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Therapeutic Effects of Biguanide Vs. Statin in Polycystic Ovary Syndrome: A Randomized Clinical Trial

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Abstract: Various classes of medication are currently being used in Polycystic Ovary Syndrome (PCOS) patients including the biguanides and the statins. However, their efficacies are rarely compared. This study aimed to compare efficacy of a biguanide and a statin in treating PCOS. In a randomized double-blind clinical trial, 400 women with PCOS were recruited within 15 months in Taleghani Hospital. They randomly received either a biguanide (metformin 500 mg three times daily) or a statin (simvastatin 20 mg daily) for three consecutive months. Changes of clinical and laboratory variables were compared. In the biguanide group the serum glucose status (abnormal fasting and non-fasting sugar and insulin levels and percentage of hyperinsulinemic cases) and menstrual abnormalities improved significantly after treatment ($p<0.05$). In the statin group the lipid profile status (abnormal total cholesterol, high and low density lipoproteins), C-Reactive Protein (CRP), serum dehydroepiandrosterone sulfate, hyperinsulinemia, severity of acne and menstrual abnormalities improved significantly after treatment ($p<0.05$). Comparing the two groups, the improvements in fasting blood sugar and serum insulin levels were significantly better in the biguanide group ($p = 0.04$ for both parameters); whereas the improvements in serum total cholesterol ($p<0.001$), low density lipoprotein ($p<0.001$), CRP ($p<0.001$) and acne status ($p = 0.04$) were significantly superior in the statin receivers. Based on these results, each medication is only effective on some aspects of the disease. Overall, the simvastatin was superior to metformin with regard to the number of beneficial effects.

Key words: Polycystic ovary syndrome, biguanide, statin, metabolic complications, hirsutism and acne

INTRODUCTION

Polycystic Ovary Syndrome (PCOS) is a frequent endocrine disease among women with a prevalence of 5%- 10% during the reproductive age. It is also a common cause of anovulatory-related infertility (Boomsma *et al*., 2008; Palacio *et al*., 2006; Azziz *et al*., 2004). Presence of PCOS is not confined to fertility issues and causes a variety of pathogenic conditions such as acne, hirsutism, obesity, abnormal periods, glucose intolerance and Diabetes Mellitus (DM) (Goldenberg and Glueck, 2008). Although, the condition has been fully evaluated in different settings, the exact pathophysiology remains unknown. Hyperandrogenism, abnormal folliculogenesis and steroidogenesis and hyperinsulinemia are the main underlying abnormalities (Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004). A combination of various genetic and environmental factors is believed to be associated with development of PCOS (Lee *et al*., 2005). Due to uncertain physiopathology, there are not yet definite treatments in PCOS patients. Weight loss (Ornstein *et al*., 2011), transvaginal ovarian drilling (Ghasemzad *et al*., 2007), antiandrogens (Krotkiewski *et al*., 2003), oral contraceptives (Kebapcilar *et al*., 2010), ovulation stimulators (Papaleo, 2011), medications routinely used in diabetes mellitus (Kuscu and Koyuncu, 2002) and lipid/cholesterol lowering agents (Kaya *et al*., 2010) have been proposed by different studies. The last two groups of medication, i.e., antidiabetic agents and lipid/cholesterol lowering medications are consisted of a verity of drugs with different profiles, mechanisms of action, potency and side effects (Katzung, 2000). This study aimed to compare the therapeutic effects of a biguanide (antidiabetic agent) and a statin (cholesterol lowering agent) in patients with PCOS.

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MATERIALS AND METHODS

Patients: In a randomized double-blind randomized clinical trial, 400 hundred women with PCOS were recruited. This study was performed in Tabriz Taleghani Teaching Centre in a 15-month period of time from February 2010 to May 2011. This centre is a big referral one in north-west of Iran in the field of obstetrics and gynecology.

