A Comparative Study for the Level of Serum Insulin-Like Growth Factor-1 in Normal and Polycystic Ovarian Syndrome Women

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Abstract
Background: PCOS is described in some articles as a common condition seen in 7 to 15 per cent of women of reproductive age. The occurrence of PCOS is very complicated and its surrounded by many reasons that involve inheritable, environmental, and lifestyle factors that have not yet been determined. Definition of PCOS is restricted to at least two of the three Rotterdam criteria: Oligo/anovulation, clinical or natural hyperandrogenism, and a micro polycystic pattern (ovarian volume > 10 ml and more than 12 follicles by the ovary). Objective: This study was carried out in order to investigate the contribution of IGF-1 to PCOS and meanwhile to cast light on the means of IGF-1 in women with and without PCOS. MethodsWomen of their reproductive age were first divided into two main groups; those with PCOS (26 subjects) and without PCOS (24 subjects). Each of the two groups was subdivided once again according to BMI into obese (BMI ≥ 27 kg/m2) and nonobese (BMI < 27 kg/m2). IFG-1 was the primary concern of this research work, and blood samples were collected from all participants.Results: Women with PCOS have significantly higher waist circumference mean than those without, which is valid for both groups of BMI. Women with IGF-1 greater than 37.6 are likely to have PCOS with a sensitivity of 68.8% and specificity of 69.2%. Moreover, women more excellent than 32.2 are more likely to have PCOS with a sensitivity of 75% and specificity of 69.2%.Conclusion: This research work revealed that IGF-1 could be used as a biomarker in the diagnosis process of PCOS. Body mass index and waist circumference can also be used as indicators for PCOS according to their sensitivity and specificity. According to the results of the ROC curve, waist circumference was found to be the best among other predictors of PCOS, including IGF-1. IGF-1 was significantly correlated only with the waist circumference of normal participants.
Keywords: Polycystic ovary syndrome, BMI, IGF-1, ROC curve.

1. Introduction

Polycystic ovary syndrome PCOS is a medical problem occurred at completely different rates in step with several cultural and socioeconomic factors, including education level and lifestyle.
PCOS is described in some articles as a common condition seen in 7 to 15 per cent of women of reproductive age. Stein and Leventhal identified and characterized PCOS in 1935. The occurrence of PCOS is very complicated and its surrounded by many reasons that involve inheritable, environmental, and lifestyle factors that have not yet been determined. Definition of PCOS is restricted to at least two of the three Rotterdam criteria: Oligo/anovulation, clinical or natural hyperandrogenism, and a micro polycystic pattern (ovarian volume > 10 ml and more than 12 follicles by the ovary)1.
A major endocrinopathy among reproductive-aged women, PCOS is still not regarded as a significant health problem globally. It affects 4%-20% of women worldwide. Related issues such as prevalence, diagnosis, aetiology, dealing with patients, and psychological aspects are still uncertain and need more attention2.
In many studies, PCOS seems to be interrelated with obesity or even overweight in general worldwide. PCOS is also associated with many bad aspects related to infertility and pregnancy3.
Insulin-like growth factor-1 (IGF-1) is a 70-amino-acid polypeptide hormone with endocrine, paracrine, and autocrine actions. The liver primarily creates it in response to endocrine stimulation by growth hormone and insulin, and it is produced locally in all bodily tissues4.
PCOS is an endocrine disorder that leads to various health complications, such as irregular menstrual cycles, hirsutism, infertility, acne, and other metabolic disorders, including obesity. In addition, PCOS is believed to raise the likelihood of type 2 diabetes mellitus (T2DM) and other cardiovascular complications (CVD) in women. Different diagnostic criteria are used to determine PCOS prevalence in different geographical regions according to Rotterdam criteria. Concerning the whole population, PCOS prevalence lies within 5–10% in women of reproductive age. About 40% of women with PCOS suffer from depression. Anxiety and depression are among the most common psychological complications in PCOS5.
According to the previous argument, PCOS aetiology is not well known. However, some

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indications characterize women with PCOS syndrome to be more likely exposed to chronic low-grade inflammation. Furthermore, inflammation is likely associated with other prominent aspects of PCOS, including insulin resistance and cardiovascular disease risk factors. Indeed, inflammation is considered the defining feature of endothelial dysfunction and atherosclerosis. According to dual x-ray absorptiometry (DEXA), women with PCOS are predisposed to increase visceral adiposity regardless of BMI. Patients with PCOS have similar percentages of total and trunk fat but higher percentages of abdominal fat. As mentioned above, visceral adipose tissue is associated with insulin resistance, hyperglycemia, and dyslipidemia, all of which are associated with PCOS6.

