Original Article

COMPARISON OF METFORMIN AND CYPROTERONE-ESTRODIOL COMPOUND EFFECT ON HS C-REACTIVE PROTEIN AND SERUM ANDROGEN LEVELS IN PATIENTS WITH POLY CYSTIC OVARY SYNDROME

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ABSTRACT

Objectives: The aim of this study was comparison of the effects of Metformin and Cyproterone**-**estradiol compound on serum androgens & highly sensitive C-reactive protein levels.

Methodology: Sixty patients with Poly Cystic Ovary Syndrome (PCOS) were enrolled in this study conducted during a period of 16 months from December 2004 to March 2006. Thirty subjects were in each group and treated with Metformin one gram per day or Cyproterone-estradiol compound 21 days monthly and at the beginning and after 3 and 6 months, weight, height, testosterone, dehydroepiandrosterone sulfate (DHEA-S) and hs-CRP levels were measured.

Results: Mean age of patients was 23.5±8.7 years with the range of 15 to 49 years. In both groups significant decreases in DHEA-S levels and in Cyproterone-estradiol compound group a significant decrease in testosterone levels were seen after 6 months, but there were no significant decrease on hs- CRP levels. Comparison of two groups showed that there were no significant differences in the effects of these two drugs on serum testosterone, DHEA-S and hs-CRP levels. In our study the level of hs- CRP at the beginning of treatment were significantly higher in patients who were overweight and obese. Also we found that Cyproterone-estradiol compound causes significant decrease at the level of hs-CRP in overweight and obese patients.

Conclusion: The results of this study are different from those of previous studies about beneficial effects of Metformin on hs-CRP levels but are similar to the results of studies that revealed probably obesity and overweight has important role in inducing inflammation and increasing CRP levels.

KEY WORDS: Poly Cystic Ovary Syndrome, Metformin, Cyproterone-estradiol compound, hs-CRP.

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INTRODUCTION

Poly Cystic Ovary Syndrome (PCOS) is one of the most common endocrine disorders in women at reproductive ages and is the most common cause of infertility due to unovulation and its frequency in these ages at different

studies is from 4% to 10%.[1-7] This syndrome is classically defined by clinical and/or biochemical signs of hyper androgenism such as hirsutism, acne and alopecia, irregular menstrual cycles and in a significant proportion of patients with insulin resistance and obesity.[8,9] Although for many years the interest in PCOS has been focused on the cutaneous and reproductive manifestations of this disorder, the recent evidence suggests that metabolic and cardiovascular risk factors cluster in these patients.[8] PCOS is associated with increased prevalence of several cardiovascular risk factors, including hypertension and dyslipidemia. In addition, women with PCOS display surrogate markers for early atherosclerosis, such as increased C-reactive protein concentration.[10] Increased insulin resistance and hyper insulinemia may contribute to the androgen excess seen in women with PCOS.[11] Recently insulin resistance syndromes such as type 2 diabetes mellitus and PCOS have been linked to slightly elevated serum C-reactive protein levels in the normal range, which has been shown to predict risk for cardiovascular disease.[7] Insulin lowering agents such as Metformin and Rosiglitazone dose-dependently have been shown to increase insulin sensitivity, lowered serum concentrations of CRP and restored ovulation.[7,12]

The etiology of PCOS is unknown, but current theories emphasize genetic and intrauterine origins coupled with environmental factors such as diet and altered lifestyle patterns.[13] The genetic basis of PCOS is unknown. There is a strong familial component but the mode of inheritance is uncertain and several candidate genes have been proposed to contribute to susceptibility.[14] Diagnostic criteria of PCOS derived from the conference held at the National Institutes of Health in 1990 and the revised 2003 consensus in the Netherlands.[8,9,15]

C- reactive protein is the prototypic acute phase reactant; indeed its level increases rapidly after an inflammatory stimulus and may raise hundreds of fold according to the intensity of stimulus.[16] CRP levels measured with a high sensitivity assay are less than 10 mg/L in 98% of healthy persons. Even when relatively elevated within this normal range, CRP has been shown to be predictive of a first cardiovascular event in previously healthy men and women.[17,18] The aim of our study was to compare the effects of Metformin and Cyproterone-estradiol compound on CRP and androgens level in patients with PCOS.