The inclusion and exclusion criteria: The inclusion criteria were diagnosis of PCOS, age between 20 and 40 years and normal levels of serum bilirubin, aminotransferases, blood urea nitrogen and creatinine. The exclusion criteria were as follows:

- Congenital adrenal hyperplasia
- Hyperprolactinemia
- Cushing's syndrome
- Androgen-secreting tumors
- Thyroid disease
- Hypertension
- Previous cardiovascular disease
- A positive history of taking Oral Contraceptive Pills (OCPs)
- Steroidal hormones or any medication potentially influencing ovarian function in the last three months
- Pregnancy
- Drug allergy

Diagnosis of PCOS: Diagnosis of PCOS was made when there were clinical signs and symptoms (obesity, subfertility, infertility, acne, hirsutism, etc.), biochemical hyperandrogenism and oligomenorrhea (number of periods = 8 per year) or unovulation (absence of ovulation during periods) (Cunningham *et al*., 2009).

Randomization: The patients were randomly allocated in two equal groups, including 200 patients in each one. These two groups were matched for the age, Body Mass Index (BMI) and type of period abnormality.

In the first group oral biguanide (Metformin, 500 mg three times daily) and in the second group oral statin (Simvastatin, 20 mg daily) were prescribed for three consecutive months (Cunningham *et al*., 2009). Dietary and activity profiles were similar in both groups during the interventional period.

Ethics: Informed signed consents were obtained from all the patients. This study was approved by the Ethics Committee of Tabriz University of Medical Sciences.

Variables: The following variables were evaluated before and after intervention in both groups:

- Weight to Hip Ratio (WHR)
- Body Mass Index (BMI)
- Abnormal periods
- Abnormal Oral Glucose Tolerance Test (OGTT)
- Acne
- C-Reactive Protein (CRP)
- Hyperinsulinemia
- Hirsutism score
- Follicle Stimulating Hormone (FSH)
- Luteinizing Hormone (LH)
- Fasting Blood Sugar (FBS)
- Post-Prandial Blood Sugar (PPBS)
- Serum insulin
- Insulin Sensitivity Index (ISI)
- Serum cholesterol
- Serum High-Density Lipoprotein (HDL)
- Serum Low-Density Lipoprotein (LDL)
- Serum triglyceride
- Serum total and free testosterone

All the mentioned laboratory tests were performed at morning follicular phase of a normal period or after injection of progesterone. Hirsutism was evaluated by Ferriman and Gallwey scoring system (Wild *et al*., 2005). Oral Glucose Tolerance Test (OGTT) was performed after ingestion of 75 g of pure glucose. The Insulin Sensitivity Index (ISI) was calculated automatically from plasma glucose and insulin concentrations in fasting state and during OGTT. Hyperinsulinemia was defined when post-prandial serum insulin level was >151 $\mu U\ mL^{-1}$ (Larsen *et al*., 2002).

Statistical analysis: The data are shown as Mean±Standard Deviation or frequency (percentage). Analysis was performed by SPSS software V.15.0 (Chicago, IBM Co). Independent or paired samples t-tests were employed for numeric data and Chi-Squares, Fisher's Exact or McNemar's tests were used in descriptive data analysis. $p<0.05$ was considered statistically significant (Petrie and Sabin, 2000).

RESULTS

The metformin and simvastatin receivers were matched for age (Mean: 26.43±4.67 vs. 26.87±4.45 years, respectively; $p = 0.65$) (Fig. 1).

Within the metformin receivers, percentage of abnormal periods ($p = 0.01$) and hyperinsulinemia ($p<0.001$), as well as the mean FBS ($p = 0.001$), PPBS

Table 1: Pre- and post-interventional variables in two groups receiving metformin or simvastatin

