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Trabajo Original

Obesidad y síndrome metabólico

Serum betatrophin level increased in subjects with metabolic syndrome: a case-control study

Aumento del nivel de betatrofina en suero en sujetos con síndrome metabólico: estudio de casos y controles

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Abstract

Background: Betatrophin is a novel adipokine that provokes pancreatic β-cell proliferation and is involved in lipid metabolism.

Aims: This study aims to evaluate the role of serum betatrophin in metabolic syndrome (MetS).

Methods: A hospital-based, age-/gender-matched case control study was conducted. The serum betatrophin level was evaluated by enzyme-linked immunosorbent assay. Serum concentrations of 12 adipokines were measured to assess their associations with serum betatrophin, using commercial Adipokine Magnetic Bead Panel kits. Statistical analyses included bivariate correlation, receiver operating characteristic (ROC) curve, and multivariate stepwise linear regression.

Results: Serum betatrophin showed a higher level in MetS patients (997.36 ± 475.92 pg/ml, p = 0.001) compared with controls (735.35 ± 526.51 pg/ml). Compared with the lowest tertile, the highest tertile of serum betatrophin level indicated an association with higher risk of MetS (adjusted odds ratio = 3.521, 95% confidence interval [CI] [1.191-10.413], p = 0.023). ROC curve of betatrophin was developed to predict the presence of MetS (area under ROC = 0.682 [95% CI, 0.597-0.767], p < 0.001). Furthermore, betatrophin correlated with several parameters, e.g. age (r = 0.286, p < 0.001), body mass index (r = 0.160, p = 0.046), waist-to-hip ratio (r = 0.241, p = 0.002), high-density lipoprotein cholesterol (r = -0.167, p = 0.037), low-density lipoprotein cholesterol (r = -0.195, p = 0.015), fasting plasma glucose (r = 0.266, p = 0.001), hemoglobin A1C (r = 0.314, p < 0.001), homeostasis model assessment of insulin resistance (r = 0.272, p = 0.001), and various adipokines, e.g. resistin (r = 0.571, p < 0.001), interleukin-8 (r = 0.435, p < 0.001), tumor necrosis factor-α (r = 0.295, p = 0.011) and lipocalin-2 (r = 0.346, p = 0.003).

Conclusions: This study supports that serum betatrophin plays an important role in MetS, involving the regulations of glucose and lipid metabolism and inflammation.

Key words:

Betatrophin. Angiopoeitin-like 8 (ANGPTL8). Adipokine. Hepatokine. Metabolic syndrome.

Resumen

Introducción: la betatrofina es una novedosa adipoquina que provoca la proliferación de células β pancreáticas e interviene en el metabolismo de los lípidos.

Objetivos: el propósito de este estudio es evaluar el papel de la betatrofina en el síndrome metabólico.

Método: se llevó a cabo un estudio hospitalario de casos y controles según sexo y edad. El nivel de betatrofina en suero fue evaluado mediante ensayo por inmunoabsorción ligado a enzimas. Se midieron las concentraciones en suero de 12 adipoquinas para evaluar las asociaciones con la betatrofina usando los kits comerciales Adipokine Magnetic Bead Panel. Los análisis estadísticos incluyeron correlación bivariada, análisis de curva ROC y análisis de regresión lineal multivariable.

Resultados: el nivel de betatrofina en suero fue más elevado en pacientes con síndrome metabólico (997,36 ± 475,92 pg/ml, p = 0,001) que en los controles (735,35 ± 526,51 pg/ml). Frente al tercil más bajo, el tercil más alto del nivel de betatrofina mostró una asociación con mayor riesgo de síndrome metabólico (odds ratio ajustado = 3,521, intervalo de confianza [IC] 95% [1,191-10,413], p = 0,023). Se desarrolló la curva ROC de betatrofina para pronosticar la presencia de síndrome metabólico (área bajo la curva ROC = 0,682 [95% IC, 0,597-0,767], p < 0,001). Además, la betatrofina mostró correlación con distintos parámetros, como edad (r = 0,286, p < 0,001), índice de masa corporal (r = 0,160, p = 0,046), índice cintura-cadera (r = 0,241, p = 0,002), lipoproteína de alta densidad (r = -0,167, p = 0,037), lipoproteína de baja densidad (r = -0,195, p = 0,015), glucosa plasmática en ayunas (r = 0,266, p = 0,001), hemoglobina A1C (r = 0,314, p < 0,001), índice de resistencia a la insulina mediante HOMA (r = 0,272, p = 0,001) y diversas adipoquinas, entre ellas resistina (r = 0,571, p < 0,001), interleucina-8 (r = 0,435, p < 0,001), factor de necrosis tumoral alfa (r = 0,295, p = 0,011) y lipocalina-2 (r = 0,346, p = 0,003).

