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ORIGINAL ARTICLE

Association of Spexin with Metabolic and Reproductive Features of Polycystic Ovary Syndrome in Women with Eating Disorders

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Background Polycystic ovary syndrome (PCOS) is connected with metabolic, reproductive, and psychiatric disorders such as depression, anxiety and eating disorders (ED). Gonadotropin-releasing hormone secretion is regulated by neurohormones, such as spexin (SPX). This study aimed at assessing the serum level of SPX in women with PCOS and to evaluate its association with eating disorders, metabolic and reproductive features.

Subjects and Methods A case control study was conducted on 80 women; 40 women with PCOS and 40 healthy women as a control group. Serum SPX was assessed by an enzyme-linked immune absorbent assay. Depression, anxiety and ED were assessed using the Structured Clinical Interview for DSM-IV-TR axis I disorders, Hospital Anxiety and Depression scale and Eating Disorder Examination Questionnaire.

Results Serum SPX values were lower in the PCOS group (0.62±0.312) compared to the control group (1.16±0.49, P <0.001). The prevalence of ED among PCOS group was 32.5% (n= 13) vs 15% in the control group (n= 6) with binge eating disorder (BED) having the highest prevalence of ED among patients with PCOS. PCOS women with ED had lower values of SPX compared to PCOS women without ED (0.532±0.275 vs. 0.747±0.33, respectively, P <0.001). There were significant negative correlations between serum SPX and phenotypic features of the PCOS group, as well as ED parameters. BMI, depression, and anxiety scores were independently correlated with SPX level in the PCOS group.

Conclusions PCOS is associated with metabolic and eating disorders in particular BED. SPX levels were significantly lower in PCOS women and ED and inversely associated with metabolic, reproductive, and eating disorders.

Keywords BED, Eating disorders, Metabolic, PCOS, Reproduction, Spexin.
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INTRODUCTION

The prevalence of polycystic ovary syndrome (PCOS) is estimated to be about 21% in women of reproductive age. PCOS is a multisystem reproductive metabolic disease. Striking evidence of crosstalk between metabolic and reproductive disorders in the pathogenesis of PCOS, though, no single feature is a requisite for the diagnosis (Teede *et al.,* 2018).

In the last decades, multiple, though sparse, evidence has accumulated suggesting that many conventional cardiometabolic and infertility disorders are linked to

PCOS in addition to psychiatric disorders, such as anxiety, depression, and eating disorders (ED) (Lee *et al.,* 2019).

It is noteworthy to mention that ED are characterized by binge eating behaviors, such as bulimia nervosa (BN) and binge eating disorder (BED) which had the highest prevalence according to previous research (Lee *et al.,* 2019).

Spexin (SPX) is a neuropeptide that is expressed all over the body's organs and tissues (Gu *et al.,* 2015). Despite these pieces of evidence, there is a substantial disparity in our experience about the physiological role of SPX in adipose tissue. In a recent comprehensive study, Walewski *et al.* detected lower expression of SPX in adipose tissue (Walewski *et al.,* 2010).

There is a known association between SPX and energy homeostasis, which is mostly associated with obesity. These observations are confirmed by accumulating studies that reported that SPX could play important roles in the pathogenesis of metabolic disorders and reproductive dysfunctions (Ma *et al.,* 2018).

Neuropeptide dysregulation and ED are frequently associated with each other. However, it remains unclear whether these correlations influence the association between PCOS and ED. Therefore, we aimed in the current study to estimate the level of serum SPX in PCOS. Also, to estimate its correlation with the eating pattern, metabolic features, and reproductive PCOS phenotypes.

SUBJECTS AND METHODS

Eighty subjects were recruited in the current research consecutively; of those forty were women with PCOS and the remaining forty were body mass index (BMI) and age matched as a control group. The flowchart of the study, inclusion and exclusion criteria are described in Fig. 1.