Although PCOS prevalence is continuously increased due to different etiologies, a protocol for standardization diagnosis seems difficult to frame2.

Infertility is presupposed to be examined in twelve months without pregnancy in couples having regular sexual issues virtually twice a week1.

Insulin resistance in PCOS can be caused by a post-binding malfunction in insulin receptor signalling pathways, and high insulin levels can increase gonadotropin levels in the ovary. Hyperinsulinemia can also decrease the production of sex hormone-binding globulin (SHBG) in the liver, leading to an increase in androgenicity4.

IGF-1 has been implicated in the prevalence of insulin resistance syndrome in several investigations4.

Subjects and methods

1. During the period March to April 2021, 26 women (patients' group) with PCOS and 24 women with normal ovaries (control group) attended a private gynaecology clinic for fertility purposes were considered in this study.
2. All subjects enrolled in this study were approved to have normal serum prolactin levels and thyroid function tests, with no clinical signs of cushion syndrome or adrenal hyperplasia.
3. Information about age, height, weight and waist circumference were recorded for all subjects. Ultrasound had done for all participants on the 12th or 13th day of the cycle. Blood samples were collected three hours after a meal, and hence the IGF-1 was checked together with prolactin hormone and thyroid-stimulating hormone (TSH) on the second or third day of the cycle.

Inclusion criteria

4. After excluding all etiologies other than fertility, all subjects attending the private clinic during this period within the reproductive age were involved in this study.
5. Diagnosis of PCOS relied on Rotterdam criteria which required at least two constraints of the following three:

1. Oligo/Anovulation
2. Clinical and/or biochemical hyperandrogenism
3. Polycystic ovaries morphology.

Exclusion criteria

a. Every subject who failed to meet the requirements of the Rotterdam criteria was excluded from the study.

Ethical concerns

b. The ethical committee of the district's medical director approved the research work, and all were informed of the scientific nature of the research and agreed to participate.

c. Collected data were organized in excel sheets first, and then the well-known statistical software SPSS ver. 25 was used for the analysis of data.

2. Results

Figure 1 shows the age frequency distribution for the two groups of subjects (Normal and POCS). In both groups of subjects, ages ranged between 18 to 40 years, with an overall mean of 28.22 years and a standard deviation of 6.5 years. Per cent of obese women (BMI≥27) in the PCOS group was 61.54%, while it was 54.17% in the Normal group.

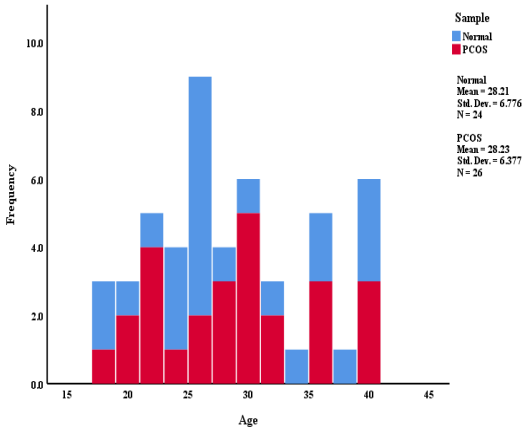

Figure 1: Frequency distribution of age of subjects concerning their groups.

Table 1 shows the means of age, weight, waist circumference and IGF-1 for nonobese (highlighted entries) and obese subgroups as compared by t-test. Mean age was not significantly different in both groups; Normal and PCOS according to obese and nonobese subgroups. The huge fluctuation in IGF-1 readings prevents using the t-test properly as a procedure for comparing two means. In this instance, the Mann-Whitney test, one of the commonly used non-parametric tests in such a situation, was also used. Both tests revealed similar conclusions indicating that the mean and median IGF-1 of PCOS subjects are significantly higher than that of their counterpart in the Normal group of subjects for both obese and nonobese cases.

When the obese group of subjects is considered, despite age, all other variables' means were significantly different, as presented in table 1. PCOS subjects showed higher means than their counterparts in the Normal group even with no significant difference.

