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Investigation of the Relationship Between Serum Retinol-Binding Protein 4 Levels and Insulin Resistance, Homocysteine, and CRP Levels in Patients with Polycystic Ovary Syndrome

Polikistik Over Sendromlu Hastalarda Serum Retinol Bağlayıcı Protein 4 Seviyeleri ile İnsülin Direnci, Homosistein ve CRP Düzeyleri Arasındaki İlişkinin Araştırılması

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ABSTRACT

Aim: Polycystic ovary syndrome (PCOS) is the most common endocrinopathy in reproductive-age women, characterized by anovulation, hyperandrogenism, and menstrual irregularities. Its prevalence is approximately 6–8%, and insulin resistance is observed in 30–70% of affected individuals. Retinol-binding protein 4 (RBP4), a newly identified adipokine and specific carrier of vitamin A, has been shown to increase in insulin-resistant states. This study aimed to investigate serum RBP4 levels in women with PCOS and evaluate their association with metabolic parameters.

Materials and Methods: The study included 45 patients with PCOS and 45 healthy controls from Dr. Zekai Tahir Burak Training and Research Hospital. Fasting blood samples were collected and stored at -80 °C. Serum RBP4 levels were measured using the Enzyme-Linked Immunosorbent Assay (ELISA). Statistical analyses were performed using SPSS.

Results: No statistically significant difference in serum RBP4 levels was found between the two groups. However, HOMA-IR, androstenedione, total testosterone levels, LH/FSH ratio, and Ferriman-Gallwey Hirsutism Score were significantly higher in the PCOS group. HDL cholesterol levels were significantly lower in the PCOS group.

Conclusion: Our data suggest that RBP4 is not significantly associated with metabolic parameters such as insulin resistance and lipid profile in patients with PCOS. Therefore, the utility of RBP4 as an independent biomarker in the metabolic risk assessment of PCOS is limited. Further studies with larger sample sizes and prospective designs are needed.

Keywords: Polycystic ovary syndrome (PCOS); Retinol-binding protein 4 (RBP4); Insulin resistance; Homocysteine; C-reactive protein (CRP)

ÖZ

Amaç: Polikistik over sendromu; anovulasyon, amenore, adet düzensizliği ve hirsutizm gibi birçok klinik bulgusu olan, reprodüktif dönem kadınlarda en sık görülen endokrinopatidir. Toplumda prevalansı %6-8 dir. PKOS'lu kadınların büyük bir kısmında (%30–70) insülin rezistansına rastlanmaktadır. Retinol-bağlayacı protein 4 (RBP4) karaciğerden üretilen ve vitamin A için tek spesifik taşıyıcı protein olarak bilinen yeni keşfedilen bir adipokindir. RBP4 birçok insülin rezistanslı fare modellerinde seviyesi artan, adipositlerden salgılanan hormon olarak yayınlamıştır. Biz de çalışmamızda bir insülin rezistans durumu olan PKOS'lu kadınlarda serum RBP4 seviyelerini araştırdık.

Gereç ve Yöntemler: Çalışmamıza, Dr. Zekai Tahir Burak Eğitim ve Araştırma Hastanesi Jinekoloji polikliniğine başvuran PKOS tanısı konulan 45 hasta dahil edildi. Kontrol grubuna ise 45 sağlıklı kadın dahil edildi.Açlık serum RBP4 seviyeleri ölçümü için alınan örnekler serumları ayrılarak –80 derecede saklandı. Serum RBP4 seviyeleri ölçümü için tüm serumlar aynı anda 'Enzyme-Linked Immunosorbent Assay' (ELISA) yöntemi ile çalışıldı. Verilerin analizi SPSS for Windows programında yapıldı.

Bulgular: Serum RBP4 seviyeleri için iki grup arasında istatistiksel anlamlı farklılık saptanmadı. PKOS grubunun HOMA-IR, androstenedion, total testosteron düzeyleri ve LH/FSH oranları, Ferriman-Gallwey Hirsutizm Skoru anlamlı olarak yüksek bulundu. HDL Kolesterol seviyeleri ise PKOS grubunda anlamlı olarak daha düşük bulundu.

