






Association of Spexin Hormone Levels with Metabolic Disturbance in Women with Polycystic Ovarian Syndrome

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Abstract

Background: Polycystic ovarian syndrome is affecting around 5–15% of females. Spexin hormone, identified as neuropeptide Q, has been newly recognized by bioinformatics methods.

Objective: To evaluate the relationship concerning levels of spexin hormone with metabolic disruption in women with polycystic ovarian syndrome.

Patients and Methods: A case-control study carried out in the department of Obstetrics and Gynecology in Al-Imamain Al-Khademain medical city/Baghdad, Iraq, from Jan 1, 2022, to the end of Dec 31, 2022. The study sample comprises, 192 participants aged 18-45 years were joined and allocated into a case group (96 women with PCOS) and a control group (96 women without PCOS).

Results: Mean value of spexin hormone was (2.7±0.3 ng/mL) in the PCOS group, while it was (3.5±0.7 ng/mL) in the control group; fasting blood sugar shows significant association with a negative, weak correlation with Spexin in patients (P-value= 0.005), Insulin shows significant association with inverse correlation with Spexin in patients (P-value= 0.04), Homeostasis model valuation of insulin resistance (HOMA-IR) shows significant association with inverse correlation with Spexin in patients (P-value= 0.003). Spexin had a significant inverse correlation with LH, SHBG, testosterone, FAI, and Dehydroepiandrosterone.

Conclusion: Serum level of spexin hormone was meaningfully decreased in patients with PCOS than that in healthy women.

Keywords: Polycystic ovary syndrome, Spexin, Hormonal, Metabolic Disturbance.

Introduction

Polycystic ovary syndrome (PCOS) is a mutual endocrine-reproductive-metabolic disorder in women which remains a significant cause of unproductiveness, disturbing around 5–15% of females global (1-6). The principal hormonal irregularities in PCOS are categorized by greater androgen and estrogen but lesser progesterone ranks; the occurrence of gestational diabetes, asthma, and repeated miscarriage is 3–7-fold, 10-fold, and 3–5-fold higher in females with PCOS than in the overall people, correspondingly (6-13). A latest work has revealed that a greater body mass index is connected with hypertriglyceridemia in PCOS women, which is ascribed to the obesity-induced variation of adipokines, comprising tumor necrosis factor-alpha (TNF α), interleukin (IL)-6, and adiponectin (7-9,12-16). PCOS is a complex and multifactorial disease, and not all investigators agree with the classifications (14,20-26). In Germany, Greece, and other countries, no significant differences in insulin resistance (IR), dyslipidemia, or BMI were observed (24,25-32). Spexin (SPX), also known as neuropeptide Q, has lately been recognized by bioinformatics procedures. SPX is a secreted 14-amino-acid peptide exceedingly preserved from fish to mammals. It is broadly conveyed in the central nervous system and outlying tissues such as the liver, gonad, and kidney in rodents, fish, and humans (33-41). Hence, SPX has been described to have a diversity of purposes, comprising roles in stomach tightening, adrenocortical cell propagation, cardiovascular and renal task, nociception, nourishing, and replica (42-44). A new revision stated that intracerebroventricular (icv) inoculation of SPX augmented hypothalamic mRNA ranks of leptin receptor and melanocortin four receptor in mice, signifying a possible part of SPX in the act of leptin in the hypothalamic center for dynamism homeostasis (45-48). Latest articles have emphasized SPX purposes in governing obesity and energy metabolism founded on the witnessed interactions amid SPX and obesity: the circulating level of SPX is little in fat people matched to their steady equivalents (44,48-52).

Patients and Methods

Design of the study

A case-control study, carried out in Al-Imamain Al-Khademain Medical City/Baghdad, from Jan 1, 2022,

to Dec 31, 2022. This research was ethically accepted by the scientific congress of Obstetrics and Gynecology, the Iraqi Board for medical specialization, and the scientific committee of the hospital setting. As well as verbal consent from all patients, the objective and processes were clarified to all contributors, and they were specified the right to contribute or not; oral agreement was taken with assurance that the information would be reserved confidential. 192 participants aged between 18-45 years old were enrolled and allocated into two sets: Case group: 96 women with PCOS. Control group: 96 non-PCOS women healthy women coming to the hospital for checkup and follow up.