Table 1: Results of two-sample t-test obtained from comparison of means according to BMI subgroups versus Normal and PCOS groups of subjects.						
			n	Mean±Sd	t-test	p-value
Age	BMI≥27	Normal	13	28.15±6.44	-0.339	0.737
		PCOS	16	29.06±7.71		
	BMI<27	Normal	11	28.27±7.47	0.486	0.632
		PCOS	10	27.00±3.71		
Weight	BMI≥27	Normal	13	73.38±10.32	-3.291	0.003
		PCOS	16	89.63±15.14		
	BMI<27	Normal	11	58.36±9.63	-1.76	0.094
		PCOS	10	63.80±1.55		
Waist circumference	BMI≥27	Normal	13	84.00±8.58	-3.869	0.001
		PCOS	16	103.06±15.95		
	BMI<27	Normal	11	72.18±7.44	-2.84	0.01
		PCOS	10	80.50±5.76		
IGF-1	BMI≥27	Normal	13	38.07±30.03	-2.834	0.009
		PCOS	16	90.91±61.39		
		Normal	13	32.8(7.4-125.3)	292.5	0.023*
		PCOS	16	89.6(16.3-171.1)		
	BMI<27	Normal	11	36.66±31.76	-2.393	0.027
		PCOS	10	97.05±76.95		
		Normal	11	29.6(8.0-125.3)	139	0.045*
		PCOS	10	87.6(13.7-144.7)		
* Results based on Mann-Whitney test						

Table 2 shows a matrix of the bivariate correlation coefficients (only significant correlations) between variables of interest. Insulin-like growth factor was only significantly correlated with waist circumference for the standard group of subjects.

In addition to IGF-1, waist circumference was significantly correlated with weight and BMI (Normal and PCOS groups).

Table 2: Matrix of bivariate correlation coefficients (only significant) between variables of interest.						
		Age	Weight	BMI	Waist Cir	IGF-1
Age	Normal					
	PCOS					
Weight	Normal			0.879	0.595	
	PCOS			0.913	0.859	
BMI	**Normal**		0.879		0.664	
	PCOS		0.913		0.82	
Waist Cir	**Normal**		0.595	0.664		0.523
	PCOS		0.859	0.82		
IGF-1	**Normal**				0.523	
	PCOS					

1. Since IGF-1 is the variable of most interest in this study, scatter diagrams of this variable versus age, BMI and waist circumference were obtained for Normal and PCOS groups separately (figures 2 and 3).
2. Figure 2 shows the scatter diagrams concerning the Normal group of subjects. A general negative trend of IGF-1 with age can be observed with extreme observations located beyond the aggregation of other points. In the cases of BMI and waist circumference, IGF-1 seems to reveal a positive general trend except for some observations that lie far enough from other data which make such dispersion in the plot.
3. Figure 3 revealed that IGF-1 shows a positive general trend for all variables. The current dispersion in all three plots refers to the great fluctuations of readings recorded for these variables.

