Myo-inositol *vs.* D-chiro inositol in PCOS treatment

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***Aim*. Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women in fertile age. It is an endocrine and metabolic disorder characterized by oligo-anovulation, hyperandrogenism and insulin-resistance. Various therapeutic approaches have been attempted in PCOS, including diet and the use of pharmacological agents such as oral contraceptives (OCs) or anti-androgens. Recently, the introduction of inositol in the treatment plan has proved to be as reasonable as useful in countering the endocrine-metabolic disorders of this syndrome.**

***Methods*. The aim of our study was to compare the clinical, endocrine and metabolic response after 6 months of therapy in 137 PCOS women characterized by oligomenorrhea and/or acne and/or mild hirsutism and insulin-resistance. The patients were treated with myo-inositol or with D-chiro-inositol or with placebo.**

***Results*. Our study showed that both myo-inositol (MI-PG) and D-chiro inositol (DCI-PG) treatments are able to significantly improve the regularity of the menstrual cycle, the Acne Score, the endocrine and metabolic parameters and the insulin-resistence in young, overweight, PCOS patients.**

***Conclusion*. Definitely, we assumed that both treatments with myo-inositol and with D-chiro inositol could be proposed as a potential valid therapeutic approach for the treatment of patients with PCOS. Additionally, further examination and for a longer period of treatment are needed.**

KEY WORDS: Polycystic ovary syndrome - Therapeutics - Inositol.

Polycystic ovary syndrome (PCOS) is an endocrine and metabolic disorder, which can be defined as a group of patterns of symptoms or abnormalities that indicate a particular medical situation. This syndrome interests approximately the 6-10% of the female population in reproductive age.[1] The current definition of PCOS requires the presence of two of the following three conditions: 1) oligo- and/or anovulation; 2) clinical and/or biochemical signs of hyperandrogenism; 3) polycystic ovaries and the exclusion of other etiologies.[2] Chronic anovulation most often manifests as oligomenorrhea; anovulatory cycles may lead to dysfunctional uterine bleeding and decreased fertility. Cutaneous manifestations of hyperandrogenemia in the polycystic ovary syndrome include hirsutism, acne, and male-pattern hair loss (androgenic alopecia), whereas acanthosis nigricans is a cutaneous maker

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of hyperinsulinemia.[3] Other features of PCOS are obesity, insulin resistance, dyslipidemia, cardiovascular disease, obstructive sleep apnea and infertility. A percentage of women with PCOs between 40 and 80%, has overweight/obesity.[4] Although obesity itself is not considered the inciting event in the development of the syndrome, excess adiposity can exacerbate associated reproductive and metabolic derangements.[5] Insulin resistance has been demonstrated in both obese and nonobese women with PCOS.[6] For these women has been hypothesized genetic predisposition to this anomaly of metabolism. Much of the variability in the levels of insulin resistance is due to the type of fatty tissue accumulated, even in the presence of normal weight (at the level of the trunk and abdomen with increased visceral fat).[7] In fact, the adipose tissue-trunk visceral, is more easily mobilizable compared to that in peripheral distribution, typical of the normo-ovulatory women, and its metabolism passes through the liberation of free fatty acids, which are related to an increase in resistance to insulin both in the liver and peripheral. D-chiro-inositol (DCI-PG) and myo-inositol (MI-PG) are both important second messengers in signal transduction of insulin, intervening in the activation of serotonin receptors in the Central Nervous System; at the ovarian level, MI and DCI mediate the insulin response, also mediating the action of FSH in the regulation of follicular growth. They have different functions: the MI-PG promotes the entry of glucose into the cell, the DCI-PG rules instead the conversion of glucose into glycogen. In insulin-resistant subjects is evident the reduction in the levels of DCI in the tissues that regulate the storage of glycogen. Alterations of the metabolism of inositols may cause Insulin Resistance, PCOS and type II diabetes. The importance of insulin resistance in PCOS is also suggested by the fact that insulin-sensitizing compounds have been proposed as putative treatments to solve the hyperinsulinemia-induced dysfunction of ovarian response to endogenous gonadotropins, reducing thus hyperandrogenemia and re-establishes menstrual cyclicity and ovulation, increasing the chance of a spontaneous pregnancy.[8] Several studies in literature report the results obtained from the use of both MI -Inositol that of DCI in PCOS patients, demonstrating their effectiveness in improving clinical symptoms, the endocrine and metabolic systems. The aim of our study is to compare the clinical, endocrine and metabolic response after 6 months of therapy in 142 PCOS women, treated with MI or with DCI or with placebo.

