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Original Article

Evaluation of the Relationship Between Insulin Resistance and Selenoprotein P in Patients with Polycystic Ovary Syndrome

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ABSTRACT

Objective: Polycystic ovary syndrome (PCOS) is the most frequently seen disorder in women of childbearing age, and is characterized by insulin resistance (IR). Selenoprotein P (SeP) is a hepatokine associated with IR. The aim of the present study was to determine SeP levels in PCOS and to investigate its relationship to IR.

Methods: A total of 27 patients and 27 age- and body mass index (BMI)-matched healthy controls were included in the study. Demographic data, anthropometric measurements, and biochemical parameters were evaluated. IR and free androgen index were calculated. Analysis of the correlation of biochemical and anthropometric parameters with SeP was performed.

Results: There was a significant difference in the mean fasting insulin and homeostasis model assessment of insulin resistance (HOMA-IR) between patients and controls (both $p<0.05$), while the SeP level was similar (1.05±0.7ng/mL, 1.61±1.9ng/mL, respectively; $p=0.7$). There was no correlation between SeP and HOMA-IR in either group. There was a negative correlation between SeP and waist circumference (WC) in the PCOS group ($p=0.03$; $r=-0.485$), but not in the control group. In the control group, there was a negative correlation between SeP and BMI and fat percentage ($r=-0.506$, $p=0.007$; $r=-0.643$, $p=0.024$, respectively), but not in the PCOS group. In addition, there was a significant positive correlation between testosterone and SeP in the patients ($r=0.456$; $p=0.017$).

Conclusion: The SeP level was similar in patients and controls, and there was no correlation between SeP and IR in the PCOS group. However, the correlation of SeP with WC and testosterone in PCOS suggests a possible metabolic relationship.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a chronic, complex disease with adverse effects on quality of life that affects 10% to 15% of women of childbearing age. It is characterized by oligo-anovulation, hyperandrogenism, infertility, and polycystic ovaries.[1] These patients are often obese (50–65%), have insulin resistance (IR) (35–45%), and Type 2 diabetes (DM) (7–10%).[2,3] IR (especially in striated muscle and adipose tissue), and beta cell dysfunction are basic mechanisms that represent long-term metabolic risks, though the pathophysiology of IR has not been clarified conclusively. Neither obesity nor androgen excess alone sufficiently explains the IR seen in PCOS.[4,5]

Selenoprotein P (SeP) is a glycoprotein that contains 22% to 65% of the selenium in plasma, and it is the best marker of the selenium taken with food.[6] SeP is expressed by most tissues; however, approximately 90% of SeP is expressed in hepatocytes. Adipose tissue, which plays an im-

portant role in lipid and glucose metabolism, plays a role in the regulation of SeP.[7,8]

When compared with individuals of normal weight, a higher serum SeP level has been found in overweight and obese individuals, and the SeP level in circulation has been associated with glucose metabolism in human beings.[9,10] Although a role in the cerebral, reproductive, and immune systems; thyroid function; and protection from cancer have been demonstrated,[11–13] the correlation between selenium and glucose metabolism has not yet been completely displayed. It was initially thought that antioxidative and insulinomimetic effects of selenium would provide protection against the development of DM.[14,15] However, selenium intake was observed to be associated with potential risk for type 2 DM or metabolic syndrome in epidemiological studies.[16–19] Other studies cited in the literature have reported that intake of high doses of selenium might decrease the risk of developing type 2 DM.[20–22] Available data suggest that SeP is negatively regulated by insulin in the liver in cases of normal insulin sensitivity. Increased glucose concentrations stimulate the release of insulin from the pancreas and SeP from the liver.[23,24] Since, in the event of IR, expression of SeP cannot be suppressed, glucose levels will rise further. When this mechanism is considered, an increased SeP level in the circulation appears to be the outcome, rather than the cause, of impaired glucose metabolism.

In the present study, the aim was to investigate the relationship between IR and SeP.