Identification of women with PCOS was established on the following

Clinical parameters:

BMI calculated according to Kg/m²

Waist circumference

Modified Ferriman-Gallwey score for hirsutism (women with FG >8 considered as hirsute)

Presence of acne. Menstrual irregularity (oligo anovulation)

U/S: (ovarian volume >10 ml without cyst or dominant follicle and appearance of more than 12 follicles was seen and 2-9 mm in diameter.

Hormonal parameters

Progesterone, LH/FSH, Free testosterone, DEHEA, SHBG, Estradiol, FAI, and Spexin.

Metabolic parameters

FBS, insulin level, and HbA1c

HOMA-IR hemostatic model assumes that IR

While the women in the control set were designated from those, who consult our department in the hospital for a routine check-up or from patients' relatives with no disorders (hirsutism, acne, and hyperandrogenism).

The inclusion criteria used for recruitment of women with PCOS

PCOS women were identified agreeing to the 2003 Rotterdam criteria.

Range of age between 18-45 years old

Married and unmarried women.

Exclusion criteria

Patients aged more than 45 years and less than 18 years

Chronic disease

Congenital adrenal hyperplasia

Cushing syndrome

Androgen secreting tumor

Autoimmune disease

Thyroid disease

Matching criteria:

Age and BMI were matched for both groups in the study.

Methods

Blood samples from all participants were taken from antecubital veins during the initial follicular phase of the cycle (3-5 days) after the selection of the patients, and the blood sample was taken after 10 hours of fasting. Next, the researchers place the blood samples at room heat for at a minimum of 30 min to touch the coagulated form. Then, the coagulated models were centrifuged for 15 min. at 2000 X g for parting. Then, the serum samples were centrifuged and kept the separated pieces in aliquots at -80 C0 to analyze circulating spexin levels by ELISA test.

Insulin resistance (IR)

was evaluated by homeostasis model assessment of insulin resistance: $HOMA-IR = \text{fasting insulin (mU/mL)} \times \text{fasting glucose (mg/dL)} / 405$.

Statistical Exploration

Data were scrutinized by using the SPSS IBM program version 25 Statistics are offered as means \pm variance matched using an unpaired t-test.

Chi-square or Fisher s exact 'tests matched means and percentages when suitable.

Probability values < 0.05 were deliberated statistically noteworthy in all results.

Results

The mean age of the PCOS group was (29.9 ± 5.84) years and (30.3 ± 6.0) for the control group, mean BMI level in the PCOS group was (30.82 ± 4.67) kg/m² and (29.67 ± 4.39) kg/m² in the control group, mean Waist: Hip ratio level in PCOS group was (0.80 ± 0.06) and (0.79 ± 0.02) in the control group, mean FBS level in PCOS group was (85.20 ± 12.33) and (84.8 ± 11.79) in the control group, mean insulin level in PCOS group was (15.12 ± 3.63) and (10.6 ± 3.29) in the control group, and mean HOMA-IR level in PCOS group was (3.15 ± 0.09) and (2.07 ± 0.08) in control group. There was no substantial variance between PCOS and control (p -value ≥ 0.5) concerning age, BMI, Waist: Hip ratio, and FBS. At the same time, Insulin and HOMA-IR were meaningfully greater in PCOS matched to the control (p -value < 0.001), as illustrated in table 1.

Table 1: Characteristic parameters of PCOS* and control set

Group	PCOS	Control	P-value
Number	96	96	
Age (years), mean ± SD	29.9±5.84	30.3±6.0	0.6
BMI (kg/m ²), mean ± SD	30.82±4.67	29.67±4.39	0.08
Midriff: hip ratio, mean ± SD	0.80±0.06	0.79±0.02	0.1
FBS (mg/dL), mean ± SD	85.20±12.33	84.8±11.79	0.8
Insulin (mU/mL), mean ± SD	15.12±3.63	10.6±3.29	<0.001
HOMA-IR, mean ± SD	3.15±0.09	2.07±0.08	<0.001

