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The Relation Between Insulin Resistance and Sympathetic Skin Response in Patients with Polycystic Ovary Syndrome

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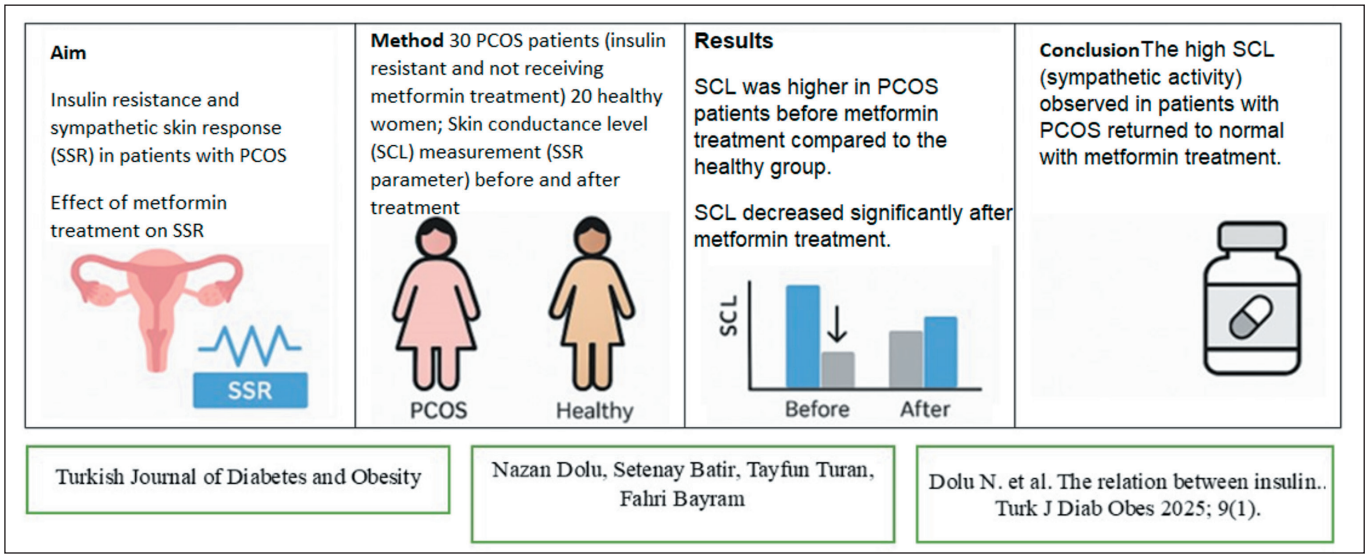
GRAPHICAL ABSTRACT



ABSTRACT

Aim: Changes in sympathetic activity are responsible for hypertension and insulin resistance observed in polycystic ovary syndrome (PCOS). The Sympathetic skin response (SSR) reflects the activity of the sudomotor glands stimulated by the sympathetic nerves. In this study, we aimed to investigate the relationship between insulin resistance and SSR in PCOS patients. In addition, the effect of insulin resistance treatment with the antidiabetic agent metformin on SSR was explored.

Material and Methods: Thirty PCOS patients with insulin resistance who did not receive metformin therapy and twenty healthy women were included in the study. Hormone, oral glucose tolerance test, and HOMA score (Homeostasis Model Assessment) measurements were performed on all participants. Skin conductance level (SCL), which is a parameter of SSR and reflects sympathetic activity, was recorded from all participants without anxiety or depression. All measurements were repeated after treatment with 1500-2000 mg/day metformin for 6 months in PCOS patients.

