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Original Article

The relationship between betatrophin levels and HbA1c

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Abstract

Aim: In our study, we first aimed to investigate the effect of betatrophin in uncontroled diabetes patients with HbA1c above 14. Another focus of our study is the effect of betatrophin levels on the biochemical parameters of the patients.

Material and Methods: This is an observational study with a prospective case-control design. The study was carried out between July 2018 and November 2018 at the internal medicine clinic of the tertiary university hospital. Our study was conducted with participants divided into 3 groups. Group 3 (uncontrolled T2DM) consisted of 40 participants who met the study criteria and HbA1c above 14% . Group 2 (controlled T2DM) consisted of 40 participants who met the study criteria and HbA1c below %10 and the group 1 (control group) consisted of 40 people who did not have a history of diabetes mellitus.

Results: There was no statistical difference in age and sex between the 3 groups included in the study. Betatrophin levels of patients with uncontrolled diabetes were significantly higher than control group and controlled diabetic group.($p<0.001$). HbA1c value of the participants was found to have a significant effect on betatrophin level, unlike other parameters.($p<0.001$).

Conclusion: We found higher betatrophin levels in the group with uncontrolled diabetes in our study. There was no significant difference in betatrophin levels between the controlled T2DM group and the healthy group. Our data found that betatrophin level showed a significant positive correlation with HbA1c level.

Keywords: Betatrophin; HbA1c; diabetes mellitus

INTRODUCTION

Diabetes Mellitus (DM) is a chronic disease characterized by microvascular and macrovascular complications due to insulin deficiency or problems with insulin effect (1). Diabetes is responsible for 30-40% of all end stage renal disease in the United States, therewithal one of the most important causes of long-term complications that cause mortality and morbidity (2) Today, although there are methods such as taking antidiabetic drugs or injecting insulin for diabetes treatment, there is no way of thorough treatment (1,2). Recently, Yi et al. found a new hormone and named it betatrophin, which, closely related to diabetes treatment, could increase the quantity of cells that produce insulin in mice quickly (3). Chen et al. and Jiao et al. confirmed afterwards the potential role of betatrophin in the proliferation of beta cells and the regulation of glucose metabolism (4,5). Betatrophin is secreted from human liver and adipose tissue and it named differently according to its different functions, including angiotensin amyloid 8 (ANGPTL8), lipoprotein lipase inhibition (Lipasin), and refeeding induced in fat and liver (RIFL) betatrophin has been reported to play a role in lipid metabolism as well as glucose metabolism (3,6,7). The effect of betatrophin on lipid and glucose metabolism in humans is controversial. Gokulakrishnan et al. reported a higher significance level of betatrophin in type 2 diabetic patients compared to healthy controls (8). Gomez Ambrosi et al. found that betatrophin level was low in T2DM unlike Gokulakrishnan et al.(9) Betatrophin levels were variable in type 2 diabetes mellitus (T2DM), either increased (10-12) or decreased (8,9). In a betatrophin-related meta-analysis study, betatrophin was reported to be significant in non-obese type 2 diabetes patients (13) . Recent studies of

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betatrophin have focused on the effect of betatrophin on complications in diabetic patients (14,15). In the literature, betatrophin has been reported to be significantly higher in patients with diabetic complications. In many studies, there was a correlation between HbA1c, glucose levels and betatrophin. Based on the data that betatrophin plays a role in diabetic complications, In our study, we first aimed to investigate the effect of betatrophin in uncontrolled diabetes patients with HbA1c above 14. Another focus of our study is the effect of betatrophin levels on the biochemical parameters of the patients.

MATERIAL and METHODS

This is an observational study with a prospective case-control design. The study was carried out between July 2018 and November 2018 at the Internal medicine clinic of the tertiary university hospital. Ethical approval was obtained from the Ethics Committee of Non-Interventional Research of Firat University (19.04.2018/08.33). Those who met the inclusion criteria were included in the study and written consent form was obtained from all participants. Participants were excluded if they had malignant tumors, severe cardiopulmonary disorders, renal/thyroid dysfunction, type 1 DM, severe inflammatory diseases, viral-/drug induced/autoimmune liver diseases, pregnancy or excessively alcoholic consumption.

Our study was conducted with participants divided into 3 groups. Group 3 (uncontrolled T2DM) consisted of 40 participants who met the study criteria and HbA1c above 14%. Group 2 (controlled T2DM) consisted of 40 participants who met the study criteria and HbA1c below %10 and the group 1 (control group) consisted of 40 people who did not have a history of diabetes mellitus . Selections of participants were based on the principle of age and gender matching. All subjects gave written informed consent before participation. This study was approved by the Ethics Committee of the First Affiliated Hospital, Zhejiang University, in accordance with the Helsinki Declaration of 1975.

