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THE RELATIONSHIP BETWEEN CIRCULATING BETATROPHIN LEVELS AND INSULIN RESISTANCE IN LEAN AND OVERWEIGHT /OBESE PCOS

ZAYIF VE OBEZ PCOS' DA İNSÜLİN REZİSTANSI VE KAN BETATROFİN DÜZEYLERİ ARASINDAKİ İLİŞKİ

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ÖZ

Amaç: Polikistik over sendromlu (PKOS) kadınların yaklaşık %70'inde insülin direnci ve buna bağlı metabolik bozukluklar vardır, ancak insülin direncine yol açan altta yatan mekanizma bilinmemektedir. Betatrofin, karaciğerde ve yağ dokusunda eksprese edilen ve insülin direnci ve β-hücre proliferasyonu ile ilişkili olduğu bulunan bir proteindir. Bu çalışmanın amacı, PKOS olgularında dolaşımdaki betatrofin düzeyini değerlendirmek ve obezite ve insülin direnci ile ilişkisini araştırmaktır.

Yöntemler: Bu prospektif kesitsel çalışmada, ELİSA test kitleri kullanılarak normo-ağırlıklı 35 tane PCOS vakasında ve 38 tane fazla kilolu/obez PCOS vakasında (BMI≥25) dolaşan betatrofin seviyeleri ölçüldü. Betatrofin seviyeleri, antropometrik ölçümler, açlık kan şekeri, glikoz yüklemesinden 2 saat sonra kan şekeri ve insülin direncinin homeostaz modeli değerlendirmesi (HOMA-IR) değerleri karşılaştırıldı.

Bulgular: Normal ağırlıklı PKOS grubunun dolaşımdaki betatrofin düzeyleri aşırı kilolu/obez PKOS grubuna göre anlamlı derecede yüksek bulundu (p=0,023). Betatrofin ve HOMA-IR seviyeleri arasında anlamlı bir ilişki yoktu.

Sonuç: Betatrofin, aşırı kilolu/obez grupta normo-ağırlıklı PKOS grubuna göre anlamlı derecede düşük bulundu. Betatrofinin PKOS ve insülin direncindeki rolü yeterince aydınlatılamadığından PKOS hastalarında insülin direncinin iyi bir öngörücüsü olmadığı söylenebilir.

Anahtar Kelimeler: Betatrophin; PCOS; obesite; insulin direnci; metabolik sendrom.

ABSTRACT

Objective: About 70% of women with polycystic ovary syndrome (PCOS) have insulin resistance and related metabolic disorders but the underlying mechanism leading to insulin resistance remain unknown. Betatrophin is a protein expressed in the liver and adipose tissue that has been found to be related to insulin resistance and β-cell proliferation. The aim of this study is evaluate the circulating betatrophin level in PCOS cases and to investigate its relationship with obesity and insulin resistance.

Methods: In this prospective cross-sectional study circulating betatrophin levels were measured in 35 PCOS cases with lean and 38 overweight/ obese PCOS cases (BMI≥25) using spesific enzyme-linked immunosorbent assay kits. Betatrophin levels, antropometric measurements, fasting blood glucose, 2 -hour post-glucose load blood glucose and homeostasis model assessment of insulin resistance (HOMA-IR) values were compared.

Results: Circulating betatrophin levels of the lean PCOS group were found to be significantly higher than the overweight/obese PCOS group (p=0.023). There were no significant association between betatrophin and HOMA-IR levels.

Conclusions:Betatrophin was found to be significantly lower in the overweight/obese group than in the lean PCOS group. Since the role of betatrophin in PCOS and insulin resistance has not been sufficiently clarified, it can be said that it is not a good predictor of insulin resistance in PCOS patients.

Key words: Betatrophin; PCOS; obesity; insulin resistance;metabolic syndrome

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INTRODUCTION

PCOS is the most common endocrine disorder in the fertile female age group and hyperandrogenism,oligoanovulation, and polycystic ovarian morphology are the main features of disease(1,2). These features are related to future metabolic risks for the patient such as obesity, insulin resistance (IR), glucose intolerance, diabetes and metabolic syndrome (3-5). The pathogenesis of PCOS is not clear today. According to studies, insulin resistance and hyperinsulinemia have been found together in obese PCOS. (3,4,6). Insulin resistance is thought to be responsible for hormonal and metabolic disorders observed in PCOS. PCOS has two phenotypes, obese and normal weight, the latter being a much less common presentation of the syndrome(7).

