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Research Article

Betatrophin is correlated with glucagon and insulin release rather than insulin resistance marker in type 2 diabetes mellitus Iraqi women

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ABSTRACT

Background: Betatrophin mainly expressed in liver and adipose tissue, stimulates pancreatic β-cell proliferation in insulin resistance state and improves metabolic process regulation. This study aimed to understand effective roles of betatrophin in diabetic and non-diabetic Iraqi women. Also, it's correlation with some insulin markers, metabolic parameters and glucagon.
Methods: Eighty women participated in this cross-sectional study, (mean body mass index: 21 - 49 kg/m^2; mean age: 25-50 years) were enrolled and classified according to the presence of diabetes into 2 groups (40 diabetic and 40 non-diabetic). Anthropometric, biochemical and metabolic parameters measured.
Results: Betatrophin level had no statistically significant differences between non-diabetics and diabetics. Serum betatrophin levels had no statistically significant positive or negative correlations with age, anthropometric, lipid profile, diabetic parameters, thyroid stimulating hormone, glucagon, irisin, glucagon like peptide -1 and hepatocyte growth factor except uric acid (r=0.2539, P =0.0231). Serum betatrophin had no statistically significant correlations with all variables in non-diabetic and diabetic groups except with homoeostasis model assessment- for β-cell function (HOMA-β) and glucagon (r=0.3647, P=0.0207; r=0.3403, P=0.0317 respectively) in the diabetic group. Stepwise regression showed that only uric acid was independently related factors to circulating betatrophin β=0.8500, P=0.02.
Conclusions: Betatrophin was positively correlated with HOMA-β and glucagon in type 2 diabetes mellitus women. Uric acid was a direct independent predictor of betatrophin level.

Keywords: Betatrophin, Glucagon, Type 2 diabetes, HOMA-β, Homeostasis model assessment insulin resistance (HOMA-IR), Uric acid

INTRODUCTION

Diabetes and obesity are a public health problem all over the world and it is particularly important to explore the potential treatments that focus on the mechanisms of diabetes, impaired pancreatic β-cells function, and insulin resistance. It has been recommended recently that the best treatment, for type 2 diabetes (T2DM), is to replace or regenerate the pancreatic β-cell mass.[1] The recently identified hormone, betatrophin, could be contributed to the regeneration of β-cell mass.[2] Betatrophin, discovered by Yi and colleagues, has a role in increment β-cell mass in mice, and it may be raising hopes for regenerative β-cell therapy in humans. Betatrophin, also known as lipasin, re-feeding induced fat and liver (RIFL), hepatocellular carcinoma-associated protein TD26 and angiopoietin-like protein (ANGPTL8).[3-8]

It has been established that betatrophin is a liver and a fat-derived hormone.[3] The quite recent discovery of a novel peptidic hormone called irisin has also been reported by Spiegelman's group. Irisin essentially acts on

the white adipose tissue cells and its concentrations rise after exercise in both mice and humans, thus increasing total energy expenditure and lightened diet-induced insulin resistance in certain animal models.[8]

PGC1-α expression in muscle stimulates an increment in secreted irisin and the ultimate acts on white adipose cells to stimulate UCP1 expression, mediated via activation of p38 MAPK, and promote the expression of betatrophin. Gomar et al concluded that irisin and betatrophin may be involved in the same pathway, ROS →p38 MAPK→PGC1α → irisin → betatrophin→β-cell regeneration.[9]

This conclusion may be involved in both, the insulin resistance and β-cell function mechanism, which would provide new possibilities for exploring defective pathways involved in regenerative capacity and the β-cells function of diabetic and obese patients. The objective of this study is to understand the role of betatrophin and its relation with insulin resistance, β-cells function%, glucose homoeostasis, glucagon, anthropometric, lipid profile and uric acid in diabetic and non-diabetic Iraqi women.

METHODS

Design and subjects

This study was conducted at the Department of Biology, College of Sciences, University of Baghdad. Eighty Iraqi women were recruited consecutively during the period from April 2014 to February 2015. Subjects recruited at the Obesity Research and Therapy Unit, Alkindy College of Medicine, University of Baghdad and from the Specialized Center for Endocrinology and Diabetes-Baghdad, Iraq. For this cross-sectional study 80 women (age: 25 - 50 years) and classified according to diabetes presences into two groups (40 diabetic and 40 non-diabetic).

