

# Metabolic and hormonal effects of a combined Myo-inositol and D-chiro-inositol therapy on patients with polycystic ovary syndrome (PCOS)

Marcin Januszewski<sup>1</sup>, Tadeusz Issat<sup>1,2</sup>, Alicja A. Jakimiuk<sup>3</sup>,  
Malgorzata Santor-Zaczynska<sup>1</sup>, Artur J. Jakimiuk<sup>1,2</sup>

<sup>1</sup>Department of Obstetrics and Gynecology, Central Clinical Hospital of Interior, Warsaw, Poland

<sup>2</sup>Center of Reproductive Health, Institute of Mother and Child, Warsaw, Poland

<sup>3</sup>First Faculty of Medicine, Medical University of Warsaw, Poland

## ABSTRACT

**Objectives:** To evaluate the effects of a combined Myo-inositol (MI) and D-chiro-inositol (DCI) therapy on the hormonal and metabolic parameters of women with PCOS. Prospective clinical study. Clinical Study registration number — EUPAS25705

**Material and methods:** Seventy women diagnosed with PCOS according to the Rotterdam criteria were enrolled in this study. Patients received a combined therapy of one tablet that contained 550 mg of inositol (myo-inositol (MI) and D-chiro-inositol (DCI) in a ratio of 10:1) twice a day for 6 months. At each of 3 visits, the body weight, height and BMI were all recorded; and serum levels of free testosterone (fT), sex hormone-binding globulin (SHBG), luteinizing hormone (LH), follicle-stimulating hormone (FSH) and glucose with insulin during standard OGTT (75 g) were measured. Also at each visit, transvaginal ultrasonography and skin condition assessments were performed.

**Results:** Significant body weight reduction and decreases in fT, FSH, LH and insulin levels, as well as significant increase of serum SHBG concentrations were observed. Serum glucose levels during OGTT decreased after 6 months of treatment. Also, skin conditions improved after only three months of treatment.

**Conclusions:** Combination of MI and DCI in a ratio 10:1 seems to be efficient in improving both metabolic and hormonal parameters in patients with PCOS.

**Key words:** inositol; PCOS; OGTT; MI DCI ratio

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## INTRODUCTION

Polycystic ovary syndrome (PCOS) is one of the most common endocrinopathies in women of reproductive age, with a prevalence of 4–18% [1]. According to the 2003 Rotterdam criteria, diagnosis of PCOS is made when 2 out of 3 features are present: oligo- and/or anovulation, clinical and/or biochemical signs of hyperandrogenism, and/or ultrasonographic findings of polycystic ovaries; and any other etiologies of hyperandrogenism are excluded. PCOS typically presents with irregular menstrual cycles, infertility, and clinical signs of hyperandrogenism, including hirsutism, acne and androgenic alopecia [2–4].

Increasing evidence supports the important role played by insulin resistance and compensatory hyperinsulinemia,

that are commonly observed in these patients, both obese and lean [5–7]. It was hypothesized that in patients with PCOS, insulin resistance and compensatory hyperinsulinemia stimulates the secretion of both ovarian and adrenal androgen, and they suppress hepatic synthesis of the sex hormone binding globulin (SHBG). This leads to hyperandrogenism and subsequent premature follicular atresia and anovulation as well as leading to gonadotropin imbalance (an increase in LH and a decrease in FSH), which are characteristic of PCOS [8, 9]. This insulin resistance also determines an increased risk of cardiometabolic disorders such as obesity, impaired glucose tolerance, type 2 diabetes (DM2), dyslipidemia, hypertension, metabolic syndrome and cardiovascular disease [10, 11].

### Corresponding author:

Artur J. Jakimiuk

Center of Reproductive Health, Institute of Mother and Child, Warsaw, 17a Kasprzaka St., 01–211 Warsaw, Poland  
e-mail: jakimiuk@yahoo.com

The important roles of insulin resistance and hyperinsulinemia in the pathogenesis of PCOS are confirmed by the favorable response of PCOS patients to insulin-sensitizing drugs, with improved ovulatory function and reduced circulating androgens [12].

Insulin resistance is hypothesized to be related to altered insulin signaling, probably due to a defect in the inositolphosphoglycan (IPG) second messenger pathway [13–15].

The cellular content of INS is represented almost entirely by MI (> 99%) and for the remaining part by D-chiro-inositol (DCI) [16].

The aim of the present study was to evaluate the effect of a combined MI + DCI therapy on the metabolic and hormonal parameters in PCOS patients.

