

Effect of Administration of Metformin on Lipid Profile in Patients with Polycystic Ovary Syndrome after Six Months of Treatment

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ABSTRACT

Objective: Women with polycystic ovary syndrome (PCOS) exhibit risk factors for cardiovascular diseases such as abdominal obesity, insulin resistance and dyslipidemia. Insulin sensitizers, especially metformin, have been shown to improve these metabolic disturbances, but there are only a few studies on their effects on serum lipids in polycystic ovary syndrome. The aim of the present study was to evaluate the effects of metformin on lipid profile changes in patients affected by PCOS.

Methods: In this study, 60 women aged 16-40 years with PCOS were selected. Diagnostic criteria were based on the diagnostic criteria of PCO syndrome in Rotterdam ESHRE (European Society for Human Reproduction)/ ASRM (American Society of Reproductive Medicine) Sponsored PCOS Consensus Workshop Group (2004). Samples of fasting peripheral blood were taken from all patients to test serum Cholesterol, Low density lipoprotein (LDL), Triglycerides (TG) and High density lipoprotein (HDL) at the start of the treatment and were repeated after 6 months of metformin treatment in a dosage of 1500 mg in divided doses. Also, BMI was compared before and after the treatment.

Results: The mean BMI before treatment was 24.6 ± 2.9 kg/m² and after treatment was 23.8 ± 2.8 kg/m² ($p < 0.0001$). The mean cholesterol level before treatment was 192.9 ± 30.2 mg/dl and after treatment was 174.0 ± 21.7 mg/dl ($p < 0.0001$).

The mean Triglyceride value before treatment was 148.1 ± 43.2 mg/dl and after treatment was 129.9 ± 29.6 mg/dl ($p < 0.0001$). The mean LDL level before treatment was 127.5 ± 31.7 mg/dl and after treatment was 106.8 ± 21.6 mg/dl ($p < 0.0001$). The mean HDL level before treatment was 36.6 ± 7.9 mg/dl and after treatment was 41.1 ± 6.4 mg/dl ($p < 0.0001$).

Conclusion: In women with PCOS, metformin treatment had beneficial effects on lipid profile and therefore it could be useful in the prevention of cardiovascular complications in these women.

Key words: Lipid profile, Metformin, PCO syndrome.


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INTRODUCTION

Polycystic ovary syndrome (PCOS) is a heterogeneous condition characterized by chronic anovulation and hyperandrogenism, and it is typically associated with insulin resistance and hyperinsulinemia – especially in obese women.^{1,2} This disorder affects women in reproductive age. The signs of PCOS include hyperandrogenism and anovulation. Since the cause of this syndrome has not been diagnosed yet, therefore its treatment will be depending on signs and patient characteristics such as: hirsutism, obesity, menstrual disorder and infertility.³

Women with PCOS have an atherogenic lipid profile characterized by lower high-density lipoprotein (HDL) cholesterol and higher triglyceride (TG) and low-density lipoprotein (LDL) cholesterol levels than the age- and weight-matched control women.^{4,6}

Metformin, a biguanide antihyperglycemic drug, has been used for decades for the treatment of type 2 diabetes mellitus. In diabetic patients, metformin treatment has been shown to have a beneficial effect on circulating lipid levels by decreasing the concentrations of plasma triglycerides, total and LDL cholesterol

and by increasing the levels of HDL cholesterol and the HDL: LDL cholesterol ratio, independently of the improvement of glycemic control. ⁷ However, there are only a few studies specifically concerning the effects of metformin therapy on the lipid profile in women with PCOS.

Keeping this in mind, the aim of our study was to investigate the effect of metformin on lipid profile changes, in women with PCOS.

MATERIALS AND METHODS

The present study was conducted in the Department of Biochemistry in collaboration with Department of Obstetrics and Gynaecology, Govt. Medical College, Patiala. The study was approved by the institutional ethical committee.

A total of 60 patients(in the range of 16-40 years) reporting to the outpatient department of Obstetrics and Gynaecology, Department of Rajindra Hospital, Patiala with clinical features suggestive of PCOS were included in the study.

The presence of any two of the following criteria was used to diagnose PCOS as laid down by the Rotterdam ESHRE/ ASRM Sponsored PCOS Consensus Workshop Group (2004):

- Oligo-ovulation or anovulation
- Clinical and/ or biochemical hyperandrogenism
- Polycystic ovaries and exclusive of congenital adrenal hyperplasia, androgen secreting tumours and Cushing’s syndrome.