	Metformin				Simvastatin				
Variables	Before	After	Change	P*	Before	After	Change	P*	P**
WHR	0.95±0.20 (0.59-1.62)	0.90±0.17 (0.49-1.34)	-5.26	0.13	0.81±0.13 (0.59-1.62)	0.90±0.20 (0.56-1.10)	-10.00	0.22	0.27
BMI	27.71±0.73 (26.80-29.50)	27.64±0.63 (26.80-29.20)	-0.25	0.12	27.40±0.69 (27.00-29.80)	27.72±0.66 (26.60-29.30)	-1.15	0.31	0.20
Abnormal periods	136 (68)	72 (36)	-47.06	0.01	80 (40)	132 (66)	-39.39	0.04	0.67
Abnormal OGTT	42 (21)	26 (13)	-38.10	0.25	40 (20)	56 (29.2)	-28.57	0.06	0.06
Acne	80 (40)	54 (27)	-32.50	0.25	42 (21)	72 (36)	-41.67	0.04	0.04
CRP+	104 (52)	92 (46)	-11.54	0.69	38 (19)	120 (6)	-68.33	<0.001	<0.001
Hyperinsulinemia	124 (62)	14 (7)	-88.71	<0.001	14 (7)	133 (66.5)	-89.47	<0.001	0.35
Hirsutism score	4.73±3.76 (0.00-9.00)	3.20±3.57 (0.00-9.00)	-32.35	0.08	3.73±3.60 (0.00-9.00)	4.60±3.64 (0.00-8.00)	-18.91	0.19	0.53
FSH (IU L^{-1})	7.26±2.07 (1.40-10.60)	7.40±1.83 (2.25-10.80)	+1.93	0.15	7.67±1.30 (3.40-10.80)	7.76±1.69 (4.40-10.50)	-1.16	0.54	0.18
LH (IU L^{-1})	12.32±5.38 (4.80-21.40)	12.08±5.65 (4.40-21.40)	-1.95	0.22	10.99±4.22 (4.80-21.00)	11.42±3.79 (5.10-22.00)	-3.77	0.22	0.68
FBS (mg dL^{-1})	93.87±17.37 (63.00-147.00)	86.43±8.94 (66.00-104.00)	-7.93	0.001	87.40±9.87 (75.00-140.00)	89.40±13.82 (75.00-110.00)	-2.24	0.16	0.04
PPBS (mg dL^{-1})	118.67±27.40 (63.00-168.00)	104.23±19.90 (63.00-150.00)	-12.17	0.01	122.77±36.52 (94.00-218.00)	126.97±37.78 (84.00-212.00)	-3.31	0.21	0.08
Insulin (mg dL^{-1})	11.33±13.62 (3.90-82.00)	10.24±13.71 (3.90-82.00)	-9.62	0.01	9.93±11.13 (3.80-68.00)	10.21±11.14 (3.80-68.00)	-2.74	0.06	0.04
ISI	6.67±1.13 (4.70-9.00)	6.77±0.87 (5.00-8.70)	+1.50	0.58	6.92±0.71 (4.60-8.70)	7.06±1.00 (5.00-8.10)	-1.98	0.45	0.35
Cholesterol (mg dL^{-1})	184.90±54.82 (120.00-329.00)	185.13±49.89 (115.00-332.00)	+0.12	0.95	142.30±42.80 (119.00-329.00)	183.47±49.24 (121.00-329.00)	-22.44	<0.001	<0.001
HDL (mg dL^{-1})	54.53±14.95 (41.00-114.00)	52.07±15.82 (16.00-98.00)	-4.51	0.49	55.63±8.63 (41.00-75.00)	52.87±10.41 (41.00-75.00)	+5.22	0.02	0.16
LDL (mg dL^{-1})	116.73±28.60 (78.00-202.00)	115.03±27.79 (70.00-198.00)	-1.46	0.12	98.80±17.54 (86.00-202.00)	113.40±25.92 (69.00-156.00)	-12.87	<0.001	<0.001
Triglyceride (mg dL^{-1})	123.90±52.79 (42.00-271.00)	112.92±47.28 (8.90-180.00)	-8.86	0.27	118.37±54.08 (75.00-380.00)	113.20±60.69 (75.00-307.00)	+4.57	0.42	0.17
Total testosterone (mg dL^{-1})	0.74±0.15 (0.40-1.00)	0.67±0.12 (0.40-0.88)	-9.46	0.12	0.65±0.13 (0.40-1.00)	0.74±0.16 (0.40-0.98)	-12.16	0.23	0.48
Free testosterone (mg dL^{-1})	1.48±1.01 (0.10-3.80)	1.48±0.95 (0.10-3.90)	0.00	0.98	3.42±3.71 (0.10-13.50)	3.59±4.20 (0.10-13.20)	-4.74	0.43	0.45
DHEAS (mol mL^{-1})	8.67±0.75 (6.90-10.00)	8.04±2.03 (0.90-9.60)	-7.27	0.14	8.11±0.84 (6.90-10.40)	8.60±0.85 (6.80-9.90)	-5.70	<0.001	0.73
SHBG (mol mL^{-1})	40.73±3.99 (34.00-49.00)	41.17±3.38 (34.00-49.00)	+1.08	0.25	39.80±3.28 (34.00-49.00)	39.93±3.88 (34.00-46.00)	-0.33	0.85	0.47
Prolactin (mg mL^{-1})	16.20±2.52 (12.00-22.00)	16.43±3.31 (11.00-22.00)	+1.42	0.55	15.94±2.23 (12.00-21.00)	16.03±2.28 (12.00-21.00)	-0.56	0.43	0.43

