

A Potential Pathological Role of Wingless Type1 Inducible Signaling Pathway Protein-1 and Betatrophin in Obese Women with Polyststic Ovary Syndrome

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Authors' contributions

This work was carried out in collaboration among all authors. All authors designed the study and author AGAEH performed the statistical analysis. Author AGAEH wrote the protocol and wrote the first draft of the manuscript. Authors ATAEM, DMMAE and AGAEH managed the analyses of the study. Authors AGAEH and ATAEM managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Background: Polycystic Ovary Syndrome is a common female endocrinopathy. It is associated with adipokines dysfunctional secretion pattern and insulin resistance, which is considered as the main reason for its clinical feature. Wingless type1 inducible signaling pathway protein-1 is a novel adipokine that displays insulin resistance and adipose tissue inflammation where it strongly related to adipocyte accumulation and regeneration. Betatrophin has a potential role in pancreatic beta-cell

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proliferation and obesity and several studies showed inconsistent betatrophin levels in patients with diabetes and obesity but, its relation to polycystic ovary syndrome is unclear.

Aim: Investigation of the role of serum wingless type1 inducible signaling pathway protein-1 and betatrophin in normal weight and obese patients with polycystic ovary syndrome. Studying their association with other markers, then determine whether obesity and insulin resistance is associated with them.

Methods: Wingless type1 inducible signaling pathway protein-1 and betatrophin serum levels were measured in 44 patients with polycystic ovary syndrome (22 obese and 22 non-obese) and 44 matched control (22 obese and 22 non-obese) females using specific ELISA kits.

Results: Betatrophin and wingless type1 inducible signaling pathway protein-1 levels were elevated in the polycystic ovary syndrome group (49.4 pg/ml, 187.6 pg/ml) than in the control group (32.08 pg/ml, 108.4 pg/ml) respectively. Moreover, their levels were higher in the obese subgroup than in normal weight subgroup. There were positive correlations between wingless type1 inducible signaling pathway protein-1 and betatrophin in non-obese ($r=0.89$, $p=0.0001^{***}$) and in obese ($r=0.78$, $p=0.0001^{***}$) polycystic ovary syndrome groups.

Conclusion: Betatrophin and wingless type1 inducible signaling pathway protein-1 are associated with adiposity and insulin resistance in polycystic ovary syndrome. Hence wingless type1 inducible signaling pathway protein-1 and betatrophin may play a role in the incidence of polycystic ovary syndrome. They may be valuable in diagnosis and prediction of polycystic ovary syndrome patients.

Keywords: *Betatrophin; insulin resistance; polycystic ovary syndrome; WISP1.*

1. INTRODUCTION

Polycystic Ovary Syndrome (PCOS) is the most common cause of chronic anovulation and hyperandrogenism (HA) in young women and affects 5–10% of the female population. PCOS patients suffer from menstrual disorders and, dysfunctional uterine bleeding in addition; they have the risk of cardiovascular disease and diabetes [1]. Obesity in women with PCOS is the most important environmental factor implicated in its etiology and greatly increases the risk of insulin resistance (IR) [2]. Extensive studies indicated that IR plays a central role in the pathogenesis of PCOS with prevalence of 80% of all affected female and of 95% in obese women with PCOS [3]. Adipokines are hormones, cytokines and other bioactive substances produced by adipose tissue. Disturbed secretion of adipokines may impact the pathophysiology of PCOS [4]. There are relationships between adipokines levels and IR in PCOS patients [5].

Wingless type1 inducible signaling pathway protein-1 (WISP1) is a recently determined adipokine in human adipose tissue, is expressed in several organs and tissues, including the pancreas, ovaries, brain and placenta. It was found that WISP1 regulates tissue repair, regeneration and development [1]. WISP1 is substantially overexpressed in obese subjects and reflects IR and adipose tissue inflammation;

hence, WISP1 may play a role in linking obesity to inflammation and IR and could be a novel therapeutic target for obesity [6].

Betatrophin identified as secretory protein secreted mainly by hepatocytes with a potential role in lipid metabolism by regulating the level of plasma triglycerides and cholesterol through inhibition of lipoprotein lipase (LPL) [7]. Betatrophin has been reported to be a regulator of lipid metabolism and overexpression of betatrophin may reduce insulin sensitivity, and enhance IR in hepatocytes [8].

