Evaluation of Betatrophin Hormone and Alpha-Fetoprotein Levels in Gestational and Type 2 Diabetic Pregnant Women in Basrah Province

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Abstract

BackgroundBetatrophin and alpha-fetoprotein are widely used as diagnostic markers for type 2 diabetes mellitus (T2DM), but their clinical utility in diagnosing gestational diabetes (GDM) is unclear. Therefore, this study aims to evaluate the levels, relationship between betatrophin and alpha-fetoprotein, and the risk as well as the ability to predict postpartum outcomes in GDM and T2 DM. Methods: A case-control study, that involved 61 volunteer pregnant women with GDM and T2 DM, who attended and received antenatal care services at Al- Fayhaa Teaching Hospital and Basrah for Women and Children Teaching Hospital, during the period from October 2021 to February 2022. Betatrophin and alpha-fetoprotein and other parameters were measured by standard methods. Results: pregnant women with DM were shown significantly higher betatrophin, AFP, and glucose levels than healthy pregnant women; while they showed non-significant differences in total cholesterol (T.C), low-density lipoprotein-cholesterol (LDL-C), and insulin levels than healthy women. Triglyceride and HOMO-IR showed significant differences in GDM &T2DM groups compared with the healthy group. The statistical analyses revealed that there were no significant differences between GDM and T2DM groups in all variables ($p>0.05$). Linear regression models revealed significantly high levels of betatrophin, fasting glucose, and BMI in GDM and T2DM. The linear model (ROC) analysis revealed that betatrophin is the best predictor of GDM compared to controls (area under the curve; AUC = 0.797). The model also revealed that alpha-fetoprotein and BMI are the best predictors of GDM and T2DM. Conclusions: Betatrophin and alpha-fetoprotein levels were increased in diabetic pregnant women and betatrophin and AFP are predictors of risk in pregnant women with diabetes.

Keywords: Betatrophin, Alpha-fetoprotein, Gestational diabetes mellitus, Pregnancy, T2DM.

1. Introduction

Diabetes mellitus (DM) is a severe health problem that has far-reaching consequences for global health and the economy (Alabbood& Marzoq, 2021). It develops as a result of insulin deficiency or resistance, with more young women being diagnosed during their reproductive years (Choudhury& Rajeswari, 2021). A local study of over 5400 people in the southern Iraqi city of Basrah found a 19.7 percent age-adjusted prevalence of diabetes in subjects aged 19 to 94 years (Mansour et al,2014). Diabetes is classified into three main types: type 1 diabetes (T1DM), type 2 diabetes (T2DM), and gestational diabetes mellitus (GDM) (Sole et al,2021). During pregnancy, diabetes can be T1DM, T2DM, or GDM (Choudhury& Rajeswari, 2021). Pregestational diabetes refers to type 1 and type2 diabetes that occurs before pregnancy (Muhas & Naseef, 2017). T2DM was found in 90–95 % of diabetes patients (Hong et al, 2020) and is recognized by hyperglycemia, insulin resistance, and insulin deficiency (Al-Hejaj, 2021). Gestational diabetes mellitus (GDM) is defined as glucose intolerance that begins or is first detected during pregnancy (Reitzle et al, 2021). Globally, the prevalence of GDM ranges from 5% to 25.5 %, depending on race, ethnicity, age, body composition, and screening and diagnostic criteria (Kim et al, 2021).

The availability of biomarkers that allow for early intervention (some as early as the first trimester). This is important since early intervention aims to improve future mothers' health. Also, reducing illness prevalence in succeeding generations (Giannubilo et al, 2022; Poon et al, 2018). Biomarkers are measurable biological characteristics to distinguish normal from pathological states or responses to a therapeutic drug given. Therefore, the sensitivity and specificity of a biomarker to the disease, are intended to indicate of utmost importance (Gan et al,2020).

Betatrophin (ANGPTL8) is a newly identified circulatory hormone secreted by the liver and adipose tissues, that is thought to promote cell proliferation (Luo & Peng, 2018). It is an important cytokine that is significantly increased in type 2 diabetes mellitus (T2DM), obesity, and metabolic syndrome. ANGPTL8 has been shown in numerous studies to be a biomarker for these metabolic disorders-related diseases (Guo et al, 2021).

Alpha-fetoprotein (AFP) is a plasma protein generated by the fetal liver and the embryonic yolk

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sac (Adigun et al, 2021). 35% of pregnant women with unexplained elevated AFP levels had at least one adverse perinatal outcome (Ozturk et al, 2014).
The present study aims to determine serum biochemical markers levels of betatrophin and alpha-fetoprotein in pregnant women with gestational or type 2 diabetes; to examine whether serum levels of these biomarkers are valuable for assessing disease severity, risk stratification, pregnancy outcomes; and also, to validate the diagnostic accuracy of parameters in GDM & T2DM diagnosis.

