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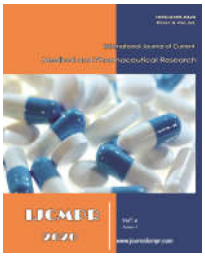

Research Article

ELEVATED LEVELS OF CYSTATIN C, A CARDIOMETABOLIC RISK FACTOR IN POLYCYSTIC OVARIAN SYNDROME

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ABSTRACT

Polycystic ovarian syndrome (PCOS) is a endocrine disorder characterized by irregular menstrual cycle, hyperandrogenism and polycystic ovaries. It is been reported that there is strong association between PCOS and cardio-metabolic risk. Cystatin C is non-glycosylated protein, acts as cysteine protease inhibitor and synthesized at a constant rate in all nucleated cells. Cystatin C are strongly associated with cardiovascular risk and correlated with changes inflammatory biomarkers and reliable marker for assessment of renal function. This study was to evaluate cystatin C levels in the PCOS cases and to correlate with BMI, Waist circumference and lipid levels. This cross-sectional study enrolled total of 108 women with PCOS and a group of 54 healthy volunteers as controls. Body mass index (BMI/kg m2) and waist circumference (cm) were measured and evaluated the Cystatin C and lipid levels in patients with PCOS and controls as well. Total cholesterol, triglyceride, LDL, and cystatin C levels were significantly higher and the HDL cholesterol levels were lower in comparison with healthy subjects ($p < 0.05$). We also found positive correlations between the cystatin C levels and BMI, Waist circumference, Total cholesterol and LDL levels in the PCOS patients. As PCOS is associated with higher levels of cystatin C and recent studies have suggested a role for cystatin C in progression of cardiovascular disease and its complications. More research and clinical studies are needed on the precise role of cystatin C as a cardiovascular risk factor in PCOS and measures to be taken to reduce the overall cardiovascular risk.

INTRODUCTION

Polycystic ovarian syndrome(PCOS) is a heterogeneous group of endocrine disorder characterized by irregular menstrual cycle, hyperandrogenism and polycystic ovaries, with prevalence of 6 to 15% of reproductive-age women.(1–3). In one of the study conducted in India, the prevalence of PCOS has been reported to be 9 to 11% (Mendeley - Prevalence of Polycystic Ovarian Syndrome in Indian Adolescents).The diagnosis of PCOS using Rotterdam criteria requires presence of two of the three following diagnostic features: Polycystic ovaries, Oligo/anovulation and/or Clinical or Biochemical evidence of hyperandrogenism (4). In recent years, many studies have reported a strong association between PCOS and cardiometabolic risk factors including obesity, insulin resistance, and dyslipidemia (2,3). Indeed, the incidence of PCOS is very high in overweight or obese women(5,6). Dyslipidemia in PCOS is characterized by elevated Total Cholesterol, Triglyceride (TG), low density lipoprotein cholesterol (LDL-C), very low density lipoprotein cholesterol (VLDL-C) and decreased high density lipoprotein cholesterol (HDL-C) (7).The clustering of these metabolic indices is implicated in the earlier onset and development of type 2 diabetes and Cardiovascular disease(CVD) in PCOS(8–12) .

Cystatin C is non-glycosylated protein, acts as cysteine protease inhibitor and synthesized at a constant rate in all nucleated cells(13)(16). Cystatin C has been proposed as a reliable marker for assessment of renal function, owing to its free filtration across glomerular capillaries, complete reabsorption by renal tubules, lack of tubular secretion and does not excrete in urine.(14,15)(10,11).

Serum Cystatin C is correlated with changes in inflammatory biomarkers like fibrinogen, serum albumin, D-dimer, antithrombin III(16,17) and this shows strong association between Cystatin C and inflammation. Inflammatory state contributes to development of atherosclerotic plaque, risk of plaque rupture and thrombotic complications(18).

Obesity, increased BMI, higher waist circumference, and increased % of body fat are associated with high levels of serum cystatin C in normal healthy individuals(19,20). Cystatin C is highly expressed in human adipose tissue, equivalently in subcutaneous and omental fat depots. Adipose

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tissue expression of cystatin C is increased in obesity. A graded association is existing between high BMI and elevated serum Cystatin C levels(19,21). This increase could arise from enlarged adipocytes and macrophages, which express cystatin C mRNA and infiltrate the adipose tissue in obesity (22).

Cystatin C is strongly associated with cardiovascular risk, but its precise role in the development and progression of cardiovascular disease is not clearly understood(23,24). Studies suggest that cystatin C shows a stronger linear correlation with cardiovascular morbidity and mortality in comparison with serum level of creatinine (11).Elevated levels of Cystatin C have been shown to predict coronary heart disease, liver fibrosis, and stroke(8,25,26). The purpose of this study was to evaluate cystatin C levels in the PCOS cases and to correlate with BMI, Waist circumference and lipid levels.

MATERIALS AND METHODS

Ethical statement

This study was approved by the Human ethics committee, Mamata medical college and general hospital, Khammam, Telengana. Informed consent was obtained from each member before enrolling in the study.

