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The effects of overt hypothyroidism on adipose tissue and serum betatrophin levels

Serum aşikar hipotiroidizmin adipöz dokuda etkileri ve serum betatrophin düzeyleri

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Abstract

Aim: Betatrophin, also known as angiopoietin-like peptide-8, is an adipokine in glycoprotein structure synthesized from adipose tissue and liver. Betatrophin plays a role in fat and energy metabolism by inhibiting lipoprotein lipase, the key enzyme in the hydrolysis of plasma lipoproteins. Although thyroid hormones have an active role in energy metabolism, their relationship with cholesterol and lipid metabolism is not clear. In our study, we aimed to investigate the relationship of serum betatrophin levels with energy and lipid metabolism in patients with overt hypothyroidism.

Methods: This is a case-control study. The mean age of 44 patients (20 males, 24 females) with hypothyroidism was 44.7 (13.8). A total of 40 healthy volunteers, including 19 males and 21 females, were included in the study as a control group. The mean age of healthy volunteers was 44.6 (14.4) years. Fasting blood glucose, AST, ALT, urea, creatinine, TSH, free T3, free T4, HDL-cholesterol, LDL-cholesterol, triglyceride (TG), total cholesterol, anti-TPO, anti-TG, insulin, HOMA-IR levels and serum betatrophin levels were measured by ELISA and compared in both groups.

Results: Serum betatrophin levels were significantly higher in patients diagnosed with hypothyroidism compared to the control group (P=0.001). Serum betatrophin levels were positively correlated with TSH, TG and total cholesterol, and negatively correlated with HDL, free T3 and free T4 levels. There was no significant difference in the comparison of patients regarding anti-TPO levels in the hypothyroidism group (P=0.78).

Conclusion: In our study, we found that serum betatrophin levels were high in hypothyroid patients. This study may be useful in the development of treatments targeting betatrophin in clinical practice.

Keywords: Hypothyroidism, Betatrophin, Lipoprotein lipase

Öz

Amaç: Angiopoietin like peptit-8 olarak da bilinen betatrofin, adipöz doku ve karaciğerden sentezlenen glikoprotein yapısında bir adipokindir. Betatrofin, plazma lipoproteinlerinin hidrolizinde anahtar enzim olan lipoprotein lipaz'ı inhibe ederek yağ ve enerji metabolizmasında rol oynar. Tiroid hormonları enerji metabolizmasında aktif rol almasına rağmen kolesterol ve lipid metabolizmasıyla ilişkisi net değildir. Yaptığımız çalışmada hipotiroidi tanılı hastalarda serum betatrofin düzeylerinin enerji ve lipid metabolizması ile ilişkisini incelemeyi amaçladık.

Yöntemler: Bu bir vaka kontrol çalışmasıdır. Çalışmaya katılan hipotiroidi tanılı 44 hastanın (20 erkek, 24 kadın) yaş ortalaması 44,7 (13,8) idi. 19 Erkek ve 21 kadın olmak üzere toplam 40 sağlıklı gönüllü de kontrol grubu olarak çalışmaya katıldı. Sağlıklı gönüllülerin yaş ortalaması: 44,6 (14,4) yıl idi. Her iki grupta da açlık kan şekeri, AST, ALT, üre, kreatinin, TSH, serbest T3, serbest T4, HDL-kolesterol, LDL-kolesterol, trigliserit (TG), total kolesterol, anti-TPO, anti-TG, insülin, HOMA-IR düzeyleri ve ELISA yöntemiyle serum betatrofin düzeyleri ölçüldü.

Bulgular: Kontrol grubuna kıyasla hipotiroidi tanısı konan hastalarda serum betatrofin düzeyleri anlamlı derecede yüksekti. (P=0,001). Serum betatrofin düzeyleri ile TSH, TG ve total kolesterol arasında pozitif yönde; HDL, serbest T3 ve serbest T4 ile negatif yönde korelasyon vardı. Hipotiroidili hasta grubunda anti-TPO yüksekliğine göre yapılan karşılaştırmada anlamlı farklılık yoktu (P=0,78).

Sonuç: Çalışmamızda hipotiroidi hastalarında serum betatrofin düzeylerinin yüksek olduğunu bulduk. Bu çalışma, klinik uygulamada betatrofeni hedef alan tedavilerin geliştirilmesinde faydalı olabilir.

