Türk Klinik Biyokimya Derg 2024; 22(2): 41-49

Araştırma Makalesi / *Research Article*

https://doi.org/10.56615/tkbd.2024.05

Evaluation of Kisspeptin Levels in Women with Polycystic Ovary Syndrome

Polikistik Over Sendromlu Kadınlarda Kisspeptin Düzeylerinin Değerlendirilmesi

Ruhi Doğan[1] Muhammed Emin Düz[2] Burak Yasin Avcı[2]

Elif Menekşe[2] Ecem Avcı[2] Alpaslan Öztürk[3]

1 Sabuncuoğlu Şerefeddin Eğitim ve Araştırma Hastanesi, Kadın Doğum Hastalıkları, Amasya, Türkiye

2 Sabuncuoğlu Şerefeddin Eğitim ve Araştırma Hastanesi, Tıbbi Biyokimya, Amasya, Türkiye

3 Etlik Şehir Hastanesi, Tıbbi Biyokimya, Ankara, Türkiye

Received / Başvuru Tarihi: 26 Şubat 2024 *Accepted* / Kabul Tarihi: 31 Mayıs 2024

ABSTRACT

Aim: Polycystic ovarian syndrome (PCOS) is a multifactorial disorder with different phenotypic characteristics, the most frequent endocrine disorder in women, and the leading cause of anovulatory infertility. Kisspeptin is recognized to have a crucial function in regulating reproductive hormone production through signaling its G protein-coupled receptor to the hypothalamic-pituitary-gonadal axis. High kisspeptin levels have been found in PCOS patients, although other investigations show the reverse. Our study aims to contribute to the scientific literature by discussing our patient population data on this subject.

Material and Methods: Forty-two women with PCOS (mean age: 22.1±3.9) and thirty-nine healthy women (mean age: 21.3±2.6) were included in the study. Kisspeptin and routine laboratory tests were analyzed with the blood samples on the third day of menstruation. Height, weight, homeostatic model assessment-insulin resistance (HOMA-IR), body mass index (BMI), age, hirsutism, waist circumference, smoking, and irregular period data were also recorded. Comparison and correlation analyses were performed between groups, within PCOS patients, and in all individuals.

Results: Kisspeptin levels did not differ between PCOS patients and healthy women (p=0.086). PCOS patients had greater weight, BMI, free thyroxine, luteinizing hormone, insulin, hemoglobin A1c, platelet, and HOMA-IR values. Kisspeptin and thyroid-stimulating hormone correlated within all individuals, and kisspeptin and progesterone correlated within PCOS patients.

Yazışma adresi: Ecem Avcı

Sabuncuoğlu Şerefeddin Eğitim ve Araştırma Hastanesi, Tıbbi Biyokimya, Amasya, Türkiye

e-posta: ecembaltann@gmail.com

Etik onay: Amasya Üniversitesi Etik Kurulu, 22.09.2022 tarihi, 91568 sayılı kurul kararı

Conclusion: Contrary to the literature, kisspeptin levels in PCOS patients did not differ from healthy women. The absence of differences in kisspeptin levels between PCOS patients and healthy women may be attributed to the hypothalamic or ovarian subtypes of PCOS. Further research is needed to enlighten the topic entirely.

Key Words: Polycystic Ovary Syndrome, Kisspeptin, Metabolic Syndrome

ÖZET

Amaç: Polikistik over sendromu (PKOS), farklı fenotipik özelliklere sahip, kadınlarda en sık görülen endokrin bozukluk olan ve anovulatuar infertilitenin önde gelen nedeni olan çok faktörlü bir hastalıktır. Kisspeptinin, G proteinine bağlı reseptörünü hipotalamik-hipofiz-gonadal eksenine sinyal göndererek üreme hormonu üretimini düzenlemede çok önemli bir işleve sahip olduğu kabul edilmektedir. PKOS hastalarında yüksek kisspeptin seviyeleri bulunmuştur, ancak diğer araştırmalar bunun tersini göstermektedir. Çalışmamız bu konudaki hasta popülasyonu verilerimizi tartışarak bilimsel literatüre katkı sağlamayı amaçlamaktadır.