Research procedures

All anthropometric and biochemical measurements were taken in the morning after 12 hours fast using standardised methods. Anthropometric measurements were obtained using standard protocols and techniques.

After removal of shoes and heavy clothing, each subject underwent weight was measured to the nearest 0.5 kg using a digital weighing scale, the height of each subject was measured to the nearest 1 cm using a stadiometer. The WC measurement was made at minimal inspiration to the nearest 1 cm, midway between the last rib and the iliac crest.[10,11]

Waist circumference (CW) < 80 cm defined as normal, a WC ≥ 80 defined as obese.[12] Body mass index (BMI) was calculated as BMI=weight (kg)/ square height (m^2).[13] Arterial blood pressure was measured with a digital electronic tensiometer subjects had been sitting more than 5 minutes with appropriate cuff size or by an automatic device. Participants seated with their left arm resting at the level of the heart and two measurements were taken after the subject had been at rest. Values used in the analysis are the averages of two readings were taken at 5 min intervals.

The criteria for diagnosis and inclusion of subjects with T2DM has depended on careful patient's history and/or the measurements of serum glucose levels ≥ 126 mg/dl, also, by a consultant physicians of obesity research and therapy unit, Alkindy College of Medicine, Baghdad, Iraq.

The basis of the criteria of the WHO for a person to be defined as has obesity or diabetes.[14] The homoeostasis model assessment (HOMA) was applied to estimate degree of IR and β cells as described below.[15] HOMA-insulin resistance (HOMA-IR) was calculated by (fasting insulin (mU/ml)* fasting glucose (mmol/L)/22.5). A HOMA-β cell was calculated by: (20 * fasting insulin (mU/ml) / (fasting glucose (mmol/L) -3.5)). The exclusions criteria including; pregnant, lactating, menopause, smoker, alcohol drinker, endocrine or genetic or drug causes of obesity, T1DM, cardiac, renal, hepatic diseases, anaemia and hypoproteinemia.

Laboratory measurements

The phlebotomy protocol specified a blood draw after at least a 12-h fast for all study participants. Serum was taken from blood samples which allowed to clot and then sera separated by centrifugation at 3000 rpm for 10 min at room temperature.

A part of extracted serum used for measuring metabolic and biochemical analysis on the same day. While the rest of the serum aliquot into storage phials, labelled and frozen at -20°, until used for the hormones assay. Biochemical tests were estimated according to manufacturer's instructions (Roche Diagnostics).

The *in-vitro* tests for the quantitative determination in human serum and plasma measured with the Roche Cobas c111 clinical chemistry analyser. Sera of hormones levels were determined with a commercially available human ELISA kits (Mybiosource Company/ San Diego, CA, USA) according to the manufacturer's instructions (Irisin catalogue number MBS706887, Betatrophin (angiopoietin-like protein 8) catalogue number MBS706992, glucagon-like protein 1 (GLP-1) catalogue number MBS2513877, hepatocyte growth factor (HGF) catalogue number MBS2021513, insulin catalogue number MBS2509572, and glucagon catalogue number MBS2502180.

Thyroid stimulating hormone (TSH) product Code: 325-300 was supplied by Monobind Inc. CA, USA. All assays were done in the Department of Immunology / Teaching Laboratories, Baghdad Teaching Hospital by using enzyme-linked immunosorbent assay (ELISA).

Statistical analysis

The statistical analysis system- SAS (2012) was used to analyse the effect of different factors in non-diabetic and diabetic groups. The least significant difference - LSD test was used to significant compared between study groups. Estimate of correlation coefficients between betatrophin with all variables of the study. Univariable and stepwise multiple linear regression analysis was used to identify variables independently associated with serum betatrophin levels for all population, non-diabetic and diabetic groups separately. A P-value of ≤ 0.01 and ≤0.05 was used as the level of significance differences.

RESULTS

The results in a Table 1 showed there were highly significant differences between groups in age, weight, WC, BMI, TGs, HDL-C, FPG, FI, HOMA-IR1, HOMA-β (P<0.0001), SBP, LDL-C (P<0.005), and TC (P<0.003).