Anahtar kelimeler: Hipotiroidizm, Betatrofin, Lipoprotein lipaz

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Introduction

Overt hypothyroidism affects between 4 and 10% of the world population [1]. Thyroid hormones regulate energy metabolism and affect the tissue response of other hormones in the organism [2,3]. Changes in the levels of thyroid hormones may affect muscle and visceral fat tissue mass, and may be involved in the pathogenesis of insulin resistance, type 2 diabetes mellitus and cardiovascular events [4]. TSH affects the function of the TSH receptor (TSHR) protein and stimulates adipokine production in abdominal adipose tissue and preadipocytes in humans [5]. Despite the important effects of thyroid hormones on intermediate metabolism and energy homeostasis, its relationship with cytokines secreted from adipose tissue is still unclear [6]. Betatrophin, also known as ANGPLT-8, is a 188 amino acid and 22 kDa glycoprotein produced in the liver and adipose tissue [7,8]. Betatrophin inhibits LPL, one of the key enzymes for lipid metabolism [9]. LPL is the enzyme that catalyzes the breakdown of triglycerides to free fatty acids [10]. LPL hyperactivity was associated with decreased plasma TG levels and decreased cardiovascular risks, whereas LPL function loss was associated with hypertriglyceridemia and increased cardiovascular risk [10,11]. Serum betatrophin levels and triglyceride levels were positively correlated in previous studies [8,12].

Betatrophin, unlike the other members of the ANGPTL family, does not carry the fibrinogen-like region, coiled spiral area and disulfide bond [13]. Therefore, betatrophin is considered as an atypical member in the ANGPTL family and a newly emerged player in lipid metabolism [9,14].

There are recent studies investigating the effects of betatrophin on beta-cell expansion and islet function [15]. In this study, we tried to explain the relationship between hypothyroidism and fat metabolism by serum betatrophin levels. This study may help demonstrate the effects of hypothyroidism on adipose tissue.

Materials and methods

Design and patients

44 patients between the ages 20 and 69, who were diagnosed with overt hypothyroidism in Internal Medicine Department between September 2017 and February 2018 and 40 healthy volunteers were included in this study.

In our study, TSH> 4.94 mIU / L, FT4 <9.01 ng / dL and / or freeT3 <2.5 pg / mL were defined as overt hypothyroidism. Patients with diabetes mellitus, acute and chronic renal failure, hypertension, coronary heart disease, congestive heart failure, peripheral arterial disease, cerebrovascular accident, malignancy, acute and chronic liver diseases, pituitary gland and hypothalamus diseases, major operation history in the last three months, rheumatic diseases, severe psychiatric conditions, malabsorption syndrome, pregnancy, alcohol intake and smoking were excluded. Blood was obtained from all participants for routine laboratory tests including fasting glucose, urea, creatinine, AST, ALT, TSH, free T3, free T4, TPO-Ab, TG-Ab, HDL-cholesterol, LDL-cholesterol, triglyceride, and total cholesterol levels. Routine laboratory tests were performed using Cobas Elecsys 601 (Roche Diagnostics, Switzerland). An additional tube of blood was obtained from the volunteers for the measurement of serum betatrophin levels. Blood tubes rested at room temperature for 30 minutes, then centrifuged at 4000 rpm for 10 min. The resulting sera were stored at -80 ° C.

BMI was obtained by dividing the patient's weight in kg by the square of height in meters. Insulin resistance was calculated by HOMA-IR index: Fasting serum insulin (uIU / mL) * Fasting serum glucose (mg / dL) / 405. Patients with HOMA-IR index> 2.5 were accepted as insulin resistance.

Measurements of betatrophin

Human ANGPTL-8 (betatrophin) levels were measured by using an enzyme-linked immunosorbent assay. Performance characteristics of betatrophin assay were as folows: The analytical (linear) measurement range was 11.4-1200 ng / mL and the minimum detection limit was 10.2 ng / mL. The reported intraassay and interassay CV’s were 8.5% and 7.7%, respectively.

Ethical committee approval

Our study was approved by the Committee of Ethics Committee of Okmeydanı Training and Research Hospital of Health Sciences University and it was complied with the principles of Helsinki Declaration (date: 19.12.2017; no: 784).