Materials and methods

During the 6 months of enrollment, a total of 137 women affected by PCOS were selected for our study. The criteria of enrollment were: the age (not over 30 years), symptoms such as acne, oligomenorrhea, irsutism and insuline resistance. The mean age of patients was 25±2.4 years and the BMI was 28±1.3 kg/m^2. All the patients were characterized by oligomenorrhea and/or acne (2.5±0.5, evaluated by Cremoncini Score) and/or mild hirsutism (<15, evaluated by Ferriman-Gallwey Score), and insulin-resistance (3.2±0.6 evaluated by HOMA-IR). According to a randomized double blind, the patients were divided into 3 groups: Group A (51 PCOS patients), treated with 2 g of myo-inositol (+ folic acid) twice a day, per os; Group B (48 PCOS patients), treated with DCI (+ folic acid, B12 vitamin and manganese) 500 mg twice a day, per os, group C (38 PCOS patients, controls) treated with multivitaminic supplement without folic acid, B12 vitamin and manganese, twice a day, per os. The number of before treatment, and after 6 months of therapy, were evaluated clinical subjective and objective parameters (menstrual-cycle, acne score and hirsutism score), metabolic parameters (total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, glycemia, insulinemia and HOMA-IR) and endocrine parameters (LH, FSH, PRL, Total T, fT, Δ4-A, 17-OH-P ,DHEA, DHEA-S, SHBG).

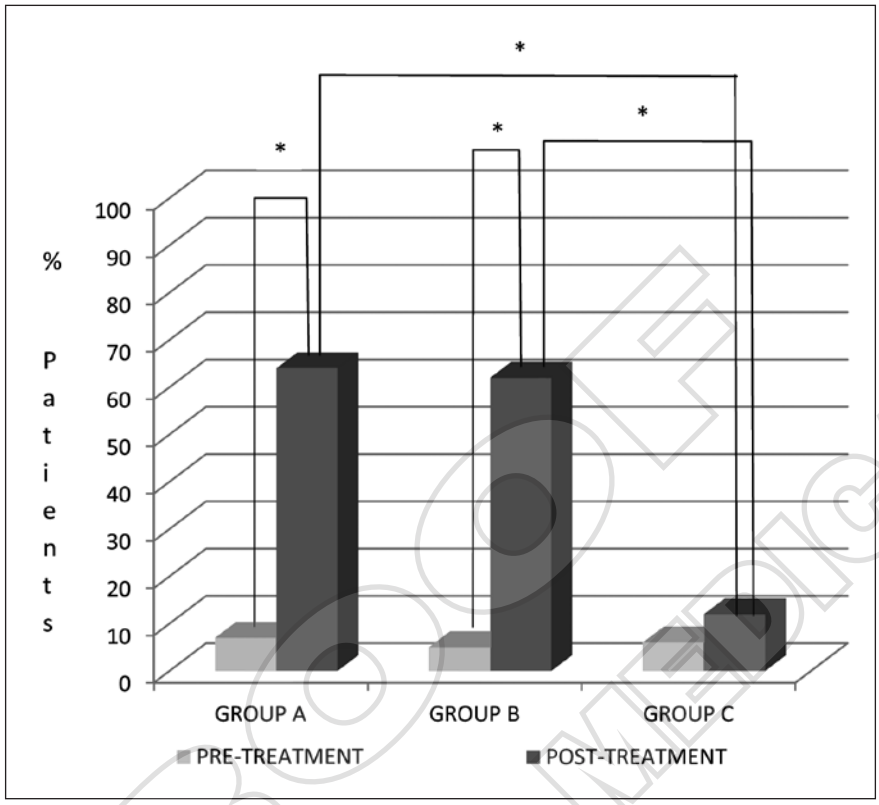

Figure 1.—Menstrual cycle regularity (%) before and after treatment with myo A), D-chiro inositol (group B) and placebo (group C) (*P.<0.001).

