

Relationship Between Serum Adiponectin and Kisspeptin Levels and Insulin Resistance in Patients With Pcos

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ABSTRACT

Objective: In this study, it is aimed to investigate the relationship between serum adiponectin and kisspeptin levels and insulin resistance in patients with PCOS.

Methods: 144 patients diagnosed with PCOS in a tertiary center, were included in the study. At the first visit, the height and weight measurements were recorded and menstrual functions were questioned. After ultrasonographic evaluation and hormonal assessment, patients were divided into groups according to insulin resistance (IR), then were compared in terms of hormonal parameters.

Results: Weight and BMI were significantly higher in the insulin-resistant group ($p=0.018$, $p=0.012$). Mean fasting glucose, fasting insulin levels and HOMA indexes of the insulin-resistant group were significantly higher than the non-resistant group, respectively ($p<0.001$). LH/FSH ratios were significantly lower in the IR+ group (1.33 vs 1.58, $p<0.05$). No significant difference was observed between the groups in terms of adiponectin and kisspeptin levels, but the mean kisspeptin level in the IR- group was higher than the IR+ group (32.72 vs 19.36, $p=0.067$). Adiponectin and kisspeptin were both found to have a very weak positive relationship with FSH ($r=0.169$ and 0.171).

Conclusion: Adiponectin is known to decrease in obesity and type 2 diabetes, but does not show the difference in insulin-resistant PCOS patients. Kisspeptin, which is a hypothalamic peptide and associated with increased LH levels in patients with PCOS, was found to be lower in the IR+ group. In order to clarify the role of kisspeptin and adiponectin in the mechanisms of PCOS and insulin resistance, it is needed to be examined in a larger sample with BMI-matched healthy controls.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a prevalent metabolic and endocrine condition that affects 5–22% of reproductive-age women and is known for its features of chronic anovulation, hyperandrogenism, and ovaries with multiple cysts.^[1,2] The cause of PCOS has not been fully understood, however, factors such as disruptions in ovarian steroid production and gonadotropin secretion, genetic predisposition, as well as hyperinsulinemia/insulin resistance (IR) are mechanisms that focused on.^[3]

Kisspeptin, a peptide produced in the hypothalamus that is

important in regulating the Hypothalamic–Pituitary–Gonadal axis,^[4] is been reported to increase luteinizing hormone (LH) levels by more than double, with only a minor or no change in follicle-stimulating hormone (FSH) levels after intravenous administration.^[5,6] In addition, it has been suggested that the effects of the kisspeptin molecule on the gonadal axis may be the cause of hyperandrogenism, reproductive and metabolic changes in PCOS.^[7,8] It has been shown that kisspeptin-10 administered to rats had increased insulin levels in a dose-dependent manner.^[9]

Adiponectin, first described in the mid-1990s^[10] has a crucial role in regulating the sensitivity of insulin and has been

Table 1. Demographic characteristics comparisons between the groups

	IR[+] Group n=69 Mean±SD	IR[-] Group n=75 Mean±SD	p-value
Age	28.35±3.95	28.16±4.28	0.785
Weight (kg)	72.68±12.88	67.24±14.28	0.018*
Height (m)	162.67±5.68	162.16±6.39	0.617
BMI (kg/m ²)	27.45±4.53	25.49±4.68	0.012*

*: p<0.05; t-test; SD: Standard Deviation; BMI: Body Mass Index; IR[+]: Insulin Resistant; IR[-]: Non-insulin Resistant.

Table 2. Comparison of fasting glucose and fasting insulin levels and HOMA indices between the groups

	IR[+] Group n=69 Mean±SD	IR[-] Group n=75 Mean±SD	p-value
Fasting Glucose (mg/dL) ²	95.33±16.30	87.04±6.22	0.000*
Fasting Insulin (mIU/mL) ¹	17.08±7.06	6.93±1.85	0.000*
HOMA index ²	4.04±2.27	1.47±0.38	0.000*

*p<0.001; 1: t test; 2: Mann–Whitney U test; SD: Standard Deviation; IR[+]: Insulin Resistant; IR[-]: Non-insulin Resistant.

shown to have protective effects against type 2 diabetes.^[11,12] It has also been suggested that adiponectin may have an effect on the metabolic background of PCOS and was found to be low in PCOS patients with high insulin levels.^[13,14] In the study, it was determined that adiponectin level was negatively correlated with fasting insulin, HOMA model sensitivity, BMI, and testosterone, but not with LH/FSH ratio in patients both with and without PCOS.^[15]

The purpose of this study is to look into the association between serum adiponectin and kisspeptin levels and IR in PCOS patients.

