# A comparison of effects of Atorvastatin and OCP on biochemical profile of PCOS patients

Majid Mobasseri[1], Jafar Shadi[1], Amir Bahrami[1], Akbar Aliasgarzadeh[1], Esmaeil Faraji[1], Morteza Gojazadeh[2]

1- Department of Endocrinology, Imam Reza Hospital, Faculty of Medicine, Tabriz University of Medical Sciences, Iran.
2- Department of Physiology, Faculty of Medicine, Tabriz University of Medical Sciences, Iran.
*_Corresponding author: Jafar Shadi (Jafar_shadi30@yahoo.com)

**Abstract: Introduction**: Poly cystic ovary syndrome (PCOS) is one of the most common endocrine disorders which affect approximately 5 to 10 percent of women in reproductive age. Beside all common treatments, statins have recently been discussed in the treatment of PCOS. It is shown that statins can improve the biochemical profile and hemostatic status leading in improvement of prognosis of patients. **Methods**: In a randomized clinical trial, we studied 40 patients with poly cystic ovary syndrome after achieving inclusion criteria in the form of two groups (intervention and control groups respectively Atorvastatin and OCP, 20 patients in each groups). Parameters regarding to the biochemical and hemostatic status of patients was compared before and after a 3 months treatment period. **Results**: The mean age of patients was 24.1±6.1 years (minimum 14 years, maximum 37 years of old). Within the biochemical parameters the changes in FBS, total cholesterol, LDL, DHEA-S was significant in Atorvastatin group (P<0.001), while the changes was significant in OCP group just in FBS (P<0.001), TG (P<0.001), LH (P=0.002) and Insulin (P=0.01). The mean fibrinogen levels in Atorvastatin groups decreased from 319.4±47.4 before treatment to 293.8±43 after the treatment that had a significant difference (P=0.01). Fibrinogen had decreased from 327.4±38.2 to 310.5±50.1 in control group which this decrease was not statistically significant (P=0.19). The changes in other hemostatic parameters were not significant in both groups. Conclusion: With regard to the findings of present study and decrease in some parameters of biochemical profile in both groups and with considering to the decrease in DHEA-S and fibrinogen levels in patients under treatment of Atorvastatin. We cannot certainly prefer these drugs to each other. Other studies with more cases seems to be necessary for prove or rejection of the subject.

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## 1. Introduction

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders which affect 5-10% of women in reproductive age. Androgen excess is observed in 60- 80% of the women with PCOS. Hyperandrogenemia is a dependent risk factor which is associated with increased risk of cardiovascular events and hypertension in women with polycystic ovary syndrome. The women with PCOS as well as anovulation are characterized with an increase in abdominal obesity, insulin resistance, risk of type 2 diabetes and cardio vascular diseases. Hyperandrogenemia, hirsutism and acne cause psychosocial complications in these patients (Raval, 2011).

The mechanisms of increased cardiovascular disease in patients with PCOS include: Dyslipidemia, hypertension, increase in atherogenic markers (CRP, Fibrinogen, and Homocysteine). Considering the pathophysiology of the disease, different treatments have been given like: changes in life style, spironolactone, OCP, metformin, clomiphene citrate and… (Raval, 2011). Recently, different clinical studies have been conducted on statins in PCOS treatment. The advantages of statins have been discussed in primary and secondary prevention of cardiovascular diseases. Statins, by improving the biochemical profile and hemostatic status of PCOS patients improve the prognosis of patients.