MATERIAL AND METHODS

Patient selection

Twenty-seven patients with PCOS aged between 18-35 years and 27 healthy, age- and BMI-matched control subjects who presented at the outpatient clinics of the Department of Endocrinology, and Diseases of Metabolism were included in the study. Diagnosis of PCOS was made based on the presence of at least 2 of the following 2003 Rotterdam European Society for Human Reproduction/American Society of Reproductive Medicine consensus criteria: oligo or anovulation, findings of clinical and/or biochemical hyperandrogenism, and detection of polycystic ovary on ultrasonogram.[25] Patients with any systemic disease (cardiovascular disease, rheumatologic disease, hypertension, DM, malignancy, chronic renal disease, etc.), and patients who used an oral contraceptive agent; antihypertensive, antidiabetic, antiobesitic, antihyperlipidemic agents; a glucocorticoid; or who had received ovulation induction therapy within the previous 6 months were excluded. Other causes of hyperandrogenism and oligo-anovulation, such as Cushing syndrome, non-classical congenital adrenal hyperplasia, thyroid dysfunction, hyperprolactinemia, and androgen secreting tumors, were ruled out.

The control group consisted of healthy women without oligo-anovulation, hirsutism, or biochemically detected hyperandrogenism.

Before initiation of the study, approval of the ethics committee was obtained. All study participants were informed about the procedures to be performed, and written, informed consent was provided.

Anthropometric measurements

At first admission, height (m) and bodyweight (kg) of all participants was measured and BMI was calculated and expressed as kg/m^2. Waist circumference was measured from the umbilicus after expiration, and hip circumference was measured at the level of the greater trochanter. Waist/hip ratio was calculated. Distribution of fat in the body was estimated using bioelectrical impedance analysis (Jawon, Kangnung, South Korea).

Biochemical assessments

Following 8 to 12 hours of fasting, biochemical analyses were performed during the early follicular phase (2nd-5th days of menstrual period). Baseline venous blood samples were drawn from all participants to measure serum levels of fasting blood glucose (FBG) fasting insulin, total cholesterol (total–C), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglyceride (TG), total testosterone, sex hormone-binding globulin (SHBG), dehydroepiandrosterone sulfate (DHEA-S), and SeP. Next, 75 g oral glucose tolerance test was performed, and venous blood samples were drawn at 30, 60, 90, and 120 minutes to determine blood glucose and insulin levels. Blood samples drawn for the SeP levels were centrifuged at 4000 rpm for 20 minutes, the serum was separated, and then stored at -80°C.

Patients whose second-hour postprandial plasma glucose level was ≥200 mg/dL and who were diagnosed as type 2 DM were not included in the study. The patients were diagnosed as impaired glucose tolerance or impaired fasting blood glucose based on American Diabetes Association criteria.[26] IR was calculated based on the homeostasis model assessment of insulin resistance (HOMA-IR): [fasting blood glucose (mg/dL) x fasting glucose (µIU/mL)/405].[27] Free androgen index (FAI) (total testosterone x100/SHBG) was used to determine androgen status.[28] Areas under the curve (AUCs) for glucose and insulin during OGTT were calculated by the trapezoidal method.

Glucose, total-C, TG, and HDL-C levels were determined based on enzymatic colorimetric method using an AU5800 Clinical Chemistry System analyzer (Beckmann Coulter, Inc., Brea, CA, USA). Total testosterone, SHBG, and DHEA-S were measured using UniCel DxI 600 Access Immunoassay System (Beckmann Coulter, Inc., Brea, CA, USA), and the chemoluminescence method, using original

Cobas E-411 Immunologic Analyzer System kits (Roche Diagnostics, Basel, Switzerland) for insulin.

SeP was measured with the enzyme linked immune assay method, using a commercial kit (USCN Life Sciences, Inc., Wuhan, China). Intra-assay coefficient of variation (CV) and inter-assay CV values of the kit were <10% and <12%, respectively.