Also, results demonstrated there were on significant differences between groups in height (P=0.633), DBP (P=1.000), UA (P=0.178), Glucagon (P=0.445), TSH (P=0.687), irisin (P=0.061), betatrophin (P= 0.144), GLP-1 (P=0.967) and HGF (P=0.071).

Table 1: Baseline clinical characteristics of the study subjects.

Variables	Non-diabetic (N= 40)	Diabetic (N= 40)	LSD value	P value
Age (years)	34.40±7.62	41.42±5.28	2.918 **	<0.0001
Weight (kg)	77.57±19.77	96.15±14.68	7.749 **	<0.0001
Height (cm)	159.35±5.92	158.72±5.75	2.598 NS	0.633
WC (cm)	93.35±16.22	114.82±11.15	6.195 **	<0.0001
BMI (kg/m^2)	30.55±7.68	38.22±5.85	3.039 **	<0.0001
SBP (mm Hg)	118.00± 5.39	123.07±9.67	3.485 **	<0.005
DBP (mm Hg)	79.45±3.29	79.45±4.67	1.797 NS	1.000
FPG (mg/dl)	84.22±7.46	175.15±45.75	14.67**	<0.0001
TC (mg/dl)	169.95±31.99	192.52±33.67	14.621 **	<0.003
TGs (mg/dl)	108.42±60.85	180.67±69.56	29.092 **	<0.0001
HDL-C (mg/dl)	51.82±11.57	41.05±10.37	4.891 **	<0.0001
LDL-C (mg/dl)	102.52±25.82	120.82±30.75	12.640 **	<0.005
U.A (mg/dl)	4.10±0.99	4.04±1.20	0.491 NS	0.816
TSH (µIU/ml)	3.08±1.31	2.97±1.21	0.561 NS	0.687
FI (mU/ml)	4.97±1.45	16.38±3.34	1.153 **	<0.0001
HOMA-IR	1.04±0.33	7.21±2.95	0.939 **	<0.0001
HOMA- β	92.26±37.63	60.23±25.51	14.38 **	<0.0001
Glucagon (pg/ml)	843.37±230.35	808.83±167.16	89.590 NS	0.445
GLP-1 (ng/ml)	18.32±16.46	18.16±18.62	7.823 NS	0.967
HGF (pg/ml)	20.43±6.93	23.93±9.91	3.806 NS	0.071
Irisin (ng/ml)	118.01±76.74	91.35±44.75	28.108 NS	0.061
Betatrophin (pg/ml)	10.04±4.41	8.84±2.67	1.620 NS	0.144

*Significant correlation (P <0.05); **Significant correlation (P <0.01); BMI: body mass index; WC: waist circumference; SBP: systolic blood pressure; DBP: diastolic blood pressure; FPG: fasting plasma glucose; TC: total cholesterol; TGs: triglycerides; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; UA: uric acid; TSH: thyroid stimulating hormone; FI: fasting insulin; HOMA-IR: homeostasis model assessment-insulin resistance; HOMA-β: homeostasis model assessment-β cells; GLP-1: glucagon like peptide- 1 ; HGF: hepatocyte growth factor.

Multiple regression analysis of betatrophin as dependent variables

The bivariate associations cannot be considered at face value since they are not free from confounding. To adjust for potential confounders of the circulating betatrophin concentration, so stepwise multiple linear regression analysis was performed.

Univariable and stepwise multiple linear regression performed to determine variables that had independent associations with circulating irisin and betatrophin. Table 3 showed all results of univariable and stepwise multiple regressions for betatrophin results of univariable regression showed that only UA was positively significant determinant (r= 0.8500, P=0.02), also, results of stepwise linear multiple regression showed that only UA was independently related factors to circulating betatrophin β=0.8500, P=0.02.

Correlations of betatrophin with various variables

Correlation results of serum betatrophin levels showed no statistically significant positive or negative relation with all variables except UA (r=0.2539, P=0.0231). In addition, betatrophin correlation results demonstrated no statistically significant correlations in a non-diabetic

group with all variables. In diabetic group, serum betatrophin levels had statistically significant positive correlations with HOMA-β and glucagon only (r=0.3647, P=0.0207; r=0.3403, P=0.0317 respectively).

