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Decrease Of High Sensitivity C-Reactive Protein (hsCRP), A Cardiovascular Risk Marker By Metformin Treatment In Polycystic Ovarian Syndrome Patients.

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ABSTRACT

Polycystic ovary syndrome (PCOS) is a common endocrine disorder among the women with a prevalence between 5 and 10% In addition to chronic anovulation and androgen excess, PCOS is associated with insulin resistance (IR), metabolic abnormalities and an increased cardiovascular risk. hsCRP is an independent major risk marker of cardiovascular complications. Chronic low-grade inflammation seems to play an essential role in the pathogenesis of PCOS, and might lead to the development of metabolic consequences. There are contradictory reports about the beneficial effects of metformin treatment on CRP levels in patients with PCOS. So we studied the effect of metformin treatment on hsCRP levels in PCOS patients.

Keywords: PCOS, Insulin resistance, Cardiovascular risk, Metformin Treatment, CRP.

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INTRODUCTION

Polycystic ovarian syndrome (PCOS) is one of the commonest endocrine disorders affecting female fertility [1]. It is characterized by insulin resistance, dyslipidemia, hyperandrogenism, chronic anovulation and polycystic ovaries [2]. Currently the prevalence of PCOS is increasing throughout the world, which might be attributed to westernization, stress and lifestyle changes [3]. It affects 8-20% of women in the younger age group worldwide [4]. There is a high prevalence of PCOS in Indian women than their Caucasian counter parts [5], with an estimated prevalence of up to 22.5% [6]. adding to health burden of the country. Besides fertility problems, PCOS women have a high risk for developing insulin resistance and prediabetes /diabetes, dyslipidemia, heart disease, stroke, endometrial cancer and obesity [7].

Insulin resistance is considered as a central feature of PCOS. Insulin resistance was assessed as HOMA-IR and Insulin sensitivity as QUICK-I check index. HOMA IR was calculated using the formula [fasting plasma glucose (mg/dL) × fasting insulin (IU/mL)]/405 and the qualitative insulin sensitivity check index (QUICKI) was calculated using the formula 1/[log fasting insulin (μU/mL) + log fasting glucose (mg/dL)]. HOMA IR (cut off >2.5) and QUICK-I (cut off <0.333) was used to assess insulin resistance in our study subjects [8]. Both obese and non-obese PCOS women exhibit insulin resistance and are hyperinsulinemic than age and weight matched normal women. The decrease in insulin sensitivity in PCOS seems to be an intrinsic defect in genetically susceptible women. Defect in insulin signaling either at the ligand –receptor level or the post receptor binding triggers the metabolic abnormalities culminate in the pathogenesis of PCOS [9]. Usually insulin action is mediated through tyrosine kinase receptor. Tyrosine auto-phosphorylation increases the insulin receptor tyrosine kinase activity, whereas serine phosphorylation inhibits it. The possible mechanism of insulin resistance is attributed to the excessive serine phosphorylation of insulin receptors. Serine phosphorylation has also been shown to increase cytP450 enzyme activity leading to increased androgen synthesis as a result women with insulin resistance have significantly higher level of testosterone and increased prevalence of hirsutism than non-insulin resistant women [10]. Several large-scale prospective studies have demonstrated that CRP is a strong independent predictor of future CVD and/or stroke [11,12]. CRP seems to be more potent as a predictor of cardiovascular events and it may be an ideal marker for screening of apparently healthy young PCOS patients than normal healthy women. Hence serum hsCRP levels were analyzed in PCOS women to assess the CVD risk.

MATERIALS AND METHODS

Thirty PCOS women 18- 30 years selected as per modified Rotterdam criteria. The diagnosis of PCOS was made according to modified Rotterdam criteria: 1) The presence of clinical and/or biochemical signs of hyperandrogenism; 2) At least one of the following: Oligo or anovulation and/or polycystic ovaries. Under Interventional study design, Metformin was given at a dose of 500 mg/day for 90 days. Patients with cardiovascular disorders, infections, diabetes mellitus and thyroid disorders are excluded. Fasting blood samples were collected at the beginning and at the end of three months. BMI, insulin assay, high sensitivity CRP were analyzed. All statistical analysis was performed using SPSS statistics version 20.0. Students' t test was applied and the results are expressed as mean ± SD, $p < 0.05$ – significant.

