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Comparison of the Effects of Metformin and Oral Contraceptives (Cyproterone Compound) on Serum Lipid Profiles in Patients with Polycystic Ovary Syndrome

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ABSTRACT

This study aimed to compare the effects of Metformin and oral contraceptive (cyproterone compound) on serum lipid profiles in patients with Polycystic Ovary Syndrome (PCOS).This randomized controlled trial study was performed on 60 patients with PCOS referred to gynecological clinics of BesatHostpital in Sanandaj , Iran between March 2014 and May 2014.All patients were examined by a researcher, and they were diagnosed with PCOS using the Rotterdam criteria. The participants were randomly allocated into two equal groups (n = 30, each group); one group received Metformin and another group received cyproterone. A written informed consent was obtained from all participants, and then 2 mL blood sample was taken from the participants and sent to the reference laboratory. Data were entered into SPSS version 22 software, and then were analyzed using the Shapiro-Wilk test, mean comparison test, t-test, and Mann-Whitney U test. A statistically significant difference was seen in Triglyceride (TG) levels between the two groups (P < 0.001); so that the level of TG was lower in the Cyproterone compound group compared to the Metformin group, and this difference was increased over time. Also, there was a statistically significant difference in the cholesterol levels between the two groups (P < 0.001). The cholesterol levels were decreased in both groups; however, the level of cholesterol was significantly lower in the Cyproterone compound group compared to the Metformin group, and this difference was increased over time. Moreover, the results showed that there was a statistically significant difference in High-Density Lipoprotein (HDL) and Low-Density Lipoprotein (LDL) levels between the two groups. According to the results of the current study, Metformin treatment has beneficial effects on serum lipid profiles in PCOS.

Keywords: Metformin; Oral contraceptives; Lipid profile; polycystic ovary syndrome

INTRODUCTION

Polycystic Ovary Syndrome (PCOS) is a condition in which the imbalance of sex hormones could be seen in women. This could result irregularity of monthly cycles, the emergence of numerous cysts on ovaries, infertility and many health changes [1].

This syndrome is the most common endocrine disorder in women and its prevalence is about 15-20 percent and 5-10 percent during childbearing ages [2, 3]. Polycystic ovary syndrome is associated with metabolic disorders, such as insulin resistance and dyslipidemia [2, 3]. In the past, an action would have been taken for effective treatment and

preventing specific complications of this syndrome such as infertility, hirsutism, but today, we must affect the life quality and quantity of these patients [2]. In addition, this would not happen except with more researches and understanding of the components of this syndrome such as metabolic problems. Patients with PCOS are at risk of metabolic syndromes including diabetes, high blood pressure, high cholesterol, and high insulin levels [4]. Also, dyslipidemia has an adverse effect on human health especially on cardiovascular health that is caused by many risk factors in PCOS.

Today, a growing need for developing pharmaceutical interventions has been identified to improve metabolic functioning in women with PCOS [5].Among the drugs that have been used in various studies on PCOS patients, Metformin, thiazolidinedione, oral contraceptive pills, acarbose, statins, vitamin D, and so on could be pointed out [6, 7]. Metformin is commonly prescribed due to its favorable and multilateral effects and its low complications [8]. Recent studies on this drug suggest indirect reduced levels of insulin, reduced lipid abnormalities and reduced systemic inflammation. However, new trials have been questioned the beneficial metabolic effects of Metformin when compared with placebo [5].

Among other medications that are prescribed for the improvement of ovarian functioning, which their dysfunction is the main features of PCOS, are Oral Contraceptive Pills (OCPs); because of its low side effects and its well tolerance by the patients, the prescription of cyproterone compound types of these pills has been used as a common treatment by physicians [7].

Given different metabolic effects of different drugs, studying and comparing these differences will help treatment decisions. The studies done so far on patients with PCOS, have been focused on the metabolism of carbohydrates [2, 7], and only in some of these studies, the metabolism of fats have been considered briefly [5]. This study was designed to compare the effects of Metformin and oral contraceptive (cyproterone compound) on serum lipid profiles in patients with PCOS.