PCOS diagnosis was done according to the Rotterdam criteria (Rotterdam ESHRE/ASRM Sponsored PCOS Consensus Workshop Group, 2004). The diagnosis of depression, anxiety, and eating disorders was based on the Arabic version of the Structured Clinical Interview for DSM-IV-TR axis I disorders (First, 1997; El Missiry *et al.,* 2003), the Arabic version of the Eating Disorder Examination Questionnaire (EDE-Q) (Fairburn and Beglin, 1994; El-Bakry *et al.,* 2018). And the Arabic version of Hospital Anxiety and Depression scale (Zigmond and Snaith, 1983; Terkawi *et al.,* 2017).

Menstrual history, clinical examination, and history taking were reported from all participants. This study was approved by the Institutional Review Board and all participants were assigned informed agreement before their inclusion in the study.

Biochemical tests

Blood samples were taken from all participants during the early follicular phase of the menstrual cycle and were done according to operating procedures in Zagazig university hospital laboratories.

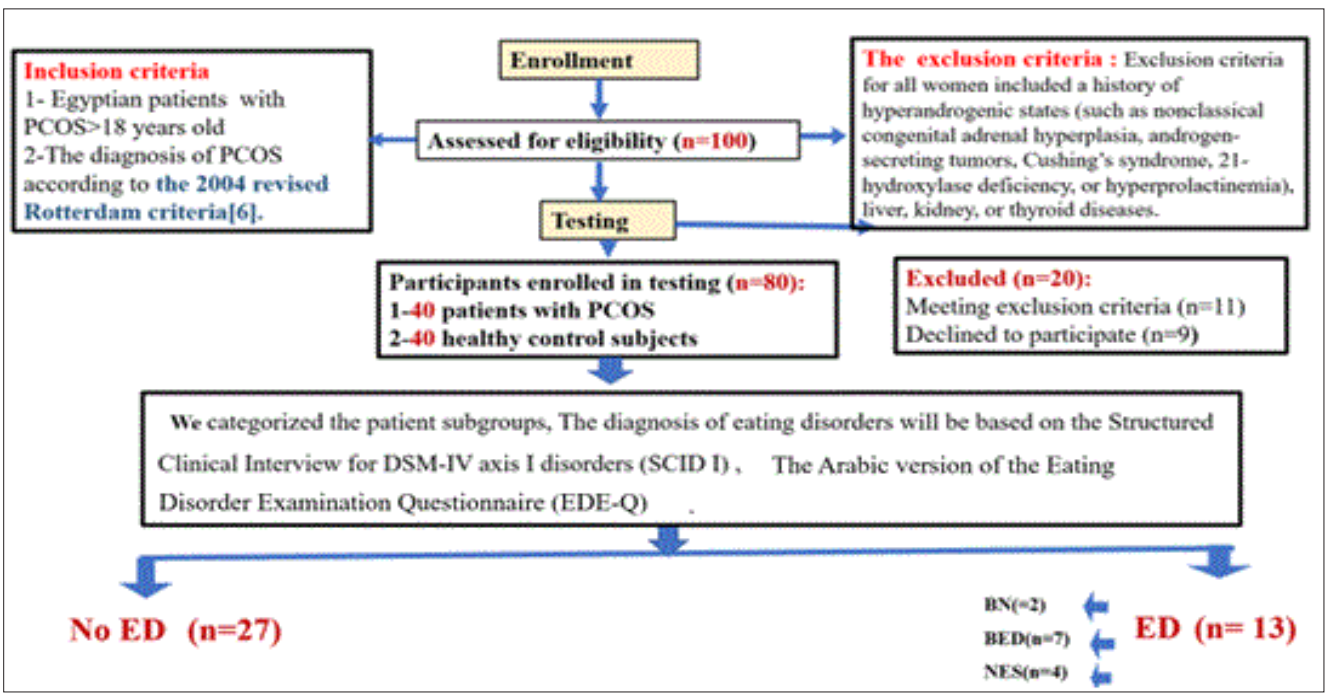

Figure 1: Flowchart of the study, inclusion and exclusion criteria.

Assessment of serum Spexin

Serum SPX concentrations were assessed by ELISA technique using a kit supplied by (Bioassay Technology Laboratory, China, Cat. No E3507Hu) permitting the manufacturer's directions.

