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Elevated circulating level of xenopsin related 1-are associated with PCOS (Polycystic Ovarian Syndrome)

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Abstract
Background: Polycystic ovary syndrome is a common metabolic and endocrine disorder affecting 6 to 21% of reproductive aged women depending on population, mean body mass index and diagnostic criteria used. High prevalence is rates seen in women whom are overweight or have an Indigenous or Asian background. Xenin is a peptide hormone produced by a subpopulation of chromogranin A-positive endocrine cells in the mucous membrane of the duodenum. In humans, xenin circulates in the blood plasma.
Aim of the study: To determine the role of xenopsin level in polycystic ovarian syndrome.
Patients and methods: Observational case control study, conducted in Salah Aldin general hospital in Obstetrics and gynecological department, from (the first of Fab 2018 to the end of Dec. 2018). 40 patients with PCOS and 40 healthy women were included in the study.
Results: the mean age of PCOS group was 29±2.30 years and 28±7.20 years for control group. Sensitivity of the test to diagnose the PCOS were (88.0%), the specificity (89.0%), positive predictive value (86.0%), negative predictive value (84.0%) and the accuracy of the test to diagnose the PCOS was (88.6%).
Conclusion: Highly significant increase in Xenopsin level in PCOS group than that in control group.

Keywords: Polycystic ovary syndrome, Xenopsin, menstrual dysfunction, infertility

Introduction
Polycystic ovary syndrome (PCOS) is a common metabolic and endocrine disorder affecting 6 to 21% of reproductive aged women depending on population, mean body mass index (BMI) and diagnostic criteria used. High prevalence is rates seen in women whom are overweight or have an Indigenous or Asian background. [1]
The features of PCOS, including menstrual dysfunction, infertility and hirsutism have been described in medical records for more than 2,000 years. [2] The syndrome was officially recognised in the 1930's by Stein and Leventhal who associated polycystic ovaries (PCO) to the clinical features of menstrual dysfunction, infertility, hirsutism and obesity. Since the 1980's, researchers expanded on these observations to report an association between hyperinsulinaemia and hyperandrogenism bringing to light possible etiologies and a complicated metabolic and reproductive condition with psychosocial and economic consequences across the lifespan. These ground-breaking studies also caused great debate as to whether insulin resistance (IR) is a unique feature of PCOS contributing to clinical features and health consequences. [3]

Xenin
Xenin is a peptide hormone produced by a subpopulation of chromo-granin A-positive endocrine cells in the mucous membrane of the duodenum. The peptide has been found in humans, dogs, pigs, rats, and rabbits**.** In humans, xenin circulates in the blood plasma. There is a relationship between peaks of xenin concentration in the plasma and the third phase of the Migrating Motor Complex. For example, infusion of synthetic xenin in fasting volunteers will cause phase III activity. After a meal (the 'postprandial state'), infusion of xenin increases both frequency and the percentage of aborally propagated contractions. In higher concentrations xenin stimulates exocrine pancreatic secretion and inhibits the gastrin-stimulated secretion of acid in dogs. Xenin is also produced in neuroendocrine tumors of the duodenal mucosa. [3]

Structure and sequence
Xenin is a 25-amino acid polypeptide. The amino acid sequence of xenin is identical to the N-

terminal end of cytoplasmic coatomer subunit alpha, from which xenin can be cleaved by aspartic proteases. Xenin is structurally related to the amphibian peptide xenopsin and to the neuropeptide neurotensin. [3]

Xenopsin-related peptide-1 (XP-1) is an octapeptide that shares some specific structural and biological characteristics with neurotensin (NT)/xenopsin/xenin family. [4] Xenopsin-related peptide(s) have been localized in dog**,** monkey and human gastric mucosal cells. Researches indicate that synthetic xenopsin caused hyperglycemia and had a potent activity of secretion of insulin and glucagon from pancreas and gastrin from gastric G cells in anesthetized dogs. The effect of XP-1 on glucagon secretion is more potent than the effect on insulin and gastrin secretion. Nevertheless, the impact of XP-1 on many organs is still unknown. [5]

Aim of the study

To determine the role of xenopsin level in polycystic ovarian syndrome.

