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C-REACTIVE PROTEIN AND ADIPOSITY IN WOMEN WITH POLYCYSTIC OVARY SYNDROME

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Abstract: C-reactive protein (CRP) is one of the biomarkers that elevated in obese women with polycystic ovary syndrome (PCOS). PCOS is the most common endocrine disorder, affecting 5-10% of women at reproductive age. This syndrome is characterized by overproduction of androgen and ovulatory dysfunction which are accompanied by many clinical and biochemical features including hirsutism, acne, ovary cysts, menstrual irregularities, obesity, dyslipidemia, hyperinsulinemia and glucose intolerance**. This study was aimed to: 1.** measure serum levels of CRP, total cholesterol, triglyceride, LDL, HDL, VHDL, in addition to calculate Body Mass Index (BMI), in women with PCOS and to compare the results with that of healthy women (Controls). **2.** Compare serum CRP, total cholesterol, triglyceride, LDL, HDL and VHDL in patient subgroups with BMI matched control subgroups. The present study includes thirty (30) women with PCOS and thirty (30) healthy women served as control. All subjects' age range was between 15 to 40 years, then each group classified into two subgroups depending on BMI. Blood samples were collected and serum was obtained to measure CRP and lipid profile. Polycystic ovarian women group exhibited significantly increased serum levels of CRP ($p= 0.001$), cholesterol ($p= 0.009$), triglyceride ($p=0.0001$) and LDL ($p= 0.0001$) when compared to healthy control group. BMI also increased in polycystic ovarian women group although it is statistically not significant when compared to controls. Our results indicated that CRP is one of biomarkers in obese women with PCOS. Its high level associated with adiposity rather than PCOS itself.

Keywords: Polycystic ovary syndrome, Adiposity, C-reactive protein, lipid profile, BMI.

Introduction

C-reactive protein (CRP) is acute phase protein, synthesized and secreted by the liver in response to the stimulus by interleukin-6 which is present in adipose tissue. It is a predictor of acute inflammation which has main role in the progression of atherosclerosis that leads to the cardiovascular diseases [1,2]. Adiposity is a risk factor that leads to cardiovascular and metabolic diseases, also is a predisposing factor to PCOS. PCOS is a disorder that is generally characterized by androgen excess, ovulatory disorders, and polycystic ovaries. Hyperandrogenism causes clinical (hirsutism, persistent acne and alopecia) and/or biochemical changes (raised serum testosterone level) [3].

Ovulatory dysfunction is characterized by irregularity and unpredictability of menstrual periods (less than 21 or more than 35 days). On the other hand, normal menstrual period (between 21 to 35 days) does not exclude ovulatory disorder in hyperandrogenism women. Moreover, between 15-40% of women with hyperandrogenism and normal menstrual period have ovulatory disorder [4]. PCOS occurs

from a genes and environmental factors combination. In addition, many factors can increase the probability of this disorder like a family history of diabetes, obesity and unhealthy lifestyle [5]. As a result of relationship between PCOS and overweight or obesity, level of C-reactive protein is increasing in response to the stimulus by interleukin-6 which originates from adipose tissue, excessive exercise and reducing BMI proved their efficiency in normalization of ovulation and subsequent menstrual cycle. However, most female patients find difficulty in achieving and maintaining a reasonable body weight. A review article published in 2013 showed significant improvements in pregnancy, regular menstrual period, ovulatory function and hyperandrogenism can occur with weight loss[6]. Most PCOS women have obesity and/or insulin resistance. This raised insulin levels can cause dysfunction in the hypothalamic-pituitary-ovarian axis that contribute to PCOS. Hyperinsulinemia elevates GnRH pulse frequency, LH/FSH ratio that leads to increase ovarian androgen production [7]. The diagnosis of polycystic ovary syndrome is approved in the presence two of the following features:

1- Clinical or biochemical signs of excessive androgen production after the exclusion of other hyperandrogenic disorders.
2- Oligomenorrhea and/or anovulation.
3- Ultrasound inspection of ovaries showed more than 12 follicles in each ovary with diameter of 2-9 mm and/or ovarian size more than 10 ml [8].

