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Effect of simvastatin versus metformin on biochemical profile of polycystic ovary syndrome: a randomized clinical trial

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ABSTRACT: Background: Metformin has been widely investigated for treating Polycystic ovary syndrome(PCOS), however, it doesn't improve total biochemical profile of the disorder. The aim of this study was to assess the efficacy of simvastatin on PCOS and to compare its effect with metformin on biochemical and clinical symptoms of polycystic ovary syndrome.Methods: In a randomized clinical trial 60 women at reproductive age with PCOS were allocated to receive either 1500 mg dose of metformin tablets, or simvastatin tablets in 20 mg daily dosage. Several lipid, carbohydrate and steroid profile assessments were done at baseline and three months afterwards.Results: In this study Fasting blood sugar(FBS), serum insulin, menstrual cycle irregularities and hyperinsulinemia decreased significantly after treatment with metformin. Moreover, cholesterol, LDL, HDL, DHEAS, hyperinsulinemia, acne, and positive CRP tests decreased significantly in simvastatin group. Conclusion: Biochemical pattern of PCOS is differently affected by metformin and simvastatin and a complementary efficacy of combined treatment may also be anticipated.
Keywords: biochemical parameters, polycystic ovary syndrome, metformin, simvastatin

INTRODUCTION

Polycystic ovary syndrome is an endocrine disorder that affects about 6.5 percent of women worldwide. In Iran also, metabolic syndrome is considered to be of concern(Heidari et al. 2010;Sarrafzadegan et al. 2008) with a prevalence of 32% among Tehran adults based on definition by international diabetes federation(Zabetian, Hadaegh, &Azizi 2007).The major endocrine abnormality in this syndrome is excessive androgen secretion or activity, and the patients many also sufferinsulin activity problems(Norman et al. 2007).The typical biochemical features of PCOS are hyperandrogenemia and increased serum luteinizing hormone (LH) but PCOS is also associated with a characteristic metabolic syndrome that includes hyperinsulinemia, insulin resistance, and dyslipidaemia(Franks 1997).

Polycystic ovary syndrome(PCOS)as a prevalent endocrine disorder in reproductive age is the most common cause of infertility due to anovulation and cause of the 73 % of hirsutism cases(Franks 1995). Infertility may be the one of the first patient concerns regarding PCOS but is not the last or the most serious one. Women with PCOS have higher risk of cardiovascular diseases due to clustering risk factors(Wild 2002). The main mechanism to blame on is the progression of atherosclerosis, a major determinant of which is dyslipidemia. So higher levels of lipids in women with PCOS needs further notice to be addressed in treating PCOS and reducing lipidemia may help in lowering the risk of cardiovascular diseases(Wild et al. 2011). It seems reasonable that if the treatment of PCOS can address all aspects of biochemical and clinical abnormalities in this syndrome, better outcomes can be expected. Metformin has been widely investigated and used for treating PCOS, however it doesn't affect some aspects of the disorder including dyslipidemia(Lord, Flight, & Norman 2003).Recently few studies have started to assess simvastatin in treating PCOS(Banaszewska et al. 2007;Banaszewska et al. 2009;Duleba et al. 2006;Kaya et al. 2010;Kazerooni et al. 2010), but very few have tried to compare it with metformin(Banaszewska, Pawelczyk, Spaczynski, & Duleba 2009;Kazerooni, Shojaei-Baghini, Dehbashi, Asadi, Ghaffarpasand, & Kazerooni 2010). The aim of this study was to assess efficacy of simvastatin on PCOS and compare its effect with metformin on biochemical and clinical symptoms of polycystic ovary syndrome.

MATERIALS AND METHODOLOGY

Study was conducted during 2009-2010 in Tabriz, Iran. In a randomized clinical trial, 60 women atreproductive age with PCOS who referred to Taleghani University Hospital clinic were enrolled. Using a parallel design subjects were allocated into two treatment modalities in equal groups of 30 patients each. Block randomization was used to ensure equal sized comparison groups(Asghari-Jafarabadi & Sadeghi-Bazargani 2014), and randomization list was generatedusing Randlist11 software package. The first group received 1500 mg dose of metformin as oral tablets while the second group received simvastatin tablets in 20 mg daily dosage. Both groups received similar nutritional and exercise protocols.PCOS diagnosis was confirmed by agynecologist in patients with hyperandrogenism and existence of oligomenorrheaor anovulation. Blinding was done for the outcome assessors(blinded evaluation).

The inclusion criteria were as:

Age in a range of20-40 years

PCOS diagnosed

Normal levels of bilirubin, aminotransferases, BUN, and creatinine.