Gereç ve Yöntem: Çalışmaya PKOS tanılı 42 kadın (ortalama yaş: 22.1±3.9) ve 39 sağlıklı kadın (ortalama yaş: 21.3±2.6) dahil edildi. Adetin üçüncü gününde alınan kan örneklerinden Kisspeptin ve rutin laboratuvar testleri incelendi. Ayrıca boy, kilo, homeostatik model değerlendirmesi-insülin direnci (HOMA-IR), vücut kitle indeksi (BMI), yaş, hirsutizm, bel çevresi, sigara kullanımı ve adet düzensizliği verileri de kaydedildi. Gruplar arasında, PKOS hastalarında ve tüm bireylerde karşılaştırma ve korelasyon analizleri yapıldı.

Bulgular: Kisspeptin düzeyleri PKOS hastaları ile sağlıklı kadınlar arasında farklılık göstermedi (p=0.086). PKOS'lu hastaların kilosu, BMI, serbest tiroksin, luteinize edici hormon, insülin, hemoglobin A1c, platelet ve HOMA-IR değerleri daha yüksekti. Kisspeptin ve tiroid stimüle edici hormon tüm bireylerde korelasyon gösterirken, kisspeptin ve progesteron PKOS hastalarında korelasyon gösterdi.

Sonuç: Literatürün aksine PKOS hastalarında kisspeptin düzeyleri sağlıklı kadınlardan farklı değildi. Hipotalamik veya yumurtalık kaynaklı PKOS alt tipleri, PKOS hastaları ile sağlıklı kadınlar arasında fark göstermeyen kisspeptin düzeylerini açıklayabilir. Konunun tamamen aydınlatılması için daha fazla araştırmaya ihtiyaç vardır.

Anahtar Kelimeler: Polikistik Over Sendromu, Kisspeptin, Metabolik Sendrom

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a multifactorial condition with various phenotypic factors, with clinical diagnosis typically requiring at least two of the following features: polycystic ovaries, androgen excess (hyperandrogenemia), and chronic anovulation, characterized by the former two frequently being the most prominent (1). The most prevalent endocrine condition in women and a primary cause of anovulatory infertility is PCOS. Even though the cause of PCOS is unknown, it is considered a complex condition involving genetic, metabolic, endocrine, and environmental abnormalities (2). PCOS is characterized by increased gonadotropin-releasing hormone (GnRH) pulse velocity, elevated luteinizing hormone (LH), decreased follicle-stimulating hormone (FSH), and progesterone insensitivity (3,4). Disruptions in the neuroendocrine reproductive axis, in addition to hyperandrogenemia, lead to abnormal ovarian maturation and decreased fertility (5). In addition, PCOS is frequently associated with metabolic disorders, such as obesity, increased abdominal adiposity, insulin resistance, glucose intolerance, and a greater risk of type 2 diabetes (6).

Kisspeptin is now known to have a critical role in the control of reproductive hormone secretion, according to two fundamental studies published in 2003 that showed that diminished signaling of its G protein-coupled receptor (KISS1R) led to hypothalamic-pituitary-gonadal (HPG) axis dysfunction (7,8). Furthermore, Kisspeptin was further

linked to positive and negative estrogen feedback after the reproductive activity of neurokinin B (NKB) was found (9). Kisspeptin, NKB and dynorphin (Dyn) are all expressed in the hypothalamus and are typically colocalized in a highly conserved area known as KNDy (Kisspeptin, NKB, and dynorphin) neurons (10,11). Arcuate nucleus (ARC) kisspeptin neurons regulate kisspeptin release by modulating NKB and Dyn secretion, hence mediating the negative feedback of sex hormones (12). Furthermore, kisspeptin neurons, which are found in the rostral periventricular region of the third ventricle (RP3V) in rodents and the preoptic area (POA) in humans, regulate estradiol positive feedback by expressing estradiol and cotransmitters such as tyrosine hydroxylase, gamma-aminobutyric acid (GABA) and glutamate, that last two of which have the effect of stimulating GnRH neurons (13).

Given PCOS's strong neuroendocrine underpinning, it is critical to evaluate Kisspeptin's involvement in its pathogenesis (14). Researchers discovered that serum Kisspeptin levels positively correlate with BMI, free androgen index, and insulin resistance indices in PCOS (15). Conversely, some studies showed comparable, negatively correlated, or insignificant results (14,16). Our aim in carrying out the study is to contribute to the literature in which different opinions are presented by investigating the change in kisspeptin levels in PCOS patients. We aim to find out if there exists a substantial disparity in kisspeptin levels between those diagnosed with PCOS and women who are in good health.