Patients and Methods

Sixty subjects with age range (15-40) years shared in this study during the period from December/ 2016 to April/ 2017. The individuals were divided into: patient group included thirty women with PCOS, that were diagnosed by clinical signs and/ or symptoms, ultrasound detection of polycystic ovaries and measuring sex hormones profile that are FSH, LH, PRL and testosterone as diagnostic criteria, then patient group subdivided into 2 subgroups that are normal body weight subgroup (n=15) with BMI $<$25 Kg/m^2 and obese women subgroup (n=15) with BMI $>$ 25 Kg/m ^{2} who attended Azadi Teaching Hospital in Duhok City, Iraq. Control group included thirty apparently healthy women without PCOS and subdivided according to their BMI into normal body weight subgroup (n=15) with BMI $<$ 25 Kg/m^2 and obese women subgroup (n=15) with BMI $>$ 25 Kg/m ^{2}. They were volunteers from friends and outpatient clinics, not taking any drug that affecting metabolism of adrenal hormone. Exclusion criteria included diabetes mellitus, impaired hepatic, renal and thyroid function, a cardiac diseases, infection and inflammation cases.

Sample collections and measurements:

Informed consent was obtained from all subjects and blood samples were collected in the morning (of not less than 14 hours fasting). Then samples were left standing for one hour and serum was

separated by centrifugation at 3000 rpm for 10 minutes to measure levels of serum CRP levels by photometric measurement of turbidity that corresponding to reaction of Ab-Ag using end point method (at 340 nm) by Biolabo kit (France), total cholesterol, triglyceride, low density lipoprotein- cholesterol (LDL), high density lipoprotein- cholesterol (HLD was separated from serum and measuring cholesterol that present in HDL) by enzymatic method using Biolabo kit (France) and very low density lipoprotein-cholesterol (VLDL mg/ml =Triglyceride/5), In addition the body mass index (BMI) was calculated as weight in kilograms per height (square meter) [weight/ (height)2], women were considered as normal weight at BMI (18.5-24.9 kg/m^2), overweight women (25-29.9 kg/m^2) and obese women at BMI(>30kg/m^2) [9]. The measurement of sex hormones profile (FSH, LH, PRL, and testosterone) were done by Enzyme Linked Flourescent Assay using a kit supplied by BioMerieux (France). In addition to calculate LH/FSH ratio.

Statistical analysis:

The variables were reported as mean ± SD, Chi ($\chi 2$) square test was used to compare the difference among of variables. The differences are considered to be statistically significant if $p \leq 0.05$. The analysis was performed with the statistical package SPSS collection (version 18).

Results:

There was no significant statistical difference in BMI between study group (PCOS women) and control group. A mean serum levels of CRP (6.84±0.24), cholesterol (152.07 ± 6.88), triglyceride (124.78 ± 8.62) and LDL (25.38 ± 1.78) were significantly increased in women with PCOS when compared to healthy control group. Also the mean serum level of HDL was higher in PCOS women (72.03 ± 7.00) than that of the control group (although not significant). Whereas, the mean concentration of LDL (52.39 ± 2.33) was lower in PCOS women than that of control group (also not significant). Moreover, normal body weight PCOS women exhibited significantly increase in serum levels of cholesterol (p= 0.02), and LDL (p= 0.01) with a mean of (151.50 ± 12.79) and (59.35 ± 3.05) consequently when compared to healthy normal body weight control group. The normal body weight of PCOS women showed not significant increasing in the levels of CRP, triglyceride, HDL and VLDL when compared to the weight matched controls. Obese PCOS women were compared to obese control women to show the effect of PCOS on serum lipid profile. The results indicated that a significant increases in the mean serum levels of triglyceride (156.14±11.57), LDL (45.42±2.40) and VLDL (32.08±2.31) in the obese PCOS women with p-value (0.001), (0.003) and (0.001) consequently. Increased levels of cholesterol and HDL were noticed in the obese PCOS women that statistically not significant when compared to the weight matched controls. Mean serum of CRP (7.43±0.34) was significantly increased in the obese PCOS women with p- value (0.05) comparing to BMI matched controls. Significant increasing was noticed in the mean of CRP

(7.43±0.34) in obese PCOS women with p- value (0.001) when compared to normal weight of PCOS women.

