

GLYCEMIC STATUS IN PATIENTS WITH POLYCYSTIC OVARY SYNDROME AND DYSLIPIDEMIA BEFORE AND AFTER THREE MONTHS TREATMENT WITH ATORVASTATIN

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Abstract

Background and Aims. Polycystic ovary syndrome (PCOS) is associated with disturbances in carbohydrate and lipid metabolism. Statins appear to have beneficial effects in PCOS, although some meta-analyses showed an increased risk of developing diabetes mellitus. The aim of this study was to evaluate the effect of treatment with 20 mg of atorvastatin daily for three months on glucose tolerance in a group of 8 normal weight patients with PCOS and dyslipidemia. **Material and Methods.** We evaluated 8 patients aged between 29 and 40 years, with normal weight, diagnosed with PCOS and dyslipidemia. The carbohydrate metabolism was assessed by oral glucose tolerance test (OGTT) before and after 3 months of therapy with 20 mg of atorvastatin daily. **Results.** Treatment with atorvastatin resulted in a statistically significant reduction in total cholesterol ($p = 0.001$), LDL cholesterol ($p = 0.001$), triglycerides ($p = 0.01$) and statistically significant increase in HDL cholesterol ($p = 0.003$). Fasting plasma glucose ($p = 0.59$) and the 2-hour OGTT glycemia ($p = 0.54$) were not significantly changed. Total testosterone decreased significantly ($p = 0.04$). **Conclusions.** At baseline, all patients included in our study showed unaffected carbohydrate metabolism. Even after 3 months of therapy with atorvastatin 20 mg daily no changes in glucose homeostasis were noted.

key words: polycystic ovary syndrome, dyslipidemia, glucose tolerance, atorvastatin.

Background and Aims

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders in women of reproductive age, with a prevalence of 6.5 to 8% in Europe [1-3]. Besides endocrine disorders, many patients with PCOS exhibit metabolic disorders. Insulin resistance

is the most common of these, affecting approximately 50-60% of PCOS women compared with 10-25% of women in the general population. Thus, patients with PCOS have an increased cardiovascular risk, because of insulin resistance and the raised level of serum lipoproteins [4-8].

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Statins, besides lowering lipids, (particularly LDL-cholesterol), may reduce insulin resistance, hyper-androgenism, the oxidative stress and inflammation in PCOS [9,10].

Lately, some meta-analyses showed that statin therapy is associated with a slightly increased risk of diabetes. The risk is however low, both in absolute terms and in comparison with the reduction of cardiovascular events and, consequently, statin therapy must not be abandoned [11].

The aim of this study was to evaluate the effect of treatment with 20 mg of atorvastatin daily for three months on glucose tolerance in a group of 8 normal weight patients with PCOS and dyslipidemia.

Material and Methods

We evaluated 8 patients aged between 29 and 40 years (33.3 ± 3.8 years) with normal weight and confirmed diagnosis of PCOS and dyslipidemia (at least one of total cholesterol > 200 mg%, LDL cholesterol > 130 mg%, HDL cholesterol < 40 mg%, triglyceride > 150 mg%). PCOS diagnosis was confirmed on the basis of Rotterdam criteria [12] – Presence of at least two of:

- oligo or anovulation manifested by oligo or amenorrhea;
- biochemical or/and clinical evidence of androgen excess;
- documented polycystic ovaries by ultrasound (12 or more cysts on an ovary with a diameter of 2-9 mm or ovarian volume > 10 cm³).

We identified menstrual disorders by history, clinical signs of virilization (hirsutism, seborrhea, acne, alopecia, genital virilization) by clinical examination, we dosed

total testosterone. We asked for the ultrasound appearance of the ovaries. We determined lipid profile and glucose tolerance by oral glucose tolerance test (OGTT) before and after 3 months of therapy with 20 mg atorvastatin daily.

Glucose, total and HDL cholesterol, triglycerides were determined in laboratories RENAR of Drobeta Turnu Severin by spectrophotometric method (enzymatic colorimetric) from venous blood glucose collected in fasting state. The value of LDL cholesterol was determined by an indirect method from the value of total cholesterol, triglycerides and HDL cholesterol according to the Friedewald formula: LDL-cholesterol = total cholesterol - HDL cholesterol - triglyceride / 5. This method of determination is used only for triglyceride levels lower than 250 mg%. Total testosterone (normal range in adult woman = 0.13-1.08 ng/ml) was determined by electro-chemi-luminescence immunoassay (ECLIA).

