Metformin and changes in serum lipid profile in lean patients with polycystic ovary syndrome

Wpływ metforminy na profil lipidowy pacjentek z zespołem policystycznych jajników i prawidłową należną masą ciała

Introduction: The aim of our study was to assess the values of total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) and triglycerides before and after treatment with metformin in lean patients with polycystic ovary syndrome (PCOS).

Material and methods: 32 patients received metformin 1500 mg per day in three divided doses. Lipids measurements were performed twice: before and after 6 months of treatment with metformin.

Results: In lean patients with PCOS after treatment with metformin we observed: statistically significant lower LDL-C levels (4.16±0.79 mmol/l vs 3.4±0.86 mmol/l; p<0,05) and triglycerides levels (1.8±0.53 mmol/l vs 1.12±0.64 mmol/l; p<0,05). We observed an increase in HDL values and a decrease in total cholesterol values, but these changes were not statistically significant (1.5±0.71 mmol/l vs 1.71±0.69 mmol/l, p=0,09; 5.87±0.92 mmol/l vs 5.69±0.97 mmol/l, p=0,11).

Conclusion: Our study showed that treatment of 1500 mg metformin for about six months among PCOS women results in an improvement in serum lipid profiles. We observed a significant decrease in LDL-C and triglycerides values after metformin therapy.

Wstęp: Celem pracy była ocena stężenia cholesterolu całkowitego, cholesterolu HDL, LDL oraz triglicerydów u pacjentek z PCOS (zespół policystycznych jajników) i prawidłową należną masą ciała, przed i po leczeniu metforminą.

Materiały i metodyka: 32 pacjentki otrzymały metforminę w dawce 1500 mg dziennie, w 3 dawkach podzielonych. Pomiar profilu lipidowego wykonano u każdej pacjentki z PCOS dwukrotnie, przed i po 6 miesiącach leczenia metforminą.

Wyniki: U pacjentek z PCOS i prawidłową należną masą ciała zaobserwowano istotne statystycznie obniżenie poziomu cholesterolu LDL (4,16±0,79 mmol/l vs 3,4±0,86 mmol/l; p<0,05) i triglicerydów (1,8±0,53 mmol/l vs 1,12±0,64 mmol/l; p<0,05) po 6-cio miesięcznej terapii metforminą. Odnoszą się również wzrost stężenia HDL i zmniejszenie stężenia cholesterolu całkowitego, jednak zmiany te nie były istotne statystycznie (1,5±0,71 mmol/l vs 1,71±0,69 mmol/l; p=0,09; 5,87±0,92 mmol/l vs 5,69±0,97 mmol/l; p=0,11).

Wnioski: Wykazano, że leczenie metforminą w dawce 1500 mg przez okres sześciu miesięcy skutkuje poprawą profilu lipidowego u pacjentek z PCOS i prawidłową należną masą ciała. Zabookserwowano istotny spadek wartości cholesterolu LDL i triglicerydów po leczeniu metforminą.
2 diabetes treatment since 1957 in Europe [14]. Nowadays metformin is also used in PCOS, pre-diabetes, and in patients with type 1 diabetes and insulin resistance [15,16]. Another beneficial effects of metformin in clinical practice are considering, e.g. in gestational diabetes, in cancer treatments, in lipids lowering therapy or in prevention of cardiovascular diseases [15]. Some recent studies showed that metformin administration results in decrease in low-density lipoprotein cholesterol (LDL-C) level, total cholesterol and triglycerides [17-20], although the review showed that metformin has no effect on serum cholesterol or triglycerides [21]. A meta-analysis of randomized controlled trial reported that metformin administration had no effect on cholesterol, LDL-C, HDL-C levels but had a significant impact on serum triglycerides level compared to placebo [22].

There is a growing concern on impact of metformin on lipids. We aimed to evaluate the effectiveness of metformin therapy on serum lipids in lean PCOS women.