MATERIALS AND METHODS

Subjects

Forty-two non-pregnant women with PCOS (mean age: 22.1±3.9) as patients and thirty-nine healthy non-pregnant women (mean age: 21.3±2.6) as controls between March and November 2023 were included in the study. A gynecologist made the diagnosis of PCOS based on three criteria (anovulation or oligo-ovulation, clinical and/or biochemical hyperandrogenism, and polycystic ovarian morphology (PCOM) seen on ultrasound) according to the European Society of Human Reproduction and Embryology/American Society for Reproductive Medicine Rotterdam consensus (ESHRE/ASRM) (1). The study excluded postmenarchial women, those with known or suspected additional illnesses other than insulin resistance caused by PCOS, women with corticoid therapy, and used oral contraceptives.

Ethical Considerations

All participants provided written informed consent. In addition, the Amasya University Institutional Review Board gave ethical approval for the study with a 22.09.2022 date and 91568 number. The study follows the World Medical Association's Helsinki Declaration on the ethical conduct of research involving human beings and/or animals.

Study Design

After fasting on the third day of the menstrual period, blood samples were taken from all individuals in tube with K_3EDTA for the complete blood count (CBC) and tube with gel, without additives for clinical chemistry, immunoassay tests, and kisspeptin. CBC was analyzed the same day with a Sysmex XN-1000 analyzer (Sysmex, Kobe, Japan). For clinical chemistry, immunoassay tests, and kisspeptin, gel tubes without additives were centrifuged at 1500*g for 15 minutes, portioned, and stored at -80°C until the day of the study. On a working day, samples were thawed at room temperature (25°C). FT_3, FT_4, TSH, 17-hydroxy progesterone (17-OHP), free testosterone, follicular stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2), progesterone, prolactin, beta-human chorionic gonadotropin (beta-HCG), dehydroepiandrosterone sulfate (DHEAS), 25-OH vitamin D, testosterone, and insulin were analyzed with an immunoassay method by

Siemens Advia Centaur XP analyzer (Siemens, Erlangen, Germany). In addition, glucose, urea, creatinine, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) were analyzed with a spectrophotometric method on a Beckman Coulter AU-5800 analyzer (Beckman, California, USA). Serum kisspeptin levels were measured with the Enzyme-Linked ImmunoSorbent Assay (ELISA) via ELK Biotechnology Elisa kit (ELK Biotechnology CO., Wuhan, PRC) kit (Catalog Number: ELK4058) with a detection range of 31.25-2000 pg/mL and a sensitivity of 13.1 pg/mL, and calculated on a Thermo Scientific Multiscan GO plate reader (Thermo Fisher Scientific, Massachusetts, USA). The HOMA-IR (homeostatic model assessment insulin resistance) was calculated as (Fasting insulin, uIU/mL)*(Fasting glucose, mg/dL) / 405, with 0.7-2.0 reference ranges (17). Height (m), weight (kg), and body mass index (BMI; kg/m^2) were calculated. The average BMI range was set as 18-24.9 kg/m^2. Women with a BMI of 25-29.9 kg/m^2 were classified as overweight, while those with a BMI of 30 kg/m^2 or more were categorized as obese (18). According to the Ferriman and Gallwey hirsutism score, out of 36, those with a score of ≥ 8 were considered to have hirsutism, and those with a score of <8 was considered absent (19). Smokers (20 pieces a day) and patients with irregular periods were also recorded. Finally, according to the International Diabetes Federation, persons with a waist circumference higher than 80 cm were deemed high risk (20). In comparison, those with a waist circumference of less than 80 cm were considered low risk. Regarding the factors and measures mentioned earlier, comparisons were made between PCOS patients and healthy individuals. Furthermore, the patient group was investigated in terms of several indicators above.

Statistics

Categorical values were expressed as percentages or frequency, and noncategorical variables were expressed as median, minimum, maximum, mean, and standard deviation. Chi-square tests were used to examine categorical data. Parametric values were compared using the t-test, and non-parametric ones were compared with the Mann-Whitney-U test. Data were also investigated regarding correlation statistics such as Pearson's or Spearman's, depending on whether they are parametric or not. The result is considered statistically significant when the p-value is less than 0.05. Statistical analyses were performed using JASP 0.14 statistical software (JASP team, Amsterdam, Netherlands) and Excel 2016 (Microsoft Inc., Redmond, Washington, USA).

