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HIGH SENSITIVE C-REACTIVE PROTEIN AND APOLIPOPROTEIN B LEVELS IN POLYCYSTIC OVARY SYNDROME

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ABSTRACT

Polycystic ovary syndrome [PCOS] is associated with abdominal obesity, insulin resistance and dyslipidemia. Women with PCOS may be at an increased risk for the development of type 2 diabetes mellitus. Atherosclerosis is characterised by an inflammatory response of the arterial wall due to endothelial injury. Hence low grade chronic inflammation may independently predict coronary heart disease [CHD]. Serum high sensitive C-reactive protein [hsCRP], a marker of chronic subclinical inflammation which is actively involved in atherogenesis is considered a predictor of future CVD. We investigated hsCRP and apolipoprotein B [apoB] levels in a small population of 30 women with PCOS and 30 control subjects. In women with PCOS the levels of hs-CRP, apolipoprotein B and waist-to-hip ratio were significantly elevated when compared with controls. Screening with hsCRP and apolipoprotein B may provide a better risk assessment in patients with PCOS.

KEY WORDS

Apolipoprotein B, atherosclerosis, cardiovascular risk, diabetes, hsCRP, inflammation, PCOS.

INTRODUCTION

Polycystic ovary syndrome [PCOS] is a common disorder of chronic abnormal ovarian function which affects 5-10% of the female population of reproductive age[1]. PCOS is characterized by i) chronic anovulation ii) androgen excess iii) insulin resistance iv) abdominal obesity and v) dyslipidemia[2, 3]. Thus PCOS shares some or most components of the metabolic syndrome. There is an increased prevalence of cerebrovascular disease and cardiovascular risk factors in PCOS women compared with controls[4].

Inflammation is recognized as a major contributor to the pathogenesis of atherosclerosis[5]. C-reactive protein rather than being only a marker of inflammation, may directly promote endothelial dysfunction and therefore play an active role in atherogenesis[6]. Prospective epidemiological studies have demonstrated that CRP, when measured with new high sensitivity assays (hsCRP), strongly and independently predicts risk of myocardial infarction, stroke, peripheral arterial disease and sudden cardiac death. hsCRP levels correlate with several components of the metabolic syndrome, including those not easily measured in clinical practice such as insulin sensitivity, endothelial dysfunction and hypofibrinolysis[7]. Thus CRP may be considered as an ideal marker for screening of apparently healthy young PCOS patients[4].

More recently, adipose tissue is recognized as a rich source of proinflammatory mediators like TNF-α, IL-6, leptin, plasminogen activator inhibitor-I, resistin and C - reactive protein that may directly contribute to vascular injury, insulin resistance and atherogenesis[8]. Intra-abdominal fat appears to produce several of the adipokines in greater amounts than other fat depots[9]. Increased abdominal fat accumulation has been reported in PCOS patients compared with age and BMI matched controls[10]. Evidence is mounting to suggest that adipokines may directly influence endothelial function through their proinflammatory properties[8]. Atherosclerosis is an inflammatory process that initially begins with endothelial dysfunction[11].

It has been reported that CRP is present and synthesized in atherosclerotic tissues[12]. CRP binds the phosphocholine of oxidized low density lipoprotein[LDL], upregulates the expression of adhesion molecules in endothelial cells, increases LDL uptake into macrophages, inhibits endothelial nitric oxide synthase expression in aortic endothelial cells and increases plasminogen activator inhibitor-I expression and its activity[13].

Data from the Women Health study has shown hsCRP to be a strong predictor of the risk than LDL cholesterol[14]. hsCRP levels less than 1, 1 to 3, and greater than 3mg/L may be interpreted as low, moderate and high vascular risk respectively[7]. Several large prospective studies have demonstrated that CRP levels are elevated in patients with PCOS and may be a marker of early cardiovascular risk[4]. But some studies have suggested that PCOS is not associated with increased CRP levels[15]. Thus there are varied reports regarding increased levels of hsCRP in PCOS patients. In this context we have analysed hsCRP, apolipoprotein B and lipid profile between women with PCOS and healthy controls.

