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RESEARCH ARTICLE

Study The Association Between Betatrophin Level (Angiopoietin-Like Protein 8) And Insulin Resistance in Patients with Type 2 Diabetes

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ABSTRACT

Background: The exact relationship of betatrophin with insulin resistance remains controversial. Some studies report elevated betatrophin levels in insulin-resistant states, while others show inconsistent findings. Therefore, this study aims to investigate the association between betatrophin level and insulin resistance in T2DM patients, using marker homeostatic model assessment of insulin resistance (HOMA-IR); offering new insights into its potential as a biomarker for metabolic dysfunction or insulin resistance in T2DM. **Methods:** a case-control study and was conducted over a period of 12 months. A total of 100 participants were enrolled, including 50 patients with type 2 diabetes mellitus (T2DM) and 50 age and sex matched healthy controls. The diagnosis of patients with T2DM was established according to the American Diabetes Association (ADA) criteria. All parameters were estimations by standard methods. **Results:** Betatrophin levels were revealed significantly increase of betatropin, total cholesterol, triglyceride, low density lipoprotein, insulin and decrease high density lipoprotein in the T2DM patients group compared with the control group, ($p = 0.001$). Also, betatrophin showed 11600 area under the curve. **Conclusion:** Betatrophin levels was high in patients' group, and this association is likely mediated through insulin resistance.

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Introduction

Diabetes mellitus is a long- term metabolic condition marked by consistently high blood glucose levels due inadequate insulin production, the body's inability to use insulin effectively, or a combination of both. These factors can result in various health complications, such as heart disease, nerve damage, kidney failure, and vision impairment [1]. Type 2 diabetes mellitus (T2DM) makes up over 90% of all diabetes mellitus cases [2]. The main causes of type 2 diabetes mellitus include reduce insulin secretion by pancreatic beta cells and decreased insulin sensitivity in peripheral tissues, resulting in a progressive decline in natural insulin production [3].

Diabetes mellitus poses a global public health burden, as it is projected that the number of affected individuals will increase by an additional 200 million by 2040 [4]. Diabetes is responsible for over 1 million deaths annually, ranking as the ninth leading cause of mortality worldwide [5]. Type 2 diabetes mellitus is marked by high blood glucose levels due to the gradual decline in insulin- secreting β-cell function, often accompanied by varying levels of insulin resistance. In addition to these primary pathological mechanisms, other disruptions in glucose regulation, such as abnormal hyperglucagonemia and a compromised incretin response, are commonly present [6]. Following a healthy diet, staying physically active, keeping a normal weight, and stopping smoking can help prevent or delay the onset of diabetes [7]. Genetic factors contribute significantly to the onset of type

2 diabetes and elevate the likelihood of developing the condition. The risk of developing T2DM is approximately 40% if one parent has the disease, and it rises to 70% when both parents are affected.

Betatrophin is a protein that is mostly expressed in the liver and adipose tissues. It is also referred to as TD26, LPL inhibitor (lipasin), and ANGPTL8. Its primary function is in lipid metabolism, according to preliminary research. Betatrophin, also known as angiopoietin-like protein 8 (ANGPTL8), is a hormone consisting of 198 amino acids with a molecular weight of approximately 22 kDa. It functions as an adipokine involved in promoting the proliferation of pancreatic β-cells and plays a role in the regulation of lipid metabolism. Betatrophin plays a dual role in regulating glucose homeostasis and lipid metabolism. However, its function in glucose metabolism in humans remains debated. Multiple studies have reported elevated betatrophin levels in conditions such as insulin resistance, obesity, and type 2 diabetes Betatrophin, also referred to as TD26, LPL inhibitor (lipasin), and ANGPTL8, is a protein predominantly found in the liver and adipose tissues. Initial research has demonstrated that its primary function is regulating lipid metabolism [8]. The identification of betatrophin as a hormone represents a significant scientific advancement, as it enhances insulin resistance by promoting β-cell proliferation [8].

Materials and Methods

A case-control study, involved 50 patients with T2DM, were collected from Al- Fayhaa Teaching Hospital in Basra city, Iraq; and 50 healthy controls. All participants were interviewed during their current medical workup to collect important information, including; age, family history, weight, height, duration of illness and body mass index (BMI). Fasting blood glucose (FBG), triglycerides (TG), total cholesterol (TC) and high-density lipoprotein cholesterol (HDL) were measured using kits supplied by (Spainreact, Spain). Serum was stored at -20ºC deep freeze for others future determinations.

-Materials: ANGPTL8 tik (ELK Biotechnology, China).

- **Methods**: Specific biomarkers associated with diabetes and some chemical biomarkers. These were done by using standard techniques; Automated analyzer (Cobas Integra 400 Plus), ELISA.