The mean FSH level was (8.07±4.12 IU/L) in the PCOS group and (9.35±3.53 IU/L) in the control set. The mean LH level was (17.29±8.56 mIU/ml) in the PCOS group and (6.66±2.99 mIU/ml) in the control group, mean Progesterone level was (1.03±0.04ng/ml) in the PCOS group and (1.04±0.07ng/ml) in the control group, mean Estradiol level was (53.82±5.71 pg/dl) in PCOS group and (52.87±4.92 pg/dl) in control group, mean Testosterone level was (2.03±0.39 nml/L) in PCOS group and (1.71±0.32 nml/L) in control group, mean Androgen level was (7.86 ± 1.85) in

PCOS group and (2.41 ± 0.31) in control group, mean SHBG level was (34.40±12.33 nmol/l,) in PCOS group and (55.62±17.15 nmol/l,) in the control group, mean DEHEA level was (169.27±64.18 µg/dl) in PCOS group and (151.87±41.69 µg/dl) in the control group. No important dissimilarity among both clusters in the study among FSH and Estradiol (P≥0.05). At the same time, significant differences were found among (LH, progesterone, TT, FAI, SHBG, and DEHEA, as illustrated in Table 2.

Table 2: Comparison between mean hormonal assay in the studied groups

Group	PCOS	Control	p-value
Number	96	96	-
FSH (IU/L), mean ± SD	8.07±4.12	9.35±3.53	0.36
LH (mIU/ml), mean ± SD	17.29±8.56	6.66±2.99	0.001
Progesterone (ng/ml), mean ± SD	1.03±0.04	1.04±0.07	0.02
Estradiol,(pg/dl) mean ± SD	53.82±5.71	52.87±4.92	0.1
Testosterone (nml/L), mean ± SD	2.03±0.39	1.71±0.32	<0.001
Free Androgen index, mean ± SD	7.86 ± 1.85	2.41 ± 0.31	<0.001
SHBG nmol/l, mean ± SD	34.40±12.33	55.62±17.15	<0.001
DEHEA µg/dl, mean ± SD	169.27±64.18	151.87±41.69	0.02

The mean level of LDL was (133.42±29.65 mg/dL) in the PCOS group while (130.32±27.13 mg/dL) in the control cluster, the mean level of HDL was (44.16±8.43 mg/dL) in the PCOS group, and (54.12±11.09mg/dL) in the control group, mean TG level was (141.01±22.57 mg/dL) in PCOS while (94.87±16.03 mg/dL) in the control group, and mean

level of cholesterol was (162.70±15.13 mg/dL) in PCOS group and (161.20±13.23 mg/dL) in control group. No major variance between two clusters regarding LDL and serum cholesterol ($P \geq 0.05$). At the same time, HDL and TG were significantly different in PCOS compared to control, as illustrated in Table 3.

Table 3: Lipid profile of PCOS cases and control group

Group	PCOS	Control	<i>P-value</i>
Number	96	96	-
LDL (mg/dL), mean ± SD	133.42±29.65	130.32±27.13	0.4
HDL (mg/dL), mean ± SD	44.16±8.43	54.12±11.09	<0.001
TG (mg/dL), mean ± SD	141.01±22.57	94.87±16.03	<0.001
Cholesterol (mg/dL), mean ± SD	162.70±15.13	161.20±13.23	0.4 Ns

The Mean value of Spexin was (2.7±0.3 ng/mL) in the PCOS group, while it was (3.5±0.7 ng/mL) in the

control cluster; this level showed that there was considerably decreased in PCOS compared to control, as illustrated in Fig.1.

