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ORIGINAL ARTICLE

The Relation between Serum Kisspeptin Level in PCO Women and Its Metabolic and Hormonal Profiles, Case-Control Study

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ABSTRACT

Background: Polycystic ovarian syndrome (PCOS) is a metabolic disorder, and its pathogenesis is still unclear, but the changes in the hypothalamic-pituitary-gonadal (HPG) axis are considered one of the main causes in the development of PCOS. Kisspeptin is a peptide encoded by the KISS gene that regulates the hypothalamus-pituitary-gonadal (HPG), which may be concerned with the pathogenesis of PCO. **Aim:** To identify the relation between serum Kisspeptin and sex hormones and metabolic parameters among normal and PCO women. **Methods**: A prospective case-control study was conducted among 64 subjects (32 with PCO and 32 with the control group). The serum Kisspeptin level was measured using enzyme-linked immunosorbent assay (ELISA) and correlated with other hormones such as LH, FSH, DHEA, testosterone, and prolactin**. Results:** Serum kisspeptin level was significantly higher in the PCOS group when compared to the control group. There was a statistically significant positive correlation between kisspeptin and each of HOMA IR, LH, FSH, DHEA, testosterone, and prolactin. **Conclusions:** The increase in kisspeptin level may play a role in pathogenesis of PCOS, and may represent a novel link between metabolic and hormonal disturbance in PCOS females since this peptide was correlated with HOMA-IR, LH, FSH, DHEA, testosterone and prolactin.

Keywords: PCO; Kisspeptin; FSH; LH; Metabolic

INTRODUCTION

Polycystic ovarian syndrome (PCOS) is one of the most common hormonal problems that affects women in the reproductive age group and usually starts during adolescence. It is characterized by oligomenorrhea or amenorrhea, hyperandrogenism, and the presence of cysts in the ovaries [1]. The prevalence of PCOS is between 8 and 13%, as confirmed by guidelines, and about 70% of cases are still undiagnosed [2]. It is associated with other conditions such as insulin resistance, obesity, and gestational diabetes; in addition, it is considered one of the most common causes of anovulatory infertility [3]. The pathogenesis of PCOS is still unknown; however, some studies have shown that PCOS is associated with an elevation of reactive oxygen species (ROS), oxidative stress, and suppression of antioxidants [4]. Indeed, there was a decrease in the level of superoxide dismutase (SOD) in the serum and follicular fluid among patients [5]. Also, the pathophysiology of the disease may be due to an alteration of LH/FSH ratios, which resulted from an increase in the level of luteinizing hormone (LH); however, this mechanism is still poorly understood [6]. These gonadal hormones have a role in modifying the neuronal function of gonadotrophin-releasing

hormone (GnRH) either through negative or positive feedback [7].

Kisspeptins are neuropeptides that are essential for regulation of reproductive hormone secretion, brain sex differentiation and fertility, as loss of their function is usually associated with pubertal failure. In addition to studies among animal models and patients, the generation of PCOS results from the alteration of kisspeptin signals [8]. Moreover, it was found that kisspeptin has a direct effect on the upstream of GnRH with upregulation of GnRH-mRNA, which explains the overfold increase of LH after kisspeptin administration [9].However, the clear relation between kisspeptin and the hypothalamic pituitary gonadal axis remains inconclusive. Some studies showed a high concentration of kisspeptin levels among PCOS women when compared with the control group [10], and other studies revealed no significant difference between PCOS and control group [11]. Based on the evidence, it is mainly found a positive correlation between kisspeptin neurons and LH level. Therefore, we conducted this study to assess the relation between kisspeptins (serum level) with sex hormones and metabolic parameters among normal and PCO women.

METHODS

This study was carried out as a prospective case control over a period of four months in the Obstetrics and Gynecology outpatient clinic at Zagazig University Hospitals.

