-21 reduced the amounts of controlled cell death 4 (P.D.C.D-4), which is a marker of resistant to insulin as well as a trigger of apoptotic (16). According to the current results, there was a significantly significant ($P < 0.001$) variance in the amount of expression of the miR-21-5p gene between G.D.M patients & healthy controls. The current findings are consistent with the research that was done. (17), The GDM group's level of miR-21-5p expression were significantly lower than those of the control group.(18), used a microarray to examine the expression of miRNA-21 in the placental tissues of GDM rats. In GDM rats, miRNA-21 was shown to be downregulated. Interestingly, miRNA-21 knockdown enhanced apoptosis and decreased insulin production in INS-1 cells, whereas miRNA-21-overexpressed INS-1 cells showed the opposite effects. However, (19) discovered that a later risk of acquiring G.D.M was linked to increased levels of miR-21-5p. Only women who were overweight or obese prior to becoming pregnant showed this connection, and Jamalpour (*20*) demonstrated that patients with G.D.M had considerably higher levels of miRNA.21. There could be a number of reasons for the conflicting results of previous studies regarding the relative expression of miRNAs. Numerous studies have demonstrated that miRNA expression varies among groups that share the same environment and is influenced by genetic background. (21). How miR21 is related to G.D.M is still unknown, though. One tenable theory is that mi.R21 suppresses cell development and invasion while increasing glucose absorption in G.D.M patients by inducing the PPA.Rα gene. (22). They observed sexily multifaceted miRNA transcription in the human placenta throughout gestation. *(23*). They discovered that in women in the first

and third periods, miR-21 was up-regulated and displayed differently .The aforementioned findings point to a possible function of miR-21-5p expression in tracking GDM patients' treatment.

According to the current findings, the researchers discovered a substantial positive association between the miRNA-222 gene and the miRNA-16 gene (r=0.322 & p=0.022) as well as between the miRNA-222 gene and the level of FBS (r=0.301 &p=0.027). This suggests that there may be a connection between the mi.RNA and the metabolism of glucose during pregnancy, which is known to have a significant impact on birth weight. These findings are consistent with those of Filardi (24), who discovered a positive correlation ($p < 0.001$) between the expression of circulating miR-222-3p & fasting plasma glucose (F.P.G). Jie (25) demonstrated that miR-222-3p expression was positively correlated with FPG and Hb.A1c in the patient population. Additionally, in patients with GDM, there is a favorable correlation between FPG and increased miR-222-3p expression (27).These findings contradict the work of (28) that found a substantial positive association between the miRNA21 gene and patients with gestational diabetes mellitus (P=0.03). Despite the fact that the current results indicate a significant negative correlation between miRNA21 (r=-0.327).(29). Additionally, the current findings are in conflict with those of Zhao and Tao (30), who observed a negative correlation between the level of miRNA-21 and blood glucose, & Seyhan *et al*. (2016), who reported a significant link between the level of miR-21 and Hb.A1c.

Conclusion

This study suggests that miR-21-5p may serve as a potential biomarker for G.D.M. Also that miR-21 may influence glucose uptake and insulin resistance, while miR-222-3p appears to be positively correlated with fasting plasma glucose, reinforcing its role in glucose metabolism. The elevated levels of miRNA-222 in G.D.M patients suggest that it may serve as a potential biomarker for the diagnosis or monitoring of gestational diabetes mellitus. These findings suggest that miR-21-5p could be useful in monitoring G.D.M treatment, while miR-222-3p may influence glucose metabolism and birth weight.

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Conflict of Interest:

"The authors declare no conflict of interest."

Data availability
Completely obtained information was involved in this training.

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