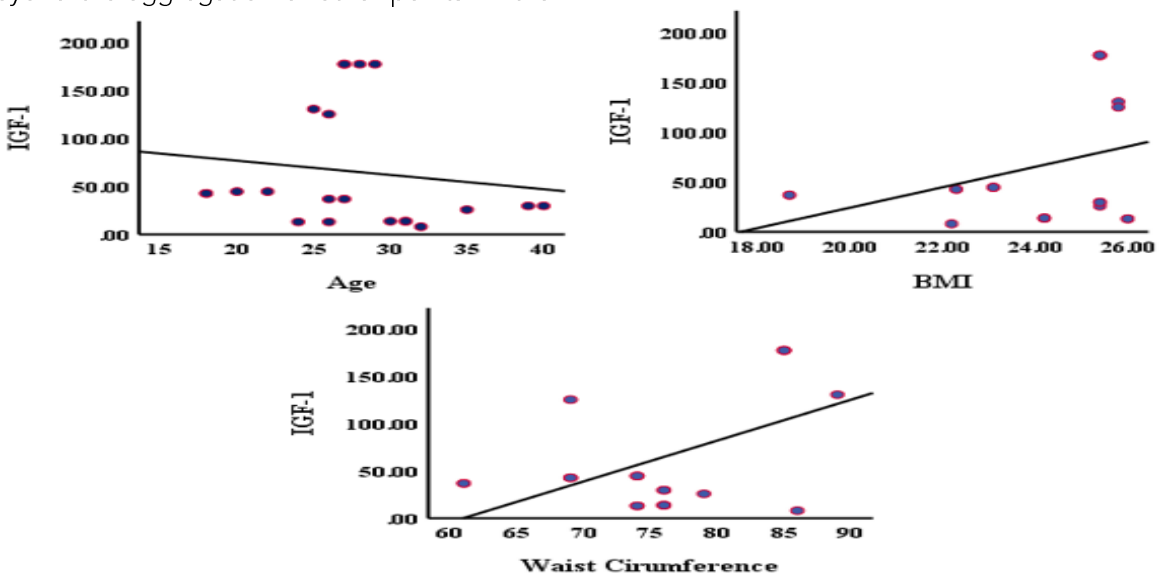

Figure 2: Scatter plot of IGF-1 versus age, BMI and waist circumference for Normal group of subjects.

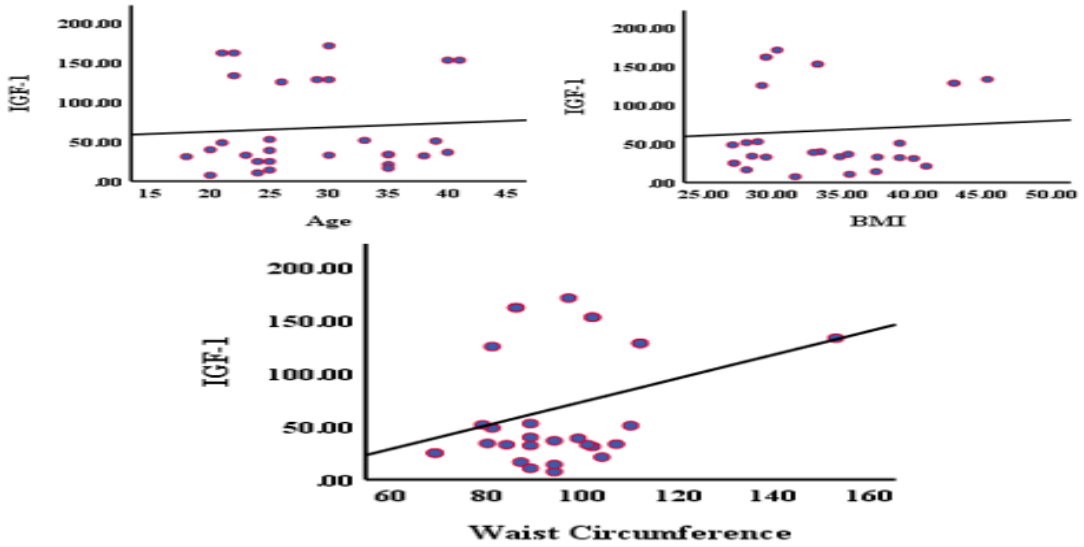

Figure 3: Scatter plot of IGF-1 versus age, BMI and waist circumference concerning PCOS group of subjects.

Receiving operating characteristic (ROC) curve

1. This statistical technique has been formed in order to identify cutoff points for the variables weight, BMI, waist circumference, and IGF-1 to be used in the diagnosis of subjects as to belong to either one of the relevant groups (Normal, PCOS). Sensitivity and specificity will play an essential role in the classification process of the subjects. Deciding on the cutoff point is a complicated task; it needs a rational balance between how risky is a decision when a positive case is diagnosed mistakenly as a negative case. In this context, the cutoff points are determined with a high level of caution.
2. The curve is not a precise diagnosis procedure, but it can point out how likely a particular patient, from the readings of the considered variable, is said to be a case of PCOS.
3. Table 3 shows the area and the curve (AUC) for each curve presented in figure 4. If AUC is below 0.6, then it should be neglected, and hence its corresponding variable should be discarded. Although IGF-1 shows an acceptable AUC, it is the lowest among all others.
4.

Table 3: Area under the curve AUC as obtained by using the ROC curve.