We postulated that WISP1 and betatrophin levels may be changed in PCOS patients and obesity as well as IR may be associated with betatrophin and WISP1.

2. SUBJECTS AND METHODS

2.1 Subjects

This study was carried out at Obstetrics and Gynecology department, Sayed Galal University Hospital. This study was performed on 88 Egyptian normal weighed and obese, premenopausal women aged 20–40 years with and without PCOS. The safety of patients from disease may be affected on study's parameters such as diabetes mellitus, cardiovascular disorders, renal diseases, dyslipidemia, and thyroid disturbance. The questionnaire was filled

for each woman include: name, age, married state, presence of abortion states, menstrual states, disease symptoms, length of disease period, weight and height. Women with PCOS were diagnosed according to the revised Rotterdam criteria (2003), by the presence of two of the following three manifestations: Oligo ovulation and/or anovulation, clinical and/or biochemical signs of hyperandrogenism, polycystic ovaries on ultrasound examination. The control cases had regular menstrual cycles and normal ultrasonography findings, without clinical or biochemical hyperandrogenism. Normal weight was defined as BMI of 18.5 to 24.9 kg/m² and obesity was defined as a BMI of 30 kg/m² or higher according to the WHO criteria).

2.2 Methods

Blood samples (10 ml) were drawn from each participant at day 2 or day 3 of menstrual period after an overnight fasting. The venous blood sample was divided into two tubes. 2 ml were put on fluoride for estimating fasting plasma glucose. The remaining blood was collected in vacutainers without additives, allowed to clot for 30 minutes at room temperature and centrifuged at 4000 rpm for 10 minutes, to obtain serum supernatant which was labeled and stored at -40°C until analyzed.

Lipid profile and fasting plasma glucose (FPG) were measured by endpoint technique using (Spectrum-diagnostics®; Egypt). Fasting insulin was measured by ELISA using (Perfect Ease Biotech Beijing®; USA). Hormonal profile (luteinizing hormone (LH) was measured by ELISA using (Bio Tina® GmbH; Germany, follicle stimulating hormone (FSH) was measured by ELISA using (Chemux® BioScience; USA), progesterone and total testosterone (TT) were measured by ELISA using (NovaTec® immundiagnostica GmbH; Germany)). Anti-Müllerian Hormone (AMH) was measured by ELISA using (CUSABIO®; China). WISP1 and betatrophin were measured by ELISA using (Cloud-Clone Crop®; USA). Homeostatic model assessment-insulin resistance (HOMA-IR) was calculated using the standard formula: $HOMA-IR = \text{Insulin (mU/ml)} \times \text{Glucose (mmol/l)} / 22.5$ [9].

2.3 Statistical Analysis

Data were analyzed by GraphPad Prism 5 version 5.01. Data were summarized as mean ± SEM. Differences between groups were

analyzed by one-way ANOVA. Post-hoc testing was performed by the Tukey test to compare the difference among the groups. Simple linear correlation (Pearson correlation coefficient test) (r) was also done. Probability (P-value) is considered significant if < 0.05. ROC curves have been analyzed by SPSS version 20.0.

3. RESULTS

3.1 Baseline Characteristics

Characteristics of the subgroups including clinical, lipid profile, hormones and adipokines parameters are shown in (Table 1). Both PCOS groups had higher FPG, fasting insulin, HOMA-IR, TC, TAG, LDL-C, LH, LH/FSH ratio, TT and AMH values than the non PCOS groups. Serum WISP1 and betatrophin values were elevated in the obese and non-obese PCOS group compared to the control groups with *P* value equal 0.0001*** for all (Figs. 1 and 2). Also both obese subgroups had higher BMI, fasting insulin, HOMA-IR, TC, TAG, LDL-C, WISP1 and betatrophin values than the normal weight subgroups.

3.2 Correlation Analysis

Serum WISP1 and betatrophin concentrations were positively correlated with BMI, FPG, fasting insulin, HOMA-IR, TC, TAG, LDL-C, LH and TT in obese and non-obese PCOS group. Also WISP1 and betatrophin showed positive correlation with AMH in non-obese PCOS only. Importantly there was positive correlation between betatrophin and WISP1 in obese and non-obese PCOS group (Table 2) and (Figs. 3 and 4).

3.3 Receiver Operating Characteristics Curves

The ROC curves were carried out to assess the diagnostic performance of both WISP1 and betatrophin for PCOS (Figs. 5 and 6) and (Table 3).

