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Comparison of effect of simvastatin and metformin monotherapy on lipid profile and testosterone levels in polycystic ovary syndrome

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ABSTRACT

Background: Polycystic ovary syndrome has consequences like insulin resistance, hyperandrogenism and dyslipidemia. Metformin is commonly used for treatment of this disorder and its effects on various biochemical parameters are compared with a cardioprotective drug simvastatin. Method: Fifty patients of polycystic ovary syndrome were divided into two groups depending on metformin or simvastatin administration for a period of 6 months. Levels of serun glucose, insulin, and testosterone and lipid profile were estimated before and after treatment and compared statistically for both the groups.Results: Metformin and simvastatin reduced levels of insulin and testosterone and improved lipid profile in patients of polycystic ovary disease. The effects of two groups were found to be statistically comparable. Conclusion: Efficacy of simvastatin is comparable to metformin for treatment of polycystic ovary syndrome, though more studies are required to support this view.
Keywords: Polycystic ovary syndrome, metformin, simvastatin, testosterone, lipid profile

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Introduction

Polycystic Ovary Syndrome (PCOS) is a complex and heterogenous clinical condition characterised by hyperandrogenism and chronic oligoovulation and anovulation[1]. PCOS is a common endocrinopathy affecting women of reproductive age group and is commonly associated with obesity, menstrual irregularity, insulin resistance, infertility and/ or hyperandrogenism[1]. It is also associated with increased risk of abnormal lipoproteins and hypertension as well as cardiovascular or cerebrovascular morbidity[2]. It has been reported recently that a significant proportion of overweight women with PCOS have hyperinsulinemia[3].

Treatment for PCOS subjects typically includes lifestyle modification which brings about weight loss and pharmaceutical intervention which includes oral contraceptives, antiandrogen therapy, insulin lowering agents such as metformin and lipid lowering agents like statins[4, 5].

Metformin is a biguanide which brings about increase in insulin sensitivity and pregnancy rate accompanied by decreased insulin and androgen levels in PCOS[6]. It inhibits hepatic glucose production and increases peripheral insulin sensitivity at post receptor level[3].
Simvastatin is 3-hydoxy-3-methyl glutaryl coenzyme A reductase (HMG Co A reductase) inhibitor which is the rate limiting step in cholesterol biosynthesis. It has also been reported to have antioxidant, anti-inflammatory and antiandrogenic properties by inhibiting the proliferation and steroidogenesis in ovarian theca interstitial cells[4].

Metformin is the established modality for treatment of PCOS, but there is paucity of literature regarding

effects of simvastatin and its comparison with metformin in patients of PCOS. Therefore, this study was planned to evaluate and compare the effects of metformin and simvastatin as monotherapy on lipid profile and testosterone levels in patients of PCOS.

Material and Methods

The present study was a prospective, randomized study conducted on 50 consecutive women diagnosed with PCOS after obtaining informed consent and approval from institutional board of studies. Patients were selected as per Rotterdam criteria[7] 2003 who were fulfilling two or more of the following criteria:

- Oligomenorrhoea and/ or anovulation
- Clinical and/ or biochemical signs of hyperandrogenism
- Polycystic ovaries

Patients having any endocrinal disorder, kidney or liver disease or taking oral contraceptive pills or any other hormonal medication were excluded from the study. The 50 patients were divided into two groups of 25 each using systematic randomization method:

Group I: PCOS patients who were given metformin 500 mg TDS per oral for 6 months.

Group II: PCOS patients who were given simvastatin 20 mg OD per oral for 6 months.

Detailed clinical history including menstrual history was taken and thorough clinical examination was done for all patients. Body mass index (BMI) was calculated by weight (Kg) divided by height (m) squared. Abdominal fat distribution was defined by waist hip ratio (WHR). Ultrasound assessment was conducted at baseline to evaluate the ovarian volume, number of follicles and endometrium as a criterion to diagnose the PCOS in patients at enrollment. The ovaries were defined as 'polycystic' when they were enlarged with volume more than 10 cc or with more than 12 follicular cysts (size of 2-9 mm) in any one ovary.

Fasting venous blood samples were collected for both the groups at the time of diagnosis and after 6 months of treatment. The serum samples were estimated for levels of glucose, insulin, lipid profile and testosterone. Serum glucose and lipid profile were analysed on autoanalyser (Konelab 30 i) using standard kit techniques while serum insulin and testosterone were estimated by chemiluminescence technique (Advia Centaur CP, Siemens) [8,9,10].

Data was reported as mean ± standard deviation and was analysed using unpaired't' test, paired 't' test and chi square test with Yates correction. Student's two-tailed't' test was used for a comparison between groups of normally distributed variable. Statistical analysis of frequency differences between the groups was evaluated using χ^2 test.