Results:

The baseline of some characteristics of this study of both groups (patients & control) were presented in Table (1). The percipients ages range was between 45-65 years with a mean ±SD of 52.78 ± 5.26 for control and 54.2 ± 6.95 for patients. The results were showed significant statistical differences between diabetic patients and the control group regarding to most variables, except foe age, BMI, urea, creatinine and VLDL.

Table 1: general and biochemical characteristics of study participants:

Variables	T2DM Patients (N= 50) Mean± SD	Control Group (N= 50) Mean± SD	P. +Value
Age (Years)	54.2 ± 6.95	52.78 ± 5.26	0.252
BMI (Kg/M^2)	26.67 ± 1.92	25.93± 2.68	0.18
FBS (mg/dl)	221.00 ± 97.86	93.62 ± 6.68	< 0.001
Urea (mg/dl)	31.65 ± 11.39	29.4 ± 10.85	0.314
Creatinine (mg/dl)	0.92 ± 0.36	0.85 ± 0.27	0.253
Cholesterol (mg/dl)	195.52 ± 51.78	145.72 ± 49.91	0.001
Triglyceride (mg/dl)	195.79 ± 111.47	125.08 ± 38.44	0.001
HDL (mg/dl)	38.32 ± 10.8	46.71 ± 10.88	0.001
LDL (mg/dl)	116.18 ± 38.71	98.04 ± 43.19	0.029
VLDL (mg/dl)	37.27 ± 16.69	34.39 ± 12.73	0.334
Insulin (uU/mL)	27.38 ± 13.4	7.39 ± 3.14	0.001
HOMA- IR (mg/dl)	13.91 ± 7.62	1.91 ± 0.74	0.001
Betatrophin (ng/mL)	0.69 ± 0.89	0.38 ± 0.48	0.001

SD: Standard Deviation, P-value < 0.05 is significant.

Comparison of biochemical parameters between the age groups 45-55 years and 56- 65 years showed some statistical differences between patients and healthy controls (P < 0.05) as shown in the table (2).

Table 2: Comparison of biomarkers between age subgroups of patients.

Variables	Patients 45-55 (Years) (N= 26) Mean± SD	Patients 55-65 (Years) (N= 24) Mean± SD	P. Value
FBS (mg/dl)	172.39 ± 91.1	172.46 ± 107.23	0.997
Urea (mg/dl)	31.14 ± 11.24	29.63 ± 11.04	0.505
Creatinine (mg/dl)	0.85± 0.41	0.91 ± 0.49	0.577
T. Cholesterol (mg/dl)	176.66 ± 59.61	161.91 ± 51.02	0.188
Triglyceride (mg/dl)	166.98 ± 95.84	151.01 ± 81.76	0.373
HDL (mg/dl)	42.33 ± 11.71	42.78 ± 11.53	0.851
LDL (mg/dl)	106.84 ± 42.25	107.49 ± 41.7	0.94
VLDL (mg/dl)	36.18 ± 14.31	35.34 ± 15.73	0.787
Insulin (uU/mL)	17.76 ± 15.26	16.84 ± 11.98	0.735
HOMA- IR	8.24 ± 8.4	8.5 ± 9.05	0.882
Betatrophin (ng/mL)	0.5 ± 0.74	0.57 ± 0.72	0.632

Comparison between males and females'patients showed no significant statistical differences between the two groups.

Table 3: Differences of biomarkers between patients according to sex.

Variables	Females (N= 25) Mean± SD	Males (N= 25) Mean± SD	P. Value
BMI (Kg/M^2)	26.46± 3.81	26.88± 5.45	0.454
FBS (mg/dl)	155.52 ± 54.08	189.32 ± 125.31	0.083
Urea (mg/dl)	30.57 ± 12.51	30.47 ± 9.67	0.964
Creatinine (mg/dl)	0.85 ± 0.42	0.94 ± 0.44	0.180
Cholesterol(mg/dl)	177.64 ± 58.36	163.59 ± 54.13	0.215
Triglyceride (mg/dl)	150.23 ± 63.44	170.64 ± 110.53	0.261
HDL (mg/dl)	43.27 ± 10.09	41.76 ± 12.96	0.518
LDL (mg/dl)	111.73 ± 41.16	102.49 ± 42.36	0.272
VLDL (mg/dl)	33.74 ± 13.45	37.93 ± 15.97	0.159
Insulin (uU/mL)	18.08 ± 14.29	16.69 ± 13.72	0.621
HOMA- IR	7.52 ± 6.72	9.18 ± 10.19	0.338
Betatrophin (ng/mL)	0.55 ± 0.86	0.51 ± 0.57	0.762

The biomarker FBS had an area under the Tab le (4) and Figure (1) were shown the discriminative ROC curve (AUC) of 0.990, with a p-value of <0.001. This value means that the result is highly statistically significant. This strengthens confidence that FBS is an effective and reliable indicator. Insulin reported AUC of 0.992, with a p-value of <0.001. This value means that the result is highly statistically significant. HOMA- IR had an area under the ROC curve (AUC) of 0.958, with a p-value of <0.001. This value means that the result is highly statistically significant. Betatrophin reported AUC of 0.611, with a p. value of 0.187. This value means that the result was not significant.

