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Study of Serum Betatrophin Level as a Biochemical Marker in Patients with Type-2 Diabetes Mellitus

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ABSTRACT

Background: Type 2diabetes mellitus [T2DM] is a global health problem with high morbidity and mortality. Betatrophin is a novel circulating protein produced by the adipose tissue and the liver. It is a newly identified endocrine regulator associated with insulin resistance [IR], metabolism of lipid and glucose homeostasis. It increase under states of IR to increase the proliferation of β-cell and stimulate insulin secretion.

The Aim of The Work: The study aim is to evaluate the serum betatrophin-levels in normal and in subjects with diabetes .To investigate the association of betatrophin with IR and other study parameters.

Patients and Methods: Forty nine patients with T2DM [different ages and both sex] and forty healthy subjects [sex and age matched] as a control group were included in the study. Betatrophin was measured using Human Betatrophin ELISA Kit. Fasting blood glucose [FBG], lipid profile, fasting insulin, glycated hemoglobin, serum creatinine, albumin -creatinine ratio [ACR] and protein to creatinine ratio [PCR] in urine were assessed.

Results: Betatrophin was higher in patients with diabetes than in the control group. In the group with diabetes, serum betatrophin level ranged from 18-25.5ng/l with a median value of 20, while in the control group betatrophin level ranged from 15-19 ng/l with a median value of 18 [P< 0.001]. Betatrophin at a cut off ≥ 19.5 ng/ml can discriminate patients with DM from non-DM participants [AUC=0.75, P <0.001] being specific rather than sensitive.

Conclusion: The concentrations of betatrophin were significantly increased in patients with diabetes and were further increased in parallel to the decrease in the beta cell function. Thus, the level of serum betatrophin plays a potential role in the pathogenesis and detection of T2DM.

Keywords: Insulin Resistance; Diabetes Mellitus; Adipose Tissue; Betatrophin.

INTRODUCTION

Diabetes mellitus [DM] is a metabolic disease results from insulin action or secretion defects. It is a worldwide chronic pandemic disease associated with many complications [1].

It is the leading cause to blindness, end-stage renal disease and stroke [2].

DM affects more than 170 million people and by 2030 nearly 370 million people will be affected [3].

T2DM present in 90% of adults with DM [4].The rising incidence is presumably due to rapid urbanization, population growth, aging, increased obesity, physical inactivity and changing dietary habits [4].

Betatrophin is a protein secreted from liver and adipose tissue [white and brown adipose tissue]. It is composed of 198 amino acids [5].

This protein has been given many names; as Angiopoietin-like protein 8 [ANGPTL8], "hepatocellular carcinoma-associated gene" [TD26], "refeeding induced in fat and liver" [RIFL] and "lipasin" [6].

ANGPTL8 regulate the lipoprotein lipase activity, which is a key enzyme in pathways of lipoprotein lipolysis [7].

Betatrophin is an endocrine regulator of insulin resistance [IR], metabolism of lipids and glucose homeostasis, which all are thought to be involved in the pathogenesis of T2DM complications [8].

Betatrophin increase β cell proliferation and insulin secretion in IR [9].

It was significantly elevated in nonalcoholic fatty liver disease [NAFLD] due to endoplasmic reticulum stress [10].

In women, it could offer a prediction for polycystic ovarian syndrome [PCOS] [11].

THE AIM OF THE WORK

The study aim is to evaluate the serum betatrophin-levels in normal and in subjects with diabetes .To investigate the association of betatrophin with IR and other study parameters

PATIENTS AND METHODS

This study is a case–control study included 49 patients with T2DM with mean age of 56.6 ± 10 years [17 males and 32 females].

Patients were selected from the Mansoura University Hospital, Faculty of Medicine, Egypt, from April 2019 to March 2020. Also, 40 healthy controls were also selected from the same locality [matched for sex and age]. Informed consent from all participants were obtained and approval was given by the ethics committee in our institution.

DM was diagnosed according to the American Diabetes Association criteria [12].

Patients who refuse participation in the study, patients with malignancy, liver failure patients, end-stage renal diseases patients, patients with type1diabetes and patients with chronic inflammatory conditions as systemic lupus and rheumatoid arthritis were excluded from the study.