MATERIALS AND METHODS

This study included 144 patients with PCOS at the ages of 18 and 40 years, who applied to the infertility polyclinic of Zeynep Kamil Women and Children Disease Training and Research Hospital between January 2019 and 2022. At the first visit, the height and weight measurements of the patients were recorded, and body mass indices (BMI) were calculated. Ultrasonographic assessments were done by the transvaginal probe and patients were questioned in terms of menstrual functions. Patients with polycystic ovaries are instructed to give blood test to evaluate fasting glucose, fasting insulin, adiponectin, kisspeptin, FSH, estradiol (E2), LH, thyroid-stimulating hormone (TSH), free thyroxine (FT4), and prolactin (PRL) levels on the 2nd and 4th days of menstruation.

IR was used to divide the patients into two groups. HOMA index was calculated for each patient according to [Fasting glucose (mg/dL) X Fasting insulin (mIU/mL) X 0,055]/22,5 formula, the value <2.1 were considered to have no IR[-],

and those with a HOMA index value equal to or >2.1 were considered to have IR[+]. Serum adiponectin and kisspeptin levels were compared with patients with and without IR and it was also examined whether there was a significant difference in terms of age, BMI, HOMA indices, FSH, LH, LH/FSH, E2, TSH, FT4, and PRL levels.

Statistical Analysis

The data analysis was done using the IBM SPSS program. Since the data were analyzed in two groups' patients with and without IR, the t-test, which is one of the parametric analyses, was used to compare the data with normal distribution, and the Mann–Whitney test, which is one of the non-parametric analyses, was used to compare the data that did not comply with the normal distribution.

RESULTS

There was not a significant difference in the groups' average ages and heights (p>0.05). Weight and BMI of the insulin-resistant group were significantly higher than those of the non-insulin-resistant patients (72.68±12.88 vs. 67.24±14.28 and 27.45±4.53 vs. 25.49±4.68, respectively) (p<0.05) (Table 1).

On account of higher mean fasting glucose (95.33±16.30) and fasting insulin (17.08±7.06) levels of the insulin-resistant group, HOMA indices were significantly higher in them than those in the non-resistant group (4.04±2.27 vs. 1.47±0.38) (p<0.001) (Table 2).

Early follicular phase assessments of FSH, LH, E2, TSH, and PRL levels of the groups were similar (p>0.05). LH/FSH ratios were lower (1.33±0.58 vs. 1.58±0.83) and free T4 values were higher (1.22±0.19 vs. 1.14±0.17) in

Table 3. Hormone parameter comparisons between the groups

	IR[+] Group n=69 Mean±SD	IR[-] Group n=75 Mean±SD	p-value
FSH (mIU/mL) ¹	5.69±1.71	5.77±1.81	0.785
LH (mIU/mL) ¹	7.39±3.55	8.68±4.37	0.055
LH/FSH ¹	1.33±0.58	1.58±0.83	0.043*
E2 ²	41.79±14.47	45.16±21.21	0.555
TSH ¹	2.46±1.14	2.42±1.29	0.846
FT4 ¹	1.22±0.19	1.14±0.17	0.010*
PRL ²	18.02±8.34	17.85±9.30	0.517

*: p<0.05; 1: t-test; 2: Mann–Whitney U test; SD: Standard Deviation; FSH: Follicle-stimulating Hormone; LH: Luteinizing Hormone; E2: Estradiol Hormone; TSH: Thyroid-stimulating Hormone; FT4: Free Thyroxine Hormone; PRL: Prolactin Hormone.

Table 4. Serum adiponectin and kisspeptin levels comparisons between the groups

	IR[+] Group n=69 Mean±SD	IR[-] Group n=75 Mean±SD	p-value
Adiponectin (mg/dL) I	9.53±7.25	8.93±8.20	0.646
Kisspeptin (mIU/mL) I	19.36±29.80	32.72±52.92	0.067

I: t-test; SD: Standard Deviation.