MATERIALS AND METHODS

This study was conducted on 60 patients with PCOS referred to gynecological clinics of BesatHostpital affiliated to Kurdistan University of Medical Sciences, Sanandaj, Iran between March 2014 and May 2014. At the beginning of the study, 120 patients were participated in the study; of this number, 24 cases did not have the inclusion criteria, 30 others did not sign the consent form to participate in the study and 6 cases were excluded during the study because we could not contact them. A total of 60 patients were analyzed to the end of the study; and they were enrolled in the study based on clinical symptoms, physical examination, laboratory tests, Rotterdam criteria and a confirmed diagnosis by a specialist physician.

The patients were randomized through the random blocks of four and divided into two equal groups (n=30, each group). One group was treated with 500 mg Metformin daily from a manufactured drug company (Aboureihan) to minimize gastrointestinal side effects for a week on the first day of spontaneous menstruation or no menstruation of women after rejection of pregnancy and the treatment was continued with 3 pills of Metformin 500 mg. Women received Metformin were advised to use nonchemical methods of birth-control during the study.

Another group was treated with cyproterone compound from pharmaceutical companies (Iran Hormones). There was no possibility of matching the drugs because we used packages prepared in the market from pharmaceutical companies. However, the drugs were prepared from the same pharmaceutical company. Once during a month of the study, the proper use of medications was ensured by the investigator by telephone. Because the drugs were supplemented from the market and due to different shapes and dosages of the drugs, the research could not be blinded, but patients were not aware of the treatment groups that they were assigned to.

Inclusion criteria (before simple randomization) were women aged 18 to 40 years with PCOS according to the Rotterdam criteria (at least 2 out of three criteria, including: the lack of ovulation or low ovulation, signs of biochemical or clinical hyperandrogenism and polycystic ovaries diagnosed by ultrasonography) and the exclusion criteria included hormonal disorders such as hyperprolactinemia, Cushing's syndrome, late onset of adrenal hyperplasia, chronic disorders of the liver, kidney, heart and thyroid, positive pregnancy tests, medications such as Danazol, androgen progestin consumption, consumption of other drugs that reduce blood sugar and blood fat in the last three months, the presence of diabetes mellitus and refusal to participate in the study.

The Shapiro-Wilk test has been used to test whether data were normally distributed. Descriptive baseline characteristics for two groups (Diane and Metformin) comparisons were tabulated as Mean±SD. Comparing between two groups for continuous data were statistically analyzed using t-test and Mann-Whitney U test. The

primary efficacy data on GTT and lipid profile were examined using intention-to-treat analysis. Using General Linear Model (GLM) score of lipid profile between two groups were compared by repeated measurement ANOVA test. Time of evaluation was considered as within subject factor, intervention state (Diane and Metformin) as between subject factor. The time groups (interaction term) was considered as group differences (between Diane and Metformin) in their response over time. We tested Mauchley'sSphericity test for compound symmetry assumption. A p-value of 0.05 or less was considered statistically significant and p value of less than 0.1 considered marginally statistically significant. Data were analyzed using IBM SPSS statistics version 16 and Stata version 10.

A total of 120 patients who were presented to our clinic were screened during the study period. Of these, 24 patients did not meet the inclusion criteria and 30 patients declined to participate in the study. The remaining 66 patients were randomly allocated to two groups. Of these, 6 patients were lost to follow-up during the study period. In total, 60 patients completed the present study and data from all these patients were analyzed (Figure 1).

