

Full Length Research Paper

The effect of metformin on the lipid profile of women with polycystic ovary syndrome: A randomized controlled trial

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Polycystic ovary syndrome (PCOS) is one of the most common endocrinopathies affecting 4 to 7% of women in the reproductive age. The purpose of this study was to investigate the effects of metformin on the lipid profile of women with PCOS. This randomized controlled study was conducted in public and private obstetrics clinics in Sanandaj city, Northwest Iran. One hundred women with polycystic ovarian syndrome diagnosed by the Rotterdam criteria were enrolled in the study. Patients with premature ovarian failure, hyperprolactinemia, diabetes mellitus, thyroid disease, adrenal hyperplasia, and androgen-secreting tumors, were excluded. The patients were randomly divided into case (n=50) and control (n=50) groups. Metformin was prescribed for the case group for 6 months. The patients in the control group received tablet of pepper mint. Fasting insulin, cholesterol, triglycerides, low- and high-density lipoproteins (LDL and HDL) levels were checked 3 and 6 months after for all the participants. Data were analyzed using *t* and analysis of variance (ANOVA) tests. No statistically significant difference between the two groups was found before and after intervention regarding the serum cholesterol, and triglycerid levels.

Key words: Lipid profile, metformin, polycystic ovary syndrome.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is one of the most common endocrinopathies affecting 4 to 7% of women in the reproductive age. PCOS manifests in variety of clinical presentations including hirsutism, irregular menstruation, anovulation, insulin resistance, obesity and infertility. Moreover, hyperandrogenemia, increased luteinizing hormone (LH), decreased follicle stimulating hormone (FSH) and sex hormone binding globulin (SHBG), and hyperinsulinemia are also observed in most cases (Knochenhauer et al., 1998; Asuncion et al., 2000; Banaszewska et al., 2006). Anovulation is a rife health issue with various clinical manifestations such as amenorrhea, irregular menstruation, and hirsutism

(Knochenhauer et al., 1998).

An elevated level of insulin due to insulin resistance is observed in 50 to 70% of patients with PCOS, which will lead to increased androgen levels. *In vitro* studies have proven the stimulatory effect of insulin on the production of androgen, estrogen, and progesterone (Knochenhauer et al., 1998). Increased insulin levels followed by hyperandrogenemia will lead to hypertension, glucose intolerance and dyslipidemia (Asuncion et al., 2000). Hyperandrogenemia and insulin resistance play the most important role in the pathology of lipid disorder (Onalan et al., 2005). Dyslipidemia is probably the most common metabolic disorder in patients with PCOS (Banaszewska

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et al., 2006).

Metformin is an oral biguanide that inhibits hepatic gluconeogenesis and stimulates peripheral glucose uptake, reduces the production of fatty acids, and increases their oxidation. Metformin also enhances the sensitivity of skeletal muscles, reduces appetite, improves metabolic abnormalities leading to low androgen levels and improves and regulates ovarian function and menstrual cycles (Onalan et al., 2005). Various studies confirm the positive effect of metformin on most metabolic functions such as better blood glucose control, lipid profile improvement, and decrease in cystic inflammation (Yu Ng et al., 2001; Onalan et al., 2005; Banaszewska et al., 2006). Also, various clinical trials have examined the effects of metformin in women suffering from PCOS, in most of which the daily dose of metformin was 1500 to 2000 mg. These studies have indicated that treatment with metformin increases insulin sensitivity and reduce weight and body mass index (BMI), blood pressure, and cholesterol levels (Knochenhauer et al., 1998; Onalan et al., 2005).

The most common gastrointestinal side effects of metformin includes nausea and vomiting, bloating, diarrhea, loss of appetite, and metallic taste. However, these side effects will reduce or perish when the drug is taken with food (Moggetti et al., 2000). There is still controversy regarding the effects of metformin. Some studies have shown decreased cholesterol, low-density lipoprotein (LDL) and triglycerides levels following metformin consumption (Knochenhauer et al., 1998; Onalan et al., 2005), while other researchers reported no significant change in the lipid profile (Asuncion et al., 2000). Several other findings have also shown that metformin reduces triglycerides, but has no effect on cholesterol (Knochenhauer et al., 1998).

The aim of the present study was to investigate the effect of metformin on the lipid profile of women with PCOS.