Betatrophin is a protein originated from liver and adipose tissue known in the following names refeeding-induced fat and liver protein-RIFL (8, 9), lipasin (8,10) or atypical angiopoetin-like protein 8 (ANGPLT8) (8,11). It is a novel glucolipid metabolic regulation factor and plays a key role in insulin metabolism by controlling beta cell proliferation in pancreatic beta cell islets in mice (3,12). It is also related with glucose homeostasis and lipid metabolism by taking dual roles (13,14). In humans, the role of betatrophin in glucose metabolism is controversial. Several reports indicated that betatrophin levels were increased in insulin resistance (8), obesity and type 2 diabetes (15-18) whereas other data claims the opposite (19,20). Betatrophin was also investigated in PCOS patients in comparison with non-PCOS healthy women (18,20-21). Most of the studies and a current meta-analysis (22) revealed the betatrophin levels increased in PCOS patients as compared to non-PCOS cases and these sudies showed a positive correlation between serum betatrophin concentration and HOMA-IR in women with PCOS (20). On the contrary some other studies showed that a negative correlation between fasting serum betatrophin concentration and HOMA-IR (23).

The aim of the present study was to compare the serum betatrophin levels in patients with overweight/obese and normal weight PCOS and and to investigate the relationship between betatrophin and insulin resistance.

MATERIALS AND METHOD

A total of 73 reproductive age women with PCOS according to 2003 Rotterdam ESHRE/ASRM PCOS Consensus Workshop Group diagnostic criteria were included in this prospective cross-sectional study(24). Patients were recruited from the Reproductive Endocrinology Clinic of Zekai Tahir Burak Women's Health and Research Hospital. This study was approved by the Institutional Review Board of the aforementioned hospital. Informed consent was obtained from every included patient.

Exclusion criteria included the following: Pregnancy and breastfeeding, morbid obesity, an additional systemic disease (i.e.,hyperprolactinemia, thyroid dysfunction, hypertension, liver or kidney diseases, cardiovascular disease, dyslipidemia, type 1 or type 2 diabetes, chronic or acute infection within the previous 30 days), smoking, and using hormonal contraception or antiandrogen therapy.

The patients were divided into two groups according to their BMI values : Group 1 consisted of lean (BMI<25 kg/m2) PCOS cases (n=35) and Group 2 (n=38) consisted of overweight/obese (BMI≥ 25 kg/m2) PCOS cases.

Waist-to-hip ratio(WHR), fasting blood glucose (FBG) and fasting insulin(FI), serum betatrophin concentrations at baseline were estimated. Blood samples were obtained after fasting overnight for at least 10 hours.

The modified Ferriman Gallwey score for the detection of hirsitismus was obtained in all patients. A score of 8 and above was considered significant for hirsutmus(25,26).

A 2-h oral glucose tolerance test was used to evaluate impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) that reveals the presence of IR in clinical practice. After a 12-h overnight fasting, participants ingested 75 g glucose, and glucose and insulin concentrations were determined at baseline and after 120 min. Fasting glucose was measured using a glucose oxidase assay. Impaired glucose tolerance (IGT) was defined as two-hour glucose levels of 140 to 199 mg/dL. Insulin was measured by the immunoradiometric method.

Homeostasis model assessment insulin resistance (HOMA-IR) was calculated using this formula: fasting glucose (mg/dL) x fasting insulin (mU/L)/405. A HOMA-IR value of 2,5 was taken as a cut-off point (27). All results were compared between the groups.

Fasting maternal blood samples were obtained from the mother in the form of venous blood . Serum samples were separated by centrifugation at 5000 revolutions/min (2236 g) for 10 min within 15–20 min of blood sampling. They were frozen immediately and kept at -80 C until final analysis.

Serum betatrophin levels was detected by enzyme-linked immunosorbent assays (CHEMWELL 2900, ALGEN, ELISA) using commercially available kit (Human betatrophin, YL Biont, ELISA.) in duplicate. Results were reported as ng/L. Intraassay and interassay %CV (Coefficient Variation) values are given as <8%, <10%, respectively.