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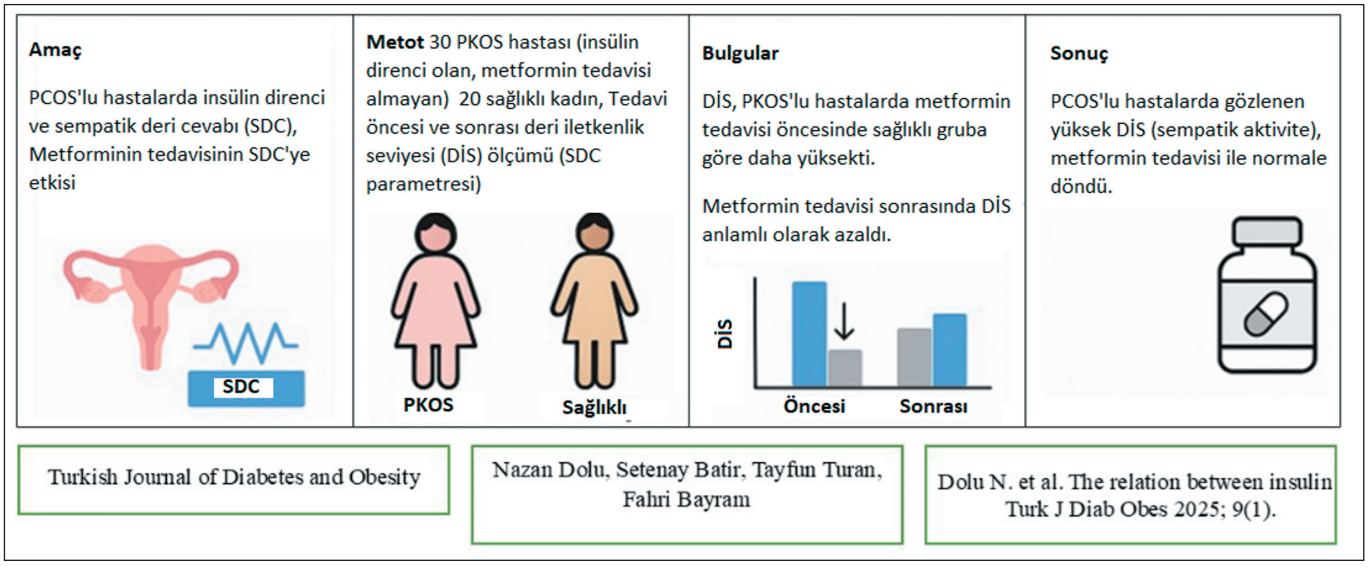
Results: Testosterone, androstenedione levels, and HOMA-insulin resistance values were significantly higher in PCOS than healthy controls (p <0.001). SCL was higher in PCOS patients than in the healthy group before metformin treatment (p<0.05), but significantly decreased after metformin treatment and approached the value of the control group (p<0.05).

Conclusion: The high SCL observed in PCOS patients indicates increased sympathetic activity in these patients. The decrease in SCL after treatment of PCOS patients with metformin shows that metformin may have an ameliorative effect on some PCOS symptoms by reducing sympathetic activity.

Keywords: *Polycystic Ovary Syndrome, Sympathetic skin response, Insulin resistance, Sympathetic activity, HOMA*

Polikistik Over Sendromlu Hastalarda İnsülin Direnci ile Sempatik Deri Cevabı Arasındaki İlişki

GRAFİKSEL ÖZET



ÖZ

Amaç: Polikistik over sendromunda (PKOS) görülen hipertansiyon ve insülin direnci gibi bozukluklardan sempatik aktivitedeki değişiklikler sorumludur. Sempatik deri cevabı (SDC), sempatik sinirler tarafından uyarılan sudomotor bezlerin aktivitesini yansıtır. Bu çalışmada, PKOS hastalarında insülin direnci ile SDC arasındaki ilişkiyi araştırmayı amaçladık. Ayrıca antidiyabetik ajan metformin ile insülin direnci tedavisinin SDC üzerindeki etkisi araştırıldı.

Gereç ve Yöntemler: Çalışmaya metformin tedavisi almayan insülin direnci olan 30 PKOS hastası ve 20 sağlıklı kadın dahil edildi. Tüm katılımcılara hormon, oral glukoz tolerans testi ve HOMA skoru (Homeostasis Model Değerlendirmesi) ölçümleri yapıldı. SDC'nin bir parametresi olan ve sempatik aktiviteyi yansıtan deri iletkenlik seviyesi (DİS), anksiyete-depresyon olmayan tüm katılımcılardan kaydedildi. PKOS hastalarında 6 ay süreyle 1500-2000 mg/gün metformin tedavisi sonrasında tüm ölçümler tekrarlandı.