Conclusiones: este estudio demuestra que la betatrofina en suero desempeña una importante labor en el síndrome metabólico, implicando la regulación del metabolismo de la glucosa y los lípidos y la inflamación.

Palabras clave:

Betatrofina. Angiopoyetina-8 (ANGPTL8). Adipoquina. Hepatoquina. Síndrome metabólico.

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INTRODUCTION

The prevalence of obesity-related metabolic disorders is mounting to epidemic proportions in the world (1-3). Obesity, insulin resistance (IR), dyslipidemia, hyperglycemia, and hypertension are frequently coincident in one individual, in a disorder defined as metabolic syndrome (MetS) (4).

Yi et al. (5) identified betatrophin, also called angiopoeitin-like 8 (ANGPTL8) or lipasin as a 22-kDa novel adipokine that promotes a remarkable pancreatic beta cells proliferation and expand beta cells mass in IR mice. Chen et al. (6) and Jiao et al. (7) confirmed afterwards the potential role of betatrophin in the proliferation of beta cells and the regulation of glucose metabolism.

In the meantime, recent evidence supports a link between betatrophin and lipid metabolism. Ren et al. (8) found that betatrophin was significantly induced during adipogenesis in 3T3-L1 cells, as well as primary cultures of human adipocytes, whereas knockdown of betatrophin gene leaded to down regulated adipogenesis. Quagliarini et al. (9) supported that betatrophin was involved in the regulation of postprandial triglyceride (TG) and fatty acid metabolism. Furthermore, Zhang et al. (10) identified betatrophin as a hepatokine that increases serum TG content, via reducing TG clearance. Finally, Gusarova et al. (11) confirmed again that overexpression of betatrophin in mice liver doubled plasma TG levels.

Inspired by the experimental advance, a series of clinical studies were performed to evaluate the role of betatrophin in obesity-related metabolic disorders, e.g. diabetes and morbid obesity (12-16). A case-control study of T2DM by Xie et al. (17) indicated that, compared with subjects of normal glucose tolerance, patients with T2DM witnessed a higher level of serum betatrophin. Furthermore, a cross-sectional study in 149 women by Barja-Fernández et al. (13) showed that, compared with normal weight, women with anorexia presented an elevated level of serum betatrophin, whereas its level decreased in morbid obese women.

Crujeiras et al. (18) performed previously a clinical intervention study which showed that serum betatrophin increased in obese MetS patients, compared with subjects with normal weight. In this study, thus, we conducted a hospital-based case-control study to evaluate the role of serum betatrophin in MetS and to investigate its associations with biochemical parameters and serum adipokines.

SUBJECTS AND METHODS

SUBJECTS

Seventy-eight MetS subjects were consecutively recruited from the subjects who attended to the outpatient department of the First Affiliated Hospital, Zhejiang University, from January to May 2015. Based on a principle of age- and gender-match, 78 controls were selected from the annual health examination during the same period. Participants were excluded if they had malignant tumor, severe cardiopulmonary disorders, renal/thyroid dysfunction, severe inflammatory diseases, viral-/drug-induced/autoimmune liver diseases, pregnancy, or excessively alcoholic consumption.

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

Anthropometric examinations were performed as previously described (19). Besides, all subjects were informed to complete an overnight fast. About 10 ml whole blood samples were collected from every subject, and then serum samples were separated for immediate analysis or further analysis (stored at -80 °C). Serum analyses were measured using a Hitachi 7600 Auto-Analyzer (Hitachi, Tokyo, Japan) or an Abbott-Architect Immunoanalyzer (Abbott Laboratories, Abbott Park, IL).