METHODOLOGY

The subjects included in this clinical trial were 70 patients with PCOS from specialty and sub specialty clinics of Tabriz University (Medical Sciences). We used the National Institutes of Health criteria for diagnosis of patients. All of the patients visited with an endocrinologist and demographic and biochemical parameters collected by a questionnaire. In all patients, we measured height, body weight, BMI, testosterone, DHEA-S and CRP.

Testosterone and DHEA-S were measured with ELISA and CRP was measured with a high sensitive quantitative photometric assay. Patients randomly divided in two equal groups. In one group we used Metformin 1000 mg/d and in another group we used Cyproterone-estradiol compound (Ethinyl estradiol 35µg plus Cyproterone acetate 2mg) 21days a month. Biochemical parameters and body weight rechecked after 3 and 6 months of treatment in all patients, and results collected in a questionnaire. Our exclusion criteria's were: rheumatic disease, infective disease, therapy for hirsutism and scalp hair loss such as spironolactone and finasteride and therapy for acne such as antibiotics. In Metformin group five patients did not continue therapy, three patients due to pregnancy and two patients due to epigastric pain. In Cyproterone-estradiol compound group 5 patients did not continued therapy due to nausea, increasing in body weight and drug intolerance. The collected data were analyzed with SPSS; version 11.5.We used paired T test and chi square for analysis and $P<0.05$ considered significant.

RESULTS

Mean age of patients in Metformin group was 24.9±11 years and in Cyproterone-estradiol

compound group was 22±5.2 years. There were no significant statistical differences between them (P=0.19). Mean of body mass index in Metformin group was 26.5±5.7 kg/m2 and in Cyproterone-estradiol compound group was 24.6±4.9 kg/m2, with no significant statistical differences between them (P=0.17). Clinical signs and biochemical parameters of 60 patients with PCOS before treatment are shown in Table-I and comparison of biochemical parameters and alterations in body weight and BMI in two groups during and at the end of treatment are shown in Table-II.

In both groups significant decreases in DHEA-S levels and in Cyproterone-estradiol compound group a significant decrease in testosterone levels were seen after 6 months, but there were no significant decrease in hs- CRP levels.

Comparison of two groups showed that there were no significant differences in the effects of these two drugs on serum testosterone, DHEA-S and hs-CRP levels. In our study the level of hs- CRP at the beginning of treatment were significantly higher in patients who were overweight and obese. Also we found that Cyproterone-estradiol compound causes significant decrease at the level of hs-CRP in overweight and obese patients.

Table-I: Clinical signs and biochemical parameters of 60 patients with PCOS before treatment with Metformin and Cyproterone-*estadiol* compound

Clinical signs	*Number (%)*
Hirsutism	46(76.6)
Acne	35(58.3)
Scalp hair loss	33(55)
BMI and lab findings	*mean ± SD*
Mean age (year)	23.4±8.1
Height (cm)	157.6±6.1
Weight (kg)	63.4±14.7
BMI (kg/m^2)	25.57±5.4
Testosterone (ng/mL)	0.91±0.4
DHEA-S (µg/dL)	1.65±1
hs-CRP (mg/L)	9.08±3.9

DISCUSSION

Although still debatable and equivocal, there have recently been increasing suggestions that PCOS women without any other apparent chronic disease may be at increased risk for CVD compared with normal cycling women of similar age and BMI.[19] Many PCOS patients have an adverse lipid profile and an increased prevalence of glucose intolerance, type 2 diabetes, and hypertension.[19,20] These women may also have an increase in sub clinical atherosclerotic disease, as suggested by greater carotid intima-media thickness and higher levels of coronary calcifications.[21] Although the association between PCOS and CVD has been repeatedly suggested by several reports,[19,22] it has not yet

Table-II: Comparison of biochemical parameters and alterations in body weight and BMI in two groups during and at the end of treatment