BMI: Body Mass Index, CRP: C-Reactive Protein, DHEAS: Dehydroepiandrosterone sulfate, FBS: Fasting blood sugar, FSH: Follicle-stimulating hormone, HDL: High density lipoprotein, ISI: Insulin sensitivity index, LDL: Low density lipoprotein, LH: Luteinizing hormone, OGTT: Oral glucose tolerance test, PPBS: Post-Prandial blood Sugar, SHBG: Sex hormone binding globulin, WHR: Waist-Hip ratio. Data are presented as Mean±Standard deviation (range) or frequency (percentage). Changes of variables are presented as percentage. -: Indicates decrease and +: Indicates increase of that variables after treatment. P*: Intra-group, P**: Inter-group $p<0.05$ is considered statistically significant

($p = 0.01$) and serum insulin ($p = 0.01$) decreased significantly after treatment. Decrease of the hirsutism score was nonsignificant in a marginal fashion ($p = 0.08$). Changes of other variables were not significant ($p>0.05$) (Table 1).

In the group of simvastatin receivers (intra-group analysis), percent of abnormal periods ($p = 0.04$), acne ($p = 0.04$), positive CRP ($p<0.001$) and hyperinsulinemia ($p<0.001$), as well as the mean serum total cholesterol ($p<0.001$), LDL ($p<0.001$) and DHEAS ($p<0.001$) decreased and the mean serum HDL ($p<0.001$) increased significantly after treatment. Percent of abnormal OGTT ($p = 0.06$) and mean serum insulin ($p = 0.06$) decreased nonsignificantly in a borderline manner after treatment. Changes of other variables were not significant ($p>0.05$) (Table 1).

Comparing the changes of variables between the metformin and simvastatin receivers, the mean FBS (7.93% vs. 2.24%, $p = 0.04$) and serum insulin (9.62% vs. 2.74%, $p = 0.04$) decreased significantly more in the metformin group after treatment. Decrease of abnormal OGTT (38.1% vs. 28.57%, $p = 0.06$) and PPBS (12.17% vs. 3.31%, $p = 0.08$) was higher in the metformin receivers nonsignificantly but statistically borderline. Percentages of cases with acne (32.50% vs. 41.67%, $p = 0.04$) and positive CRP (11.54% vs. 68.33%, $p<0.001$), as well as the mean serum total cholesterol (by 0.12% vs. 22.44%, $p<0.001$) and LDL (1.46% vs. 12.87%, $p<0.001$) decreased

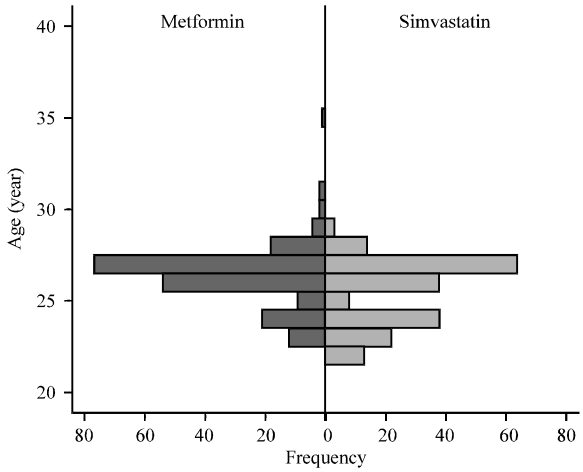

Fig. 1: Frequency of patients' age in metformin and simvastatin receivers

significantly more prominent after treatment in the simvastatin group. Changes of other variables were comparable between the 2 groups (Table 1).

No significant side-effects or complications were documented in the patients within the study period.