The study population and sample size: The target population included females in the reproductive age group presented in the outpatient clinic. Sample was calculated using Open Epi software to be 64 subjects, 32 with PCOS , and 32 in the control group, assuming the level of kisspeptin was 10.12±5.8 in the case group and 6.51±3.13 in the control group, with a non-response rate of 10% at CI of 95% and a power of test of 80%. [12]

Inclusion criteria:The PCOS group included Females who showed a clinical diagnosis of PCOS This diagnosis was made according to the Rotterdam criteria made by ESHRE-ASRM in 2004 (13), which are defined as the presence of two out of three criteria;Oligomenorrhea and/or anovulation, which means menstruation less than six menses a year or menstrual length greater than 35 days , clinical and/or biochemical signs of hyperandrogenism determined by the Modified Ferriman-Gallwey score (14) when the score is 8 or more are considered hirsutism and/or the presence of acne, and biochemical evidence of hyperandrogenism detected by total testosterone and the free androgen index and The presence of > 12 follicles in each ovary measuring 2–9 mm in diameter and/or an increase in ovarian volume (>10 ml) made by trans-vaginal U/S.

***The control group*:** was defined as a patient with regular menses and a normal appearance of the ovary by pelvic U/S scan and free from any other symptoms of hyperandrogenism.

***Exclusion criteria* were** women with other endocrinal disorders have the same picture of hyper-androgenism or producing oligomenorrhea, like Cushing syndrome, androgen-secreting tumors, hypo-gonadotrophic hypogonadism, and hyperprolactinemia, which can be determined by clinical and routine workup,pregnant females, as pregnancy itself may increase kisspeptin release from the placenta and mislead the results and known diabetic patients who have obvious insulin resistance.

Tools of Data Collection

Patient characteristics and physical examination:All patients in the 2 groups were enrolled in a basic history and clinical examination including age, length of

menstrual cycle, clinical scoring of hirsutism, weight, and height to calculate BMI and classified according to the WHO classification of obesity: BMI= 18.5 to 24.9 means average weight, 25 to 29.9 means over weight, and ≥ 30 means obese. Also, a Trans-vaginal Ultrasound scan was made on all patients from days 2-3 of the cycle to estimate Antra follicular count (AFC) and diagnose PCO patient.

***Insulin resistance, Hormonal and Biochemical assay*:**Serum levels of fasting plasma glucose and fasting plasma insulin were measured to calculate the hemostatic model of insulin resistance (HOMA-IR), as normal insulin sensitivity was defined on the basis of fasting serum glucose and insulin levels and hemostatic model of insulin resistance (HOMA IR). Patient with a fasting insulin level greater than 20 iu/ml and HOMA-IR greater than 2.5 were accepted as insulin resistance groups.

HOMA-IR was calculated by equation: HOMA-IR= fasting blood glucose (mg/dl) × fasting insulin (u ml/ml)/405.

Serum kisspeptin, LH, FSH, DHEA, AMH, Testosterone, prolactin and estrogen were also measured in both groups. Human kisspeptin1 (Kiss1) ELISA kit (Catalog Number 201-12-4106 - SunRed Biotechnology, shanghai, China): A sandwich enzyme immunoassay for the quantitative measurement of human kisspeptin in samples of serum and blood plasma).

STATISTICAL ANALYSIS

Data analysis was performed using the software SPSS (Statistical Package for the Social Sciences) version 25, while quantitative data was designated using means and standard deviations. Spearman's rank correlation coefficient was calculated to assess relationship between various study variables, (+) sign indicate direct correlation & (-) sign indicate inverse correlation, also values near to 1 indicate strong correlation & values near 0 indicate weak correlation. All tests were two-sided. P-value <0.05 was considered statistically significant (S), P-value ≥ 0.05 was considered statistically insignificant (NS).

ETHICAL APPROVAL

The Institutional Review Board (IRB) of the Faculty of Medicine approved the study, Zagazig University approved the study protocol (ZU-IRB #11171). An informed consent was taken from the participants who agreed to participate in the study. Patients were also assured about the confidentiality of their information given to carry out the study, which will be used only for the study.

