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Kisspeptin levels in polycystic ovary syndrome and its manifestations

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Abstract

Background: The altered luteinizing hormone to follicle-stimulating hormone (LH/FSH) ratio- an important component in the pathogenesis of polycystic ovary syndrome (PCOS), is regulated by a brain peptide kisspeptin. This study aimed to explore the association of serum kisspeptin levels with PCOS and its manifestations. **Methods:** This cross-sectional study included 80 participants with PCOS on the basis of International evidence-based guidelines, 2018, and 71 healthy matched controls. Along with clinical information, fasting blood was drawn to measure total testosterone, sex hormone binding globulin, thyroid stimulating hormone, prolactin, 17-hydroxyprogesterone, and kisspeptin in all, and glucose, lipids, insulin, LH, FSH in only PCOS participants in the follicular phase of the menstrual cycle. Kisspeptin was measured by sandwiched enzyme-linked immunosorbent assay method with a lower limit detection level of 0.01 pg/mL. **Result:** Kisspeptin levels were undetectable in 25 out of 80 and 16 out of 71 controls. Among the participants with detection levels (55 in each group), kisspeptin did not differ between PCOS and control [31.2 (19.2 – 43.1) vs. 40.4 (14.9 – 70.4), pg/mL, p=0.446]. Among participants with PCOS, kisspeptin levels had no significant associations or correlations with any manifestations (ns for all). ROC curve analysis showed kisspeptin as not an acceptable marker for PCOS [AUC (95% CI): 0.57 (0.46 – 0.68), p= 0.221]. **Conclusion:** Our study failed to show any association of kisspeptin levels with PCOS and its manifestations.

Key Words: Polycystic ovary syndrome, Kisspeptin, Luteinizing hormone, Follicle stimulating hormone

Introduction : Polycystic ovary syndrome (PCOS) is a common reproductive endocrine and metabolic condition with unknown pathophysiology.[1] Although hyperandrogenism and insulin resistance are the main contributors, the effects of these two are centrally modulated in the gonadotropin-releasing hormone (GnRH) neurons of the hypothalamus. The final output of the neurons are luteinizing and follicle-stimulating hormone and their ratio (LH/FSH ratio) mediates different reproductive events in healthy persons as well as the manifestations of PCOS.[2] However, the GnRH neurons are regulated by gamma-aminobutyric acid (GABA), Kisspeptin-Neurokinin B-Dynorphin (KNDy), and other neurons that receive information on different steroids including androgens, antimullerian hormone, and metabolic status of the person.[3,4] Thus a vicious cycle is produced that maintains the manifestations of PCOS.

Kisspeptin is a key regulator of GnRH neurons. This peptide is encoded by the KISS1 gene and binds with the G-protein-coupled receptor (GPR54/KISS1R) in the GnRH neurons.[5] It is considered to be responsible for the timely activation of hypothalamic-pituitary hormones at puberty and in maintaining normal cyclical function during adult life.[5,6] Kisspeptin stimulates the release of GnRH into

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the portal circulation, which in turn stimulates the secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the gonadotroph cells of the anterior pituitary. It is thought that the dysregulated gonadotropin secretion in PCOS is a reflection of altered kisspeptin inputs to GnRH neurons.[5-7] The complex relationships of kisspeptin with the different pathophysiological factors as well as heterogeneous presentations of PCOS need the exploration of the association between them.

Our study was intended to measure the kisspeptin levels in PCOS and to analyze correlations between kisspeptin and PCOS in Bangladeshi women.

Methods

This was a cross-sectional study done over one year in the Department of Endocrinology of a University hospital after being approved by the university's institutional review board. Informed written consent was taken from all study participants. The study was conducted according to the Helsinki Declaration.

Using the following formulae [$n = \{(Z_\alpha + Z_\beta)^2 \times (\sigma_1^2 + \sigma_2^2)\} \div (\mu_1 - \mu_2)^2$], taking the mean and standard deviation from a previous study, at 95% confidence interval and 80% power, the sample size was 70.[8] We included 80 newly diagnosed PCOS participants (age: 13-35 years) and 71 apparently healthy controls for the study.