Pleiotropic effects of Statins include an improvement in CRP, endothelial dysfunction, increased nitric oxide bioavailability, antioxidant properties, and inhibition of inflammatory responses and stabilization of atherosclerotic plaques. In other word, the advantages of 3-Hydroxy-3methylglutary coenzyme A (HMG-CoA) reductase inhibitors (statins) have been shown in primary and secondary prevention of cardio- vascular diseases. In patients with polycystic ovary syndrome, serum testosterone and DHEA-S levels are significantly higher than the healthy women. Statins improved endocrine/clinical aspects of PCOS by decreasing these markers. (Sthyapalan, 2012; Sthyapalan, 2010; Raja, 2011; Hoeger, 2009; Kadaman and Duleba, 2008; Sohrabvand, 2009; Shahrezaei, 2011; Banaszewska, 2007; Sathyapalan, 2009; Duleba, 2006; Baldassarre,

2009). With regard to the fact that different studies with different findings have been conducted all over the world, but such a study has not been conducted about the patients of our area, the researchers have decided to assess Atorvastatin effects in improving biochemical profile and hemostatic status of patients with PCOS for the first time in north west of Iran.

## 2. Material and Methods

A randomized, double-blind, control study was undertaken using Atorvastatin 20 mg daily at a tertiary care center in Tabriz-Iran. The diagnosis of PCOS was based at least on two of three diagnostic criteria of the Rotterdam consensus, namely clinical and biochemical evidence of hyperandrogenemia (Ferriman- Gallwey score>8), oligomenorrhea or amenorrhea and polycystic ovaries by ultrasound. Subjects had no concurrent illness, and were not on any prescription or over-the counter medication that was likely to affect insulin sensitivity, lipids or ovarian function including hormonal contraceptives for the preceding six months, change in life style during the study period, pregnancy and lactation. Non-classical 21-hydroxylase deficiency, hyperprolactinemia, Cushing`s disease and androgen-secreting tumors were excluded by appropriate tests. Forty subjects who fulfilled the inclusion and exclusion criteria were randomly assigned to atorvastatin (A) and OCP (O) group, (20 patients in each group). The patients underwent medical treatment for 3 months with atorvastatin 20 mg daily (manufactured by Shafa Co.) or OCP [Cyproterone Acetate 2 mg + Ethinyl Estradiol 0.035mg( Cyproterone compound)] manufactured by Aburaihan Co. The study was conducted in 15 months from December 2011 to January 2013.

All patients were assigned into two groups by using Rand List software. The sample size was considered 20 subjects for each group. Weight, height, BMI, waist circumference, biochemical and hemostatic profile including total cholesterol, triglyceride, high-density lipoprotein cholesterol (HDL-C), Low density lipoprotein cholesterol (LDL-C), fasting plasma glucose, fibrinogen, total testosterone, dehydroepiandrosterone sulphate (DHEA-S), homocysteine, and serum insulin were measured before and after the treatment at the end of a three month period. Prolactin, LH, TSH, cortisol (after overnight 1 mg dexamethasone), and 17 Hydroxyprogesterone were measured at base line. Biochemical tests were measured using ADVIA 1200 chemistry system-Hitachi 912. Hormonal parameters were assayed using Chemiluminescence. ADIVA centaur CP was used to measure homocysteine. Serum 17 OH progesterone and hs-CRP were determined using Eliza Micro Reader 4 plus.

**Statistical analysis**

Results are presented as mean ± SEM. The statistical analysis was performed using SPSS for Windows NT, version 16.0. For comparing quantitative parameters repeater measurement of Anova (RMA) test and for qualitative parameters Chi-square test was used. Fisher`s exact test was used when needed .For all analyses, a two-tailed $p<0.05$ was considered to indicate statistical significance.

## 3. Results

Forty-three patients were screened before the study, and one patient in A group and two patients in O group were excluded due to personal reasons in the course of the study. Finally, 20 patients were studied in each group. The mean age of the patients was 24.1±6.1 (A group 24.1±6.1 vs. O group 24±5.9). The age difference between the two groups was not statistically significant. (p= 0.92).

Before treatment, ovarian ultrasonography was done in all patients. In group A nine cases (45%) and in group O three cases (15%) had normal imaging. The remaining subjects had characteristic ultrasonographic findings of polycystic ovaries. The difference was not statistically significant between two groups (p=0.08).

Anthropometry indices such as weight, height were not significantly different between the two groups (Table 1).

