

Study of Serum Betatrophin Level in The Patients of Type 2 Diabetes Mellitus

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ABSTRACT

Background: Type 2 DM is due primarily to lifestyle and genetic factors. A number of lifestyle factors are known to be important to the development of type 2 DM. Betatrophin, also known as angiopoietin-like protein (ANGPTL8), is a circulating protein predominantly produced in the liver and adipose tissue. Betatrophin is induced as a result of insulin resistance. It is reported to modulate pancreatic β -cell mass and glucose homeostasis reflectable on lipid metabolism.

Aim of the Study: Evaluation of the role of betatrophin in patients with type 2 diabetes mellitus.

Patients and Methods: This clinical study was carried out at Clinical Pathology Department, Tanta University Hospital and included 80 subjects who were divided into two groups: Group 1:40 Patients diagnosed with type 2 diabetes mellitus. Group 2: 40 normal subjects with matched age and sex as a control group.

Results: In type 2 diabetes mellitus patients group, serum betatrophin ranged from 25.83 to 860.65 ng/l with a median value of 54.815 ng/l while in control group, betatrophin ranged from 7.5-53.2 ng/l with a median value of 11.250 ng/l. There was significant statistical difference in betatrophin between the two groups. ($P < 0.001$). Betatrophin was significantly higher in type 2 diabetes mellitus patients as compared to control group.

Conclusion: Circulating betatrophin concentrations were significantly increased in patients with T2 DM and associated with glucose homeostasis and insulin sensitivity. Thus, the level of serum betatrophin has a potential role in detection and pathogenesis of T2DM.

Keywords: betatrophin, type 2 diabetes mellitus.

INTRODUCTION

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin action, insulin secretion, or both. The chronic hyperglycemia of diabetes leads to long-term damage, dysfunction, and failure of various organs, especially the kidneys, eyes, heart, nerves, and blood vessels⁽¹⁾.

Symptoms of marked hyperglycemia include polydipsia, polyuria, weight loss, sometimes with polyphagia, and blurred vision. Acute life threatening complications of uncontrolled diabetes are hyperglycemia with ketoacidosis or the non ketotic hyperosmolar syndrome.

Long-term consequences of diabetes include nephropathy causing renal failure, peripheral neuropathy with a risk of foot ulcers, amputations, retinopathy with potential loss of vision.

Also, autonomic neuropathy leading to gastrointestinal, genitourinary, and cardiovascular symptoms and sexual dysfunction.

Patients of diabetes have an increased incidence of atherosclerotic cardiovascular, peripheral arterial and cerebrovascular disease. Hypertension and abnormalities of lipoprotein metabolism are often found in people with diabetes⁽²⁾.

Type 2 DM previously known as non-insulin dependent diabetes, or adult-onset diabetes, accounts for about 85% of diabetic cases⁽³⁾.

The pathophysiology of type 2 DM is complex. It depends on three major abnormalities:

1. Insulin resistance in peripheral tissue, (defined as decreased biological response to normal concentrations of circulating insulin), especially fat, muscle, and liver.
2. Impaired insulin secretion.
3. Excess glucose production by liver.

A combination of multiple genetic and environmental factors contributes to the pathogenesis of type 2 diabetes (T2DM)⁽⁴⁾.

Betatrophin Protein belongs to angptl family which consists of eight members (angpt 1 to angptl 8). This protein is an atypical ANGPTL protein as it lacks the fibrinogen-like domain and only possesses the N-terminal coiled-coil domains⁽⁵⁾.

Betatrophin, angiopoietin-like protein (ANGPTL-8) or lipasin secreted from the liver and adipose tissue controversially was reported to modulate pancreatic β -cell mass and glucose homeostasis reflectable on lipid metabolism⁽⁶⁾.

Lipoprotein lipase (LPL) is determining in the disposal of plasma TAGs where its dysregulation increased incidents of cardiovascular disease and T2DM. One of the key regulators of LPL is betatrophin⁽⁷⁾.

Betatrophin may be responsible for the increased plasma TAGs levels in obese and T2DM⁽⁸⁾.

Betatrophin protein, also known as hepatocellular carcinoma-associated protein TD26. It has been identified as a specific hormone that promotes pancreatic β cell proliferation and lipid regulation⁽¹¹⁾.