Results

All the patients in the present study were in the age group of 17-39 years. Majority of patients (80% in group I and 72% in group II) were suffering from menstrual disturbances (oligomenorrhoea/ amenorrhoea) and all the patients (100%) had hirsutism. 52% patients in group I and 64% in group II had acne on presentation.

Table 1:

Biochemical profile in groups I and II before and after 6 months of treatment:

Group	Baseline Levels (Mean±SD)	Levels after 6 months (Mean±SD)	p value[a]
Glucose (mg/dL)			
I	93.20±14.0	92.88±16.12	0.91
II	92.40±15.10	92.44±12.24	0.98
pValue[b]		0.87	
Insulin (μIU/mL)			
I	19.93±9.01	18.18±8.28	0.01
II	21.45±6.87	17.06±5.47	0.001
pValue[b]		0.57	
Total Testosterone (ng/mL)			
I	54.16±29.87	49.80±28.15	0.006
II	57.64±36.64	53.24±30.78	0.019
pValue[b]		0.84	
Triglycerides (mg/dL)			
I	125.08±28.21	120.96±23.17	0.09
II	137.64±36.64	130.24±30.78	0.014
pValue[b]		0.23	
Total Cholesterol (mg/dL)			
I	151.80±32.58	144.76±30.05	0.008
II	160.4±31.72	147.80±27.85	0.004
pValue[b]		0.71	
HDL-C (mg/dL)			
I	38.36±5.52	39.92±4.33	0.019
II	39.04±3.57	40.80±3.09	0.005
pValue[b]		0.41	
LDL-C (mg/dL)			
I	104.28±27.79	101.60±25.43	0.11
II	115.52±23.01	111.88±19.91	0.04
pValue[b]		0.11	
VLDL-C (mg/dL)			
I	26.32±4.95	26.08±4.56	0.686
II	28.48±5.20	27.00±4.06	0.054
pValue[b]		0.45	

$p<0.05$ was considered statistically significant, [a] Comparison for measurements within groups, [b] Comparison between the groups at 6 months of treatment, Bold p values represent significant difference **Abbreviations:** HDL-C, high density lipoprotein

cholesterol; LDL-C, low density lipoprotein cholesterol; VLDL-C, very low density lipoprotein cholesterol.

84% patients of group I and 68% of group II had evidence of polycystic ovaries on ultrasound. At enrollment, 52% patients in group I and 68% in group II had body mass index equal to or more than 25 while 60% of patients in group I and 80% of the patients in group II had WHR more than 0.80.

Discussion

PCOS is associated with menstrual dysfunction, infertility, hirsutism and clinical consequences like dyslipidemia, hypertension, cardiovascular morbidity and insulin resistance[11]. In the present study also, majority of the patients presented with complaints of menstrual irregularities, hirsutism, acne and weight gain. The serum levels of fasting glucose were found to change non-significantly in both the groups after 6 months of treatment which is in agreement with other studies in literature[4,12].

Baseline concentration of fasting serum insulin levels decreased significantly after 6 months of treatment with metformin. Similar findings have been reported by other authors also[13,14,15]. Metformin, being an insulin sensitizer, exerts its effect by promoting peripheral glucose utilization[16]. In group II patients treated with simvastatin, serum insulin levels decreased significantly after 6 months of treatment. In literature, simvastatin has been reported to dercrease insulin levels but additional benefit of adding simvastatin to metformin has contradictory reports by different authors[4, 14] .The change in two groups was non-significant in the present study.

The decrease in serum testosterone levels 6 months after treatment with metformin was found to be more profound as compared to that by simvastatin therapy though the difference in two groups was found to be non-significant statistically. Insulin levels were also found to be decreased in two groups, suggesting that alleviation of hyperandrogenism may be mediated by decreased insulin action. These results may also be explained by decreased ovarian steroidogenesis, probably due to reduced serum insulin concentration in these patients.

Besides endocrinal, another important aspect of PCOS is increased risk of cardiovascular morbidity brought about predominantly by derangement of lipoprotein metabolism[17]. Though the levels of different lipids were found to be within the normal range in both the groups, the levels improved [↓ in triglycerides (TG), total cholesterol (TC), low density lipoprotein cholesterol (LDL-C) and very low density lipoprotein cholesterol (VLDL-C) while ↑ in high density lipoprotein cholesterol (HDL-C)] significantly after treatment with simvastatin only. Metformin was found to decrease levels of only total cholesterol significantly. Simvastatin acts by inhibiting HMG Co A reductase enzyme which is activated by insulin and as this drug produces a hypoinsulinemic state, its activation is also hindered[18].

