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Serum Mannose Level and Its Association in Women with Polycystic Ovarian Syndrome: a Case Control Study of Al-Najaf City / 2020

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Abstract

Background: Polycystic ovarian syndrome is a common public health issue around the world. Insulin resistance and glucose intolerance play important role in the etiology of polycystic ovarian syndrome and the serum mannose is incorporated in metabolism of glucose.

Aim of study: Determination of the association between serum mannose level and polycystic ovarian syndrome.

Patients and Methods: A case control study enrolled eighty eight women were divided as forty four women with polycystic ovarian syndrome and forty four women without polycystic ovarian syndrome presented to outpatient clinic at Fertility Center/Al Sader Medical City and outpatient clinic of Al- Zahraa Teaching Hospital in Najaf city-Iraq during the period from 1st of February till 31st of December, 2020.

Results: The mean Serum Mannose level of women with polycystic ovarian syndrome 7.37 was significantly higher than mean serum mannose of controls 1.32 ($p<0.001$). Cutoff serum mannose level of 1.98 had acceptable validity results (90.9% sensitivity, 90.9% specificity, 94% PPV, 90.5% NPV and 90% accuracy). The means of serum level testosterone and luteinizing hormones were significantly higher among women with polycystic ovarian syndrome, while mean follicular stimulating hormone level was significantly lower among women with polycystic ovarian syndrome.

Conclusions: The serum mannose level is significantly increased in women with polycystic ovarian syndrome which may indicate its possible role in the pathophysiology of polycystic ovarian syndrome.

Keywords: Polycystic ovarian syndrome (PCO), testosterone, luteinizing hormones, follicular stimulating hormone, Serum Mannose.

Introduction

Polycystic ovarian syndrome (PCOS) is the most common endocrine pathology and is a leading cause of ovulatory dysfunction in the reproductive-aged female around the world were its prevalence ranges around 5% to 15% depending on the diagnostic criteria. It is a hyperandrogenic state with oligoanovulation that cannot be explained by any another disorder and is diagnosed by exclusion. [1]. The main pathophysiology of PCOS is still unknown but several theories have been proposed to explain the pathogenesis of PCOS [2] and ovarian hyperthecosis and hyperandrogenism in addition to insulin resistance are considered the main pathological disturbance in PCOS, in addition to numerous genetic and environmental factors which has been postulated to interact and play a role in the underlying pathophysiology of this syndrome. Limited data are available regarding newer biomarkers, except for Anti-Müllerian hormone (AMH) and several other biomarkers like testosterone which may be associated with PCOS.

Mannose is predominantly monosaccharide for protein glycosylation and is account for the majority of mannose found in mammalian blood [5,6]. The importance of mannose in PCOS-related metabolic disorders has been increasingly recognizeed, for example, plasma mannose levels are significantly elevated in women with insulin resistance [6,7]. In addition to that obese women with metabolic abnormalityes express a significant decline in mannose metabolism and utilization genes in the livers [6,7].other studies found that elevated plasma mannose levels may be associated with common chronic diseases like type 2 diabetes and cardiovascular disease, which may be used as a predictive biomarker [8]. Despite these advances in knowledge, the role of mannose in the pathogenesis of PCOS remains not clear [8]. So the aim of the present study is to determine the association between serum mannose level and polycystic ovarian syndrome.

Patients & Methods

A case control study was done at Fertility center/ Al- Sader Medical City and Al-Zahra'a Teaching Hospital for Maternity and Pediatrics /Najaf/Iraq, during the period from 1st of February till 31st of December, 2020.The protocol of the study was approved by scientific council and ethical committee of the Iraqi board of medical specialization were 88 women included in the study after an informed consent. The study sample consisted of 44 PCOS women and 44 controls their age between 18-45 years. The final diagnosis of polycystic ovarian syndrome was done according to Rotterdam criteria [9]. The exclusion criteria are tobacco smoking, hormonal treatment such as oral contraceptive pills, gonadotropins releasing hormones agonist or antagonist, hyperprolactinemia, endocrine disorders such as Cushing's syndrome, congenital adrenal hyperplasia, hypothyroidism pituitary tumors and refuse to participate.