Statistical analysis

All statistical analyses were performed SPSS 26, and P <0.05 was considered statistically significant.

Ethical consideration

The study was approved by the Zagazig University institutional review board (IRB no. 10236/22-12-2022), assuring that this study was conducted according to the ethical guidelines outlined in the Declaration of Helsinki. Informed consent was obtained from all participants.

RESULTS

The characteristics of the studied participants

There were statistically significant differences between studied groups regards metabolic, reproductive features (Table 1). Among PCOS women, the total number of PCOS women with ED according to DSM-IV-TR criteria, was 13 patients; two women had BN, seven women had BED and four women had night eating syndrome (NES). Regards the control group the total number of women with ED was six patients; one woman had BN, three women had BED and two women had night eating syndrome. Regarding the EDE-Q subscales; global scale, restraint subscale, shape concern subscale, weight concern subscale, and eating concern subscale, there were statistically significant differences between cases and control groups. In addition, regarding the scores of anxiety and depression, there was statistically significant differences between the studied groups, (P <0.05) (Table 2).

The characteristics of the PCOS women

Among PCOS groups (n= 40), patients with ED (N= 13) had significantly higher values of metabolic and reproductive disorders in the form of hirsutism score, BMI, waist/hip ratio, ovarian volume, AFC, total cholesterol, triglycerides, LDL, fasting plasma glucose, luteinizing hormone, dehydroepiandrosterone-sulphate (DHEA-S), androstenedione, total testosterone compared to PCOS patients without ED (n= 27), (P <0.05) (Table 3).

Comparison of serum spexin in studied groups

The current study detected that woman with PCOS had significantly lower values of serum SPX (ng/mL) (0.62±0.312) compared to controls (1.16±0.49) (P <0.001) (Table 1). Interestingly, PCOS women with ED had significantly lower values of serum SPX (ng/mL) (0.532±0.275) compared to PCOS women without ED (0.747±0.33), (P <0.001*) (Fig. 2).

Correlation between serum spexin, clinical, metabolic features among PCOS patients

Interestingly we observed in the current research that among the PCOS group, there were significant negative correlations between serum SPX and hirsutism score, BMI, ovarian volume, AFC, triglycerides, and FPG, as well as the scores of anxiety and depression (P <0.05) (Table 4).

Linear regression analysis

To increase the reliability of the present study, we applied Linear regression, and we detected that BMI, and depression scores were independently associated with serum SPX (P <0.05) (Table 5).

The accuracy of serum spexin for differentiating PCOS women

To evaluate the power of serum SPX we used the ROC test. The area under the curve (AUC) was 0.881(95% CI= 0.812–0.951) with sensitivity= 83.3%, specificity= 95%, and the cutoff values (0.749), (P <0.05) (Fig. 3).

The accuracy of serum spexin for distinguishing ED from the other group among PCOS women

Interestingly we observed that the AUC of SPX was 0.865 (95% CI= 0.787–0.944) with sensitivity= 92.3%, specificity= 65%, and cutoff values (0.587), (P <0.05) (Fig. 4).

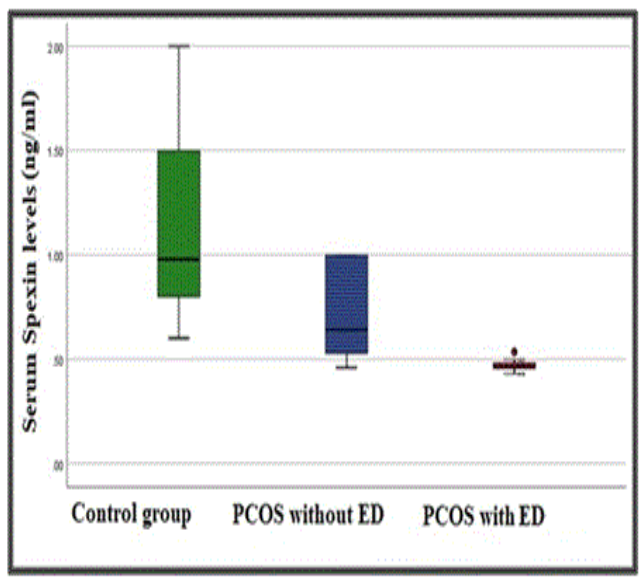

Figure 2: Comparison between the studied groups regarding serum spexin levels.