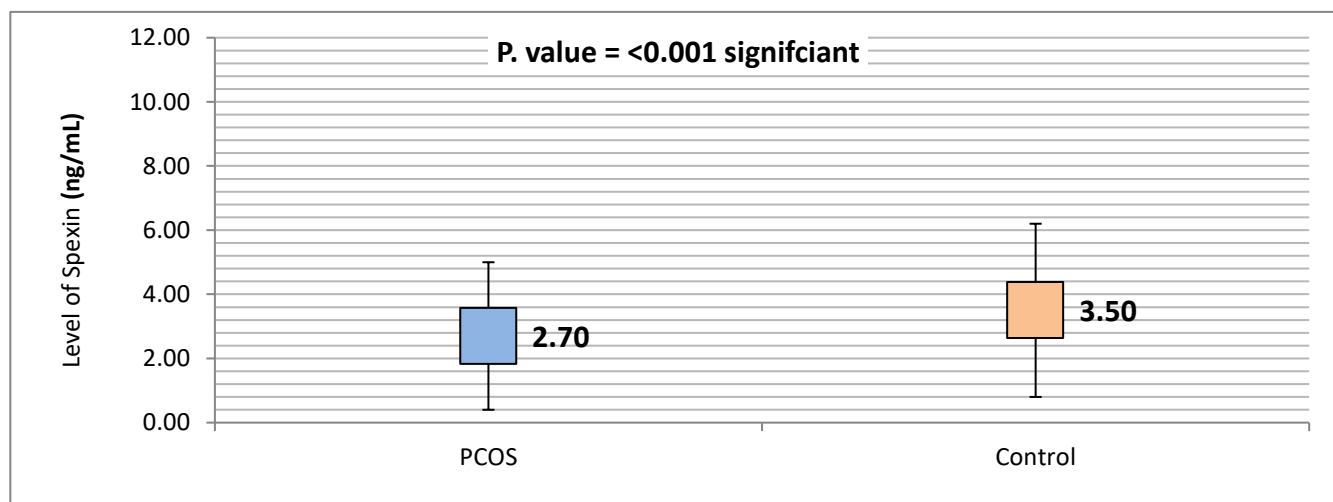


Figure 1: Distribution of serum levels of Spexin (ng/ml) in both PCOS patients & controls

There was no significant association between spexin hormone with age (P-value= 0.210), While inverse significant correlation with BMI (P-value =0.027), moreover waist: hip ratio shows considerable association with spexin level in patients group (P-value= 0.027), FBS shows significant association with negative, weak correlation with spexin in patients (P-value= 0.005), Insulin shows

significant association with negative, weak correlation with Spexin in patients (P-value= 0.04), while HOMA-IR shows significant association with negative, weak correlation with Spexin in patients (P-value= 0.003).and there is no association between Spexin with LDL, HDL, TG, and cholesterol. All these are shown in Table 5.

Table 5: Correlation between spexin hormone and metabolic assay in the PCOS group

Variables	Spexin	
	PCOS	
	(r)	P-value
Age (years)	0.190	0.210
BMI (kg/m ²)	-0.252	0.027
Waist: hip ratio	-0.237	0.020
FBS (mg/dL)	-0.231	0.005
Insulin	-0.338	0.04
HOMA-IR	-0.294	0.003
LDL (mg/dL)	-0.088	0.565
HDL (mg/dL)	0.268	0.3
TG (mg/dL)	-0.141	0.38
Cholesterol (mg/dL)	-0.143	0.349

Table 6 showed no significant correlation between Spexin and hormonal assay (FSH, E2, and progesterone) in patients with PCOS. At the same

time, Spexin had a significant correlation with LH, SHBG, testosterone, FAI, and DEHEA but with a negative, weak correlation (r <0.4) except for SHBG, with a weak positive correlation.

Table 6: The correlation between Spexin with the hormonal assay in PCOS

Variables	Spexin	
	PCOS	
	(r)	P-value
FSH	0.06	0.121
LH	-0.202	0.03
Estradiol	-0.117	0.8
Progesterone	0.17	0.36
SHBG	0.147	0.03
Testosterone	-0.342	0.004
FAI	-0.199	0.02
DEHEA	-113	0.05

