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Predictive Value of First Trimester Measurements of Adiponectin and 1,5 Anhydroglucitol in Diagnosis of Gestational Diabetes Mellitus

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Abstract

Background: The search for diagnostic biomarkers in diabetes is rapidly expanding, increasing efforts devoted to new diabetes diagnostic biomarker discovery. Current, early screening and diagnostic tests for D.M. depend on studies on biomarkers.

Aim of the work: The current research aimed to predict the occurrence of gestational diabetes by measuring serum adiponectin and 1, 5 anhydroglucitol during the first trimester.

Methods: OGTT was done using 75 g of anhydrous glucose, which was given to the pregnant women, and measurement of 1,5 AG was simultaneously performed to all cases in the first, and ≥ 24 weeks of their pregnancy, respectively. Serum 1, 5, A.G. and adiponectin levels were assessed using an enzymatic, colorimetric assay kit by ELISA method.

Results: 1,5 AG and adiponectin concentrations were significantly lower in women with high-risk for GDM during the first trimester. The area under the ROC curve was 0.968 for 1,5 A.G, and 0.737 for adiponectin. The maximal sensitivity and specificity (100% and 80%, 100% and 66.7% for 1,5 A.G. and adiponectin respectively). A 1,5-AG cut-off level of 1,5 A.G was 7.55 µg/mL and 17.30 for adiponectin.

Conclusion: We concluded that first-trimester measurement of serum 1,5 anhydroglucitol concentration and adiponectin is a good biomarker for GDM, and 1,5 A.G. is the most reliable.

Keywords: Predictive value; Gestational diabetes mellitus; Adiponectin; 1,5-Anhydroglucitol

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Introduction

In the past decade, the International Diabetes Federation (IDF) illustrated that the estimated prevalence of diabetes worldwide has continuously grown each year 366 million in 2011, three hundred seventy-one million in 2012, 382 million in 2013, four hundred fifteen million in 2015. This number may rise to 451 million in 2017 and expected to rise to 552 million by the year 2030 [1-5]. Current screening and diagnostic tests for D.M. are established on studies on biomarker candidates in diagnosing type 1, type 2, and gestational D.M [6].

1,5 Anhydroglucitol (1,5 AG) is one of the naturally occurring monosaccharide's found in nearly all foods and is structurally similar to glucose [7]. It is absorbed mainly from ingested food and is distributed to all organs and tissues [8]. Clinical studies have also reported 1,5 AG as a short-term postprandial marker for hyperglycemia [9]. Adiponectin is primarily expressed and synthesized in maternal adipose tissue but not by the placenta and does not cross to fetal circulation [10]. Previous investigations ascribe adiponectin to promote β-cell function and survival as well as to lower systemic glucose levels *via* suppression of hepatic glucose output. There is evidence for an inverse association of serum adiponectin with progressing insulin resistance [11]. The applicability of adiponectin as a prognostic biomarker for GDM risk is currently under debate. There is evidence that decreased adiponectin levels at early pregnancy predict the occurrence of GDM [12].

The objective of this study is to assess the value of measuring serum adiponectin, and 1,5 anhydroglucitol during the first trimester in the prediction of gestational diabetes.

Patients and Methods

The study subjects for this case-control study were recruited from antenatal clinics of the Obstetrics and Gynaecology Department at Tanta University Hospital. The duration of the study was two years, starting from October 2018 till April 2020.

Inclusion criteria

- Pregnant woman less than 14 weeks of gestation.
- Single pregnancy.
- Age of the female between 18 and 35 years.
- Obesity (BMI>25 kg/m^2).
- Women with a previous history unexplained intrauterine fatal death.
- Women with a previous history of delivery of a macrocosmic baby.
- Past-history of gestational diabetes.
- Poly hydramnios with unidentifiable cause as open spina bifida or esophageal atresia.
- History of polycystic ovary syndrome.
- Family history of diabetes.

Exclusion criteria

- Well established diabetes.
- Patients with chronic liver disease, or patients with hepatitis B virus infection (HBV), and/or patients with hepatitis C virus (HCV) affection.