Statistical Analysis

Statistical analyses were perfrmed with IBM SPSS (Statistical Package for Social Sciences) software, version 21.0 (https://www.ibm.com/support/pages/how-cite-ibm-spss-statistics-or-earlier-versions-spss). The normality of the data was evaluated for all of the quantitative variables by using the Kolmogorov–Smirnov test, and the descriptive statistics were expressed as the Mean±Standard deviation or median (min–max). When the data were not normally distributed, a Mann–Whitney U test was used to compare the two groups. The comparison between the categorical variables was performed using the Chi-square test and $p<0.05$ was accepted as significant. Multiple Lineer Regression analisis was used to determine the variables affecting betatrophin. In this regression model, betatrophin was taken as the dependent variable. Age, WHR, HOMA-IR, BMI and IGTT were taken as independent variables.

Power analysis was performed using G-power software (G-power v3.1.9.2, Universitat Kiel, Kiel, Germany). Difference between two independent means (two groups) power analysis demonstrated that we achieved a power of 0.80 with a 5% level of significance. Accordingly, 35 patients from each group were sufficient.This analysis was performed between the two groups using comparison of the Betatrophin values.

RESULTS

A total of 73 cases were included. Mean age, BMI and WHR values of participants were 23.6±4.4 years, 26.11±5.3 kg/m2 and 0.92±1,05 respectively; mean total testosterone concentration, mean baseline plasma glucose concentrations, mean blood glucose values of 2 -hour post-glucose load and mean HOMA-IR values were 0,57 ±0,2 ng/mL, 92.5±7.5 mg/dl, 107±23.6 mg/dl and 2.6±0.5, respectively. Mean betatrophin level and were found 1041±148 ng/L. Only 20% of the all cases had a mFG score of 8 and above.

When the groups were compared, subjects with overweight/obese PCOS had a significantly higher FI, plasma glucose of 2 -hour post-glucose load, HOMA-IR and WHR values. The circulating betatrophin concentration was higher in the lean PCOS patients than in overweight/obese PCOS patients (691,8±996 ng/L vs 1421,4±1279 ng/L, p=0.023).The clinical and biochemical characteristics of the studied groups are presented in Table 1.

Table 1. The clinical and biochemical characteristics of the studied groups

Mean±SD	Lean PCOS (n=35)	Overweight/obese PCOS (n=38)	P value
Age(year)	22,26 ± 3,9	24,7± 4,5	**0,016**
WHR	0,8 ± 0,2	1,02 ±1, 5	**0,000**
FBG (mg/dl)	90 ±7,2	93 ± 7,6	0,140
FI(mIU/mL)	9,2±3,3	13,6±8,9	**0,005**
2-hour post-glucose load blood glucose (mg/dl)	98 ± 19,6	114±24,7	**0,004**
HOMA-IR	2,1±0,8	3,1±2,1	0,008
Betatrophin(ng/L)	1421,4±1279	691,8±996	0,023

SD: Standard deviations;BMI: Body mass index;WHR: Waist/Hip Ratio;FBG: Fasting Blood Glucose;

FI: Fasting ınsulin; HOMA-IR: Homeostasis Model Assessment-Insulin resistance

Clinical indexes with significant differences ($P < 0.05$) are in bold.

To further explore the association of plasma betatrophin level with metabolic characteristics, groups were divided into two sub-groups according to WHR, 2-h post-glucose load blood glucose and HOMA-IR values. In 80 % of the overweight/obese PCOS group, WHR was above 0.85. Comparison of the WHR, 2-hour post-glucose load blood glucose and HOMA-IR values in normal weight and overweight/obese PCOS are presented in Table 2.

Table 2. Comparison of the WHR, 2-hour post-glucose load blood glucose and HOMA-IR values in normal weight and overweight/obese PCOS

	Lean PCOS (n=35)	Overweight/obese PCOS (n=38)	P value
Waist-to-hip ratio			
<0.85	58.5% (n=31)	41.5% (n=22)	
≥0.85	20% (n=4)	80% (n=16)	**0.008**
2-hour post-glucose load blood glucose (mg/dl)			
<140	50.8% (n=33)	49.2% (n=32)	
≥140	25% (n=2)	75% (n=6)	0.264
HOMA-IR			
<2.5	68,57% (n=24)	52,63 % (n=20)	
≥2.5	31,43 % (n=11)	47,37 %(n=18)	0.250

HOMA-IR: Homeostasis Model Assessment-Insulin resistance P-values in bold are statistically significant (p<0.05)

It was found that there was no statistically significant difference in circulating betatrophin levels of those with WHR below and above 0.85 (p=0.097). In terms of serum betatrophin concentrations, no significant association was found between those with 2 -hour post-glucose load <140 and those with ≥140 (p=0.230). There was no significant association between HOMA-IR values (below and above 2.5) and circulating betatrophin concentrations (p=0.420). Associations of clinical and laboratory parameters with serum betatrophin concentration are presented in Table 3.