Table 1: Clinical and laboratory characteristics of the studied groups:

	PCOS patients (mean±SD) (*n*= 40)	Control group (mean±SD) (*n*= 40)	*P* value
Age (years)	28.7±6.9	29.2±5.96	0.962
Infertility	10(25%)	0(0%)	<0.001*
Primary	4(10%)	0(0%)	
Secondary	6(15%)	0(0%)	
Systolic blood pressure (mmHg)	132.6±9.3	125.4±2.16	<0.001*
Diastolic blood pressure (mmHg)	88.5±6.9	80.6±5.96	<0.001*
Hirsutism score	11.41±4.2	5.38±0.594	<0.001*
Body mass index (kg/m^2)	37.2±5.731	23.9±2.48	<0.001*
Waist/hip ratio	1.26±0.28	0.98±0.191	<0.001*
Ovarian volume	9.35±3.744	3.58±0.612	<0.001*
AFC	15.35±3.74	7.58±2.612	<0.001*
Total cholesterol (mg/dl)	185.0±124.7	167.5±19.26	<0.001*
Triglycerides (mg/dl)	221.2±42.05	144.55±20.4	<0.001*
LDL cholesterol (mg/dl)	175.8±18.11	106.24±4.24	<0.001*
HDL cholesterol (mg/dl)	40.3±9.42	57.5±7.33	<0.001*
Fasting plasma glucose (mg/dl)	119.3±15.61	83.9±8.40	<0.001*
FSH (mIU/ml)	3.9±1.51	3.6±0.91	0.117
LH (mIU/ml)	9.97±2.53	4.52±1.21	<0.001*
LH/FSH	1.8±0.39	1.1±0.43	<0.001*
DHEA-S (mg/ml)	5.3±1.27	1.89±0.21	<0.001*
Androstenedione (ng/ml)	2.5±0.35	1.44±0.14	0.015
Total testosterone (ng/ml)	0.92±0.41	0.50±0.145	<0.001*
Serum spexin (ng/ml)	0.62±0.312	1.16±0.49	<0.001*

AFC: antral follicle cells; DHEA-S: dehydroepiandrosterone sulphate; FSH: follicle stimulating hormone; LH: luteinizing hormone; *: Statistical significance where *P* <0.05.

Table 2: Eating disorders, depression and anxiety among the studied groups:

	PCO patients (mean±SD) (*n*= 40)	Control group (mean±SD) (*n*= 40)	*P* value
Eating disorders			
All ED diagnoses	13(32.5%)	6(15%)	<0.001*
AN	0(0%)	0(0%)	<0.001*
BN	2(5%)	1(2.5%)	<0.001*
BED	7(17.5%)	3(7.5%)	<0.001*
NES	4(10%)	2(5%)	<0.001*
Prevalence of abnormal EDE-Q score			
Global Scale	8(20%)	1(2.5%)	<0.001*
Restraint Subscale	5(12.5%)	1(2.5%)	<0.001*
Shape Concern Subscale	25(62.5%)	5(12.5%)	<0.001*
Weight Concern Subscale	14(35%)	4(10%)	<0.001*
Eating Concern Subscale	4(10%)	1(2.5%)	<0.001*
HADS scores			
Anxiety	9.55±4.76	6.81±3.56	<0.001*
Depression	4.39±3.59	3.64±3.21	<0.001*

AN: anorexia nervosa; BED: binge eating disorder; BN: bulimia nervosa; ED: Eating Disorders; EDE-Q: Eating Disorder Examination Questionnaire; HADS: Hospital Anxiety and Depression scale; NES: night eating syndrome; *: Statistical significance where *P* <0.05.