Written consent: Was obtained from the women on whom the study executed, and they informed about the objectives and hazards of the study

Study population: The study groups comprised 100 women with high-risk for GDM (Group-I), and 50 women without risk for GDM (Group-II).

Group-I (100 cases): with high risk for gestational diabetes:

- Previous macrocosmic baby>4 kg
- BMI>30 kg/m^2
- Previous unexplained stillbirth
- History of PCOS (polycystic ovarian syndrome)
- Family history of first-degree relatives diabetes

Group-II (50 cases): With no risk locates for developing gestational diabetes. For both groups, serum glucose level and adiponectin 1,5 anhydroglucitol were measured by ELISA method in the first trimester. Then Oral Glucose Tolerance Test was done for both groups at ≥ 24 weeks of gestation and the patients were followed for the development of gestational diabetes mellitus and its complications.

All patients were subjected to

Personal history: Name, age, parity, occupation, and peculiar habits of medical importance.

Menstrual history: Gestational age of present pregnancy determination according to last menstrual period (if patient sure about the date and had three regular cycles before the pregnancy or has ultrasound report done in the first trimester) and confirmation by ultrasound assessment.

Present history: Associated symptoms: (bleeding, abdominal pain) and routine treatment first trimester like a folic acid supplement.

Obstetric history: Including the number of previous deliveries, previous preterm labour, and abortion, postpartum, and puerperium period, prior history of miscarriage, prior history of gestational diabetes mellitus.

Surgical history: Any cervical surgeries and previous cesarean section.

General Examination: Vital signs (heart rate, temperature, respiratory rate, body mass index (BMI). and blood pressure), BMI calculated as weight (kg)/height (m^2), chest and heart examination, limbs examinations.

Abdominal examination: Including inspection and palpation of the abdomen. Anthropometric measurement Height, weight, BMI, and blood pressure (B.P.) were measured. Height, weight, and B.P. were evaluated at the antenatal visit. Height measured by using standard wall-mounted tape and in a standing position, weight calculated by using a digital scale. A manual sphygmomanometer was used for measuring the B.P in sitting position and the arm laid at the level of the heart and the same arm used for measurement at all antenatal visits. All mothers rested for 5 minutes before measurement. BMI was calculated by dividing weight/height (kg/m^2).

Methods

The Oral Glucose Tolerance Test (OGTT) was done using 75 g of anhydrous glucose, which was dissolved in 300 ml of water and given to the pregnant women. Further venous samples were drawn at fasting, one and two hours on oral glucose tolerance test, and measurement of 1,5 AG was simultaneously performed to all cases in the first, and ≥ 24 weeks of their pregnancy, respectively. Serum 1,5 AG and adiponectin levels were assessed using an enzymatic, colorimetric assay kit by ELISA method.

Provision of privacy

There are adequate provisions to maintain the privacy of participants and confidentiality of the data; the patient name is substituted by serial number, her address as confidential.

Statistical analysis of the data

Data was fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp) Qualitative data described using numbers and percentages. The Kolmogorov-

Smirnov test was used to verify the normality of distribution. Quantitative data defined using range (minimum and maximum), mean, standard deviation, median, and Interquartile Range (IQR). The significance of the obtained results judged at the 5% level.

The used tests were

1. Spearman coefficient: To correlate between two distributed abnormally quantitative variables

2. Sensitivity: The capacity of the test to correctly identify diseased individuals in a population "TRUE POSITIVES." The higher the sensitivity, the smaller the number of unidentified cases "false negatives."

3. Specificity: The capacity of the test to correctly exclude individuals who are free of the disease "TRUE NEGATIVES." The higher the specificity, the fewer "false positives" will be included.

4. Receiver Operating Characteristic Curve (ROC): It is done by plotting sensitivity (T.P) on Y-axis versus 1-specificity (F.P) on the X- axis at the different cut off values. The area under the ROC curve denotes the diagnostic performance of the test. Area more than 50% gives acceptable performance and is about 100% is the best performance of the test. The ROC curve also allows a comparison of performance between two tests.

5. Positive Predictive Value (PPV): The probability of the disease being present, among those with positive diagnostic test results

6. Negative Predictive Value (NPV): The probability that the disease was absent, among those whose diagnostic test results were negative

7. Odd Ratio (OR): Used to calculate the odds ratio at 95% confidence interval of an event occurring in one risk group to the odds of it happening in the non-risk group

Follow up

Patients proved diabetic were transferred to the diabetes clinic for diabetes control and submitted to antenatal care, as high-risk cases.