MEASUREMENT OF SERUM BETATROPHIN

Serum betatrophin was measured by a commercial enzyme-linked immunosorbent assay (ELISA) (catalogue no. E11644h; Wuhan Eiaab Science, Wuhan, China; intra-assay coefficient of variation [CV] < 4.8%; interassay CV < 7.2%) (14). Meanwhile, its level was validated by an ELISA kit from another provider (catalogue no. SEW803Hu; USCN Life science Inc., Wuhan, China; intra-assay CV < 10%; interassay CV < 12%) (16) and western blotting (Anti-C19orf80, catalogue no. ab180915; Abcam Ltd., Cambridge, UK, and β-Actin Rabbit mAb, catalogue no. 8457; Cell Signaling Technology, Inc., Danvers, MA) (20).

MILLIPLEX® HUMAN ADIPOKINE MAGNETIC BEAD PANEL KITS

The MILLIPLEX® Human Adipokine Magnetic Bead Panels were performed to measure 12 serum adipokines as previously described (19) (cat. # HADK1MAG-61K and cat. # HADK2MAG-61K).

DIAGNOSTIC STANDARD OF METS

The MetS was defined using the updated National Cholesterol Education Program/Adult Treatment Panel III criteria for Asian Americans as having at least three of the following parts (21): a) waist circumference ≥ 90 cm for men or ≥ 80 cm for women; b) TG ≥ 1.7 mmol/l; c) high-density lipoprotein cholesterol (HDL-C) ≤ 1.03 mmol/l for men or ≤ 1.30 mmol/l for women; d) blood pressure ≥ 130/85 mmHg or current use of antihypertensive medications; or e) fasting plasma glucose (FPG) ≥ 5.6 mmol/l, T2DM previously diagnosed by a physician, or current use of antidiabetic medications.

STATISTICAL METHODS

Normally distributed variables were presented as mean ± standard deviation (SD). Normality of distribution was tested with the Kolmogorov-Smirnov test, and variables with a skewed distribution underwent an lg (x) transformation to achieve a normal distribution and were presented as median value (interquartile range). The Student's t test or Mann-Whitney U test for continuous variables, and $\chi 2$ test or Kruskal-Wallis test for categorical variables were used to compare parameters between two groups. To assess the relationship between betatrophin and MetS, we calculated the adjusted odds ratio (OR) and 95% confidence interval (CI) with a multivariable binary logistic regression. The receiver operating characteristic (ROC) curve of betatrophin was developed to predict the presence of MetS. Bivariate correlation analyses were performed using Pearson's correlation analysis or Spearman rho correlation analysis. Multivariate stepwise linear regression analysis was conducted for betatrophin (dependent variable), including the variables that significantly correlated with betatrophin as independent variables. All statistical analyses and plotting were performed using Stata (version MP 11.2, StataCorp LP, College Station, Texas, USA) and GraphPad Prism (version 6.0, GraphPad Software, Inc., San Diego, CA, USA). Power of sample size was calculated by G*Power (version 3.1, Heinrich-Heine-Universität Düsseldorf, Germany) (22). A two-sided $p < 0.05$ was considered as statistically significant.

RESULTS

VALIDATION OF ELISA

The validation of betatrophin levels revealed a fine consistency ($r = 0.8703$, $p < 0.001$) between ELISA kits from two providers (Fig. 1).

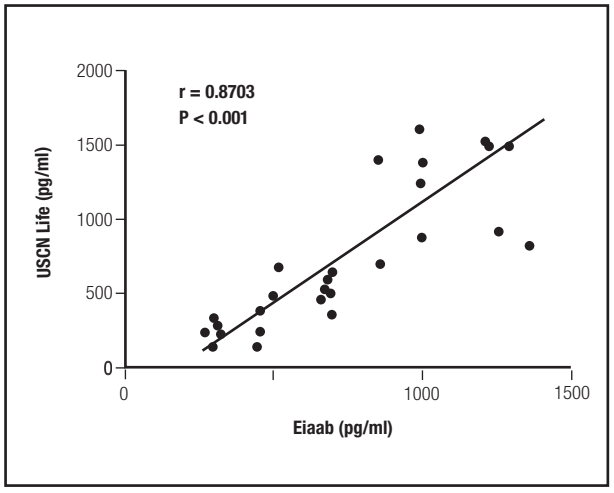

Figure 1.