SUBJECTS AND METHODS

This was a case-control cross sectional study to compare the levels of hsCRP, apolipoprotein B and lipid profile in a group of 30 PCOS patients and 30 controls. All of the subjects were in the age group of 18-35 years. PCOS was defined as menstrual irregularity due to oligomenorrhea (fewer than

nine menstrual periods per year) or amenorrhea (no menstrual periods for 3 or more months) and clinical evidence of hyperandrogenism (hirsutism, acne or male pattern balding)[4]. None of them were diabetic or treated with hormonal contraceptives, statins or any other medications for at least 2 months before blood examination. None of them had any clinical evidence of acute infection or recent trauma. The study was approved by the institutional ethical committee of SRM Medical College Hospital and Research Center. Informed consent was obtained from all the subjects.

Methods

5 ml of venous blood was collected from the subjects after a 12-h fast. Plasma glucose and serum total cholesterol, triglycerides and HDL were analysed on the same day of collection using Beckman-Coulter analyser and kits from the same company. LDL-C was calculated by Friedewald formula.

The serum was stored at -20ºC and analysis of hsCRP and apolipoprotein B was performed by immunoturbidimetric assay (Beckman Coulter). Data analysis was performed using SPSS, version 17.0.

RESULTS

The PCOS group had a higher BMI [28 ±4.39 vs. 25 ±2.46 kg/m^2, p<0.01] and waist-to-hip ratio [0.87±0.04 vs., 0.84±0.04, p<0.05]. In women with PCOS, levels of hs-CRP [4.02±2.3 vs. 2.6±1.9, p<0.05], apolipoprotein B [103.9 ± 22.09 vs. 82.7±10.55, p< 0.01], Total cholesterol [174.5±21.5 vs. 157±20.7, p<0.01] and LDL-Cholesterol [113.6± 17.3, vs. 98±19.3, p<0.01] were statistically significant compared with controls. There was no significant difference in the concentration of serum triglycerides [p>0.05], high density lipoprotein cholesterol [p>0.05] and plasma glucose [p>0.05] between PCOS patients and healthy controls.

Table 1

Comparison of mean±SD of measured parameters between PCOS and control groups and the statistical significance of the differences

PARAMETERS	CONTROLS(n=30)	PATIENTS(n=30)	pvalue
	mean ± S.D	mean ± S.D	
hsCRP (mg/L)	2.6 ± 1.9	4.02 ± 2.3	p<0.05
ApoB(mg/dl)	82.7 ± 10.55	103.9 ± 22.09	p<0.01
BMI(kg/m2)	25 ± 2.46	28 ± 4.39	p<0.01
Waist-to-hip ratio	0.84 ± 0.04	0.87 ± 0.04	p<0.05
TC(mg/dl)	157 ± 20.7	174 ± 21.5	p<0.01
TGL(mg/dl)	95 ± 28.1	105 ± 53.4	NS
HDL-C (mg/dl)	40 ± 8.8	39.8 ± 6.01	NS
LDL-C (mg/dl)	98 ± 19.3	113.6 ± 17.3	p<0.01
VLDL-C (mg/dl)	19 ± 5.6	19.7 ± 7.62	NS
Plasma Glucose (mg/dl)	89 ± 13.1	92.8 ± 9.9	NS

The values are considered statistically significant if the p value is less than or equal to 0.05(p≤0.05) NS = not significant

Figure 1

The significantly different CRP levels and waist-to-hip ratio in PCOS vs. Control groups