Table 2 showed correlation results of betatrophin and other variables in non-diabetic and diabetic groups.

Table 2: Correlation coefficient between betatrophin and other variables in whole study population, non-diabetic, and diabetic groups.

Variables	All subjects -r (n= 80)	P value	Non-diabetic-r (n= 40)	P value	Diabetic-r (n=40)	P-value
Age (years)	-0.2018	0.0726	-0.1612	0.3204	-0.0978	0.5483
Weight (kg)	0.0114	0.9198	0.1374	0.3977	0.0291	0.8585
Height (cm)	0.0342	0.7631	0.0726	0.6562	-0.0522	0.7490
WC (cm)	0.0060	0.9560	0.0355	0.8280	-0.1366	0.4007
BMI (kg/m^2)	-0.1192	0.2925	0.1100	0.4609	0.0655	0.6879
SBP (mm Hg)	-0.0713	0.5296	0.0650	0.6906	-0.1069	0.5115
DBP (mm Hg)	-0.1046	0.3558	-0.1308	0.4211	-0.0982	0.5465
FPG (mg/dl)	-0.1955	0.0822	0.0606	0.7103	-0.2047	0.2052
TC (mg/dl)	-0.1279	0.2581	-0.1763	0.2764	-0.1276	0.4328
TGs (mg/dl)	0.0861	0.4474	-0.0434	0.7905	-0.0788	0.6287
HDL-C (mg/dl)	-0.0821	0.4689	-0.0156	0.9237	0.0710	0.6632
LDL-C (mg/dl)	-0.1279	0.2581	-0.1081	0.5066	0.0665	0.6833
U.A (mg/dl)	0.2539*	0.0231	0.2560	0.1109	0.2836	0.0762
TSH (µIU/ml)	-0.0648	0.5680	-0.1626	0.3161	0.0811	0.6189
FI (mU/ml)	-0.1100	0.3320	0.1733	0.2850	0.0881	0.5887
HOMA-IR	-0.1480	0.1890	0.1654	0.3077	-0.0721	0.6582
HOMA- β	0.1590	0.1580	-0.0133	0.9350	0.3647*	0.0207
Glucagon (pg/ml)	0.1495	0.1856	0.0494	0.7623	0.3403*	0.0317
GLP-1 (ng/ml)	0.0458	0.6865	-0.0145	0.9295	0.1389	0.3927
HGF (pg/ml)	0.0519	0.6473	0.1018	0.5319	0.0906	0.5781
Irisin (ng/ml)	0.1699	0.1320	0.2281	0.1569	-0.1085	0.5052

*Significant correlation (P <0.05); BMI: body mass index; WC: waist circumference; SBP: systolic blood pressure; DBP: diastolic blood pressure; FPG: fasting plasma glucose; TC: total cholesterol; TGs: triglycerides; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; UA: uric acid; TSH: thyroid stimulating hormone; FI: fasting insulin; HOMA-IR: homeostasis model assessment-insulin resistance; HOMA-β: homeostasis model assessment-β cells; GLP-1: glucagon like peptide- 1 ; HGF: hepatocyte growth factor.

DISCUSSION

Correlation between betatrophin and anthropometric variables

There were several limitations of this study, a major one is the small number of sample, the absolute value of betatrophin was usually different between different studies, and matching of the sample was complicated by clinical differences between women who were recruited consecutively. Guo et al reported that serum betatrophin levels did not differ between lean and obese or between normal glucose tolerance (NGT) and T2DM participants, which is consistent with the current study.