Selection Criteria

- Oligomenorrhoea (< 6 cycles/ year), secondary amenorrhoea or hypomenorrhoea (bleeding <1 day) with obesity.
- Oligomenorrhoea (< 6 cycles/ year), secondary amenorrhoea or hypomenorrhoea (bleeding < 1 day) with hirsutism.
- Oligomenorrhoea (< 6 cycles/ year), secondary amenorrhoea or hypomenorrhoea (bleeding < 1 day) with acne.
- Oligomenorrhoea (< 6 cycles/ year), secondary amenorrhoea or hypomenorrhoea (bleeding < 1 day) with infertility.

The menstrual cycle was described as being oligomenorrhoeic (a cycle interval of longer than 35 days but less than six months) amenorrhoeic (no menstruation for more than six months) or hypomenorrhoeic (bleeding lasting less than 1 day).

Exclusion criteria

1. Infertility due to male factors
2. Infertility due to tubal factors
3. Infertility due to cervical factors
4. Hyperprolactinemia
5. Thyroid disorders
6. Adrenal hyperplasia
7. Cushing’s syndrome
8. Androgen producing tumors

The fertility status was classified as “proven fertile” (those with a previous pregnancy and non-subsequent infertility), “fertility untested” (those who had never tried to conceive) or “infertile”.

METHODOLOGY

The patients fulfilling the above criteria were included in the study. A detailed history was recorded with particular reference to menstrual irregularity, obesity, hirsutism, acne and infertility. Informed consent was taken from every patient before including her in the study. It was a 6 month prospective randomized study involving 60 patients of PCOS. Serum levels of Cholesterol, HDL, LDL and Triglycerides were estimated at the start of treatment and were repeated after 6 months of metformin treatment in a dosage of 1500 mg in divided doses.

Height and weight measurements were done to calculate the BMI. Evidence of hirsutism, acne was looked for.

Assays: Lipid Profile

Fasting blood sample was collected from the patients and serum was separated for estimation of the following:

1. S.Cholesterol: By in vitro enzymatic colorimetric method.⁸
2. S. Triglycerides: By in vitro enzymatic colorimetric method.⁹
3. Estimation of LDL: By Friedewald’s formula.¹⁰
 $LDL-C = Total\ cholesterol - (TG/5 + HDL-C)$
4. HDL-Cholesterol: By enzymatic method after precipitation of serum by phosphotungstate and magnesium chloride.¹¹

SSPS version 13 was used to do the appropriate statistical tests including Student’s T Test (two- tailed), Fisher exact test. The results are expressed as means and standard deviation. Differences were considered to be statistically significant if p-value was <0.05.

Table 1: Distribution of patients according to clinical presentation

Clinical Presentation	No. of patients	%age
Menstrual irregularity	54	90
Infertility	15	25
Clinical hyperandrogenism	43	71.67
Overweight	16	26.67
Obesity	5	8.33
Polycystic ovaries on ultrasonography	50	83.33

Note: Discrepancy in total number of patients due to overlapping of symptoms.

Table 2: BMI changes after giving metformin for 6 months

	BMI (kg/m ²)				
	Before	After	t	P	S
Range	20.2 – 32.5	17.6 – 31.6	9.72	< 0.0001	HS
Mean ± SD	24.62 ± 2.91	23.80 ± 2.85			

Table 3: Changes in lipid profile after 6 months of treatment with metformin

Parameter (mg/dl)	Before	After	p	T	S	% Change
S.Cholesterol (mg/dl)	192.95 ± 30.32	174.03 ± 21.72	<0.0001	6.3	HS	↓ 9.80
Triglyceride levels (mg/dl)	148 ± 43.21	129.97 ± 29.68	<0.0001	6.3	HS	↓12.2%
LDL levels (mg/dl)	127.52 ± 31.73	106.87 ± 21.67	<0.0001	5.57	HS	↓16.19%
HDL levels (mg/dl)	36.67 ± 7.94	41.1 ± 6.48	<0.0001	4.34	HS	↑12.08%

RESULTS

In the present study, 60 patients with clinical features suggestive of PCOS who attended the outpatient department of Obstetrics and Gynaecology Department of Rajindra Hospital attached to Govt. Medical College, Patiala were evaluated. Serum levels of serum Cholesterol, HDL, LDL and Triglycerides were estimated and were repeated after 6 months of treatment with metformin.

The study was done over a period of 12 months and the following observations were made. The mean age of patients was 22.8 ± 4.65 years with a range of 16 years to 38 years. The maximum number of patients (25) was in the 21 – 25 years age group.