Statistical analysis

SPSS Statistics for Windows, Version 17.0 (SPSS Inc., Chicago, IL, USA) software was used to analyze the data, which were expressed as mean±SD. Since fewer than 30 participants were enrolled in the study, non-parametric tests were used. For intergroup comparisons, the Mann Whitney-U test was applied. Correlation analyses were performed using Spearman's rank correlation coefficient. For all statistical analyses, the cut-off value of significance was $p<0.05$.

RESULTS

Twenty-seven patients with PCOS and 27 healthy controls were included in the study. The mean age of the patient group and the control group was 24.89±3.87 years and 26.26±3.30 years (p=0.167), respectively, and mean BMI in each group was 24.23±3.98 kg/m^2 and 23.28±3.16 kg/m^2, respectively (p=0.332). In the patient group, body fat percentage, fasting insulin, HOMA-IR, $AUC_{Glucose}$, and TG levels were significantly higher, while HDL-C levels were lower ($p<0.05$). Serum SeP level was comparable in the 2 groups (p=0.755). The clinical and biochemical characteristics of the patient and control groups are presented in Table 1.

When all of the participants were evaluated, a significant negative correlation was detected between SeP level, waist circumference, BMI, and fat percentage (r=-0.308, p=0.035; r=-0.375, p=0.006; r=-0.444, p=0.030, respectively). When the groups were evaluated separately, a negative correlation was observed between SeP and waist

Table 1. Clinical and biochemical characteristics of patients with polycystic ovary syndrome and controls

	PCOS (n=27)	Control (n=27)	p
	Mean±SD	Mean±SD	
Age (years)	24.89±3.87	26.26±3.30	0.167
Anthropometric measures			
Body mass index (kg/m^2)	24.23±3.98	23.28±3.16	0.332
Waist-to-hip ratio	0.78±0.05	0.77±0.07	0.153
Waist circumference (cm)	76.50±8.12	73.96±9.06	0.091
Hip circumference (cm)	97.50±6.67	97.04±7.34	0.633
Percent trunk fat mass (%)	35.80±5.81	30.81±6.20	0.026
Metabolic measures			
Fasting blood glucose (mg/dL)	85.03±8.96	81.33±8.58	0.188
Fasting insulin (µIU/mL)	12.38±5.27	8.52±3.58	0.005
Homeostasis model assessment of insulin resistance	2.62±1.24	1.74±0.81	0.004
Total cholesterol (mg/dL)	181.28±41.93	167.67±45.91	0.347
Low-density lipoprotein cholesterol (mg/dL)	110.32±32.07	108.83±35.92	0.810
High-density lipoprotein cholesterol (mg/dL)	50.76±9.50	56.67±9.74	0.028
Triglyceride (mg/dL)	106.46±63.82	67.42±21.95	0.004
Hormonal measures			
Dehydroepiandrosterone sulphate (µg/dL)	296.80±139.76	201.15±67.80	0.008
Sex hormone binding globulin (nmol/L)	41.66±29.21	68.39±48.32	0.012
Total testosterone (ng/dL)	63.41±22.62	35.85±11.04	<0.001
Free androgen index	8.42±7.04	2.75±2.03	<0.001
Selenoprotein P	1.05±0.70	1.62±1.97	0.755
Area under curve fasting blood glucose	13533.98±1927.39	12001.67±2027.74	0.013
Area under curve insulin	6527.48±3048.70	5257.22±3105.06	0.081

PCOS: Polycystic ovary syndrome; SD: Standard deviation.