Full history was taken from all participants and clinical examination was done. Body mass index [BMI] as weight in kilograms divided by height in meters squared [kg/m^2] was calculated [13].

Blood pressure was taken by a random-zero sphygmomanometer in the sitting position.

Venous blood samples were collected after overnight fasting. FBG, lipid profile, liver functions, kidney functions, complete urinalysis and protein excretion in urine as ACR and PCR were measured.

Serum insulin was assayed using ELISA kits [supplied by ImmunoScape Corporation [Netherland]].

Calculation of homeostasis model assessment- insulin resistance [HOMA-IR]:

HOMA-IR = FBG [mg/dl] x fasting insulin [mIU /ml]/ 405;

HOMA of β-cell function [HOMA-B %] and HOMA of insulin sensitivity [HOMA- S %];

HOMA-B% = 20 x fasting insulin [20*mI.U. /ml] / FBG [mmol/ml] - 3.5

Hemoglobin A1c [HbA1c] was measured in the whole blood chromatographically and colorimetrically using ion-exchange resin method with the aid of using vitro science kits.

Serum betatrophin was measured using Human Betatrophin ELISA Kit. First, human betatrophin antibody pre-covered the plate. Then, the antibodies coated on the wells bound to betatrophin, which is present in the sample.

By the addition of biotinylated human betatrophin antibody, it connects to betatrophin in the specimen. After this, streptavidin-HRP is added and ties to biotinylated betatrophin antibody.

During the washing phase, unbound streptavidin-HRP are washed away after incubation. Then, the substrate arrangement is included generating a shading, which is proportional to the amount of human betatrophin. Then after, the reaction is terminated after the acidic stop

solution is added and the absorbance at 450 nm is measured.

Statistical analysis:

For data entry and analysis, SPSS software [version 25.0; IBM Corp., Armonk, NY, USA] was used. Qualitative data were described as frequency [N] and rate [%].

Quantitative data were described as mean ± standard deviation [SD] if typically dispersed with no significant outliers or median and interquartile range [IQR] if not. Qualitative data comparison were done by chi-Square test or fisher's exact test.

Free Samples t-test was utilized for ordinarily dispersed information. Mann-Whitney U test was utilized if not. Identification of the betatrophin cut point that distinguish diseased from non-diseased cases [DM from non-DM participants] was done using receiver operating characteristic [ROC] curve analysis. Diagnostic accuracy, sensitivity, specificity, PPV and NPV were all calculated. AUC was graphed.

Spearman's correlation was used to assess the direction and strength of association between an ordinal variable and a quantitative variable. Point biserial correlation was used to assess the association between a dichotomous variable [e.g., sex] and a quantitative variable [e.g., betatrophin level].

Partial correlation was used to assess the direction and strength of association between two quantitative variables after adjustment for age and sex.

The results were considered non-significant when the probability of error is more than 5% [$p > 0.05$] while significant when the probability of error is less than 5% [$p \leq 0.05$].

RESULTS

This study involved 89 participants divided into; 49 patients with T2DM and 40 apparently healthy individuals. The studied diabetic patients has median duration of diabetes 9 years [ranging from 2 to 29 years], median ACR 217 mg/g [ranging from 40 to 1547 mg/g] and median PCR495.2 mg/g [ranging from 365 to 2891 mg/g]. The mean HbA1c ± SD was 7.8% ± 1.5% as shown in table [1].

There was insignificant difference between the two groups regarding sex [P = 0.976]. However, age, ischemic heart disease [IHD], systolic blood pressure [SBP], BMI and grade 2 obesity were higher among patients with diabetes than in the control group [p<0.001].

The mean values of triglyceride [TG], cholesterol, FBG, creatinine and HOMA-IR were higher in patients with diabetes than in the control group [p<0.001].

HOMA- B% and HOMA- S% were significantly lower in patients with diabetes than in the control group. It was observed that 15 % of apparently healthy control subjects had IR without overt diabetes as shown in table [2].

The betatrophin [ng/l] levels among the study groups were higher in T2DM patients than in the control group [P <0.001]. Its median value in patients with diabetes was 20ng/l ,while in the control group was 18 ng/l.