The exclusion criteria were as: Pregnancy; Using hormonal contraceptives and drugs affecting related hormonal patterns or affecting blood sugar and lipids; Congenital adrenal hyperplasia, Hyperprolactinemia, Cushing syndrome, androgen secreting tumoral disease, thyroidal diseases, diabetes mellitus, hypertension, Ischemic heart disease; contra-indications to use or continue using trial drugs

Medical history was taken fromall the participants and they were followed up for three months and underwent anthropometric assessments, clinical examinations. Hirsutism was assessed using Ferriman and Gallwey score.Laboratory assessments were also done both at baseline and after three months through the follicular phase of a normal menstrual period or after progesterone injection.FSH, LH, Free testosterone, TSH, FBS, triglyceride, total cholesterol, HDL, CRP, serum insulin, Insulin sensitivity index(ISI), and GTT were assessed.

Data were analyzed using SPSS 16 statistical software package. Independent samples t-tests were employed for comparing numeric data regarding the between group changes and paired samples t-tests were used to test before-after changes in the values of numeric data. Independent categorical comparisons were made using Chi-Squares test and McNemar's tests were used to assess before-after change of the categorical scaled variables like existence of menstrual cycle irregularities.

Considering the large number of profile measurements, linear discriminant analysis was used to assess whether the two treatment modalities could be discriminated based on biochemical profile of the patients. At all analysis steps a*P*-value less than 0.05 was considered statistically significant.

Study was approved by the regional committee of ethics in Tabriz University of Medical Sciences.

RESULTS

Mean age of the participants was 26.7(SD=4.5) years. Mean systolic and diastolic blood pressure values at baseline were 110.8 mmHg and 80.8 mmHg respectively. The differences observedbetween groupswere not statistically significant. Regarding the anthropometric measurements, mean BMI and mean waist to hip ratio at baseline were 26.8 $Kg/m^2$and 0.59 respectively. Three months after treatment the figures were 26.6 and 0.49 respectively. Neither the change over time, nor the between group differencesof these figures were statistically significant.

The proportion of women with menstrual cycle irregularities in metformin group, decreased from 66.7% to 36.7 %. Throughthe paired comparisons, 10 women turned from irregular menstruation to regular menstruation after treatment and only one patient turned to develop menstrual irregularity versus baseline regular pattern ($P<0.05$). The proportion of women with menstrual cycle irregularities in simvastatin group decreased from 60% to 40 %. During the paired comparisons, nine women turned from irregular menstruation to regular menstruation after treatment and three patients showed a reverse pattern. This improvement pattern was not statistically significant. However, the between group difference was found to be a tendency rather than statistical significance.Regarding other categorical assessments, hyperinsulinemia significantly decreased in metformin group and hyperinsulinemia, acne, and positive CRP tests decreased significantly($P<0.05$). Hirsutism improvement was not also different between groups. No important drug side effects were observed in both groups.As through linear discriminant analysis the primary model to assess discrimination between treatment groups was constructed with nine first variables. The misclassification rate at this phase was calculated to be 28% which was not a good score. Model was extended to include more variables at several phases and finally after including 41 variables the model

achieved zero misclassification rate showing that the two treatment modalities could be differentiated assessing biochemical profile. Laboratory findings at the beginning and after treatment are compared between groups in table 1.

Scaled measures of change in different laboratory findings over treatment time is compared for different findings between groups(Figure 1). Serum cholesterol and LDL decreased largerin simvastatin group($p<0.001$) while, blood sugar and insulin decreased largerin metformin group.

DISCUSSION

In this study FBS, serum insulin, menstrual cycle irregularities and hyperinsulinemia significantly decreased after treatment with metformin.Also cholesterol, LDL, HDL, DHEAS, hyperinsulinemia, acne, and positive CRP tests decreased significantly in simvastatin group. The first positive results in using metformin for PCOS was first presented in 1994(Velazquez et al. 1994). Later studies also showed the improvement of menstrual cycle in PCOS after using metformin(Costello et al. 2007;Glueck et al. 2001;Pasquali et al. 2000;Vrbikova et al. 2002). Metformin is also studied in an Iranian population showing positive effects in treating PCOS(Tabatabei&Mojibian 2011). Other than the effects of metformin on menstrual cycle, it was found that efficacy of metformin in PCOS may be higher among obese people(Morin-Papunen et al. 1998). Consistently with previous studies, metformin showed to be effective in our study, but as stated by previousresearch, it doesn't affect the lipid profile thatno doubt is of importance in PCOS(Luque-Ramirez et al. 2007;Morin-Papunen, Koivunen, Ruokonen, & Martikainen 1998).