Patient and methods

Study design and setting

Observational case control study, conducted in Salah Aldin general hospital in Obstetrics and gynecological department, from (the first of Fab 2018 to the end of Dec. 2018). 40 patients with PCOS and 40 healthy women were included in the study.

All respondents (case group & control group) assessed by history about menstrual cycle (regular or not), fertilization, and BMI.

Method

Sample of 10cc blood were taken from the all respondents and send to the hospital lab to measure (FBS, fasting insulin, CRP, testosterone, LH, prolactin, FSH), and isolated serum were send to private lab (Al-Bashir lab.) to measure the level of xenopsin by ELIZA.

Ethical consideration

The study was approved by each of the council of Iraqi board of health specializations and hospital administration. The purpose and procedures were explained to all participants and they were given the right to participate or not, verbal consent was taken with reassurance that interpret gained will be kept confidentially.

Statistical analysis

All patients' data entered using computerized statistical software; Statistical Package for Social Sciences (SPSS) version 21 was used. Descriptive statistics presented as (mean ± standard deviation) and frequencies as percentages.

In all statistical analysis, level of significance (p value) set at ≤ 0.05 and the result presented as tables and/or graphs.

Results

Figure 1 shows that by using the U/s for diagnosis of polycystic ovaries, it was found only 6/40 (15%) of the patients was with it and the rest 34/40 (85%) was without PCO.

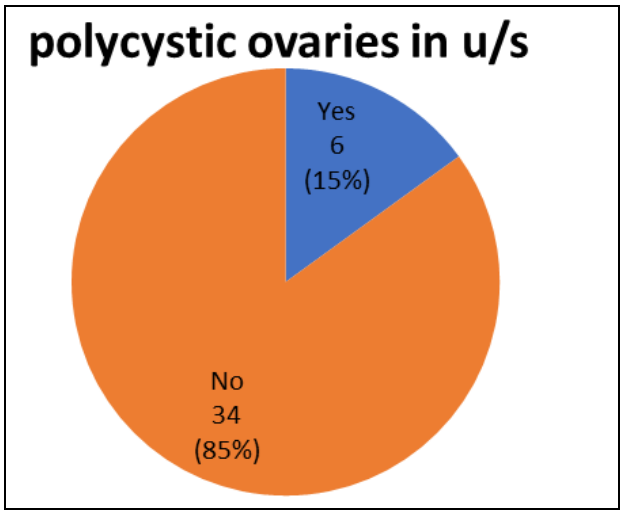

Fig 1: Polycystic ovaries diagnosed by U/s

As shown in figure 2: 30/40 (75.0%) of the PCOS patients presented with both clinical and biochemical hyper androgen, 7/40 (17.5%) of them was with clinical only, 2/40 (5%) were none and 1/40 (2.5%) were biochemical.