After explanation of the whole procedure, patients' information was documented in details in a prepared questionnaire including age, parity, family history drugs history, surgical history, smoking habit, menstrual history. A physical examination and baseline assessment was done for the patients at the day 2 or 3 of menstrual cycle; BMI was calculated as body weight in kilograms divided by height in squared meters (kg/m^2) [10]. Transvaginal ultrasound scan was performed for all participants. A blood samples were withdrawn at the first 2-3 days of the menstrual cycle and

centrifuged to collect serum. Part of the serum was used to measure hormones including FSH, LH, serum prolactin and total testosterone.

Total serum mannose was assessed in an enzyme linked immunosorbent assay (ELISA). All women's data analyzed using computerized statistical software; Statistical Package for Social Sciences (SPSS) version 22 was used. Descriptive statistics presented as (mean ± standard deviation) and frequencies as percentage-es. Multiple contingency tables conducted and appropriate statistical tests performed, Chi square test was used for categorical variables (Fishers exact test was used when expected variable was less than 20% of total variable). Independent sample t-test was used to compare between two means. ROC curve was used for prediction of PCOS by serum mannose and testosterone levels. In all statistical analysis, level of significance (p value) set at ≤ 0.05 and the result presented as tables and/or graphs.

Results

This study included forty-four women with polycystic ovarian syndrome (PCOS) with mean age of 27.8±4.9 years; mean age of women with PCOD was insignificantly higher than mean age of control women (p=0.14). No significant differences were observed between women with PCOS and controls regarding marital status (p=1.0) and parity (p=0.8). There was non-significant difference in body mass index between women with PCOS and controls (p=0.16); 27.3% women with PCOS were obese, while 13.6% of controls were obese. Mean BMI of women with PCOS was non significantly higher than mean BMI of control women (p=0.25) (Table 1).

Mean serum testosterone level of women with PCOS (0.74 ng/dl) was significantly higher than mean serum testosterone of (0.24 ng/dl) for controls (p<0.001). Mean follicular stimulating hormone level of women with PCOS was significantly lower than mean follicular stimulating hormone of controls (p=0.001). Mean luteinizing hormone level of women with PCOS was significantly higher than mean luteinizing hormone of controls (p<0.001). Mean serum mannose level of women with PCOS (7.37±4.68 ng/ml) was significantly higher than mean serum mannose of (1.32±0.74 ng/ml) for controls (p<0.001). (Table 2) (Fig.1, 2, 3). The cut off serum mannose level of 1.98 had acceptable validity results (90.9% sensitivity, 90.9% specificity, 94%PPV, 90.5% NPV and accuracy 90%) while the cutoff serum testosterone level of 0.55 had acceptable validity results (93.2% sensitivity, 100% specificity, 92.5%PPV, 100% NPV and accuracy 95%) and the cutoff serum LH level of 8 had acceptable validity results (80% sensitivity, 91% specificity, 89.7%PPV, 81.6% NPV and accuracy 85.2%) (Table 3) (Fig. 4,5,6).

Discussion

Hyperandrogenism is accompanied with a profound risk of insulin resistance, metabo-lic syndrome and liver steatosis which are all features of polycystic ovarian syndrome (PCOS) [11,12]. Some authors detected a link between testosterone and glucose intolerance, among women with PCOS [13]. The serum mannose is important peptide that is associated significantly with hyper-androgenism and insulin resistance [14].

The present study found that mean serum mannose level of women with PCOS was significantly higher than mean serum mannose of controls (p<0.001). This finding is similar to results of Mi *et al* [15] study in USA which stated that serum mannose level is directly linked to androgens especially higher levels are detected in polycystic ovarian syndrome.

Table 1: Demographic characteristics of the study groups.

Variable	Study groups				P value
	PCO		Control		
	No.	%	No.	%	
Age					0.2*
<20 years	0	-	1	2.3	
20-29 years	27	61.4	32	72.7	
30-39 years	17	38.6	11	25.0	
Mean±SD (years)	27.8±4.9		26.3±4.5		0.14 **
Body mass index					0.16***
Normal	8	18.2	14	31.8	
Overweight	24	54.5	24	54.5	
Obese	12	27.3	6	13.6	
Mean±SD (Kg/m^2)	27.7±3.00		26.9±3.4		0.25**
Marital status					1.0*
Married	34	77.3	34	77.3	
Single	10	22.7	10	22.7	
Parity					0.8***
Nulliparity	10	22.7	10	22.7	
Primi-parity	8	18.2	8	18.2	
Multi-parity	18	40.9	21	47.7	
Grand-multiparity	8	18.2	5	11.4	
Mean±SD	2.2±1.8		2±1.7		0.6^{**NS}

*Fishers exact test,**Independent sample t-test, ***Chi-square test, NS=Not significant. P value <0.05 was significant

Table 2: Distribution of serum luteinizing hormone, follicular stimulating hormone, testosterone and mannose level ac- cording to study groups.