Validation of ELISA Kits. Correlation of serum betatrophin levels between USCN Life ELISA kit and Eiaab ELISA kit (n = 30, r = 0.8703, p < 0.001).

Western blotting detection of serum betatrophin among four serum samples indicated a consistent trend with the ELISA result (Fig. 2).

POWER OF SAMPLE SIZE

Given the serum betatrophin concentrations and the numbers of case and control, the power of the sample size was 0.945 (effect size d = 0.522) (Fig. 3).

CHARACTERISTICS OF ALL SUBJECTS

The characteristics of 156 subjects (78 cases and 78 age-/gender-matched controls) are shown in table I. Serum betatrophin presented a higher level in MetS subjects (997.36 ± 475.92 pg/ml, p = 0.001), compared with controls (735.35 ± 526.51 pg/ml) (Table I and Fig. 4A).

BETATROPHIN TERTILES

All 156 subjects were divided into three groups, according to the tertiles of serum betatrophin concentrations. The frequency of MetS showed an upward trend (T1: 26.9%, T2: 55.8%, and T3: 67.3%; $p < 0.001$), as betatrophin concentration increased among its tertiles (Fig. 4B).

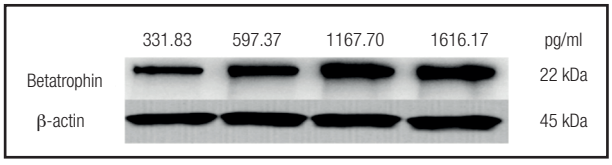

Figure 2.

Validation of ELISA by Western Blotting. Representative western blot detection of betatrophin in four serum samples.

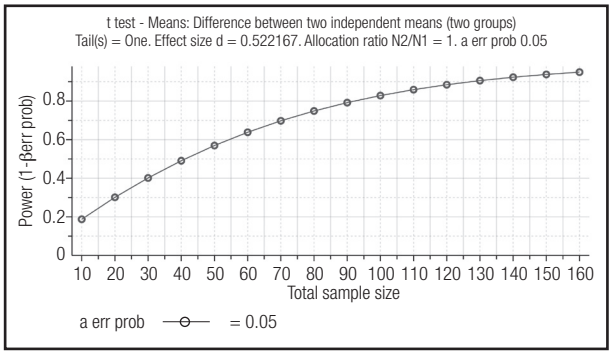

Figure 3.

Power of sample size. Given the serum betatrophin concentrations and the numbers of case (n = 78) and control (n = 78), the power of the sample size was 0.945 (effect size d = 0.522).

Table I. Characteristics of subjects according to NAFLD

Parameters	Control	NAFLD	p value
No. of subjects	78	78	
Age (years)	53.72 ± 9.14	56.56 ± 10.76	0.077
Male, n (%)	50, 64.1%	50, 64.1%	1.000
BMI (kg/m^2)	23.77 3.11	25.60 3.54	0.001#
WHR	0.880 0.085	0.943 0.048	< 0.001#
Betatrophin (pg/ml)	735.35 526.51	997.36 475.92	0.001#
TG (mmol/l)	1.15 (0.85-1.56)	1.68 (1.13-2.63)	< 0.001#
TC (mmol/l)	4.71 0.95	4.41 1.13	0.077
HDL-C (mmol/l)	1.31 0.33	1.00 0.26	< 0.001#
LDL-C (mmol/l)	2.77 0.73	2.35 0.91	0.002#
VLDL-C (mmol/l)	0.68 (0.49-0.84)	0.61 (0.82-1.10)	< 0.001#
FPG (mmol/l)	5.18 (4.69-5.75)	6.65 (5.47-9.14)	< 0.001#
HbA1c (%)	5.90 (5.48-6.90)	7.45 (6.20-9.73)	< 0.001#
FINS (μU/ml)	12.10 (8.20-17.73)	13.20 (9.55-20.15)	0.209
HOMA-IR	2.84 (2.08-4.20)	4.00 (2.62-6.60)	0.001#
Fasting C peptide (ng/ml)	0.80 (0.55-1.40)	1.08 (0.81-1.60)	0.007#

Data are mean ± SD or median (interquartile range) for continuous variables. #p value is less than 0.01.