AIM OF THE WORK

The aim of this study is to gauge the role of betatrophin in patients with type two diabetes mellitus.

SUBJECTS AND METHODS

This clinical study was carried out at Clinical Pathology Department, Tanta University Hospital and included 80 subjects who were divided into two groups:

Group 1: 40 patients diagnosed with type2 diabetes mellitus.

Group 2: 40 normal subjects with matched age and sex as a control group.

All patients were selected from Internal Medicine Department in Tanta University.

The study was conducted during 2018.

Inclusion Criteria

1. Patients with age ranging from 20-60 years.
2. Patients diagnosed as type2 diabetes mellitus.

Exclusion Criteria

Patients with infection, cardiac, renal and liver disease, prior malignancy and pregnant patients were excluded.

All participants were subjected to the following parameters:

1. Full history taking.
2. Clinical examination.
3. Laboratory Investigations including:

❖ **Routine investigations:**

1. Fasting and two hours postprandial blood glucose level.
2. liver function tests.
3. lipid profile including total cholesterol, HDL cholesterol, LDL cholesterol and serum triglycerids.
4. HbA1c.
5. HOMA insulin resistance.

❖ **Specific investigation:**

6. Serum betatrophin level using ELISA technique
Written informed consent was taken from all participants in this research.

Methods

A) Routine investigation:

1-Liver functions, fasting, post prandial blood glucose, cholesterol, triglycerides, LDL and HDL levels were analyzed by automated chemistry analyzer, random access (INDIKO PLUS).

2- Estimation of glycated Hb:

Kit provided by (Biosystem Company), Catalog No. (254 002)

Statistical analysis

Statistical presentation and analysis of this study was conducted, using the mean, standard deviation and chi-square test by SPSS V.20.

RESULTS

This study was conducted on 80 subjects divided into two groups as follow:

- I) Group 1:** 40 Patients diagnosed with type 2 diabetes mellitus.
- II) Group 2:** 40 normal subjects as a control group.

• **Demographic data**

As regards sex, the patients group included 18 males and 22 females, and control group contained 21 males and 19 females. There was no significant statistical difference between the studied groups according to gender (P = 0.502) (**Table 1**).

Regarding age, in patients group, it ranged from 26 to 69 years with a mean of 45.075 ± 10.133 years old, while in control group, it ranged from 21 to 64 years with a mean of 43.7±12.759 years old with no statistical significant difference (P = 0.595). (**Table 1**)

Table (1): Sex and age of the studied groups.

Age	Groups						T-Test	
	Patients			Control			t	P-value
Range	26	-	69	21	-	64	0.534	0.595
Mean ± SD	45.075	±	10.133	43.700	±	12.759		
Sex	Groups						Chi-Square	
	Patients		Control		Total		X ²	P-value
	N	%	N	%	N	%		
Male	18	45.00	21	52.50	39	48.75	0.450	0.502
Female	22	55.00	19	47.50	41	51.25		
Total	40	100.00	40	100.00	80	100.00		

Laboratory data:**I. Blood glucose, glycated hemoglobin (HbA1c) and HOMA IR levels:**

In type2 diabetes mellitus patients group, the mean fasting blood glucose (FBG) level was 165.350 ± 44.846 mg/dl. In control group, the mean fasting blood glucose was 86.375 ± 9.486 mg/dl. Statistical analysis showed significant difference between values of fasting blood glucose levels between the two studied groups (P value < 0.001) (**Table 2**).

In type2 diabetes mellitus patients group, the mean postprandial blood glucose (PPBG) level was 236.400 ± 48.344 mg/dl. In control group, the mean postprandial blood glucose level was 127.300 ± 9.809 mg/dl. Statistical analysis showed significant difference between values of postprandial blood glucose levels among the studied groups (P value < 0.001) (**Table 2**).