RESULTS

A total of 64 participants were included in this study. ٣٢ were categorized as the control group, and the other 32 were the PCO group. There was a non-statistically significant difference when comparing the two groups regarding age, BMI, waist, hip, and Waist-Hip ratio. (Table 1)

Regarding the serum levels of LH, DHEA, AMH, and testosterone hormones, there was a statistically significant increase (p<0.001) in the PCOS group when compared to the control group; however, the FSH level was significantly lower when compared to the control group. On the other hand, there was a non-statistically significant difference when comparing between both groups regarding prolactin hormone (p=0.219). (Table 2) .

While regarding the blood glycemic parameters, there was a statistically significant increase in serum insulin level (p<0.001) in the PCOS group (10.62 µIU/ml ±0.49) when compared to the control group (9.72µIU/ml ±0.5). However, there was a non-statistically significant difference when comparing theglucose level of both groups

(p=0.675). Moreover, HOMA IR showed a significant increase (p<0.001) in the PCOS group (2.64±0.25) when compared to the control group (2.40±0.23). (Table 2)

Regarding serum kisspeptin level there was statistically significant increase in PCO group (2.44 ng/ ml ±1.38) when compared to control group (1.19 ng/ ml ±0.54), p-value=<0.001 (Table 2 & figure1). Moreover, there was a statistically significant positive correlation betweenkisspeptin and each of HOMA IR, LH, FSH, DHEA, Testosterone andProlactin. (Table 3).

The ROC curve was performed to test the predictive power of kisspeptin at cut off=1.055 which had a sensitivity of 71.9% and a specificity of 43.7%, predictive value for positive (PVP) = (56.1%), predictive value for negative (PVN) = (60.9%), and (57.8%) accuracy (Table 4 & figure 2)

Table (1): Demographic characteristic of the studied group

Characteristic	**control group** Mean ±SD	**PCO group** Mean ±SD	**t**	**P value**
Age	28.03±3.89	28.34±4.32	-0.304	0.762
BMI (kg/m 2)	24.50±2.66	23.94±2.46	0.877	0.384
Waist (Cm)	82.44±6.26	82.75±6.09	-0.202	0.840
Hip (cm)	107.28±3.91	106.78±4.24	0.490	0.626
Waist Hip ratio	0.77±0.04	0.78±0.05	-0.646	0.521

(t) Independent Samples Test

Table (2): Serum levels of sex hormones, prolactin, glycemic parameters and kisspeptin of the studied groups

Characteristic	**control group (n=32)** mean ±SD	**PCO group (n=32)** mean ±SD	**t**	**P value**
LH (IU/ml)	6.78±3.77	14.96±2.2	-10.607	**<0.001***
FSH (IU/mL)	12.83±4.84	7.23±2.34	5.894	**<0.001***
Testosterone (ng/ ml)	0.49±0.24	1.01±0.46	-5.764	**<0.001***
DHEA (ng/ ml)	3.79±1.92	6.49±2.33	-5.054	**<0.001***
E2 (pg/mL)	44.64±3.38	65.28±6.8	-15.374	**<0.001***
AMH (ng/ ml)	4.61±0.69	7.88±0.44	-22.639	**<0.001***

Characteristic	control group (n=32) mean ±SD	PCO group (n=32) mean ±SD	t	P value
Prolactin (µIU/ml)	552.17±44.21	568.89±62.05	-1.241	0.219
Glucose (mg/dl)	100.22±5.4	100.92±7.77	-0.421	0.675
Insulin (µIU/ml)	9.72±0.5	10.62±0.49	-7.215	**<0.001***
HOMA IR	2.40±0.23	2.64±0.25	3.8	**<0.001***
Kisspeptin (ng/ ml)				
Mean ±SD Median (IQR)	1.19±0.54 1.09 (0.69-1.69)	2.44±1.38 **2.44 (0.94-3.79)**	(z) -3.538	**<0.001***

Anti-Mullerian Hormone (AMH), Dehydroepiandrosterone (DHEA)
(t) Independent Samples Test. (Z) Mann-Whitney Test

