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ORIGINAL ARTICLE

Comparison of two insulin sensitizers, metformin and myo-inositol, in women with polycystic ovary syndrome (PCOS)

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Abstract

Insulin resistance (IR) plays a pivotal role in PCOS. Insulin-sensitizer agents such as metformin and inositols have been shown to improve the endocrine and metabolic aspects of PCOS. The purpose of this study is to compare their effects on the clinical and metabolic features of the women with PCOS. Fifty PCOS women with IR and/or hyperinsulinemia were randomized to treatment with metformin (1500 mg/day) or myo-inositol (4 g/day). IR was defined as HOMA-IR >2.5, while hyperinsulinemia was defined as a value of AUC for insulin after a glucose load over the cutoff of our laboratory obtained in normal women. The Matsusa Index has been calculated. The women have been evaluated for insulin secretion, BMI, menstrual cycle length, acne and hirsutism, at baseline and after 6 months of therapy. The results obtained in both groups were similar. The insulin sensitivity improved in both treatment groups. The BMI significantly decreased and the menstrual cycle was normalized in about 50% of the women. No significant changes in acne and hirsutism were observed. The two insulin-sensitizers, metformin and myo-inositol, show to be useful in PCOS women in lowering BMI and ameliorating insulin sensitivity, and improving menstrual cycle without significant differences between the two treatments.

Keywords

Androgens, amenorrhea, insulin resistance, insulin sensitizer, polycystic ovary syndrome

History

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Introduction

The polycystic ovary syndrome (PCOS) affects about 6–10% of women in the reproductive age, characterized by chronic anovulation, hirsutism and acne, sterility and polycystic ovarian ultrasound morphology (PCOM) [1,2]. More than 50% may be obese [3]. Most of the patients with PCOS are affected by insulin resistance [2,4], dyslipidemia [5], a low grade of chronic inflammation, vascular and endothelial dysfunctions [6,7]. These metabolic features are worsened by obesity and can increase the risk of glucose intolerance, type 2 diabetes mellitus, hypertension, and cardiovascular diseases [8,9].

Insulin resistance plays a pivotal role in the development of the clinical and metabolic abnormalities of PCOS. Consequently, PCOS patients have a higher insulin production that in turn stimulates ovarian androgen secretion, as well as the release of other factors from different tissues that are involved in the metabolic damage [10].

To prevent the long-term health consequences of PCOS, besides lifestyle modifications [11,12], the use of insulin-sensitizers has been proposed, and metformin has been commonly used [13,14]. A large body of evidence shows that metformin may have metabolic and reproductive benefits, including weight reduction, decrease in plasma insulin and lipid levels, decrease in blood pressure, decrease in androgen plasma levels, restoration of a normal menstrual cyclicity and ovulation [14–16]. However, the use of metformin may be limited by gastrointestinal side effects [15,16].

Recently, new insulin sensitizers containing inositol have been proposed in the treatment of PCOS patients. Inositol is a physiological compound belonging to the sugar family and nine stereoisomers are known, of which myo-inositol and D-chiroinositol are the two main ones present in our body [17]. Myo-inositol administration improves insulin sensitivity [18,19]. Moreover, it produces a second messenger, the inositol triphosphate, that regulates some hormones such as TSH and FSH [20,21]. In contrast to metformin, no side effects have been reported during treatment with myo-inositol [22–24], while improving reproductive and metabolic parameters in PCOS women [23,24]. However, the number of studies is limited and no study has been performed to compare the efficacy of myo-inositol versus a more “classical” and most frequently used insulin sensitizer. The purpose of this study was to compare the effects of myo-inositol and metformin treatment on the clinical and metabolic features of women with PCOS.

Materials and methods

Subjects

The study protocol was approved by the Institutional Review Board of Pisa University. Informed consent was obtained from all participants. Fifty women with PCOS, aged from 18 to 28 years were included in the study. These women were selected among patients referred to the Outpatient Clinic of Reproductive Endocrinology of the University of Pisa between 2014 and 2015 for oligomenorrhea and clinical signs of hyperandrogenism. The diagnosis of PCOS was made according to the Rotterdam criteria [25]. Subjects with hyperprolactinemia, hypo or hyperthyroidism, congenital adrenal hyperplasia, Cushing’s syndrome or androgen-secreting tumors were excluded from this study.