Results

The clinical and biochemical disclosures of this case-control study appear in nine tables and six figures.

Table 1 creates the impression of the important clinical data for differentiation between the two groups regarding age, body weight, BMI, and gestational age. There was no basic qualification between the analyzed packs concerning the clinical disclosures.

	Group-I			Group-II			P-value
Age (years)	27.4	±	4.7	27.1	±	4.8	0.846
Weight	82.8	±	11.9	71.6	±	14.5	0.044*
BMI	36.4	±	4.2	30	±	5	0.041*
Pulse	100.6	±	9.8	99.3	±	11.5	0.366#
Systolic blood pressure	110	±	11.6	110.2	±	10.2	0.698#
Diastolic blood pressure	69.3	±	12.5	70.6	±	14.1	0.913#
Hemoglobin (Hb)	10.7	±	3.1	10.6	±	4	0.898#
Mean Parity	1.21	±	1.13	1.35	±	1	0.853
Mean Gravidity	2.21	±	1.14	2.44	±	1	0.843
Mean Gestational age	10.41	±	3.76	10.2	±	1.11	0.942

Table 1: Comparison between both groups regarding some clinical findings.

There was no genuine qualification between the considered packs for hypertension and C.S. All things considered, there was a basic quantifiable difference between the two gatherings concerning the family ancestry of diabetes and reiterated unconstrained baby expulsion as in **Table 2**.

	Group-I		Group-II		P-value
Family History of diabetes	n	%	n	%	
Yes	76	76%	0	0	0.003*
No	24	24%	50	100%	
Hypertension (HTN)					
Yes	40	40%	6	12%	0.586
No	60	60%	44	88%	
Repeated spontaneous abortion					
Yes	32	32%	0	0	0.042*
No	68	68%	50	100%	
C.S					
No	48	48%	20	40%	0.758
Yes	52	52%	30	60%	

Table 2: Comparison between both groups regarding past history.

In the **Table 3**, it is obvious that there was a significantly essential qualification between the two packs as regard BMI >30 Kg/M^2 and an impressive complexity as regards p-esteem.

	Group-I		Group-II		P value
	n	%	n	%	
BMI >30 KG/M2	84	84%	0	0	0.021
Previous unexplained stillbirth					
Yes	5	20.60%	0	0%	0.038*
No	80	80.00%	50	100%	
Previous macrosomic baby > 4kg					
Yes	8	8.00%	0	0%	0.062*
No	92	92%	50	100%	
History of PCOS					
Yes	20	20.00%	0	0%	0.038*
No	80	80.00%	50	100%	
Family History of diabetes					
Yes	76	76%	0	0	0.003*
No	24	24%	50	100%	

*Chi-square test, #independent sample t-test; 1,5 AG=1, 5 anhydroglucitol.

Table 3: Comparison between both groups regarding the risk for gestational diabetes.

Table 4 gives the idea that the mean values of the 1,5 AG and adiponectin concentrations were significantly lower in women with high-risk for GDM during the first trimester.

	Group-I			Group-II			P value
1,5 AG	6.8	±	5.7	9.8	±	4.2	0.001*
Adiponectin (µg/ml)	5.2	±	2.1	7.8	±	2.4	0.001*

rs: Spearman correlation co-efficient.

Table 4: Comparison between 1, 5 A.G. and adiponectin at 1st trimester in both groups.

Table 5, Figures 1 and 2 exhibit the correlation between adiponectin and 1, 5 A.G., and BMI>30 Kg/m^2 .

	Adiponectin		1, 5 A.G.	
BMI >30 KG/M^2	rs	-0.787	rs	-0.948
	p	0.001*	p	0.021
Fasting plasma glucose	rs	-0.528	rs	-0.156
	p	0.005*	p	0. 041

Table 5: Correflafion beftween Adfiponecfin and 1, 5 A.G., and BMI >30 KG/M^2, Fasting plasma glucose in the study groups.