Bulgular: Testosteron ve androstenedion düzeyleri ile HOMA-insülin direnci değerleri PKOS'lularda sağlıklı kontrollerden anlamlı olarak yüksekti (p<0,00). DİS, PKOS'lu hastalarda metformin tedavisi öncesinde sağlıklı gruptan daha yüksekti (p<0,05), ancak metformin tedavisi sonrasında anlamlı düzeyde azalarak kontrol grubuna yaklaştı (p<0,05).

Sonuç: PKOS hastalarında gözlenen yüksek DİS, bu hastalarda sempatik aktivitenin arttığını göstermektedir. PKOS hastalarının metformin ile tedavisi sonrasında DİS'deki azalma, metforminin sempatik aktiviteyi azaltarak bazı PKOS semptomları üzerinde iyileştirici etkisi olabileceğini göstermektedir.

Anahtar Sözcükler: *Polikistik Over Sendromu, Sempatik deri cevabı, İnsülin direnci, Sempatik aktivite, HOMA*

INTRODUCTION

Polycystic Ovary Syndrome (PCOS) is an endocrine disease occurring in women of reproductive age, characterized by chronic anovulation and hyperandrogenism (1). Hyperlipidemia, obesity, and insulin resistance often accompany the disease (2-4). Metformin is among the treatment modalities used in women with PCOS, with its beneficial effects on both hyperandrogenism and insulin resistance (5).

Although the formation mechanism of PCOS has not yet been elucidated, various hypotheses have been put forward. LH hypersecretion, insulin resistance and hyperinsulinemia may be among the causes. Increased sympathetic-adrenal medullary (SAM) activity has been associated with insulin resistance (6).

It has been stated that increases in sympathetic activity may be responsible for symptoms such as hypertension in PCOS (7-9). Increased norepinephrine levels were found in estrogen-induced polycystic ovaries in rats. Hashim et al also reported that women with PCOS showed altered autonomic function and sympathetic activity, and plasma epinephrine levels were high (10).

Sympathetic skin response (SSR) is a proven method to measure sympathetic autonomic nervous system activity and to evaluate neurocognitive functions such as attention, anxiety, and cognition (11,12). Skin conductivity level (SCL), one of the measured parameters of SSR, reflects the activity of sweat glands innervated by sympathetic nerves. Since sympathetic nervous system activity increases in stressful situations, SCL is also measured as an indicator of stress (13,14).

There are SSR studies conducted on patients with PCOS in the literature. SSR was found to be increased in some studies (10,15) and decreased in one study (16).

In this study, we aimed to explore the relationship between the skin conductance level and insulin resistance in women with PCOS. We also studied the effects of insulin resistance treatment on sympathetic skin response. The relationship between insulin resistance and skin conductance levels in patients with PCOS was examined for the first time in this study.

MATERIALS and METHODS

Study Groups

This study was carried out at the Laboratory of the Department of Physiology, Erciyes University, Faculty of Medicine from January 1st, 2011 to February 25th, 2012. Thirty PCOS patients (mean age: 25.65±1.96), and 20 healthy women (mean age: 24.89±1.65) participated in the study. The Erciyes University Faculty of Medicine Ethics Committee approved the study (2010/57). Informed consent and permission were obtained from all participants. PCOS was defined according to the 2003 Rotterdam consensus criterion (17). Thirty women diagnosed with PCOS in Erciyes University Faculty of Medicine, Department of Endocrinology, were included in the study.

The minimum number of participants was determined by the G Power Version 3.1.3 software. The sample size was calculated as 0.50 effect size, 80% test power, and 95% confidence level. Power analysis revealed that a sample size of at least 35 was required.