Table1. Comparisons of BMI and serum CRP in patient subgroups with BMI matched controls subgroups and between patient subgroups. (n= 15)Mean ± SD

Parameter	Normal body weight PCOS	Normal body weight control	p-value	Obese PCOS subgroup	Obese control subgroup	p-value	Normal body weight PCOS	Obese PCOS subgroup	p-value
BMI<25 Kg/m2	19.94 ± 0.32	17.74 ± 0.19	0.001	33.80± 0.97	31.84 ± 0 .65	NS	19.94 ± 0.32	33.80± 0.97	0.001
CPR mg/L	4.36±0.83	2.35±0.11	NS	7.43±0.34	4.76±0.34	0.05	4.36±0.83	7.43±0.34	0.001

Parametric data represented as mean ±SD, NS= (not significant), p- value ≥0.05, significant difference (p-value ≤ 0.05).

Table2. A Comparison of mean demographic and biochemical parameters of women with PCOS (n=30) with control groups (n= 30).

Parameters	Control group Mean ± SE	PCOS group Mean ± SE	P-value
BMI kg/m2	24.79 ± 1.39	26.87 ± 1.42	NS
CPR mg/L	3.62 ± 0.2	6.84±0.24	0.001
Cholesterol mg/dl	130.85 ± 4.51	152.07 ± 6.88	0.009
Triglyceride mg/dl	87.03 ± 4.46	124.78 ± 8.62	0.0001
HDL mg/dl	60.02 ± 4.93	72.03 ± 7.00	NS
LDL mg/dl	52.82 ± 2.02	52.39 ± 2.33	NS
VLDL mg/dl	17.41 ± 0.89	25.38 ± 1.78	0.0001
LH(mIU/ml)	6.14 ± 0.48	2.81 ± 0.18	0.0001
FSH(mIU/ml)	5.09 ± 0.38	4.81 ± 0.28	NS
Testerone(ng/ml)	0.75 ± 0.02	0.46 ± 0.03	0.0001
Prolactin (ng/ml)	24.92 ± 0.88	29.50 ± 0.66	0.0001
LH/FSH ratio	1.21 0.04	0.61 0.05	0.0001

Parametric data represented as mean ±SD, NS= (not significant), p- value ≥0.05, significant difference (p-value ≤ 0.05).

Table3. Comparison of lipid profile in patient subgroups with BMI matched controls subgroups. (n=15) Mean ± SD

Parameters	Normal body weight PCOS subgroup	Normal body weight control subgroup	*p*-value	*Obese PCOS subgroup*	*Obese control subgroup*	*p*-value
Cholesterol mg/dl	151.50 ±12.79	121.42± 4.54	0.02	152.64± 5.74	140.28± 7.08	NS
Triglyceride mg/dl	93.42± 4.86	87.64 ±4.48	NS	156.14± 11.57	86.42± 7.90	0.001
HDL mg/dl	66.58 ± 12.53	53.90 ±5.91	NS	77.48± 6.49	66.14 ± 7.76	NS
LDL mg/dl	59.35 ± 3.05	48.78 ± 2.88	0.01	45.42 ± 2.40	56.85± 2.50	0.003
VLDL mg/dl	18.68 ± 0.97	17.55 ±0.90	NS	32.08 ± 2.31	17.28± 1.58	0.001

Parametric data represented as mean ±SD, NS= (not significant), p- value ≥0.05, significant difference (p-value ≤ 0.05).