Table 5. Correlation analysis of serum adiponectin and kisspeptin levels with other hormones

	Weight	BMI	Fasting Insulin	Fasting Glucose	HOMA	FSH	LH	LH/FSH	E2	TSH	PRL
Adiponectin											
r	-0.058	-0.009	0.072	0.001	0.063	0.169	0.016	-0.109	-0.032	-0.045	-0.068
p	0.492	0.919	0.393	0.993	0.456	0.042*	0.848	0.194	0.701	0.590	0.416
n	144	144	144	144	144	144	144	144	144	144	144
Kisspeptin											
r	-0.067	-0.078	-0.022	-0.007	-0.007	0.171	-0.017	-0.064	-0.018	-0.132	-0.089
p	0.423	0.353	0.795	0.933	0.937	0.040*	0.841	0.443	0.834	0.115	0.290
n	144	144	144	144	144	144	144	144	144	144	144

*: p<0.05; r: Pearson Correlation; For r<0.20=weak correlation; FSH: Follicle-stimulating Hormone; LH: Luteinizing Hormone; E2: Estradiol Hormone; TSH: Thyroid-stimulating Hormone; PRL: Prolactin Hormone.

the insulin-resistant group compared to the IR[-] group, (p<0.05) (Table 3).

As presented in Table 4, no significant difference was observed between the groups in terms of serum adiponectin levels (IR[+]: 9.53±7.25 vs. IR[-]: 8.93±8.20). Although it was not significant, serum kisspeptin levels in the insulin-resistant group were found to be quite lower than in the other group (IR[+]: 19.36±29.80 vs. IR[-]: 32.72±52.92) (p>0.05).

When correlation analyses were done for serum adiponectin and kisspeptin levels and other hormones; adiponectin was found to be positively correlated with FSH, very weakly (p=0.042, Table 5 and Figure 1a). Similarly, kisspeptin was found to have a very weak positive

correlation with FSH (0.171, p=0.040, Table 5 and Figure 1b). Adiponectin or kisspeptin had no significant relationship with weight, BMI, fasting insulin, fasting glucose, HOMA index, and other hormones (Table 5).

DISCUSSION

There is broad agreement that the majority of women with PCOS is insulin resistant and have a higher incidence of obesity.^[16,17] In line with the literature, our data revealed that weight and BMI were significantly higher in the group with IR than in age-matched PCOS patients who had normal glucose tolerance. In the studies, it was declared that obesity and IR resulted from decreased insulin-mediated glucose disposal (IMGD).^[18] Dunaif et al.^[19] showed in

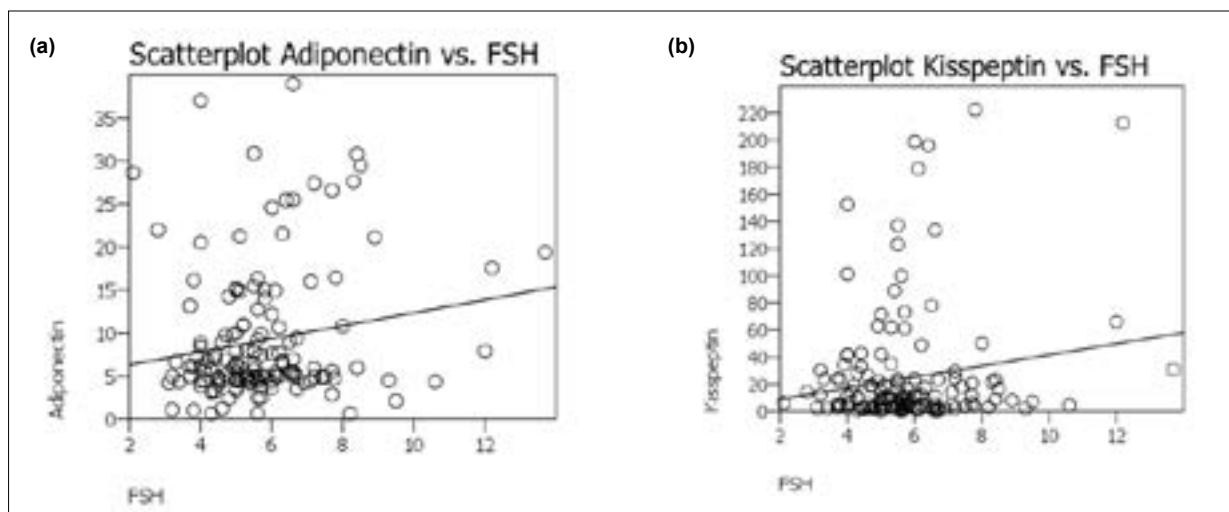


Figure 1. (a) Scatterplots for adiponectin vs FSH. (b) Scatterplots for kisspeptin vs. FSH.