Participants who received hormone and insulin resistance therapy and had a history of ovarian surgery were excluded from the study. All patients had normal thyroid function tests. Twenty non-obese healthy women volunteered as controls. The Psychiatry Department of Erciyes University performed a psychiatric evaluation in all groups, and in our study, which included people with normal anxiety, people were included. SSR (tonic and phasic SCL and Skin conductance fluctuation rate -SCFr) was recorded after performing the anxiety depression scale. Insulin resistance was diagnosed according to fasting glucose, fasting insulin, Oral Glucose Tolerance Test (OGTT), and Homeostatic Insulin Resistance (HOMA-IR) test results. After the SSR records of PCOS patients with insulin resistance were obtained, 6-month metformin (1500 mg/day) treatment was applied. The tests were repeated after 6 months.

Psychiatric Evaluation

Hamilton Depression Rating Scale (HDRS) was used for depression scores and Hamilton Anxiety Rating Scale (HARS) was used to determine the personality and anxiety scores of the groups. Standardized Mini-Mental State Examination (MMSE) was applied to evaluate the cognitive functions (18,19). All the people who participated in the study group had normal anxiety and depression scales.

Hormonal Analysis

Hormonal analysis was performed in the follicular phase (3-6 days of the menstrual cycle). Basal serum concentrations of sex hormone-binding globulin (SHBG), estradiol (E2), total (tT) and free testosterone (fT), androstenedione (A), and dehydroepiandrosterone-sulfate (DHEA-S) were analyzed by the ELISA (Enzyme-Linked ImmunoSorbent Assay) technique.

Oral Glucose Tolerance Test

After fasting for 10-12 hours, OGTT was performed between 08.00-10.00. After blood was drawn in the fasting state, 75 g of glucose was administered orally. Blood was then drawn at 30-minute intervals over 2 hours to measure glucose and insulin levels (20,21).

Homeostatic Measurement Assessment of Insulin Resistance

HOMA-IR evaluates blood glucose levels and insulin resistance using insulin while fasting. Blood is given only once and is calculated by the formula: fasting serum insulin (mIU/L) × fasting plasma glucose (mmol/L)/22.5 (20,22).

SSR Measurement

SSR was recorded with the MP36 system (BIOPAC). SSR were recorded with two Ag/AgCl electrodes (with 0.05 molar NaCl gel) from the medial phalanges of the index and middle fingers' palmar surface of the right and left hands.

Tonic response: Responses (μmho/cm2) were recorded for 2 minutes without stimulation. Two parameters were calculated in tonic responses, the skin conductivity level (SCL) and the number of non-specific skin conductance fluctuations (NS-SCFr). NS-SCFr are spontaneous fluctuations in sweat gland activity. NS-SCFr occurs without stimuli (23).

Phasic response: The 15 auditory stimuli were presented for 10 minutes after the tonic measurement. All were 1-sec, 90 dB, 1000-Hz tones. The interstimulus interval was changed from 30 sec to 65 sec. The mean SCL values were calculated for phasic SSR. Skin conductivity responses greater than 0.02 μmho in 12 seconds were considered as the response (24).

Statistical Analysis

Statistical analyses were performed with IBM SPSS Version 21.0. First, a normality test was applied with the Kolmogorov-Smirnov test. Comparison of PCOS and control group baseline data was performed with one-way ANOVA analysis of variance and post hoc Scheffe test. Relationships between BMI and insulin, HOMA, or G/I value were evaluated with regression and Pearson correlation tests. Values are presented as mean ± SE. Statistical significance was defined as $p < 0.05$.

RESULTS

Demographic characteristics of PCOS and control groups are given in Table 1. There was no significant difference between the ages of women with PCOS (25.65±1.96) and the control group (24.89±1.65) (p=0.39). PCOS patients exhibited significantly increased body mass index (BMI, kg/cm^2) (control group: 22.55±0.52, PCOS group: 25.72±1.18, p=0.003). The degree of hirsutism ranged from mild to severe (scores 10 to 17 according to Ferriman and Gallwey) in most of the PCOS patients (hirsutism score: 17.00±1.13; p<0.001) (25). Twenty-five patients with PCOS had severe acne, moderate acne was observed in two patients and three patients had mild acne (Acne (+) = 25 (83.3%); (Number, %) (++) = 2 (6.6%), (+++) = 3 (10%).