2. Methods

Our study involved 61 pregnant women who attended antenatal care services at Al- Fayhaa Teaching Hospital and Basrah for Women and Children Teaching Hospital, from October 2021 to February 2022. The medical histories were obtained by interviewing pregnant women who were prepared to participate in the study. The participants were divided into three groups (22 healthy pregnant women without diabetes mellitus (control),19 pregnant women with GDM, and 20 pregnant women with T2DM). Pregnant with any other chronic diseases were excluded from the study.
Fasting serum glucose and lipid profile concentrations were measured by colorimetric method, using a commercial Kit (The Architect Abbott C 4000 system \USA). Insulin was measured chemiluminescence technique (The Architect Abbott i1000\USA). Enzyme-linked immunosorbent assay kits (ELISA) were used to determine serum betatrophin and alpha-fetoprotein levels.

3. Statical Analysis

The SPSS software version 26 was used for statistical analysis. All collected data were expressed as mean ± standard deviation. The statistical significance level was $p< 0.05$.

4. Results

Table (1) showed significant increases (P-value <0.05) in BMI, fasting glucose, HOMA IR, TG, betatrophin, and alpha-fetoprotein in the diabetes group compared with the control group; while there were nonsignificant increases in levels of insulin hormone, total cholesterol, HDL-C, and LDL-C.

Table (1) Comparison between Control and Patients' Groups in 3rd Trimester of Pregnancy.

Variables	Control (n = 22) Mean ± SD	Diabetic patients (GDM&T2DM) (n=39) Mean ± SD	P. Value
Age	30.86±6.58	33.54±5.61	0.099
BMI (kg/m^2)	28.67±4.49	32.77±5.72	0.005*
Fasting glucose (mg/dl)	91.50±16.74	137.36±72.89	0.000*
Insulin (µIU/ml)	16.25±14.96	21.28±18.51	0.281
HOMA IR	3.94±4.39	7.31±7.09	0.026*
Total cholesterol (mg/dl)	207.36±35.55	206.03±53.68	0.907
Triglycerides (mg/dl)	195.50±59.91	256.87±127.92	0.014*
HDL-C (mg/dl)	53.12±10.50	56.98±15.64	0.306
LDL-C (mg/dl)	152.09±41.55	131.67±51.85	0.119
VLDL-C (mg/dl)	39.29±11.75	48.52±24.17	0.050*
Betatrophin (pg/ml)	345.16±199.07	582.56±249.25	0.000*
Alpha-fetoprotein (ng/ml)	67.88±52.44	36.98±19.90	0.014*
* = Significant; P-value <0.05.			

Table (2) revealed significant increases (P-value <0.05) in BMI, fasting glucose, and betatrophin in GDM and T2DM groups, while alpha-fetoprotein was significantly decreased ($p<0.05$) in comparison with the control group according to the 3rd trimester of pregnancy. On the other hand, data revealed that the insulin hormone, HOMA IR (P-value > 0.05) were non significantly different in GDM and T2DM groups in comparison with the control group. Lipid profile concentrations showed no significant differences compared with the control, according to the 3rd trimester of pregnancy.

Table (2) Comparison among Control, GDM, and Type 2 DM in the 3rd-Trimester of Pregnancy.

Variables	Control (n =22) Mean ±SD	GDM(n=19) Mean ± SD	T2DM (n= 20) Mean ± SD	P. value
Age (Years)	30.86±6.58	32.47±5.04	34.55±6.06	0.144
BMI (kg/m2)	28.67±4.50	34.01±7.22	31.60±3.63	0.008*
Fasting glucose (mg/dl)	91.50±16.74	129.16±41.09	145.15±94.32	0.015*
Insulin(µIU/ml)	16.25±14.96	22.06±23.87	20.54±12.01	0.541
HOMA IR (MCU/ml)	3.94±4.39	6.98±8.10	7.62±6.17	0.137
Total cholesterol (mg/dl)	207.36±35.55	212. 89±49.74	199.50±57.67	0.684
Triglycerides (mg/dl)	195.50±59.91	249.20±121.07	264.17±136.85	0.109
HDL-C (mg/dl)	53.20±53.12	60.07±60.07	54.05±54.05	0.243
LDL-C (mg/dl)	152.09± 41.44	134.53±51.03	128.95±53.80	0.281
VLDL-C (mg/dl)	39.30±11.75	48.64±24.70	48.41±24.30	0.258
Betatrophin (pg/ml)	345.16±199.07	589±264.44	576.44±240.68	0.002*
Alpha-fetoprotein (ng/ml)	67.88±52.44	34.77±20.05	39.07±20.05	0.007*
* Significant; P-value <0.05				

Regarding the type of disease, there were no significant differences between pregnant women

with GDM and pregnant women with T2DM in all parameters, table 3.