Discussion

The present study demonstrated that CRP was significantly higher in patient women with PCOS than controls, this agrees with Iuhas et al ., (2012) who measured serum CRP in PCOS group and controls, they contributed the increasing in serum CRP to adiposity and abdominal fat in women with PCOS [10] . Ramanand et al., (2014) study found that a significant increasing of serum CRP in women with PCOS compared to controls due inflammation that associated with PCOS in patient group [11]. This result is also in agreement with Tosi et al., (2009) study who found high level of CRP in women with PCOS and the researchers had indicated that women with PCOS are carrying a marker of low – level inflammation [12]. Mean serum CRP was not significantly increased in normal body weight PCOS subgroup compared to weight matched controls whereas it significantly increased in obese PCOS subgroup compared to obese healthy women subgroup and to normal body weight patients, these findings are agree with Koppalli et al.,(2016) who compared the mean of CRP between obese patients and BMI matched controls and also compared it between normal body weight patients and obese patients, a significant increasing in both comparing were contributed to a state of inflammation in PCOS which aggravated by adiposity [13] . These results also in agreement with Morreale et al., (2011) study that contributed high level of CRP in obese women with PCOS comparing to control group to adiposity in PCOS group [14]. Obesity is stated as inflammatory marker and is related to elevated biomarker levels of IL-6 and TNF-α which originated from adipose tissue that are stimulate synthesis of CRP in the liver [15]. The results of present study are disagreeing with Karoli et al., (2012) who study association of CRP with obesity in women with PCOS and they did not find relation between them [16]. In this we study found that there was alteration in lipid profile. There were significant increases in serum cholesterol, triglycerides and very low density lipoprotein

cholesterol (VLDL) levels in women with PCOS comparing to healthy women without the syndrome, these results are in agreement with Manjunatha et al.,(2014) study who found that there were a significant increases in serum cholesterol, triglycerides and VLDL. He contributed the significant increasing in serum triglycerides may be due to the accumulation of triglycerides, which was due to the increased lipogenesis, decreased clearance by liver or reduced oxidation of fatty acid in addition to increased secretion of VLDL particles by the liver resulted in elevated plasma triglycerides levels which might be due to insulin resistance that was found in women with PCOS [17].

Barter et al., (2003) contributed dyslipidemia in PCOS patients to insulin resistance due to obesity that leads to more catabolism of HDL particles, formation of LDL particles and causing more cholesterol ester transfers protein which might be contributed for this. In addition to the insulin resistance which was seen in PCOS patients, hyperandrogenism also plays an important role in the alteration of serum lipid profile. It has been associated with increased activity of hepatic lipase which has a role in catabolism of HDL particles. Thus women with PCOS have more atherogenic lipid profile than healthy women control [18]. Lambrinoudaki et al.,(2006) found that high level of triglycerides can be contributory factor adiposity in women with PCOS.

Thus it was concluded that dyslipidemia (atherogenic), obesity, insulin resistance may lead to cardiovascular diseases [19]. When comparing serum lipid profile between normal body weight women with PCOS and women with normal body weight we found that there was a significant high level of serum triglyceride, LDL and low HDL in normal body weight women with PCOS which was agreed with Teede et al.,(2007) study who measured serum triglycerides and high density lipoprotein in polycystic ovary syndrome and he found that high triglycerides and low (HDL) in PCOS compared to weight matched controls. Dyslipidemia is a common metabolic abnormality occurs independently of BMI in PCOS, although obesity has a synergistic deleterious effect on PCOS [20]. In addition, Sidhwani et al., (2011) showed that dyslipidemia occurs independently of BMI, PCOS can cause changes in lipoprotein level, increasing risk of cardiovascular disorder. Dyslipidemia was present in normal body weight women and appeared more closely related to androgens. This study also confirm the elevation in particle number of LDL and a critical reduction in LDL size and assume that androgens might play an important role in pathogenesis of dyslipidemia in women with PCOS [21].

The exact mechanism of dyslipidemia and subsequent hyperandrogenism in PCOS is not clear; hyperandrogenism might lead to changes in lipoprotein levels either by affecting directly at the liver, or by changing body composition by favoring central adiposity [22]. Serum levels of triglycerides, LDL and VLDL was significantly higher in obese PCOS women comparing to weight matched controls. In obese women with PCOS, there was an increase in free fatty acid formation and decreased in lipoprotein lipase activity due to increased insulin resistance. The elevated levels of androgen, a biochemical feature in PCOS, leads to dysfunction in lipid metabolism. It has been confirmed that around 70% of PCOS patients have changes

in lipoprotein profile. Moreover, the disturbances in lipid profile still present even after weight loss [23.] The present study supports those findings. The association is present between PCOS and levels of triglyceride and LDL, but not with the BMI. However there was a negative impact effect of adiposity on women with PCOS. The etiology of dyslipidaemia in PCOS women is multifactorial. Hperandrogenism and insulin resistance appears to have important role in disturbance of lipid metabolism by increasing lipolysis process and decreasing lipoprotein lipase and hepatic lipase activites [24].