In the statistical comparison of psychiatric evaluations of PCOS and control groups, no significant difference was found. All subjects had normal anxiety and depression scale findings (p>0.05) (Table 1).

The patients and healthy women of SHBG, E2, tT, fT, A, and DHEA-S were analyzed. The tT (p<0.02), fT (p<0.00), and A (p<0.03) levels were significantly increased in the PCOS group. There was no significant difference for other hormones (Table 1).

As shown in Table 2, there were no statistically significant differences in hormone levels in the PCOS patient groups between pre- and post-treatment (p>0.05).

Table 1: The comparison of psychiatric evaluation and hormonal parameters of PCOS and control groups

	Controls (n=20)	PCOS (n=30)	F	P
Psychiatric evaluation				
HDRS	0.92±0.54	0.86±0.45	0.43	0.73
HARS	4.82±1.36	3.73±1.28	0.95	0.43
MMSE	29.04±0.92	28.66±0.43	0.10	0.95
Hormones				
SHBG nmol/L	49.10±8.53	39.82±4.34	0.49	0.68
tT ng/dL	36.77±5.65	79.96±5.56	4.89	0.00
fT pg/mL	1.56±0.20	2.60±0.19	3.31	0.02
A ng/mL	1.41±0.19	2.32±0.20	3.14	0.03
E_2 pg/mL	62.92±5.97	59.07±6.76	0.57	0.63
DHEAS ng/mL	2320.20±262.38	3208.69±256.76	1.85	0.15

Data are expressed as the mean ± SD. **HDRS:** Hamilton Depression Rating Scale 7↓ normal), **HARS:** Hamilton Anxiety Rating Scale (14↓ normal), Standardized Mini Mental State Examination (MMSE) (24↑ normal), **SHBG:** Sex Hormone Binding Globulin (32-100 nmol / L), **tT:** Total Testosterone (11-80 ng / dL), **fT:** Free Testosterone (0.29 - 3.18 pg / mL), **A:** Androstenedione (0.10 - 3.08 ng / mL), **E2:** Estradiol (30-119 pg/ml), **DHEAS:** Dehydroepiandrosterone Sulfate (1330-441ng / mL)

Table 2: The comparison between pretreatment and posttreatment in the PCOS group for hormonal parameters

Hormone	Pretreatment (n=20)	Posttreatment (n=20)	F	P
SHBG nmol/L	33.00±3.00	47.50±13.50	-1.38	0.39
tT ng/dL	65.50±6.25	96.00±13.25	-3.00	0.20
sT pg/mL	2.36±0.38	2.28±0.50	0.13	0.90
A ng/mL	2.50±0.64	3.45±1.08	-0.76	0.48
DHEAS ng/mL	2446.40±444.13	2249.20±659.22	0.53	0.62

Data are expressed as the mean ± SD. **SHBG:** Sex Hormone Binding Globulin (32-100 nmol / L), **fT:** Free Testosterone (0.29 - 3.18 pg / mL), **tT:** Total Testosterone (11-80 ng / dL), **A:** Androstenedione (0.10 - 3.08 ng / mL), **DHEA:** Dehydroepiandrosterone Sulfate (1330-4410 ng / mL), **TSH:** Thyroid Stimulating Hormone (0.27 - 4.20 mIU / mL)

Table 3: The comparison of PCOS and control groups for metabolic parameters

Metabolic parameters	Controls (n=20)	PCOS pretreatment (n=30)	PCOS posttreatment (n=30)	F	P
Fasting glucose (mg/dl)	83.90±0.9	88.24±1.57	85.32±3.25	2.26	<0.08
Fasting insulin (μU/ml)	3.56±1.54	9.74±0.83	7.51±3.21	5.29	<0.002
HOMA-IR	0.49±0.17	2.31±0.22	1.51±2.73	10.42	<0.001