Considering the existence of atherosclerosis risk factors in PCOS, the idea to use cholesterol lowering agents in PCOS was introduced into the research in recent years. In a crossover trial, simvastatin and OCP were compared. They found that, total and free testosterone, andhirsutism decreased more after Statin + OCP, than the OCP alone. Statin lowered serumLH, but not the FSH andprolactin. Generally simvastatin was found to improve endocrine/clinical aspects of PCOS and had beneficial effects on lipid profile and systemic inflammationmarkers(Banaszewska, Pawelczyk, Spaczynski, Dziura, & Duleba 2007).

Another study in 2010 comparing simvastatin and atorvastatin, found that both the statins were effective in reducing inflammation, hyperandrogenemia, oxidative stress and metabolic parameters,while, simvastatin wasmore effective on total testosterone in PCOS women(Kaya, Pabuccu, Cengiz, & Dunder 2010).

Simvastatin was also compared with OCP in another study finding that, i addition to the effects on lipid profile, serum testosterone and LH levels as well as LH/FSH ratio also declined more in the statin group than in the OCP groupafter 12 weeks of treatment(Duleba, Banaszewska, Spaczynski, & Pawelczyk 2006).

We retrieved only two studies comparing or using metformin and simvastatin together in PCOS. In one clinical trial, metformin was compared with simvastatin and simvastatin plus metformin. Similar to our study evaluations were done at baseline and after threemonths. Total testosterone decreased in all groups but decreased larger in simvastatin-only group. Moreover, body mass index and C-reactive protein values decreased,but DHEAS declined significantly only in the Simvastatin group. None of the treatments were associated with significant changes in LH or FSH levels. Total cholesterol and low-density lipoprotein cholesterol significantly declined only in Simvastatin and Simvastatin-Metformin groups. They concluded that simvastatin was superior to metformin alone, whereas a combination of simvastatin and metformin was not significantly superior to simvastatin alone(Banaszewska, Pawelczyk, Spaczynski, & Duleba 2009).

Contrary to the aforementioned study, Kazerooni et al. found that the combination of metformin and simvastatin could lead to a better reduction of testosterone and LH levels thus reversing the LH:FSH ratio, lipid profile, and insulin resistance(Kazerooni, Shojaei-Baghini, Dehbashi, Asadi, Ghaffarpasand, & Kazerooni 2010).

Based on our results, that different descriptive patterns(as in figure 1) and statistically significant differences between groups, it seems that a complementary efficacy of combined treatment may be anticipated if approved by future studies comparing combined metformin and simvastatin with both treatments separately but in larger scale to fulfill the necessary statistical power of study. However the results of discriminant analysis in this study supported an overall difference between groups.