In type2 diabetes mellitus patients group, the mean glycated hemoglobin (HbA1c) level was (8.394 ± 0.998 %) ranging from. In control group, the mean glycated hemoglobin (HbA1c) level was (4.855 ± 0.446 %). Statistical analysis showed significant difference between values of glycated hemoglobin (HbA1c) among the studied groups (P value < 0.001) (**Table 2**). In type 2 diabetes mellitus patients group, the mean Homeostatic Model Assessment Insulin Resistance (HOMA IR) level was 2.890 ± 0.694 % ranging from 1.9-4.5 %. In control group, the mean Homeostatic Model Assessment Insulin Resistance level was 0.588 ± 0.240 % ranging from 0.2-1 %. Statistical analysis showed significant difference between values of Homeostatic Model

Assessment Insulin Resistance (HOMA IR) among the studied groups (P value < 0.001) (**Table 2**).

II. Lipid profile:

In type2 diabetes mellitus patients group, the mean serum cholesterol level was 251.250 ± 57.538 mg/dl ranging from 155-440 mg/dl. In control group, the mean serum cholesterol level was 153.125 ± 23.136 mg/dl ranging from 112-196 mg/dl. Statistical analysis showed significant difference between values of serum cholesterol levels between the studied groups (P value < 0.001) (**Table 3**).

In type2 diabetes mellitus group, the mean serum triglycerides level was 186.475 ± 42.194 mg/dl ranging from 140-373 mg/dl. In control group, the mean serum triglycerides level was 98.375 ± 18.209 mg/dl ranging from 65-125 mg/dl. A significant statistical difference was found between the two studied groups (P value < 0.001) (**Table 3**).

In type 2 diabetes mellitus group, HDL level ranged from 34-45 mg/dl with a mean value of 39.775 ± 4.003 mg/dl, while in control group, HDL ranged from 43-66 mg/dl with a mean value of 54.475 ± 5.840 mg/dl. There was a significant statistical difference among the studied groups (P value < 0.001) (**Table 3**). In type2 diabetes mellitus group, low-density lipoprotein (LDL) ranged from 84.4-321.4 mg/dl with a mean value of 173.855 ± 51.146 mg/dl, while in control group, LDL ranged from 34.8-127 mg/dl with a mean value of 78.753 ± 25.410 mg/dl. There was a significant statistical difference between the studied groups (P value < 0.001) (**Table 3**).

Table (2): Blood glucose, glycated hemoglobin (HbA1c) and HOMA IR levels among the studied groups
 $P < 0.05$ * \rightarrow Significant

Variables	Groups				T-Test	
	Patients		Control		t	P-value
FBG (mg/dl)						
Mean \pm SD	165.350	\pm 4.846	86.375	\pm 9.486		
PPBG (mg/dl)						
Mean \pm SD	236.400	\pm 48.344	127.300	\pm 9.809		
HBA1c (%)						
Mean \pm SD	8.394	\pm 0.998	4.855	\pm 0.446		
HOMA IR (%)						
Mean \pm SD	2.890	\pm 0.694	0.588	\pm 0.140		

Table (3): Lipid profile of the studied groups:

Variables	Groups				T-Test	
	Patients		Control		t	P-value
Cholesterol (mg/dl)						
Mean \pm SD	251.250	\pm 7.538	153.125	\pm 23.136		
Triglycerides (mg/dl)						
Mean \pm SD	186.475	\pm 2.194	98.375	\pm 8.209		
HDL (mg/dl)						
Mean \pm SD	39.775	\pm 4.003	54.475	\pm 5.840		
LDL (mg/dl)						
Mean \pm SD	173.855	\pm 5.146	78.753	\pm 5.410		

II. Betatrophin (ng/l) among the two studied groups:

In type 2 diabetes mellitus patients group, serum betatrophin showed a median value of (54.815 ng/l) while in control group, betatrophin median value was

11.250 ng/l. There was significant statistical difference in betatrophin between the two groups ($P < 0.001$). Betatrophin was significantly higher in type 2 diabetes mellitus patients as compared to control group. (**Table 4**).

Table (4): Betatrophin (ng/l) between the two studied groups

Betatrophin (ng/l)	Groups				Mann-Whitney Test	
	Patients		Control		Z	P-value
Median (IQR)	54.815	7.813	11.250	2.025		

• **Correlation between Betatrophin and the studied parameters in the two groups:**

- There was a significant positive correlation between betatrophin and FBG in type2 DM (**Table 5**).
- There was a significant positive correlation between betatrophin and PPBG in type2 DM. (**Table 5**).
- There was a significant positive correlation between betatrophin and HOMA IR in type2 DM (**Table 5**).
- There was a significant positive correlation between betatrophin and Hb A1c (**Table 5**)
- There was a significant positive correlation between betatrophin and t
- riglycerides. (**Table 5**).