Anthropometric and biochemical examinations

In our study, the anthropometric measurements of the participants were taken first. Height, weight and waist circumference of the participants were measured by the same researcher. BMI of participants were calculated with (BMI=kg/m2) formula after height and weight measurements. The patients' blood pressures were measured from both arms after at least 15 minutes of rest and their mean values were recorded. Blood samples were taken from the participants who declared that they were hungry all night (12 hours hunger). Biochemical values of all participants (Total cholesterol (TC) , triglycerides (TG) , HDL, VLDL, LDL, glucose, HbA1c, insulin, 25 D-vit) were measured. After measuring glucose and insulin values of all participants, HOMA-IR values were calculated. (HOMA-IR = [Fasting Insulin (μU / mL x Fasting Glucose (mg / dl)] / 405).

Additional samples were taken to check the Betatrophin levels of all participants. Blood samples for betatrophin were centrifuged and their serums were separated. The collected samples were kept at -20 ° C until working.

Measurement of serum betatrophin

Betatrophin measurements were performed in the 3rd step hospital biochemistry laboratory by a commercial enzyme-linked immunosorbent assay (ELISA) (catalogue no. YLA2042HU; Shanghai YL Biotech Co.,Ltd., Shanghai. Assay range: 10ng/L- 2000ng/l, sensitivity: 5.21 ng/l, intra-assay CV < 8%; inter-assay CV < 10%)

Statistical Analysis

Statistical analysis of the data was performed by IBM SPSS 22 statistics package program. Shapiro-Wilk test was used to determine whether the data showed normal distribution. Descriptive statistics of the data were expressed as mean ± standard deviation for variables with normal distribution in continuous data, [median (minimum: maximum)] for non-normal distribution variables, and frequency for categorical variables as percentage [n (%)]. In comparison of more than two independent groups, One-Way ANOVA and LSD test for post-Hoc test were used for normal distributed continuous data, Kruskal Wallis test and Dunn test for post-Hoc test for non-normal distributed continuous data. Significance level was $\alpha = 0.05$. Statistically significant values are indicated in bold in the tables.

RESULTS

There was no statistical difference in age and sex between the 3 groups included in the study. Betatrophin levels of patients with uncontrolled diabetes were significantly higher than control group and controlled diabetic group ($p<0.001$) (Table 1).

HbA1c value of the participants was found to have a significant effect on betatrophin level, unlike other parameters.($p<0.001$) Table 2.

DISCUSSION

Studies on mice showed that betatrophin increases pancreatic cell proliferation and plays a role in glucose metabolism. After these data, researches about betatrophin levels in patients with diabetes mellitus started to increase. Although the relationship between diabetes and betatrophin is controversial, it is emphasized that betatrophin levels increase in type 2 diabetes patients. Based on the data in the literature, unlike previous studies, we investigated the effect of betatrophin levels on participants with uncontrolled T2DM. In our study, we investigated the relationship between betatrophin levels of healthy individuals, individuals with controlled T2DM, and uncontrolled T2DM with HbA1c above 14.

In our study, it was found that betatrophin level was higher in uncontrolled T2DM group compared to both non-diabetes and controlled T2DM group. There was no statistically significant difference between betatrophin levels in patients with controlled T2DM and non-diabetes group. Song et al. reported an increase in betatrophin levels in patients with T2DM in meta-analysis. As a result

Table 1. Characteristics of participants

Characteristics	Control group (group 1)	Controlled T2DM (group 2)	Uncontrolled T2DM (group 3)		
	Mean ±Std		Mean ±Std	p* value	p** value
Gender n(%)					
Female	30 (75)	30 (75)	30 (75)	0.60	
Male	10 (25)	10(25)	10(25)		
Age	49.35±5.11	49.35±5.14	51.80±6.22	0.076	
BMI	23.60±2.60	25.80±2.23	29.43±5.31	**<0.001**	1-2:**0.024** 1-3:<**0.001** 2-3:<**0.001**
Waist circumference	85.35±7.31	86.50±6.11	105.58±14.45	**<0.001**	1-2:1.00 1-3:<**0.001** 2-3:<**0.001**
Total cholesterol	163.98±26.10	168.78±20.28	202.28±51.02	**<0.001**	1-2:0.98 1-3:<**0.001** 2-3:<**0.001**
Triglycerides	91.20±36.70	107.78±22.20	181.48±45.20	**<0.001**	1-2:0.553 1-3:<**0.001** 2-3:<**0.001**
HDL	53.30±12.64	47.42±12.32	47.42±12.32	0.066	1-2:1.00 1-3:0.087 2-3:0.216
VLDL	18.42±6.80	18.27±6.04	36.10±17.01	**<0.001**	1-2:0.99 1-3:<**0.001** 2-3:<**0.001**
LDL	91.95±19.78	98.18±12.15	118.12±44.19	**<0.001**	1-2:0.98 1-3:<**0.001** 2-3:0.009
Systolic blood pressure	110.00±8.17	115.90±10.41	121.38±14.76	**<0.001**	1-2:0.069 1-3:<**0.001** 2-3:0.104
Diastolic Blood Pressure	76.50±8.18	79.98±7.62	76.63±11.51	0.168	1-2:0.289 1-3:1.00 2-3:0.326
HbA1c	5.55±0.32	7.42±0.71	14.43±0.37	**<0.001**	1-2:<**0.001** 1-3:<**0.001** 2-3:<**0.001**
HOMA-IR	1.69(0.72-8.90)	3.38 (1.52-10.95)	8.15(1.20-66.60)	**<0.001**	1-2:1.00 1-3:<**0.001** 2-3:<**0.001**
Betatrophin	126.87±11.32	167.68±38.82	364.76±86.14	**<0.001**	1-2:0.091 1-3:<**0.001** 2-3:<**0.001**