Of the baseline paraclinical indices, only LH was significantly different between the two groups.

Table 1. Comparison of baseline information between two groups of the patients

| Parameter | A group (N=20) | O group (N=20) | P |
|---|---|---|---|
| Weight (kg) | 74.3 ±17.5 (46-115) | 65.9 ±11.8 (43.5-89) | 0.08 |
| Height (cm) | 161.2 ± 35.1 (150-170) | 160.2 ±34,8 (149-177) | 0.61 |
| BMI (kg/m2) | 28.5±6.3 (18.9-44.9) | 25.6±4 (16.9-31.2) | 0.96 |
| Waist circumference (cm) | 93.4±13.9 (70-120) | 85.5±15.7 (34-103) | 0.10 |
| Systolic BP (mmHg) | 109.5±12.3 (90-130) | 112±13.1 (90-135) | 0.53 |
| Diastolic BP (mmHg) | 72.5±9.5 (60-90) | 74.2±9.2 (60-90) | 0.55 |

Data are presented as mean±SEM.

After treatment, only FBS, TG and total Chol were significantly different between the two groups.

Atorvastatin induced statistically significant decrease of total cholesterol, LDL cholesterol and FBS by 21.7%, 35.9% and 11.4% respectively. In Contrast OCP induced a modest increase in total cholesterol. Triglycerides increased significantly by 93% after OCP. Also, OCP had a significant effect on the reduction of FBS, LH and insulin by 17.5%, 11.8% and 35.7% respectively (Table 2).

The 56% reduction in DHEAS was statistically significant ($p<0.001$) in patients taking Atorvastatin, whereas there was a modest increase in OCP group. In Atorvastatin group, there was a 13.3% reduction ($p=0.29$) in testosterone, in contrast to 83% increase in OCP group (Figure 1).

## 4. Discussions and conclusion

Hyperandrogenemia is a risk factor for increased risk of cardiovascular diseases and hypertension in women with polycystic ovary syndrome (Raval, 2011). Pleiotropic effects of Statins include an improvement in CRP, endothelial dysfunction, increased nitric oxide bioavailability, antioxidant properties, inhibition of inflammatory responses, and stabilization of atherosclerotic plaques (Sathyapalan, 2009).

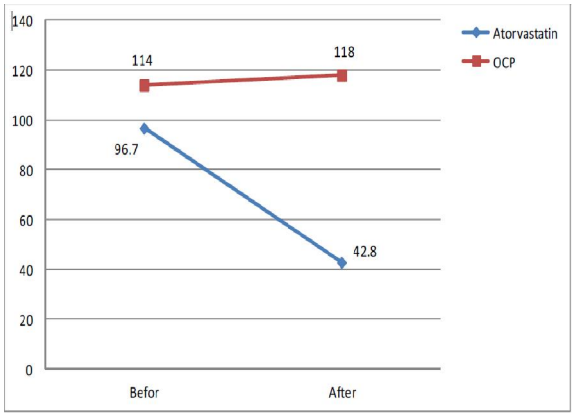


Figure 1: Changes in DHEA-S between two groups

Sohrabvand et al (2008) compared serum homocysteine levels in Iranian women with and without PCOS. The findings suggest that there is an inverse correlation between homocysteine and serum folic acid levels in PCOS. Therefore, it seems that proper administration of folic acid can reduce homocysteine levels in patients with PCOS and help prevent the attributed cardiovascular risk associated with disease (Kadaman and Duleba, 2008).

The findings of a study by Raja, et al (2011) in patients with PCOS, showed that in contrast to other studies, Atorvastatin appeared to worsen hyperinsulinemia demonstrating a small increased risk of diabetes in Atorvastatin-treated PCOS women. Also, there was no difference in testosterone levels between two groups (Raja, 2011). In Atorvastatin group, the reduction of fibrinogen (about 8%) is statistically significant. In contrast to our study, fibrinogen serum changes were not studied by Raja et al (2011) as one of hemostatic markers. In the study by Raja, et al, hsCRP changes were not statistically significant between two groups like our study (Raja, 2011). In contrast to the study by Raja, et al, in current study there was an increase in hsCRP level after intervention in both groups. This might be due to small sample size of our study.