Variable	Study groups		P value
	PCO	Control	
	Mean± SD	Mean± SD	
LH (IU/L)	9.41±3.64	5.75±1.52	<0.001
FSH (IU/L)	6.65±2.62	8.79±3.24	0.001
Serum testosterone(ng/dl)	0.74±0.1	0.24±0.09	<0.001
Serum mannose (ng/ml)	7.37±4.68	1.32±0.74	<0.001

*Independent sample t-test, P value <0.05 was significant

Table 3: ROC coordinates for prediction of PCO by serum man- nose, testosterone and LH level

ROC coordinates for prediction of PCO by serum mannose level					
Cutoff point	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**Accuracy**
1.8	93.2%	77.3%	90.8%	80.5%	86%
1.98	90.9%	90.9%	94%	90.5%	90%
2.2	81.8%	97.7%	88.8%	93%	85%
ROC coordinates for prediction of PCO by serum testosterone level					
Cutoff point	Sensitivity	Specificity	PPV	NPV	Accuracy
0.46	100%	55%	100%	57%	73%
0.55	93.2%	100%	92.5%	100%	95%
0.61	84.1%	100%	80%	100%	89%
ROC coordinates for prediction of PCO by serum LH level					
Cutoff point	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**Accuracy**
7	77%	60%	74%	72.2%	68.1%
8	80%	91%	89.7%	81.6%	85.2%
9	61%	90%	87.1%	70.1%	76.2%

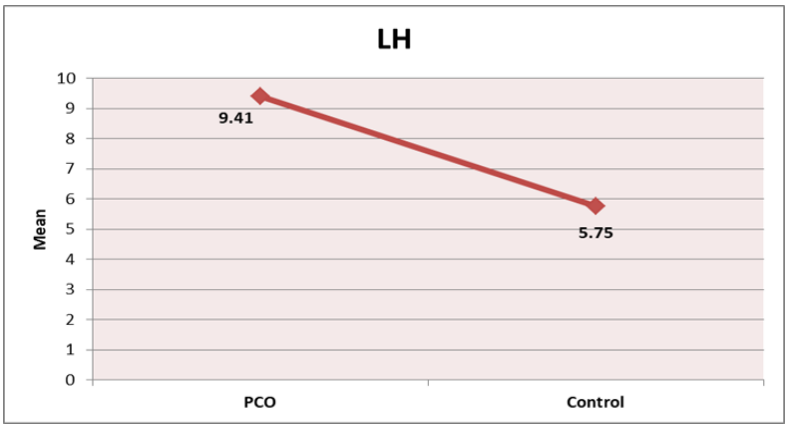

Figure 1. Distribution of serum LH mean according to study groups.

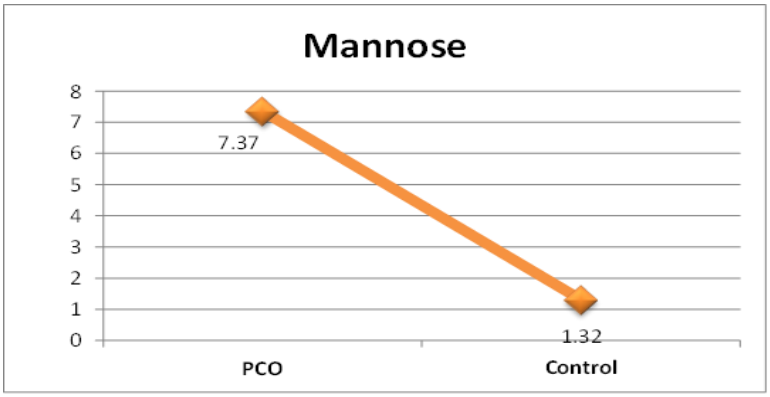

Figure 2. Distribution of serum mannose mean according to study groups.