No subject was using medication known to influence the endocrine and the metabolic profiles. Only subjects affected by insulin resistance and/or hyperinsulinemia (see after for definition) were included in the study. No subjects had an abnormal glucose response to the OGTT. All women were affected by acne and/or hirsutism. Thirty healthy subjects (18–28 years), with normal cycles and no symptoms of hyperandrogenism were included as control.

All the PCOS women were randomly assigned to the treatment with two insulin-sensitizers: 25 women were treated with metformin 1500 mg/daily (500 mg orally thrice daily) (the metformin group) while women in the other group received myo-inositol 4 g plus folic acid 400 mcg/daily (the inositol group). The allocation sequence of the treatments was decided by a third party (D.P.) before the recruitment of patients by random-number tables.

Protocol

All subjects were studied during the follicular phase of the menstrual cycle (3–7 days after the onset of spontaneous or progestin-induced menstrual bleeding). Height and weight were measured and BMI was calculated. At entry hirsutism was evaluated by modified Ferriman Gallway score. The cycle menstrual length was expressed as the average of days between cycles in the previous six months before the study.

Blood samples were obtained between 08.00 and 10.00 am after an overnight fast for the determination of LH, FSH, prolactin, estradiol, 17-hydroxyprogesterone (17OHP), total testosterone (T), DHEAS, Androstenedione (A) and cortisol (F). An OGTT was performed. Plasma samples for glucose and insulin concentrations were collected before and after 30, 60, 90, 120 and 180 minutes from a 75 g oral glucose administration. Insulin plasma concentrations were expressed as the area under the curve (AUC). The AUC was calculated using the trapezoidal rule and was expressed as $\mu\text{U per ml} \times 180$ minutes. Hyperinsulinemia was defined as a value of the AUC over the cutoff of our lab obtained in normal women. As an indicator of insulin resistance, the homeostasis model assessment of insulin resistance (HOMA-IR) was calculated. Patients with values of HOMA-IR > 2.5 were considered insulin resistant [26]. As an indicator of insulin sensitivity, from OGTT the insulin sensitivity index was also calculated using the formula reported by Matsuda and DeFronzo [27].

All patients were submitted to pelvic trans-abdominal or transvaginal ultrasounds, according to their sexual activity for the evaluation of ovarian morphology. The presence of an ovarian volume >10 cc and or more than 12 follicles per ovary was consistent for a diagnosis of PCO morphology (PCOM).

During the sixth month of treatment a new evaluation of the clinical (BMI, menstrual cycle length, acne and hirsutism), the hormonal (17OHP, T, DHEAS, A) and the metabolic (HOMA-IR, AUC-insulin, Matsuda index) parameters was performed. The changes in the signs of hyperandrogenism (acne and hirsutism) were evaluated as subjectively reported by the women as no change, slightly or significant improvement, worsening. During the observation period, the patients did not modify their Mediterranean diet and did not follow a low-carbohydrate diet.

The concentrations of LH, FSH, estradiol, prolactin, A, T, DHEAS, 17OHP F, glucose and insulin were determined as previously reported [28].

All data were reported as the mean \pm SD. The differences between the group of PCOS women and controls at the baseline were calculated using the Student *t*-test for unpaired data. To evaluate the differences in the response to each treatment in each group, the Wilcoxon test was used while the Mann–Whitney test was used to evaluate the differences between the two groups. For

all the analyses, a value of $p < 0.05$ was considered statistically significant.

Results

The clinical, the endocrine, and the metabolic features at the baseline of the PCOS women and the controls are reported in Table 1. Three patients of the metformin group (diarrhea and abdominal pain) and one patient in inositol group (poor compliance) dropped out from the study.

Baseline insulin sensitivity and the androgens levels in PCOS women were significantly different from the controls ($p < 0.05$). PCOS women included in the metformin and the inositol groups did not differ for age, BMI, insulin secretion and sensitivity, and hormonal profile.

BMI significantly decreased from 28.4 ± 5.2 to 26.8 ± 5.8 in the metformin group ($p < 0.01$) and from 27.3 ± 4.5 to 25.3 ± 3.9 in the inositol group ($p < 0.01$) with no difference between the two groups.