Table 2. Correlation between selenoprotein P level and other parameters

	PCOS		Control		All subjects	
	p	r	p	r	p	r
Age (years)	0.946	0.014	0.643	0.094	0.759	0.043
Body mass index (kg/m^2)	0.186	-0.268	0.007	-0.506	0.006	-0.375
Waist circumference (cm)	0.030	-0.485	0.252	-0.228	0.035	-0.308
Waist-to-hip ratio	0.079	-0.402	0.648	-0.094	0.343	-0.143
Percent trunk fat mass (%)	0.286	-0.284	0.024	-0.643	0.030	-0.444
Fasting blood glucose (mg/dL)	0.057	-0.371	0.566	0.116	0.475	-0.099
Fasting insulin (µIU/mL)	0.386	-0.174	0.361	-0.183	0.361	-0.127
Homeostasis model assessment of insulin resistance	0.174	-0.263	0.454	-0.151	0.271	-0.152
Low-density lipoprotein cholesterol (mg/dL)	0.138	-0.305	0.827	0.047	0.346	-0.138
High-density lipoprotein cholesterol (mg/dL)	0.558	0.123	0.766	0.064	0.555	0.086
Triglyceride (mg/dL)	0.366	-0.185	0.328	-0.209	0.272	-0.158
Dehydroepiandrosterone sulphate (µg/dL)	0.183	0.275	0.089	-0.334	0.788	-0.038
Sex hormone binding globulin (nmol/L)	0.241	-0.244	0.642	0.100	0.395	-0.124
Testosterone (ng/dL)	0.017	0.456	0.085	-0.337	0.946	0.009
Free androgen index	0.058	0.385	0.192	-0.276	0.475	0.104

PCOS: Polycystic ovary syndrome.

circumference in the PCOS group (r=-0.485; p=0.03), contrary to the control group. In the control group, a negative correlation existed between SeP and BMI, and fat percentage (r=-0.506, p=0.007; r=-0.643, p=0.024, respectively), such a correlation was not observed in the PCOS group. There was no correlation between SeP and HOMA-IR in both groups. However, there was a negative correlation in the significance limit between SeP and FBG in the PCOS group (r=-0.371, p=0.057). There was no correlation between SeP and total testosterone levels in the whole group; however, in the patient group, a positive correlation was found between total testosterone and SeP level (r=0.456 and p=0.017). Results of the correlation analysis performed for SeP and other parameters are provided in Table 2.

DISCUSSION

PCOS is a chronic disease of women of childbearing age with systemic effects, coursing with hyperandrogenism, oligo-anovulation, and IR. Studies have demonstrated a close relationship between SeP and glucose metabolism, and also reported increased plasma SeP level in the presence of IR.[21,22] In a study performed after the administration of metformin, dose-related decreases in the expression and secretion of SeP mRNA was observed,[29] and some researchers have indicated that SeP might be a treatment target in DM with IR.[30]

In a review article written by Mao and Teng, the authors indicated that in a case of normal insulin sensitivity, insulin will suppress release of SeP from the liver, while in the case of IR, this feedback mechanism fails to function and an increase in SeP level occurs, which may induce an increase in blood glucose level.[31] In another study in which 100 patients with varying glucose tolerance levels were evaluated, a higher plasma SeP concentration was detected in cases with normal glucose tolerance relative to cases with type 2 DM or prediabetes, and enhanced plasma SeP levels were found to be positively correlated with BMI and IR.[9] In our study, higher IR was detected in patients with PCOS, though not statistically significantly different, and mean plasma SeP level was lower than that of the control group. Furthermore, we did not find any relationship between the parameters of glucose metabolism and SeP in the 2 groups based on the correlation analysis we performed. However, in the PCOS group, a negative borderline correlation was detected between FBG and SeP. Since none of our patients had DM, a decreased SeP level in patients with PCOS may be correlated with suppression of SeP level secondary to a higher insulin level. Generally, increased SeP level has been associated with DM and other cardiometabolic risks,[31] though it should be noted that this mechanism has not been clearly established. In a study conducted by Yang et al. with 8 patients with IR and 8 control subjects, suppression of SeP gene expression in the subcutaneous tissue was demonstrated in patients with IR.[7]

In a study that was an evaluation of visceral obesity using computed tomography, a correlation between visceral

obesity and SeP level was observed.[32] However, some studies have demonstrated a negative correlation between SeP level, gene expression, obesity and IR.[31] In the present study we performed a correlation analysis between SeP and anthropometric parameters, and found negative correlations between SeP and waist circumference in the patient group, and also between SeP and BMI and the percentage of adipose tissue in the control group.