Table (3): Correlation betweenkisspeptin (ng/ ml) and different parameters

Variables		Kisspeptin (ng/ ml)
LH	r	**.621****
	p	**0.000**
FSH	r	**.484****
	p	**0.005**
Testosterone	r	**.569****
	p	**0.001**
DHEA	r	**.746****
	p	**0.000**
E2	r	0.237
	p	0.191
AMH	r	0.082
	p	0.654
Prolactin	r	**.385***
	p	**0.029**
Glucose	r	0.138
	p	0.460
insulin	r	0.212
	p	0.245
HOMA IR	r	**0.31***
	p	**.0٣٧**

P= Sig. (2-tailed), r= Correlation Coefficient

Table (4): Predictive values of kisspeptin as a predictor of PCO

Variables	AUC	95%CI	Cutoff	Sensitivity	Specificity	PVP	PVN	Accuracy
Kisspeptin (ng/ ml)	0.757	0.635-0.879	1.055	71.9%	43.7%	56.1%	60.9%	57.8%

AUC=Area under curve, PVP=Predictive value for positive, PVN= Predictive value for Negative, CI=Confidence Interval

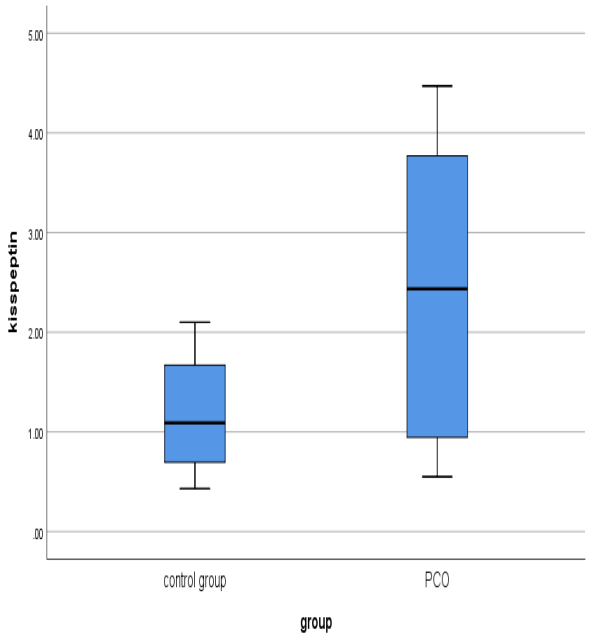

Figure (1): Box bolt showing comparison of kisspeptin (ng/ ml) level within the studied groups

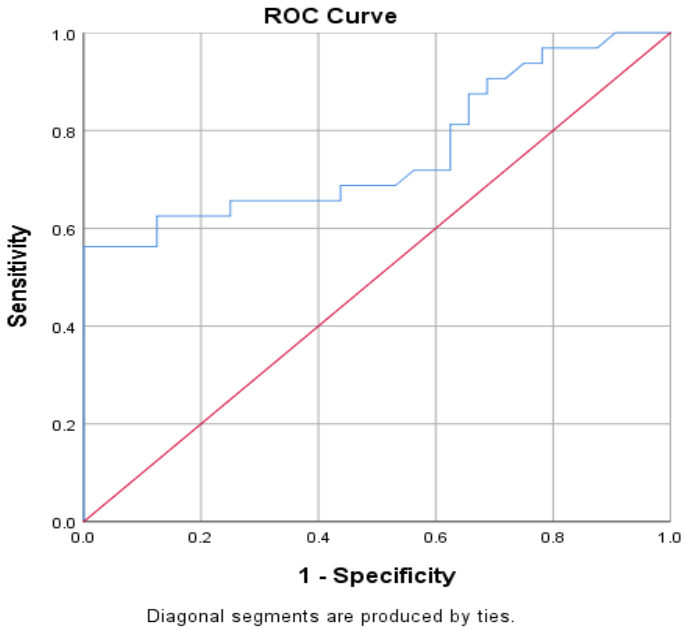

Figure (2): Roc curve representing Predictive values of the kisspeptin as a predictor of PCO.