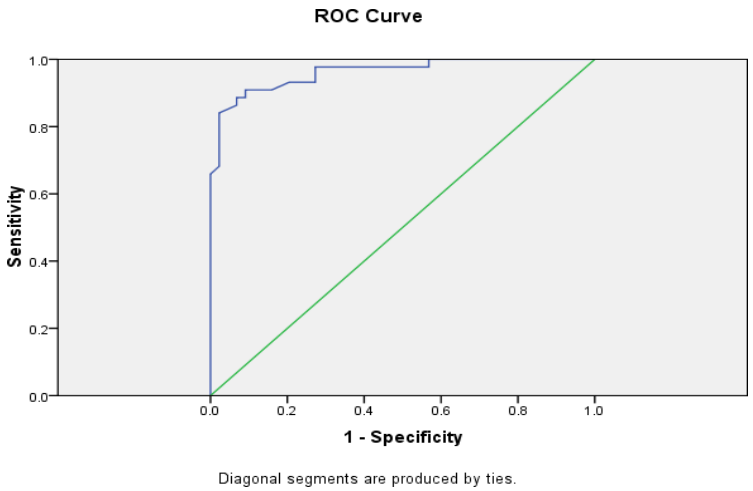

Figure 3. ROC for serum mannose level prediction of PCO (AUC=0.96).

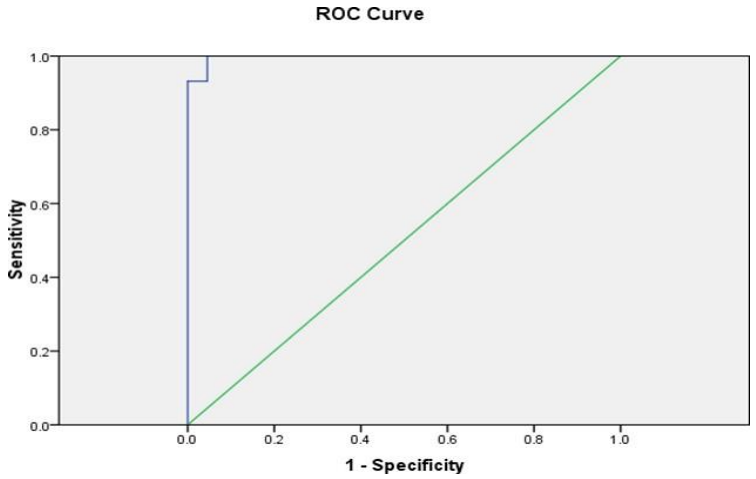

Figure 4. ROC for serum testosterone level prediction of PCO (AUC=0.99).

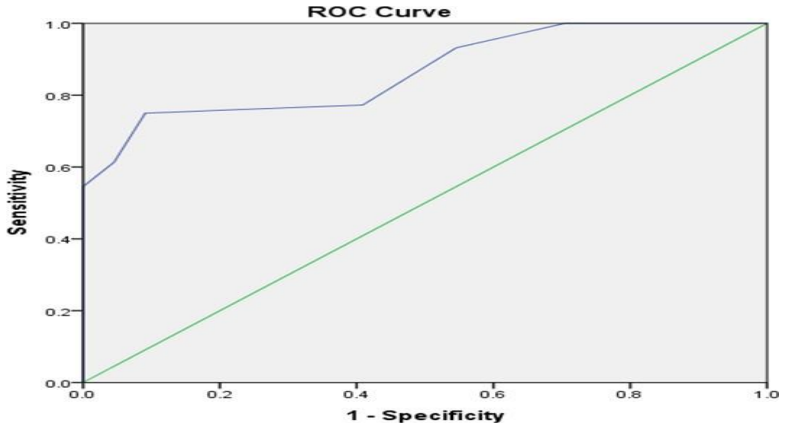

Figure 5. ROC for serum LH level prediction of PCO (AUC=0.865).