Table 3: Clinical and laboratory characteristics of the PCOS group with and without ED:

	PCO patients without ED (*n*= 27)	PCO patients With ED (*n*= 13)	*P*
Age (years)	28.3±5.16	29.3±4.3	0.783
Infertility	2(7.4%)	8(61.5%)	<0.001*
Primary	1(3.7%)	3(23.1%)	<0.001*
Secondary	1(3.7%)	5(38.4%)	<0.001*
Systolic blood pressure (mmHg)	131.4±4.16	133.6±6.3	0.181
Diastolic blood pressure (mmHg)	88.4±4.4	88.5±5.5	0.942
Hirsutism score	8.47±2.4	12.51±4.2	<0.001*
Body mass index (kg/m^2)	31.9±1.5	38.2±6.72	<0.001*
Waist/hip ratio	1.21±0.191	1.32±0.38	<0.001*
Ovarian volume	8.58±3.612	10.35±6.73	<0.001*
AFC	14.58±2.7	22.35±2.92	<0.001*
Total cholesterol (mg/dl)	157.5±19.26	195.0±124.7	<0.001*
Triglycerides (mg/dl)	184.55±20.4	233.2±52.05	<0.001*
LDL cholesterol (mg/dl)	106.24±44.5	175.8±68.3	<0.001*
HDL cholesterol (mg/dl)	44.5±7.33	38.3±9.42	<0.001*
Fasting plasma glucose (mg/dl)	93.9±15.3	129.3±12.5	<0.001*
FSH (mIU/ml)	4.52±1.6	4.1±1.3	0.523
LH (mIU/ml)	8.11±2.6	10.23±3.1	<0.001*
LH/FSH	1.7±1.34	2.2±1.33	<0.001*
DHEA-S (mg/ml)	4.89±0.4	6.3±1.4	<0.001*
Androstenedione (ng/ml)	2.1±0.22	2.6±0.44	0.015
Total testosterone (ng/ml)	0.71±0.23	0.94±0.4	<0.001*

AFC: antral follicle cells; DHEA-S: dehydroepiandrosterone sulphate; FSH: follicle stimulating hormone; LH: luteinizing hormone; *: Statistical significance where *P* <0.05.

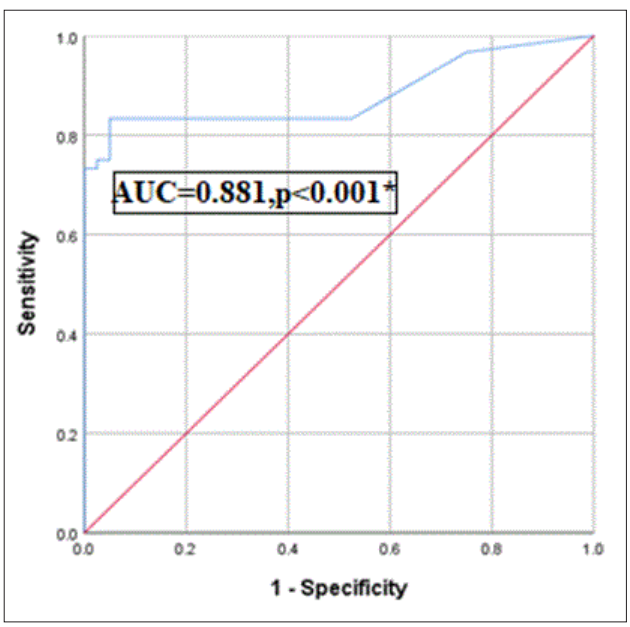

Figure 3: The accuracy of serum spexin for differentiating PCOS women from the control group by ROC curves.

