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Myo-inositol administration positively affects hyperinsulinemia and hormonal parameters in overweight patients with polycystic ovary syndrome

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Abstract

Objective. To evaluate the effects the administration of myo-inositol (MYO) on hormonal parameters in a group of PCOS patients.

Design. Controlled clinical study.

Setting. PCOS patients in a clinical research environment.

Patients. 20 overweight PCOS patients were enrolled after informed consent.

Interventions. All patients underwent hormonal evaluations and an oral glucose tollerance test (OGTT) before and after 12 weeks of therapy (Group A ($n = 10$): myo-inositol 2 gr. plus folic acid 200 μg every day; Group B ($n = 10$): folic acid 200 μg every day). Ultrasound examinations and Ferriman-Gallwey score were also performed.

Main outcome measures. Plasma LH, FSH, PRL, E2, 17OHP, A, T, glucose, insulin, C peptide concentrations, BMI, HOMA index and glucose-to-insulin ratio.

Results. After 12 weeks of MYO administration plasma LH, PRL, T, insulin levels and LH/FSH resulted significantly reduced. Insulin sensitivity, expressed as glucose-to-insulin ratio and HOMA index resulted significantly improved after 12 weeks of treatment. Menstrual cyclicity was restored in all amenorrheic and oligomenorrheic subjects. No changes occurred in the patients treated with folic acid.

Conclusions. Myo-inositol administration improves reproductive axis functioning in PCOS patients reducing the hyperinsulinemic state that affects LH secretion.

Keywords: *Myo-inositol, LH, hyperinsulinemia, policystic ovary syndrome, inositolphosphoglycan*

Introduction

Polycystic ovary syndrome (PCOS) is the most common cause of menstrual irregularity, ovarian dysfunction and infertility [1–3]. Typically PCOS is characterized by hyperandrogenism, chronic anovulation, polycystyc ovaries at ultrasound evaluation and dermatological problems such as acne, hirsutism, seborrhea, though the latter might be extremely variable in their occurrence [2,3]. In these last years a great body of evidence has demonstrated the important role of altered insulin sensitivity in many, though not all, PCOS patients [3–6]. In fact such altered insulin sensitivity or compensatory hyperinsulinemia has been frequently reported not only in overweight/obese PCOS [7] but also in lean/normal weight PCOS patients [5,6,8,9], thus supporting the hypothesis that insulin resistance might be independent from body weight.

Insulin sensitizing compounds, such as metformin, pioglitazone, troglitazone have been proposed as a putative treatment to solve the hyperinsulinemia-induced dysfunction of ovarian response to endogenous gonadotropins in order to improve ovulation, spontaneous pregnancy, menstrual cyclicity and hyperandrogenemia [4–6,8].

However recent studies suggest that some abnormal action of insulin might be dependent from inositolphosphoglycan (IPG) mediators of insulin action [10,11] and suggest that a deficiency in a

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specific D-chiro-inositol (DCI)-containing inositol-phosphoglycan may underlie insulin resistance, similarly to type 2 diabetes [12,13]. DCI administration has been demonstrated to reduce insulin resistance both in lean and obese PCOS patients improving ovarian function and decreasing hyperandrogenism [14,15]. Such studies have suggested the putative presence of a defect in the insulin-signaling pathway in which DCI-PG is the mediator of insulin action, thus contributing to the pathophysiology of the insulin resistance of PCOS [16]. Besides DCI, another inositol, Myo-Inositol (MYO), has been reported to be greatly correlated to ovarian function [17] and oocyte quality in patients undergoing IVF procedures, independently from circulating plasma levels [18]. Such data support a specific role also for MYO on gonadotropin-induced ovarian function [18,19] though not confirmed by others [16].

On these bases we aimed to evaluate the effects of myoinositol administration on hormonal parameters in a group of oligomenorrheic/amenorrheic patients with PCOS.

Material and methods

Subjects

A group of 20 PCOS patients were recruited for this study after informed consent. These patients were selected among a population attending the Gynecological Endocrinology Center at the University of Modena and Reggio Emilia, Italy, according to the following criteria: a) presence of micropolycystic ovaries at ultrasound, b) mild to severe hirsutism and/or acne; c) oligomenorrhea or amenorrhea d) absence of enzymatic adrenal deficiency and/or other endocrine disease, e) normal PRL levels (range 5–25 ng/ml), f) no hormonal treatment for at least 6 months before the study.