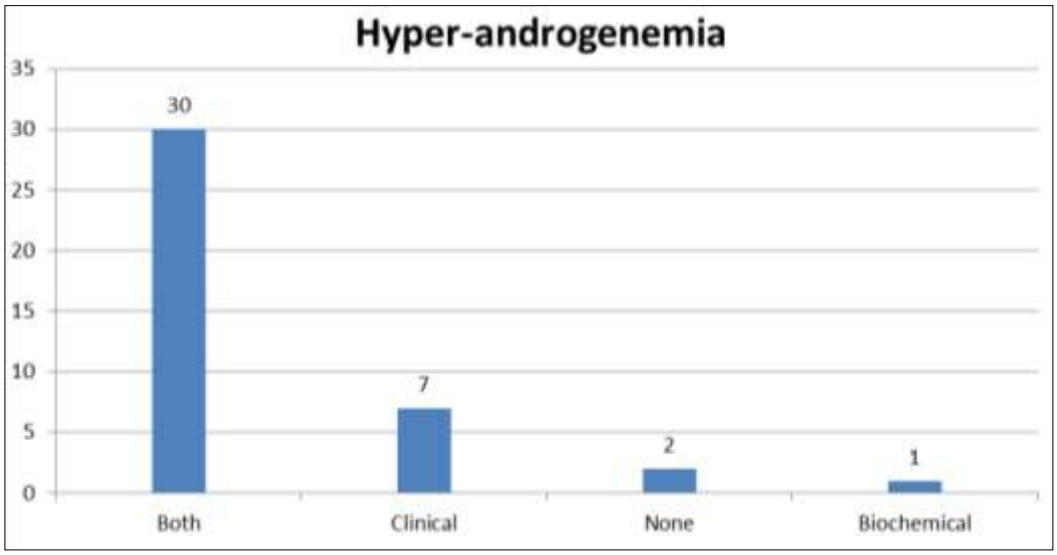

Fig 2: Distribution of the PCOS according to the hyper-androgenemia

Table 1 shows that the PCOs were diagnosed by U/s in only 6/40 (15%) patients. There is no significant association were found between age, hyper-androgenemia, fertile and menstrual cycle with us diagnosis of the disease.

Table 1: Association between PCOS diagnosed by U/s with studied variables

		Polycystic Ovaries in u/s				P value
		Yes		No		
		No.	%	No.	%	
Age Group	≤ 20	1	14.30	6	85.70	0.5
	21-29	3	27.30	8	72.70	
	30-39	1	6.70	14	93.30	
	≥40	1	14.30	6	85.70	
Hyper-androginemia	Clinical	1	14.30	6	85.70	0.9
	Biochemical	0	0.00	1	100.00	
	Both	5	16.70	25	83.30	
	None	0	0.00	2	100.00	
Fertile	Yes	2	9.50	19	90.50	0.3
	No	4	21.10	15	78.90	
Menstrual cycle	Regular	2	10.00	18	90.00	0.3
	Irregular	4	20.00	16	80.00	

As shown in table 2, there is a highly significant increase in the level of Xenopsin in PCOS group than that in control group, moreover highly significant associations between fasting insulin, total testosterone, prolactin and FSH levels with the PCOS group. Significant association were found between FBS and Insulin resistance with the PCOS group, while no significant association were found between age, BMI and LH level with PCOS group.

Table 2: Relation between many variables and PCOS group

Variable	PCOS (group) Mean±SD	Control (group) Mean±SD	P value
Age	29±2.30	28±7.20	0.4 NS
BMI	30.4±4.5	28.9±4.8	0.1 NS
Fasting blood sugar level	119.6±25.7	107.3±10.1	0.006*
Fasting insulin	11.83±6,8	5.40±3.2	<0.001**
Insulin resistance	2.57 ± 2.10	1.51 ± 1.07	0.005*
Xenopsin peptide level	6.6±2.0	5.0±1.4	<0.001**
CRP	2.9±1.3	2.1±1.1	0.003*
Total testosterone	0.67 ± 0.21	0.45 ± 0.24	<0.001**
LH	28.0±6.0	27.4±4.1	0.6 NS
Prolactin	22.8±3.6	10.1±2.0	<0.001**
FSH	3.2±1.5	5.3±1.2	<0.001**

NS = not significant, * = significant, ** = highly significant

The validity test of xenopsin when the cutoff value ≥ 5.9 as follow: the sensitivity of the test to diagnose the PCOS were (88.0%), the specificity of the test were (89.0%), positive predictive value was (86.0%), negative predictive value was (84.0%) and the accuracy of the test to diagnose the PCOS was (88.6%) (Table 3)

Table 3: Validity test of xenopsin patients with PCOS

Cutoff value of xenopsin	Sensitivity	Specificity	PPV	NPV	Accuracy
≥5.9	88.3	89.0	86.0	84.0	88.6