Data are expressed as the mean ± SD. **HOMA-IR:** Homeostasis Model Assessment

Table 4: The comparison of PCOS and control groups for EDA measurements

EDA measurements		Controls (n=20)	PCOS (n=30)	F	p
SCFr (μmho)		2.85 ±0.61	4.20 ± 0.71	1.62	0.19
Tonic SCL (μmho)	right hand	8.41±0.62	12.42 ±0.68	8.94	0.00
	left hand	8.16±0.43	10.85±0.63	6.27	0.00
Phasic SCL (μmho)	right hand	7.35±0.70	12.47±0.84	8.71	0.00
	left hand	7.34±0.62	11.31±0.69	8.15	0.00

Data are expressed as the mean ± SD. **SCFr:** skin conductance fluctuations, **SCL:** skin conductance level

Table 5: The comparison of pretreatment and posttreatment in the PCOS group for EDA parameters

EDA measurements		PCOS pretreatment (n=30)	PCOS posttreatment (n=30)	F	p
SCFr (μmho)		3.33 ±1.22	2.77 ± 0.68	0.69	0.50
Tonic SCL (μmho)	right hand	13.68±1.28	9.65 ±1.80	2.34	0.04
	left hand	11.63±0.92	8.25±1.01	2.40	0.04
Phasic SCL (μmho)	right hand	14.06±1.72	9.25±2.01	3.59	0.007
	left hand	12.49±1.48	8.42±1.64	2.63	0.03

Data are expressed as the mean ± SD. **SCFr:** skin conductance fluctuations, **SCL:** skin conductance level

Although there was no significant difference between the groups for fasting glucose concentration (p>0.05), pre- and post-treatment groups of PCOS had significantly higher fasting insulin levels (p< 0.002) and HOMA-IR index (p< 0.001) than the control group (Table 3).

When fasting glucose levels were compared before and after metformin treatment in PCOS patients, there was no significant difference between fasting glucose levels. However, fasting glucose concentration decreased after treatment (p>0.08). Fasting insulin levels (p<0.002) and HOMA-IR index (p<0.001) decreased significantly after metformin treatment in PCOS patients compared to before treatment (Table 3).

As shown in Table 4, tonic SCL (p<0.00) and phasic SCL (p<0.00) were significantly higher in the pre-treatment PCOS group than in the control group. The posttreatment levels of tonic SCL and phasic SCL were found to be lower than the pre-treatment levels. Tonic SCL (p<0.04), and phasic SCL (p<0.007) levels were significantly lower in the posttreatment group when compared with pretreatment's (Table 5).

There were no statistically significant differences for SCFr between PCOS and the control group (p>0.05) and between the pretreatment and posttreatment levels in the PCOS group (p>0.05).

Correlation analyses were performed for fasting blood glucose level and SCL. There was no significant correlation between the groups for fasting glucose concentration and SCL.

DISCUSSION

The high incidence of insulin resistance in patients with PCOS and the demonstration of the relationship between some metabolic disorders and sympathetic activation have popularized the idea that sympathetic activity may increase in patients with PCOS, cause some PCOS symptoms, and may be responsible for the etiopathogenesis of the disease.

In this study, we investigated the relationship between sympathetic activity via SSR and insulin resistance in women with PCOS. We also studied the effects of insulin resistance treatment on SSR.

According to our findings, as expected, free testosterone, total testosterone, and androstenedione levels were higher in the PCOS group than in the control group. There were no statistical differences for SHBG, E2, and DHEA-S between PCOS and control groups.

It has been reported that increased sympathetic nerve activity and secretion of catecholamines may stimulate the formation of insulin resistance (26). In our study, the higher HOMA-IR index and fasting insulin levels of patients with PCOS before metformin treatment than the control group, and after treatment, these values decreased.