Statistical analysis

IBM SPSS version 25.0 (SPSS Inc, Chicago Illinois) statistical program was used. The distribution of variables was measured by Kolmogorov-Smirnov test. The data were expressed as mean (standard deviations, SD) for normally distributed variables and % frequencies for non-normally distributed and categorical variables. In the comparison of parametric data between two independent groups, independent sample t-test was performed. Mann-Whitney U test was used for the analysis of non-normally distributed data. The correlation of betatrophin, a non-normally distributed variable, to other parameters was analyzed by non-parametric Spearman test.

Multivariate regression analysis and stepwise option were used to evaluate all independent variables with serum betatrophin as the dependent variable. As a result of the regression analysis, independent variables other than TSH and triglyceride were excluded, because they were not related to serum betatrophin levels. All calculated *P*-values were bidirectional and *P*-values <0.05 were considered statistically significant.

Results

The demographic and laboratory data of study groups are summarized in table 1.

When compared with healthy controls, TSH, anti TPO, anti TG, serum triglyceride and serum betatrophin levels significantly increased in patients with hypothyroidism, while free T4 and free T3 decreased. Age, sex, BMI, Fast glucose, HOMA-IR, AST, ALT, urea, creatinine, HDL cholesterol, LDL-cholesterol and total cholesterol levels were not different.

The results of the correlation analysis between serum betatrophin levels and other parameters are summarized in table 2 and figure 1. There was a positive correlation between betatrophin levels of all participants and TSH, TG and total cholesterol levels. A negative correlation was found between

betatrophin levels of all participants and free T3, free T4 and HDL-cholesterol levels.

Multivariate regression analysis results are presented in table 3. Comparison of Anti-TPO> 9 and Anti-TPO <9 patients using the Mann-Whitney-U test is presented in table 4.

Table 1: The demographic and laboratory features for the two groups of hypothyroidism and euthyroidism (control group)

	Control group mean (SD) (n:40)	Hypothyroid patients mean (SD) (n:44)	*P*-value
Age (year)	44.65 (14.4)	44.7 (13.83)	0.986[a]
Sex			
Male (%)	19 (47.50%)	20 (45.45%)	0.788[b]
Female (%)	21 (52.50%)	24 (54.55%)	
BMI (kg/m^2)	25.80 (3,27)	26.75 (3.95)	0.236[a]
Fasting glucose (mg/dL)	92.52 (8.68)	91.93 (16.18)	0.795[c]
Fasting insülin (mg/dL)	5.33 (1.29)	8.25 (2.42)	0.056[c]
HOMA-IR	2.77 (1.96)	3.05 (1.84)	0.078[c]
Urea (mg/dL)	28.25 (8.97)	29.23 (10.12)	0.642[a]
Creatinine (mg/dL)	0.74 (0.18)	0.67 (0.14)	0.250[a]
AST (U/L)	19.45 (7.16)	20.15 (6.73)	0.492[c]
ALT (U/L)	19.55 (7.94)	18.02 (7.28)	0.422[c]
HDL-cholesterol(mg/dL)	50.15 (7.88)	44.25 (9.10)	0.308[a]
LDL-cholesterol(mg/dL)	117.78 (36.41)	124.02 (35.35)	0.428[a]
Triglyceride(mg/dL)	117.07 (50.15)	148.36 (55.93)	0.007[c]
Total cholesterol(mg/dL)	185.13 (36.88)	198.75 (35.62)	0.089[a]
TSH (µIU/mL)	1,91 (0.82)	9.30 (3.36)	0.001[c]
Free T4 (ng/dL)	11.99 (4.34)	3.53 (2.12)	0.001[c]
Free T3 (pg/mL)	2.85 (0.86)	1.46 (0.74)	0.001[c]
TPOAb (IU/mL)	6.35 (3.19)	12.90 (3.54)	0.001[c]
TGAb (IU/mL)	3.24 (1.56)	12.72 (2.60)	0.001[c]
Betatrophin (ng/mL)	324.58 (92.48)	417.40 (127.84)	0.001[c]

a: t-test; m, b: chi-square test, c: Mann–Whitney U test; ALT: alanine aminotransferase, AST: aspartate aminotransferase, BMI: body-mass index, HOMA-IR: homeostatic model of assessment-insulin resistance, LDL-cholesterol: low-density lipoprotein-cholesterol, HDL-cholesterol: high-density lipoprotein-cholesterol, TSH: thyroid stimulating hormone, Anti TPO: thyroid peroxidase ab, Anti TG: thyroglobulin ab