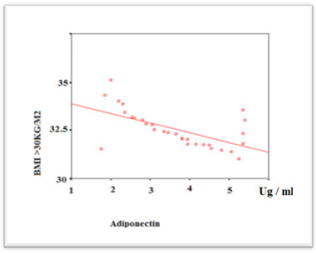

Figure 1: Correflafion beftween adfiponecfin and BMI >30 KG/M^2 in the study Group-I.

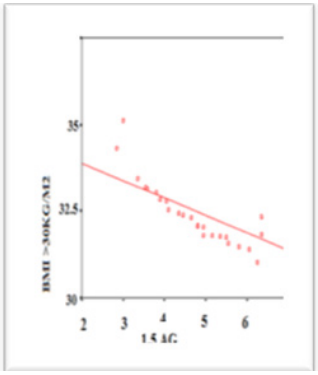

Figure 2: Correflafion beftween 1, 5 A>G> and BMI >30 KG/M^2 in the study Group-I.

Table 6 gives the idea that the mean values of the 1,5 AG and adiponectin concentrations were significantly lower in women with high-risk for GDM during the last trimester.

	Group-I			Group-II			P-value
Adiponectin(µg/ml)	5.1	±	1.3	7.4	±	1.5	0.001*
1,5 AG	6.1	±	2.7	9.3	±	4.1	0.001*

Table 6: Comparison between both groups as the adiponectin, and 1,5 AG (µg/ml) at ≥ 24- week gestation ≥ 24 weeks gestation.

Table 7, Figure 3 and 4 display the correlation between adiponectin and 1, 5 anhydroglucitol, and BMI and fasting plasma glucose levels.

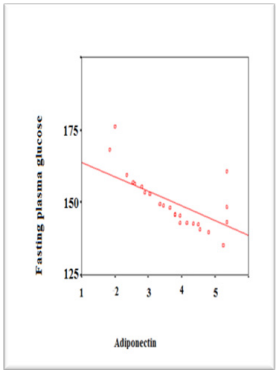

Figure 3: Correlation between Adiponectin and Fasting plasma glucose in the study Group-I.

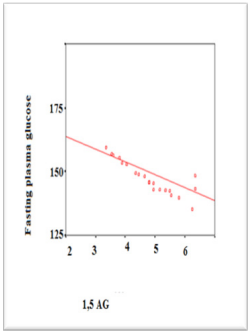

Figure 4: Correlation between 1, 5 anhydroglucitol and Fasting plasma glucose in the study Group-I.

	Adiponectin		1, 5 A.G.	
BMI >30KG/M^2	rs	-0.889	rs	-0.957
	p	0.001*	p	0.021
Fasting plasma glucose	rs	-0.628	rs	-0.458
	p	0.005*	p	0. 041

rs: Spearman correlation co-efficient

Table 7: Correlation between Adiponectin, and 1, 5 A.G., and BMI >30 KG/M^2, and Fasting plasma glucose in the study groups.

Table 8 shows a comparison between 1,5 AG and adiponectin levels ≥ 24 weeks gestation.

	1st			≥ 24 week			P-value
1,5 AG	6.8	±	5.7	6.1	±	2.7	0.842
Adiponectin	5.2	±	2.1	5.1	±	1.3	0.983

*Chi-square test, # independent sample t-test.

Table 8: Comparison between 1,5 AG, adiponectin at 1st, and 3rd trimester in the Group-I.

Table 9, Figures 5 and 6 depict the ROC curve findings of 1,5 AG and adiponectin for high-risk women for GDM. For 1,5 A.G, there is an excellent AUC was found (AUC=0.968, p<0.001). At the cut off value of 17.55, sensitivity was 100%, specificity was 80%, PPV was 88.3%, NPV was 87%, and accuracy was 90%. Concerning adiponectin, AUC was found (AUC=0.737, p<0.001). At the cut off value of 17.30, sensitivity was 100%, specificity was 66.7%, PPV was 83.2%, NPV was 80%, and accuracy was 94%.