Table (5): Correlation between Betatrophin and the studied parameters in the two groups

Correlations		
	B. Trophin (ng/l)	
	r	P-value
Age	-0.281	0.079
FBG (mg/dl)	0.968	<0.001*
PPBG (mg/dl)	0.671	<0.001*
HOMA IR (%)	0.757	<0.001*
Cholesterol (mg/dl)	0.255	0.113
Triglycerides (mg/dl)	0.635	<0.001*
HDL (mg/dl)	-0.170	0.296
LDL (mg/dl)	0.256	0.110
Albumin (g/dl)	-0.170	0.295
ALT (u/l)	0.096	0.557
AST (u/l)	0.150	0.354
T. Bilirubin (mg/dl)	0.157	0.332
D. Bilirubin (mg/dl)	0.201	0.214
HbA1c (%)	0.782	<0.001*

Table (6): Receiver Operating Characterestic Curve

ROC curve between Patients and Control					
Cutoff	Sens.	Spec.	PPV	NPV	Accuracy
>34.2	97.50	92.50	92.9	97.4	97.5%

Table (6) showed a cut off value of betatrophin equal 34.2 ng/l discriminating between patients group from control group, with a sensitivity of 97.5%, specificity of 92.5%, accuracy of 97.5%, positive predictive value of 92.9% and negative predictive value of 97.4%.

DISCUSSION

Diabetes mellitus is one of the commonest endocrine disorders encountered in clinical practice. It is characterized by hyperglycemia due to an absolute or relative lack of insulin and/or insulin resistance. Chronic hyperglycemia of diabetes leads to long-term damage, dysfunction, and failure of various organs, especially the eyes, kidneys, nerves, heart and blood vessels ⁽¹⁰⁾.

Type 2 DM was first described as an element of metabolic syndrome in 1988. Type 2 DM (formerly known as non-insulin dependent DM) is the most common form of DM characterized by hyperglycemia, insulin resistance, and relative insulin deficiency. Type 2 diabetes mellitus (T2DM) is the predominant form of diabetes and accounts for at least 90% of all cases of diabetes mellitus. It is caused by a combination of genetic factors related to impaired insulin secretion, insulin resistance and environmental factors such as obesity, over eating, lack of exercise, and stress as well as aging ⁽¹¹⁾. Type 2 Diabetes is sometimes a part of the metabolic syndrome, which is associated with alternative risk factors from early in the disease process, including abdominal obesity, high blood pressure, dyslipidaemia, a prothrombotic state and insulin resistance. Although macrovascular disease is the major cause of morbidity and mortality in type 2 diabetes, microvascular complications are often present when diabetes is diagnosed, even in people with no symptoms ⁽¹²⁾.

The present study showed no significant difference in age (years) distribution between the two groups.

As regards gender in the present study, type 2 DM group included 18 males and 22 females and control group included 21 males and 19 females. There was no significant difference in sex distribution between the 2 groups. This is in accordance with previous study by **Yamada *et al.*** ⁽¹³⁾ who found that there was no significant difference in sex between the two groups.

In present study, Fasting blood glucose mean values were 165.350 ± 44.846 and 86.375 ± 9.486 in type 2 DM group and control group respectively. FBG was significantly higher in type 2 diabetes mellitus patients as compared to control group.

In type 2 diabetes mellitus group, post prandial blood glucose (PPBG) level was significantly higher in type 2 diabetes mellitus patients as compared to control group. This is in agreement with **Hu *et al.*** ⁽¹⁴⁾ who stated that FBG and PPBG were significantly increased in type 2 DM when compared to the control group.

In present study, in type 2 diabetes mellitus group, glycated hemoglobin (Hb A1c) was significantly higher in type 2 diabetes mellitus patients as compared to control group.