In the study by Raja, et al, there was an increase in DHEA-S level only in placebo group; in contrast we can show a reduction (about 30 µg/dl) in the group taking Atorvastatin (Raja, 2011). In our study, accordant to the study conducted by Raja et al (2011), there was a reduction of 56% in DHEA-S level (54 µg/dl) in the group taking atorvastatin, whereas there was a modest increase in the group taking OCP (Raja, 2011).

Most of the clinical trials have shown the positive effect of statins on reduction of atherosclerotic and cardiovascular diseases. Therefore, statins are used in dyslipidemia treatment as well as prevention of atherosclerosis and cardiovascular events (Shahrezaei, 2011). In our study, there was a significant reduction in LDL-C and total cholesterol in the group taking Atorvastatin after three month period.

Banaszewska et al (2007), in a study on statins in PCOS showed that OCP plus simvastatin in comparison with OCP alone can significantly reduce total testosterone, LH and inflammatory markers (Banaszewska, 2007). The reduction of total cholesterol and LDL was statistically significant like our study. In contrast to our study, the reduction in hsCRP was statistically significant in the study by Banaszewska et al (2007) (Banaszewska, 2007). Duleba et al (2006) studied the effect of simvastatin plus metformin on reduction of serum testosterone level and inflammatory markers in PCOS. There was a reduction in total cholesterol in the group taking simvastatin and an increase in OCP group (Duleba, 2006). In our study, also, a 21.8% reduction in total cholesterol was significant in the group taking Atorvastatin, whereas there was a modest increase in total cholesterol in OCP group. In the patients with PCOS, DHEA-S and testosterone serum levels were significantly higher than that in healthy women (6).

In our study, there was 56% reduction of DHEA-S in Atorvastatin group.

Table 2. Comparison of the Comparison of the paraclinical indices before and after intervention between two groups