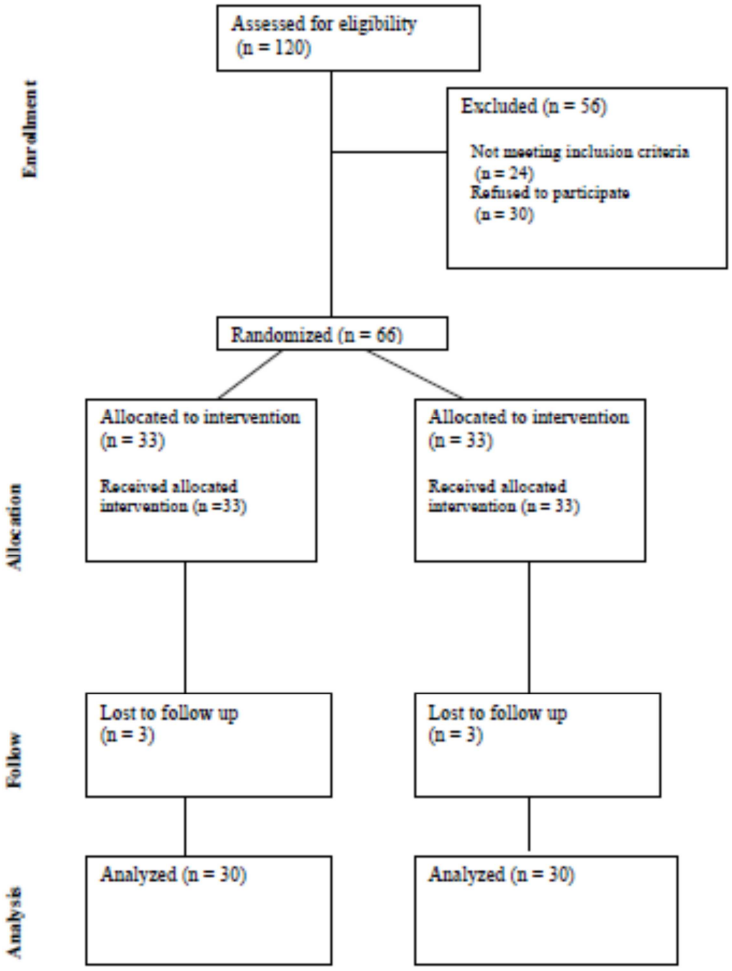

Figure 1. CONSORT diagram of patients' randomization, intervention, and analysis

RESULTS

Basic demographic and clinical characteristics of patients in two groups (group A: Diane and group B: Metformin) are presented in Table 1. As shown in table 1, no significant difference was detected in average age (23.33±3.18 vs 23.23±3.01; P= 0.9)and BMI (28.39±3.95 vs 27.58±7.11; P= 0.31). Table 2 shows the values of the pre-and post-intervention GTT and lipid profile parameters of each group.

Effect of treatment on GTT

As shown in table 2, there was a statistically significant time trend decline in both groups (within-subject differences or time effect) for GTT (P<0.01). Glucose tolerance test in Metformin group was lower than Diane group but there was no statistically significant differences between groups (between-subject differences or group effect) (p=0.65). The groups have parallel lines, decreasing over time and the reduction slope of two groups were nearly the same (no group time interaction or interaction effect) (P=0.79).

Effect of treatment on lipid profile

Triglyceride level

As shown in Fig. 2 and table 2, there is a statistically significant time trend (within-subject differences or time effect) for TG levels (P<0.001) and both groups are getting less depressed over time. Triglyceride levels in Diane group was letter than Metformin group and there is statistically significant differences between groups (between-subject differences or group effect) (p=0.03). In the graph we see that the groups have non-parallel lines that decrease over time and are getting progressively away from each other over time. The reduction slope of Diane group was greater than Metformin group (group time interaction or interaction effect) (P<0.001).

Cholesterol level

As shown in Fig. 2 and table 2, there is a statistically significant time trend (within-subject differences or time effect) for cholesterol levels (P<0.001) and both groups are getting less depressed over time. Cholesterol levels in Diane group was letter than Metformin group and there is statistically significant differences between groups (between-subject differences or group effect) (p<0.001). In the graph we see that the groups have non-parallel lines that decrease over time and are getting progressively away from each other over time. The reduction slope of Diane group was greater than Metformingroup (group time interaction or interaction effect) (P=0.008).

High-density lipoprotein level

As shown in Fig. 2 and table 2, there is a marginally statistically significant time trend (within-subject differences or time effect) for HDL levels (P= 0.08). High-density lipoprotein levels in Diane group was greater than Metformin group but this difference was not statistically significant (no between-subject differences or group effect) (p= 0.92). In the graph we see that the groups have non-parallel lines and there is group time interaction or interaction effect (P=0.001).

