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Metformin Treatment Reduces Insulin Resistance And Also Corrects Dyslipidemia In PCOS Women

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Abstract
Background: *Dyslipidemia is a common metabolic complication occurring in polycystic ovarian syndrome. Studies suggest that insulin resistance is associated with dyslipidemia. Metformin is an insulin sensitizing agent commonly used in the management of PCOS. In the present study we assessed the effect of metformin on insulin resistance and dyslipidemia in PCOS women.*
Methods: *Thirty PCOS women of 18-30 years who fulfilled the Rotterdam criteria were treated with metformin (1000mg/day) for 3 months. Fasting Plasma glucose, insulin, HOMA-IR and Lipid profile were measured at the baseline and after 3 months of treatment.*
Results: *Three months of metformin treatment significantly reduced fasting insulin levels, HOMA-IR value and also improved lipid profile in pcos women.*
Conclusion: *Metformin treatment would be more beneficial in the management of PCOS with respect to improvement of insulin sensitivity and dyslipidemia.*
Keywords: *Polycystic ovary syndrome, HOMA-IR, Lipid.*

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I. Introduction

Polycystic ovary syndrome (PCOS) is a common endocrine disorder among the women of reproductive age, which is characterized by chronic anovulation, clinical or biochemical hyperandrogenism, insulin resistance, obesity and dyslipidemia. [(1)]. Prevalence of dyslipidemia is higher in women with PCOS as compared with regularly cycling women [(2)]. Dyslipidemia is characterized by raised concentrations of plasma triglyceride, marginally elevated low density lipoprotein (LDL)-cholesterol, and reduced high density lipoprotein (HDL)-cholesterol [(3)]. Insulin resistance is the key factor in the pathogenesis of PCOS and thus dyslipidemia may be consistent with the insulin resistant state [(4)]. Metformin is an extensively used insulin sensitizing agent in the treatment of PCOS [(5)]. Different beneficial effects of Metformin on insulin resistance and dyslipidemia have been reported previously [(6,7)]. Hence in the present study we assessed the effect of metformin treatment on insulin resistance and dyslipidemia in PCOS women.

II. Materials And Methods

The study was done in department of Biochemistry in collaboration with Department of Obstetrics and Gynecology from April 2017 to November 2017 at Rajah Muthiah Medical College & Hospital, Annamalai University. The study was approved by Institutional Human ethics committee. Informed written consent was obtained from participants of the study.

2.1 Inclusion criteria: Thirty women of age group 18-30 years who were diagnosed as PCOS by Rotterdam criteria, after exclusion of other etiologies such as congenital adrenal hyperplasia, androgen-secreting tumors, Cushing's syndrome were treated with Metformin 1000 mg (500 mg twice daily) for 3 months.
2.2 Exclusion criteria: Subjects with the history of diabetes, hypertension, systemic inflammatory conditions and clinical evidence of acute infections, systemic diseases, renal and hepatic diseases and Oral contraceptive pill usage were all excluded from the study. Complete physical examination was recorded including anthropometric measurements (Height and weight, BMI, Blood pressure, waist circumference, Hip circumference and Waist hip ratio), fasting plasma glucose, lipid profile and fasting insulin were all measured before and after metformin treatment. Plasma glucose, Serum total cholesterol, triglycerides and HDL-C were

measured using standard kits in auto analyzer. LDL and VLDL were calculated using Friedewald formula and Insulin resistance was estimated via Homeostasis Model Assessment insulin resistance index: HOMA IR = [fasting plasma glucose (mg/dL) × fasting insulin (IU/mL)]/405

23 Statistical analysis: All statistical analysis was performed using SPSS statistics version 20.0. The results are expressed as mean ± SD. For comparison of all quantitative variables, within the group at the baseline and after the third month, paired t-test was used**.** A p value of <0.05 was considered to be statistically significant.

