A Combined Treatment with Myo-Inositol and Monacolin K Improve the Androgen and Lipid Profiles of Insulin-Resistant PCOS Patients

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Abstract

Objective: We sought to assess and compare the effects of myo-inositol combined with monacolin k (Group A) versus inositol only (Group B) and metformin (Group C), on the clinical, hormonal, metabolic and lipid profiles of insulin-resistant PCOS patients.

Study design: 60 insulin resistant PCOS patients were randomly assigned into three groups. All groups were treated for 6 months with either myo-inositol and monacolin k, inositol only or metformin. Patients clinical, hormonal and metabolic profiles were compared between all groups, and within each group, prior and following the aforementioned treatment.

Results: All treatment arms improved patients’ clinical, hormonal and metabolic profiles, with a tendency toward better results in patients using the combination of myo-inositol and monacolin k.

Conclusion: The combined treatment with the natural products: monacolin K and myo-inositol represents a valid and well tolerated alternative to the common medical therapy, improving the PCOS related symptoms, with minimal side effects.

Keywords: Cholesterol; Inositol; Insulin resistance; Monacolin k; PCOS

Introduction

Polycystic Ovary Syndrome (PCOS) is a multifactorial endocrinopathy, affecting 5-10% of reproductive age women. The clinical presentation varies from eumenorrhea and a sonographic picture of polycystic ovaries but with subtle phenotypic abnormalities or signs of hyperandrogenism, to advanced Stein and Leventhal syndrome [1,2] and its associated long- term sequelae. Moreover, most women with PCOS also exhibit metabolic syndrome features, including insulin resistance, obesity and dyslipidaemia [3-5]. For a long time, treatments for PCOS were focused on androgen suppression and induction of ovulation. More recently it has been clearly demonstrated that the effective reduction of insulin resistance obtained with metformin restores regular menstrual cycles, ovulation and therefore fertility [6,7]. This substance has an insulin-sensitizing activity and it is currently used to reduce blood sugar levels in patients with diabetes mellitus since it improves the peripheral utilization of glucose, acting on the liver by increasing insulin sensitivity and inhibiting glucose production, whereas it improves glucose storage and utilization in skeletal muscle cells [8,9]. Interestingly it is been clearly demonstrated that metformin improves insulin action at least in part, by increasing insulin mediated release of D-Chiro-Inositol Phosphoglycan (DCI-IPG) in PCOS women [10].

The Inositol Phosphoglycans (IPGs) are putative mediators in non-classical insulin signaling cascade for glucose uptake and use, they play an important role in cell development and morphogenesis. Insulin-resistant PCOS women display decreased insulin-stimulated release of D-Chiro-Inositol (DCI)-Containing IPGs (DCI-IPGs) during an oral glucose tolerance test, as compared to control women [11], which was related to impaired coupling between insulin action and the release of the DCI-IPG [12,13].

Oral nutritional supplementation with inositol, part of the vitamin B complex (B8) and an intracellular second messenger, was demonstrated to enhance insulin sensitivity and improves the clinical and hormonal characteristics of PCOS patients [14-18]. Moreover inositol supplementation was shown to restore spontaneous ovulation with the consequent increase in conception, either alone [19-21] or when combined with gonadotropins [22].

Systemic inflammation associated with endothelial vascular dysfunction and metabolic dysfunction are commonly present in women with PCOS, with the consequent exaggerated risk for Cardiovascular Disease (CVD), compared with those without PCOS [23-25]. Moreover, Triglyceride (TG), Low-Density Lipoprotein (LDL) and non-high-density lipoprotein (HDL) cholesterol levels are also higher in PCOS as compared with non-PCOS women. Red yeast rice, a Chinese dietary supplement, has gained popularity due to its properties as a natural statin. It contains varying amounts of natural monacolin K (mevinolin) - a metabolite of Monascus rubber, which specifically inhibit 3-hydroxy-3-methylglutaryl (HMG)-CoA reductase, the rate-limiting enzyme in cholesterol synthetic pathway [18].

Monacolin K was suggested to have a similar effect on lipid metabolism, as shown for the mechanism of action of pharmacological statins [26], and it was demonstrated to effectively reduce the levels of cholesterol in patients with hypercholesterolemia [27]. Moreover, its ability to inhibit steroid synthesis was claimed to be responsible for the observed decrease in hyperandrogenism, which may further restore ovulation in those PCOS patients, as was already demonstrated following the use of simvastatin alone or in combination with metformin [28]. Furthermore, the antioxidative properties of statins and monacolin K, may further control cellular proliferation and improve ovulatory function [29].
Prompted by these findings, we sought to assess and compare the effects of myo-inositol combined with monacolin k versus insulin alone and versus metformin treatment, on the clinical, hormonal, metabolic and lipid profiles of insulin-resistant PCOS patients.