Discussion

New biochemical markers are identified in patients with PCOS. In a study carried out by Ehrmann DA et al., 2006 in which Twenty-six (6.6%) subjects had diabetes; among the 368 nondiabetics, it mentioned that Hypothalamic-pituitary-ovarian axis dysfunction plays a crucial part in the progress of the disease, however the specific mechanism character is not entirely agreed so far (13). This alliance is chiefly controlled via reaction contrivances by gonadal steroids. It is understood that spexin shows a part in regulating the hypothalamic-pituitary-ovarian axis via the downregulation of Luteinizing hormone excretion (43). We found the mean insulin level in the PCOS set was (15.12±3.63) and (10.6±3.29) in the control cluster, and the mean HOMA-IR level in the PCOS cluster was (3.15±0.09) and (2.07±0.08) in the control cluster, Insulin and HOMA-IR were expressively greater in PCOS matched to controller (p-value < 0.001). This finding is in agreement with Behboudi-Gandevani et al., 2016 in a cohort of 754 reproductive-aged females, comprising 704 eumenorrheic non-hirsute patients and 50 PCOS ladies choose agreeing to the national institutions of health's (NIH) principles in which HOMA-IR (2.22 vs. 1.74, p-value = 0.017) (44). Moreover, Temur et al., 2016 when Fifty-two women with PCOS and 55 well females were involved in the study, accorded for oldness and body mass index (45). A significant difference was found in HOMA-IR between the studied groups (2.40±1.44 vs 1.37±1.10, p-value = 0.001). Also, this is in agreement with Ates et al., 2018 Subjects (n = 77) were categorized into two sets: oligomenorrhea (O) and clinical and biochemical hyperandrogenism (HA) (n = 38), without PCO and O + HA with PCO (n = 39). The control set comprised of 33 age-matched pubescent with HOMA-IR (3.54 ± 2.72 vs 5.02 .025, p-value = 0.011) [46], and These studies and the current

findings indicate that PCOS is related to insulin resistance (IR) and an increased IR is present in PCOS. In the present study, all lipid parameters (TG and HDL) were expressively variance in PCOS, and HDL was considerably lower in PCOS matched to control; these findings are consistent with several studies such as González A et al. study in 2011 in which a total of 117 subjects were enrolled. Of these, 93 females with IR were compared against 24 females without IR. Raised TGL/HDL ratio was noticed in 89 (61.4%) and 12 (38.6%) subjects with and without IR, correspondingly. The high TGL/HDL ratio was considerably linked to IR (OR 2.64, 95% CI = 1.12-6.29) (47). The most critical finding in this study was a important decrease in levels of spexin in the PCOS cluster than in the control cluster. This is the same as that mentioned by Ilhan GA 2018 in a Turkish study; 120 females with PCOS and 50 age and body mass index (BMI) harmonized healthy panels were joined. Clinical, hormonal, and metabolic considerations and serum spexin levels were matched between the clusters. This study was carried out to demonstrate the levels of spexin in females suffering from PCOS. And he revealed a significant decrease in Spexin levels in the patient's set paralleled with the average healthy respondents in the control group, with no differences in baseline criteria, lipid profile (except for triglyceride levels), HOMA-IR, and unrestricted androgen index in both groups. But in Ilhan GA 2018 study, significant differences were found according to Waist to hip ratio and triglyceride levels. Spexin levels were clearly interrelated with HDL and depressingly interrelated with HOMA-IR in women with PCOS (50,51,52). Moreover, in Beyazit F et al (49), in their study determined 91 women with PCOS and 86 well controls found that spexin concentration did not differ significantly between patients and controls. It is of pronounced worth since there is no study in literature describing the part of spexin in

PCOS patients. Also, Beyazit F et al. do not agree with this study as they cannot detect any link between flowing spexin and other metabolic or hormonal features, comprising body structure or IR (49). Chen et al. 2019, considered the ranks of serum SPX in 40 fat and 32 average-weight adolescent children and found that Spexin levels were considerably diminished in fat teen-agers matched to controls. Additionally, serum SPX ranks were lesser in IR-fat individuals than in non-IR-fat individuals. Serum SPX amounts connected deleteriously and considerably with triglycerides, systolic blood pressure, diastolic blood pressure, fasting insulin level, HOMA-IR, insulinogenic index, and HOMA- β levels in fat kids (50). Similarly Al-Daghri et al found in their study which comprised 124 contributors Established that small serum ranks of the marker are somewhat correlated with parts of metabolic disorder (51). Further analysis of spexin in PCOS patients with baseline characteristics and metabolic assay shows a significant correlation with BMI. In contrast, for Waist: hip ratio, FBS, Insulin, and HOMA-IR show substantial association with a negative, weak correlation with spexin in patients. This result was comparable to a recent study by Guler A, 2021 when 160 women were joined in the case-control study, 80 PCOS women, and 80 age- and body mass index (BMI) accorded topics with regular menstrual cycles. The selected women were between 18- and 45-year-old; they revealed a significant decrease of markers in the case cluster than that in the control cluster in addition to converse link between spexin and insulin resistance, BMI, while for Waist: hip ratio, FBS, Insulin, and HOMA-IR in females with PCOS (52). In addition to that, Ilhan GA concluded that women with polycystic ovaries have Spexin levels confidently associated with HDL levels and deleteriously with HOMA-IR (48).