Materials and Methods
A retrospective study was performed to assess the metformin influence on lipid profiles in lean PCOS patients. Thirty two women with polycystic ovarian syndrome were enrolled in the study. The diagnosis of PCOS among all examined patients was based on the Androgen Excess Society criteria [23]. We included patients with phenotype of free androgen index (FAI) only greater than or equal to 5. Hyperprolactinemia, androgen secreting tumors, Cushing’s disease, congenital adrenal hyperplasia were excluded based on clinical and laboratory data.

The mean age of study population was 28 years (25-31 years). All patients have BMI (body mass index) within the normal range (18.5-24.9 kg/m²). All subjects had normal renal and hepatic function and had not received any medication for at least six months before the study. Patients who showed evidence of thyroid dysfunction, diabetes mellitus, cardiovascular diseases, hypertension or other internal pathologies were excluded from the study.

Each patient underwent a full clinical evaluation. Fasting blood samples were collected at 8 am from a forearm vein between 1-5 day of menstrual cycle. The following parameters were measured: luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol, testosterone, triiodothyronin (FT3), thyroid stimulating hormone (TSH), thyroxin (FT4), sex hormone binding globulin (SHBG), all according to the routine methods. Free testosterone was calculated by using FAI ratio- the total testosterone level (nmol/l) was divided by the SHBG level (nmol/l) and then multiplying by a 100. The clinical characteristic of study population was presented in Table I.

All patients were treated with metformin 1500 mg daily, in three divided doses, for 6 months.

Collected data included lipids values measured before and after 6 months of metformin administration. Both total cholesterol and HDL-cholesterol concentrations were measured directly. The concentrations of LDL cholesterol were calculated according to the method of Friedewald et al. [24]: LDL cholesterol=total cholesterol - HDL cholesterol -(triacylglycerol/5).

The study was performed in the Department of Gynecological Endocrinology, Jagiellonian University Hospital, Cracow, Poland.

Statistical analysis
Clinical and laboratory parameters, expressed on continuous scale, were presented as means with standard deviation. Data did not present any significant outliers. Kolmogorov-Smirnov test revealed a normal distribution of data. Differences in lipid profiles pre- and post-metformin intervention were analyzed using paired t-tests. Statistical analysis was made using Statistica 12 (Statsoft, Tulsa, OK, USA). Pearson were used to assestion between.

Results
Serum lipids values at the beginning of the study and after 6 months metformin therapy were presented in Table II in lean patients with PCOS we observed statistically significant lower LDL-C levels (4.16±0.79 mmol/l vs 3.40±0.86 mmol/l, p<0.05) and lower triglycerides levels (1.8±0.53 mmol/l vs 1.12±0.64 mmol/l, p<0.05) after treatment with metformin. There was also an increase in HDL values and a decrease in total cholesterol values, but these changes were not statistically significant (1.5±0.71 mmol/l vs 1.71±0.69 mmol/l, p=0.09; 5.87±0.92 mmol/l vs 5.69±0.97 mmol/l, p=0.11).

Discussion
Our study showed that treatment of 1500 mg metformin for six months among PCOS women result in improvement in serum lipids. We observed a significant decrease in LDL-C and triglycerides values after metformin treatment. Changes in HDL values and total cholesterol values were not statistically significant.

There are some studies on the influence of metformin on serum lipid profile but the results remain inconclusive. Mhao et al. in their randomized control trial study (RTCs) also showed that metformin treatment in dose of 500 mg twice daily decrease LDL-C and decrease triglycerides levels [25]. Result of analysis of 2372 studies and 12 RTCs presented that metformin treatment and lifestyle intervention versus lifestyle intervention alone or with placebo did not differ in lipids levels in PCOS women [26]. Some studies showed a beneficial influence of metformin therapy on lipid profiles [27-30], some did not [31-33]. The effect of metformin on lipid parameters differed between studies. Chou et al. reported amelioration of influence of metformin only on total cholesterol [29], Lord et al. presented beneficial influence on total cholesterol and LDL-C [27], Trolle et al. showed increased LDL-C [33], while Onalan et al. reported decreased triglycerides levels after metformin therapy [34]. Some studies showed improvement in metabolic profile only in obese PCOS women [35,36]. Sahin et al. presented that metformin therapy in lean patients with PCOS has no beneficial effect on lipid profiles and cardiovascular risk factor [37]. The baseline characteristics of patients might play a role in effectiveness of metformin therapy. Inconsistence results regarding the effect of metformin on lipid profiles in PCOS women can result from differences between study populations (BMI, insulin