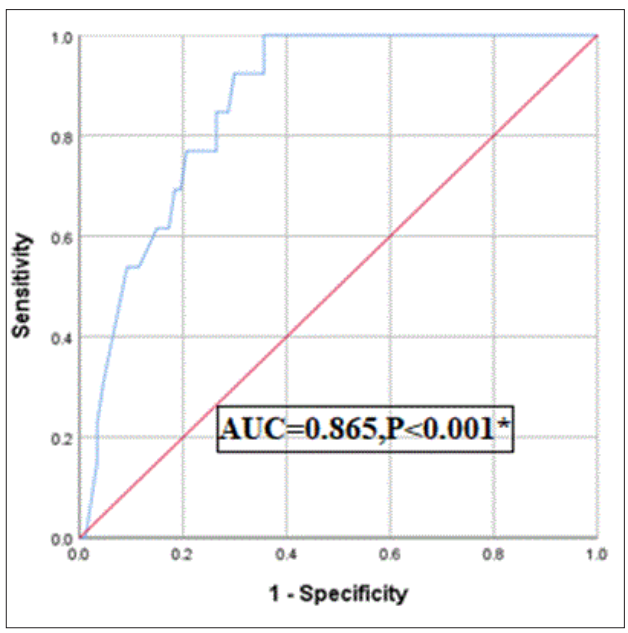

Figure 4: The accuracy of serum spexin for differentiating PCOS women from the control group by ROC curves.

Table 4: Pearson correlation of serum spexin levels with clinical, anthropometric as well as biochemical characteristics in studied subjects:

	Serum spexin levels	
Characteristics	***r***	***P***
Hirsutism score	−0.469	<0.001*
Body mass index (kg/m^2)	−0.583	<0.001*
Waist/hip ratio	−0.611	<0.001*
Ovarian volume	−0.484	<0.001*
AFC	−0.475	<0.001*
Total cholesterol (mg/dl)	−0.189	0.147
Triglycerides (mg/dl)	−0.475	<0.001*
LDL cholesterol (mg/dl)	−0.061	0.643
HDL cholesterol (mg/dl)	0.226	0.082
FPG (mg/dl)	−0.721	<0.001*
Total testosterone (ng/ml)	−0.098	0.456
LH (mIU/ml)	−0.271	0.036
DHEA-S (mg/ml)	−0.190	0.145
Androstenedione (ng/ml)	−0.207	0.112
HADS score		
Anxiety	−0.452	<0.001*
Depression	−0.527	<0.001*

AFC: antral follicle cells; DHEA-S: dehydroepiandrosterone sulphate; FPG: fasting plasma glucose; HADS: Hospital Anxiety and Depression scale; LH: luteinizing hormone; *: Statistical significance where P <0.05.

DISCUSSION

A growing number of studies reported that endocrine and metabolic dysfunction can influence the phenotypic features of PCOS (Dumesic *et al.,* 2015; Trikudanathan, 2015; Patel, 2018). Several pieces of evidence have revealed that PCOS progression is connected to hyperandrogenemia, which leads to ovulatory dysfunction and dysregulation of luteinizing hormone and Gonadotropin-releasing hormone secretion (Trikudanathan, 2015).

As expected, the current study detected those women with PCOS had a higher prevalence of ED in comparison to the control group, in the form of global scale, restraint subscale, shape concern subscale, weight concern subscale, and eating concern subscale.

A similar prevalence was observed in Cesta *et al.* research as their results revealed that women with PCOS and their first-degree relatives had higher risks for a range of psychiatric disorders than the general population thus it was suggested that genetic predisposition could be the link between PCOS and psychiatric disorders (Cesta *et al.,* 2016). Dokras *et al.* (Dokras *et al.,* 2011). and Hollinrake *et al.* (Hollinrake *et al.,* 2007). observed similar results.

The results of the current study demonstrated that PCOS is associated with higher scores of anxiety and depression than the control group. Also, similar results were described by Barry *et al.* (Barry *et al.,* 2011). There is a lot of evidence that obesity-associated disfigurement contributes to the increased risk of mood disorders among women with PCOS (Garner, 1981).

The results of the current study demonstrate that concerning the prevalence of ED among PCOS women, the total number of PCOS women with ED was 13 patients (32.5%). Unsurprisingly, BED had the highest prevalence of ED among patients with PCOS. Similarly, reports by Bernadett and Szemán observed that about 21% of PCOS patients had ED (Bernadett, 2016). The interesting findings of Lee *et al.* study detected that ED with PCOS were more than four times those without PCOS (Lee *et al.,* 2017).

