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Betatrophin in polycystic ovary disease and its association with insulin resistance

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Abstract
Background: Betatrophin, a newly identified peptide hormone secreted mainly by liver and adipose tissue, is a member of a family of angiopoietin-like proteins and is implicated in the regulation of lipid and glucose metabolism. Originally, betatrophin was determined to function in lipid metabolism by reducing triglyceride clearance through lipoprotein lipase inhibition.
Objective: To assess the association between Betatrophin and insulin resistance in polycystic ovary disease women.
Patients and Method: A case control study carried in our hospital, at the period from the 1st of October 2019 to the end of January 2020. One hundred women were enrolled in the current study and divided into 2 groups.
Results: S. Betatrophin levels were significantly higher increases in case group (PCOS patients) than that in control group (P<0.001). The correlation analysis between serum Betatrophin and various parameters in table 4 showed that there is a positive correlation between circulating Betatrophin levels with fasting insulin, and HOMA-IR. While negative correlation found with fasting blood glucose.
Conclusion: Betatrophin highly significantly increase in PCOS patients, and betatrophin is independently associated with insulin resistance.

Keywords: betatrophin, polycystic ovary syndrome, Insulin resistance

Introduction
Polycystic ovary syndrome (PCOS) is a common metabolic and endocrine disorder affecting 6 to 21% of reproductive aged women depending on population, mean body mass index (BMI) and diagnostic criteria used. High prevalence is rates seen in women whom are overweight or have an Indigenous or Asian background [1].
The features of PCOS, including menstrual dysfunction, infertility and hirsutism have been described in medical records for more than 2,000 years [2]. The syndrome was officially recognized in the 1930's by Stein and Leventhal who associated polycystic ovaries (PCO) to the clinical features of menstrual dysfunction, infertility, hirsutism and obesity. Since the 1980's, researchers expanded on these observations to report an association between hyperinsulinemia and hyperandrogenism bringing to light possible etiologies and a complicated metabolic and reproductive condition with psychosocial and economic consequences across the lifespan. These ground-breaking studies also caused great debate as to whether insulin resistance (IR) is a unique feature of PCOS contributing to clinical features and health consequences [3].

Etiology
PCOS is a multifactorial disease. Several susceptible genes have been identified as contributors to the pathophysiology of the disease. These genes are involved in various levels of steroidogenesis and androgenic pathways. Twin studies have estimated about 70% heritability. Also, the environment is a fundamental component in the expression of these genes and development and progression of the disease [4, 5].

Epidemiology
PCOS is the most common endocrine pathology in the reproductive-aged female around the world. The prevalence ranges around 5% to 15% depending on the diagnostic criteria. Rotterdam criteria include a broader prevalence than National Institute of Health 1990 Criteria. Based on the NIH 2012 workshop report, it is estimated that PCOS affects about 5 million

reproductive-aged females in the United States, and the cost to the healthcare system for diagnosing and treating PCOS is approximate $4 billion annually not including the cost of serious comorbidities associated with PCOS.

Multiple conditions have been associated with PCOS including infertility, metabolic syndrome, obesity, impaired glucose tolerance, DM-2, cardiovascular risk, depression, OSA, endometrial cancer, NAFLD/NASH. Higher prevalence has been associated in first-degree relatives with PCOS, prepubertal obesity, congenital virilizing disorders, above average or low birth weight for gestational age, premature adrenarche, use of valproic acid as an antiepileptic drug. Studies have also suggested that there is a higher prevalence in Mexican-Americans than non-Hispanic whites and African Americans [6, 7].

Betatrophin

Betatrophin, a newly identified peptide hormone secreted mainly by liver and adipose tissue, is a member of a family of angiopoietin-like proteins and is implicated in the regulation of lipid and glucose metabolism. As the peptide was discovered independently by different groups, it is known by various names that include 're-feeding induced fat and liver (RIFL)protein,' 'lipasin,' 'angiopoetin-like 8 proteins' (ANGPLT8), and 'hepatocellular carcinoma-associated protein' (TD26). Originally, betatrophin was determined to function in lipid metabolism by reducing triglyceride clearance through lipoprotein lipase inhibition [8].

It has been implicated that the hormone is a key mediator of the postprandial trafficking of triglyceride-fatty acids to adipose tissue. In addition, betatrophin sequence variations were reported in lipid metabolism [9-11].

Furthermore, the results of the studies evaluating the relationship between diabetes and betatrophin are not uniform and any causal relationship between these two remains to be established. Several recent studies have reported betatrophinlevelsin type2diabetesandobesity. Different research groups have shown elevated, reduced, or unchanged betatrophin values depending on the features of the recruited population [12, 13].