Metformin had a reducing effect on sympathetic activity and insulin resistance. So, treatment of insulin resistance may improve both insulin resistance and PCOS symptoms related to sympathetic activity. The ameliorative effect of

metformin on insulin resistance has been attributed to its increased activity of insulin receptor tyrosine kinase, glycogen synthesis, and GLUT4 glucose transporters. It has also been reported that metformin improves insulin sensitivity by inhibiting lipolysis and reducing lipotoxicity in adipose tissue (27).

It has been shown that metformin treatment in obese rats can normalize the cholinergic response via muscarinic acetylcholine receptors (M3) in pancreatic beta cells and improve autonomic nervous system function in obese rats. According to Franco et al.'s study, the healing effect of metformin in PCOS may also be mediated by the autonomic nervous system (28, 29). In line with these studies, a decrease in fasting insulin and HOMA values was found in our study, indicating an improvement in insulin resistance levels with metformin treatment. The decrement in EDA parameters after treatment also reflects a decrease in sympathetic activity.

The relationship between PCOS and insulin resistance indicates that insulin resistance may play a role in the etiopathogenesis of PCOS (30). Individuals with PCOS have higher insulin resistance than women without PCOS. There is also a positive relationship between androgen and insulin concentrations in PCOS (31,32). Hyperinsulinemia suppresses SHBG synthesis in the liver. Metformin treatment has been reported to decrease circulating androgen concentration and increase SHBG concentration (33-35).

In our study, tonic and phasic SCL were higher in the PCOS group than in the control group. The post-treatment levels of tonic and phasic SCL were found to be lower than the pretreatment levels. This result showed us that the treatment improved SCL levels in PCOS patients. SCL level decreased with treatment, similar to healthy subjects. In the study of Hashim et al., SSR latency was found to be lower and SSR amplitude was higher in PCOS patients with obesity than in the obesity control group (10).

In non-obese PCOS patients, lower SSR latency and higher amplitude were detected in the non-obese control group (10). In the study of Okyay et al., SSR amplitude was higher in the PCOS group than in the control group. They reported that these findings are due to increased sympathovagal activity in PCOS patients (15). The findings of both studies are consistent with our findings and show increased sympathetic activity.

In the study of Dag et al., unlike our study, it was found that SSR latency was prolonged and amplitude decreased in PCOS patients compared to the control group. It was concluded that this may be due to impaired parasympathetic and sympathetic dysfunction in PCOS patients (16).

In PCOS patients, higher SCL results from high hormone levels and/or sympathetic hyperactivity. Our pateints had normal BMI (non-obese). Non-obese patients showed sympathetic hyperactivity and higher plasma epinephrine levels (10). In our study, higher SCl levels and insulin resistance may result from high sympathetic activity. Furthermore, SCL was decreased with treatment in PCOS patients. Insulin resistance therapy was used in our patients. After the therapy, plasma hormone levels didn't change. So, insulin resistance therapy may be responsible for decreased SCL or low sympathetic activity in the post-treatment PCOS group.

Studies are reporting that metformin can be used as a treatment, especially in obese women with PCOS (36). Although the acute and chronic autonomic effects of metformin are found to be contradictory, our study found that metformin had a reducing effect on sympathetic activity in patients with insulin-resistant PCOS.

In conclusion, higher SSR was observed in PCOS patients due to increased sympathetic activity. A decrease in SSR occurred after treatment with the anti-glycemic-antidiabetic agent metformin. This decrease indicates that metformin has a reducing effect on sympathetic activity. So, treatment of insulin resistance may improve both insulin resistance and PCOS symptoms related to sympathetic activity.

Acknowledgments
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Author's Contributions
All authors were responsible for the conceptualization and design of the study. All authors collected the data. Setenay Batir and Nazan Dolu analyzed the data. All authors contributed to the interpretation of the findings and the writing process.

Conflict of Interest
The authors have no conflicts of interest to declare.

Financial Disclosure
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Ethical Approval and Informed Consent
The study was approved by the Ethics Committee of Erciyes University Faculty of Medicine (2010/57). Written informed consent was obtained from the patients who agreed to participate in the study.

Peer Review Process
Extremely and externally peer-reviewed.

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