**Patients and Methods**

The study population consisted of 60 PCOS patients, aged between 24 and 32 years, with insulin resistance (as evaluated by homeostasis model assessment of insulin resistance-HOMA index). Informed consent was obtained from all patients before participation in the study, and the study was approved by the Clinical Research Committee. All patients met the PCOS criterion of the recent ESHRE/ASRM consensus [1], with the exclusion of other endocrinopathies. HOMA index was calculated as the product of fasting plasma insulin (mU/L) and glucose [1], with the exclusion of other endocrinopathies. HOMA index was calculated as the product of fasting plasma insulin (mU/L) and glucose (mmol/L) concentrations divided by 22.5 [23,30].

Upon enrollment, all patients underwent a basic workup, including the completion of a referral status form that covered demographic characteristics, basic medical and gynecological history and comprehensive physical examination, including Body Mass Index (BMI) and Ferriman-Gallwey score [28] evaluations. We considered hirsute women with Ferriman-Gallwey score >8 [31,32]. Moreover, blood was drawn from all patients for hormonal [FSH, LH, Total Testosterone (TT), free Testosterone (fT), SHBG and Androstenedione (A)], metabolic (glucose, insulin) and lipid (total cholesterol, LDL, HDL, triglycerides) profiles.

Eligible women were randomly assigned into three groups. Group A (n=20) achieved myo-inositol 1.5 g and monacolin k 3 g (AZELEP-ProgineFarmaceutici), twice a day, for 6 months; and Group B (n=20) was treated with a galenic preparation containing inositol 1.5 g twice a day for 6 months and Group C (n=20) was treated with metformin 850 mg twice a day, for 6 months.

After 6 months of therapy, all patients had repeated the aforementioned evaluations.

**Statistical analysis**

Statistical analysis was performed by SPSS statistical software version 17 (SPSS I Chicago, IL, USA), with Mann-Whitney test, as appropriate. Results are presented as medians ± confidence interval (IC) 95%; p< 0.05 was considered significant.

**Results**

The baseline clinical, hormonal, metabolic and lipid profiles were comparable between the three study groups (Table 1). Following 6 months of treatment, the duration of the menstrual cycles was significantly shortened in all study groups (Table 1). Moreover, while all the BMI (Table 1 and Figure 1) and the Ferriman-Gallwey (Table 1) were significantly improved after 6 months of treatments in the three study groups, the reductions were pronounced in group A (myo-inositol+monacolin k) compared to group B (inositol only).

While, we observed no differences in FSH levels following the 6-months, LH levels were significantly reduced in all three patient groups. As shown in Table 1, the menstrual cycles were significantly shortened following 6 months of treatment. Furthermore, BMI was significantly reduced in all study groups. The metabolic and lipid profiles were also improved in all groups, with the most pronounced effects observed in group A (myo-inositol+monacolin k). The metabolic and lipid profiles were also improved in all groups, with the most pronounced effects observed in group A (myo-inositol+monacolin k).

**Figure 1**: Evaluation of basal BMI and after 6 months of treatment in women treated with monacolin k + myo-inositol (group A), inositol only (group B), or metformin (Group C). Values are presented as median and IC 95%. *p<0.05, **p<0.005, ***p<0.001.

**Table 1**: Clinical, hormonal, metabolic and lipidic profiles of the three study groups.

<table>
<thead>
<tr>
<th>GROUP A</th>
<th>GROUP B</th>
<th>GROUP C</th>
</tr>
</thead>
<tbody>
<tr>
<td>BASAL</td>
<td>AFTER 6 MONTHS</td>
<td>P</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28.2 ± 1.3</td>
<td>25.7 ± 1.1</td>
</tr>
<tr>
<td>Menstrual cycles (days)</td>
<td>45-60</td>
<td>30-35</td>
</tr>
<tr>
<td>F. Gallwey (score)</td>
<td>11.7 ± 2.7</td>
<td>7 ± 3.9</td>
</tr>
<tr>
<td>LH (mU/ml)</td>
<td>10.3 ± 1.3</td>
<td>7.3 ± 0.4</td>
</tr>
<tr>
<td>FSH (mU/ml)</td>
<td>4.5 ± 0.3</td>
<td>5.8 ± 0.6</td>
</tr>
<tr>
<td>T (pg/ml)</td>
<td>0.8 ± 0.1</td>
<td>0.5 ± 0.1</td>
</tr>
<tr>
<td>FT (pg/ml)</td>
<td>1.2 ± 0.2</td>
<td>0.6 ± 0.1</td>
</tr>
<tr>
<td>A (ng/ml)</td>
<td>2.0 ± 0.1</td>
<td>0.9 ± 0.1</td>
</tr>
<tr>
<td>SHBG (nmol/L)</td>
<td>42.5 ± 3.2</td>
<td>96 ± 10.8</td>
</tr>
<tr>
<td>Glucose (mg/dl)</td>
<td>99.5 ± 2.1</td>
<td>91 ± 1.7</td>
</tr>
<tr>
<td>Insulin (mU/ml)</td>
<td>14.1 ± 2.8</td>
<td>10.2 ± 1.1</td>
</tr>
<tr>
<td>HOMA</td>
<td>3.8 ± 0.4</td>
<td>2.5 ± 0.4</td>
</tr>
<tr>
<td>Total Cholesterol (mg/dl)</td>
<td>220 ± 12.4</td>
<td>194 ± 8.5</td>
</tr>
<tr>
<td>HDL (mg/dl)</td>
<td>59.5 ± 3.4</td>
<td>68.5 ± 3.2</td>
</tr>
<tr>
<td>TG (mg/dl)</td>
<td>164 ± 9.4</td>
<td>134 ± 9.4</td>
</tr>
<tr>
<td>LDL (mg/dl)</td>
<td>127.5 ± 3.2</td>
<td>96.5 ± 7.3</td>
</tr>
</tbody>
</table>