The glucose to insulin ratio [5,21] and the HOMA index [20], at baseline, were computed to estimate the sensitivity to insulin. Such ratio was >4.5, i.e. within the normal range, in all subjects. Five patients were amenorrheic (last menstrual cycle 3 months before or more) and 15 oligomenorrheic (menstrual cycle every 50 days or more).

Ten out of the twenty patients (Group A) were randomly assigned to be treated with myo-inositol 2 gr. plus folic acid 200 μg every day (Inofolic, LO.LI. Pharma, Italy), dissolved in a glass of water, between 9 and 11 in the morning, for 12 weeks. The other patients (Group B, $n=10$) were administered only folic acid at the daily dosage of 200 μg, for 12 weeks and were considered as the control group. No changes of life style or diet was required from the patients.

Amenorrheic patients were studied the first time on a random day, while oligomenorrheic patients were studied on day 7 of the menstrual cycle. The post treatment endocrine control was performed on day 7 of the first menstrual cycle occurring after the 10–12th week of treatment.

All patients were evaluated for LH, FSH, PRL, estradiol (E2), androstenedione (A), 17-hydroxy-progesterone (17OHP), insulin, cortisol and testosterone (T). Oral glucose tolerance test (OGTT), for insulin, glucose and C-peptide determinations, was performed sampling 15 minutes before, and 30, 60, 90, 120 and 240 minutes after the oral assumption of 75 gr. of glucose, before and after 12 weeks of treatment.

Vaginal ultrasound examination and the Ferriman-Gallway score were performed before and after 12 weeks of treatment. Each patient kept a diary of their menstrual cyclicity, reporting the date of menstrual occurrence. The study protocol was approved by the Human Investigation Committee of the University of Modena and Reggio Emilia, Italy.

Assay

All samples from each subject were assayed in duplicate in the same assay. Plasma LH and FSH concentrations were determined using a previously described immunofluorimetric assay (IFMA) [22,23]. The sensitivity of the assay expressed as the minimal detectable dose was 0.1 IU/ml. The cross reactivities with free α- and ß- subunits of LH, FSH and TSH were less than 2% [22]. Intra-assay and inter-assay coefficients of variation were 5.1 and 7.3%, respectively.

Plasma E2, 17-OHP, A, cortisol and T were determined by radioimmunoassay (Radim, Pomezia, Rome, Italy) as previously described [24]. Based on two quality control samples the average within- and between-assay coefficients of variation were 4.1% and 9.5%.

Plasma insulin was determined using an immunoradiometric assay (Biosource Europa S.A., Nivelles, Belgium). Based on two quality control samples the average within- and between-assay coefficients of variation were 4.5% and 11.7%.

Plasma C-peptide concentrations were determined using a chemiluminescence assay (DBC immulite one, Los Angeles, CA, USA). Based on two quality control samples the average within- and between-assay coefficients of variation were 4.5% and 8.0%.

Statistical analysis

We tested data for significant differences between groups, after analysis of variance (one-way ANOVA), using Student's t-test for paired (within the same group) and unpaired data (between the two groups), as appropriate. The area under the curve of OGTT (AUC, subtracted from the baseline value) was computed using the trapezoid formula so that to evaluate the insulin response to oral glucose load. Data are expressed as mean $\pm$ SEM.

Insulin sensitivity was computed as glucose-to-insulin ratio since this ratio has been shown to be a

good index of insulin sensitivity in women with PCOS [25,26]. HOMA index, computed as [basal glucose] × [basal insulin]/22,5, was also evaluated since it indicates the insulin resistance [20].

Results

Data are shown as mean ± SEM. Table I shows the homogeneity of the two studied groups. Consistent significant changes were observed in Group A (under MYO + folic acid administration) since several hormonal parameters changed during the treatment interval. Indeed mean plasma LH, PRL, T and insulin levels significantly decreased, as well as LH/FSH ratio, the index of insulin sensitivity glucose/insulin ratio and the HOMA index (Table I). Insulin response, evaluated thirty minutes following oral glucose load, was significantly reduced ($p < 0.01$) in group A patients (Figure 1) as well as the AUC of insulin with respect to baseline conditions ($p < 0.05$) (Figure 2) while no changes were observed in group B.