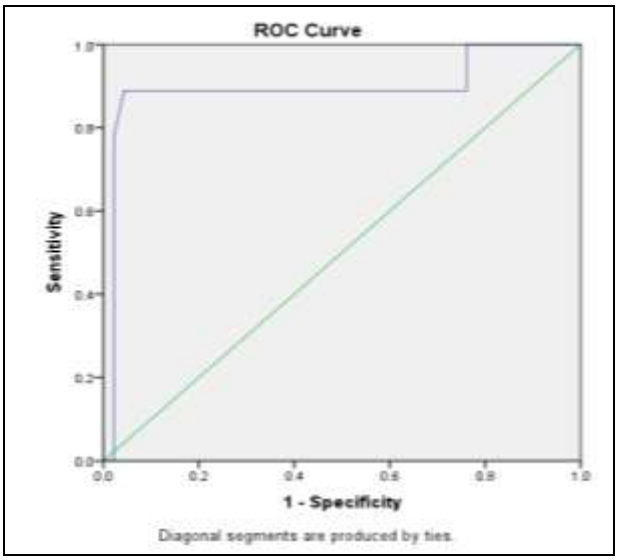

Fig 3: ROC curve for serum level of xenopsin for prediction of PCOS.

Discussion

Until now the pathophysiology of polycystic ovaries is not fully understood, but they thought that insulin resistance plays a central role in the development process. Many patients with PCOS, especially those that have a higher body fat mass presented insulin resistance [3]. Nonetheless, even in thinner women with polycystic ovarian syndrome, there is increase in insulin resistance compared to the control group [6].

The mean age of PCOS group was 29±2.30 years and 28±7.20 years for control group. Hussein B *et al*. [3] found that the mean ages in the PCOS and non-PCOS groups were 29.5 ± 5.45 years versus 32.9 ± 6.95 years, respectively.

The most common factors of infertility in infertile women is PCOS and ahigher frequency among women aged 20-29, this result in Hanaa and Enas Iraqi study which agreement with my study [7].

PCOS is considered as one of the important risk factors for developing type 2 DM and impaired glucose tolerance. In Italian long-term longitudinal design studies, they conclude that type 2 DM in Italian women with PCOS is higher 2.6 times than that of the healthy general female population. Furthermore, as a cumulative effect of such a higher incidence, the age-standardized prevalence of T2DM in PCOS women at middle age is 6.8 times greater than that of healthy female population of a similar age [8].

Regarding to the BMI, the current study found that there is significant increase of BMI in PCOS group than that in healthy group. In a recent study carried in Spain by Alvarez-Blasco F *et al*, [9] found that PCOS was 5-fold more common among unselected premenopausal overweight or obese women seeking advice for weight loss compared to that of the general population. In this study, the increased prevalence of PCOS in overweight and obese women was irrespective of the degree of obesity and was independent of the presence or absence of the metabolic syndrome or its features [9].

The current study mentioned that total testosterone level was significantly increasing in PCOS women than that in healthy women. This is in accordance to Legro R *et al*. [10]

No significant association was found between BMI and PCOS group, which are in agreement with that found by Temur M *et al*, study carried in Turkey in 2017. [11]

The current study found that CRP was increased significantly in PCOS patients group than control group, this may be due to the PCO syndrome is considered as one of the low grade chronic inflammatory disease. Which is in agreement with an Iranian studies conducted by Moti M *et al*. [12] when they reported that the levels of CRP in PCOS are higher than that in other, Moreover it is in accordance with that found by Tarkun I *et al*. [1]

The level of LH were increased and FSH is slightly decreased agree with that found by Deshmukh S [13], and he attributed this results to pulsatile secretion of GnRH and to the high estrogen environment.

In our study, xenopsin level was found to be significantly higher than control group, this is in agreement with that revealed by Temur M *et al*. [11] Cochrane and colleagues study found that xenopsin have a role in cellular inflammation which is done by affecting macrophages and triggering the histamine elevation in mast cells [14].

Moreover Carraway *et al*. [15] revealed that xenopsin may act on granulocytes directly when they study the mice and lead to inflammatory effects. Current study found that the level of CRP increased significantly in PCOS group as we mentioned above but we don't have data regarding the relationship between xenopsin and CRP.

In a study by Chowdhury *et al*., [16] xenin molecule receptors from the xenopsin family have been identified in pancreatic neurons, and it has been shown that this molecule together with neurotensin receptor 1, may act on beta cells indirectly and cause T2DM conversion from normal glucose tolerance.

Conclusion

Highly significant increase in Xenopsin level in PCOS group than that in control group.

No Conflicts of Interest

Source of Funding: Self

Ethical Clearance: Was taken from the scientific committee of the Iraqi Ministry of health

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