Clinical, hormonal, metabolic and lipidic profiles of the two study group, before and following 6 months of treatment. (Group A: inositol plus monacolin; Group B: inositol only; Group C metformin). Data are presented as median ± confidence interval (IC) 95%. P values are significant if p<0.05.
Considering the glycemic profile, glucose and insulin levels, as well as the HOMA-index were significantly reduced following treatment in both study groups (Table 1). These reductions were more pronounced following treatment in group A, compared to B (Figure 2).

Regarding the lipid profile (Table 1 and Figure 3), total cholesterol level was reduced in all three groups but significantly only in group A treated with myo-inositol + monacolin k. The same pattern was observed...

**Figure 2:** Representation of HOMA, insulin and glucose at basal time and after 6 months of treatment with monacolin k + myo-inositol (group A), only inositol (group B) or metformin (Group C). Values are presented median and IC 95%. *p<0.05, **p<0.005, ***p<0.001.

**Figure 3:** Cholesterol (Chol.), triglycerides (TG), HDL and LDL values at basal time and after 6 months treatment with monacolin k + myo-inositol (group A), inositol only (group B), or metformin (Group C). Values are presented as median and IC 95%. *p<0.05, **p<0.005, ***p<0.001.
for TG and LDL-cholesterol with significantly reduction in group A, (Figure 3). Furthermore treatment with myo-inositol and monacolin k (group A) resulted in a significant increase in HDL cholesterol level, no change in inositol only instead (group B) and metformin treatment (Group C) (Table 1 and Figure 3).

Almost all women in each group have endured well the two treatments: only two women in group A and one in group B reported moderate diarrhea carefully controlled with lactic ferments intake, while the women treated with metformin (Group C) reported severe side effects like nausea and diarrhea and two women interrupted the treatment.

Discussion

In the present study, we demonstrated that all treatments improved patients’ clinical, hormonal and metabolic profiles, with a tendency toward better results using the combination of myo-inositol and monacolin k.

Our data confirm previous observations demonstrating the beneficial effect of inositol on overweight, hyperinsulinemic and hirsute PCOS patients with menstrual irregularities [17,20]. Moreover our study confirms that metformin can improve metabolic aspects in PCOS patient, even if the literature is discrepant about metformin effects on lipid, menstrual and ovulation characteristics [8,9,33,34].

Actually, after 6 months of therapy all study groups have demonstrated shorter menstrual cycles, lower Ferriman-Gallwey scores and decreased BMI and LH/FSH ratio. Observations, which are probably the consequence of weight loss and improvement in insulin-resistance, associated with inositol intake. In fact, the reduction in BMI was more pronounced in group A (myo-inositol + monacolin k), compared to group B (inositol only).

Ferriman-Gallwey score, as well androgen levels were significantly reduced in all study groups, with a tendency toward a better improvement following the combined treatment with myo-inositol and monacolin k. This probably results from the significant increase in SHBG levels observed following treatment with myo-inositol+monacolin k [34,35].

While glucose, insulin and HOMA index were significantly decreased in all groups, the HOMA index in patients treated with myo-inositol and monacolin k were within the normal range.

Regarding the lipid profile, total cholesterol, triglycerides and LDL levels were significantly reduced in all groups, with a more pronounced reduction in LDL following the combined treatment with myo-inositol and monacolin k. Moreover, while HDL cholesterol was not significantly modified in inositol therapy, the combined treatment with myo-inositol and monacolin k significantly increased in HDL levels. The show an increased risk of cardiovascular disease [9], the aforementioned observations emphasize the important role of myo-inositol and monacolin k intake on lipid metabolism, and more specifically in improving lipid profile and reducing patients’ cardiovascular risk.

Since metformin and statins administrations are associated with several side effects such as nausea, vomiting, gastric pain causing the end of therapy [36], the combined treatment with the natural products: monacolin k and myo-inositol represents a valid alternative, well tolerated and with a similar mode of action. This new combination of myo-inositol and monacolin k may oppose the etiopathologies responsible for the onset and deterioration of PCOS related symptoms, and may represents a reasonable alternative to other treatments modalities, such as combined oral contraceptive or antiandrogenic drugs, which are associated with a variety of side effects, especially in adolescents. Moreover this natural choice is much more accepted by patients and clinicians who consider metformin only an antiandrogenic drug and then other uses are “off label” [37].

References