Item	1, 5 Anhydrogflucitofl	Adiponecin
AUC	0.907	0.881
95% CI	0.968	0.737
p	<0.001	<0.001
Cut off	17.55	17.3
Sensitivity (%)	100	100
Specificity (%)	80	66.7
PPV (%)	88.3	83.2
NPV (%)	87	80
Accuracy (%)	90	94

Table 9: ROC AUC and performance characteristics of 1, 5 anhydroglucitol, and adiponectin for developing gestational diabetes.

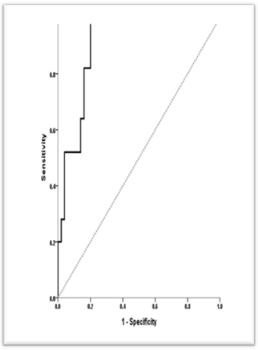

Figure 5: ROC curve of 1, 5 A.G. for developing gestational diabetes.

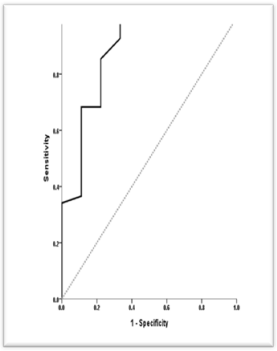

Figure 6: ROC curve of adiponectin for developing gestational.

Discussion

The search for diagnostic biomarkers in diabetes is rapidly expanding, increasing efforts devoted to new diabetes diagnostic biomarker discovery. Current, early screening and diagnostic tests for D.M depend on studies on biomarker candidates in diagnosing type 1, type 2, and gestational D.M [6].

The work of the current research aimed to predict the occurrence of gestational diabetes by measuring serum adiponectin and 1,5 anhydroglucitol during the first trimester.

In the present study, the mean age of the participants was 27.4 ± 4.7 years, mean of BMI (Body Mass Index) was (36.4 ± 4.2), and lastly (76%) had a positive family history of D.M. In contrast (24%) had an adverse family history of D.M. Adiponectin is primarily expressed and synthesized in maternal adipose tissue but not by the placenta and does not cross to fetal circulation [9]. Previous investigations ascribe adiponectin to promote β-cell function and survival as well as to lower systemic glucose levels *via* suppression of hepatic glucose output. There is evidence for an inverse association of serum adiponectin with progressing insulin resistance [10]. The applicability of adiponectin as a prognostic biomarker for GDM risk is currently under debate. There is evidence that decreased adiponectin levels at early pregnancy predict the occurrence of GDM [11].

Association between increased body mass index and gestational diabetes mellitus well established [12]. Kiani and collaborates found that the mean BMI in cases of GDM was 27.53, which found the overweight range [13]. Irving and coworkers reported a positive family history of Diabetes mellitus in 23% of their studied cases [14]. Also, In a study by Bhograj et al. [15] the adiponectin serum level was measured in pregnant women. The pregnancy age at the time of obtaining the sample was 24 to 28 weeks. In this study, the serum level of adiponectin in women with GDM was lower than that in healthy women of the same age [15].

Haem et al. [16] conducted a study on pregnant women and healthy pregnant women. Serum levels of adiponectin, fasting blood sugar, and lipid level are measured in these women in pregnancy age of 28 to 34 weeks. There was no statistically significant difference in the serum level of adiponectin between two groups of GDM and control. However, the women with GDM with over 30 years old, had a serum level of adiponectin lower than than the control group [16]. Wojcik and Associates reported that adiponectin appears to be a factor linking I.R. to β-cell dysfunction in the pathogenesis of diabetes [17].

In the present study, the correlation between adiponectin and BMI>30 Kg/m^2, Fasting plasma glucose in the study group I with a significant correlation in between in the first trimester and 3rd trimester that agrees with the study done by Bhograj et al. [15]. and Haem et al. [16]. That is in line with the results of Wang et al. [17], who reported that 1,5-AG could be a useful index of glycaemic excursions in patients with reasonably well-controlled diabetes [18].

The current survey revealed that the mean levels of the adiponectin (µg/ml) during the first trimester were significantly lower in GDM women (5.2 ≥ 2.1 µg/ml) compared to women without GDM (7.8 ± 2.4 µg/ml) (p=0.001). Besides, the mean levels of the adiponectin (µg/ml) were significantly lower in women at high-risk for GDM (5.1 ± 1.3 µg/mL) compared to women without risk for GDM (7.4 ± 1.5 µg/mL (p=0.001) at 3rd trimester.