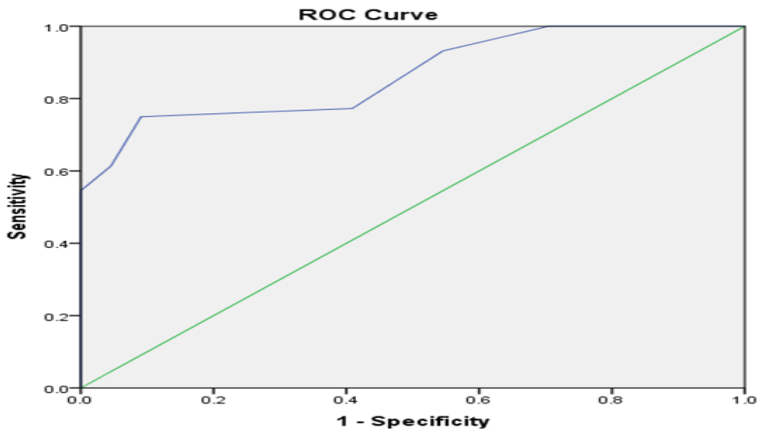

Figure 6. ROC for serum LH level prediction of PCO (AUC=0.865).

However many authors reported a novel relationship between serum mannose level with both of testosterone and luteinizing hormones in PCOS women. Witchel *et al.,* [16] study in USA document-ted that glucose abnormality like high serum mannose level and insulin resistance play an important role in etiology of polycystic ovarian syndrome. Another American study carried out by Hsiao *et al*., found a significant relationship between excess of androgens and higher level of serum mannose especially among women with polycystic ovarian syndrome. Kowalska *et al.,* [17] study in Poland documented that serum mannan binding lectin is markedly declined among women with PCOS and no signific-ant relationship was observed between serum mannose level and androgens.

Current study found that serum mannose level of 1.98 ng /ml had accept-able validity results (90.9% sensitivity, 90.9% specificity, 94% PPV, 90.5% NPV and 90% accuracy). Feng et al [18] on 71 women with PCOS and 61 healthy women which revealed that serum mannose was increased among women with PCOS and serum mannose could predict the polycystic ovarian syndrome with accept-able validity findings (66.2% sensitivity, 73.8% specificity, 74.6% PPV, 65.2% NPV and 68% accuracy). Peña et al [19] study in Cuba found that insulin resistance is significantly increased among women with PCOS than women with normal ovarian function. A Japanese study by Yoshimura *et al.,* [20] showed a profound relationship between serum mannose level and glucose tolerance in humans. For that, the serum mannose level could be used as a significant predictor for early diagnosis of polycystic ovarian syndrome [20].

In this study, mean serum testosterone level of women with PCOS was significantly higher than mean serum testosterone of controls ($p<0.001$). This finding coincides with results of Alsaadi and Mohamad study [21] in Iraq which found that mean testosterone level was significantly higher among women with PCOS as compared to healthy women, It is also consistent with results of Lerchbaum et al [22] in Austria which documented those PCOS women is significantly related with high serum testosterone level and the higher levels of free testosterone in PCOS women is indicator of adverse metabolic reactions. Zhang *et al.,*[23] study in China found that androgen hormones increase (such as testosterone) is directly linked to increase in glucose intolerance as these

hormones increased the insulin resistance and beta cell dysfunction among women with polycystic ovarian syndrome. Our study found that serum testosterone level of 0.55 had acceptable validity results (93.2% sensitivity, 100% specificity, 92.5% PPV, 100% NPV and accuracy 95%), which is in agreement with results of Iwasa et al [24] study in Japan which revealed an important role in serum testosterone level of 0.71 for diagnosis of polycystic ovarian syndrome with acceptable validity results (78% sensitivity and 54% specificity) [24].

Regarding mean luteinizing hormone level of women with PCOS we detected that it is significantly higher than mean luteinizing hormone of controls ($p<0.001$) and the serum LH level of 8 iu/l had acceptable validity results (80% sensitivity, 91% specificity, 89.7%PPV, 81.6% NPV and accuracy 85.2%). Kanamarlapudi *et al.,* [24] study in UK reported that luteinizing hormones were over-expressed among women with polycystic ovarian syndrome and Nicholas *et al.,*[25] study in USA clarified the relationship between luteinizing hormone and insulin resistance.

Conclusion

The serum mannose level is significantly elevated in polycystic ovarian syndrome which might indicate its role in pathophysiology of polycystic ovarian syndrome.

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Competing interests

The authors declare that there is no conflict of interest.

Author Contributions

The authors prepared the questionnaire, collect and analyses the cases, wrote, read and approved the final manuscript.

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