Study population and design

This cross-sectional study enrolled total of 108 women with PCOS and a group of 54 healthy volunteers as controls at department of Obstrectics and Gynaecology unit of Mamata General Hospital and Shymala Hospital in the Khammam town, Telangana. The diagnosis of PCOS was made according to the 2003 Rotterdam criteria(4). The subjects having Diabetes mellitus, hypertension, coronary heart disease and endocrine disorders were excluded. Alcoholics, smokers, pregnant women, subjects on vitamin supplementation and subjects with altered kidney function (random urinary protein >16mg/dl, serum creatinine >1.1mg/dl) are also excluded from the study.

Body mass index (BMI/kg m^2) and waist circumference (cm) were measured in each subject. 5 ml of blood sample was collected from the subjects as well as controls after overnight fasting (12hr) by venipuncture and then centrifuged; aliquots of serum were stored at -80^oC until assayed. Total Cholesterol, Triglycerides and High-density lipoprotein (HDL) were measured using cholesterol oxidase/peroxidase, glycerol phosphate oxidase/peroxidase, and phospho-tungstate precipitation methods respectively. Low-density lipoprotein (LDL) was calculated using Friedewald formula. Serum levels of cystatin C were measured using Latex enhanced Immuno turbidimetry method.

Statistical Analysis

All values were expressed as mean ± SEM. The results obtained were analysed statistically using the unpaired student't' test to evaluate the significance of difference between the mean values. Pearson's correlation coefficient was used for correlation among variables. Differences were considered statistically significant at a level of P <0.05.

RESULTS

The mean BMI and waist circumference were increased in PCOS cases when compared to controls. Serum cholesterol, TG, LDL-C and cystatin C levels were higher and HDL cholesterol levels were lower in PCOS patients when compared with non PCOS controls. (Table 1). Cystatin C has shown positive correlation with obesity (BMI and waist), cholesterol and LDL-C. (Table 2)

Table 1 Comparison of anthropometric and clinical parameters between healthy volunteers and subjects with PCOS.

Parameter	Healthy Volunteers (n=54)	PCOS (n=108)	P-value
BMI(kg/m2)	24.3 ± 0.7	24.2 ± 0.4	NS
Waist(cm)	79.46 ± 1.3	82.11 ± 0.9	NS
Cholesterol (mg/dl)	162.6 ± 4.4	189.1 ± 3.3	<0.0001*
TG(mg/dl)	119.0 ± 4.5	147.9 ± 4.4	<0.0001*
HDL(mg/dl)	41.81 ± 0.4	38.06 ± 0.4	<0.0001*
LDL(mg/dl)	96.98 ± 4.2	122.1 ± 3.2	<0.0001*
CystatinC (mg/L)	0.82 ± 0.02	1.10 ± 0.02	<0.0001*

Values expressed as mean±SEM. NS - Not Significant; *statistically significant.

BMI: Body mass index; TG-Triglycerides; HDL-High density lipoprotein; LDL-Low density lipoprotein

Table 2 Pearson's correlation with r-value (Cystatin C vs other parameters)

Variable	Cystatin c *R*
BMI(Kg/m^2)	0.529***
Waist(cm)	0.345***
Cholesterol(mg/dl)	0.261**
TG(mg/dl)	-0.119NS
HDL-C(mg/dl)	-0.124NS
LDL-C(mg/dl)	0.292**

**significant at 1% ***significant at 0.1%NS: Not significant

BMI: Body mass index; TG-Triglycerides; HDL-High density lipoprotein; LDL-Low density lipoprotein

DISCUSSION

This study compared the levels of Cystatin C in PCOS patients and healthy volunteers and evaluated the correlation of Cystatin C with BMI, Waist circumference and lipid levels. Total cholesterol, triglyceride, LDL, and cystatin C levels were significantly higher and the HDL cholesterol levels were lower in comparison with healthy subjects ($p < 0.05$). We also found positive correlations between the cystatin C levels and BMI, Waist circumference, Total cholesterol and LDL levels in the PCOS patients.

Cystatin C, an established serum marker of renal function is becoming acknowledged as a marker of elevated risk of death from cardiovascular complications, myocardial infarction and stroke(27).We found that serum cystatin C levels were significantly higher in PCOS women than controls and these results are in line with earlier study conducted by Mohammad Hossein *et al* (28).

The increasing global prevalence of obesity may play a key role in promoting the development of PCOS in susceptible individuals. In addition, obesity aggravates preexisting clinical, hormonal and metabolic features in most women with PCOS(29,30).

Dyslipidemia was observed in PCOS cases when compared with controls. The increase in mean cholesterol, TG and LDL-C were more pronounced in obese women. Servais *et al* (31) showed that cystatin C level is significantly related with metabolic syndrome components like blood pressure, triglycerides and waist circumference. Recent studies have demonstrated increased cystatin C as independent risk factor for CVD, hypertension, atherosclerosis and stroke that may reflect an increased inflammatory statethat contributes to

atherosclerotic plaque vulnerability and a high risk of plaque rupture and thrombotic complications (18). In our study cystatin C has shown positive correlation with obesity (BMI and waist), cholesterol and LDL-C.

CONCLUSION

As PCOS is associated with higher levels of cystatin C and recent studies have suggested a role for cystatin C in progression of cardiovascular disease and its complications. More research and clinical studies are needed on the precise role of cystatin C as a cardiovascular risk factor in PCOS and measures to be taken to reduce the overall cardiovascular risk. This will supplement PCOS treatment and can help in minimizing future cardiovascular risk.

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