Table (3) Comparison between Patients with GDM and T2DM.			
Variables	GDM(n=30) Mean ± SD	T2DM(n=24) Mean ± SD	P. value
Age	31.43 ± 5.44	34.38 ±6.27	0.228
BMI (kg/m2)	32.68 ± 6.57	31.66 ± 3.68	0.751
Fasting glucose (mg/dl)	125.83 ± 42.39	154.33 ± 96.99	0.194
Insulin (µlu/ml)	22.64 ± 21.28	22.56 ±14.41	1.0
HOMA IR (MCU/ml)	7.02 ±7.39	8.63 ±7.03	0.659
Total cholesterol (mg/dl)	202.20±49.54	200±59.69	0.987
Triglycerides (mg/dl)	208.99 ±113.42	257.92 ±129.83	0.222
HDL-C (mg/dl)	54.56±14.99	54.64±16.81	1.0
LDL-C (mg/dl)	130.73±49.80	127.92±52.68	0981.
VLDL-C (mg/dl)	41.05±22.73	74.90±23.15	0.441
Betatrophin (pg/ml)	580.11±227.13	581.81±241.86	1.0
Alpha-fetoprotein (ng/ml)	31.79±20	36.85±20.97	0.876

The cut-off points and the corresponding validity test values (sensitivity & specificity) of parameters in the diagnosis of DM in the 3rd trimester of pregnancy were shown in table (4) and figure (1).

Table (4) Receiver-Operating Characteristic (ROC) Curve Analysis for the Diagnosis of DM in pregnancy.							
Variables	The area under the ROC curve (AUC)	P. Value (AUC0=0.5)	Best cut-off criterion	Sensitivity (%)	Specificity (%)	Positive Predictive value	Negative Predictive value
BMI (kg/m2)	0.694	0.012*	29.5	69.2%	59.1%	75%	52%
HOMA_IR	0.671	0.027*	3.6050	59%	59.1%	71.9%	44.8%
Glucose (mg/dl)	0.801	0.059 NS	92.5	82.9%	68.2%	82.9%	75%
Insulin (µIU/ml)	0.606	0.172 NS	11.62	69.2%	50%	71.1%	47.8%
AFP (ng/ml)	0.631	0.026*	43.64	56.4%	50%	66.7%	39.3%
Betatrophin (pg/ml)	0.797	0.000*	516.4	76.9%	72.7%	83.3%	64%

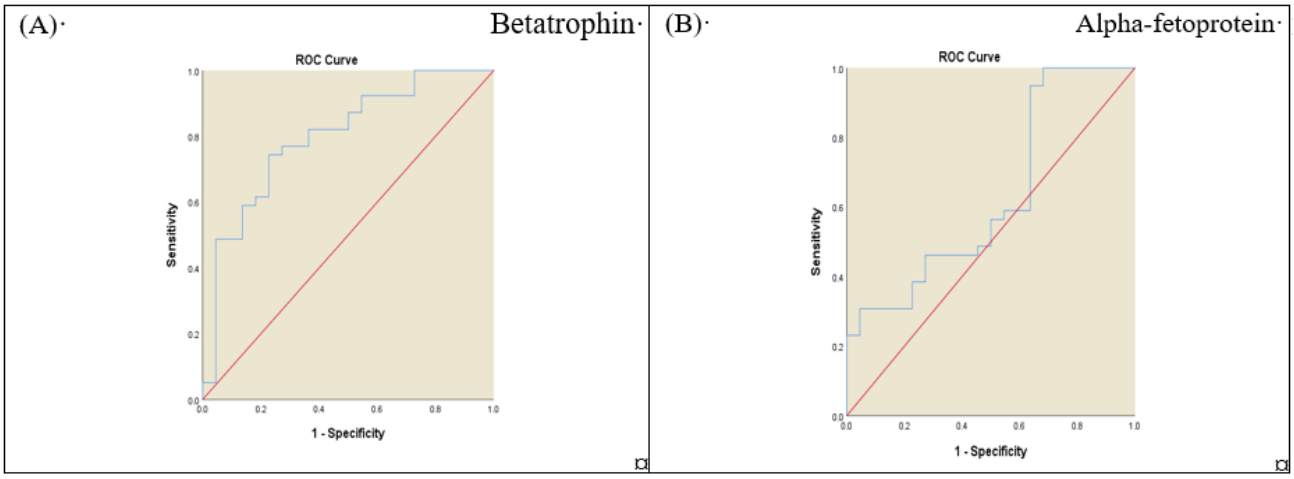

Figure (1) Receiver Operating Characteristic Curves, Showing the Area under the Curve of Betatrophin (A) and Alpha-fetoprotein (B) in Diabetes Patients.

Odds ratios were shown in Table (5), which indicated the predictive capacity of the model; glucose (1.072), and betatrophin (1.006).