Sonuç: Çalışma verilerimizin sonuçlarına göre; RBP4'ün PKOS'lu hastalarda glukoz metabolizmasında ve insülin rezistansında henüz kullanılabilir bir marker olmadığını düşünmekteyiz. Bu testlerin klinikte kullanımı ve yüksek riskli grupların belirlenebilmesi için daha fazla sayıda çalışmaya ihtiyaç duyulmaktadır.

Anahtar Kelimeler: Polikistik Over Sendromu (PCOS); Retinol-bağlayıcı protein 4 (RBP4); Insulin Direnci; Homosistein; C-reaktif protein (CRP)

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INTRODUCTION

Polycystic ovary syndrome (PCOS) is a common endocrinopathy in women of reproductive age, characterized by clinical findings such as anovulation, amenorrhea, menstrual irregularities, and hirsutism. Its prevalence varies between 6-8% depending on different diagnostic criteria. A significant proportion of women with PCOS (30-70%) exhibit insulin resistance (1).

Retinol-binding protein 4 (RBP4) is an adipokine produced by the liver and known as the specific carrier protein for vitamin A. Yang et al. reported that RBP4 is secreted by adipocytes and has increased levels in various insulin-resistant mouse models (2). Initially considered only as a retinol transporter, RBP4 has gained attention as an adipokine that may link GLUT4 expression in adipocytes to insulin resistance (3).

Animal studies have demonstrated a correlation between high RBP4 levels and reduced insulin sensitivity, body mass index (BMI), lipid profiles, and other metabolic syndrome components (2). However, human studies have yielded conflicting results (4,5).

In this study, we aimed to investigate serum RBP4 levels in women with PCOS, a condition associated with insulin resistance. Given that previous research has suggested an association between RBP4 and lipid metabolism, we also examined the correlation between serum RBP4 levels and lipid profiles. Additionally, we evaluated the relationship between serum RBP4 levels and µCRP, a marker of inflammation linked to obesity and insulin resistance, as well as homocysteine levels, which have been found to be elevated in some studies of PCOS patients.

Based on these findings, our objective was to determine whether RBP4 could serve as a potential biomarker for glucose and lipid metabolism in PCOS patients.

MATERIALS AND METHODS

This study was originally planned and conducted prospectively between 2008–2009 as a medical thesis at Zekai Tahir Burak Women's Health Training and Research Hospital. This study included 45 patients diagnosed with PCOS who visited the gynecology outpatient clinic at Dr. Zekai Tahir Burak Training and Research Hospital between January 2008 and June 2009. The diagnosis of PCOS was based on the revised Rotterdam criteria, requiring the presence of at least two of the following three features: oligo-anovulation (cycle length >45 days or fewer than six cycles per year), clinical or biochemical hyperandrogenism (Ferriman-Gallwey score >12 or serum testosterone levels above normal), and polycystic ovary morphology on transvaginal ultrasound (TV-USG).

Thyroid function tests, LH/FSH ratio, prolactin, 17-OHP, androstenedione, total and free testosterone levels were evaluated in all patients and controls. Patients with thyroid disease, hyperprolactinemia, Cushing's syndrome, congenital adrenal hyperplasia, or those who had used hormonal medications, ovulation induction agents, glucocorticoids, antiandrogens, or antihypertensive drugs in the past six months were excluded from the study. Women with comorbid conditions that could affect RBP4 levels were also excluded.

The control group consisted of 45 healthy women who attended the gynecology or family planning outpatient clinics during the same period. These women were clinically normal, normoovulatory, and were selected without considering body weight. All participants provided written informed consent after being fully informed about the study.