1989 that IMGD was significantly decreased in 35–40% of women with PCOS than control women of comparable BMI. Thus, IR seems to be increased in PCOS independently from BMI.

The studies which investigated the relationship between body fat topography and insulin sensitivity suggested that the increase in upper body obesity is associated with IR in PCOS.^[20,21] Since then, indirect evaluation of adipose tissue like the measurement of adipokines had come to the fore. Adiponectin is an adipokine that is expressed and secreted by adipocytes and presented to play an important role in the pathogenesis of obesity, IR, and type 2 diabetes mellitus^[14,15,22] It has been shown that obese subjects expressed lower levels of adiponectin; however, the relationship between hypoadiponectinemia and IR was stronger than that of obesity.^[23]

In the study of Sepilian and Nagamani adiponectin level had been reported to be negatively correlated with BMI in the control group where there was no correlation between BMI and adiponectin in the patients with PCOS. They have presented IR as a main determinant of hypoadiponectinemia and not adiposity in patients with PCOS.^[14] In another case-control study conducted by Spranger et al.^[15] in 2005, plasma levels of adiponectin were linked to BMI, HOMA index, and fasting insulin in both PCOS women and healthy controls. It was revealed by multiple regression analysis that circulating adiponectin concentrations were independently correlated with the level of obesity and IR. Despite these findings, we observed that adiponectin levels were similar in PCOS patients with and without IR, and there was no relationship between IR and adiponectin levels (9.53 vs. 8.93 mg/dL, $p=0.646$).

Studies investigating the relationship between serum adiponectin and the hormonal axis have reported opposing results. Spranger et al.^[15] have declared an increased LH/FSH ratio in patients with PCOS with no correlation with the adiponectin levels ($r=-0.05$, $p=0.7$). Two studies reported a positive correlation between adiponectin and

LH and LH/FSH ratio and put forward the hypothesis of LH and gonadotropin-releasing hormone (GnRH) secretion were inhibited by adiponectin.^[24,25] In our study, while the FSH and LH levels of the groups did not differ, the LH/FSH ratios were significantly higher in the group without IR (1.58 vs. 1.33, $p=0.043$), but there was no correlation with the adiponectin levels ($r=0.016$, $p=0.848$).

In a recent study by Artimani et al.,^[26] a positive correlation between the expressions of adiponectin and FSH was found at a strong ($r=0.84$) and significant ($p=0.001$) level. Similarly, in our study, adiponectin was found to have a positive and significant relationship with FSH, but this relationship was very weak ($r=0.169$). In addition, we have noticed a positive correlation between kisspeptin and FSH, similarly ($r=0.171$, $p=0.040$). Contrarily, Gorkem et al.^[27] reported a negative relationship between kisspeptin and FSH, while another study found no significant relationship between these two in patients with PCOS.^[28]

According to our data, in the group without IR, the mean LH levels were higher than that of the patients with IR (8.68 vs. 7.39 IU, $p=0.055$), and although not significant, it was observed that the mean kisspeptin level in the IR-negative group was approximately 69% (32.72 vs. 19.36 mIU/mL, $p=0.067$) higher than IR+ group. In addition, we have found no correlation between LH and LH/FSH ratio with kisspeptin levels ($r=0.017$, $r=-0.064$).

Previous studies in the literature reported that an increase in kisspeptin significantly increases LH levels, thus more than twice the LH/FSH ratio, with little or no change in FSH levels.^[6,29] While several investigators have noticed a positive correlation between kisspeptin and LH levels, they have failed to find significantly higher kisspeptin levels in patients with PCOS compared with non-PCOS women,^[30] Daghestani et al.^[28] found a negative significant relationship between these two in obese PCOS patients. Therefore, the association between kisspeptin and LH secretion in PCOS patients is unclear due to the varied constitution of participants in various research.^[30]

Strengths and Limitations

The short sample size and lack of healthy controls are the study's principal limitations. If the groups were chosen by randomization and the control group was added, the study power would increase, and more significant differences would be produced. On the other hand, this is thought to be the first prospective study to look into the relationship between kisspeptin and adiponectin and IR and PCOS.