RESULTS

PCOS patients had considerably greater weight and BMI values than healthy women. In addition, the PCOS group had significantly increased mean FT_4, LH, insulin, HbA1c, platelet (PLT), and HOMA-IR values. Table 1 demonstrates the data and statistical analyses of the specified parameters. However, kisspeptin values did not differ between PCOS patients and healthy women (p=0.086).

Considering all individuals, kisspeptin levels did not change in patients with hirsutism and irregular period complaints (p=0.255 and p=0.250, respectively) than in healthy women. HbA1C levels were significantly increased in patients with hirsutism and irregular period complaints (p=0.007 and p=0.003, respectively) than in healthy women.

When the PCOS group is examined within itself, while kisspeptin levels in PCOS individuals with hirsutism were not different from those without hirsutism (p=0.910), DHEAS levels were considerably greater (p=0.020). Furthermore, there is a positive relationship between kisspeptin and progesterone levels (r=0.376, p=0.038). On the other hand, no correlation was found between waist circumference and kisspeptin levels (r=0.344, p=0.396). A positive relationship was found between kisspeptin and TSH (r=0.489, p=0.049) in the PCOS group.

Table 1. Demonstration of the data and statistical analyses of the specified parameters.
BMI: Body mass index, FT_3: free thyroxine 3, FT_4: free thyroxine 4, TSH: thyroid stimulating hormone, 17-OHP: 17-hydroxy progesterone, FSH: follicle-stimulating hormone, LH: Luteinizing hormone, E_2: Estradiol, Beta-HCG: Beta-Human chorionic gonadotropin, DHEAS: dehydroepiandrosterone sulfate, HBA1C: hemoglobin A1C, AST: aspartate aminotransferase, ALT: alanine transaminase, HB: hemoglobin, HCT: hematocrit, PLT: platelet, WBC: white blood count, HOMA-IR: homeostasis model assessment-insulin resistance. P value<0.05 was considered significant and shown as bold.

Tablo 1. Belirtilen parametrelere ait verilerin ve istatistiksel analizlerinin gösterilmesi.
BMI: Vücut kitle indeksi, FT3: Serbest tiroksin 3, FT4: Serbest tiroksin 4, TSH: Tiroid uyarıcı hormon, 17-OHP: 17-hidroksi progesteron, FSH: Folikül uyarıcı hormon, LH: Luteinize edici hormon, E2: Estradiol, Beta -HCG: Beta-İnsan koryonik gonadotropini, DHEAS: dehidroepiandrosteron sülfat, HBA1C: hemoglobin A1C, AST: aspartat aminotransferaz, ALT: alanin transaminaz, HB: hemoglobin, HCT: hematokrit, PLT: trombosit, WBC: beyaz kan sayımı, HOMA-IR: homeostaz modeli değerlendirmesi-insülin direnci. p değeri<0,05 anlamlı kabul edildi ve koyu renkle gösterildi.