Area Under the Curve					
Test Result Variable(s)	Area	Std. Error	Asymptotic Sig. b	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
Weight	0.817	0.079	0.004	0.663	0.971
BMI	0.774	0.089	0.012	0.600	0.948
WaistCir	0.892	0.059	0.000	0.775	1.000
IGF-1	0.752	0.090	0.021	0.576	0.928
The test result variable(s): Weight, BMI, WaistCir, and IGF1 has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.					
a. Under the non-parametric assumption					
b. Null hypothesis: true area = 0.5					

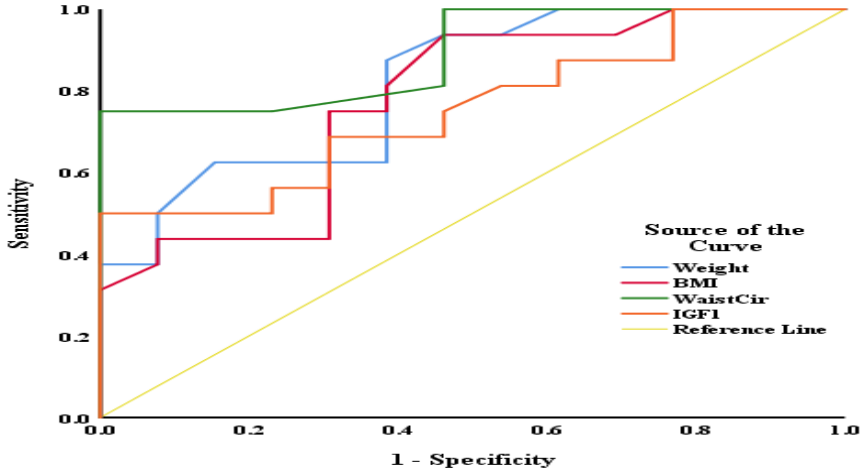

Figure 4: The ROC curve for the weight, BMI, waist circumference and IGF-1 by considering PCOS as distinguished criteria.

Table 4: Cutoff points and their corresponding sensitivity and specificity as obtained from the ROC curve.			
Variable	Cutoff value	Sensitivity	Specificity
Weight	84.5	62.5	84.6
BMI	32.25	75	69.2
Waist circumference	91.5	75	66.9
IGF-1	37.6	68.8	69.2

3. Discussion

1. PCOS is a very common endocrinopathy confronting women in their reproductive period. Although the prevalence of this medical phenomenon is almost known worldwide7, no official statistics have been available about it in Iraq. However, in private gynaecological clinics, as in the official hospital of obstetrics and gynaecology, women of reproductive age are usually attended to for the cases of fertility problems.
2. Regarding BMI levels, the percentage of obese women found in this underwent study is remarkable higher than that (52.8%) found by Kaur et al., 20218 and that (55%) found byPremoli et al., 20059.
3. Some epidemiological data suggest an association between PCOS and obesity10. Obesity is noticed as a leading characteristic that may help identify women with PCOS. Weight reduction is found to significantly enhance the likelihood of fertility and pregnancy11.
4. Obesity is considered a critical indicator in the process of PCOS because Bariatric surgery is supposed to take place when (BMI≥35 kg/m2)1. In this context, weight reduction is considered a non-pharmacological treatment for patients with PCOS.
5. Waist circumference, which is significantly associated with weight and BMI, is another feature of obesity and what is valid for BMI is also true for waist circumference logically.
6. IGF-1 is significantly associated with a waist circumference of Normal subjects only. IGF-1 level is significantly higher in subjects with PCOS than in normal ovarian, which agrees with Javaid et al., 202012.
7. IGF-1 is known to have many biological effects on different body organs. It is believed to stimulate cell growth and proliferation. Research suggests that this component has an action on the ovarian tissue as well, which makes it very essential in the medical evaluation of the PCOS13.
8. In favour of a healthy pregnancy, regular observations should be made on all women with PCOS, whether they were undergoing oral treatment or surgical.
9. Complications during pregnancy are essentially higher for women with PCOS than those without, and these involve pre-eclamptic toxaemia, pregnancy-induced hypertension and the birth of small-for-gestational-age. It has been noticed that risks of adverse pregnancy, fetal and neonatal are significantly high occurred in women with PCOS than in women without14.

4. Conclusion

This research work revealed that IGF-1 levels are significantly higher in PCOS women than normal. According to the results of the ROC curve, waist circumference was found to be the best among other predictors of PCOS, including IGF-1. IGF-1 was significantly correlated only with the waist circumference of normal participants.

Conflict of interest

The authors declare that they have no conflict of interest.

5. Funding

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