Table 3. Association of evaluated parameters with serum betatrophin concentration

Mean±SD	Serum betatrophin concentration (ng/L)	P value
Waist-to-hip ratio <0.85(n=53) ≥0.85 (n=20)	1214±1249 583±892	97
2-hour post-glucose load blood glucose (mg/dl) <140 (n=65) ≥140 (n=8)	1090±1214 647±946	230
HOMA-IR <2.5 (n=44) ≥2.5 (n=29)	1290±1379 877.9±1032	420
BMI(kg/m2) <25 (n=35) ≥25 (n=38)	1421±1279 691±996	23

Considering all the other factors affecting circulating betatrophin concentration according to Anova regression analysis, it was concluded that serum betatrophin concentration decreased with increasing age and WHR (p = 0.008 and p = 0.049, respectively). The variables affecting circulating betatrophin concentration are presented in Table 4.

Table 4. Regression analysis of the variables affecting circulating betatrophin concentration: standardized regression coefficients

	Standardized Coefficients	P values
Age	-.326	**0.008**
2-hour post-glucose load blood glucose (mg/dl)	.000	0.999
HOMA-IR	.176	0.137
WHR	-.236	**0.049**
BMI(kg/m²)	-.008	0.952

P-values in bold are statistically significant (p<0.05)

DISCUSSION

In the present study, circulating betatrophin concentrations were found significantly lower in the overweight/obese PCOS group compared to the lean PCOS group. Additionally, circulating betatrophin concentrations in groups were found similar according to the FBG, 2-hour post-glucose load blood glucose, HOMA-IR and WHR values. Considering all the factors affecting circulating betatrophin concentration, it was found that serum betatrophin concentration correlates only with age and WHR.

Previous studies have shown that betatrophin, a protein-derived hormone produced from liver and adipose tissue, plays a role in insulin secretion by pancreatic islet cell induction (28,29). In addition, betatrophin is not only involved in glucose metabolism but also in lipoprotein metabolism(28,30). In animal studies, betatrophin was found to increase insulin production and regulate glucose metabolism by beta cell proliferation (28) and circulating betatrophin was found to be higher in patients with type 2 diabetes (31,32). In the gestational diabetes group, betatrophin was found to be high in the third trimester if the

pregnant were overweight (33,34).

According to the in vivo and in vitro studies it has been emphasized that the regulation of betatrophin is a useful marker for insulin resistance and metabolic diseases (21). Circulating betatrophin has also been examined in PCOS patients. Available studies in the literature have reported conflicting results with elevated (18,20), decreased or similar (8,21) serum concentrations of betatrophin in PCOS patients as compared to controls.

In some studies, serum concentration of betatrophin has been found to be associated with IR and metabolic syndrome in PCOS patients regardless of being obese or lean (8,35). On the contrary, in the study of Kahraman et al., it was stated that in PCOS patients had no relation to insulin resistance and circulating betatrophin concentration Conversely, in the study of Kahraman et al., no significant relationship was found between serum circulating betatrophin and insulin resistance (1). In a different study exploring the association of betatrophin levels with metabolic parameters in lean and overweight/obese women with and without PCOS, it was found that betatrophin level was higher in lean PCOS with compared to overweight/obese PCOS. The authors were stated that the reason for this contradictory situation may be due to different metabolic types of PCOS(3). As a result of a current meta-analysis of 11 studies, circulating betatrophin was significantly higher in PCOS patients than non-PCOS controls most likely regardless of lean or obese BMI (22).

In this meta-analysis, according to the results of subgroup analysis, it was found that the increased betatrophin concentrations were basically due to the presence of PCOS, regardless of BMI. In addition, this meta-analysis suggests that elevated betatrophin levels in PCOS become more prominent with higher age and IR.

Since betatrophin levels were found to be different in patients with PCOS compared to normal individuals in previous studies, we only included obese and normal weight patients with PCOS in this study. Furthermore, based on the hypothesis that the dominant expression site of betatrophin is in adipose tissue, we divided our study population into two groups according to their BMI values and compared lean and overweight/obese PCOS cases. As a result of our study, betatrophin concentration was found to be statistically significantly lower in the overweight/obese PCOS group compared to the lean group. Similarly, in a prospective cross sectional study, it was stated that significantly higher plasma betatrophin levels in lean PCOS compared with overweight/obese PCOS(3).