4. DISCUSSION

Overexpression of betatrophin can reduce insulin sensitivity, and enhance IR in hepatocytes [8]. The results of our study confirmed that serum levels of betatrophin were increased in women with PCOS when compared to control subjects. Also the obese subgroups had higher

Table 1. Comparisons between statistics of clinical, lipid profile, hormones and adipokines data of all studied groups

Parameter	Non-obese groups		P-value	Obese groups		P-value
	Group I (Non-obese control) N=22 Mean ± SEM	Group II (Non-obese PCOS) N=22 Mean ± SEM		Group III (Obese control) N=22 Mean ± SEM	Group IV (Obese PCOS) N=22 Mean ± SEM	
BMI (kg/m ²)	25.4 ± 0.8	23.9 ± 0.7	NS	35.3 ± 1.06	39.3 ± 2.05	NS
FPG (mg/dl)	93.2 ± 2.6	107.9 ± 3.02	0.0001***	94.3 ± 2.6	113 ± 2.1	0.0001***
Insulin (uIU/ml)	8.8 ± 0.6	15.5 ± 1.3	0.0001***	10.4 ± 1.02	20.3 ± 1.2	0.0001***
HOMA-IR	2.05 ± 0.1	4.1 ± 0.3	0.0001***	2.4 ± 0.2	5.7 ± 0.4	0.0001***
TC (mg/dl)	138.9 ± 6.3	170 ± 6.1	0.0001***	226.5 ± 7.2	274.7 ± 11.9	0.0001***
TAG (mg/dl)	86.3 ± 4.1	129.6 ± 4.06	0.0001***	131.2 ± 7.2	185.7 ± 6.4	0.0001***
HDL-C (mg/dl)	61.7 ± 1.8	39.9 ± 0.7	0.0001***	32.8 ± 0.9	25.9 ± 1.1	0.0001***
LDL-C (mg/dl)	59.9 ± 4.3	106.7 ± 5.3	0.0001***	167.4 ± 6.1	204.6 ± 9.8	0.0001***
LH (mIU/ml)	4.4 ± 0.2	13.3 ± 0.4	0.0001***	4.9 ± 0.1	13.9 ± 0.3	0.0001***
FSH (mIU/ml)	8.5 ± 0.3	8.7 ± 0.3	NS	8.7 ± 0.3	8.4 ± 0.3	NS
LH/FSH	0.5 ± 0.01	1.6 ± 0.1	0.0001***	0.5 ± 0.02	1.7 ± 0.08	0.0001***
P4 (ng/ml)	0.9 ± 0.04	0.9 ± 0.04	NS	0.9 ± 0.04	0.9 ± 0.04	NS
TT (pg/ml)	0.2 ± 0.01	0.6 ± 0.04	0.0001***	0.2 ± 0.02	0.6 ± 0.03	0.0001***
AMH (ng/ml)	4.4 ± 0.08	13.8 ± 0.6	0.0001***	4.4 ± 0.1	14.4 ± 0.6	0.0001***
WISP 1 (pg/ml)	86 ± 3.2	145 ± 8.1	0.0001***	108.4 ± 7.04	187.6 ± 16.5	0.0001***
ANGPTL8 (pg/ml)	25.2 ± 0.7	33.9 ± 1.01	0.0001***	32.08 ± 1.1	49.4 ± 2.8	0.0001***

Data described by mean ± SEM and the significance using the P-value, NS = Non significant (P-Value > 0.05); ***P < 0.0001: Statistically Significant. AMH = Anti-Müllerian hormone, ANGPTL8 = Angiopoietin-like proteins 8, BMI = Body mass index, FPG = fasting plasma glucose, FSH = Follicle stimulating hormone, HDL-C = High density lipoprotein-cholesterol, HOMA-IR = Homeostatic model assessment-insulin resistance, LDL-C = Low density lipoprotein-cholesterol, LH = Luteinizing hormone, TAG = Triacylglycerol, TC = Total cholesterol, TT = Total testosterone, WISP1 = Wingless integrated (WNT)-inducible signaling pathway proteins-1

Table 2. Correlations between WISP1 and betatrophin with other data of PCOS groups