Low-density lipoprotein level

As shown in Fig. 2 and table 2, there is a statistically significant time trend (within-subject differences or time effect) for LDL levels (P<0.001). Low-density lipoprotein levels in Diane group was greater than Metformin group and there is statistically significant differences between groups (between-subject differences or group effect) (p<0.001). In the graph we see that the groups have non-parallel lines that decrease over time and are getting progressively away from each other over time and there is a group time interaction or interaction effect (P<0.001).

Table 1.Basic demographic and clinical characteristics of patients in the two groups

	Group		P value
	Diane (n=30)	**Metformin (n=30)**	
Age (yr)	23.33±3.18	23.33±3.01	0.9
BMI (Kg/m^2)	28.39±3.95	27.58±7.11	0.59
Prolactin (ng/dl)	190.74±199.68	197.56±215.72	0.94
Insulin (mg/dl)	14.94±5.95	24.48±38.93	0.85
FBS (mg/dl)	85.1±11.15	82.8±12.62	0.46

Table 2. GTT and lipid profile levels at baseline, 3 and 6 month follow-up in both groups

		Time			F statistics		
		Baseline	**3 month**	**6 month**	**Time**	**Group**	**Time*group**
GTT	Diane	128.23±33.72	102.31±22	81.08±14.15	99.57 [a]	0.2 [c]	0.18 [c]
	Metformin	124.38±25.47	99±23.67	80.83±13.2			
TG	Diane	146.97±57.4	139.3±5.01	135.9±50.55	25.12 [a]	14.86 [a]	12.22 [a]
	Metformin	150.7±48.35	113.4±39.7	87.87±34.41			
CH	Diane	136.2±39.1	119.07±31.88	115.5±37.09	11.6 [a]	71.78 [a]	5.07 [a]
	Metformin	175.47±38	181.83±36.42	135.7±27.83			
HDL	Diane	51.63±23.73	59.97±15.08	75.17±39.01	2.57 [b]	0.009 [c]	8.07 [a]
	Metformin	69.53±30.98	56.09±23.22	59.5±35.62			
LDL	Diane	118.5±27.86	129±22.6	127.45±28.7	15.76 [a]	21.07 [a]	27.62 [a]
	Metformin	115.63±23.95	107.97±26.83	76.43±23.21			

[a] Significance level less than 0.01; [b] Significance level less than 0.05; [c] Significance level less than 0.1