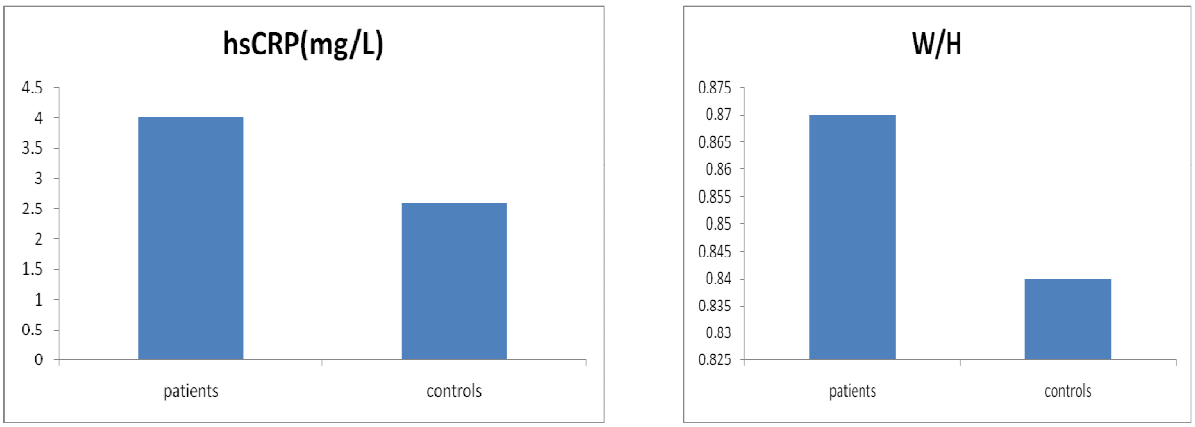
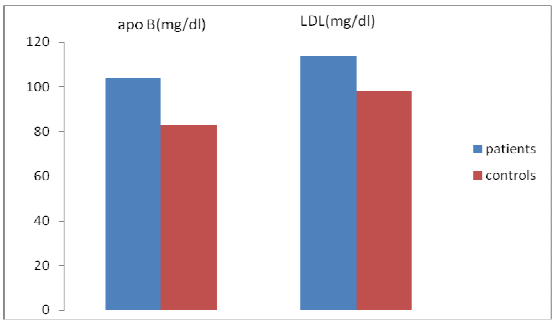


Figure 2

The significantly different apolipoprotein B and LDL-C levels in PCOS vs. Control groups.



DISCUSSION

In our study, levels of hsCRP(mg/L), apolipoprotein B(mg/dl), total cholesterol (mg/dl) and low density lipoprotein cholesterol (mg/dl) were higher in PCOS group compared with controls and statistically significant. BMI and waist-to-hip ratio were also higher in the PCOS group and statistically significant. Boulman et al, (2004) has reported that PCOS women with hsCRP concentration greater than 3mg/L had a higher prevalence of moderate cardiovascular risk compared with BMI matched controls[4].

In our study, the abdominal fat accumulation in PCOS patients is more as indicated by increased waist-hip ratio. Women with PCOS often have the phenotype associated with increased abdominal girth[16]. Excess abdominal fat is usually associated with chronic low-grade inflammation[17]. Tarkun et al., (2004) has concluded that women with PCOS have increased visceral fat mass relative to the BMI matched control group because the waist circumference was higher in the PCOS group[2]. Despres et al., (2000) has found that visceral adiposity correlates with CRP concentration independently of total adiposity in a cross sectional study of 168 participants[18].

We have found that the apolipoprotein B levels were also significantly higher in the patients. Apo B is contained in all the atherogenic lipoproteins, including VLDL, IDL and LDL. Thus the plasma concentration of apoB indicates their cumulative number[19]. A high serum level of apoB is considered a risk factor for arteriosclerosis[20].According to Legro et

al.(2001) women with PCOS are at an increased risk for the development of type II diabetes mellitus at all weights and at an young age[21]. The study by Christian et al., (2000) has concluded that the prevalence of coronary artery calcification in pre-menopausal women with PCOS was significantly greater[22].

In a prevalence study of women referred for coronary angiography, Birdsall et al.,(1997) found that women with PCOS had more extensive CAD[23]. Paul Ridker et al., (2000) noted that even among women with low total cholesterol levels, the risk of cardiovascular events were higher in the presence of increased levels of hsCRP[5]. The levels of hsCRP was a significant predictor of risk even in the subgroup of women with LDL-C levels below 130mg/dl. Individuals with LDL-C concentrations less than 130mg/dl and hsCRP levels more than 3mg/L represent a high risk group often missed in clinical practice[24].

Unlike other markers of inflammation, CRP levels are stable over long periods, have no diurnal variation and can be measured inexpensively. Limitations are noted. This study did not include insulin and androgen assays, repeat hsCRP testing and was not a prospective analysis.

CONCLUSION

The results of this study show elevated hsCRP levels in PCOS patients along with an increase in waist-to-hip ratio. These results suggest that an increase in central obesity is observed in PCOS women contributing to increased levels of inflammation. As CRP is a non-specific inflammatory marker, the levels may need to be interpreted along with relevant clinical findings and related biochemical investigations. The current study also suggests that serum apolipoprotein B measurements may also be considered for risk assessment in these patients. Prospective studies with a larger group would be ideal to know if hsCRP and other inflammatory markers may be considered as indicators of future coronary heart diseases in patients with PCOS.

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