Correlation of WISP 1 with	Group II		Group IV		Correlation of betatrophin with	Group II		Group IV	
	r	P-value	R	P-value		r	P-value	r	P-value
BMI (kg/m ²)	0.75	0.0001***	0.77	0.0001***	BMI (kg/m ²)	0.8	0.0001***	0.9	0.0001***
FPG (mg/dl)	0.42	0.0498*	0.53	0.0102*	FPG (mg/dl)	0.43	0.0434*	0.59	0.0034**
Insulin (uIU/ml)	0.42	0.0490*	0.48	0.0102*	Insulin (uIU/ml)	0.52	0.0127*	0.49	0.0189*
HOMA-IR	0.52	0.0120*	0.57	0.0048**	HOMA-IR	0.64	0.0012**	0.59	0.0033**
TC (mg/dl)	0.46	0.0308*	0.54	0.0083**	TC (mg/dl)	0.5	0.0163*	0.71	0.0002***
TG (mg/dl)	0.44	0.0396*	0.42	0.0485*	TG (mg/dl)	0.55	0.0077**	0.59	0.0038**
LDL-C (mg/dl)	0.43	0.0420*	0.63	0.0015**	LDL-C (mg/dl)	0.44	0.0360*	0.72	0.0001***
HDL-C (mg/dl)	0.19	0.3757	0.17	0.4253	HDL-C (mg/dl)	0.35	0.1023	-0.03	0.8877
LH (mIU/ml)	0.70	0.0003***	0.42	0.0499*	LH (mIU/ml)	0.75	0.0001***	0.57	0.0052**
FSH (mIU/ml)	-0.41	0.0523	0.12	0.5916	FSH (mIU/ml)	-0.45	0.0336*	0.009	0.9660
P4 (ng/ml)	-0.13	0.5544	0.07	0.7317	P4 (ng/ml)	-0.13	0.5529	-0.011	0.9588
TT (pg/ml)	0.66	0.0008***	0.49	0.0182*	TT (pg/ml)	0.69	0.0003***	0.53	0.0098**
AMH (ng/ml)	0.72	0.0001***	0.21	0.3348	AMH (ng/ml)	0.8	0.0001***	0.069	0.7576
ANGPTL8 (pg/ml)	0.89	0.0001***	0.78	0.0001***	WISP1 (pg/ml)	0.89	0.0001***	0.78	0.0001***

*Correlation is significant at $P < 0.05$, **Correlation is significant at $P < 0.01$, *** Correlation is significant at $P < 0.0001$, AMH = Anti-Müllerian hormone, ANGPTL8 = Angiotensin-like proteins 8, BMI = Body mass index, FPG = fasting plasma glucose, FSH = Follicle stimulating hormone, HDL-C = High density lipoprotein-cholesterol, HOMA-IR = Homeostatic model assessment-insulin resistance, LDL-C = Low density lipoprotein-cholesterol, LH = Luteinizing hormone, P4 = progesterone, TAG = Triacylglycerol, TC = Total cholesterol, TT = Total testosterone, WISP1 = Wingless integrated (WNT)-inducible signaling pathway proteins-1

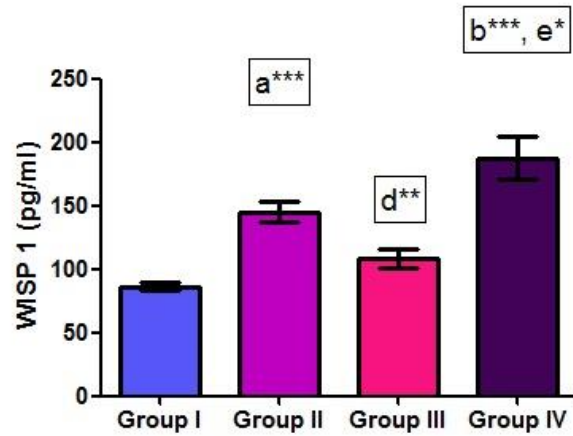


Fig. 1. Mean ± SEM of WISP1 of all studied groups

* $P < 0.01$, *** $P < 0.0001$: statistically significant

^a $p < 0.0001$ group II versus group I, ^b $p < 0.0001$ group IV versus group III, ^d $p < 0.001$ group I versus group III, ^e $p < 0.01$ * group IV versus group II