Table 2: Correlations between serum ANGPTL-8 (betatrophin) levels and covariates

Covariates	Correlation coefficient	*P*-value
BMI (kg/m^2)	0.03	0.808
HOMA-IR	0.03	0.750
HDL (mg/dL)	-0.23	0.034
LDL (mg/dL)	0.21	0.058
TG (mg/dL)	0.40	0.001
T.CHOL (mg/dL)	0.29	0.008
TSH (µIU/mL)	0.32	0.003
FT4 (ng/dL)	-0.30	0.006
TPOAb (IU/mL)	0.09	0.433
TGAb(IU/mL)	0.25	0.220

BMI: body-mass index, HOMA-IR: homeostatic model of assessment-insulin resistance, LDL-C: low-density lipoprotein-cholesterol, HDL-C: high-density lipoprotein-cholesterol, T.CHOL: total cholesterol, TSH: thyroid stimulating hormone, TPOAb: thyroid peroxidase ab, TGAb: thyroglobulin ab

Table 3: Multivariate regression analysis

Covariates	Coefficient B (SE)	%95 CI	*P*-value
Constant	220.8 (30.5)	158.9 - 281.6	0.001
TSH	7.7 (2.5)	2.768 – 12.6	0.003
TG	1.1 (0.2)	0.679 – 1.5	0.001

Model R^2: 0.40 and p<0.001. Regression equation for serum betatrophin on the basis of this model was 220,782 -10,290 * TSH +1,070 * TG

Table 4: Comparison of TPOAb >9 (n=21) and TPOAb ≤9 (n=23) patients with Mann-Whitney-U test

	P-value[1]
BMI	0.026
HOMA-IR	0.176
TSH	0.235
Free-T4	0.842
Triglyceride	0.823
HDL-C	0.999
LDL-C	0.823
Total-cholesterol	0.565
Betatrophine	0.778

BMI: body-mass index, HOMA-IR: homeostatic model of assessment-insulin resistance, TSH: thyroid stimulating hormone, HDL-C: high-density lipoprotein-cholesterol, LDL-C: low-density lipoprotein-cholesterol, [1] Mann-Whitney U test

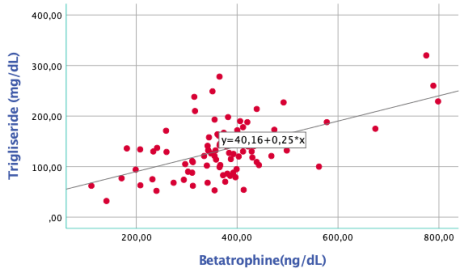

Figure 1: Relationship between serum betatrophin and triglyceride levels

Discussion

Thyroid hormones govern energy metabolism by activating glucose, fat and protein oxidation in tissues. In hypothyroidism, decreased T3 and T4 levels and increased TSH levels are characteristic. With the decrease in thyroid hormones, instead of being oxidized for energy, lipids are stored in the body. Consequently, body weight increases and lipid profile changes [16,17].

As is known, visceral adipose tissue is the main adipose tissue producing various adipokines. Numerous evidences have shown that cytokines secreted from adipose tissue lead to endothelial dysfunction and cause atherosclerosis with dyslipidemic effects [18-21]. In a study, visceral adipose tissue volume was increased in patients with hypothyroidism [22]. Despite the intense interaction of thyroid hormones and regulatory hormones secreted from adipose tissue, this relationship has not been fully elucidated. In our study, we investigated the level of ANGPTL family cytokines secreted from adipose tissue in patients diagnosed with overt hypothyroidism and found it was closely related to lipid metabolism, in accordance with the previous studies.

ANGPTL-8, also known as betatrophin, is a regulator and stabilizer in lipid metabolism by its LPL inhibition, which is also a feature of other cytokines in the ANGPTL family [23,24]. As is known, LPL provides clearance of TG-rich plasma lipoproteins [25]. LPL is located in the capillary endothelium and catalyzes the hydrolysis of endogenous VLDL-TG and exogenous chylomicron-TG to glycerol and FFAs [26].

