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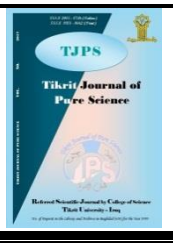

C-REACTIVE PROTEIN AND ADIPOSITY IN WOMEN WITH POLYCYSTIC OVARY SYNDROME

Fatimah Haitham Fathi

Department of Clinical Laboratory Science, College of Pharmacy, University of Mosul , Mosul , Iraq

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Corresponding Author:

Name: Fatimah Haitham Fathi

E-mail: fatmahaitham2013@gmail.com

Tel:

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. It is also called hyperandrogenic anovulation (HA) due to a hormones imbalance in women. Risk factors that predisposing to PCOS including; obesity, decreased physical exercise and family history with PCOS. 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 normal weight women patients with BMI matched controls. 3. Compare serum CRP, total cholesterol, triglyceride, LDL, HDL and VHDL in obese women patients with BMI matched controls. 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. Moreover, the serum levels of LDL and HDL in polycystic ovarian women showed non statistical differences when compared to the 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. PCOS has negative impact on lipid metabolism in normal body weight women and adiposity is played 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 are more prone to dyslipidemia (atherogenic) and they should routinely screen to prevent further metabolic and cardiac diseases.

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 Follicle stimulating hormone (FSH), Luteinizing hormone (LH), Prolactin (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 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 Minividas kit (BioMerieux)®. 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 is 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) are significantly increased in the women with PCOS when compared to healthy control group. Also the serum level of HDL is higher in the polycystic ovarian women with a mean (72.03 ± 7.00) than that of control group (although not significant). Whereas, the mean concentration of LDL (52.39 ± 2.33) is lower in the polycystic ovarian women than that of control group (also not significant). Moreover, normal body weight polycystic ovarian women exhibited significantly increased serum levels of cholesterol (p= 0.02), and

LDL (p= 0.01) with a mean (151.50 ±12.79) and (59.35 ±3.05) consequently when compared to healthy normal body weight control group. The normal body weight polycystic ovarian women showed not significant increasing in the levels of CRP, triglyceride, HDL and VLDL when compared to the weight matched controls. Obese polycystic ovarian 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 polycystic ovarian women with p- value (0.001), (0.003) and (0.001) consequently. Increased levels of cholesterol and HDL were noticed in the obese polycystic ovarian women that statistically not significant when compared to the weight matched controls. Mean serum CRP (7.43±0.34) is significantly increased in the obese polycystic ovarian women with p- value (0.05) comparing to BMI matched controls. Significant increasing is noticed in mean of CRP (7.43±0.34) in obese PCOS women with p- value (0.001) when compared to normal weight PCOS women.

Table1: Comparisons of BMI and serum CRP in patient subgroups with BMI matched controls subgroups and between patient subgroups.

Parameter	Normal body weight PCOS subgroup (n=15) Mean ± SD	Normal body weight control subgroup (n=15) Mean ± SD	*p*-value	*Obese PCOS subgroup (n=15)* Mean ± SD	*Obese control subgroup (n=15)* Mean ± SD	*p*-value	Normal body weight PCOS subgroup (n=15) Mean ± SD	*Obese PCOS subgroup (n=15)*	*p*-value
BMI<25 Kg/m^2	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.

Parameters	Normal body weight PCOS subgroup (n=15) Mean ± SD	Normal body weight control subgroup (n=15) Mean ± SD	*p*-value	*Obese PCOS subgroup (n=15)*	*Obese control subgroup (n=15)*	*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 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 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 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 who compare mean CRP between obese patients and BMI matched controls and also comparing it between normal body weight patients and obese patients, a significant increasing in both comparing were contributed to state of inflammation in PCOS which aggravated by adiposity[13]. These results also in agreement with Morreale et al 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 with elevated biomarker levels of IL-6 and TNF-α which originate from adipose tissue that are stimulate synthesis of CRP in the liver[15]. The results of present study are disagreeing with Karoli et al who study association of CRP with obesity in women with PCOS and they did not find relation between them[16]. In this 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 in agreement with Manjunatha et al study who found that there were 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 may be due to insulin resistance that was found in women with PCOS[17].

Barter et al 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 may contribute for this. In addition to the insulin resistance which is seen in PCOS patients, hyperandrogenism also play important role in 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 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 there was significant high serum triglyceride, LDL and low HDL in normal body weight women with PCOS that agrees with Teede et al study who measure 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 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 may 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 may 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 is significant high in obese PCOS women comparing to weight matched controls. In obese women with PCOS, there is an increased free fatty acid formation and decreased 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]. In the present study support these finding. The association is present between PCOS and levels of triglyceride and LDL, but not with the BMI. However there is 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 increased lipolysis

process and decreased lipoprotein lipase and hepatic lipase activites [24].

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