	SD ±(mean) Metformin group			*SD ± (mean) Cyproterone compound*			*Comparison between groups P value*		
	Pretreatment	*After 3 month's*	*After 6 month's*	*Pretreatment*	*After 3 month's*	*After 6 month's*	*Pretreatment*	*After 3 month's*	*After 6 month's*
Testosterone (ng/mL)	0.88±0.4	0.82±0.4	0.71±0.3	0.94±0.5	0.8±0.4	0.58±0.3	0.57	0.8	0.31
DHEA-S (µg/dL)	1.88±1.1	1.8±0.9	1.2±0.5	1.43±0.91	1.67±1	1.1±0.6	0.09	0.62	0.63
hs-CRP (mg/L)	8.89±4.5	8.27±3.5	8.39±2.9	9.2±3.1	8.87±3.7	8.35±4.5	0.76	0.53	0.97
BW(kg)	66.3±15.7	64.8±17.1	62.0±12.2	60.7±13.7	60.2±13.5	57.0±9.1	0.14	0.26	0.19
BMI (Kg/m^2)	26.5±5.7	25.8±6.4	24.5±4.1	24.6±4.9	24.4±4.9	23.6±3.2	0.17	0.33	0.5

been unequivocally substantiated.[23] These findings and high CRP in the PCOS group suggest that women with PCOS may indeed be at risk for early-onset CVD. Moreover, a recent prospective study has linked menstrual irregularity, about 80% of which is attributed to PCOS, to an increased risk of mortality due to fatal coronary heart disease.[23]

In Boulman N and coworkers study[6] the mean CRP concentrations were significantly higher in the PCOS subgroups at normal BMI (<25) and in the obese group (BMI, >30) compared with the control subgroups of similar BMI ($P < 0.001$). For the subgroup of overweight PCOS and controls (BMI, 25–29), the CRP was higher in the PCOS subgroup (3.55 vs. 2.08, respectively), but the difference did not reach statistical significance ($P = 0.07$), probably due to the smaller number of patients in this subgroup (n = 17 vs. 31–68 in the two other PCOS subgroups of BMI). In the National Health and Nutrition Examination Survey III study, the metabolic syndrome was found in 23.7%, of 1887 Caucasian women.[19,24] The 27.7% prevalence of CRP greater than 3 mg/liter in Boulman N preselected (high BMI) control group is keeping with this finding in the National Health and Nutrition Examination Survey III cohort study.[19,24]

Boulman N and coworkers concluded that treatment regimens directed toward lowering CRP levels, (such as diet, smoking cessation, exercise, blood pressure control, low dose aspirin, metformin, and possibly statins)[7,25] in the future should probably be more aggressive for those PCOS women with increased CRP, as recently suggested by Glueck et al.[19] Of course, the applicability and efficiency of this hypothesis await the results of long-term clinical testing.

In Morin-Papunen L and coworkers study[7] metformin decreased significantly serum CRP levels by 31% (nonobese subjects) and 56% (obese subjects) at 6 months of treatment. Previous studies have suggested that metformin primarily decreases central obesity and secondarily improves insulin action and metabolic disturbances in obese and nonobese women with PCOS.[26] Accordingly, in the Morin-Papunen L and coworkers study, the improvements of both waist circumference and WHR during metformin treatment were the only significant determinants of serum CRP decrease, whereas BMI and fasting insulin play probably a less important role.

In this study, we found a statistically significant decrease in BMI, DHEA-S and testosterone level in all patients after 6 month's therapy but there was no statistically significant decrease in hs-CRP level after 6 month's therapy in overall. In comparison between two Metformin and Cyproterone-estradiol Compound groups, we found that there were no statistically significant differences in the effects of these two drugs on BMI, serum androgens (DHEA-S and testosterone) and hs-CRP levels, but we showed that Cyproterone-estradiol Compound causes a statistically significant decrease at the level of hs-CRP, only in overweight and obese patients. This is in contrast to Morin-Papunen L and coworkers study[7] that showed a statistically significant decrease in hs-CRP in patients who were treated with Metformin. Probably decreasing in hs-CRP in their study is related to other factors such as decreasing in body weight that needs more studies to prove it.

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