The diagnosis of PCOS was based on International evidence-based guidelines for the assessment and management of polycystic ovary syndrome 2018. Irregular cycles and polycystic ovarian morphology were considered by gynecological age.[9] Clinical hyperandrogenism was considered with a modified Ferriman-Gallwey (mFG) score of ≥6 and hyperandrogenemia by a free androgen index (FAI) of ≥5%.[9,10] Participants having regular menstrual cycles without any clinical and biochemical features of hyperandrogenism were considered healthy controls. Those having related endocrine disorders [thyroid stimulating hormone: 0.5< TSH >5.5 mIU/mL; hyperprolactinemia (>25 ng/mL); non-classic congenital adrenal hyperplasia (synacthen stimulated 17-hydroxyprogesterone, 17OHP >10 ng/mL)], significant systemic diseases, pregnancy/ lactation, or taking any insulin sensitizers, hormonal contraceptives, antiandrogens, or any related drugs were excluded from both the groups.

After taking informed written consent, relevant histories were taken and physical examinations [height, weight, waist circumference (WC), hip circumference (HC), blood pressure (BP), acne, hirsutism, and acanthosis nigricans] were done. Blood was drawn in the follicular phase of the menstrual cycle in a fasting state to measure total testosterone (TT), sex hormone-binding globulin (SHBG), prolactin, TSH, 17-OHP, and kisspeptin levels in all the study participants. Additionally, insulin, glucose, lipid profile in the fasting state, and glucose in fasting and after an oral glucose tolerance test (OGTT) were measured only in the PCOS group. Ultrasonography for polycystic ovarian morphology (PCOM) was also done during the follicular phase of the menstrual cycle by trans-abdominal or transvaginal route depending on the marital status and participants' choice.

All the hormones including SHBG were analyzed by chemiluminescence microparticle immunoassay. The serum concentrations of kisspeptin were measured with a commercially available ELISA kit with a lower limit detection level of 0.01 pg/mL. The inter-assay and intra-assay coefficient of variations were 4.0 – 5.9% and 4.3 – 5.9% respectively. A cut-off of 25 kg/m2 for body mass index

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(BMI), LH/FSH ratio >1.0, and homeostasis model assessment (HOMA-IR) of 2.6 were considered obesity, altered LH/FSH ratio, and insulin resistance respectively.[11-13] Presence of 3 out of 5 [WC ≥80 cm, BP ≥130/85 mm-Hg, fasting plasma glucose (FPG) ≥ 5.6 mmol/L, hypertriglyceridemia (TG) ≥150 mg/dL, and low high density lipoprotein (HDL)-cholesterol <50 mg/dL or equivalent for children) was considered a metabolic syndrome.[14,15]

Data were analyzed by Statistical Package for Social Sciences (SPSS) software (version 23.0). Qualitative variables were expressed in frequency (%) and quantitative variables were expressed in median (inter-quartile range, IQR). Associations of medians of serum kisspeptin between the study groups and different manifestations of PCOS were analyzed by the Mann-Whitney U test or Kruskal Wallis one-way ANOVA (analysis of variants) test as appropriate. The association between two qualitative variables was tested by the chi-square test. A Spearman correlation test was done to see the correlation between kisspeptin levels with different manifestations among participants with PCOS. Receiver operating characteristics (ROC) curve analysis was done to see serum kisspeptin as a marker of PCOS and its manifestations. Statistical significance was considered by two-tailed p-values below 0.05.

This study was approved by the Institutional Review Board of Bangabandhu Sheikh Mujib Medical University where the study took place (NO. BSMMU/2020/9717). Informed written consent was taken from all participants and legal guardians (for minors) before enrollment.

Results

Among 80 participants with PCOS and 71 control, 25 (31.3%) and 16 (22.5%) had undetectable levels of serum kisspeptin respectively. Finally, data from 55 participants of each group with detectable kisspeptin levels were analyzed.