Conclusion

Serum level of Spexin hormone was considerably

decreased in ladies with PCOS than in non-PCOS women with an inverse significant correlation with BMI, Waist: hip ratio, FBS, Insulin, and HOMA-IR. While no association was found between spexin with LDL, HDL, TG, and cholesterol. Spexin has a significant correlation with LH, SHBG, testosterone, FAI, and DEHEA.

Recommendations

A multicenter study may be recommended with investigations to identify the effect and relationship between spexin and PCOS

As well as follow up the patients and reevaluate Spexin level after treatment of PCOS.

Source of funding

No source of funding

Ethical clearance

Official approval has been obtained to use data and data were analyzed without the names to protect privacy. This study was conducted according to the approval of College of Medicine/ University of Diyala and in accordance with the ethical guidelines of the Declaration of ethical committee of the College (Document no. 2023RFS786).

Conflict of interest

The author acknowledges no conflict of interest in this study

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علاقة مستويات سبيكسين مع الاضطرابات الهرمونية والتمثيل الغذائي لدى النساء المصابات بمتلازمة المبيض المتعدد الكيسات

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الملخص

الخلفية الدراسية: متلازمة المبيض المتعدد الكيسات تصيب حوالي ٥-١٥٪ من الإناث. تم التعرف حديثاً على سبيكسين، الذي تم تحديده على أنه neuropeptide Q، من خلال طرق المعلوماتية الحيوية.

الهدف من الدراسة: تقييم العلاقة بين مستويات سبيكسين والاضطرابات الهرمونية والتمثيل الغذائي لدى النساء المصابات بمتلازمة المبيض المتعدد الكيسات.

طرق العمل: دراسة الحالات والشواهد التي أجريت في قسم أمراض النساء والتوليد في مدينة الإمامين الخادمين الطبية / بغداد، من ١ كانون الثاني (يناير) ٢٠٢٢ إلى ٣١ كانون الأول (ديسمبر) ٢٠٢٢. في الدراسة الحالية، ١٩٢ مشاركاً تتراوح أعمارهم بين ١٨-٤٥ عاماً وتخصيصها لمجموعة حالة (٩٦ امرأة مصابة بمتلازمة تكيس المبايض) ومجموعة مراقبة (٩٦ امرأة بدون متلازمة تكيس المبايض).

النتائج: متوسط قيمة سبيكسين كان (٠,٣±٢,٧ نانوجرام/مل) في مجموعة متلازمة تكيس المبايض، بينما كان (٠,٧±٣,٥ نانوجرام/مل) في مجموعة التحكم. يُظهر سكر الدم الصائم ارتباطاً كبيراً مع ارتباط سلبي ضعيف مع سبيكسين في المرضى (قيمة $P=0.005$)، ويظهر الأنسولين ارتباطاً كبيراً مع ارتباط عكسي مع سبيكسين في المرضى (قيمة $P=0.04$)، وتقييم نموذج التوازن لمقاومة الأنسولين (يُظهر HOMA-IR) ارتباطاً كبيراً مع الارتباط العكسي مع سبيكسين في المرضى (القيمة $P=0.003$). كان لدى سبيكسين علاقة عكسية كبيرة مع LH، SHBG، التستوستيرون، FAI، و Dehydroepiandrosterone.

الاستنتاجات: انخفض مستوى سبيكسين في الدم بشكل ملحوظ لدى المرضى الذين يعانون من متلازمة تكيس المبايض مقارنة بالنساء الأصحاء. **الكلمات المفتاحية:** متلازمة تكيس المبايض، سبيكسين، هرموني، اضطراب التمثيل الغذائي.

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