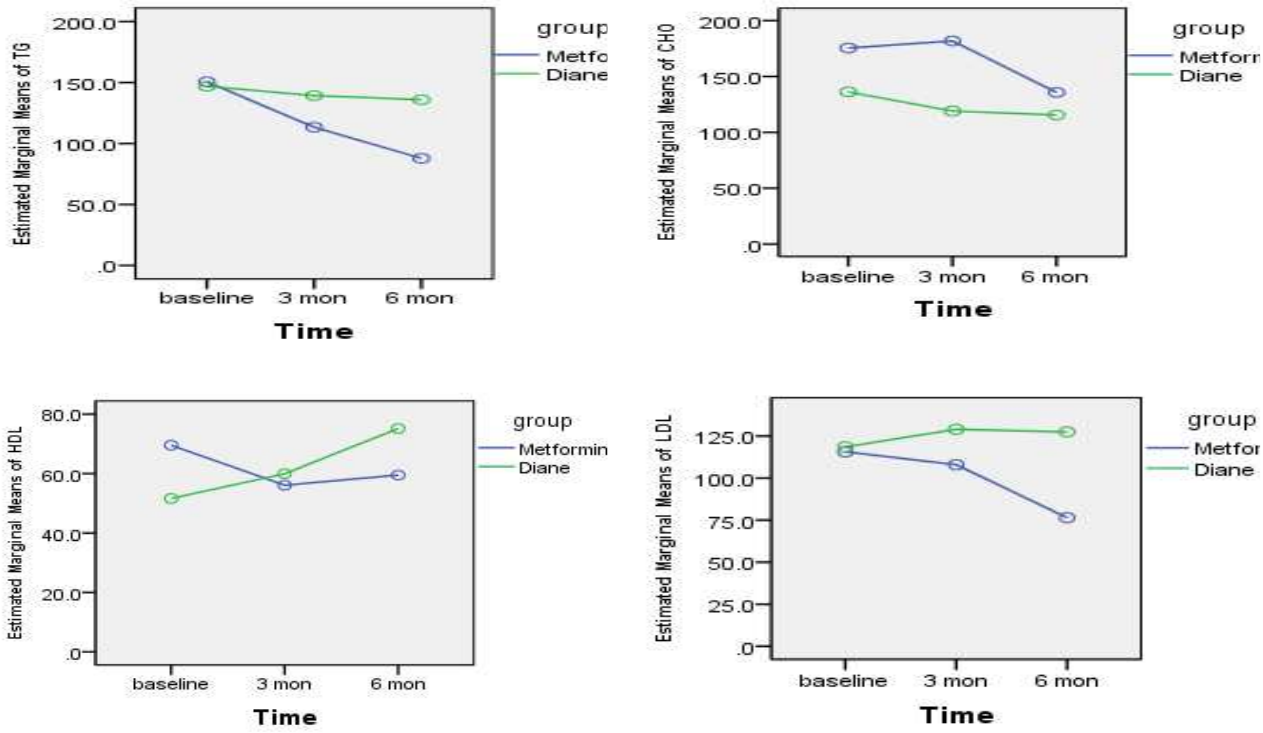

Figure 2.Trend of lipid profile before and after of interventions (Metformin vs Diane) in patients with polycystic ovarian

DISCUSSION

Regarding lipid profiles, the results showed that there is a statistically significant difference ($P < 0.001$) in Triglyceride (TG) levels between the two groups, so that TG level was significantly lower in the Cyproterone group compared to the Metformin group, and this difference was increased over time. Also, there was a statistically significant difference ($P <0.001$) in cholesterol levels between the two groups. Cholesterol levels were decreased in both groups; however, the cholesterol level in the Cyproterone group was lower compared to the Metformin group and this difference was increased over time. Also, the results of the current study showed a significant difference in the HDL and LDL levels between the two groups ($P < 0.001$).

In a meta-analysis study by Lord et al [9], they aimed to determine the effects of Metformin in women with PCOS and they studied the effects of spironolactone and Cyproterone treatments; the results showed that Metformin had a better effect in reducing lipid profiles. Kolodziejczyk et al. [10] pointed out the effective role of Metformin in a study that examined the Metformin treatment in women with PCOS.

The study of Cinar et al [11] examined ethinyl estradiol in comparison to ethinyl estradiol plus Metformin treatment in women with PCOS; and in this study, ethinyl estradiol plus Metformin has a better effect in reducing lipid profiles than ethinyl estradiol alone. A study by Fruzzetti and colleagues [12] evaluated the effects of ethinyl estradiol and cyproterone and Metformin in patients with PCOS, the lipid profiles in the Metformin group had significantly reduced compared to the other groups. The results of a study conducted by Glueck et al [13] that aimed to determine the effect of Metformin treatment in women with PCOS are similar to the results of the current study.

The results of the present study showed the beneficial effects of Metformin on lipid profiles, especially after a 6-month evaluation of these patients. The results of a study conducted by Checa et al [14] were consistent with our findings. Also, in a study conducted by Michelmore et al [15] with the aim of evaluating clinical indicators and biochemical features in young women with PCOS, these indicators decreased in people who used Metformin. Moreover, in a study by Meikle [16] the effect of Metformin on TG and cholesterol were found, that all these results confirmed the present study.

A study conducted by Lugue-Ramirez et al [17] which aimed to compare the effects of ethinyl estradiol plus cyproterone versus the effects of Metformin on classic risk factors of cardiovascular diseases in women with PCOS, showed opposite results to the results of the current study.

CONCLUSION

According to the results of the current study, it seems that Metformin has beneficial effects on lipid profiles in PCOS.