DISCUSSION

This study compared the therapeutic effects of a biguamide (metformin) and a statin (simvastatin) in patients with PCOS. By now, the blood sugar lowering agents have been evaluated in PCOS in various studies. It is generally accepted that metformin could be prescribed as the first or second line drug in infertile patients with PCOS with unovulation or in the cases candidates of receiving gonadotropin (Palomba *et al*., 2008; De Leo *et al*., 2003; Farzadi and Zadeh, 2006). Other studies have also emphasized on good effects of metformin on period cycles in women with PCOS (Glueck *et al*., 2001; Vrbikova *et al*., 2002; Pasquali *et al*., 2000; Costello *et al*., 2007; Moghetti *et al*., 2000). We did not find any beneficial effect of metformin on lipid profile in our patients. Luque-Ramirez *et al*. (2007) did not report a significant effect of metformin on lipid profile in patients with PCOS. Administration of serum cholesterol lowering agents in patients with PCOS got popularity when it was shown that the risk factors of atherosclerosis such as dyslipidemia, insulin resistance, systemic inflammation and endothelial dysfunction were more common than the normal counterparts (Lo *et al*., 2006). Banaszewska *et al*. (2007) concluded that simvastatin (for 12 weeks) was superior to Oral Contraceptive Pills (OCPs) in reducing clinical and endocrine abnormalities in PCOS. They did not find any benefit for the BMI. In our series endocrine status (including lipid profile and serum level of Dehydroepiandrosterone Sulfate or DHEAS) as well as abnormal periods and acne went better at the endpoint. We did not either find any beneficial effect of simvastatin on Waist-Hip Ratio (WHR) and Body Mass Index (BMI). Diminished number of cases with positive C-Reactive Protein (CRP) at the endpoint confirms the beneficial effect of this dug on systemic inflammation (Kelly *et al*., 2001). Kaya *et al*. (2010) showed significant improvements in inflammatory status, hyperandrogenism, oxidative stress, metabolic parameters and serum level of testosterone in PCOS patients after receiving simvastatin. Similar consequences were reported in another series by Duleba *et al*. (2006). Sathyapalan *et al*. (2009) concluded that statins for 3 months could have decreased the serum level of testosterone and CRP and ameliorate the lipid profile with no significant effect on BMI. Comparing with our results, we did not find any significant change in serum level of testosterone. This controversy might be due to small sample size in the mentioned studies (30-40 patients only). Banaszewska *et al*. (2009) evaluated 136 patients with PCOS in two groups. They concluded that simvastatin and metformin exert comparable effects on reduction of testosterone, clinical hyperandrogenism, BMI and markers of systemic inflammation. However, only simvastatin significantly improved lipid profile, DHEAS and insulin sensitivity.

In conformity with this study, improvement of lipid profile and DHEAS was significantly higher in the simvastatin receivers; however, in contrast with their findings, there were significant effects on testosterone, clinical hyperandrogenism or BMI in neither group.

There were 2 main limitations in the Banaszewska *et al*. (2009) series: the first, small sample size (finished on only 113 patients) and the second, selection of a particular population (exclusion of normoandrogenic women). The number of cases in the present study was 200 subjects in each group; a total of 400 patients which is almost 4 times higher than the recruited population in the mentioned study. This could enormously increase the power of the statistical analysis and hence; the comparisons are more valid. The normoandrogenic women were also included in the present study and this may inhibit a probable selection bias in the Banaszewska *et al*. (2009) series. Furthermore, participants of that trial were young and mostly lean; thus, they concluded that extrapolation of their observations to other populations of women with PCOS should be avoided. This limitation was not present in the current study, as well. Banaszewska *et al*. (2009) recommended that further large studies on diverse

populations are needed to reevaluate the effectiveness and safety of both medication and hence, the present study was carried out.

Based on our findings, one may conclude that combination therapy may be more beneficial in PCOS patients than every single drug. This hypothesis is also under debate (Kazerooni *et al*., 2010; Banaszewska *et al*., 2009).

CONCLUSION

Based on the results of this study in patients with PCOS, metformin significantly ameliorated abnormal periods and increased levels of serum insulin and glucose and with marginal benefits on the hirsutism score. On the other hand, simvastatin significantly decreased abnormal periods, serum levels of CRP, insulin and DHEAS and abnormal lipid profile. Comparing the two medications, the metformin was superior in relieving metabolic abnormalities associated with serum insulin and glucose; whereas the simvastatin was more effective in treatment of acne, alleviating of inflammatory condition and normalizing of lipid profile. These findings may propose that a combination therapy could lead to better consequences in these patients. However, further studies are needed in this regard.

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