MATERIALS AND METHODS

This randomized controlled trial was performed on women with PCOS who referred to public or private obstetric clinics in Sanandaj, Northwest Iran. The protocol of the study was approved by the Ethics Committee of Kurdistan University of Medical Sciences. The patients were informed about the aim and objectives of the study and written informed consent was obtained from them. Demographic data including age, educational level, weight, height, waist circumference, and blood pressure were also recorded.

PCOS was diagnosed according to Rotterdam diagnostic criteria (Marc and Speroff, 2011). Therefore, women with at least two of the following signs: chronic anovulation, hirsutism, or characteristics of a polycystic ovary in abdominal ultrasonography were enrolled.

To exclude patients with premature ovarian failure (POF), hyperprolactinemia, diabetes mellitus, thyroid disease, adrenal hyperplasia, and androgen-secreting tumors, laboratory tests such as thyroid stimulating hormone (TSH), T4, LH, FSH, and 17-OH progesterone and prolactin test were requested. Based on the test results, five patients were excluded from the study. Moreover, laboratory tests such as fasting insulin, cholesterol, triglycerides,

low-density lipoprotein (LDL), and high-density lipoprotein (HDL) were also requested for all participants.

The calculated human was 50 for each group (95% confidence interval and $\alpha=5\%$). The case (study group) group received one tablet (500 mg) metformin (Sobhan company, Iran) per day at baseline, which was gradually increased to three tablets per day over the succeeding two weeks and continued for 6 months. For the control group during the same time tablet of pepper mint (Aysuda Company, Iran) was prescribed.

The study groups were advised to avoid consuming oral contraceptive pill (OCP), steroids, and any medication that could affect lipid metabolism during the period of study. They were also advised to continue their routine daily activities and nutrition but to avoid smoking and drinking alcohol. The fasting blood sugar (FBS), triglycerides, cholesterol, LDL, and HDL tests were requested for the participants 3 and 6 months after the start of the study. Data were analyzed using Statistical Package for Social Sciences (SPSS) software, version 16. Analysis of variance (ANOVA) and *t* tests were used. The significance level was set at $p<0/05$ (Figure 1).

RESULTS

Of the total 100 patients with PCOS who referred to the obstetric (OB) clinics in Sanandaj city during the mentioned period, 19 patients were excluded, because of not meeting the inclusion criteria (11), declined to participate (6) and other reasons (2). Forty-one were assigned to the case group and the remaining 40 patients were assigned to the control group. In the case group, 9 patients refused to continue taking the medication, because of side effects such as bloating and vomiting. In the control group, 14 patients were excluded, because of the unwillingness to collaborate, distance or pregnancy.

The mean age of the participants in the case and control groups was 21.6 ± 3.2 and 21.4 ± 3.8 years, respectively. The mean BMI and waist circumference were 27.3 ± 9.9 kg/m² and 77.2 ± 11.7 cm and 23.8 ± 5.5 kg/m² and 77.5 ± 10.9 cm in the case and control group, respectively. The *t* test showed no statistically significant difference between the two groups in this regard ($p=0.065$ and 0.5 , respectively) (Table 1). No significant difference was found between the two groups with respect to thyroid hormones, prolactin, 17-hydroxyprogesterone, LH, and FSH levels ($p<0.05$).

Before intervention, FBS levels were 84.7 and 79.9 mg/dl in the case and control groups, respectively. FBS levels were normal after 3 and 6 months in both groups, and metformin had not significantly reduced blood sugar (Table 2).

No significant difference was observed between pre- and post-treatment evaluation of cholesterol level in both groups. Regarding the triglyceride level, although 20% reduction was found in triglyceride levels after metformin consumption, no statistically significant difference was found between the groups (Table 2).

HDL levels were almost similar in both groups before and after intervention. Moreover, although the HDL level in the case group decreased after 6 months, no statistically significant difference between the two groups