The important result of the current research, PCOS had significantly lower values of serum SPX values compared to controls. The results presented here show that there were significant negative correlations between serum SPX and metabolic as well as reproductive phenotypic features of the PCOS group. Even more importantly, BMI, anxiety and depression scores were independently correlated with serum SPX in the PCOS group.

Table 5: Linear regression analyses in PCOS women to test the influence of the main independent variables against serum spexin levels (dependent variable):

	Unstandardized Coefficients		Standardized Coefficients			95% CI	
Model	**B**	**SE**	**Beta**	***t***	***P* value**	**Lower Bound**	**Upper Bound**
1							
Constant	2.497	0.461		5.421	0.000	1.583	3.412
Hirsutism	−0.002	0.002	−0.181	−1.394	0.169	−0.006	0.001
BMI	0.009	0.004	0.343	2.126	<0.05*	0.000	0.017
TG	−0.026	0.009	−0.332	−2.776	0.007	−0.044	−0.007
AFC	0.006	0.005	0.217	1.251	0.216	−0 .004	0.016
Depression score	−0.013	0.004	−0.397	−3.479	<0.001*	−0.021	−0.006

*: Statistical significance where P <0.05.

In agreement with our study, Goler and Demir detected that SPX values were considerably decreased in PCOS women and negatively correlated with insulin resistance, BMI, and androgens (Guler and Demir, 2021). In line with this, a recent Egyptian study detected that serum SPX levels were significantly lower in obese diabetic patients (Mashaal *et al.,* 2022).

Though some reports are controversial, Beyazit *et al.* detected that SPX levels did not differ among PCOS in comparison to healthy controls. They contributed their finding to the theory that SPX is secreted from adipose tissue, so obesity is associated with a higher level of SPX than with normal body weight (Beyazit *et al.,* 2021).

To determine the potentially important role of serum SPX in the pathogenesis of ED and we discovered that SPX values were considerably lower in PCOS women with ED in comparison to PCOS women without ED and negatively correlated with anxiety and depression.

A growing body of evidence has corroborated that serum SPX levels affect body weight and feeding behavior (Zheng *et al.,* 2017; Tian *et al.,* 2020). On the contrary, Suhs *et al.* found no correlation between anorexia nervosa (AN) and SPX level (Suhs *et al.,* 2022). This difference between our study and Suhs *et al.* could be contributed to that according to the current study there were no patients diagnosed with AN.

To better understand the potency and diagnostic power of serum SPX, the sensitivity and specificity of serum SPX were tested, and it was detected to be (83.3% and 95%, respectively) in the diagnosis of PCOS and (92.3% and 65%, respectively) in differentiating ED from another group without ED. Thus, SPX could be a useful diagnostic test to distinguish PCOS, as well as ED from other groups.

CONCLUSION

The results of this study proved that PCOS is not only associated with reproduction but also is associated with critical metabolic and psychological health risks. BED was the highest prevalent ED among the studied sample. Serum SPX levels were significantly lower in PCOS women in particular with associated eating disorders.

ACKNOWLEDGEMENTS

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Availability of data: The data displayed in this study could be available from the corresponding author upon reasonable request.

Authors' contributions: NMR was responsible for the conceptualization and design of the research proposal. NMR, DAS, HAS, WME, MAF, DRI and SAS helped with the collection and analysis of data, and interpretation of results. NMR, DAS and WME contributed to writing the original manuscript, final editing and revision process. All authors have collectively approved the final draft.

Ethical considerations: The study protocol was approved by the Zagazig University institutional review board (IRB no. 10236/22-12-2022), assuring that this study was conducted according to the ethical guidelines outlined in the Declaration of Helsinki. After discussing the study objectives, and confirming confidentiality, written consent was obtained from all participants.

FINANCIAL SUPPORT AND SPONSORSHIP

Nil.

CONFLICTS OF INTEREST

There are no conflicts of interest.

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