After detailed anamnesis, height and weight were recorded, and blood samples were collected from all participants during the early follicular phase (between days 3 and 5 of a spontaneous or progesterone-induced menstrual cycle). Venous blood samples were obtained from the forearm between 08:00 and 10:00 AM after 12 hours of fasting. Serum samples for fasting RBP4 levels were separated and stored at -80°C until analysis. Serum RBP4 levels were measured simultaneously using the Enzyme-Linked Immunosorbent Assay (ELISA) method.

The homeostasis model assessment of insulin resistance (HOMA-IR) index was calculated using the formula: HOMA-IR = (fasting insulin × fasting glucose (mg/dL)) / 450. Hirsutism was evaluated using the Ferriman-Gallwey scoring system. The study population was matched for age and BMI before being divided into two groups. The first group consisted of 45 patients diagnosed with PCOS, while the second group included 45 healthy control subjects.

Sample Size and Randomization

The sample size was determined based on an a priori power analysis, considering the expected effect size for differences in serum RBP4 levels and the capacity of the ELISA kit used. It was estimated that at least 40 participants per group would be required to achieve 80% power at a 5% significance level, and the planned sample size was deemed sufficient and feasible for the thesis study. Due to the observational nature of the study, no randomization was applied. Eligible patients were consecutively enrolled according to predefined inclusion and exclusion criteria.

Statistical Analysis

Data analysis was performed using SPSS. The Shapiro-Wilk test

was used to determine whether continuous variables were normally distributed. Comparisons between groups were made using the Student's t-test for normally distributed variables and the Mann-Whitney U test for non-normally distributed variables. Correlations between continuous variables were evaluated using Spearman's correlation test. A p-value of <0.05 was considered statistically significant.

The study was conducted prospectively as a medical thesis at Zekai Tahir Burak Women's Health Training and Research Hospital between 2008–2009, and ethics approval for publication was subsequently obtained from Ankara Bilkent City Hospital, which continues the mission of the former institution. This approval was granted by the Ethics Committee of Ankara Bilkent City Hospital (Approval Date: 04.06.2025, Approval No: TABED 1/1350/2025) and the study was conducted in accordance with the Declaration of Helsinki and relevant national ethical standards.

RESULTS

The study population consisted of two groups: Group 1 included 45 patients diagnosed with PCOS, and Group 2 consisted of 45 normoovulatory healthy women. There was no statistically significant difference between the PCOS and control groups in terms of age and BMI (Table 1). Serum RBP4, homocysteine, and µCRP levels were not significantly different between the two groups (Table 1). However, the PCOS group had significantly higher HOMA-IR, androstenedione, total testosterone levels, and LH/FSH ratios compared to the control group. No significant differences were found between the two groups in terms of serum prolactin and 17-OH progesterone levels. However, the Ferriman-Gallwey hirsutism score was significantly higher in the PCOS group (Table 1).

Total cholesterol, LDL cholesterol, and triglyceride levels were higher in the PCOS group, but the differences were not statistically significant. However, HDL cholesterol levels were significantly lower in the PCOS group compared to the control group (Table 1).

The correlation analysis between serum RBP4 levels and HOMA-IR, homocysteine, µCRP, and total cholesterol levels was also examined. No significant correlation was found between serum RBP4 levels and these metabolic parameters in the overall study population, as well as in the PCOS and control groups separately (Table 2).

DISCUSSION

In current literature, the terms insulin resistance syndrome (IRS) and PCOS are often used interchangeably, leading to the assumption that they are closely related. However, insulin resistance cannot be demonstrated in up to 50% of obese PCOS patients using invasive tests, and this prevalence is even higher in non-obese patients (6,7). These findings indicate that PCOS and insulin resistance syndrome are not entirely equivalent. Women with PCOS exhibit impaired glucose utilization in peripheral tissues (8). In our study, we found significantly increased HOMA-IR levels in the PCOS group. Insulin resistance and related syndromes are independent risk factors for