As the difference in all these biochemical parameters after 6 months of respective treatment in both the groups was found to be statistically non-significant, thus, simvastatin may be considered comparably effective to metformin in treatment of PCOS. Though the sample size and study duration was small in this study, further research with larger groups and longer study periods is required to support these findings.

Conclusion

The results from present study show that Metformin and Simvastatin reduced levels of insulin and testosterone and improved lipid profile in patients of PCOS. But the study results may not be generalized because of small sample size used in present study. The study might have also encountered by number of biases such as measurement bias, observer bias, confirmatory bias. The findings from the present study should be validated using randomised controlled trials in large sample size.

References:

1. Lindholm A, Andersson L, Eliasson M, Bixo M, Sundstrom-Poromaa I (2008). Prevalence of symptoms associated with polycystic ovary syndrome. Int. J. Gynaecol. Obstet. 102: 39-43.
2. Danigren E, Janson PO, Johnson S (1992). Polycystic ovary syndrome and risk for myocardial infarction. Acta. Obstet. Gynaecol. Scand. 71: 559-604.
3. Kim LH, Tailor AE, Barberi RL (2000). Insulin sensitizers and polycystic ovary syndrome. Fertil Steril. 73: 1097-8.
4. Banaszewska B, Pawelczyk L, Spaczynski RZ, Duleba AJ (2009). Comparison of simvastatin and metformin in treatment of polycystic ovarian syndrome. J. Clin. Endocrine. Metab. 94: 4938-45.
5. Ghalaut VS, Sharma D, Dahiya K, Dora A, Dahiya P (2008). Rosiglitazone: Effect on spontaneous and clomiphene induced ovulation in polycystic ovary syndrome. J. Obstet. Gynecol. India. 58: 53-56.
6. Diamanti-Kandarakis AK (2005). Metformin administration improves endothelial function in women with PCOS. Eurp. J. Endocrinol. 152: 749-56.

7. Rotterdam ESHRE/ASRM-sponsored PCOS Consensus Workshop Group (2004). Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. Fertil Steril. 81: 19-25.
8. Morin LG, Prox J (1973). Single glucose oxidase-peroxidase reagent for two- minute determination of serun glucose. Clin. Chem. 19: 959-62.
9. Bahcect M, Aydemir M, Tuzcu A (2007). Effects of oral fat and glucose tolerance test on serum lipid profile, apolipoprotein, and CRP concentration, and insulin resistance in patients with polycystic ovary syndrome. Fertil Steril. 87: 1363-8.
10. Woodhead JS, Weeks I (1985). Chemiluminescence immunoassay. Deaprtment of Medical Biochemistry. Clin Chem. 57: 523-9.
11. Banaszewska B, Pawelczyk L, Spaczynski RZ, Dziura J, Duleba AJ (2007). Effects of simvastatin and oral contraceptive agent on polycystic ovary syndrome: prospective, randomized, crossover trial. J. Clin. Endocrinol. Metab. 92: 635-42.
12. Singh B, Panda S, Nanda R (2010). Effect of metformin on hormonal and biochemical profile in PCOS before and after therapy. Ind. J. Clin. Biochem. 25: 367-70.
13. Nestler JE (2008). Metformin for the treatment of the Polycystic Ovary Syndrome. N. Eng. J. Med. 358: 47-54.
14. Kazerooni T, Shojaei-Baghini A, Dehbashi S, Asadi N, Ghaffarpasand F, Kazerooni Y(2010). Effects of metformin plus simvastatin on polycystic ovary syndrome: A prospective, randomized, double-blind, placebo-controlled study. Fertil Steril. 94: 2208-13.
15. Ehrmann DA, Cavaghan MK, Imperial J, Sturis J, Rosenfield RL, Polonsky KS (1997). Effects of metformin on insulin secretion, insulin action, and ovarian steroidogenesis in women with polycystic ovary syndrome. J. Clin. Endocrinol. Metab. 82: 524-30.
16. Nazari T, Bayat R, Hamedi M (2007). Metformin therapy in girls with Polycystic Ovary Syndrome: A self-controlled clinical trial. Arch. Iranian Med. 10: 176-81.
17. Teede H, Deeks A, Moran L (2010). Polycystic ovary syndrome: A complex conditions with psychological, reproductive and metabolic manifestations that impacts on health across the lifespan. BMC Med. 8: 41.
18. Duleba AJ, Banaszewska B, Pawelczyk L, Spaczynski RZ (2006). Simvastatin improves biochemical parameters in women with polycystic ovary syndrome: results of prospective, randomized trial. Fertil Steril. 85: 996-1001.

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