Group	**Control (n=39)**		**Patients (n=42)**		**p value**
Parameter	**Median (Min-Max)**	**Mean±Std. Deviation**	**Median (Min-Max)**	**Mean±Std. Deviation**	
Age	21 (17-30)	21±3	21 (15-39)	23±5	0.101
Height (m)	1.62 (1.53-1.75)	1.63±0.05	1.63 (1.55-1.75)	1.64±0.05	0.730
Weight (kg)	55 (44-97)	58±12	64 (42-107)	67±15	**0.002**
BMI (kg/m^2)	19.6 (16.4-33.2)	21.7±4.1	24.2 (16.4-37.5)	25.0±5.2	**0.002**
Kisspeptin (pg/mL)	33.2 (32.5-41.6)	33.7±1.7	33.2 (32.5-110.0)	37.3±12.8	0.086
FT_3 (ng/L)	3.28 (2.5-4.41)	3.32±0.4	3.34 (2.85-4.36)	3.4±0.42	0.350
FT_4 (ng/dL)	1.24 (1-1.55)	1.26±0.14	1.3 (0.91-1.81)	1.33±0.17	**0.047**
TSH (mU/L)	1.92 (0.53-5.02)	2.2±1.14	2.3 (0.01-6)	2.59±1.51	0.186
17-OHP (ng/mL)	0.69 (0.3-7.9)	1.05±1.25	0.9 (0.3-2)	1±0.55	0.834
Free Testosterone (ng/L)	1.3 (0.16-16.22)	1.77±2.66	1.59 (0.41-5.5)	1.85±1.2	0.118
FSH (U/L)	5.18 (2.37-12.96)	5.26±2.07	5.81 (2-71)	8.32±11.64	0.059
LH (U/L)	7.07 (3.54-29.26)	8.21±4.83	9.7 (2.28-79.5)	13.98±15.23	**0.027**
E_2 (pg/mL)	63.8 (17.18-12)	69.89±31.77	47.51 (13.07)	72.25±68.7	0.065
Progesterone (ng/mL)	0.8 (0.13-13.7)	1.57±2.57	0.66 (0.24-13.5)	2.14±3.6	0.467
Prolactine (ng/mL)	11.29 (3.38-43.38)	13.55±7.82	11.37 (5.26-41.77)	13.61±7.97	0.970
Beta-HCG (U/L)	2 (0.2-2.7)	1.99±0.33	2 (2-2.9)	2.04±0.17	0.436
DHEAS (µg/dL)	300.94 (145-693.66)	312.02±124	280.26 (90.21-683.8)	298.3±115	0.612
25-OH Vitamin D	8.76 (5.56-31.09)	11±5.69	8.94 (4.2-21.98)	9.45±3.6	0.154
Testosterone (ng/dL)	26.2 (8.57-61.8)	29.15±12.11	27.82 (7-70.96)	28.01±11.7	0.670
Insulin (uIU/mL)	9.13 (2.28-47)	11.84±9.41	12.65 (2.86-231.88)	25.71±43.8	**0.029**
HBA1C (%)	5.1 (4.6-5.7)	5.1±0.27	5.3 (4.9-6.4)	5.4±0.36	**< 0.001**
Glucose (mg/dL)	91 (71-160)	91.64±14.9	93.5 (74-178)	95.74±16.2	0.087
Urea (mg/dL)	23 (12-48)	23.07±7.07	20 (13-34)	21.35±5.35	0.219
Creatinine (mg/dL)	0.61 (0.49-0.86)	0.61±0.08	0.59 (0.46-0.82)	0.6±0.08	0.582
AST (U/L)	16.5 (10-46)	17.6±5.91	18.5 (11-34)	18.45±4.26	0.461
ALT (U/L)	13 (6-43)	15.54±7.65	15 (7-33)	16.05±6.27	0.743
HB (g/dL)	13 (9.7-15.5)	13±1.3	13.2 (10.3-15.7)	13.16±1.25	0.571
HCT (%)	39.75 (31-45.5)	39.57±3.45	39.8 (14-46.7)	39.04±5.19	0.592
PLT (10^3/µL)	261 (195-550)	271.59±66	290 (147-427)	293.61±56.14	**0.010**
WBC (10^3/µL)	6.38 (3.89-12.43)	6.78±1.65	7.11 (4.61-235)	12.86±35.2	0.284
HOMA-IR	1.97 (0.1-11.26)	2.65±2.43	2.98 (0.67-101.91)	7.21±16.46	**0.011**