Each patient received and signed an informed consent.

Results

After 6 months of therapy, on a clinical level, our study showed a significant improvement (Figure 1) of the regularity of the menstrual-cycle in the 66% of group A (P<0.001) and in the 64% of the group B (P<0.001). No differences was reported in group C (P=NS). Similarly, a significant improvement (Figure 2) of acne score was detected both in group A and in group B (respectively, 67% of group A and 61% of group B, P<0.05 in both groups), whereas no significant differences were reported in group C. No differences about the BMI of patients were found before and after treatment (Figure 3). Concerning hirsutism score, any relevant improvement (P=NS) was detected in all patients. On the hormonal level, no significant changes were found for LH, FSH, PRL, Δ4-A, 17-OH-P and total T serum values (P=NS), whereas a significant decrease of DHEA (P<0.05), DHEA-S (P<0.05) and fT (P<0.05) and an increase of SHBG (P<0.05) serum levels was noticed only in group A and group B. The metabolic evaluation found a significant decrease of triglycerides (P<0.05), total cholesterol (P<0.05), basal insulin serum levels (P<0.05) and HOMA-IR (P<0.05) only in the group A and group B. U test for quantitative data not normally distributed (acne and hirsutism score) and Student *t* test for quantitative data normally distributed (triglycerids, cholesterol, insulin serum levels and hormones levels) was used to perform the comparison between the three groups.

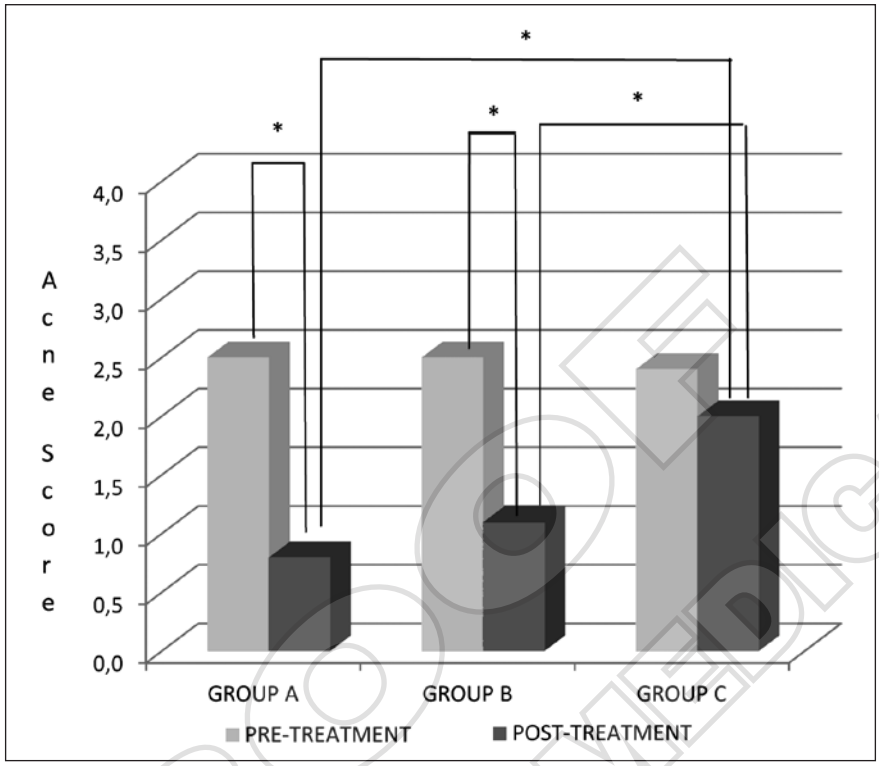

Figure 2.—Acne Score (evaluated by Cremoncini *et al.* Classification) before and after treatment with myo-inositol (group A), D-chiro inositol (group B) and placebo (group C) (*P.<0.005).