Plasma (or serum or blood) glucose concentrations have been used in the diagnosis of T2DM and therefore, estimates of T2DM prevalence and incidence have been primarily dependent on glucose measures. In the past few years, HbA_{1c}, a measure of average glycemia over the previous 8–12 weeks has been recommended as an alternative means for the diagnosis of T2DM by the WHO ⁽¹⁾ and the American Diabetes Association (ADA) ⁽¹⁵⁾. Among individuals without T2DM, increasing HbA_{1c} level is associated with not only future risk of T2DM but also a substantially increased risk of incident cardiovascular events and deaths ⁽¹⁶⁾. The cut-off of HbA_{1c} of $\geq 6.5\%$ for the diagnosis of diabetes mellitus, as recommended by the ADA and WHO, was derived based on the association between HbA_{1c} and prevalent retinopathy. The decision to use this threshold based on data from a study, which pooled data from ~ 45,000 participants from five countries and showed a narrow threshold range for HbA_{1c} at which risk of diabetes-specific retinopathy (moderate non proliferative and more severe retinopathy) increases significantly ⁽¹⁷⁾.

In present study, HOMA IR was significantly higher in type 2 diabetes mellitus patients as compared to control group. The homeostatic model assessments (HOMA) are well recognized methods for estimating β -cell function of pancreas and how well insulin is utilized by its target cell populations. HOMA-IR is a measure for insulin resistance. It is important in discerning diabetes type ⁽¹⁸⁾.

Higher HOMA-IR values reflect higher IR wherever the body is producing enough insulin, but the insulin produced is not effectively controlling plasma glucose levels; a characteristic of T2DM. A value of 3 indicates moderate insulin resistance and a value of 5 indicates severe insulin resistance ⁽¹⁹⁾.

Yi *et al.* ⁽²⁰⁾ stated that HOMA IR percentage and HbA_{1c} were significantly increased in type 2 DM when compared with the control group. This correlates with the result of the present study.

In present study, 23.136. Serum cholesterol was significantly higher in type2 diabetes mellitus patients as compared to control group. Also, serum triglycerides was significantly higher in type 2 diabetes mellitus patients as compared to control group.

Besides, serum HDL was significantly lower in type 2 diabetes mellitus patients as compared to control group. In addition, serum LDL was

significantly higher in type 2 diabetes mellitus patients as compared to control group. **Ghasemi et al.** ⁽²¹⁾ stated that serum cholesterol, serum triglycerides level and low-density lipoprotein were significantly increased in type 2 DM, while serum high-density lipoprotein was significantly decreased in type 2 DM when all of them was compared to the control group. This correlates with the result of the present study.

In diabetes several factors might have an effect on blood lipid levels, because of interrelationship between carbohydrates and lipid metabolism. Therefore, any disorder in carbohydrate metabolism causes disorder in lipid metabolism and vice versa. Insulin resistance is a primary defect in the majority of patients with T2DM. In non-diabetic individuals insulin resistance in combination with hyperinsulinemia has a strong predictive value for future development of type 2 diabetes ⁽²²⁾.

Several studies showed that insulin hormone affects the liver apolipoprotein production and regulates the catalytic activity of lipoprotein lipase and cholesterol ester transport protein, which causes dyslipidemia in diabetes mellitus. Moreover, insulin deficiency reduces the activity of hepatic lipase and several steps in the production of biologically active lipoprotein lipase ⁽²³⁾.

Hypertriglyceridemia sometimes accompanies decreased HDL cholesterol, which is also a prominent feature of plasma lipid abnormalities seen in individuals with diabetes ⁽²⁴⁾.

The cluster of lipid abnormalities related to T2DM is defined by a high concentration of TG and small dense LDL and a low concentration of HDL cholesterol. The association between reduced HDL cholesterol levels and increased risk of heart disease is, on the other hand, well established, independently of TG levels and other risk factors ⁽²⁵⁾.

The possible mechanism responsible for hypertriglyceridemia may be due to increased hepatic secretion of very low density lipoprotein (VLDL) and delayed clearance of triglyceride rich lipoproteins, which is predominantly due to increased levels of substrates for triglyceride production, free fatty acids and glucose ⁽²⁶⁾.

The notion that betatrophin might interfere with the compensative response to insulin resistance has raised hope for new diabetes therapy in humans. However, other studies found that mouse betatrophin has no effect on human beta cell proliferation and differentiation ⁽²⁷⁾.

Overexpression and silencing of the betatrophin gene in mice do not support a job for

this hormone in controlling beta cell growth but point to a clear function in controlling plasma lipid profiles ⁽²⁸⁾.