Betatrophin at a cut point of ≥19.5 ng/ml can discriminate patients with DM from non-DM participants [AUC=0.75, P <0.001] being specific rather than sensitive as shown in table [3,4].

There was a positive correlation of moderate intensity between betatrophin - levels and serum creatinine. There was a negative correlation of moderate intensity between betatrophin - levels and HOMA -B%.

A positive correlation of moderate intensity between betatrophin- levels and FPG in T2DM patients was present. There was no correlation between betatrophin- levels and other parameters under study in the control group as shown in table [5].

Table [1]: Characteristics of the studied diabetic patients

Characteristic	Distribution	Outliers	Mean	SD	Median	IQR	Range
Duration of DM [years]	Skewed	Yes	10.3	6.7	9	6-13.5	2-29
HbA1c %	Normal	No	7.8	1.5	8.1	6.5-9	4.9-11.1
ACR [mg/g]	Skewed	Yes	321.6	301.9	217	130-426	40-1547
PCR [mg/g]	Skewed	Yes	698.5	531.8	495.2	365-922	168-2891

SD: standard deviation, IQR; interquartile range. HbA1c; hemoglobin A1c, ACR; Albumin- creatinine ratio, PCR; Protein -creatinine ratio.

Table [2]: Clinical and biochemical characteristics of the study groups

Characteristic		Diabetic[N=49]	Control[N=40]	P value
Age[years]	[Mean ± SD]	56.6 ±10	38.6 ±13.7	<0.001
Sex [n, %]	Male Female	17 [34.7%] 32 [65.3%]	14 [35%] 26 [65%]	0.976
Hypertension [n, %]		37 [75.5%]	2 [5%]	<0.001
IHD [n, %]		22 [44.9%]	1 [2.5%]	<0.001
BMI[kg/m^2]	[Mean ± SD]	33.1 ±4.1	29.5 ±3.5	<0.001
BMI grades [n, %]	Ideal Overweight Obese grade 1 Obese grade 2 Obese grade 3	1 [2%] 9 [18.4%] 22 [44.9%] 15 [30.6%] 2 [4.1%]	5 [12.5%] 14 [35%] 19 [47.5%] 2 [5%] 0 [0%]	0.002
Creatinine	Median [IQR]	0.5[0.45 –0.6]	0.5 [0.4-0.58]	<0.001
Triglycerides	Median [IQR]	175[137.5-228]	120[115-132.3]	<0.001
Total cholesterol	Median [IQR]	192[157-234]	145[135.5-164.8]	<0.001
FPG	Median [IQR]	158[142.5-182.5]	100 [95-105]	<0.001
Fasting insulin	Median [IQR]	22[14-36]	10[7-12]	<0.001
HOMA-B%	Median [IQR]	69.5[45.4-103.3]	90.7[65.3-114.2]	0.014
HOMA- S%	Median [IQR]	32 [20.8-49.3]	77.6[63.2-105.7]	<0.001
HOMA- IR	Median [IQR]	3.1[2.04-4.8]	1.3[0.95-1.6]	<0.001

P value: Chi-Square test, SD: standard deviation, Data were expressed as mean ± SD [compared by Independent-Samples t-test]. Data were expressed as Median [IQR] [compared by Mann-Whitney U-test]. IHD; ischemic heart disease, BMI: body mass index, FBG: fasting blood glucose, HOMA- IR; Homeostasis model assessment- insulin resistance, HOMA-B; HOMA of β-cell function, HOMA- S%; HOMA of insulin sensitivity.

Table [3]: Betatrophin [ng/l] levels in the two studied groups

Characteristic	Diabetic [N=49]	Control [N=40]	P value
Serum betatrophin [ng/l] ; Median [IQR]	20 [18-25.5]	18 [15-19]	<0.001
Betatrophin cut point ;Median [IQR]			
<19.5 ng/ml	20 [40.8%]	34 [85%]	<0.001
≥19.5 ng/ml	29 [59.2%]	6 [15%]	

P value: Chi-Square test.