The characteristics of the study participants showed

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Table 1: Characteristics of the study participants (n= 110)

Variables	PCOS, n= 55	Control, n= 55	p
Age, years	22.0 (18.0 – 25.0)	24.0 (23.0 – 26.0)	0.245
Age of menarche, year	13.0 (12.0 – 13.0)	13.0 (12.0 – 14.0)	0.284
mFG score	11.0 (7.0 – 15.0)	3.0 (3.0 – 4.0)	**<0.001**
Acne	33 (60.0)	11 (20.0)	**<0.001**
Acanthosis nigricans	32 (58.2)	10 (18.2)	**<0.001**
Body mass index, kg/m^2	25.1 (23.6 – 28.6)	22.6 (20.4 – 25.5)	**0.002**
Waist circumference, cm	81.0 (75.0 – 85.0)	75.0 (70.0 – 81.0)	**0.004**
Waist/hip circumference	0.81 (0.76 – 0.86)	0.78 (0.74 – 0.82)	**0.012**

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Systolic BP, mm-Hg	110.0 (100.0 – 120.0)	100.0 (90.0 – 100.0)	**<0.001**
Diastolic BP, mm-Hg	70.0 (70.0 – 80.0)	60.0 (60.0 – 70.0)	**<0.001**
LH, IU/mL	8.5 (5.0 – 13.2)	2.4 (1.1 – 3.7)	**<0.001**
FSH, IU/mL	6.4 (4.9 – 7.7)	4.8 (3.4 – 5.9)	**0.001**
LH/FSH ratio	1.1 (0.9 – 2.1)	0.5 (0.32 – 0.75)	**<0.001**
Total testosterone, ng/dL	43.3 (27.1 – 75.0)	19.2 (16.4 – 22.5)	**<0.001**
SHBG, nmol/L	30.5 (25.4 – 38.6)	29.0 (21.5 – 32.0)	0.446
Free androgen index, %	5.3 (3.3 – 7.6)	2.5 (2.1 – 2.8)	**<0.001**

BP (blood pressure), mFG (modified Ferriman-Gallwey), FAI (free androgen index), OGTT (oral glucose tolerance test), LH (luteinizing hormone), FSH (follicle stimulating hormone), HOMA-IR (homeostasis model assessment of insulin resistance)

Mann-Whitney U or Kruskal Wallis test for medians was done as appropriate

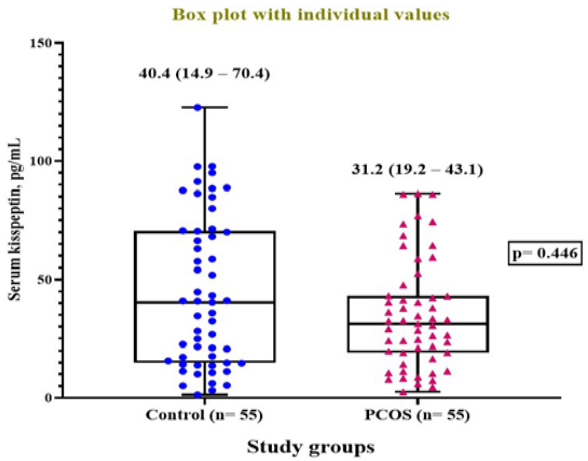
that both the study groups were similar in age, age of menarche, and SHBG levels. Different androgenic manifestations [mFG score, acne, TT, and FAI] were significantly higher in the PCOS group than in the control group. Similarly, different metabolic manifestations [BMI, WC, WHR, BP, and acanthosis nigricans] were also significantly higher in the PCOS group than in the control group. At last, LH, FSH, and their ratio were also significantly higher in participants with PCOS than in control.

The median levels of serum kisspeptin were higher in the control group than in the PCOS group without significant differences [31.2 (19.2 – 43.1) vs. 40.4 (14.9 – 70.4), pg/mL, median (IQR), p=0.446]

Legends of figures

Figure-1: Serum Kisspeptin levels in the study groups (n= 110)

Mann-Whitney U test for median was done



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Serum kisspeptin levels were similar when compared under subgroups of different manifestations among patients with PCOS.