A few studies in the literature demonstrate the relationship between hypothyroidism and serum betatrophin levels. In one study, the relationship between betatrophin levels and subclinical and overt hypothyroidism was investigated and serum betatrophin levels were found to be increased in hypothyroidism [27]. The same study suggested that betatrophin was a metabolic regulator that may affect lipid and glucose metabolism. However, it was stated that serum betatrophin elevation may be associated with thyroid autoimmunity. In our study, we also found that serum betatrophin levels were higher in patients diagnosed with overt hypothyroidism compared to the control group. Regardless of autoimmunity, we believe that betatrophin plays a regulator role in fat metabolism by its inhibitory effect of LPL, due to the fact that serum betatrophin levels were similar in patients with hypothyroidism having high or normal anti-TPO values.

In our study, although there were similar features regarding BMI, fasting plasma glucose and HOMA-IR levels in patients with hypothyroidism and control group, triglyceride levels were significantly different between both groups.

The relationship between betatrophin levels and TG levels could be detected even in patients with subclinical hypothyroidism, suggesting that hypertriglyceridemia in hypothyroidism may be mediated by increased betatrophin release [27]. In our study, there was a strong positive correlation between TG and betatrophin levels. The elevated betatrophin level inhibits LPL and prevents the breakdown of triglycerides into free fatty acids and glycerol. In hypothyroidism, lipid oxidation for energy production decreases as a result of the

decrease of fatty acid. On the other hand, elevated TG in the serum may initiate triggering mechanisms for obesity, insulin resistance and cardiovascular events, and especially for hepatosteatosis.

In a study in which we investigated the relationship between ANGPTL-4 and hepatosteatosis, we found that LPL inhibition further induces hepatosteatosis by causing TG accumulation in the tissues [14]. Betatrophin is known to exhibit the main characteristics of the ANGPTL family, with some structural differences. Stress, insulin resistance, inflammation and thermogenesis may affect betatrophin expression and signaling pathways [28]. The contradictory results in the previous studies suggest that betatrophin may be a multidimensional adipokine that can function differently under changing conditions.

Limitation

The small number of patients was the most important limitation for our study. Further studies are needed with more patient groups.

Conclusion

In our study, we found that serum betatrophin levels were high in hypothyroid patients. Consequently, considering the relationship between betatrophin and TG levels, it may give promising results as a therapeutic target.