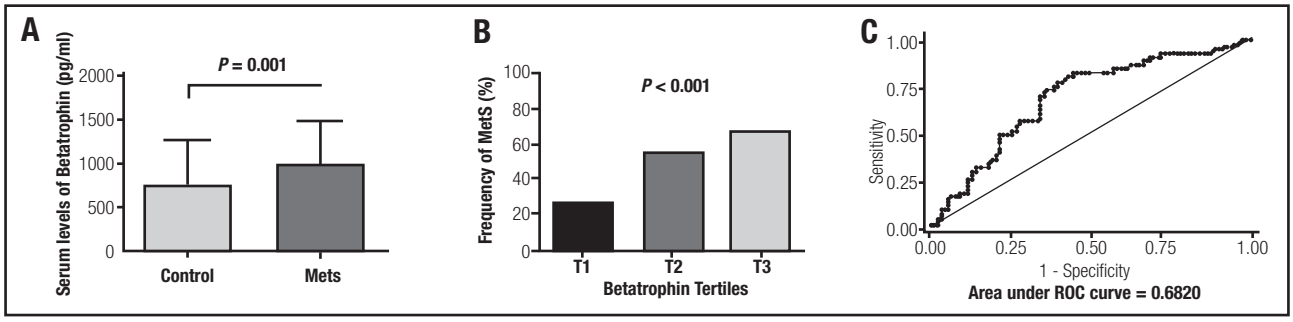

Figure 4.

Serum betatrophin levels and metabolic syndrome. A. Comparisons of serum betatrophin levels (pg/ml, mean ± SD) between control (735.35 ± 526.51) and MetS (997.36 ± 475.92), p = 0.001. B. Frequency (%) of MetS according to betatrophin tertiles (T1: 26.9%, T2: 55.8%, and T3: 67.3%, p < 0.001). C. ROC curve of betatrophin to predict the presence of MetS (AUROC 0.682 [95% CI 0.597-0.767], p < 0.001).

ODD RATIOS OF METS

Table II reveals that, in comparison with the first tertile, the second of betatrophin indicated no association with the presence of MetS (adjusted OR = 3.850, 95% CI [0.570-26.007], p = 0.167), after controlling various parameters of glucose and lipid metabolism. However, the third tertile revealed its association with higher odds of MetS (adjusted OR = 3.521, 95% CI [1.191-10.413], p = 0.023), compared with the first tertile.

ROC CURVE OF BETATROPHIN

ROC curve of betatrophin was developed to predict the presence of MetS (Fig. 4C). Area under ROC was 0.682 (95% CI 0.597-0.767, p < 0.001), with a sensitivity of 76.9%, a specificity of 60.3% and an accuracy of 68.0%, when cut-off value of betatrophin was 681.11 pg/ml.

CORRELATIONS WITH ANTHROPOMETRIC/ BIOCHEMICAL PARAMETERS AND ADIPOKINES

In table III, all subjects showed positive associations of betatrophin with age (r = 0.286, p < 0.001), body-mass index (BMI) (r = 0.160, p = 0.046), and waist-to-hip ratio (WHR) (r = 0.241, p = 0.002).

In terms of lipid and cholesterol metabolism, betatrophin presented inverse associations with total cholesterol (TC) (r = -0.232,

Table II. ORs and 95% CIs of the presence of MetS by betatrophin tertiles

		Tertile 1	Tertile 2	95% CI	p for trend	Tertile 3	95% CI	p for trend
MetS	Model 0	Reference	3.422	1.505-7.783	0.003#	2.364	1.551-3.604	< 0.001#
	Model 1	Reference	3.428	1.496-7.856	0.004#	2.319	1.486-3.619	< 0.001#
	Model 2	Reference	2.567	1.011-6.517	0.047*	1.924	1.178 – 3.145	0.009#
	Model 3	Reference	2.817	0.804-9.874	0.106	3.297	1.320-8.237	0.011*
	Model 4	Reference	2.496	0.876-7.111	0.087	1.754	1.024-3.002	0.041*
	Model 5	Reference	3.850	0.570-26.007	0.167	3.521	1.191-10.413	0.023*