Conclusion

In this study, it was concluded that adiponectin levels, which are known to decrease in obesity and type 2 diabetes, do not show a difference in insulin-resistant PCOS patients compared to those without IR. Kisspeptin, which is a hypothalamic peptide and associated with increased LH levels in patients with polycystic ovarian syndrome, was not significantly affected by insulin levels, but kisspeptin levels in the insulin-resistant group were lower than the IR-group. To clarify the role of kisspeptin and adiponectin in the mechanisms of PCOS and IR, it is needed to be examined in a larger sample with BMI-matched healthy controls.

Ethics Committee Approval

This study approved by the Zeynep Kamil Women and Children's Disease Training and Research Hospital Ethics Committee (Date: 29.04.2020, Decision No: 63).

Informed Consent

Retrospective study.

Peer-review

Externally peer-reviewed.

Authorship Contributions

Concept: M.B.Y., S.Ş., B.D.; Design: M.B.Y., S.Ş., B.D.; Supervision: M.B.Y., S.Ş., B.D.; Fundings: M.N.C.K., Z.C., B.N.O.; Materials: M.N.C.K., Z.C., B.N.O.; Data: M.B.Y., M.N.C.K., Z.C., B.N.O.; Analysis: S.Ş., M.B.Y., B.N.O., E.M.G., E.K.; Literature search: M.B.Y., S.Ş., B.D., M.N.C.K., Z.C., B.N.O., E.M.G., E.K.; Writing: M.B.Y., S.Ş., B.D., M.N.C.K.; Critical revision: M.B.Y., S.Ş., B.D., M.N.C.K., Z.C., B.N.O., E.M.G., E.K.

Conflict of Interest

None declared.

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PKOS'lu Hastalarda Serum Adiponektin ve Kisspeptin Düzeyleri ile İnsülin Direnci Arasındaki İlişki

Amaç: Bu çalışmada PKOS'lu hastalarda serum adiponektin ve kisspeptin düzeyleri ile insülin direnci arasındaki ilişkinin araştırılması amaçlanmıştır.

Gereç ve Yöntem: Üçüncü basamak bir merkezde PKOS tanısı alan 144 hasta çalışmaya dahil edildi. İlk ziyarette boy ve kilo ölçümleri kaydedildi ve adet fonksiyonları sorgulandı. Ultrasonografik değerlendirme ve hormonal değerlendirme sonrasında hastalar insülin direncine (IR) göre gruplara ayrılarak hormonal parametreler açısından karşılaştırıldı.

Bulgular: Ağırlık ve VKİ insülin dirençli grupta anlamlı olarak yüksekti ($p=0.018$, $p=0.012$). İnsüline dirençli grubun ortalama açlık glukozu, açlık insülin düzeyi ve HOMA indeksi sırasıyla dirençli olmayan gruba göre anlamlı olarak yüksekti ($p<0.001$). LH/FSH oranları IR+ grupta anlamlı derecede düşüktü (1.33'e karşı 1.58, $p<0.05$). Adiponektin ve kisspeptin düzeyleri açısından gruplar arasında anlamlı bir fark gözlenmedi, ancak IR- grubundaki ortalama kisspeptin düzeyi IR+ grubuna göre daha yüksekti (32.72'ye karşı 19.36, $p=0.067$). Adiponektin ve kisspeptinin FSH ile çok zayıf bir pozitif ilişkisi olduğu bulundu ($r=0.169$ ve 0.171).

Sonuç: Adiponektinin obezite ve tip 2 diyabette azaldığı bilinmekte olup, insülin direnci olan PKOS hastalarında farklılık göstermemektedir. Hipotalamik bir peptit olan ve PKOS'lu hastalarda artmış LH seviyeleri ile ilişkili olan Kisspeptin, IR+ grubunda daha düşük bulundu. Kisspeptin ve adiponektinin PKOS ve insülin direnci mekanizmalarındaki rolünü netleştirmek için BMI eşleşmiş sağlıklı kontrollerle daha geniş bir örneklemde incelenmesine ihtiyaç vardır.

Anahtar Sözcükler: Adiponektin; insülin direnci; kisspeptin; PKOS; polikistik over sendromu.