Table 4: Receiver-operating characteristic (ROC) curve and area under the curve (AUC) analyses for the values of serum biomarkers for the diagnosis of T2DM (Insulin resistance).

Variables	Area under the ROC curve (AUC)	p-value (AUC0=0.5)	Sensitivity (%)	Specificity (%)
FBS (mg/dl)	0.990	< 0.001	1.000	1.000
Insulin (uU/mL)	0.992	< 0.001	1.000	1.000
HOMA- IR	0.958	< 0.001	1.000	1.000
Betatrophin (ng/mL)	0.611	0.187	1.000	1.000

DeLong method. AUC: Area Under the curve

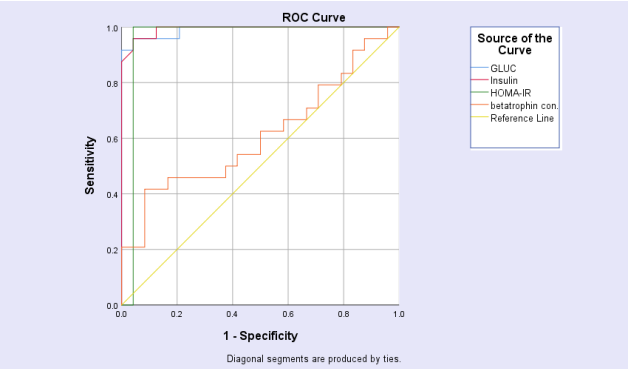

Figure1 Receiver-operating characteristic (ROC) curve and area under the curve (AUC) analyses.

Modeling of the biomarkers (identification of risk of type 2 diabetes) in a logistic regression model was shown in Table (5), that revealed no significant were reported. However, substantial increases of odd ratios were visualized for FBS (1.11), Insulin (3.22) and Betatrophin 2.25.

Table 5: Identification of risk of incident T2DM by multivariable logistic regression analysis for all Patients.

Variables	Regression coefficient	Standard error	Wald	P .Vale	Odds ratio	95% confidence Limits
FBS	0.11	0.05	4.247	0.039	1.11	1.01 - 1.23
Insulin	1.17	0.59	3.980	0.046	3.22	1.02 -10.17
Betatrophin	0.81	1.15	0.500	0.48	2.25	0.24 - 21.49

As shown in Table (6) there was no specific pattern of linear correlation was identified.

Table 6: Pearson Correlation Coefficient (r) among biomarkers included in the study.

Variables		FBG	TC	TG	HDL	LDL	Insulin	HOMA	Betatrophin
FBG	R*	1	-0.96	0.084	-0.64	-0.097	0.039	0.16	0.15
	P value	-	0.505	0.56	0.66	0.503	0.78	0.261	0.293
TC	R	-0.09	1	0.33	0.33	0.80	0.24	-0.14	0.029
	P value	0.50	-	0.01	0.019	0.001	0.86	0.92	0.84
TG	R	0.08	0.33	1	-0.41	0.24	0.08	0.17	-0.06
	P value	0.56	0.01	-	0.003	0.08	0.54	0.90	0.96
HDL	R	-0.06	0.33	-0.41	1	0.11	0.09	0.16	0.15
	P value	0.66	0.19	0.003	-	0.44	0.53	0.25	0.27
LDL	R	-0.097	0.8	0.247	0.11	1	0.002	-0.008	0.013
	P value	0.503	0.001	0.084	0.445	-	0.991	0.95	0.93
Insulin	R	0.039	0.024	0.088	0.091	0.002	1	0.868	0.143
	P value	0.786	0.867	0.54	0.53	0.99	-	0.001	0.322
HOMA	R	0.16	-0.014	0.017	0.163	-0.008	0.868	1	0.225
	P value	0.261	0.92	0.90	0.257	0.955	0.001	-	0.074
Betatrophin	R	0.15	0.029	-0.006	0.157	0.013	0.143	0.255	1
	P value	0.293	0.841	0.967	0.276	0.931	0.322	0.074	-

*Spearman's correlation coefficient

Statistical Analysis

The statistical analysis was performed using Data Tab and a P-value (<0.05) was considered statistically significant. Analyze the data to determine the association between gene polymorphisms and Biochemical Parameters. This can involve statistical tests such as chi-square, ANOVA, logistic regression and correlation analysis.