In the metformin group, after six months of treatment, the HOMA-IR decreased from 2.4 ± 0.3 to 2.0 ± 0.3 ($p < 0.01$) and the AUC-insulin decreased from 10870 ± 3555 to 8140 ± 2125 ($p < 0.05$); the Matsuda index improved from 4.9 ± 0.9 to 9.6 ± 3.9 ($p < 0.005$). In inositol group, the HOMA-IR decreased from 2.1 ± 0.5 to 1.5 ± 0.4 ($p < 0.05$) and the AUC-insulin decreased from 11890 ± 4830 to 7392 ± 5277 ($p < 0.01$), the Matsuda index improved from 5.96 ± 1.9 to 10.6 ± 3.4 ($p < 0.05$) (Figure 1). The percent changes were no different.

The mean cycle length before the study was 119 ± 63 days in the metformin group and 93 ± 60 days in the inositol group. After 6 month of treatment the mean cycle length was 54 ± 40 days in the metformin group ($p < 0.001$) and 57 ± 50 days in the inositol group ($p < 0.001$) (Figure 2). After 6 months of treatment a normal menstrual cycle length was present in 53% of the women in the metformin group and in the 44% of women in the inositol group. The cycle length improved but not normalized in 27% and in 38% of the patients, respectively. No changes in menstrual length occurred in 20% of women in the metformin group and in 18% of the inositol group (Figure 2).

No significant changes in androgen levels were seen after 6 months of treatment in both groups. No changes in hirsutism were reported by 76% and 80% of patients in the metformin and inositol

Table 1. Clinical, hormonal and insulinemic pattern of PCOS women divided into the two treatment groups (PCOS-M-metformin group and PCOS-I-inositol group) and controls.

Parameters	PCOS-M (N = 22)	PCOS-I (N = 24)	Controls (N = 30)
Age	22.3 \pm 6.0	21.6 \pm 6.6	23.1 \pm 5.4
Menstrual length (days)	119 \pm 63*	93 \pm 60*	30 \pm 3
BMI (kg/m ²)	28.4 \pm 5.2	27.3 \pm 4.5	27.2 \pm 3.9
HOMA-Index	2.4 \pm 0.3*	2.1 \pm 0.5*	1.5 \pm 0.2
AUC-Insulin ($\mu\text{U/mL} \times 180$ min)	10870 \pm 3555*	11890 \pm 4830*	6500 \pm 2370
Matsuda index	4.9 \pm 0.9*	5.9 \pm 1.9*	9.4 \pm 3.2
LH (mU/mL)	9.1 \pm 7.8*	9.0 \pm 6.8*	4.5 \pm 1.5
FSH (mU/mL)	4.7 \pm 1.6	4.4 \pm 1.2	4.2 \pm 0.2
Estradiol (pg/mL)	86.6 \pm 44.0	85.6 \pm 56.3	72.2 \pm 36.1
Prolactin (ng/mL)	16.3 \pm 8.3	16.4 \pm 8.5	15.7 \pm 3.7
Total testosterone (ng/mL)	0.7 \pm 0.3*	0.8 \pm 0.2*	0.3 \pm 0.1
Androstenedione (ng/mL)	3.0 \pm 1.2*	2.8 \pm 1.5*	1.65 \pm 0.6
DHEAS ($\mu\text{g/mL}$)	2.5 \pm 1.1*	2.3 \pm 1.2*	1.2 \pm 0.9
17-OH-P (ng/ml)	1.1 \pm 0.7	0.9 \pm 0.3	1.0 \pm 1.4
Cortisol (ng/ml)	122.5 \pm 51.8	125.5 \pm 56.5	123.3 \pm 54.2

The results are reported as mean + SD.

* $p < 0.05$ vs controls.