Aim of the study

To assess the association between Betatrophin and insulin resistance in polycystic ovary disease women.

Patients and Method

A case control study carried in our hospital, at the period from the 1st of October 2019 to the end of January 2020.

100 women were enrolled in the current study and divided into:

1. Case group: 50 women with PCOS attending the gynecological clinic, seeking for medical advice and suffering from different complain like: subfertility, menstrual disturbance, and hirsutism.
2. Control group: Another 50 women without any criteria of the disease (PCOS) they served as normal control (this sample was taken from the patients relative)

The diagnosis of PCOS women was according to Rotterdam criteria [14]:

Inclusion criteria

PCOS patients with in the age between (18-35) years

Exclusion criteria

In the current study the exclusion of the participant was done if respondents have a history of chronic medical illness (Diabetes mellitus, hypertension, thyroid disease, etc).

Data were collected by the researcher by using a specially designed questionnaire form put it by the supervisor, and all respondents were undergoing clinical examination after full history. Then measurement of: Height (cm) and weight (Kg), to calculate the BMI, Waist circumference (cm), Hip circumference (cm) to calculate Waist/Hip ratio. For the insulin resistance were calculated as follow: [15]

Because the glucose is measured in mg/dL so we use this calculation:

Fasting insulin mIU/L x fasting glucose mg/dL divided by 405

The insulin resistance range:

- Normal <3
- Borderline 3-5
- Severe IR >5

Both groups exposed to the following lab investigations:

Five ml of venous blood was taken from the respondents, at the first three days of menstrual cycle, the blood sample then centrifuged and the sera were frozen at -20 temperatures and used for various laboratory procedures, the following parameters were taken:

1. FSH, LH, total Testosterone, prolactin, estradiol, DEHEA, SHBG
2. FBS, and Insulin
3. Betatrophin

Statistical analysis

After the data were entered in a table developed by the researchers, the analysis was done by using the SPSS program, version 23 and for qualitative variables, we used frequencies and percentages, and for the quantitative variables, we used measures of central tendency and dispersion (standard deviation).

Results

Table 1 showed highly significant increase in FBG, Insulin, HOMA-IR, of the PCOS group than that in control group (P<0.001).

Table 1: Assay of blood sugar, insulin and IR

Variable	Cases	Control	P Value
	Mean ± SD	Mean ± SD	
FBG (mg/dL)	114.24±11.23	90.18±11.62	<0.001
Fasting Insulin (IU/ml)	24.7±4.1	15.94±4.8	<0.001
HOMA-IR (mlU/L)	6.97±1.61	3.55±0.49	<0.001

No significant differences were found in FSH and estradiol between the studied groups (P>0.05), moreover highly significant increase in Prolactin, Total Testosterone, and DHEA (P<0.001) of the PCOS patients than that in healthy patients, and significant increase were found in LH (P=0.003), while highly significant decrease in Sex hormone binding globulin (P<0.001) (table 2).

Table 2: Hormonal assay of the studied groups

	PCOS	Control	P Value
	Mean ± SD	Mean ± SD	
FSH (IU/L)	7.46±2.71	7.88±2.31	0.5
LH (IU/L)	18.9±5.93	7.66±6.34	0.003
Prolactin(pg/dl)	25.76±3.23	22.89±3.31	<0.001
Estradiol (pg/dl)	52.09±16.12	50.62±13.72	0.6
Total Testosterone (pg/dl)	3.1±0.48	1.72±0.53	<0.001
Sex hormone binding globulin (nmol/l)	47.7±4.9	68.7±4.5	<0.001
DHEA (µg/ml)	3.13±0.8	1.89±0.62	<0.001

S. Betatrophin levels were significantly higher increases in case group (PCOS patients) than that in control group (P<0.001) (table 3 and figure 1)

Table 3: Betatrophin level of the studied group

Variable	Cases	Control	P Value
	Mean ± SD	Mean ± SD	
Betatrophin (pg/ml)	543.4 ± 47.3	342.1 ± 32.9	<0.001