In present study, in regard to type 2 diabetes mellitus group, serum betatrophin was significantly higher in type 2 diabetes mellitus patients as compared to control group. **Abu-Farha et al.** ⁽⁸⁾ and **Hu et al.** ⁽¹⁴⁾ stated that serum betatrophin levels were significantly increased in type 2 diabetic patients compared to non-diabetic subjects. This correlates with the results of the present study.

In contrast to the present study, **Fenzl et al.** ⁽²⁹⁾ stated that serum betatrophin levels did not differ significantly between non-diabetic and T2DM subjects. These maybe due to the different sample size in the study by **Fenzl et al.** from the sample size in the present study and the subjects in the study by Fenzl et al. showed higher BMI and a different ethnicity. More importantly, the diabetic patients in the study by **Fenzl et al.** had taken oral hypoglycemic drugs (metformin_ sulfonylureas), which would potentially affect the levels of betatrophin because the main effect of metformin is to reduce insulin resistance. Also may be due to different disease duration of T2DM ⁽¹⁴⁾. **Gomez et al.** ⁽³⁰⁾ stated that serum betatrophin levels decreased in people with T2D and this disagrees with the present study. One of the main reasons for the different results reported by these two groups is likely the different ELISA kit they used.

In present study, there was a significant positive correlation between betatrophin and FBG, PPBG and HbA1c in type 2 DM. **Hu et al.** ⁽¹⁴⁾ stated that there was a significant positive correlation between betatrophin and FBG, PPBG and HbA1c in type 2 DM. This correlates with the result of the present study. While **Wang et al.** ⁽³¹⁾ stated that no relationships between betatrophin and glycemic control indices such as FBG and HbA1c. Suggesting that betatrophin might not play a very important role in controlling glucose homeostasis, which had been proved in mice models by Wang and his colleagues. They reported that mice knocked out for ANGPTL8/betatrophin showed no change in glucose homeostasis once fed either chow or high fat diet. Then, **Gusarova and his colleagues** ⁽²⁷⁾ more confirmed this issue by overexpressing betatrophin in mice livers and observed no important alteration in β -cell growth nor glucose metabolism. Nevertheless, these results were obtained from diet or S961-induced insulin resistant mice models; the role of betatrophin on β -cell growth under additional extreme conditions of β -cell destruction is still under a veil. Furthermore, the results in mice cannot be absolutely applied to

humans. **Jiao *et al.*** ⁽²⁸⁾ observed that betatrophin of mice failed to induce human β cell replication, which raised a possibility that mouse and human betatrophin might undergo different post-translational processing.

In present study, there was a significant positive correlation between betatrophin and HOMA IR in type 2 DM. This is in agreement with previous study by **Chen *et al.*** ⁽³²⁾ who showed that there was positive correlation between betatrophin and index of insulin resistance including HOMA-IR. However, it is not clear whether increased betatrophin expression is a compensatory response or only a marker of insulin resistance. It is possible that betatrophin would be increased only when the degree of insulin resistance reaches a certain threshold as a compensatory response. However, it could not be excluded that the elevated betatrophin levels may be associated with other unknown factors of diabetes, which may affect insulin resistance.

In present study, there was a significant positive correlation between betatrophin and triglycerides in type 2 DM. **Ghasemi *et al.*** ⁽²¹⁾ in a previous studies stated that there was a positive correlation between betatrophin and triglycerides in type 2 DM. This correlates with the result of the present study. Betatrophin affects TG metabolism by inhibiting lipoprotein lipase (LPL) activity and thereby increasing the TG level ⁽¹⁵⁾. This finding is in line with the results of work in betatrophin knockout mice, which had a lower serum TG concentration than did the wild type ⁽³¹⁾. **Abu-Farha *et al.*** ⁽⁸⁾ in contrast to this present study stated that there was no correlation between betatrophin and HOMA IR and also no correlation between betatrophin and triglycerides in T2DM patients.

CONCLUSION

Circulating betatrophin concentration was significantly increased in patients with T2DM and was associated with glucose homeostasis and insulin sensitivity. Thus the level of serum betatrophin has a potential role in detection in the pathogenesis of T2DM.

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