Same study, showed that insulin levels were increased in the overweight individuals, therefore, cannot ignore the possibility that elevated insulin was generally responsible for the raised betatrophin in the overweight group but he suggested that these reasons are not enough to clarify why betatrophin did not increase in obese population, owing to its lipid storage and insulin levels increased too, which may be because of the complexity of obesity.[16]

Correlation between betatrophin and diabetic variables

There is an insignificant decrease in betatrophin in diabetic subjects. Xie et al., reported no significant difference between females with T2DM and females with NGT in betatrophin level.[17] Other studies revealed that serum betatrophin level in the diabetics or pre-diabetics significantly higher than in NGT and non-diabetics.[18,19]

Correlation analysis of betatrophin demonstrated no significant correlation with FPG, fasting insulin and HOMA-IR in non-diabetic and diabetic. On other hand, results showed a significant association between betatrophin and HOMA-β in T2DM only. Ambrosi G et al reported that the association of betatrophin with any glucose metabolism marker was similar among genders.[20] Present results contradicted with some previous study that considered serum betatrophin concentrations in all

individuals were significantly positively correlated with FPG.[19]

Other studies show no significant positive correlation between betatrophin concentration and FPG concentration.[16,21] In the diabetic patients, recent studies demonstrated there was no statistically positive significant correlation between betatrophin and FPG.[16, 22] Other studies revealed a positive significant correlation of insulin and HOMA-IR relation with serum betatrophin.[16,22] In healthy and diabetic patients, the correlation between betatrophin with insulin and HOMA-IR found which contradict with these study findings.[16,17]

More recently studies results illustrated that the relation between betatrophin and HOMA-β had a negative correlation both groups.[22,23] However, it was later shown that betatrophin levels had non-significant positive relation with HOMA-β in control healthy or NDM which is not the case in the current study.[24] The paradoxical results may be related to the following observations; first, duration of T2DM where investigators reported that people with longer duration of diabetes had greater betatrophin levels.[25] Second, half subjects with T2DM receiving medication. Moreover, medications such as metformin could possibly modify the degree of insulin resistance and then affect the relation between betatrophin and insulin resistance.[26] Third, differences in sample size and ethnic groups and sampling.[18,27] Fourth, a potential diverse grade of inflammation may also exert a discrepancy impact because it impinges on both glucose and lipid metabolism.[28] Lastly, the cross-sectional design of present study shows no causal relationships between betatrophin and glucose-related variables and in this cross-sectional study betatrophin levels estimated at a single point, which cannot reflect betatrophin levels over time.[22]

Table 3: Univariable and stepwise multivariable linear regression of betatrophin with other variables as independent variables.

Variables	Univariable		Stepwise R^2= 0.064	
	Coefficient - β	P-value	Coefficient - β	P-value
Age (years)	-0.0999	0.0726	---	---
Weight (kg)	0.0021	0.9198	---	---
Height (cm)	0.0216	0.7631	---	---
WC (cm)	-0.0236	0.3178	---	---
BMI (kg/m^2)	0.0029	0.7256	---	---
SBP (mm Hg)	-0.0320	0.5296	---	---
DBP (mm Hg)	-0.0956	0.3558	---	---
FPG (mg/dl)	-0.0120	0.0930	---	---
TC (mg/dl)	-0.0208	0.0822	---	---
TGs (mg/dl)	-0.0063	0.2581	---	---
HDL-C (mg/dl)	0.0259	0.4474	---	---
LDL-C (mg/dl)	-0.0102	0.4689	---	---
U.A (mg/dl)	0.8500*	0.0200	0.8500*	0.0200
TSH (µIU/ml)	-0.1894	0.5680	---	---
FI (mU/ml)	-0.0640	0.3320	---	---
HOMA-IR	-0.1450	0.1890	---	---
HOMA- β	0.0160	0.1580	---	---
Glucagon (pg/ml)	0.0027	0.1856	---	---
GLP-1 (ng/ml)	0.0096	0.6865	---	---
HGF (pg/ml)	0.0220	0.6473	---	---
Irisin (ng/ml)	2.9560	0.1320	---	---

*Significant correlation (P <0.05); BMI: body mass index; WC: waist circumference; SBP: systolic blood pressure; DBP: diastolic blood pressure; FPG: fasting plasma glucose; TC: total cholesterol; TGs: triglycerides; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; UA: uric acid; TSH: thyroid stimulating hormone; FI: fasting insulin; HOMA-IR: homeostasis model assessment-insulin resistance; HOMA-β: homeostasis model assessment-β cells; GLP-1: glucagon like peptide- 1 ; HGF: hepatocyte growth factor.