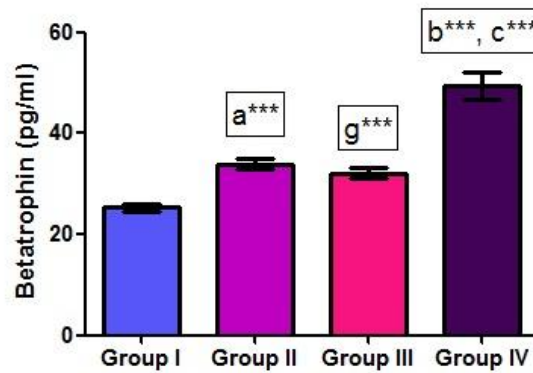


Fig. 2. Mean ± SEM of betatrophin of all studied groups

*** $P < 0.0001$: statistically significant ^a $p < 0.0001$ group II versus group I, ^b $p < 0.0001$ group IV versus group III, ^c $p < 0.0001$ * group IV versus group II, ^g $p < 0.001$ group I versus group III

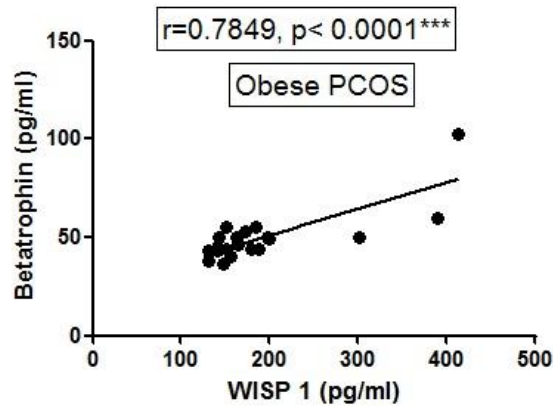


Fig. 3. Correlation between betatrophin and WISP1 in obese PCOS group

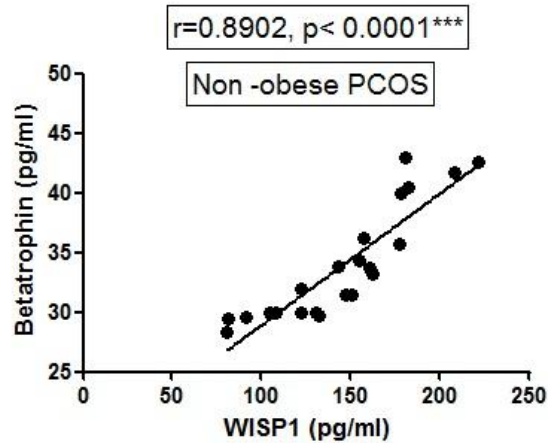


Fig. 4. Correlation between betatrophin and WISP1 non-obese PCOS group

Table 3. Characters of ROC curves for WISP1 and betatrophin levels in the diagnosis of women with and without PCOS

Variable	AUC	Cut-off point	Sensitivity	Specificity	PPV	NPV	P-value
WISP1	0.932	> 138.9	90.91%	86.36%	86.96%	90.4%	0.0001***
Betatrophin	0.987	> 38.10	95.45%	90.91%	91.30%	95.2%	0.0001***

AUC = Area under the curve, PPV = Positive predictive value, NPV = negative predictive value

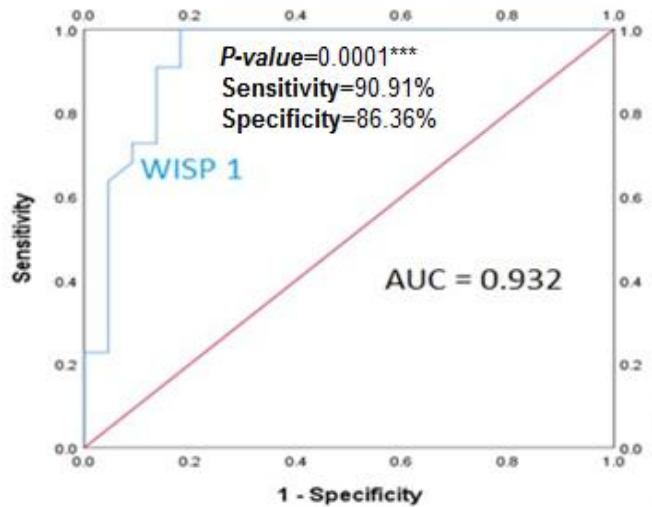


Fig. 5. ROC curve for WISP1

betatrophin level. This finding was consistent with the most of the previous studies which found increased betatrophin levels in patients with PCOS compared with those of control subjects Luo et al. [10] and Sahin et al. [1]. Varikasuvu et al. [11] suggested that IR and androgen excess might be important factors in altering circulatory betatrophin concentrations; the higher levels of