DISCUSSION

Kisspeptins, a group of brain neuropeptides, were initially discovered to act as metastasis suppressors. The 54-amino-acid peptide known as kisspeptin, which was first found in the human placenta, is produced by the KISS1 gene. Kisspeptin has been shown to control the production of luteinizing hormone (LH) during the promotion of ovulation by activating gonadotropin releasing hormone

(GnRH) from the hypothalamus and may be a factor in the onset of various PCOS symptoms. Metabolic and reproductive indicators are impacted by the pathophysiology known as polycystic ovarian syndrome (PCOS) [**15].**

The current study illustrated that there was statistically insignificant difference when comparing between both groups regarding age, BMI, waist, hip and Waist Hip ratio, which is consistent with **Gao et al. [16]** study who demonstrated that they analyzed the clinical signs after adjusting for age, height, weight, and BMI without observable changes between the study group and the control group. The lack of a clear relationship between kisspeptin and BMI may be ascribed to the experiment's results being affected by the small sample size.Unlikely, **Pérez-López et al. [17]** revealed that individuals with PCOS had greater BMI and waist-to-hip ratios than the control group. According to a meta-regression analysis, age had no effect on kisspeptin levels. **Attia et al. [18]** showed that in favor of the PCOS group, there was a difference in the waist circumference and waist-to-hip ratio between the two groups.

The present study revealed that there was statistically significant difference when comparing between both groups regarding LH, FSH, DHEA, AMH and testosterone hormones. In comparison to the control group, the PCOS group had lower mean values of FSH and higher mean values of LH, testosterone, DHEA, and AMH. On the other hand, there was statistically insignificant difference when comparing between both groups regarding prolactin hormone. In agreement with our findings, **Pérez-López et al. [17]** reported that in PCOS-afflicted women, testosterone, LH, and AMH levels were all considerably higher in the blood. Prolactin and estradiol levels in comparison between the two groups showed a statistically negligible difference. According to a meta-regression analysis, LH and AMH had no effect on kisspeptin levels. Excess androgen level is the main pathological feature responsible for PCOS, as it induces the features of PCOS through a central mechanism by increasing GnRH pulsatility via the HPG axis [19&20]. Given that GnRH neurons lack androgen receptors, other routes, such as KP neurons, that supply afferent inputs to GnRH neurons are essential in mediating the modified sex steroid feedback observed in PCOS [21].Other studiesshowed that women with PCOS had greater LH levels than non-PCOS women [22-24], which is consistent with the fact that kisspeptin may stimulate LH secretion. **Ibrahim et al. [25]** illustrated that Kisspeptin, estradiol, free testosterone, FSH, and LH levels between PCOS and control women were significantly different, which is consistent with our findings. According to **Markantes, [26]**, women with PCOS showed increased AMH, but there was not significant difference in their serum levels of testosterone, androstenedione, DEHAS, and estradiol when compared to the control group.

Concerning blood sugar investigations, there was statistically significant difference when comparing between both groups regarding insulin. PCO group showed higher mean values of insulin when compared to control group. There was non-statistically significant difference when comparing between both groups regarding Glucose level. This was in accordance with **Pérez-López et al. (17)** who stated that participants with and without PCOS had similar levels of glucose. Individuals with PCOS had substantially higher mean circulating insulin and HOMA-IR indices than non-PCOS individuals. According to a meta-regression analysis, HOMA-IR index and circulating insulin had no effect on kisspeptin levels. The full-length 54 amino acids kisspeptin may regulate glucose metabolism. **Jones et al. [27]** illustrated that Independent of gender, age, adiposity, post-load glucose, and insulin sensitivity, greater kisspeptin levels are linked to hyperinsulinism; they are also negatively connected with BMI and waist circumference.