Table [4]: Betatrophin cut point to discriminate between the two groups

ROC curve between Patients and Control							
Cut point	AUC	95% CI	P value	Sensitivity	Specificity	PPV	NPV
≥19.5 ng/ml	0.752	0.651-0.852	<0.001	59.2%	85%	82.9%	63%

AUC=Area under the ROC curve. CI=Confidence interval. PPV=Positive predictive value. NPV=Negative predictive value

Table [5]: Correlations of β-trophin with clinical and laboratory data [age- and sex-adjusted]

Data	Diabetic group		Control group	
	Coefficient	P value	Coefficient	P value
BMI	-0.080	0.591	0.032	0.848
Triglycerides	-0.012	0.939	0.060	0.719
Total Cholesterol	0.194	0.191	0.205	0.218
Serum Creatinine	-0.307	0.036	0.156	0.350
FPG	0.335	0.021	0.040	0.812
Fasting insulin	-0.257	0.081	-0.074	0.660
HOMA -B%	-0.377	0.009	-0.063	0.708
HOMA- S%	0.198	0.182	0.026	0.876
HOMA -IR	-0.132	0.378	-0.072	0.666

P value: Partial correlation test. BMI: body mass index, FBG: fasting blood glucose, HOMA; Homeostasis model assessment, IR; insulin resistance, HOMA-B%; HOMA of β-cell function, HOMA- S%; HOMA of insulin sensitivity.

DISCUSSION

In this study, we tried to find a new marker for early diagnosis of T2DM and for early prediction of its complications. There is a little or no data regarding diabetes prevalence are available from many countries especially in Africa, where it is estimated that more than 65% of individuals with diabetes remain undiagnosed [14].

Betatrophin has emerged recently as an effective metabolic regulator of glucose, lipid homeostasis and insulin secretion; however, in human, the clinical relevance of these findings remains poorly characterized.

In our study, we evaluated serum betatrophin –levels in normal and in subjects with diabetes .We investigated the association of serum betatrophin -levels with IR and other study parameters. In the present study, HOMA-IR was higher significantly in T2DM than in the control group. Higher HOMA-IR values reflect higher IR, the body is producing enough insulin, but the insulin produced is not effectively controlling the plasma glucose levels. IR is a primary defect in the majority of patients with T2DM. IR in combination with hyperinsulinemia in non-diabetic individuals has a strong predictive value for the development of T2DM in the future [15].

Yi *et al*. [16] stated that HOMA- IR percentage was increased significantly in T2DM when compared with the control group.

Serum cholesterol and triglyceride [TG] levels were higher significantly in T2DM than in the control group. Insulin hormone affects the liver apolipoprotein production, regulates the catalytic activity of lipoprotein lipase and cholesterol ester transport protein, which causes dyslipidemia in DM. Moreover, insulin deficiency reduces the hepatic lipase activity and several steps in the production of biologically active lipoprotein lipase [17].

The increased TG may be due to increased very low density lipoprotein hepatic secretion and TG rich lipo-proteins delayed clearance, which is due to increased levels of substrates for triglycerides as free fatty acids and glucose [18].

This correlates with the result of Ghasemi *et al*. [19] who stated that serum cholesterol and TG were increased significantly in T2DM.

In the present study, betatrophin -levels were higher significantly in T2DM patients than in the control group. This suggesting that impaired insulin secretion potentially increases the circulating betatrophin levels. The increase in serum betatrophin in T2DM might be attributable to a defensive response, which may represent an ability to adapt to hepatic IR or increased blood glucose concentrations by increasing β-cell proliferation and insulin secretion. This has been concomitant with the results published before by Abu-Farha *et al.*, Hu *et al.*, Yamada *et al*. and Espes *et al*. [20-23].

In contrast to our study, Fenzl *et al*. [24] stated that serum betatrophin -levels not differ significantly between T2DM subjects and non-diabetic subjects. These maybe due to the different sample size in Fenzl et al. study and a different ethnicity.

The diabetic patients in Fenzl *et al*. study had taken oral hypoglycemic drugs [metformin_ sulfonylureas], which would potentially affect the betatrophin levels, as the main effect of metformin is to reduce IR. Also may be due to different duration of T2DM. Also, Gómez-Ambrosi *et al*. [25] stated that serum betatrophin levels decreased in people with T2DM.