betatrophin may play an important role in associating androgen excess to IR in PCOS patients. Also Duan et al. [12] postulated that inflammatory cytokines secreted by macrophages have been demonstrated to augment tissue inflammation and to induce IR also had a specific role to increase betatrophin expression. However, Wang et al. [13] showed

circulating betatrophin levels were decreased in patients with PCOS. The disparities may be due to the difference in race/ethnicity, living habits, sample sizes and/or metabolic abnormalities, including the degree of IR. Eksi et al. [14] have been speculated that IR might result in decreased betatrophin levels as a negative feedback mechanism and there is a critical point at which betatrophin could start to increase. Qu et al. [15] concluded that it is unclear whether increased betatrophin expression is a compensatory response or only a marker of IR in PCOS, they postulated that there are different mechanisms involved in the regulation of betatrophin levels in PCOS, However, the possibility that elevated betatrophin levels may be associated with other etiological factors in PCOS, which may affect IR, cannot be excluded.

In the correlation analysis performed betatrophin levels showed positive correlations with BMI, FPG, insulin, HOMA-IR, TC, TAG, LDL-C, LH and TT in obese and non-obese PCOS patients. This finding was consistent with the Pu et al. [8], Luo et al. [10], Qu et al. [15], Sahin et al. [1] and Duan et al. [12]. A strongly positive correlation was found between circulating betatrophin levels and LH, free-testosterone, HOMA-IR, BMI, insulin, FBG, and lipid profile (triglycerides, LDL-C, and total cholesterol) in both groups Calan et al. [16]. Kahraman et al. [17] suggested that betatrophin may participate in hormonal disturbances, especially LH alterations, in women with PCOS. The mechanism underlying

the association between betatrophin and LH may be related to the signaling pathways between pituitary and liver, which may result in the stimulation of betatrophin by LH as a pituitary hormone. Conversely Wang et al. [13] and Pu et al. [8] founded that there were significant negative correlation between betatrophin level and insulin, HOMA-IR and BMI. These contradicting results may be due to differences in methodology, study design, participants, and sample sizes Varikasuvu et al. [11]. Sahin et al. [1] also observed a positive correlation between betatrophin and AMH. Efthymiadou et al. [18] suggested that the mechanism behind the increased AMH may be the upregulation of AMH messenger RNA by the androgens in small follicles from women with PCOS. Varikasuvu et al. [11] suggested that IR and androgen excess might be important factors in altering circulatory betatrophin concentrations. This may be explaining the positive correlation between betatrophin and AMH, where androgen excess in PCOS may be responsible for elevated levels of betatrophin and AMH.

Also in the current study there was significant increase in the mean serum level of WISP1 in obese and non-obese PCOS patients when compared to their control groups. PCOS groups showed statistically significant increase in obese women when compared to the non-obese women. Importantly, obese control women also had significantly higher circulating WISP1 levels than lean control women, regardless of PCOS.