References

1. Ouchi N, Kihara S, Arita Y, Okamoto Y, Maeda K, Kuriyama H, et al. Adiponectin, an adipocyte-derived plasma protein, inhibits endothelial NF-kappa B signaling through a c-AM*P*-dependent pathway. Circulation. 2000;102(11):1296-301.
2. Krotkiewski M. Thyroid hormones in the pathogenesis and treatment of obesity. Eur J Pharmacol. 2002;440(2-3):85-98.
3. Potenza M, Via MA, Yanagisawa RT. Excess thyroid hormone and carbohydrate metabolism. Endocr Pract. 2009;15(3):254-62.
4. Bell A, Gagnon A, Grunder L, Parikh SJ, Smith TJ, Sorisky A. Functional TSH receptor in human abdominal preadipocytes and orbital fibroblasts. Am J Physiol Cell Physiol. 2000;279(2):335-40.
5. Gierach M, Gierach J, Junik R. Insulin resistance and thyroid disorders. Endocrinol Pol. 2014;65(1):70-6.
6. Seven R. Thyroid status and leptin in Basedow-Graves and multinodular goiter patients. J Toxicol Environ Health. 2001;63(8):575–81.
7. Zimmermann-Belsing T, Brabant G, Holst JJ, Feldt-Rasmussen U. Circulating leptin and thyroid dysfunction. European Jour of Endocrinol. 2003;149(4):257-71.
8. Abu-Farha M, Abubaker J, Al-Khairi I, Cherian P, Noronha F, Kavalakatt S, et al. Circulating angiopoietin-like protein 8 (betatrophin) association with HsCRP and metabolic syndrome. Cardiovasc Diabetol. 2016;5:15-25.
9. Santaniemi M, Ukkola O, Malo E, Bloigu R, Kesaniemi YA. Metabolic syndrome in the prediction of cardiovascular events: the potential additive role of hsCRP and adiponectin. Eur J Prev Cardiol. 2014;21(10):1242-8.
10. Zhang R, Zhou SJ, Li CJ, Wang XN, Tang YZ, Chen R, et al. C-reactive protein/oxidised low-density lipoprotein/beta2-glycoprotein I complex promotes atherosclerosis in diabetic BALB/c mice via p38mitogen-activated protein kinase signal pathway. Lipids Health Dis. 2013;26:12-42.
11. Wang J, Feng MJ, Zhang R, Yu DM, Zhou SJ, Chen R, et al. C-reactive protein/oxidized low density lipoprotein/beta 2 glycoprotein i complexes induce lipid accumulation and inflammatory reaction in macrophages via p38/mitogen activated protein kinase and nuclear factor kappa B signaling pathways. Mol Med Rep. 2016;14(4):3490-8.
12. Yoon JC, Chickering TW, Rosen ED, Dussault B, Qin Y, Soukas A, et al. Peroxisome proliferator-activated receptor gamma target gene encoding a novel angiopoietin-related protein associated with adipose differentiation, Mol. Cell. Biol. 2000;20(14):5343–9.
13. Kersten S, Mandard S, Tan NS, Escher P, Metzger D, Chambon P, et al. Characterization of the fasting-induced adipose factor FIAF, a novel peroxisomeproliferator-activated receptor target gene, J. Biol. Chem. 2000;275(37):28488-93.
14. Altun Ö, Dikker O, Arman Y, Ugurlukisi B, Kutlu O, Ozgun Cil E, et al. Serum Angiopoietin-like peptide 4 levels in patients with hepatic steatosis. Cytokine. 2018;111:496-9.
15. Zhang R, Abou-Samra AB. Emerging roles of lipasin as a critical lipid regulator. Biochem Biophys Res Commun. 2013;432(3):401-5.
16. Menon VU, Sundaram KR, Unnikrishnan AG, Jayakumar RV, Nair V, Kumar H. High prevalence of undetected thyroid disorders in an iodine sufficient adult south Indian population. Jour Indian Med Assoc. 2009;107(2):72-7.
17. Pucci E, Chiovato L, Pinchera A. Thyroid and lipid metabolism. Int J Obesity Rel Metab Dis. 2000;24(2):109-12.
18. Lau WB, Ohashi K, Wang Y, Ogawa H, Murohara T, Ma XL, et al. Role of Adipokines in Cardiovascular Disease. Circ J. 2017;81(7):920-8.
19. Ahirwar AK, Singh A, Jain A, Patra SK, Goswami B, Bhatnagar MK, et al. Role of Subclinical Hypothyroidism in Association with Adiponectin Levels Causing Insulin Resistance in Metabolic Syndrome: A Case Control Study. Tokai J Exp Clin Med. 2017;42(2):96-103.
20. Hendrani AD, Adesiyun T, Quispe R, Jones SR, Stone NJ, Blumenthal RS, et al. Dyslipidemia management in primary prevention of cardiovascular disease: Current guidelines and strategies. World J Cardiol. 2016;8(2):201-10.
21. Akbaba G, Berker D, Isık S, Tuna MM, Koparal S, Vural M, et al. Changes in the before and after thyroxine treatment levels of adipose tissue, leptin, and resistin in subclinical hypothyroid patients. Wien Klin Wochenschr. 2016;128(15-16):579-85.
22. Stirrups KE, Masca NG, Erdmann J, Ferrario PG, Konig IR, Weeke PE, et al. Coding variation in ANGPTL4, LPL, and SVEP1 and the risk of coronary disease. N Engl J Med. 2016;374(12):1134-44.
23. Zhang R. The ANGPTL3-4-8 model, a molecular mechanism for triglyceride trafficking. Open Biol. 2016;6(4):150272.
24. Quagliarini F, Wang Y, Kozlitina J, Grishin NV, Hyde R, Boerwinkle E, et al. Atypical angiopoietin-like protein that regulates ANGPTL3. Proc Natl Acad Sci U S A. 2012;109(48):19751-6.
25. Wang H, Eckel RH. Lipoprotein lipase: from gene to obesity, Am. J. Physiol. Endocrinol. Metab. 2009;297(2):e271-88.
26. Goldberg IJ, Merkel M. Lipoprotein lipase: physiology, biochemistry, and molecular biology, Front. Biosci. 2001;6:388-405.
27. Han C, Xia X, Liu A, Zhang X, Zhou M, Xiong C, et al. Circulating betatrophin is Increased in patients with overt and subclinical hypothyroidism. Biomed Res Int. 2016;2016:5090852.
28. Luo M, Peng D. ANGPTL8: An Important Regulator in Metabolic Disorders. Front Endocrinol (Lausanne). 2018;9:169.

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