DISCUSSION

The main implication of our study is that Kisspeptin levels were similar between PCOS patients and healthy women. Panidis et al., the first researchers to look into Kisspeptin, found that it was inversely correlated with the elevated levels of free androgen that are common in PCOS patients (14). In a study done in Saudi Arabia with thirty healthy women and twenty-eight PCOS patients, the researchers observed no significant difference in the levels of Kisspeptin between the two groups (16). This finding is comparable to the findings that we obtained They suggested that differences in the KISS1 gene could have a role in the onset of polycystic ovary syndrome. In another retrospective investigation, researchers in Turkey found no difference in Kisspeptin levels between 285 PCOS patients and 162 controls (21). A multicenter study also found no statistically significant difference in Kisspeptin levels between 44 PCOS sufferers and 44 healthy women (22). However, a growing body of research in the literature claims that Kisspeptin levels are high in PCOS patients, which runs counter to the studies we cited and our study results. In a review of 12 investigations, four studies found that kisspeptin levels in PCOS patients did not rise, whereas eight studies found that kisspeptin levels increased considerably in PCOS (15). In another review with 699 patients and 583 controls, PCOS patients had greater serum kisspeptin levels than non-PCOS individuals. Researchers also believed Kisspeptin to be an independent biomarker for PCOS patients (23). In addition to Kisspeptin, scientists have identified 5-alpha reductase activity, leptin, insulin-like factor 3 (INSL3), and inhibin B as possible PCOS biomarkers (24). Another meta-analysis published in 2021 reaffirmed the result that PCOS patients have elevated blood levels of Kisspeptin. Since then, Kisspeptin has become increasingly prevalent as a PCOS diagnostic sign (25). There may be several reasons why the findings in our study contradict the more comprehensive data in the literature. PCOS patient group criteria may have differences between studies. For example, while one study accepted only "oligomenorrhea" and "abnormal ovary" as PCOS diagnostic criteria (16), another study did not accept "chronic anovulation" and "hyperandrogenemia" as exclusion criteria (14). Although we selected the PCOS patient group in our study using the Rotterdam criteria, the fact that our results are insignificant and do not match the literature data brings to mind different reasons. In this respect, the fact that PCOS phenotypes have a wide variety of metabolic features suggests that kisspeptin levels are not always high in all PCOS subtypes. The unfavorable results in certain studies like ours may be due to a bias in the data caused by a large proportion of one PCOS phenotype with normal kisspeptin levels. Another factor that might explain the unfavorable findings is the small sample size, vulnerable to unanticipated sampling error. For certain PCOS patients, hypothalamic overactivity may be less severe than ovarian disorder, while the role of Kisspeptin in the ovary has been rarely reported previously and appears to be unimportant, explaining why these patients have PCOS symptoms but no elevated kisspeptin levels in their blood.

Our results are compatible with literature regarding higher weight, BMI, Insulin, HbA1c, and Homa-IR values in PCOS patients (26). Metabolic syndrome is a group of metabolic disorders. The most common ones are abdominal obesity, insulin resistance, poor glucose metabolism, high blood pressure, and abnormal cholesterol levels. The risk of Type 2 diabetes mellitus (DMT2), coronary heart disease (CHD), cardiovascular diseases (CVD), and endometrial cancer goes up because of these related conditions. Many people with PCOS have signs of metabolic syndrome, like visceral obesity, high insulin levels, and insulin resistance (26,27). Apart from that, we found high FT_4, LH, and PLT values in PCOS patients. According to a study that

compared 226 women diagnosed with PCOS to 383 healthy women, the FT_4 levels in the PCOS group were found to be significantly higher (28). Also, in a cross-sectional study with 52 PCOS patients and 68 controls, researchers found significantly higher FT_4 levels in the PCOS group (29). In addition, scientists indicated higher LH levels in PCOS patients (30). In another study, using a mouse model of PCOS, researchers found dramatically elevated levels of LH and Kisspeptin (31). According to the researchers, platelet-rich plasma (PRP) can modulate hormonal interactions and boost ovarian antioxidant capability and folliculogenesis, and its auto-location might be regarded as a novel strategy to prevent/improve PCOS-induced pathogenesis (32). In this context, we hypothesize that ovarian feedback and biochemical interactions in PCOS may increase PLT levels.

We have also found a positive correlation between Kisspeptin with TSH and LH values. Consistent with our study data, a study with 30 PCOS patients and 30 healthy volunteers noted increased TSH levels in PCOS patients (33). In a second investigation involving 40 PCOS patients, researchers acquired elevated TSH levels and identified abnormalities in TSH synthesis (34). Despite this information, a study conducted with 83 PCOS patients and 66 healthy controls could not detect a correlation between Kisspeptin levels and TSH (35). In addition, the same study found a positive correlation between Kisspeptin and LH in PCOS patients, contrary to our results [35). The different results in these studies may be due to the heterogeneity of the patient group. However, the reagents and methods used may have caused different data to be obtained.

Limitations

First of all, the low number of patients and control groups was the main factor limiting our research. Secondly, the absence of disease duration of PCOS patients in the hospital database left our research incomplete. In addition, we could not study the parameters of GnRH, anti-mullerian hormone, and sex hormone binding globulin, this situation was a limiting factor in evaluating the HPG axis of the patients.

CONCLUSION

Kisspeptin, considered efficacious on the HPG axis in the literature and believed to elevate PCOS patients significantly, did not vary between our patient group and healthy women. This discrepancy may be because our patient group belongs to a different PCOS subtype than the studies in the literature or may be caused by hypothalamic and ovarian factors. Furthermore, PCOS patients had significantly elevated FT4, LH, and PLT levels. While our findings were consistent with the literature on FT_4 and LH, we could not locate a previous study that indicated PCOS individuals have a high PLT level. In conclusion, we believe that investigating Kisspeptin levels with higher patient numbers and subtyping them would shed light on the topic.