*Model 0: Unadjusted; Model 1: Adjusted for age and gender; Model 2: Adjusted for age, gender, BMI and WHR; Model 3: Adjusted for age, gender, BMI, WHR, TG, TC, HDL-C, LDL-C, and VLDL-C; Model 4: Adjusted for age, gender, BMI, WHR, FPG, HbA1c, FINS, HOMA-IR, and fasting C peptide; Model 5: Adjusted for age, gender, BMI, WHR, TG, TC, HDL-C, LDL-C, VLDL-C, FPG, HbA1c, FINS, HOMA-IR, and fasting C peptide.*p value is less than 0.05; #p value is less than 0.01.*

p = 0.004), HDL-C (r = -0.167, p = 0.037), and LDL cholesterol (LDL-C) (r = -0.195, p = 0.015), whereas betatrophin correlated positively with FPG (r = 0.266, p = 0.001), hemoglobin A1C (HbA1c) (r = 0.314, p < 0.001), fasting insulin (FINS) (r = 0.162, p = 0.043), homeostasis model assessment of insulin resistance HOMA-IR (r = 0.272, p = 0.001), and fasting C peptide (r = 0.179, p = 0.025), which are parameters of glucose metabolism and pancreatic function.

Table III also reveals the associations between betatrophin and various adipokines, including resistin (r = 0.571, p < 0.001), interleukin (IL)-8 (r = 0.435, p < 0.001), tumor necrosis factor-α (r = 0.295, p = 0.011), and lipocalin-2 (r = 0.346, p = 0.003).

MULTIVARIATE LINEAR REGRESSION

In the multiple linear regression analysis (Table IV), the model (corrected $r^2 = 0.449$, p < 0.001) that best predicted betatrophin levels included resistin, fasting C peptide, IL-8 and HbA1c as predictive variables.

DISCUSSION

This case control study revealed an elevated serum level of betatrophin in subjects with MetS, compared with controls. Moreover, a higher level of serum betatrophin revealed an association with the presence of MetS.

MetS is currently in a widely prevalent but not well-recognized situation. The complex pathogenetic condition involves glucose and lipid metabolism, pancreatic function, and various adipocyte/hepatocyte-derived cytokines (23), while betatrophin is identified as an adipokine/hepatokine related to the function of pancreatic islets and the regulation of lipid metabolism (5,9,10,24). Thus, we conducted a case control study to assess the hypothesis whether serum betatrophin relates to MetS.

To begin with, it revealed that serum betatrophin increased in subjects with MetS, compared with controls, consistent with the clinical intervention study by Crujeiras et al. (18). Furthermore, via

Table III. Correlations of serum betatrophin with various anthropometric/biochemical parameters and adipokines

Categories	Parameters	r value	p value
Anthropometrics	Age	0.286	< 0.001#
	BMI	0.160	0.046*
	WHR	0.241	0.002#
Lipid and cholesterol Metabolism	TG[a]	-0.062	0.439
	TC	-0.232	0.004#
	HDL-C	-0.167	0.037*
	LDL-C	-0.195	0.015*
	VLDL-C[a]	-0.011	0.894
Glucose metabolism and insulin function	FPG[b]	0.266	0.001#
	HbA1c[b]	0.314	< 0.001#
	FINS[a]	0.162	0.043*
	HOMA-IR[a]	0.272	0.001#
	Fasting C Peptide[a]	0.179	0.025*
Inflammation	IL-6[b]	0.145	0.222
	IL-8	0.435	< 0.001#
	MCP-1	0.014	0.903
	Lipocalin-2	0.346	0.003#
	TNF-α	0.295	0.011*
	NGF[b]	0.012	0.923
	HGF	0.079	0.509
	Adipsin	0.038	0.749
Insulin resistance	Resistin	0.571	< 0.001#
	Adiponectin	-0.079	0.509
Energy homeostasis	Leptin[a]	0.092	0.438
Fibrinolysis	PAI-1	0.130	0.273