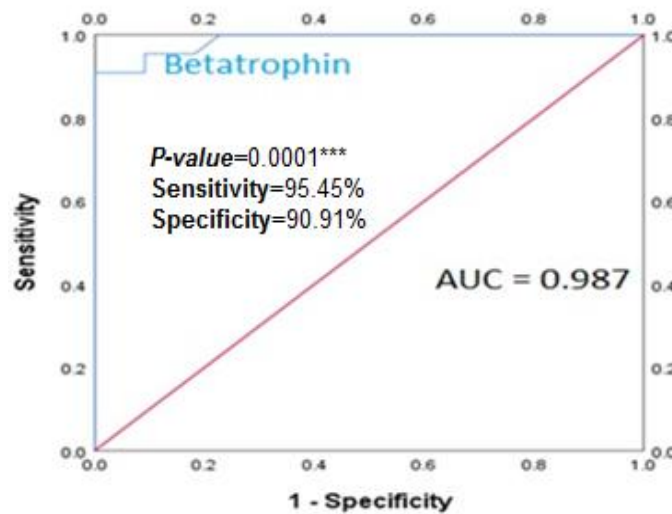


Fig. 6. ROC curve for betatrophin

This result was in agreement with Sahin et al. [1] who concluded that serum WISP1 values were elevated in the PCOS groups compared to the control groups. Circulating concentrations of WISP1 was significantly higher in obese compared to normal weight subgroups of PCOS. Also Klimontov et al. [19] and Habib et al. [20] founded that serum WISP1 levels were significantly higher in obese patients compared with healthy controls. WISP1 is associated with adiposity and adipose tissue dysfunction so, WISP1 might be a pivotal biomarker linking obesity and T2DM in addition to Ferrand et al. [21] showed that WISP1 is expressed in adipose tissue and WISP1 had been linked to adipogenesis and obesity. WISP1 acts in a highly cell-type specific manner where WISP1 is mainly expressed during organ development and under pathological conditions, such as fibrosis or cancer. Murahovschi et al. [6] postulated that where WISP1 is an adipokine released by fully differentiated human adipocytes, therefore WISP1 release increases substantially during fat cell differentiation where WISP1 gene expression and WISP1 protein production is upregulated during human adipocyte differentiation and hence WISP1 may be a useful marker of visceral fat accumulation and IR.

Serum WISP1 levels showed positive correlations with BMI, FPG, fasting insulin, HOMA-IR, TC, TAG, LDL-C, LH and TT in obese and non-obese PCOS patients. However WISP1 showed positive correlation with AMH in non-obese PCOS solely. Additionally there was positive correlation between betatrophin and WISP1 in obese and non-obese PCOS group. Our results were in line with the theoretical mechanism indicating WISP1 as an adipokine powerfully associated with adipocyte accumulation and regeneration, Sahin et al. [1] concluded that WISP1 concentrations were positively correlated with BMI, TC, LDL, TG, fasting glucose, fasting insulin, HOMA-IR, free testosterone and AMH therefore WISP1 could also be act in numerous pathways resulting in IR and inflammatory events concerning PCOS where WISP1 is thought to be found in different cell types including pancreas and adipose tissue. Also Murahovschi et al. [6] showed that WISP1 may be involved during inflammation and adipocyte differentiation in obesity and pancreatic regeneration, as well as in oxidative stress events in diabetes mellitus. Additionally Hörbelt et al. [22] demonstrated that circulating WISP1 levels were positively associated with BMI, blood glucose, HOMA-IR, and fasting

insulin levels. Throughout obesity, WISP1 adipose tissues expression and WISP1 serum levels increase, WISP1 impair phosphorylation action of insulin.

Importantly within the current study there was positive correlation between betatrophin and WISP1 in obese and non-obese PCOS group. This finding might exhibit a relationship between two metabolically active products thought to be active throughout pathways of lipid metabolism. The activation of WISP1 and betatrophin might take place through many ways; WISP1 and betatrophin would possibly either use same signal pathways or potentiate each other or they could additionally represent the serial steps of a typical pathway. There is still a lack of information for the precise mechanism concerned during this relationship. Sahin et al. [23] farcified that betatrophin and WISP1 were interactive molecules with roles in cell differentiation, proliferation and lipid metabolism. Wherever betatrophin was thought to promote beta cell proliferation and WISP1 has advanced relationship pattern with various cellular pathways during its action promoting cell survival, tissue restoration and inflammatory modulation. The impact of WISP1 and betatrophin on cell proliferation and cytoprotection may be directive while explaining the positive correlation that we observed between WISP1 and betatrophin.

5. CONCLUSION

Betatrophin and WISP1 levels were considerably higher in women with PCOS and this was powerfully associated with obesity, IR and sex hormone variations. These findings might strengthen the hypothesis of a potential role of WISP1 and betatrophin within the pathological process of PCOS. The ROC curve of WISP1 and betatrophin revealed that they had an acceptable AUC value and may be valuable in diagnosis and prediction of PCOS patients. Wherever the pathophysiology of PCOS consists of multiple complicated hormonal and metabolic relationships, our findings might offer new insight into however these mechanisms could also be functioning.

CONSENT

The patients were informed about the nature of the study, and free WRITTEN informed consent was obtained from all study subjects.

ETHICAL APPROVAL

The study was approved by the scientific research ethics committee, AL-Azhar University, faculty of pharmacy and was conducted according to the rules of Helsinki declaration for human studies, and its scientific research ethics committee code number is 161.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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