Table I
Clinical characteristics of study population.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>PCOS group</th>
<th>n=32</th>
<th>mean±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (kg/m²)</td>
<td>22.2±1.11</td>
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<tr>
<td>FT3 (pmol/l)</td>
<td>4.8±0.59</td>
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<tr>
<td>TSH (lU/ml)</td>
<td>1.8±0.5</td>
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<tr>
<td>FT4 (pmol/l)</td>
<td>15.2±1.49</td>
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<td></td>
</tr>
<tr>
<td>Prolactin (lU/ml)</td>
<td>308.5±216.0</td>
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<tr>
<td>Testosteron (nmol/l)</td>
<td>2.3±0.33</td>
<td></td>
<td></td>
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<tr>
<td>SHBG (nmol/l)</td>
<td>36.4±7.98</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FFA</td>
<td>6.6±1.25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LH (mU/ml)</td>
<td>10.9±3.97</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FSH (mU/ml)</td>
<td>7.6±1.52</td>
<td></td>
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<tr>
<td>Estradiol (pmol/l)</td>
<td>283±134.56</td>
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</tbody>
</table>

BMI-body mass index; FT3-triiodothyronine; TSH-thyroid stimulating hormone; FT4-thyroxin; SHBG-sex hormone binding globulin; FFA-free androgen index; data is presented as mean±standard deviation (SD)

Table II
Lipid profile of PCOS (polycystic ovary syndrome) women at the beginning of the study and after 6 months of metformin therapy. Data is presented as mean±standard deviation (SD).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Beginning of the study (n=32)</th>
<th>After 6 months metformin therapy (n=32)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC (mmol/l)</td>
<td>5.87±0.92</td>
<td>5.69±0.97</td>
<td>p=0.11</td>
</tr>
<tr>
<td>HDL-C (mmol/l)</td>
<td>1.5±0.71</td>
<td>1.71±0.69</td>
<td>p=0.09</td>
</tr>
<tr>
<td>LDL-C (mmol/l)</td>
<td>4.16±0.79</td>
<td>3.4±0.86</td>
<td>p=0.06</td>
</tr>
<tr>
<td>TG (mmol/l)</td>
<td>1.8±0.53</td>
<td>1.12±0.64</td>
<td>p=0.05</td>
</tr>
</tbody>
</table>

TG-total cholesterol; HDL-C-high-density lipoprotein cholesterol; LDL-C-low-density lipoprotein cholesterol; TG-triglycerides; data is presented as mean±standard deviation (SD)
resistance, baseline lipid levels), doses and length of metformin treatment. The dosage and duration of therapy varied between studies, e.g. women received 500 mg of metformin over 90 days [30], 500 mg of metformin three times a day for 3 months [27], 500 mg of metformin for 6 months [38], 500 mg of metformin twice a day and the lipids were assessed after 3 and 6 months of the therapy [32]. Studies with long follow-ups are needed to assess the long-term effects of metformin on lipid profile. It is of interest whether longer therapy or higher dose of metformin result in greater improvement of lipid profiles in comparison to lower dose of metformin or short-term therapy. It is unknown whether continuation of metformin therapy is needed to maintain beneficial effects of metformin on lipid profile.

The main limitation of the present study is the small number of patients investigated. In our opinion larger prospective trials are needed to test the hypothesis that metformin might have an beneficial impact on serum lipid profile in PCOS women.

**Conclusion**

Our study showed that therapy at daily doses of 1500 mg metformin for six months among lean PCOS women resulted in improvement in serum lipid profiles. We observed a significant decrease in LDL-C and triglycerides values after metformin treatment. This is of high importance to confirm whether metformin ameliorate or not the lipids in PCOS women because of possible clinical implications. Well-designed, randomized control trials should be conducted among numerous population of PCOS women.

**References**