## MATERIAL AND METHODS

### Subjects and study design

A group of 70 women who had been diagnosed with PCOS according to the Rotterdam criteria were enrolled in our prospective clinical study. The patients were enrolled from January 2015 to December 2016. Informed consent was obtained from all patients. The study was approved by the Bioethical Committee of the Central Clinical Hospital of the Interior in Warsaw. The gynecological history of each woman was obtained. The patients were asked about their attempts at conception, their history of oligoovulation or anovulation, acne and hirsutism; in addition we collected ultrasonographic findings of a polycystic ovary examination that we conducted with each patient on their first visit.

The patients received for 6 months, from the first visit, 1100 mg of inositol in two tablets daily (a combination of Myo-inositol and D-chiro-inositol in a ratio 10:1, with a daily dose of: 400 µg of folic acid, 1000 IU of vitamin D, 1.4 mg of vitamin B6, 6 mg of vitamin B5, and 2.5 µg of vitamin B12). The patients were followed up at 3 and 6 months from the date of their first visit. At each visit (v1 – before treatment, v2 – 3 months after initiation of treatment, v3 – 6 months after initiation of treatment), anthropometric measurements including weight, height and body mass index (BMI) were recorded. Plasma concentrations of free testosterone (fT), sex hormone-binding globulin (SHBG), luteinizing hormone (LH), follicle-stimulating hormone (FSH), fasting glucose and fasting insulin were assessed. An oral glucose tolerance test (OGTT) with 75 g of glucose was performed; and plasma glucose concentration, before oral glucose load, 1 h after, and 2 h after, was measured. Skin condition assessment, using the Acne Global Severity Scale, was performed. At each follow-up visit, the patients' compliance regarding the prescribed treatment and recommended lifestyle modifications was checked.

### Statistical analysis

Quantitative data are presented as mean ± SD. The Wilcoxon test was used to determine whether the differences

(both between the first and second visits, and between the first and third visits) were statistically significant and a Bonferroni correction was applied for multiple comparisons. The significance level was set at  $0.05/2 = 0.025$ . The percentage distribution was presented for qualitative data, such as skin condition, at the second and the third visits in relation to the first visit. To determine whether the data distribution differences were statistically significant, the X2 test was used and when the expected frequency in any cell was less than 5, the Fisher's Exact Test was applied. The significance level was set at  $\alpha = 0.05$ .

## RESULTS

A significant reduction of body weight, fT, FSH, LH and insulin plasma concentration, as well as a significant increase of the SHBG plasma concentration were observed at both the second and third visits when compared with the first visit; i.e. before administration of treatment (in all cases  $p < 0.001$ ). Moreover, statistically significant differences in the OGTT results were observed between the first and second visits, as well as between the first and third visits. The results are summarized in Table 1. Statistically significant differences were also observed between the second and third visits in regard to skin condition ( $p < 0.004$ ).

## DISCUSSION

Inositol is involved in a great variety of functions, including cell membrane formation, cell growth and survival (morphogenesis, cytoskeleton rearrangement, regulation of cell proliferation), and in intracellular signaling, the development and function of peripheral nerves, osteogenesis and reproduction [17–20].

The present study found that a combined MI + DCI therapy in a ratio of 10:1 significantly improved the metabolic and hormonal parameters in PCOS patients. In our opinion, this is the first paper in the literature which is focused on the metabolic and hormonal changes in patients with PCOS following a combined MI + DCI therapy in this 10:1 ratio. Significant decreases in body weight, fT, FSH, LH and insulin plasma concentration, as well as a significant increase in SHBG plasma concentration, were observed both after 3 months and after 6 months of MI + DCI treatment in a ratio of 10:1 (Tab. 1). Statistically significant differences were also observed regarding patients' skin condition.

Artini et al. [8] evaluated the effects of the administration of MI on hormonal parameters in a group of 50 overweight women with PCOS and reported that after 12 weeks of treatment, plasma LH, PRL, T, insulin levels and LH/FSH were significantly reduced; also that the insulin sensitivity significantly improved, and the menstrual cyclicity was restored in all amenorrheic and oligomenorrheic subjects. Similarly, Genazzani et al. [21] reported that after 12 weeks of MI

**Table 1. Quantitative data obtained at the first, second and third visits and the Wilcoxon test results (significance level set at  $p < 0.025$ )**