Table 1: Changes In Lipid Profile Before And After Metformin Treatment

Parameters	Before treatment n=28	After treatment n=28	p Value
Total cholesterol (mg/dl)	193.33±30.43	172.20±23.31	P<0.01
TG (mg/dl)	148.20±34.62	132.37± 22.27	P<0.05
HDL (mg/dl)	40.20±4.75	44.47±3.49	P<0.01
LDL (mg/dl)	123.49±27.4	101.26±21.84	P<0.01
VLDL (mg/dl)	29.64±6.92	26.47±4.45	P<0.05

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Figure 1: Changes In Lipid Profile Before And After Metformin Treatment

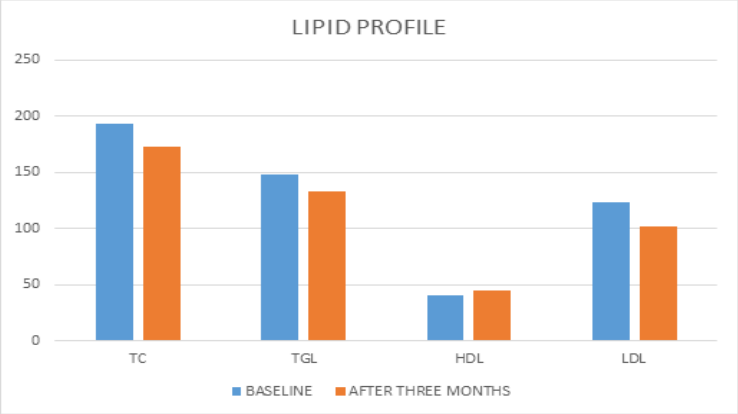

Table 2: Comparison Of Insulin Resistance Indices In Pcos Subjects Before And After Metformin Treatment

Parameters	Before treatment n=28	After treatment n=28	p Value
Glucose (mg/dl)	84.93±4.02	83.83±3.58	NS*
Insulin (µIU/ml)	17.93±3.11	14.58±2.10	P<0.01
G/I RATIO	4.91±1.08	5.87±0.92	P<0.01
TG/HDL RATIO	3.77±1.17	3±0.62	P<0.01
HOMA-IR	3.76±0.65	3.02±0.49	P<0.01
QUICK-I	0.315±0.01	0.325±0.01	p<0.01

NS* :- Not Significant

Figure 2: Insulin Resistance Indices In Pcos Patients Before And After Metformin Treatment

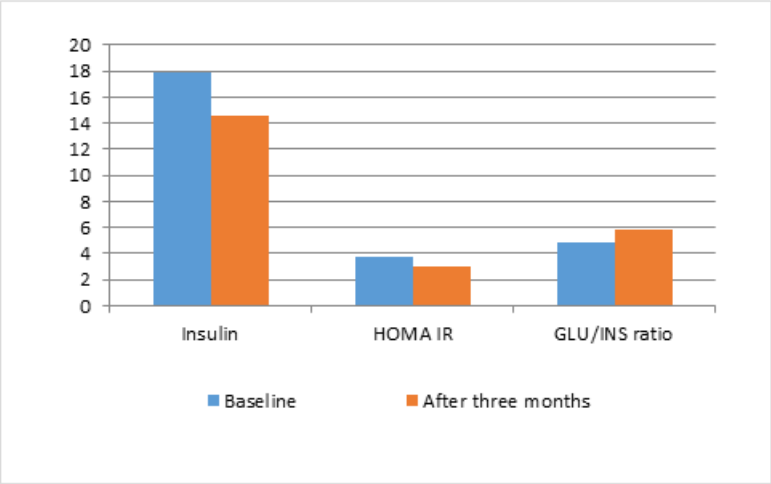

Table 3: Changes In Cardiovascular Factors In Pcos Patients Before And After Metformin Treatment

Parameters	Before treatment n=28	After treatment n=28	p Value
BMI (kg/m2)	26.29±3.14	24.46±3.18	p<0.05
LAP (cm.mmol/L)	57.56±16.91	41.57±8.96	p<0.01
Waist to ht ratio	0.59±0.03	0.55±0.02	p<0.01
VAI	3.27±0.92	2.53±0.45	p<0.01
hs-CRP (mg/L)	4.29±0.87	3.56±0.66	p<0.01