Corcoran and mates contemplated adiponectin levels among the high-risk ladies and found that their levels okay populace [18]. Pala and colleagues estimated the serum level of adiponectin in 40 ladies with GDM and 40 healthy pregnant ladies. They found that the serum level of adiponectin in patients with GDM was essentially lower than that in sound pregnant ladies in 24 to 28 weeks (2/45 ± 2/73 versus 4/3 ± 94/33 µg/ml, P=0/02) [18]. In an investigation by Mazaki-Tovi and partners, the serum level of adiponectin was estimated in 72 ladies with GDM and 149 ladies with a solid pregnancy. Thus, in this investigation, the degree of

complete adiponectin, at pregnancy age of 32 to 40 weeks in patients with GDM, was lower than solid pregnancy [19].

In agreement with our results, Bao and associates showed in their meta- analysis that the concentration of adiponectin was significantly lower in the first and early second trimester in a pregnant woman who later diagnosed as GDM [19].

The output of this investigation unrevealed that estimating 1,5 AG during the first trimester could anticipate the ensuing improvement of gestational diabetes in 88.3% of ladies and the cut-off worth was 17.55 ng/ml. The mean level of the 1,5 AG was significantly lower in GDM women (6.8 ± 5.7 µg/ml) compared to women without GDM (9.8 ± 4.2 µg/ml (p=0.001). The mean level of the 1,5 AG was significantly lower in GDM women (6.1 ± 2.7 µg/mL) during the first trimester compared to women without GDM (9.3 ± 4.1 µg/ml (p=0.001) pregnant at 3rd trimester.

Harper and colleagues found that the mean 1,5 A.G. value was 13.3 ± 5.7 µg/mL at 14-20 week and 11.1 ± 5.1 µg/ml at 24-28 week [19]. This observation supports those of Dworacka, who demonstrated a significant correlation between 1,5 AG and GDM. Nowak et al., who reported that 1,5 AG was significantly associated with maximum glucose concentration among pregnant women [15-19].

Corcoran and companions envisioned adiponectin levels among the high- chance populace and found that their levels okay populace. Pala and colleagues estimated the serum level of adiponectin in 40 ladies with GDM and 40 solid pregnant ladies. They found that the serum grouping of adiponectin in patients with GDM was essentially lower than that in healthy pregnant ladies in 24 to 28 weeks (2/45 ± 2/73 vs. 4/39 ± 4/33 µg/ml, P=0/02) [18]. In an investigation by Mazaki-Tovi and partners, the serum level of adiponectin was estimated in 72 ladies with GDM and 149 ladies with a healthy pregnancy. Thus, in this investigation, the degree of complete adiponectin, at pregnancy age of 32 to 40 weeks in patients with GDM, was lower than solid pregnancy [19].

Pramodkumar and collaborates stated that the mean level of 1,5 AG was significantly lower in women with GDM (11.8 ± 5.7 µg/mL) compared to women without GDM (16.2 ± 6.2 µg/mL). Besides, 1,5 AG showed a significant correlation with the 1 Hr post glucose value 1HrPG and 2HrPG. Also, 1,5 AG was significantly associated with GDM after adjusting for age, family history of diabetes, BMI, and gestational age. Lastly, they found that among the three individual glycemic parameters. The cut-off point of 13.21 µg/ml for 1,5 AG concentration could be used to identify 65% of GDM compared to 32.4% of individuals without GDM had values below the cut point [19].

Conclusion

We constructed the Receiver Operating Characteristic (ROC) curves of these indices to determine the optimal predictor. The area under the ROC curve was 0.968 for 1,5 A.G, and 0.737 for adiponectin. The maximal sensitivity and specificity (100% and 80%, 100% and 66.7 for 1,5 A.G. and adiponectin respectively). A 1,5-AG cut-off level of 1,5 A.G was 7.55 µg/ml and 17.30 for adiponectin. Hence, we conclude that first-trimester measurement of serum 1,5 anhydroglucitol concentration and adiponectin is a good biomarker for GDM.

Conflict of interests

The authors have no conflict of interest with anybody.

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