Menstrual irregularity was seen in 90% of the patients (Oligomenorrhoea or secondary amenorrhoea). Infertility was present in 25% patients while 71.67% of the patients presented with features of hyperandrogenism. 26.67% patients were overweight and 8.33% patients were obese. 83.33% patients had polycystic ovaries on ultrasonography. Discrepancy in total number of patients was due to overlapping of symptoms. The mean BMI levels before giving treatment were 24.62 ± 2.91 kg/m² and significantly decreased to 23.80 ± 2.85 kg/m² after giving treatment ($p < 0.0001$). Serum cholesterol levels changed from 192.95 ± 30.32 mg/dl before treatment to 174.03 ± 21.72 mg/dl ($p < 0.0001$) and there was 9.80% decrease from the baseline value of cholesterol after giving metformin for 6 months.

The mean triglyceride levels before giving treatment was 148.15 ± 43.21 mg/dl and dropped significantly to 129.97 ± 29.68 mg/dl after treatment ($p < 0.0001$). There was a decrease of 12.2% from the baseline value. The mean LDL levels before giving treatment was 127.52 ± 31.72 mg/dl and after giving treatment was 106.87 ± 21.67 mg/dl ($p < 0.0001$). There was 16.19% decrease from the baseline value. The mean HDL levels increased significantly from 36.67 ± 7.94 mg/dl before giving treatment to 41.1 ± 6.48 mg/dl after giving treatment ($p < 0.0001$) and there was 12.08% increase from the baseline value.

DISCUSSION

PCOS is an endocrine disorder seen in women of reproductive age. It describes a convergence of chronic multisystem endocrine derangements including menstrual irregularity, subfertility, obesity, hyperandrogenism, hyperlipidemia and large polycystic ovaries. Also it is a comprehensive syndrome with a variety of associated metabolic disorders which predispose these women to diabetes mellitus, coronary heart disease and myocardial infarction.

PCOS is often perimenarcheal in onset but it has not been extensively investigated in the adolescent population. In the present study, the mean age of the patients was 22.8 ± 4.6 years which was comparable to the study conducted by Diamanti-Kandarakis et al (1999) where the mean age was 24.6 ± 1.8

years.¹² Wijeyratne et al (2002) studied the clinical manifestations of PCOS among South Asians and concluded that South Asians presented at a younger age group as compared to Caucasians.¹³ Balen et al (1995) suggested that there is a substantial heterogeneity of symptoms and signs among women with PCOS.¹⁴ Several interlinking factors affect the expression of PCOS and for an individual it may change over time. In our study also patients presented with varied clinical presentation including menstrual irregularities (oligomenorrhoea, secondary amenorrhoea), hirsutism, obesity and infertility. High levels of LH and androgens have been regarded as a cause of increased number of oligomenorrhoeic patients under study.

In our study, mean values in BMI decreased significantly. Our results are comparable with the studies conducted by Gleuck et al.¹⁵ On the contrary; De Leo et al (2002) reported non-significant change in BMI after treatment with metformin.¹⁶ Reduction in BMI could be explained due to normalization of plasma insulin by metformin resulting in reduced appetite which led to weight reduction in PCOS patients. Our results demonstrated that metformin treatment improved lipid profile i.e. there is significant decrease in serum levels of cholesterol, Triglycerides and LDL-C along with significant increase in HDL-C levels. Our results are in line with previous studies on PCOS, where metformin has been shown to improve the lipid profile, mainly by increasing serum HDL cholesterol concentrations.^{17, 18} Glueck et al (2003) reported a significant decrease in triglyceride levels.¹⁵ On the other hand, Rautio et al (2005) reported non-significant change in serum cholesterol, Triglycerides and LDL-C levels.¹⁹ Glueck et al (2003) also showed a significant increase in HDL value from basal levels.¹⁵ On the other hand, some other studies have shown only a negligible or no effect on lipids in women with PCOS.^{20, 21}

The discrepancy could be explained by difference in study populations or due to different duration of treatment in various studies. The mechanisms by which metformin improves the lipid profile are not clear. Metformin has been suggested to reduce lipid uptake or synthesis in the intestine and in the hepatocytes.^{22, 23} The improvement of obesity and especially abdominal obesity with a subsequent decreased release of free fatty acids (FFAs) from adipose tissue observed during metformin therapy.²⁴⁻²⁶ could also partly explain the improvement of lipid profile during metformin treatment atleast in obese women. Atherosclerosis is more common among women who have anovulation and PCOD. Cheang and et al (2004) showed that metformin not only recommended for PCO patients because of its effect on induction ovulation, but also for its useful influence on lipid metabolism.²⁷

In conclusion, the beneficial effects of metformin on the lipid profile strengthen earlier data suggesting that metformin could be an effective drug in the prevention of CVD (Cardiovascular disease) in insulin-resistant women with PCOS.

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