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REFERENCES

[1] Franks S. Polycystic ovary syndrome. Medicine. 2013; 41(10):553-556.
[2] Jalilian N, Shahebrahimi K, Bazgir N, Rezaei M. Comparison clinical and metabolic effects of metformin and pioglitazone in polycystic ovary syndrome. Indian Journal of Endocrinology and Metabolism. 2016;20(6):805.
[3] Aroda V, Ciaraldi T, Burke P, Mudaliar S, Clopton P, Phillips S et al. Metabolic and Hormonal Changes Induced by Pioglitazone in Polycystic Ovary Syndrome: A Randomized, Placebo-Controlled Clinical Trial. The Journal of Clinical Endocrinology & Metabolism. 2009;94(2):469-476.
[4] Duleba A. Medical management of metabolic dysfunction in PCOS. Steroids. 2012;77(4):306-311.
[5] Fleming R. The use of insulin sensitising agents in ovulation induction in women with Polycystic Ovary Syndrome. HORMONES. 2006;5(3):171-178.
[6] Park E. The Prevalence of Metabolic Syndrome and its Components, and the Related Health Behavior among Adults over 20 Years Old in Jeju, South Korea. AJMAHS. 2015;5(3):91-98.
[7] Tehraninejad E, Nasiri R, Rashidi B, Haghollahi F, Ataie M. Comparison of GnRH antagonist with long GnRH agonist protocol after OCP pretreatment in PCOs patients. Archives of Gynecology and Obstetrics. 2010;282(3):319-325.
[8] De Leo V, la Marca A, Petraglia F. Insulin-Lowering Agents in the Management of Polycystic Ovary Syndrome. Endocrine Reviews. 2003;24(5):633-667.
[9] Lord J. Metformin in polycystic ovary syndrome: systematic review and meta-analysis. BMJ. 2003;327(7421):951-0.
[10] Kolodziejczyk B, Duleba A, Spaczynski R, Pawelczyk L. Metformin therapy decreases hyperandrogenism and hyperinsulinemia in women with polycystic ovary syndrome. Fertility and Sterility. 2000;73(6):1149-1154.
[11] Cinar N, Harmanci A, Bayraktar M, Yildiz B. Ethinyl estradiol-drospirenonevsethinyl estradiol-drospirenone plus metformin in the treatment of lean women with polycystic ovary syndrome. Clinical Endocrinology. 2013;78(3):379-384.
[12] Fruzzetti F, Perini D, Lazzarini V, Parrini D, Gambacciani M, Genazzani A. Comparison of effects of 3 mg drospirenone plus 20 μgethinyl estradiol alone or combined with metformin or cyproterone acetate on classic metabolic cardiovascular risk factors in nonobese women with polycystic ovary syndrome. Fertility and Sterility. 2010;94(5):1793-1798.
[13] Glueck C, Wang P, Fontaine R, Tracy T, Sieve-Smith L. Metformin-induced resumption of normal menses in 39 of 43 (91%) previously amenorrheic women with the polycystic ovary syndrome. Metabolism. 1999;48(4):511-519.
[14] Checa M. Insulin-sensitizing agents: use in pregnancy and as therapy in polycystic ovary syndrome. Human Reproduction Update. 2005;11(4):375-390.
[15] Michelmore K, Balen A, Dunger D, Vessey M. Polycystic ovaries and associated clinical and biochemical features in young women. Clinical Endocrinology. 1999;51(6):779-786.
[16] Meikle A. A comparison between rimonabant and metformin in reducing biochemical hyperandrogenaemia and insulin resistance in patients with polycystic ovary syndrome (PCOS): a randomized open-label parallel study. Yearbook of Endocrinology. 2009; 2009:240-241.
[17] Luque-Ramírez M, Álvarez-Blasco F, Botella-Carretero J, Martínez-Bermejo E, Lasunción M, Escobar-Morreale H. Comparison of Ethinyl-Estradiol Plus CyproteroneAcetateVersusMetformin Effects on Classic Metabolic Cardiovascular Risk Factors in Women with the Polycystic Ovary Syndrome. The Journal of Clinical Endocrinology & Metabolism. 2007;92(7):2453-2461.