Table 2: Kisspeptin levels in different manifestations of PCOS (n= 55)

Variables	Groups	No. (%)	Kisspeptin levels	p
Menstrual cycle	Irregular	50 (90.9)	29.8 (16.0 – 43.0)	0.327
	Regular	5 (9.1)	42.3 (29.0 – 68.9)	
Hyperandrogenism mFG≥8 &/or FAI≥5%	Present	48 (87.3)	30.9 (19.2 – 46.6)	0.959
	Absent	7 (12.7)	33.4 (10.3 – 40.3)	
Body mass index ≥25 kg/m^2	Obese	29 (52.7)	34.6 (21.5 – 50.2)	0.221
	Nonobese	26 (47.3)	24.4 (11.0 – 39.1)	
Polycystic ovarian morphology	Present	49 (89.1)	32.6 (19.5 – 45.4)	0.211
	Absent	6 (10.9)	22.8 (9.2 – 44.4)	
LH/FSH ratio >1.0	Altered	33 (60.0)	32.9 (19.5 – 47.9)	0.474
	Normal	22 (40.0)	28.8 (10.7 – 43.7)	
Insulin resistance HOMA-IR ≥2.6	Present	38 (69.1)	30.9 (19.7 – 48.9)	0.928
	Absent	17 (30.9)	32.6 (10.5 – 40.2)	
Metabolic syndrome 3 out of 5	Present	15 (27.3)	32.6 (21.8 – 52.6)	0.934
	Absent	40 (72.7)	28.5 (17.3 – 43.1)	
Phenotypes	A	37 (67.3)	31.2 (17.9 – 45.4)	0.202
	B	6 (10.9)	22.8 (9.2 – 44.4)	
	C	5 (9.1)	42.3 (29.0 – 68.9)	
	D	7 (12.7)	33.4 (10.3 – 40.3)	

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None of the variables had a significant correlation with kisspeptin levels among women with PCOS.

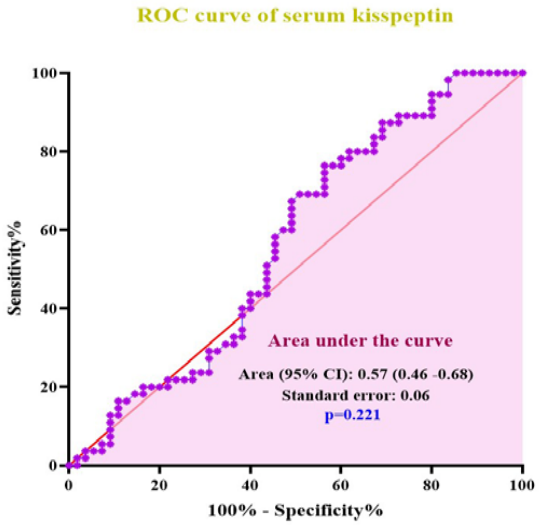
Table 3: Correlations of kisspeptin with clinical, biochemical, and hormone levels in patients with PCOS (n= 55)

Dependent of 'ρ'	ρ	p
Age, years	0.07	0.634
Age of menarche, year	-0.17	0.226
Body mass index, kg/m^2	0.20	0.145
Waist circumference, cm	0.25	0.071
Waist/hip ratio	0.27	0.056
Systolic BP, mm-Hg	0.02	0.890
Diastolic BP, mm-Hg	0.13	0.347
mFG score	0.05	0.709
LH/FSH ratio	0.22	0.105
Free androgen index, %	-0.04	0.774
Fasting plasma glucose, mmol/L	0.02	0.911
2H-OGTT glucose, mmol/L	-0.26	0.056
HOMA-IR	0.15	0.262
Total cholesterol, mg/dL	0.24	0.084
LDL-cholesterol, mg/dL	0.17	0.216
Triglyceride, mg/dL	0.24	0.082
HDL-cholesterol, mg/dL	-0.03	0.845

BP (blood pressure), mFG (modified Ferriman-Gallwey),), LH (luteinizing hormone), FSH (follicle stimulating hormone), OGTT (oral glucose tolerance test), HOMA-IR (homeostasis model assessment of insulin resistance)
Spearman's correlation test was done

Serum kisspeptin could not be used as a marker of PCOS [area under the curve, AUC (95% CI): 0.57 (0.46 – 0.68), p= 0.221]

Figure-2: Serum Kisspeptin as a marker of PCOS in the study participants



It also did not appear to be an acceptable marker of altered LH/FSH ratio [AUC) (95% CI): 0.57 (0.41 – 0.73), p=0.390], hyperandrogenism [AUC (95% CI): 0.55 (0.32 – 0.77), p= 0.705], and insulin resistance [AUC (95% CI): 0.56 (0.39 – 0.73), p= 0.518] among patients with PCOS.