Our study confirmed that betatrophin-levels correlated positively with FPG in T2DM patients. These data can point toward a novel role of betatrophin in the pathophysiology of glucose homeostasis. Betatrophin may plays a significant role in the mechanisms underlying T2DM that associated with β-cell function, replication and IR.

This comes in agreement with Chen *et al*. and Yamada *et al*. [26, 22].

This was in contrast to the study conducted by Espes *et al*. [23] who did not find any relationship between betatrophin and FBG. This inconsistency may be attributed to the different study type and the ethnic groups involved in this study.

In the current study, there was a negative correlation of moderate intensity between betatrophin-levels and HOMA- B% after adjusting for age and sex. Betatrophin -levels increase when the β-cell activity decreased. HOMA- B % was a measure of β-cell activity. As, it had been established that murine pancreatic cell proliferation is potently activated by β-cell agonists through stimulation of hepatic lipasin expression [27].

Also, Yin *et al*. [28] declared this negative correlation between betatrophin - levels and HOMA- B%. This study documented that there was a significant positive correlation of moderate intensity between betatrophin - levels and serum creatinine, which would suggest that betatrophin normally is excreted in the urine. Increased circulating concentrations of betatrophin may both reflect increased secretion and reduced clearance of the hormone in renal impairment .Also, it raises the suspicion about the involvement of betatrophin in renal impairment.

This is consistent with results by Tokumoto *et al*. [29]. In slight contrast, Yamada et al. [22] identified weak positive correlation between betatrophin -levels and serum creatinine.

In the current study, the correlation between betatrophin-levels and BMI was not significant. This may be due to the complexity of obesity. Obesity is a disease involving a number of peptides, transmitters and their receptors controlling homeostasis of the energy [30], thus many diverse factors may affect betatrophin expression and IR in obese individuals. Moreover, betatrophin may

be changed as a compensatory mechanism in response to certain factors, aimed at maintaining a certain balance. The factors affecting its increase and decrease may reach an equilibrium, so that the betatrophin-level were not changed in obesity.

Currently, we cannot explain this phenomenon due to limited understanding of molecular mechanism involved in betatrophin regulation.

This goes hand by hand with Guo *et al.* [31] that demonstrated that serum betatrophin concentrations were not increased significantly in obese subjects.

This was not matching with Fu *et al.* [32] who illustrated that serum levels of betatrophin were elevated in obesity and were positively correlated with BMI. This difference may be related to the different relatively smaller sample size of our study population.

This study revealed that the correlation between serum betatrophin -levels and total cholesterol and TG levels in patients with diabetes was not significant. The association between betatrophin and lipid values was difficult to interpret, as many of the study patients, especially among the patients with diabetes, were treated with lipid-lowering drugs [statins].

Also, this study only included 49 patients with diabetes. This resembles the results by Yi *et al.* [16]. However, this differs from the results by Fenzl *et al.* [24] that has declared that circulating betatrophin significantly correlated with total cholesterol and TG levels in patients with diabetes and betatrophin was strongly associated with atherogenic lipid profiles. We speculated this discrepancy may be resulted from the different sample sizes of both studies.

The limitations of our study, there were very few researches available about betatrophin to be compared with our results, the small sample size that might limit the generalizability of the results. Our analyses were based on single measurement of blood betatrophin in patients previously diagnosed with T2DM, which may not reflect betatrophin- levels over stages of diabetes.

Conclusion:

Serum betatrophin-levels in subjects with diabetes were increased and were further increased in parallel to the decrease in the beta cell function [HOMA -B %]. There was a positive correlation in T2DM patients between betatrophin -levels and FPG. There was a positive correlation between betatrophin -levels and serum creatinine. There was no correlation between betatrophin-levels and obesity grades. The mechanisms of action of betatrophin are still unknown. The next step is to test the effects of recombinant betatrophin protein on β-cell mass.

Recommendation:

Serial changes in the serum betatrophin need to be measured at different stages of T2DM besides newly diagnosed T2DM patients to further clarify the role of betatrophin in the pathogenesis of T2DM. Further studies are needed to elucidate whether betatrophin could have clinical applications in the development of new antidiabetic drugs or not. Follow up the diabetic patients after lifestyle changes and compare the changes of circulating betatrophin levels before and after.

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Conflicts of interest: None

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