Discussions

Type 2 diabetes mellitus (T2DM) is one of the most significant healthcare challenges of the 21st century. It is resulting from both peripheral insulin resistance and decreased insulin production [9]. The rising prevalence of T2DM in older adults is largely due to an increase in risk factors [10]. Regarding lifestyle, sedentary behavior and a high- calorie, unhealthy diet are two key environmental factors contributing to obesity, insulin resistance, and T2DM [11]. The results were shown significant differences in all glycemic parameters including fasting blood glucose, fasting serum insulin and homeostasis model assessment of insulin resistance (HOMA-IR) between study groups, these results were compatible with Gandhi. *et al.* 2017, in which the fasting blood glucose and fasting serum insulin along with HOMA-IR were elevated in patients with T2DM [12].

The rise in insulin resistance are key factors that lead to higher blood glucose levels, as they promote increased glucose production in the liver and reduce glucose uptake by muscle and fat tissues [13]. In reaction to insulin resistance, the body compensates by increasing beta-cell production and releasing more insulin to counteract the elevated blood glucose levels associated with the condition [14]. Insulin resistance have been determined by the homeostatic model assessment for insulin resistance. HOMA-IR value represents the level of IR (opposes insulin sensitivity). The optimal insulin sensitivity when HOMA-IR is less than 1; while, levels above 1.9 signal early insulin resistance and levels above 2.9 signal significant IR [15]. The results of lipid profile showed a significant difference in total cholesterol, triglycerides and low-density lipoprotein cholesterol levels which was significantly higher in the diabetic group; while, HDL level was significantly lower in T2DM compared to the control group. Previous studies observed a notable rise in TG, TC, LDL levels and a reduction in HDL among diabetic patients with poor glycemic control, highlighting the crucial role of effective diabetes management in regulating dyslipidemia [16],[17].

Hyperlipidemia is considerably more common in individuals with type 2 diabetes compared to the healthy population. This condition is marked by increased levels of TG, TC and LDL-C; all of which elevate the cardiovascular risk in individuals with type 2 diabetes. Recognizing and comprehending the risk factors contributing to hyperlipidemia in individuals with type 2 diabetes is essential for enhancing patient outcomes and optimizing therapeutic strategies [18]. Insulin resistance (IR) is well- recognized for its impact on lipid metabolism. IR impairs insulin's ability to suppress lipolysis, leading to increased mobilization of free fatty acids. This, in turn, reduces insulin's capacity to inhibit the synthesis of hepatic lipoproteins [19], [20].

The results of kidney function showed no significant difference in urea and creatinine levels between diabetic patients and the control group, because the patients were newly diagnosed and patients with renal diseases were excluded. This study was agreed with the study by Batool *et al*., (2024). Unfortunately, diabetic patients are at a higher risk of kidney damage due to diabetic nephropathy. Maintaining a balanced lifestyle with controlled blood glucose and hypertension can reduce the likelihood of developing diabetic nephropathy [21].

Betatrophin, a member of the angiopoietin family, is a circulating hormone produced by the liver. It plays a role in stimulating the proliferation of pancreatic β-cells and regulating lipid metabolism [23]. The results of betatrophin levels were showed significantly higher in the diabetic group, compared to control group. As a result, serum betatrophin levels can serve as a significant predictor of type 2 diabetes [23]. There has been increasing interest in betatrophin as a potential treatment for β-cell regeneration in diabetes [23]. Betatrophin showed non- significant highly sensitivity and specificity as diagnostic biomarker for T2DM or insulin resistance, that may due to rather small sample size. Also, the results were revealed no significant differences in all biochemical parameters between males and females. Therefore, it can be inferred that the biochemical parameters not effected by sex. Gender is crucial in understanding the development of diabetes and its associated complications. Sex hormones contribute to these differences by influencing glucose regulation, insulin secretion, and action, as well as affecting disease progression and complications. A comprehensive understanding of the interactions between the endocrine system and metabolic homeostasis is essential [24].

Conclusion:

In this study, betatrophin levels were significant elevated in patients with type 2 diabetes mellitus (T2DM). Betatrophin showed non- significant highly sensitivity and specificity. There is positive correlation between betatrophin levels and both fasting blood glucose and homeostatic model assessment of insulin resistance (HOMA-IR). Therefore, measuring of betatrophin may be useful as predictor for T2DM or insulin resistance.

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The authors declare no conflict of interest.

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