| Parameter | stage | A group (N=20) | O group (N=20) | P |
|---|---|---|---|---|
| FBS ( mg/dL) | Before | 98.2 ± 11.6 | 99.1 ± 9.5 | 0.79 |
| | After | 87 ± 7.9 | 81.7 ± 7.8 | 0.03 |
| | P | <0.001 | <0.001 | - |
| Insulin (μ IU /mL) | Before | 22.2 ± 14.6 | 21.8 ± 12.7 | 0.92 |
| | After | 18.5 ± 6.6 | 14 ± 6.8 | 0.11 |
| | P | 0.37 | 0.01 | - |
| TG (mg/dL) | Before | 73.4 ± 22.3 | 66.3 ± 24.6 | 0.34 |
| | After | 92.7 ± 41.2 | 128 ± 56.6 | 0.03 |
| | P | 0.055 | <0.001 | - |
| Total Cholesterol ( mg/dL) | Before | 192.7 ± 48.5 | 184.1 ± 36.2 | 0.52 |
| | After | 150.8 ± 50 | 188.8 ± 35.9 | 0.009 |
| | P | <0.001 | 0.61 | - |
| HDL (mg/dL) | Before | 54.6 ± 11.7 | 58.6 ± 12.4 | 0.30 |
| | After | 52.6 ± 12.1 | 60.5 ± 11.2 | 0.04 |
| | P | 0.42 | 0.34 | - |
| LDL ( mg/dL) | Before | 125.4 ± 41.4 | 116.8 ± 27 | 0.44 |
| | After | 80.3 ± 45.8 | 103 ± 34.7 | 0.08 |
| | P | <0.001 | 0.11 | - |
| AST(IU/L) | Before | 19.3 ± 8 | 17.7 ± 3.8 | 0.43 |
| | After | 19.9 ± 6.6 | 16.2 ± 3 | 0.03 |
| | P | 0.75 | 0.06 | - |
| ALT(IU/L) | Before | 27.5 ± 2.2 | 20.2 ± 9.4 | 0.19 |
| | After | 28.6 ± 2 | 17.9 ± 5 | 0.03 |
| | P | 0.76 | 0.26 | - |
| Alk.P (IU/L) | Before | 197.3 ± 66.9 | 214.8 ± 15.3 | 0.64 |
| | After | 174.4 ± 31.1 | 158.4 ± 8 | 0.41 |
| | P | 0.14 | 0.058 | - |
| LH(mIU/L) | Before | 6.9 ± 4.1 | 10.5 ± 5.7 | 0.027 |
| | After | 9.3 ± 2.4 | 4.6 ± 3.6 | 0.11 |
| | P | 0.40 | 0.002 | - |
| Testosterone (ng/dL) | Before | 0.45 ± 0.12 | 0.49 ± 0.33 | 0.057 |
| | After | 0.39 ± 0.17 | 0.99 ± 1.8 | 0.15 |
| | P | 0.29 | 0.22 | - |
| DHEA-S(μg/dL) | Before | 96.7 ± 43.9 | 114 ± 73.5 | 0.37 |
| | After | 42.8 ± 14.2 | 118.2 ± 58.5 | 0.03 |
| | P | <0.001 | 0.80 | - |
| HsCRP ( mg/L) | Before | 2.8 ± 2.9 | 2.7 ± 1.7 | 0.90 |
| | After | 3.3 ± 2.8 | 4.3 ± 3.2 | 0.27 |
| | P | 0.54 | 0.07 | - |
| Fibrinogen ( mg/dL) | Before | 319.4 ± 47.4 | 327.4 ± 38.2 | 0.56 |
| | After | 293.8 ± 43 | 310.5 ± 50.1 | 0.26 |
| | P | 0.01 | 0.19 | - |
| Homocysteine (μ MOI/L) | Before | 8.4 ± 2.6 | 7.8 ± 6.2 | 0.73 |
| | After | 5.3 ± 2.1 | 7.9 ± 4.1 | 0.32 |
| | P | 0.33 | 0.98 | - |

The findings of the study by Baldassarre et al (2009) showed that in patients with stable coronary artery disease treated with moderate doses of Atorvastatin, carotid intima-media thickness (CIMT) regression correlated with changes of inflammation, thrombosis and endothelial activation profiles (Baldassarre, 2009). In the study mentioned, the reduction of hsCRP was not significant after a one

year period, whereas, similar to our study, the reduction of fibrinogen in statin group was significant (Baldassarre, 2009). In contrast to our study, IL-6 ،IL- 8 and IL-18 were studied too. Their reduction was significant after a one year treatment with statin.

Because of the limitations of our study, investigating CIMT and its relationship with cytokines and Atorvastatin treatment were not possible. In contrast to our study, homocysteine level as a hemostatic parameter has not been studied in previous studies. In our study, there was a reduction of 37% in homocysteine in the patients taking Atorvastatin, whereas there was a modest increase in OCP group.

In general, homocysteine changes were not significant between two groups after 12 wks. We also, did not study ultrasonographic changes of ovaries after treatment.

In the study by Raja eta al (2011) polycystic ovaries size were measured by ultrasonography before and after treatment. The changes were not significant in both groups. There was a modest increase in Atorvastatin group (Raja, 2011).

This study suggests that twelve weeks of Atorvastatin significantly reduced both DHEA-S and fibrinogen. There was a reduction in some parameters of biochemical profile in both groups. Therefore, Atorvastatin was not superior to OCP in management of PCOS. Other studies with larger sample size and longer follow up seem to be necessary to prove or reject of the subject.

**Corresponding Author:**
Dr. Jafar Shadi:
Department of Endocrinology, Imam Reza Hospital, Faculty of Medicine, Tabriz University of Medical Sciences, Iran.
E-mail: Jafar_shadi30@yahoo.com

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