ACKNOWLEDGEMENTS

None.

REFERENCES

1. Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). Hum Reprod. 2004;19(1):41-47.
2. De Leo V, Musacchio MC, Cappelli V, Massaro MG, Morgante G, Petraglia F. Genetic, hormonal and metabolic aspects of PCOS: an update. Reprod Biol Endocrinol. 2016;14(1):38.
3. Blank SK, McCartney CR, Helm KD, Marshall JC. Neuroendocrine effects of androgens in adult polycystic ovary syndrome and female puberty. Semin Reprod Med. 2007;25(5):352-59.
4. Blank SK, McCartney CR, Marshall JC. The origins and sequelae of abnormal neuroendocrine function in polycystic ovary syndrome. Hum Reprod Update. 2006;12(4):351-61.

5. Azziz R, Carmina E, Dewailly D, et al. The Androgen Excess and PCOS Society criteria for the polycystic ovary syndrome: the complete task force report. Fertil Steril. 2009;91(2):456-88.
6. Moran LJ, Misso ML, Wild RA, Norman RJ. Impaired glucose tolerance, type 2 diabetes and metabolic syndrome in polycystic ovary syndrome: a systematic review and meta-analysis. Hum Reprod Update. 2010;16(4):347-63.
7. de Roux N, Genin E, Carel JC, Matsuda F, Chaussain JL, Milgrom E. Hypogonadotropic hypogonadism due to loss of function of the KiSS1-derived peptide receptor GPR54. Proc Natl Acad Sci U S A. 2003;100(19):10972-76.
8. Seminara SB, Messager S, Chatzidaki EE, et al. The GPR54 gene as a regulator of puberty. N Engl J Med. 2003;349(17):1614-27.
9. Burke MC, Letts PA, Krajewski SJ, Rance NE. Coexpression of dynorphin and neurokinin B immunoreactivity in the rat hypothalamus: Morphologic evidence of interrelated function within the arcuate nucleus. J Comp Neurol. 2006;498(5):712-26.
10. Goodman RL, Lehman MN, Smith JT, et al. Kisspeptin neurons in the arcuate nucleus of the ewe express both dynorphin A and neurokinin B. Endocrinology. 2007;148(12):5752-60.
11. Navarro VM, Gottsch ML, Chavkin C, Okamura H, Clifton DK, Steiner RA. Regulation of gonadotropin-releasing hormone secretion by kisspeptin/dynorphin/neurokinin B neurons in the arcuate nucleus of the mouse. J Neurosci. 2009;29(38):11859-66.
12. Cheng G, Coolen LM, Padmanabhan V, Goodman RL, Lehman MN. The kisspeptin/neurokinin B/dynorphin (KNDy) cell population of the arcuate nucleus: sex differences and effects of prenatal testosterone in sheep. Endocrinology. 2010;151(1):301-11.
13. Wang L, Moenter SM. Differential Roles of Hypothalamic AVPV and Arcuate Kisspeptin Neurons in Estradiol Feedback Regulation of Female Reproduction. Neuroendocrinology. 2020;110(3-4):172-84.
14. Panidis D, Rousso D, Koliakos G, et al. Plasma metastin levels are negatively correlated with insulin resistance and free androgens in women with polycystic ovary syndrome. Fertil Steril. 2006;85(6):1778-1783. doi:10.1016/j.fertnstert.2005.11.044.
15. Tang R, Ding X, Zhu J. Kisspeptin and Polycystic Ovary Syndrome. Front Endocrinol (Lausanne). 2019;10:298.
16. Albalawi FS, Daghestani MH, Daghestani MH, Eldali A, Warsy AS. rs4889 polymorphism in KISS1 gene, its effect on polycystic ovary syndrome development and anthropometric and hormonal parameters in Saudi women. J Biomed Sci. 2018;25(1):50.
17. Yoo TK, Oh BK, Lee MY, Sung KC. Association between physical activity and insulin resistance using the homeostatic model assessment for insulin resistance independent of waist circumference. Sci Rep. 2022;12(1):6002.
18. Jayanama K, Theou O, Godin J, Mayo A, Cahill L, Rockwood K. Relationship of body mass index with frailty and all-cause mortality among middle-aged and older adults. BMC Med. 2022;20(1):404.
19. Lumezi BG, Berisha VL, Pupovci HL, Goçi A, Hajrushi AB. Grading of hirsutism based on the Ferriman-Gallwey scoring system in Kosovar women. Postepy Dermatol Alergol. 2018;35(6):631-35.
20. Zhu L, Spence C, Yang JW, Ma GX. The IDF Definition Is Better Suited for Screening Metabolic Syndrome and Estimating Risks of Diabetes in Asian American Adults: Evidence from NHANES 2011-2016. J Clin Med. 2020;9(12):3871.
21. Emekci Ozay O, Ozay AC, Acar B, Cagliyan E, Seçil M, Küme T. Role of Kisspeptin in polycystic ovary syndrome (PCOS). Gynecol Endocrinol. 2016;32(9):718-722.
22. Daghestani MH. Evaluation of biochemical, endocrine, and metabolic biomarkers for the early diagnosis of polycystic ovary syndrome among non-obese Saudi women. Int J Gynaecol Obstet. 2018;142(2):162-69.
23. Liu J, Qu T, Li Z, et al. Serum kisspeptin levels in polycystic ovary syndrome: A meta-analysis. J Obstet Gynaecol Res. 2021;47(6):2157-65.
24. Phylactou M, Clarke SA, Patel B, et al. Clinical and biochemical discriminants between functional hypothalamic amenorrhoea (FHA) and polycystic ovary syndrome (PCOS). Clin Endocrinol (Oxf). 2021;95(2):239-52.
25. Pérez-López FR, Ornat L, López-Baena MT, Santabárbara J, Savirón-Cornudella R, Pérez-Roncero GR. Circulating kisspeptin and anti-müllerian hormone levels, and insulin resistance in women with polycystic ovary syndrome: A systematic review, meta-analysis, and meta-regression. Eur J Obstet Gynecol Reprod Biol. 2021;260:85-98.
26. Ali AT. Polycystic ovary syndrome and metabolic syndrome. Ceska Gynekol. 2015;80(4):279-89.
27. Jeanes YM, Reeves S. Metabolic consequences of obesity and insulin resistance in polycystic ovary syndrome: diagnostic and methodological challenges. Nutr Res Rev. 2017;30(1):97-105.
28. Zou S, Sang Q, Wang H, et al. Common genetic variation in CYP1B1 is associated with concentrations of T_4 , FT_3 and FT_4 in the sera of polycystic ovary syndrome patients. Mol Biol Rep. 2013;40(4):3315-20.
29. Karaköse M, Cakal E, Topaloğlu O, et al. Is there a link between polycystic ovary syndrome and non-thyroidal illness syndrome? J Turk Ger Gynecol Assoc. 2013;14(4):216-20.
30. Malini NA, Roy GK. Influence of Insulin on LH, Testosterone and SHBG in various PCOS Categories based on the Mode of Secretion of LH in relation to FSH Levels. Acta Endocrinol (Buchar). 2021;17(3):313-18.