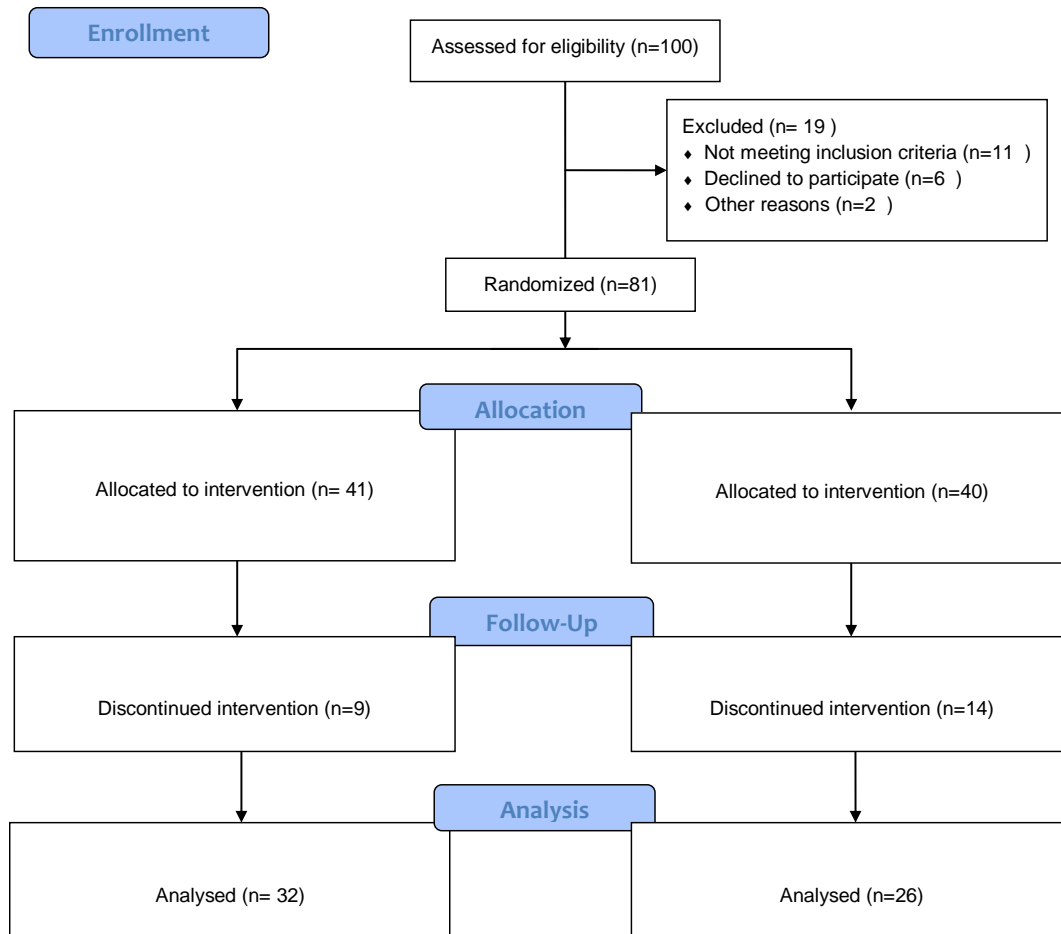


Figure 1. Flow chart of the study.

Table 1. Comparison of some variables between the case and control groups.

Variable	Group	df	Mean±SD	t- test	p value
Age	Case	79	21.6±3.2	0.25	0.8
	Control		21.4±3.8		
BMI	Case	79	27.3±9.9	1.9	0.065
	Control		23.8±5.5		
Waist circumference	Case	79	77.2±11.7	0.66	0.5
	Control		77.5±10.9		

LDL levels increased after six months in both groups. However, no statistically significant difference was found (Table 2). observed between the two groups before and after intervention ($p < 0.05$).

DISCUSSION

It was found that taking metformin compared with peppermint had no effect on the lipid profile of the

participants during our 6-month intervention. Cholesterol, LDL, HDL and triglyceride levels did change, but differences were not statistically significant. These results are consistent with some other studies (Luque-Ramirez et al., 2004; Kazerooni et al., 2010). Luque-Ramirez et al. (2004) in Brazil found that metformin had no effect on metabolic function and lipid profile. Also, Kazerooni et al. (2010) performed a study in Shiraz and found no significant change in blood sugar, insulin, cholesterol,

Table 2. Comparison of fasting blood sugar, cholesterol, triglycerides, and HDL levels between the case and control groups.