Statistical analysis

Data are presented as mean \pm standard deviation. For statistical analysis we used GraphPad software by applying paired Student test. Significance was defined at the 0.05 level of confidence.

Results

Values of biological parameters, initial and after three months of daily treatment with 20 mg atorvastatin, are shown in [Table 1](#).

Therapy with statin for three months generated significant changes in testosterone levels and in lipid profile. As expected, lipid profile improved. Total cholesterol significantly decreased from 255.3 ± 27.3

mg% to 209.5 ± 27.6 mg% ($p = 0.001$), LDL cholesterol significantly decreased from 179.2 ± 28.8 mg% to 135.5 ± 30.9 mg% ($p = 0.001$), triglycerides significantly decreased from 188 ± 32.8 mg% to 163.1 ± 18.8 mg%, ($p = 0.01$), while HDL cholesterol significantly increased from 38.5 ± 3.4 mg% to 41.4 ± 2.4 mg%, ($p = 0.003$).

Table 1. Values of biological parameters, initial and after three months of statin therapy.

	Initial	After statin therapy	p
Total testosterone (ng/ml)	1.24 ± 0.35	1.1 ± 0.23	0.04
Total cholesterol (mg%)	255.3 ± 27.3	209.5 ± 27.6	0.001
HDL cholesterol (mg%)	38.5 ± 3.4	41.4 ± 2.4	0.003
LDL cholesterol (mg%)	179.2 ± 28.8	135.5 ± 30.9	0.001
Triglyceride (mg%)	188 ± 32.8	163.1 ± 18.8	0.01
Fasting plasma glucose (mg%)	90 ± 9.2	91 ± 8.9	0.59
2h glucose (mg%) during OGTT	120.3 ± 12.3	121.8 ± 8.5	0.54

We observed a marginally significant ($p=0.04$) decrease in total testosterone levels from 1.24 ± 0.35 ng/ml to 1.1 ± 0.23 ng/ml.

We observed a slight increase of the fasting blood glucose from 90 ± 9.2 mg to 91 ± 8.9 mg%, ($p = 0.59$) and of the 2-hour blood glucose during OGTT from 120.3 ± 12.3 mg% to 121.8 ± 8.5 mg%, ($p = 0.54$), but not statistically significant.

Discussion

Lipid disorders in PCOS patients increase cardiovascular risk, therefore lipid-lowering treatment becomes necessary in many of these patients. Statins offer a novel therapeutic approach to PCOS in that they address the dyslipidemia associated with the syndrome, as well as hyperandrogenism or hyperandrogenemia. These actions may be due to an inhibition of the effects of systemic inflammation and insulin resistance/hyperinsulinemia. Evidence to date, both in vitro and in vivo, suggests that statins have potential benefits in the treatment of PCOS. Statins can be used in women with PCOS, who have dyslipidemia and are not at risk of conceiving [9,10].

But the statins' effect on patients' glucose tolerance has been a concern. Trials of statin therapy have had conflicting findings on the risk of diabetes mellitus development. A meta-analysis of 13 statin trials revealed that from 91140 participants, 4278 (2226 assigned statins and 2052 assigned control treatment) developed diabetes during a mean of 4 years. Statin therapy was associated with a 9% increased risk for incident diabetes (odds ratio [OR] 1.09; 95% CI 1.02—1.17), with little heterogeneity ($I^2=11\%$) between trials. Treatment of 255 (95% CI 150—852) patients with statins for 4 years resulted in one extra case of diabetes [11].

Dr. Puurunen MD, Oulu University Hospital, Finland, noted that statins are associated with a worsening of glucose tolerance and a slightly increased risk of type 2 diabetes in PCOS patients. 15 PCOS patients were randomized to atorvastatin 20 mg/day and 13 to placebo for 6 months. Fasting insulin levels and area under the curve increased, and whole-body insulin sensitivity decreased significantly in the atorvastatin group compared with control patients during OGTT [13]. In our study, treatment with 20

mg atorvastatin daily for three months resulted in significant reductions in total testosterone without changes in glycemic tolerance.

We consider that the statistical power is limited due to the small size of the lot, which is why we believe that further studies are needed.

Conclusion

At baseline, all patients included in our study showed unaffected carbohydrate

metabolism. After 3 months of therapy with 20 mg atorvastatin daily, no changes in glucose tolerance were noted. This therapy induced a significant decrease in total testosterone. Lipid profile was significantly improved, highlighting the main effect of atorvastatin. Taking into account the results of studies and meta-analyses, we consider that further studies are needed before statins can be recommended for routine clinical use in PCOS treatment.

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