We also detected a positive correlation between total testosterone and SeP in patients with PCOS. Very few studies have investigated the relationship between testosterone and SeP. In a study performed by Nishimura et al., after exposing Leydig cell cultures to oxidative stress, increases in SeP and testosterone were detected, and a positive correlation between them was found.[33] Also seen in our study, the correlation between testosterone and SeP is an interesting finding. An increase in SeP level in PCOS characterized by hyperandrogenemia may be a part of the anti-inflammatory and antioxidant response.

In conclusion, measurements of SeP level in PCOS patients were similar to those of healthy controls, and no correlation between glucose metabolism and SeP values was detected. The small number of patients who had normal body weight may be a limitation of our study. However, the positive correlation between total testosterone and SeP in the patient group still suggests the presence of a possible relationship. Since it was a cross-sectional study, it does not demonstrate a cause-effect relationship. Our pilot study investigated the correlation between SeP and IR in PCOS, and more comprehensive studies should be performed on this topic.

Ethics Committee Approval

Approval has been obtained from the Kartal Dr. Lütfi Kırdar Training and Research Hostipal Ethics Committee.

Informed Consent

Approval was obtained from the patients.

Peer-review

Internally peer-reviewed.

Authorship Contributions

Concept: A.Ö.; Design: A.Ö.; Data collection &/ or processing: A.Ö., İ.Y., Ş.D., M.S., M.A.U.; Analysis and/or interprotation: A.Ö, Ş.T.; Literature search: A.Ö., İ.Y., K.A.; Writing: A.Ö.; Critical review: K.A.

Conflict of Interest

None declared.

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Polikistik Over Sendromlu Hastalarda İnsülin Direnci ve Selenoprotein P İlişkisinin Değerlendirilmesi

Amaç: Polikistik over sendromu (PKOS) doğurganlık çağındaki kadınlarda en sık görülen ve insülin direnci (IR) ile karakterize bir bozukluktur. Selenoprotein P (SeP) de, insülin direnciyle ilişkili bir hepatokindir. Bu çalışmada, PKOS'da SeP düzeylerini belirlemeyi ve IR ile ilişkisini araştırmayı amaçladık.

Gereç ve Yöntem: Çalışmada 27 hastayla yaş ve vücut kitle indeksi (VKİ) eşleştirilmiş 27 sağlıklı kontrolün demografik özellikleri, antropometrik ölçümleri ve biyokimyasal parametreleri değerlendirildi. İnsülin direnci ve serbest androjen indeksi (FAI) hesaplandı. Selenoprotein P ile biyokimyasal ve antropometrik parametrelerin korelasyonu yapıldı.

Bulgular: Hasta ve kontroller arasında açlık insülini ve HOMA-IR anlamlı farklıyken (her iki $p<0.05$), SeP düzeyleri benzerdi (sırasıyla, 1.05±0.7 ng/mL ve 1.61±1.9 ng/mL, $p=0.7$). Her iki grupta da SeP ile HOMA-IR arasında korelasyon saptanmadı. Polikistik over sendromu grubunda SeP ile bel çevresi arasında negatif korelasyon mevcutken ($p=0.03$, $r=-0.485$), kontrol grubunda izlenmedi. Kontrol grubunda ise SeP ile VKI ve yağ yüzdesi arasında negatif korelasyon mevcutken (sırasıyla, $r=-0.506$, $p=0.007$ ve $r=-0.643$, $p=0.024$), PKOS grubunda izlenmedi. Ayrıca hastalarda testosteron ile SeP arasında anlamlı pozitif korelasyon saptandı ($r=0.456$, $p=0.017$).

Sonuç: Hasta ve kontroller arasında SeP düzeyleri benzer bulundu ve PKOS'de SeP ile IR arasında bir ilişki saptanmadı. Ancak PKOS'de SeP'nin bel çevresi ve testosteron ile korelasyonu olası bir metabolik ilişkiyi akla getirmektedir.

Anahtar Sözcükler: İnsülin direnci; polikistik over sendromu; selenoprotein P; vücut kitle indeksi; vücut yağ yüzdesi.