The IR in patients with PCOS is closely associated with an increase in the amount of abdominal fat and overweight. In our study, 2-hour post-glucose load blood glucose, FI and HOMA-IR values were significantly higher in the overweight/obese group Circulating betatrophin levels were found significantly lower compared to the lean group. Additionally, circulating betatrophin levels were found similar in the subgroup of PCOS patients having HOMA-IR ≥ 2.5 and HOMA-IR<2.5. Multiple linear regression analysis revealed that WHR and age were independently associated with betatrophin levels in our studied group. In the study of Li et al., the circulating betatrophin levels were found to be negatively correlated with WHR and HOMA-IR in PCOS group (3). Based on the results of a current meta-analysis that included the aforementioned study (22) statistical significance was not achieved according to betatrophin levels in obese and lean PCOS. Inconsistent with the results of our study, in this meta-analysis circulating betatrophin levels were found significantly higher in the subgroup of studies with PCOS patients having HOMA-IR >2.5 and this results was interpreted as possibility of association between increased betatrophin and IR in PCOS. As a result of a study, authors were shown that a significant increase of circulating betatrophin in untreated IR women and different effects of elevated insulin on betatrophin in vivo and in vitro which selected only women with IR. They were also found that metformin or rosiglitazone decreases circulating levels and expression of betatrophin (29). Furthermore in aforementioned meta-analysis, it was stated that the significant positive correlations were found betatrophin with age, free androgen index and free testosterone in PCOS cases (22) However, other studies in literature have conflicting results on the correlation between betatrophin and HOMA-IR.

Different opinions in previous studies on betatrophin suggest that there may be mechanisms of batatrophin that have not yet been clarified. Since betatrophin is a hormone that secretes insulin in the pancreas, it is not clear whether increased betatrophin is responsible for glucose intolerance by increasing insulin, or whether increased insulin reduces betatrophin with a negative feedback effect in already glucose intolerance. Conflicting results regarding betatrophin in obese and normal weight patients in PCOS complicates the issue. In our study, although fasting insulin, 2-hour oral glucose loading and HOMA-IR were found to be statistically significantly higher in the obese group, it was found that they did not affect betatrophin levels in the regression analysis.

The fact that we found betatrophin lower in the obese group in our study may be considered as the betatrophin-reducing effect of insulin and HOMA-IR elevation in the obese group with negative feedback. Although this is not a definitive judgment, it is a mechanism that comes to mind.

In our study, the decrease in betatrophin in the obese group suggests that the role of betatrophin not only in insulin resistance but also in fat tissue metabolism may be important. Betatrophin is not fully understood, the current results of our study may lead to some interpretations. Weight appears to be a factor influencing betatrophin levels, but it may not be the sole determinant. Various factors, including hormonal and metabolic aspects, likely contribute to the regulation of betatrophin. The interplay between weight, PCOS, and betatrophin is a complex area that requires further research for a comprehensive understanding. There are contradictory statements on the subject in the literature. There are many studies that are compatible with our results (3) and many that are not.

The inconsistency with some other studies in the literature regarding the possible relationship between IR and betatrophin levels may be related to our patient selection criteria. Most of the patients in our studied group were young, non-hyperandrogenic women with a BMI values close to the overweight limit. And also according to the HOMA-IR results, 68,5% of the lean group and 52,5% of the overweight/obese group were HOMA-IR <2.5. When 2-hour post-glucose load blood glucose levels were evaluated in terms of demonstrating impaired glucose tolerance, those with ≥140 mg/dl were in only 6 cases in the overweight/obese group. HbA1c and FAI were not evaluated in our study and our study group did not consist of full-blown PCOS cases. All these factors can be counted among the limitations of our study.

In conclusion, insulin resistance is at the center of the pathogenesis in PCOS and is responsible for most of the metabolic complications. According to the limited number of studies and meta-analysis results circulating betatrophin may be associated with IR, obesity and dyslipidemia although their results are contradictory. The relationship between betatarofin insulin resistance, betatrophin PCOS and insulin resistance, and the mechanisms related to the relationship between obesity and PCOS betatrophin have not yet been adequately clarified.In this respect, it can be said that betatrophin is not a biomarker to adequately explain insulin resistance in obese and normal weight PCOS. However, more studies are needed on which of these have a more significant relationship with circulating betatrophin.

Declaration of interest statement: The authors have no conflict of interest.

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