Table 1. Demographic and Biochemical Measurements of PCOS and Control Groups

Variables	Group I (n = 45)	Group II (n = 45)	p-value
Age (years)	27.1 ± 4.2 (19–39)	28.5 ± 4.7 (18–39)	0.134
BMI (kg/m²)	25.2 ± 4.7	26.2 ± 6.0	0.393
RBP4 (ng/mL)	53.05 (16.46–165.00)	52.48 (19.92–165.00)	0.881
HOMA-IR	1.71 (0.40–6.17)	0.91 (0.31–3.39)	**<0.001***
Homocysteine (µmol/L)	8.67 (4.50–14.20)	7.81 (4.20–14.40)	0.223
Hirsutism Score (F-G)	15.14 ± 3.68	8.04 ± 1.85	**<0.001***
CRP (mg/L)	2.91 (0.13–14.56)	1.93 (0.17–15.26)	0.253
Androstenedione (ng/mL)	2.35 (0.15–5.07)	1.60 (0.85–3.70)	**<0.001***
Total Testosterone (ng/mL)	0.53 (0.17–1.38)	0.24 (0.04–0.51)	**<0.001***
LH/FSH Ratio	1.31 (0.44–4.22)	0.76 (0.23–2.47)	**<0.001***
Total Cholesterol (mg/dL)	172.4 ± 26.84	171.0 ± 30.64	0.813
Triglyceride (mg/dL)	105.0 (42.0–213.0)	78.0 (43.0–268.0)	0.092
LDL Cholesterol (mg/dL)	99.7 ± 22.87	91.0 ± 25.09	0.089
HDL Cholesterol (mg/dL)	50.8 ± 11.98	60.0 ± 13.57	**<0.001***
Prolactin (ng/mL)	13.92 ± 4.60	15.59 ± 4.62	0.650
17-OH Progesterone (ng/mL)	1.17 ± 0.47	1.24 ± 0.48	0.720

Student's t-test[1] was used for normally distributed variables (Age, BMI, Total Cholesterol, LDL, HDL, Prolactin, 17-OH Progesterone), while the Mann-Whitney U[2] test was used for non-normally distributed variables (other parameters). A p-value of <0.05 was considered statistically significant.
Abbreviations: PCOS: Polycystic Ovary Syndrome, BMI: Body Mass Index , RBP4: Retinol Binding Protein 4, HOMA-IR: Homeostasis Model Assessment of Insulin Resistance, µCRP: Micro C-Reactive Protein, LDL: Low-Density Lipoprotein, HDL: High-Density Lipoprotein

Table 2. Correlation Between RBP4 Levels and Other Metabolic Parameters

Groups	HOMA-IR (r, p)	Homocysteine (r, p)	µCRP (r, p)	Total Cholesterol (r, p)	Triglycerides (r, p)
All Subjects RBP4 Levels	0.004, 0.968	0.033, 0.771	0.139, 0.223	0.134, 0.207	-0.015, 0.890
Group 1 (PCOS) RBP4 Levels	-0.005, 0.977	0.150, 0.330	0.215, 0.208	0.010, 0.950	-0.132, 0.388
Group 2 (Control) RBP4 Levels	0.007, 0.962	-0.092, 0.586	0.101, 0.519	0.227, 0.134	0.080, 0.600

Spearman's rank correlation test was used for analysis. A Bonferroni correction was applied, and a p-value <0.025 was considered statistically significant.
Abbreviations: PCOS: Polycystic Ovary Syndrome, RBP4: Retinol Binding Protein 4, HOMA-IR: Homeostasis Model Assessment of Insulin Resistance, µCRP: Micro C-Reactive Protein

cardiovascular disease, diabetes, hypertension, nephropathy, and dyslipidemia. These metabolic syndrome components may also be associated with elevated homocysteine levels in the long term. Sills et al. reported no statistically significant difference in plasma homocysteine levels between women with normal and polycystic ovaries (9). Similarly, in our study, there was no statistically significant difference in homocysteine levels between BMI- and age-matched PCOS and control groups. The differences in results among studies may be due to genetic, nutritional, and metabolic variations in the study populations.