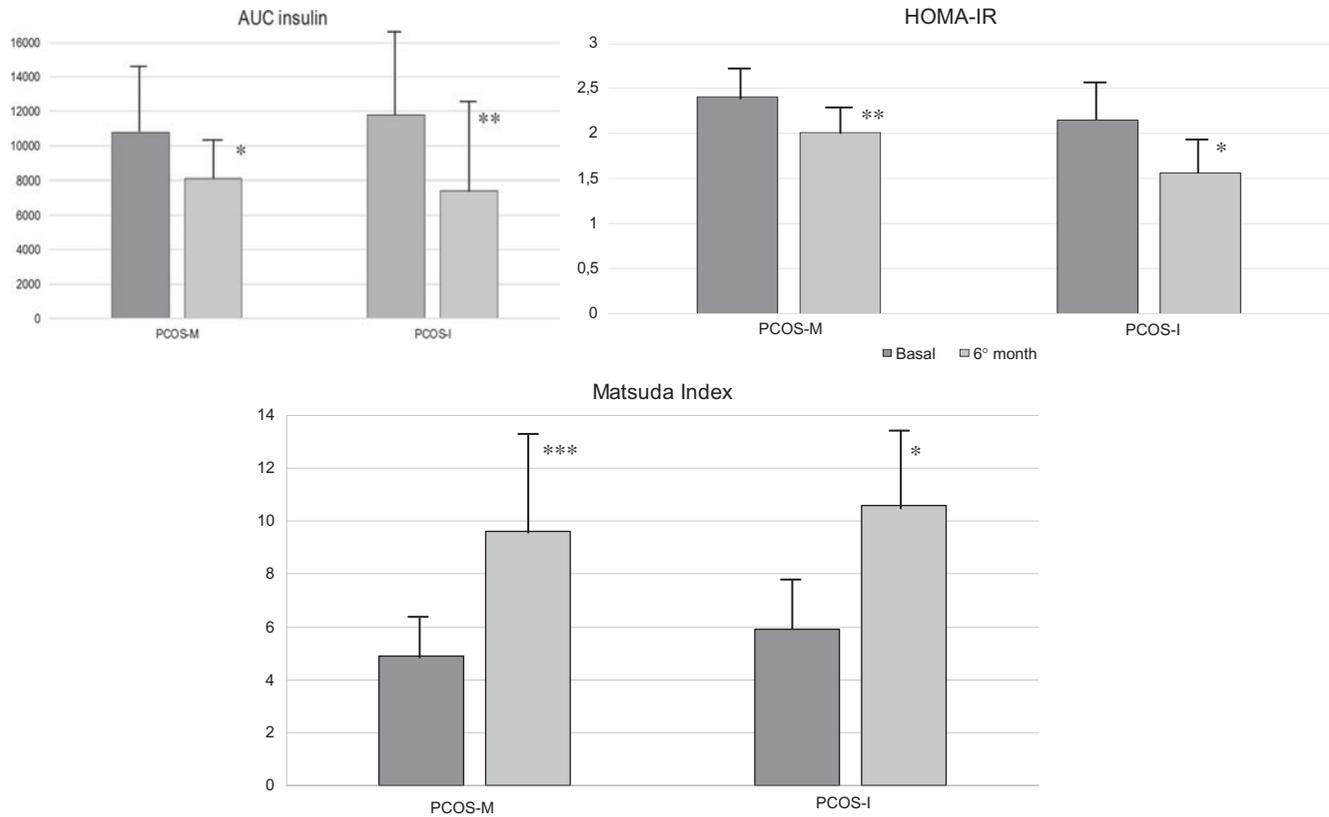
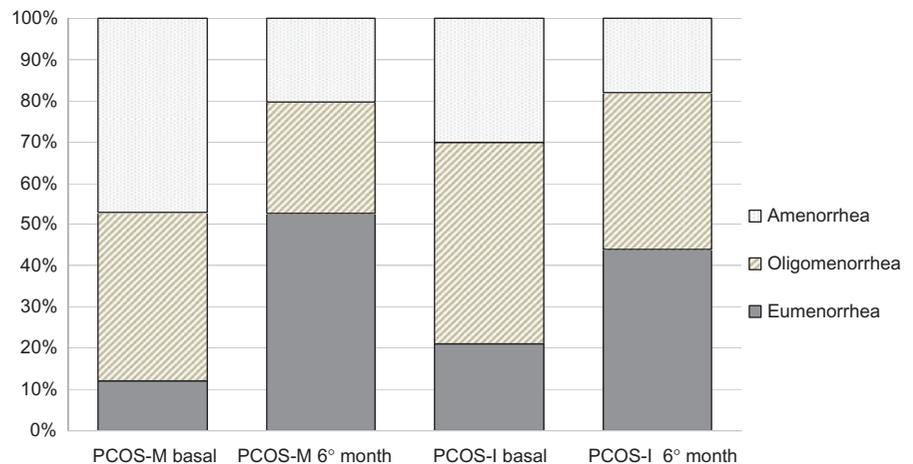