Discussion

This study did not find any significant association of kisspeptin levels with PCOS or its various manifestations including hormones and metabolic profiles.

The difference between kisspeptin levels in the present study was not statistically significant. A similar finding was reported by three previous studies that also observed similar levels of kisspeptin between PCOS and control.[16-18] But many other studies including meta-analyses found higher kisspeptin levels in PCOS than in

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control.[19-21] Kisspeptin has been shown to rise with age and its level is higher in normal weight PCOS as well as controls when compared with overweight/obese PCOS and controls.[22,23] Our study had fewer lean PCOS and higher adolescent PCOS patients than control which may explain this discrepancy.

A few previous studies found a positive correlation between kisspeptin with TT and FAI, whereas one study found kisspeptin to be negatively associated with kisspeptin.[24-26] Amongst these contradicting results of previous studies, the present study did not find any correlation of kisspeptin with either TT or FAI. Further large studies may be required to see any such correlation. Previous studies also show contradicting correlation between kisspeptin and SHBG.[25,26] The present study did not show any such correlation.

Kisspeptin has a recognized association with gonadotropin release. However, we did not find any association between kisspeptin with LH/FSH ratio. In line with our result, previous studies also failed to show any correlation between kisspeptin and LH level or LH/FSH ratio.[24,27] Altered LH:FSH ratio is not a constant finding in PCOS and like LH,

Kisspeptin may have a pulsatile secretion. Still, further studies are required to properly understand the relationship between LH and kisspeptin.

We did not find a significant association between kisspeptin levels with phenotypes of PCOS. One study has mentioned the possibility of the association of kisspeptin with phenotypes having anovulatory cycles and hyperandrogenism.[22] Small sample size, especially in the non-A phenotypes may be responsible for this insignificant association in our study.

In agreement with the previous three studies, we did not find any association between kisspeptin and BMI.[8,22] However, Rashad et al. found higher levels of kisspeptin levels in normal-BMI PCOS than in overweight/obese PCOS and an inverse association of kisspeptin levels with obesity grade.[23] There is contradicting evidence of a correlation between kisspeptin and insulin resistance.[26,27] The present study did not find any correlation between kisspeptin and blood glucose or insulin resistance.

ROC curve analysis showed that serum kisspeptin was neither an acceptable marker of PCOS nor a reliable marker of altered LH/FSH ratio, hyperandrogenism, and insulin resistance in PCOS patients. However, several studies showed kisspeptin as a fair marker of PCOS.[28,29]

Various previous studies have shown that kisspeptin levels were either too high or too low compared to ours.[30] These variable findings might be due to the use of different ELISA kits manufactured by different companies. Besides, our assay method failed to detect kisspeptin levels in around 27% of the study participants. We could not measure kisspeptin levels in the luteal phase of the menstrual cycle.

Conclusion

In conclusion, we were unable to identify any correlation between PCOS or any of its manifestations and Kisspeptin. Further studies may be needed before recommending it as a surrogate marker of PCOS.

Declarations

Competing interests: Nil

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Authors' contributions

Subi Kharel: Conceptualization, Data curation, Methodology, Investigations, Formal analysis, Writing- Original draft, Approval, Hurjahan Banu: Conceptualization,

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Methodology, Supervision, Writing- Review & Editing, Approval, Md Shahed Morshed: Conceptualization, Formal analysis, Visualization, Writing- Review & editing, Approval, Emran-Ur-Rashid Chowdhury: Data curation, Investigations, Writing- Original draft, Approval, Muhammad Abul Hasanat: Conceptualization, Methodology, Fund acquisition, Project administration, Resources, Supervision, Validation, Writing- Review & editing, Approval

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