Variable		Group	df	Mean±SD	t- test	p value
Fasting blood sugar	Before intervention	Case	78	84.7±8.2	2.1	0.038
		Control		79.9±12.1		
	After 3 months	Case	54	73.9±12.7	-0.26	0.79
		Control		74.8±10.9		
	After 6 months	Case	54	72.5±8.1	-1.44	0.15
		Control		76.1±10.3		
Cholesterol	Before intervention	Case	78	157.1±27.1	-3.2	0.002
		Control		175.7±24.6		
	After 3 months	Case	54	153.7±30.8	-0.85	0.4
		Control		160.5±29.2		
	After 6 months	Case	54	155.6±27.2	-1.6	0.11
		Control		167.4±26.6		
Triglycerides	Before intervention	Case	78	117.3±49.8	0.67	0.5
		Control		110.6±35.8		
	After 3 months	Case	54	78.3±32.2	-1.5	0.14
		Control		91.9±37.1		
	After 6 months	Case	54	86.5±28.5	-1.2	0.22
		Control		97.6±38.8		
HDL	Before intervention	Case	78	43.8±4.5	-0.1	0.95
		Control		43.9±10.2		
	After 3 months	Case	54	41.2±6.3	-1.4	0.16
		Control		43.7±6.9		
	After 6 months	Case	54	40.1±5.1	-2.6	0.01
		Control		43.9±5.8		

HDL and triglycerides levels after one year treatment with metformin.

Several other studies have shown the effect of metformin on insulin reduction, sensitivity increase and lipid metabolism improvement (Banaszewska et al., 2006; Moghetti et al., 2000; Morin-Papunen et al., 2000; Onalan et al., 2005; Zheng et al., 2002).

In the aforementioned studies, metformin increased HDL and decreased LDL and triglycerides levels. In a study conducted by Banaszewska et al. (2006) in Poland, metformin consumption lowered triglyceride levels and increased HDL levels after 6 months in the group with high insulin levels. Onalan et al. (2005) performed a study on six different groups of women with PCOS and

different BMI and insulin levels in Turkey, and reported a decrease in triglycerides levels and increase in HDL levels, especially in slim women with high insulin levels who received metformin (Onalan et al., 2005).

The existing inconsistencies between this study and a number of other studies could be because of the difference in selecting women with PCOS. In earlier studies, patients were selected based on the 1990 definition of the National Institute of Health, and diagnostic criteria were based on clinical and para-clinical hyperandrogenism and oligo-ovulation. However, patient selection is currently based on the Rotterdam criteria. These criteria include both patients who suffer from oligo-ovulation presented with polycystic ovaries, without being

hirsute as well as hirsute women with regular menstruation affected by sonographically confirmed polycystic ovaries. Therefore, this variety in definitions leads to the inclusion of patients with no metabolic disorders or minor abnormalities. In this study, patients were selected based on the Rotterdam criteria. Therefore, women with metabolic disorders were excluded.

Metformin decreases hepatic glucose production and increases peripheral sensitivity to insulin. Studies have shown that obese patients and patients with hyperinsulinemia respond better to metformin. In Banaszewska et al. (2006) study, women suffering from hyperinsulinaemia were selected according to the NIH criteria. Consequently, metformin increased their HDL and decreased their LDL and triglyceride levels. Whereas in a similar study conducted by the same group in 2011 in which the Rotterdam criteria was used, metformin had no effect on the participants with normal fasting insulin levels (Banaszewska et al., 2011).

Aleyasin et al. (2011) also conducted a study on patients suffering from PCOS with different BMIs who received an increasing dose of daily metformin up to 3000 mg. They observed that metformin was effective only on patients with BMIs greater than 35 to 40 kg/m² and elevated fasting insulin levels. Therefore, the fact that metformin had no effect in our study can be because of normal BMI and fasting insulin levels in our participants.

The limited number of participants, unfeasibility of categorizing them based on different weight and different age ranges were the limitations in this study. Thus, broader studies with greater humans, different BMIs, and different age ranges are recommended.

In conclusion, treatment with metformin in women with PCOS does not change cholesterol, HDL, LDL and triglycerides levels during a 6-month period. Therefore, further studies are needed to evaluate the lipid profile in women with different BMIs and also the effects of metformin with different doses.

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Abbreviations:

PCOS, Polycystic ovary syndrome; **LDL**, low density lipoprotein; **HDL**, high density lipoprotein; **ANOVA**, analysis of variance;

LH, luteinizing hormone; **FSH**, follicle stimulating hormone; **SHBG**, sex hormone binding globulin; **BMI**, body mass index; **TSH**, thyroid stimulating hormone; **POF**, premature ovarian failure; **OCP**, oral contraceptive pill; **FBS**, fasting blood sugar; **OB**, obstetric; **NIH**, National Institute of Health.

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