Current findings regarding kisspeptin level clearly revealed that PCOS group showed higher median values when compared to control group. Similar results were obtained by **Gao et al. [16]** who reported that the study group's kisspeptin value is greater than the control groups, and there was a statistically significant difference between the two groups

in this respect. They added there was no statistically significant difference in kisspeptin levels between the obese PCOS and non-obese PCOS groups, indicating that while kisspeptin is expressed at higher levels in PCOS patients compared to healthy individuals, there is no statistically significant relationship between the level of kisspeptin and obesity status. **Pérez-López et al. [17]** stated that, compared to control women, the amount of circulating kisspeptin was considerably higher in PCOS-afflicted women. These findings agreed with those **Katulski et al. [28]** showed that by comparing the mean levels of kisspeptin between the two groups, there was a statistically significant difference. In comparison to the control group, the PCOS group had higher median values. **Yilmaz et al. [29]** have revealed considerably greater kisspeptin levels in PCOS-affected women compared to controls, which is consistent with our current findings. In addition, even after adjusting for BMI, kisspeptin levels are greater in PCOS-positive women than in controls. **Zhao et al. [30]** demonstrated thatcomparing patients with PCOS to healthy controls, serum kisspeptin levels were considerably higher, and were positively linked with LH. **Aasif et al.,[31]** demonstrated this with the upstream direct effect of kisspeptin on GnRH neurons in terms of depolarization; these support the hypothesis that the syndrome's elevated HPG-axis activity, which causes an irregular menstrual cycle and excessive androgen secretion, may have originated from an overactive KISS1 system. This is in line with the results of **Xu et al.[32],** who showed that the level of GnRH and expression of kisspeptin and Kiss1 were increased in the hypothalamic ARC of PCOS rats.

The findings of the current study showed that there was a statistically significant positive correlation between kisspeptin and each of LH, FSH, DHEA, testosterone and prolactin. These findings were compatible with **Gao et al. (16)** who demonstrated that Kisspeptin levels and sex hormone levels in PCOS were connected, and the results revealed a favorable relationship between kisspeptin and LH, T, and AMH across the board. It wasstated that LH levels may be increased in PCOS patients due to a protracted increase in kisspeptin production, which may lead to abnormalities in the hormone feedback loop and remain permanently disrupted. **Xu et al. [32]** suggested that hyperactive GnRH/LH pulses in PCOS are linked to kisspeptin neurons, which are found in the arcuate nucleus (ARC). Through the kisspeptin-Kiss1r (Kiss1r) signalling pathway, kisspeptin controls GnRH neurons, which in turn controls the function of the hypothalamic-pituitary-gonadal (HPG) axis. AMH and kisspeptin are also linked in PCOS patients, but this is not the case in healthy women [17]. **Jeon et al. [33]** noted that Kisspeptin and testosterone have a favorable correlation. **Umayal et al. [34]**reported that Overall, there was a favorable connection between kisspeptin levels and blood testosterone and BMI.**Ibrahim et al. [22]** illustrated that positive correlations were found between blood levels of kisspeptin and free testosterone. Also, **Emekci Ozay et al. [35]** stated that in PCOS patients, kisspeptin and LH showed a favorable connection. It was in line with the theory that kisspeptin might increase LH production, albeit it is still debatable how kisspeptin's direct pituitary effects on the regulation of gonadotropin secretion work. Unlikely, **Gorkem et al. [36]** revealed that FSH and kisspeptin have a negative correlation. **Zarei et al. [15]** found that a significantly favorable correlation between kisspeptin and E2 levels was found., whereas our results suggested that there was no significant correlation between kisspeptin and E2. Differences in race, way of life, and geography may be an explanation for this variance.

A small sample size was considered one of the limitations of the current study, and the results were also affected by the genetic and demographic characteristics of the studied participants. Further studies are needed to provide a clear picture of the link between kisspeptin and studied hormones among PCOS patients.

CONCLUSIONS

Since kisspeptin was linked to HOMA-IR, LH, FSH, DHEA, testosterone, and prolactin,

it is possible that the elevated amount of this peptide contributes to the pathophysiology of PCOS and provides a new avenue for examining the relationship between metabolic and hormonal imbalance in PCOS females.**Conflict of interest:**None.

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