31. Esparza LA, Schafer D, Ho BS, Thackray VG, Kauffman AS. Hyperactive LH Pulses and Elevated Kisspeptin and NKB Gene Expression in the Arcuate Nucleus of a PCOS Mouse Model. Endocrinology. 2020;161(4):bqaa018.

32. Seyyed Anvari S, Dehgan GH, Razi M. Preliminary Findings of Platelet-Rich Plasma-Induced Ameliorative Effect on Polycystic Ovarian Syndrome. Cell J. 2019;21(3):243-52.

33. Deniz R, Yavuzkir S, Ugur K, et al. Subfatin and asprosin, two new metabolic players of polycystic ovary syndrome. J Obstet Gynaecol. 2021;41(2): 279-84.

34. Szczuko M, Splinter J, Zapałowska-Chwyć M, Ziętek M, Maciejewska D. Fluorine may intensify the mechanisms of polycystic ovary syndrome (PCOS) development via increased insulin resistance and disturbed thyroid-stimulating hormone (TSH) synthesis even at reference levels. Med Hypotheses. 2019;128:58-63.

35. Yilmaz SA, Kerimoglu OS, Pekin AT, et al. Metastin levels in relation with hormonal and metabolic profile in patients with polycystic ovary syndrome. Eur J Obstet Gynecol Reprod Biol. 2014;180:56-60.