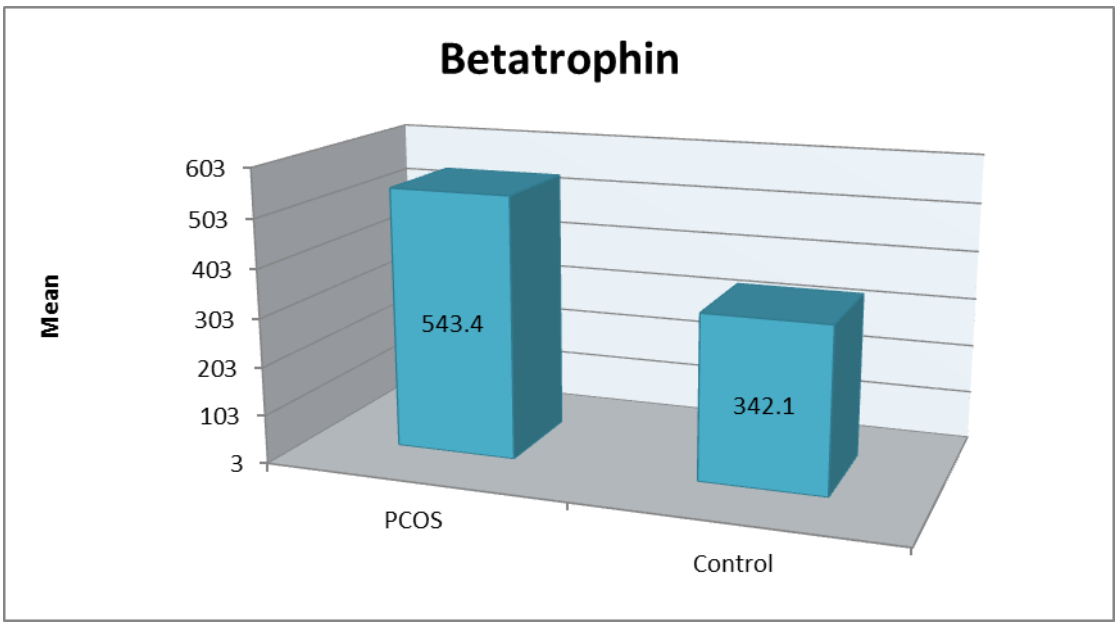

Fig 1: Level of betatrophin in studied groups

The correlation analysis between serum Betatrophin and various parameters in table 4 showed that there is a positive correlation between circulating Betatrophin levels with fasting insulin, and HOMA-IR. While negative correlation found with fasting blood glucose.

Table 4: Statistical correlation between FBG, Insulin and IR in PCOS group and Betatrophin

	Betatrophin	
	PCOS	
	r	P
FBG	-0.086	0.6
Insulin	0.73	<0.001
HOMA-IR	0.820	<0.001

Discussion

Betatrophin has recently been introduced as a novel potent stimulator of b-cell replication and improved glucose tolerance by increasing the b-cell division rate in mouse models of insulin resistance [16]. There is evidence suggesting that betatrophin expression can be induced by a high-fat diet and insulin, resulting in increased serum triglyceride levels and insulin resistance instead of improved glucose metabolism [17].

The main finding in the current study is the elevation of serum level of Betatrophin in PCOS group with significant differences with control group and positive correlation were found between Betatrophin increases with increase of insulin resistance in PCOS patients.

Adamska A *et al*, [18] results are consistent with those of other researchers who showed a positive correlation between serum betatrophin concentration and HOMA-IR in women with PCOS and in the group consisting of patients with T2D and pre diabetes and in the control group [19]. Qu *et al* [29] also observed that fasting serum betatrophin concentration positively correlated with HOMA-IR only in women with PCOS, but did

not estimate HOMA-B and Matsuda index.

Additionally, Sahin *et al*, [21] found that serum betatrophin level variability in the PCOS women was explained by homocysteine, HOMA-IR, and androstenedione levels. Erol *et al*. reported an elevated serum betatrophin concentration in the PCOS women in comparison to the control group, although they did not evaluate HOMA-IR, Matsuda index, or HOMA-B [22].

While in a study carried by Duan Y *et al*, [23] reported that the serum betatrophin concentrations were significantly decreased in women with polycystic ovary syndrome as compared with the healthy subjects in a Chinese population.

Inconsistent findings have been concluded by other researchers, who revealed a negative correlation between serum betatrophin concentration and HOMA-IR. Song *et al*, also found a negative relationship in PCOS patients between serum betatrophin concentration and HOMA-B. These different results found is due to difference in sample collection (anthropometrical differences) [24].

The link between betatrophin and glucose homoeostasis has been recently reported by Yi *et al*. [25] The group demonstrated that secretion of betatrophin increases in response to insulin resistance in mice, which stimulates beta cell replication and expansion. Administration of betatrophin was shown to improve glucose homeostasis in these mice [25].

Conclusion

Betatrophin highly significantly increase in PCOS patients, and betatrophin is independently associated with insulin resistance.

No conflicts of interest

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Ethical clearance: was taken from the scientific committee of the Iraqi Ministry of health

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