III. Results

In the present study out of thirty subjects twenty eight subjects completed the study. The clinical and anthropometric characteristics at the baseline and after three months metformin treatment were depicted in Table 1. Significant Reductions in Weight, Waist hip ratio and BMI was observed after 3 months of metformin treatment ($p<0.05$). No significant change in Blood pressure was observed during the course of metformin treatment. Table 2. represents the changes insulin resistance indices and lipid profile before and after metformin treatment. Metformin treatment showed a significant reduction in fasting insulin and HOMA-IR levels without significant change in fasting plasma glucose . There was also a significant drop in Total cholesterol, TGL, LDL-C and a raise of HDL-C after metformin treatment.

TABLES: Table.1. Clinical and Anthropometric characteristics of subjects with PCOS before and after Metformin Treatment**.**

VARIABLES	BEFORE TREATMENT	AFTER TREATMENT	P value
BMI (kg/m^2)	26.29±3.14	24.46±3.18	p<0.05
SBP (mmHg)	119.07±4.01	118.93±3.24	NS
DBP (mmHg)	78.20±2.20	78.90±1.81	NS
WAIST CIRCUMFERENCE (cm)	92±2.61	85.67±2.38	p<0.01
HIP CIRCUMFERENCE (cm)	108.10±2.26	103.70±2.68	p<0.01
WAIST HIP RATIO	0.85±0.02	0.83±0.02	p<0.05

Table .2 Insulin resistant indices and Lipid profile in PCOS women before and after Metformin Treatment.

variables	before treatment	after treatment	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
homa-ir	3.76±0.65	3.02±0.49	p<0.01
total cholesterol (MG/DL)	193.33±30.43	172.20±23.31	p<0.01
tgl (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

IV. Discussion

The present study was done to assess the effect of Metformin on Insulin resistance and dyslipidemia in PCOS women. The mean age of participants in the study was 23.65±4.18. Insulin resistance is implicated as the key player in the pathogenesis of PCOS [(8)]. Insulin resistance by stimulating lipolysis and altering the expression of lipoprotein lipase and hepatic lipase may contribute to the pathogenesis of dyslipidemia in PCOS [(9)]. Our study showed that metformin treatment exhibited significant reduction in BMI as well as Waist hip ratio. This was in line with the findings of Usanne Tan et al., (2007) who had also reported that metformin treatment significantly reduced weight, BMI and WHR in women with PCOS [(10)]. In contrast Lord et al., 2003 had demonstrated no significant reduction of BMI and Waist hip ratio by metformin in women with PCOS [(7)]. This conflicting result might be due to diversity of patient's characteristics, nature of diet and physical exercise during the course of study.ll of our patients had evidence of insulin resistance with a HOMA-IR value more than 2.5 indicating the high prevalence of insulin resistance [(11)]. In our study, there was a significant reduction of plasma insulin and HOMA-IR by metformin therapy. In contrast Zahra et al., (2017) in their study found no significant reduction in HOMA-IR value in PCOS women after metformin treatment [(6)]. This discrepancy might be due to small sample size and shorter duration in that study. However it had been shown that metformin therapy reduced serum insulin and HOMA-IR in overweight and obese women with PCOS having insulin resistance [(10)]. The improvement in insulin sensitivity by metformin could be attributed to its positive effects on insulin receptor expression and tyrosine kinase activity [(12)]. Insulin is known to exhibit stimulatory effect on lipoprotein lipase (LPL) [(15)]. In insulin resistant state like PCOS, the Lipoprotein lipase activity might get reduced leading to decreased VLDL catabolism resulting in hypertriglyceridemia and decreased HDL-C [(16)]. In this study we have observed a significant reduction serum total cholesterol, LDL-C, Triglycerides and

significant increase of HDL-C after metformin treatment. Our findings about metformin effect are in contrast to G. Karoon et al., (2016) who didn't observe any change in lipid levels during the course of metformin treatment in PCOS women [(13)]. Consistent with our findings similar result was also observed by Santana et al., (2004) upon metformin treatment in women with PCOS [(14)]. Metformin may exert this lipid lowering effect through improving insulin sensitivity and leptin sensitivity [(17)] or through activating AMP-activated protein kinase (AMPK) and consequently suppressesing fatty-acid desaturase (FADS) genes, leading to reduced levels of lipid metabolites and LDL cholesterol [(18)]. Hence metformin treatment would be more beneficial in the management of PCOS with respect to improvement of insulin sensitivity and dyslipidemia.

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