Markers of chronic inflammation, such as µCRP, have been shown to be significant predictors of type 2 diabetes. Möhlig et al. found elevated µCRP levels in PCOS patients and suggested that the increased diabetes risk in PCOS may be related to chronic inflammation. In their study, µCRP levels were particularly high in obese PCOS patients (10). However, in our study, there was no significant difference in µCRP levels between BMI- and age-matched PCOS and control groups, which may be attributed to the similarity in BMI between the two groups.

The prevalence of abnormal lipid profiles in women with PCOS is approximately 70% according to the National Cholesterol Education Program Guidelines. Insulin resistance and compensatory hyperinsulinemia are often associated with decreased HDL cholesterol levels and increased total cholesterol, LDL, and triglyceride levels. Several studies have reported similar lipid profile abnormalities in PCOS patients (11,12). In our study, HDL cholesterol levels were significantly lower in the PCOS group compared to the control group, whereas no significant differences were found in triglyceride, total cholesterol, or LDL cholesterol levels between the two groups.

Recent animal studies have provided strong evidence for the relationship between insulin resistance and RBP4 levels. Insulin-resistant mice have elevated RBP4 levels in adipose tissue and serum, which can be normalized with insulin-sensitizing agents. Increased RBP4 levels in mice induce insulin resistance, whereas decreased RBP4 levels improve insulin sensitivity (2). However, human studies on the relationship between insulin resistance and RBP4 levels have produced inconsistent results. Recent evidence further supports the involvement of RBP4 in insulin resistance and pancreatic β-cell dysfunction, highlighting its potential contribution to the pathogenesis of type 2 diabetes (13,14).

In our study, there was no significant difference in serum RBP4 levels between the PCOS and control groups. This finding is consistent with studies by Hutchison et al. and Tan et al., which found no difference in RBP4 levels between overweight PCOS patients and controls after adjusting for age and BMI (5,15). However, other studies have suggested that elevated serum RBP4 levels may act as a linking factor between adipose tissue and insulin resistance in PCOS patients. Hahn et al. reported increased serum RBP4 levels in obese PCOS women compared to controls and suggested that these elevated levels might contribute to impaired glucose metabolism (16).

Some studies have found a significant association between RBP4 levels and hypertriglyceridemia (17,18). However, in our study, we did not observe any correlation between RBP4 levels and triglyceride or total cholesterol levels, which is consistent with the findings of Choi et al. (19). Similarly, our study did not find a correlation between serum RBP4 levels and insulin resistance (HOMA-IR), which aligns with some recent studies (16,20). However, other studies have reported a positive correlation between serum RBP4 levels and insulin resistance (21,22), suggesting that high RBP4 levels are associated with reduced insulin clearance and negatively correlated with insulin secretion (23).

This study also had some limitations. The small sample size and the single-center design were major limitations.Additionally, variations in RBP4 test kits and laboratory procedures might have influenced

the measurement results. Confounding factors that could affect insulin resistance and RBP4 levels, including dietary habits, physical activity levels,and genetic polymorphisms, were not evaluated.

Future prospective studies with larger, multi-center cohorts and a more comprehensive assessment of potential confounding factors are needed to better understand the role of RBP4.

CONCLUSION

Based on our findings, serum RBP4 levels do not appear to be significantly associated with metabolic parameters such as insulin resistance and lipid profile in patients with PCOS. Therefore, the utility of RBP4 as an independent biomarker for metabolic risk assessment in PCOS is limited. Further studies with larger sample sizes and prospective designs are needed to better clarify its potential clinical relevance.

Ethics Committee Approval: This approval was granted by the Ethics Committee of Ankara Bilkent City Hospital (Approval Date: 04.06.2025, Approval No: TABED 1/1350/2025) and the study was conducted in accordance with the Declaration of Helsinki and relevant national ethical standards.

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