Conclusion

PCOS has negative impact on lipid metabolism in normal body weight women and adiposity played an important role in pathogenesis of lipid abnormality in obese women with polycystic ovary syndrome. We concluded from this study that obese women with PCOS having high CRP therefore they are more prone to dyslipidemia (atherogenic) and they should routinely screen to prevent further metabolic and cardiac diseases.

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بروتين سي التفاعلي والسمنة في النساء المصابات بمتلازمة تكيس المبايض

الملخص: بروتين سي التفاعلي (CRP) هو من المؤشرات الحيوية الذي يرتفع في النساء البدينات المصابات بمتلازمة تكيس المبايض. متلازمة تكيس المبايض هو اضطراب الغدد الصماء الأكثر شيوعاً، الذي يؤثر على 5-10% من النساء في سن الإنجاب. تتميز هذه المتلازمة بالإفراط في إنتاج الاندروجين وضعف التبويض التي تقترن بالعديد من الميزات السريرية والكيميائية الحيوية بما في ذلك كثرة الشعر، حب الشباب، تكيس المبيض، اضطرابات الحيض، السمنة، اضطراب صورة الدهون، ارتفاع الأنسولين وعدم تحمل الكلوكوز. وقد هدفت هذه الدراسة إلى: 1. قياس مستويات مصل بروتين سي التفاعلي، الكوليسترول، الشحوم الثلاثية، البروتينات الدهنية عالية الكثافة والبروتينات الدهنية واطئة الكثافة، بالإضافة إلى حساب مؤشر كتلة الجسم (BMI)، في النساء المصابات بمتلازمة تكيس المبايض ومقارنة النتائج مع مجموعة السيطرة 2- مقارنة مصل بروتين سي التفاعلي، الكوليسترول، الشحوم الثلاثية، البروتينات الدهنية عالية الكثافة والبروتينات الدهنية واطئة الكثافة في المجموعات الفرعية للنساء المصابات مع نظائرها المتكافئات لها في مؤشر كتلة الجسم للمجموعات الفرعية للنساء السليمات. شملت هذه الدراسة 30 امرأة مصابة بمتلازمة تكيس المبايض و30 امرأة سليمة. وكانت جميع النساء تتراوح أعمارهن بين 15 و 40 سنة، ثم قسمت كل مجموعة إلى مجموعتين فرعيتين اعتماداً على مؤشر كتلة الجسم. تم جمع عينات الدم والحصول على المصل لقياس بروتين سي التفاعلي وهيئة الدهون. وقد أظهرت النتائج أن مجموعة النساء المصابات زيادة كبيرة في مستويات بروتين سي التفاعلي ($p = 0.001$)، الكولسترول ($p = 0.009$)، الشحوم الثلاثية ($p = 0.0001$) والشحوم واطئة الكثافة ($p = 0.0001$) عند مقارنتها بمجموعة السيطرة. كما لوحظ ازدياد مؤشر كتلة الجسم في مجموعة النساء المصابات رغم أنها إحصائيا زيادة غير معنوية بالمقارنة مع مجموعة السيطرة. وقد أشارت النتائج إلى أن بروتين سي التفاعلي هو أحد المؤشرات الحيوية في النساء المصابات البدينات وأن مستواه العالي مرتبط مع السمنة أكثر من ارتباطه مع متلازمة تكيس المبايض نفسه.

الكلمات المفتاحية: متلازمة تكيس المبايض، السمنة، بروتين سي التفاعلي، هيئة الدهون، مؤشر كتلة الجسم.