Previous results showed that betatrophin may play a role in the mechanisms underlying T2DM associated with insulin resistance and β-cell function, and cytokine-mediated crosstalk may occur among the liver, adipose tissue, and skeletal muscle. Furthermore, one study in humans reported that betatrophin may play an essential role in the compensatory overproduction of insulin in insulin resistance state and control β-cell replication.[29] Besides, the correlation between betatrophin and glucagon in diabetics may have a role in HOMA-β relation with betatrophin. Glucagon receptor is upregulated in β-cells in response to rising concentrations of glucose.[30] This may have essential biological consequences in diabetes as fasting and postprandial glucagon levels are raised because of a loss of negative control by insulin.[31] In T2DM, hyperglucagonemia is one

of the numerous factors that participate in changing β-cell function along with islet inflammation and lipotoxicity.[32] On the other hand, to date, there has been no reliable evidence showed the role of glucagon effect on betatrophin.

We demonstrated a novel significant positive relationship between betatrophin and glucagon in diabetic subjects and this make the possible role of glucagon and possibly glucagon receptors in activation of betatrophin and that is in turn, had relation to β-cell regeneration. A clear understanding of betatrophin/glucagon interaction is very important. Glucagon activates AMPK, p38 MAPK, and JNK.[33-35] In subjects with T2DM, glucagon was elevated and participates in the change of excess hepatic glucose production and hyperglycaemia.

Puigserver et al demonstrated that glucagon activates via cAMP an important regulator of PGC-1 α gene expression, increases PGC-1 α levels, promotes transcription of the irisin precursor FNDC5.[36,8] Irisin and betatrophin may be stimulated by the current study and the concluded pathway; glucagon→ glucagon receptor → PKA/p38 MAPK→ PGC-1α→ irisin→ betatrophin→ β-cell regeneration.

However, current study found no association between betatrophin and irisin in women, which might be due to the following reasons: exercise contribution in irisin expression and secretion was not assessed in this study, diabetes mellitus is a group of metabolic diseases influenced by many factors (such as obesity, blood lipids, insulin, dietary), and not excluded the confounding factor of obesity in this study.

Current study results showed that betatrophin and irisin levels lacked a significant correlation in T2DM subjects, which might remain to be carefully interpreted when compare the results of animal models with humans, which shows that betatrophin may not regulate pancreatic β-cell expansion or control pancreatic β-cell function in T2DM patients, the positive effect of irisin on glucose homeostasis may be because of other mechanisms, like inducing browning of WAT.[26]

Correlation between betatrophin and uric acid

Correlation results of betatrophin with uric acid are consistent with findings of Yi et al which reported partially significant positive correlation between betatrophin and uric acid both groups.[22] The above findings contradict the study which found significant inverse correlations between the circulating betatrophin and uric acid.[37] A recent study shows that circulating irisin is highly significantly related to uric acid metabolism in a Chinese population. In addition, the author reported a significant direct correlation between irisin and uric acid in overweight/obese group.[38] Uric acid may have triggered the ROS generation through various mechanisms, and this may, in turn, stimulated irisin and/or in turn betatrophin through activating p38 MAPK.

Multiple stepwise regression of betatrophin and other variables show that the main predictor of circulating betatrophin was only uric acid. In reviewing most of the betatrophin articles for different authors, it was apparent that there were different predictor variables of betatrophin in a different status. In contrast, several studies revealed different variables were independently related factors to circulating betatrophin like; c-GT and HOMA-IR, BMI, FT4 and HDL-C, insulin, FPG and HOMA-IR , insulin and HOMA-IR, age and increment of C-peptide and HOMA-IR and LDL-C.[16,21,25,29,39,40] All these predictor variables interpret betatrophin independently. Several of these predictor variables not included in the current study and the others don't have a significant independent prediction for betatrophin.

CONCLUSION

From the present study it was found that serum betatrophin levels in non-diabetic subjects were not significantly higher than in T2DM subjects. Circulating betatrophin was positively correlated with HOMA-β and glucagon in the diabetic women. The results indicate that betatrophin may play a role in the mechanisms underlying T2DM associated with α and β cell function, especially in women. A serum betatrophin level shows a positive correlation with uric acid concentration.

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