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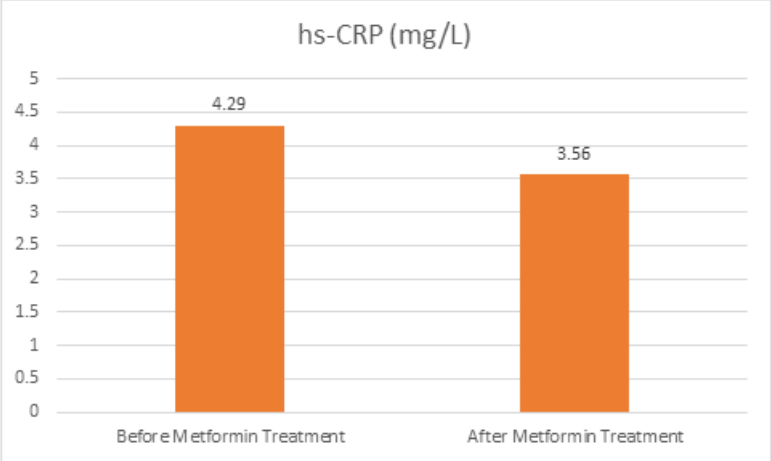
Figure 3: Cardiovascular Risk Marker Levels In Pcos Patients Before And After Metformin Treatment



RESULTS

Lipid profile – Cholesterol, TG, LDL level are decreased after metformin treatment and HDL level was increased after metformin treatment. BMI was significantly reduced by metformin treatment ($p<0.01$). HOMA-IR improved from 3.76 ± 0.65 to 3.02 ± 0.49, $P<0.01$). and hsCRP was also reduced significantly (4.19 ± 0.88 to 3.58 ± 0.7, $p<0.01$).

DISCUSSION

PCOS is one of the most common endocrine disorder affecting women of reproductive age. Several studies have suggested that insulin resistance plays an important role in the pathogenesis of the syndrome and its repercussion is responsible for the metabolic, endocrine, reproductive and long term complications. Since women with PCOS exhibit insulin resistance or some degree of hyperinsulinemia, insulin-sensitizing agents have been used in most subjects with PCOS [13]. The most extensively used insulin-lowering agent in the treatment of PCOS is metformin [14]. Though metformin has been prescribed for the management of PCOS since 1994, several studies have reported conflicting evidence regarding the role of metformin in PCOS [15,16,17].

PCOS women were reported to have an abnormal lipid profile compared to age and weight matched controls [18]. Insulin resistance plays a significant role in the development of dyslipidemia. It is characterized by raised concentrations of plasma triglyceride, marginally elevated LDL, and reduced HDL [19]. The data in our study showed that metformin treatment resulted in decrease in total cholesterol, TG and LDL levels in PCOS patients ($p<0.01$). In this study, we used QUICK-I as an index for insulin sensitivity. A quick-I value of < 0.33 was used to determine insulin resistance. The mean QUICK-I at the baseline in both the groups were found to be <0.315 suggesting the presence of an insulin resistant state in PCOS. It had been shown in several trials that metformin was unlikely to induce hypoglycaemia [20]. Our results are in agreement with the findings of earlier study which had reported that supplementation of metformin for even 6-weeks showed significant reductions in total cholesterol, LDL and TG in patients randomized to metformin and other treatment [21].

In this study the effect of metformin on a cardiovascular risk marker hsCRP was assessed. hs-CRP was increased in PCOS subjects. It could be related to obesity and/ or IR. Obesity is associated with elevated CRP in individuals with the metabolic syndrome and CRP decreases after weight loss in obese subjects. After three months of treatment with metformin, serum CRP significantly decreased. and also in our study, there was significant reduction of BMI and HOMA-IR. Thus, metformin treatment in women with PCOS showed improvement in IR and BMI and significant reduction in hsCRP level.

CONCLUSIONS

Decrease of high sensitivity C-Reactive protein (hsCRP) and HOMA-IR after metformin treatment in PCOS women clearly indicates that there is a strong positive association of obesity, insulin resistance with hsCRP and so metformin would be beneficial in cardiovascular risk reduction in PCOS patient. Since the study period was for a short duration, the clinical outcome, ovary changes, fertility issues could not be assessed and it needs a long term study. The tolerance and the adverse effects of metformin in PCOS women if any on long term use require further studies.

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