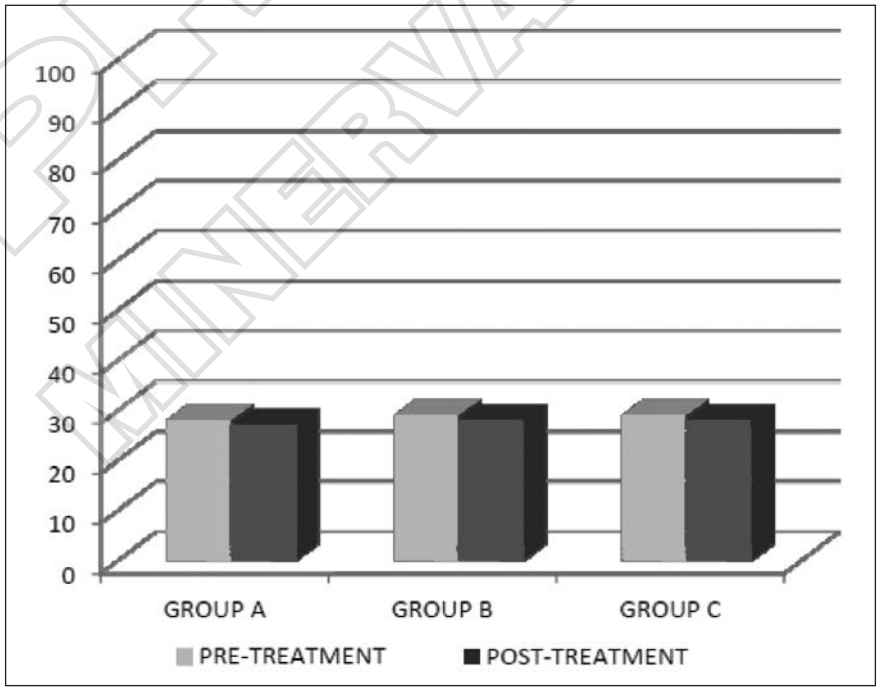

Figure 3.—BMI before and after treatment with myo-inositol (group A), D-chiro inositol (group B) and placebo (group C).

Discussion

As well known, PCOS is the most common endocrine disorder in women in fertile age. Insulin resistance and compensatory hyperinsulinemia are key features in this syndrome. The dysregulation of insulin signaling, can cause severe impact on the functional hormonal profile, as well as multiple metabolic and hemodynamic alterations.[9] Hyperinsulinemia inhibits ovulation and stimulates the production of ovarian androgens.[10, 11] The clinical features of this syndrome, such as acne, hirsutism and menstrual disorders, are the result of hyperandrogenism. Various therapeutic approaches have been attempted in PCOS, including dieting and the use of pharmacological agents such as oral contraceptives (OCs) or antiandrogens [12] even if, recently, the introduction of inositol in the treatment plan has proved to be as reasonable as useful in countering the endocrine-metabolic disorders of this disease. DCI-PG and MI-PG are both important second messengers in signal transduction of insulin; at the ovarian level, MI and DCI mediate the insulin response, also mediating the action of FSH in the regulation of follicular growth. They have different functions: the MI-PG promotes the entry of glucose into the cell, the DCI-PG rules instead the conversion of glucose into glycogen. In insulin-resistant subjects is evident the reduction in the levels of DCI in the tissues that regulate the storage of glycogen. Several studies in literature report the results obtained from the use of both MI that of DCI in PCOS patients, demonstrating their effectiveness in improving the clinical, endocrine and metabolic systems. Our study showed that both MI and DCI treatments are able to significantly improve the regularity of the menstrual-cycle and the acne score, the endocrine and metabolic parameters and insulin-resistence in young, overweight, PCOS patients. Definitely, we assumed that both treatments with MI and with DCI could be proposed as a potential valid therapeutic approach for the treatment of patients with PCOS. Additionally, further examination and for a longer period of treatment are needed.

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Conflicts of interest.—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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