	First visit Mean $\pm$ SD	Second visit Mean $\pm$ SD	Third visit Mean $\pm$ SD	p-value v1 vs. v2	p-value v1 vs. v3
Age	28.4 $\pm$ 5.1				
Height [cm]	165.2 $\pm$ 12.2				
Weight [kg]	79.2 $\pm$ 17.0	75.2 $\pm$ 14.7	72.3 $\pm$ 12.3	< 0.001	< 0.001
Free testosterone [pg/mL]	4.2 $\pm$ 2.4	3.6 $\pm$ 1.6	3.3 $\pm$ 1.3	< 0.001	< 0.001
SHBG [nmol/L]	44.1 $\pm$ 34.0	46.1 $\pm$ 29.8	48.0 $\pm$ 27.8	< 0.001	< 0.001
FSH [mIU/mL]	8.1 $\pm$ 3.1	7.2 $\pm$ 2.4	6.9 $\pm$ 2.0	< 0.001	< 0.001
LH [mIU/mL]	12.4 $\pm$ 6.7	10.8 $\pm$ 5.5	9.3 $\pm$ 4.2	< 0.001	< 0.001
Glucose-0' OGTT [mmol/L]	6.4 $\pm$ 10.7	9.3 $\pm$ 18.5	5.8 $\pm$ 8.0	0.004	< 0.001
Glucose-1-h OGTT [mmol/L]	7.5 $\pm$ 1.5	7.2 $\pm$ 1.5	7.1 $\pm$ 1.6	0.009	0.006
Glucose-2-h OGTT [mmol/L]	6.4 $\pm$ 1.3	7.7 $\pm$ 11.7	7.3 $\pm$ 10.9	< 0.001	< 0.001
Fasting insulin [ $\mu$ U/mL]	13.0 $\pm$ 6.4	11.5 $\pm$ 5.3	10.2 $\pm$ 4.2	< 0.001	< 0.001

administration, plasma LH, PRL, T, insulin levels and LH/FSH were significantly reduced and that insulin sensitivity significantly improved, in a study carried out on 20 overweight women with PCOS. Moreover, menstrual cyclicity was also restored in all amenorrhic and oligomenorrhic subjects. In another study, the efficacy of 8 weeks of treatment with MI at the dosage of 2 g per day, on the insulin sensitivity and hormonal parameters in a group of obese patients with PCOS was investigated. After the treatment interval, the patients' body mass index (BMI) and insulin resistance decreased together with LH, LH/FSH and insulin [22].

Another stereoisomer of INS, i.e. DCI, was evaluated in a study by Nestler et al. [23], in which the authors found that the administration of D-chiro-inositol to obese women with PCOS decreased the insulin response to orally administered glucose (most likely due to an improvement in peripheral insulin sensitivity), and improved ovulatory function and several metabolic abnormalities related to insulin resistance, such as serum androgen concentrations, blood pressure, and plasma triglyceride [24].

Nordio and Proietti [25], in a study of overweight women with PCOS, compared the effectiveness of a combined MI + DCI therapy in a physiological plasma ratio (40:1) with a monotherapy with MI, in reducing the risk of metabolic syndrome as well as in enhancing the ovarian functions. In that study, both MI and MI+DCI groups showed an improvement in the metabolic parameters and no significant differences between the groups were observed after six months of treatment. However, it was found that a combined therapy was able to restore the hormonal and metabolic parameters earlier than when the patients were treated with MI alone, with significant changes evident in the metabolic profile between the MI and MI + DCI groups

after three months of treatment. The researchers therefore speculated that DCI rapidly reduces the peripheral hyperinsulinemia while the presence of MI mainly improves the ovulatory function. They concluded that the combined administration of MI and DCI in a physiological plasma ratio (40:1) should be considered as the first line of approach in overweight patients with PCOS, thus reducing the metabolic and clinical alteration of PCOS and, therefore, also reducing the risk of metabolic syndrome. Results consistent with these above were reported by Benelli et al. [9] in a study of obese women with PCOS, in which the authors found the therapeutic combination of MI + DCI (in a ratio of 40:1) to improve the endocrine profile and the insulin resistance compared with the placebo (folic acid). In that study, the authors also recorded a statistically significant reduction of LH, FT, fasting insulin, and the HOMA index; and a statistically significant increase of 17-beta-Estradiol and SHBG levels.

In the present study, significant improvements in metabolic and hormonal parameters were also observed after only three months of treatment. Moreover, Colazingari et al. [26] investigated the effects on oocyte quality of the combined treatment of MI + DCI (in a ratio of 40:1) versus a DCI monotherapy, and found that only the combined therapy was able to improve oocyte and embryo quality, as well as pregnancy rates, in women with PCOS who were undergoing IVF-ET. Similarly, Brusco et al. [27] showed that MI + DCI in the lower, 5:1 ratio significantly improved the overall quality of oocytes and consequently embryo development. As was mentioned earlier, ours is the first report in the literature that is focused on the metabolic and hormonal parameters of a combined MI + DCI therapy in patients with PCOS, where the ratio of stereoisomers is 10:1.

## CONCLUSIONS

In conclusion, a combined MI + DCI treatment (in a ratio of 10:1) seems to be efficient in improving both metabolic and hormonal parameters and skin conditions in patients with PCOS.

### Conflicts of interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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