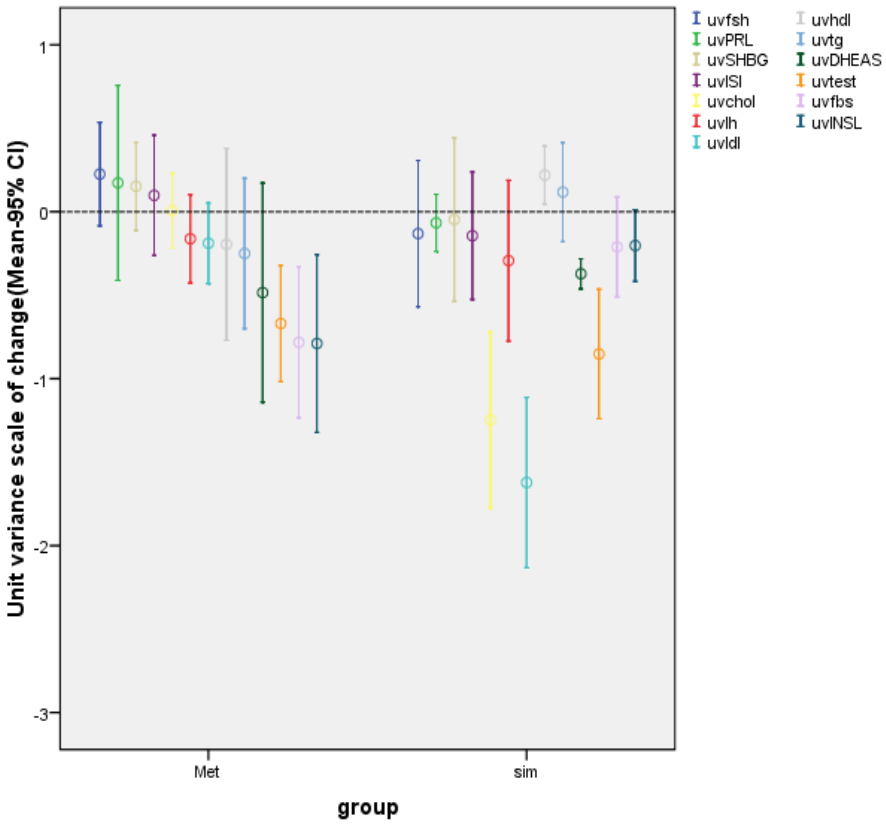

Figure 1. Error bar graph comparing mean scaled change in different laboratory measures between study groups. The dashed reference line indicates no-change level before and after treatment. Negative scores mean decrement and positive measures mean increment. Each colored figure shows mean and 95% confidence intervals. To make the comparisons possible, regarding different variability of measures, data were scaled using unit variance(uv) scaling.
Sim: Simvastatin Met: Metformine

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Table1 . Laboratory findings compared between metformin and simvastatin groups before and after treatment

	Metformin group				Simvastatin group				P value
	Mean	SD	Min	Max	Mean	SD	Min	Max	
FSH0(IU/L)	7.3	2.1	1.4	10.6	7.8	1.7	3.4	10.8	NS
FSH1(IU/L)	7.4	1.8	2.3	10.8	7.7	1.3	4.4	10.5	NS
LH0(IU/L)	12.3	5.4	4.8	21.4	11.4	3.8	4.8	21	NS
LH1(IU/L)	12.1	5.7	4.4	21.4	11	4.2	5.1	22	NS
HDL0(mg/dl)	54.5	15	41	114	52.9	10.4	41	75	NS
HDL1(mg/dl)	52.1	15.8	16	98	55.6	8.6	41	75	NS
TG0(mg/dl)	123.9	52.8	42	271	113.2	60.7	75	380	NS
TG1(mg/dl)	112.9	47.3	8.9	180	118.4	54.1	75	307	NS
FBS0(mg/dl)	93.8	17.4	63	147	89.4	13.8	75	140	NS
FBS1(mg/dl)	86.4	8.9	66	104	87.4	9.9	75	110	NS
Insulin0(mg/dl)	11.3	13.6	3.9	82	10.2	11.1	3.8	68	NS
Insulin1(mg/dl)	10.2	13.7	3.9	82	9.9	11.1	3.8	68	NS
BS0(mg/dl)	118.7	27.4	63	168	127	37.8	94	218	NS
BS1(mg/dl)	104.2	19.9	63	150	122.8	36.5	84	212	0.02
Free Testosterone0(ng/dl)	1.5	1	0.1	3.8	3.6	4.2	0.1	13.5	0.01
Free Testosterone1(ng/dl)	1.5	0.95	0.1	3.9	3.4	3.7	0.1	13.2	0.01
Prolactin0(ng/ml)	16.2	2.5	12	22	16	2.3	12	21	NS
Prolactin1(ng/ml)	16.4	3.1	11	22	15.4	2.2	12	21	NS
Cholesterol0(mg/dl)	184.9	54.8	120	329	183.5	49.2	119	329	NS
Cholesterol1(mg/dl)	185.1	49.9	115	322	142.3	42.8	121	329	0.001
Total Testosterone0(ng/dl)	0.74	0.15	0.4	1	0.74	0.16	0.4	1	NS
Total Testosterone1(ng/dl)	0.67	0.12	0.4	0.88	0.65	0.13	0.4	0.98	NS
DHEAS0(µmol/ml)	8.7	0.75	6.9	10	8.6	0.85	6.9	10.4	NS
DHEAS1(µmol/ml)	8	2	0.9	9.6	8.1	0.84	6.8	9.9	NS
SHBG0(nmol/L)	40.7	4	34	49	39.9	3.9	34	49	NS
SHBG1(nmol/L)	41.2	3.4	34	49	39.8	3.3	34	46	NS
LDL0(mg/dl)	116.7	28.6	78	202	13.4	25.9	86	202	NS
LDL1(mg/dl)	115	27.8	70	198	98.8	17.5	69	156	0.01
ISI0	6.7	1.1	4.7	9	7.1	1	4.6	8.7	NS
ISI1	6.8	0.87	5	8.7	6.9	0.71	5	8.1	NS

Index 0: Baseline Index 1: 3 months after treatment P value is for between group comparisons
NS: P-value not indicative of statistical significance