*HGF: Hepatocyte growth factor; MCP-1: Monocyte Chemoattractant Protein-1; NGF: Nerve growth factor; OR: Odds ratio; PAI-1: Plasminogen activator inhibitor-1. [a]lg(x) transformation was performed because of a skewed distribution. [b]Spearman correlation analysis.*p value is less than 0.05; #p value is less than 0.01.*

Table IV. Multiple linear regression analyses with betatrophin as dependent variable

	Variable	r^2	β	p value
Model 1		0.316		< 0.001#
	Resistin		0.571	< 0.001#
Model 2		0.387		< 0.001#
	Resistin		0.563	< 0.001#
	Fasting C peptide		0.280	0.003#
Model 3		0.422		< 0.001#
	Resistin		0.477	< 0.001#
	Fasting C peptide		0.259	0.005#
	IL-8		0.223	0.025*
Model 4		0.449		< 0.001#
	Resistin		0.446	< 0.001#
	Fasting C peptide		0.278	0.002#
	IL-8		0.221	0.023*
	HbA1c		0.186	0.041*

*Values are corrected r^2 (r^2), standardized coefficients (β) and associated p values. *p value is less than 0.05; #p value is less than 0.01.*

the analyses of binary logistic regression and the development of ROC curve, it was found that a higher level of serum betatrophin was associated with the presence of MetS.

When it comes to correlations with various parameters, serum level of betatrophin presented correlations with BMI and WHR, which are widely accepted parameters of obesity and indicators of MetS risk (25,26).

In terms of glucose metabolism and pancreatic function, the correlations of betatrophin with a series of parameters, including FPG, HbA1c, FINS, HOMA-IR and fasting C peptide, were observed, as well as with resistin, that is an adipokine associated with IR (28). Based on the experimental advance, an elevated level of serum betatrophin in subjects with MetS might be related to a compensatory regulation of the whole body, which promotes beta cells proliferation and insulin secretion, and results in a consequent adaption to higher FPG or hepatic IR (15).

Consistent with the previous studies concluding that betatrophin might regulate lipid metabolism, possibly involving lipoprotein lipase activity (8,9,10,29,30), this study presented close associations of betatrophin with serum TC, HDL-C, and LDL-C rather than TG and low-density lipoprotein cholesterol (VLDL-C).

It has been widely accepted that inflammation can be detected in a series of organs of energy homeostasis, e.g. liver, fat, muscle, and islets, when human expose themselves to the condition of over-nutrition (31,32). It has been proven that there is a remarkable accumulation of immune cells in adipose tissue, islets and liver in obese individuals. Meanwhile, increased levels of various cytokines and chemokines were found in subjects with IR and metabolic disorder (33,34). This study revealed that three serum adipokines of inflammation, i.e. TNF-α, lipocalin-2 and IL-8, significantly correlated with serum betatrophin (28,35). Lastly, a predicting model including resistin, fasting C peptide, IL-8 and HbA1c explained 44.9% of the total variability of serum betatrophin concentration.

In terms of strengths, the serum levels of 12 adipokines concerned inflammation and insulin resistance were measured using Human Adipokine Magnetic Bead Panel kits.

Some limitations of the study merit comment. A design of a follow-up study would be better to determine the pathogenetic association between serum betatrophin and MetS. Thus, in the future, a long-term cohort study with a larger population is needed.

The study suggested an elevated concentration of serum betatrophin in subjects with MetS, in comparison with controls. Serum betatrophin indicated an association with higher risk of MetS. Furthermore, circulating betatrophin correlated with the parameters concerned obesity, e.g. BMI and WHR, and biochemical parameters of glucose and lipid metabolism, e.g. TC, HDL-C, LDL-C, HbA1c, FINS, HOMA-IR, FPG, and fasting C peptide. Lastly, betatrophin presented correlations with several adipokines of inflammation and insulin sensitivity, including resistin, TNF-α, lipocalin-2 and IL-8. Therefore, it supports the idea that serum betatrophin plays an important role in MetS, involving the regulations of glucose and lipid metabolism and inflammation.

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