Table (5) Logistic Regression Analysis of Diabetes in the 3rd Trimester of Pregnancy							
variable	Unadjusted odds ratio	S.E.	Wald	P.value	Adjusted odds ratio	95% C.I.for EXP(B)	
						Lower	Upper
Glucose (mg/dl)	.070	.024	8.527	0.003	1.072	1.023	1.123
Insulin (µIU/ml)	-.127-	.075	2.885	0.089	0.881	0.761	1.020
HOMA IR MCU\ml	.486	.250	3.758	0.053	1.625	0.995	2.655
AFP (ng/ml)	-0.027	0.011	6.463	0.011	0.973	0.953	0.994
Betatrophin pg/ml	0.006	0.002	9.637	0.002	1.006	1.002	1.010

5. Discussion

Betatrophin is a hepatogenic hormone that promotes the proliferation of pancreatic β- cells and is primarily expressed in the liver and adipose tissues, which is a sign of T2DM (Hao et al, 2021). According to the results of this study, there was a highly significant increase in the betatrophin hormone concentration in pregnant women in the diabetic group (GDM & T2DM) in comparison with

the healthy control groups. Several studies agreed with the present study results, such as (QU et al, 2017 and Xu et al, 2017). These studies had shown that betatrophin promotes insulin resistance. Fasshauer, (2015), pan et al, (2019), and Erol et l, (2015) reported that betatrophin was higher in GDM. An increase in betatrophin concentration compensates for insulin resistance because it increases the liver's secretory capability and β-cell mass (Abu-Farha et al,2016; Lee et al,2016). Al-Rawashdeh et al, (2017) discovered a relationship between betatrophin concentration and glycemic control indicators in T2DM patients. It appears to be linked to the development of type 2 diabetes (Abdeltawab et al,2021). There was a significant independent relationship between betatrophin and the prevalence of GDM. Also, a relationship between metabolic disorders and an increase in betatrophin concentration leads to GDM. A result of the close relationship between insulin resistance and betatrophin is attributed to the relationship between betatrophin concentration and GDM can be explained by (Abu-Farha et al, 2015). Some researchers have found that pregnant women with GDM have significantly higher levels of betatrophin than healthy controls (Abdeltawab et al,2021; Bulmus et al,2020). According to a previous study, increased levels of ANGPTL-8 during pregnancy may be responsible for pancreatic-cell proliferation and measuring its levels can help with early diagnosis and prediction of GDM development (Martinez-Perez et al, 2016). Furthermore, research had shown that betatrophin and insulin resistance are reliable predictors of T2DM. Insulin resistance is known to improve the progression and development of GDM. As a result, despite a lack of knowledge of its underlying etiology, insulin resistance is thought to be implicated in the interaction between GDM and betatrophin (Pan et al, 2019).

Our present study demonstrated that ROC curve circulation of betatrophin concentration had high sensitivity & specificity for the diagnosis biomarker for diabetes mellitus, as suggested by Yi et al, (2015). The ROC curve showed that the sensitivity and specificity of fasting plasma glucose in detecting diabetes in the group (10 -28) weeks of gestation was high, and this result agreed with (Sevket et al, 2013). The result obtained from the current study also showed a significant decrease in alpha-fetoprotein levels in the diabetes group compared to the pregnant control group. These results are consistent with a recent study by Hur et al, (2017); who showed the relationship between AFP and GDM in the early second trimester of pregnancy. Sahin and Kocak, (2019) revealed that serum AFP levels were higher in the T2DM group compared to the control group. Prenatal levels of AFP rise in developing human embryos at the end of the first trimester and fall after 32 weeks of gestation while (Sahin & Kocak, 2019). The precise pathophysiological mechanism of low AFP levels in patients with T2DM is unknown. Turgutalap et al, (2013) demonstrated that increased urinary protein loss due to diabetic nephropathy may result in low serum AFP levels in diabetic patients.

The AUC of AFP in predicting pregnancy outcomes of DM in the third-trimester group of gestation was 0.631 in our current, this agreed with a study by Huang et al, (2021).

The results of the current study also revealed that betatrophin had a risk of DM in the pregnant women group at 10-28 weeks of gestation and the third-trimester group as suggested by (Pan et al, 2019); also, triglyceride had a risk of DM in the third-trimester group of gestation as suggested Kim et al, (2021). A similar result was obtained from another study, which reported that AFP was one of the risk factors for DM in pregnant women (Huang et al, 2021).

6. Conclusions

There was a significant increase in betatrophin and a decrease in alpha-fetoprotein in the diabetic groups when compared to the control group, and they had high sensitivity & specificity for the diagnosis or assessment of diabetes mellitus status in pregnancy.

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Conflict of Interests

No conflict of interest regarding the publication of this paper.

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