p*: Multiple Comparison p**: Dual Comparison

Table 2. Single-predictor linear regression models for mean Betatrophin concentrations

Independent variable	Linear regression models β (95% CI)		
	β-coefficient	95% confidence interval	p value
HbA1c	0.89	22,63-38.71	**<0.001**
Age	0.11	-2.43-2.97	0.84
BMI	0.08	-9.47-4.390	0.47
Waist circumference	0.005	-2.56-2.48	0.97
Total cholesterol	0.074	-1.98-1.48	0.77
Triglycerides	0.216	-1.29-0.45	0.34
HDL	0.132	-0.88-3.79	0.22
VLDL	0.203	-2.68-6.58	0.41
LDL	0.074	-2.02-1.39	0.71
Insulin	0.088	-0.52-2.49	0.19
Systolic blood pressure	0.115	-0.38-2.88	0.13
Diastolic blood pressure	0.097	-0.64-3.41	0.18
Fasting Glucose	0.091	-0.27-0.13	0.47
HOMA-IR	0.106	-1.20-4.480	0.24
D-vit	0.042	-3.59-1.64	0.46

of meta-analysis conducted by Sheyu Li et al. betatrophin was reported to be statistically higher in patients with type 2 diabetes than non-diabetic patients (13). Although it were reported that betatrophin levels increased in T2DM in the general literature datas, there was no difference between the control group and controlled T2DM group in terms of betatrophin levels in our study. Although the literature data suggest that betatrophin levels increase in T2DM, Fenzi et al reported that there was no difference between diabetic and control groups in terms of betatrophin levels (14). A.B. Hassan et al. reported that there was no difference between the control group and T2DM group in terms of betatrophin levels (17). Our data and the literature data were insufficient to show the relationship between betatrophin and T2DM. Therefore, further studies are needed to understand the effect of betatrophin on T2DM.

In our study, betarophin levels were higher in the uncontrolled T2DM group compared to those with both healthy and controlled T2DM groups. Takebayashi et al and Espes et al.reported that there was no statistical difference in betatrophin levels between the T2DM and health groups but a statistically significant correlation between HbA1c and betatrophin levels (12,18). Al-dahri et al. reported a statistical correlation between betatrophin and fasting glucose levels (19). Sheyu Li et al. reported that betatrophin increased in T2DM as a result of metaanalysis but this increase in subgroup examination was only seen in obese T2DM patients (13). Our data and literature data suggest that betatrophin levels correlate with fasting glucose and HbA1c levels. Considering the our data showing the relationship between HbA1c and betatrophin in future research may contribute to elucidation of the mechanism between betatrophin and T2DM relationship.

In current study, we evaluated the factors affecting betatrophin level by single-predictor linear regression model. In the linear regression model, it was found that HbA1c level had a significant effect on betatrophin level. Daniel et al. and J. Z. Zhou et al reported that betatrophin levels correlated only with HbA1c levels in diabetic and healthy groups (20,21). The data we obtained were similar to those of Daniel's and Zhou's datas. Takebayashi et al reported that betatrophin levels correlated with hbA1c, blood sugar and HDL levels in their study with poorly controlled diabetes patients (18). Sheyu Li et al. reported that age, sex, lipid level, insulin resistance, body mass and blood sugar affect betatrophin levels (13). Based on the general literature data and our data, there was a

significant correlation between HbA1c and betatrophin. While the controversial relationship between T2DM and betatrophin is being investigated, HbA1c levels may need to be considered. In further studies, it may be possible to obtain more reliable data by grouping participants according to HbA1c levels rather than as a diabetic and healthy group.

CONCLUSION

In conclusion we found higher betatrophin levels in the group with uncontrolled diabetes in our study. There was no significant difference in betatrophin levels between the controlled T2DM group and the healthy group. Our data found that betatrophin level showed a significant positive correlation with hba1c level. For understanding these findings, a future study with larger numbers of patients and longer observation period is needed.

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