Figure 1. AUC insulin ($\mu\text{U/mL} \times 180 \text{ min}$), HOMA-IR and Matsuda Index as mean \pm SD in both groups (PCOS-M-metformin group and PCOS-I-inositol group) at baseline (dark grey) and after six months of treatment (light grey). * $p < 0.05$, ** $p < 0.01$, *** $p < 0.005$.

Figure 2. Percentage of eumenorrhea, oligomenorrhea and amenorrhea in both groups (PCOS-M-metformin group and PCOS-I-inositol group) at baseline and after six months of treatment.



groups, respectively. A slight improvement of hirsutism was reported in 12% and in 20% of patients in the metformin group and in the inositol group, respectively. No changes in acne were reported by more than 50% of patients of both groups. A slight improvement of acne was reported in 43% of the women in the metformin and in 38% of the inositol groups. Hirsutism and acne worsened in 12% and in 7% of women in the metformin group, while in the inositol group a worsening of acne was reported by 12% of women.

Discussion

Present results show that myo-inositol is as effective as metformin in improving the clinical and metabolic profile of PCOS women. Standard doses of both drugs were used. Our results confirming

previous results obtained with each drug administered alone [13–16,29,30], showed that both approaches are equally effective in improving insulin-sensitivity. Moreover, both treatments have similar effects in inducing weight loss. As a consequence of metabolic changes, the menstrual cycle length improved in approximately 80% of women, with a complete restoration of a normal menstrual cycle in about 50% of the patients. However, if the improvement of the menstrual cyclicity corresponds to a resumption of ovulation cannot be clarified, since no determination of progesterone levels has been performed during the study. No difference between the two groups was observed in the rate of normal menstrual cycles at the end of the study. It should, however, be underlined that in a post study power analysis the sample size of the study allowed us to identify an absolute difference between the groups in the frequency of normal cycles

of 35% (with a rate of normal cycles of 45% in the control group and a power of 80%).

No significant improvement of clinical signs of hyperandrogenism occurred in both groups. In particular, no significant benefit was observed in plasma androgen levels or hirsutism suggesting that neither metformin nor myo-inositol should be used for the reduction of hirsutism in PCOS. A decrease in plasma androgen levels have been reported during insulin sensitizers administration, but the extent of the decrease probably is not sufficient to improve hirsutism in the majority of women. Conversely, an improvement of acne was reported by about 50% of PCOS women with both treatments. In no cases was the acne reported as severe and it was always reported as mild-moderate. Moreover, the improvement was subjectively reported by patients and not objectively documented with a score, because the principal focus of this study was not directed at evaluating the effect of insulin sensitizers in clinical signs of hyperandrogenism.

Metformin administration is bound to gastrointestinal side effects such as nausea, lack of appetite and diarrhea in 10% of patients in which may cause the drop out of the treatment. In addition, metformin is approved for first-line therapy for Type 2 diabetes mellitus, and thus the use in PCOS is off-label. Because of this, a signed informed consent should be obtained from PCOS women. Moreover, in the case of surgery metformin treatment must be stopped 48h before surgery because of the risk of metabolic acidosis. In this study 3 women dropped out because of gastrointestinal symptoms. In contrast, no gastrointestinal side effects were reported in the myo-inositol group, confirming the high tolerability of this drug. However, the higher economic impact of myo-inositol treatment must be taken into consideration at the time of prescription.

In conclusion, our study suggests that metformin and myo-inositol are equally effective in improving BMI, insulin sensitivity and menstrual cycle in PCOS patients. Further randomized and properly sized studies are needed in order to confirm our data.

Declaration of interest

The authors report no conflict of interest.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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