After 12 weeks of treatment no changes were observed in Group B (under folic acid administration). Significant changes were observed between Group A and B when data were compared after the treatment interval (Table I).

Ferriman-Gallway score decreased after 12 weeks of myo-inositol administration though the reduction was not statistically significant (baseline: 22.7 ± 1.4, under treatment: 18 ± 0.8). Ovarian volumes, on the other hand, were significantly reduced (before: 12.2 ± 0.6 ml, under treatment: 8.7 ± 0.8 ml, $p < 0.05$). No changes were observed in the folic acid treated group (Group B).

All patients reported menstrual bleedings on a diary. Patients under MYO administration (Group A, $n = 10$) reported menstrual cycles during the 12 weeks of treatment, in particular all five amenorrheic PCOS subjects reported eumenorrhea or oligomenorrhea after the treatment interval. Group B patients ($n = 10$) remained oligomenorrheic after the treatment interval.

Discussion

The present study reports that myo-inositol supplementation in PCOS patients positively affects metabolic parameters (i.e. insulin sensitivity) and modulates various hormonal parameters deeply involved in the reproductive axis function and ovulation.

It is well known that polycystic ovary syndrome (PCOS) is characterised by the combination of hyperandrogenism, chronic anovulation and irregular menstrual cyclicity and affects a great percentage (6–10%) of women in the repoductive age [27,28]. PCOS is indeed the most common cause of female infertility [27–29]. In addition to the abnormal hormonal parameters, patients affected by PCOS have been demonstrated to present insulin resistance, in the

Table I. Hormonal pattern of PCOS patients under study.

Patients	LH mIU/ml	FSH mIU/ml	PRL ng/ml	E2 pg/ml	P ng/ml	T ng/100ml	17OHP ng/ml	A ng/100ml	C-Peptide μg/L	Insulin μU/ml	LH/FSH	BMI	Glucose/ insulin	HOMA index
Group A (n = 10)														
Baseline	14.5 ± 2.2	6.5 ± 0.5	17 ± 4	83.6 ± 17	1.5 ± 0.8	53.4 ± 5.6	1.4 ± 0.2	171 ± 19.6	1.8 ± 0.2	12.4 ± 2.2	2.8 ± 0.4	29 ± 1.6	9.9 ± 1.8	2.8 ± 0.6
Under treatment	9.6 ± 1.6***	4 ± 0.3	12.2 ± 2.2*	90.1 ± 16.4	1.4 ± 0.4	54.8 ± 6.2	1.5 ± 0.3	170.5 ± 29	1.7 ± 0.2	6.5 ± 1.1***	2.4 ± 0.4***	28.3 ± 1.3	17.4 ± 2.9**	1.4 ± 0.3**
Patients	LH mIU/ml	FSH mIU/ml	PRL ng/ml	E2 pg/ml	P ng/ml	T ng/100ml	17OHP ng/ml	A ng/100ml	C-Peptide μg/L	Insulin μU/ml	LH/FSH	BMI	Glucose/ insulin	HOMA index
Group B (n = 10)														
Baseline	15.1 ± 2.1	4.2 ± 0.4	18.2 ± 2.3	88.5 ± 14.7	1.5 ± 0.3	61.3 ± 7.2	1.4 ± 0.3	180.5 ± 23.1	1.7 ± 0.4	12.8 ± 1.3	2.9 ± 0.5	27.8 ± 2.1	8.4 ± 3.2	2.6 ± 0.4
Under treatment	13.1 ± 3.2***	4.6 ± 0.5	16.8 ± 1.9*	78.5 ± 17	1.4 ± 0.5	55.2 ± 9.1	1.3 ± 0.4	191 ± 24	1.6 ± 0.5	11.3 ± 1.1***	2.8 ± 0.6**	28.8 ± 1.7	8.6 ± 2.6**	2.5 ± 0.7**

*$p < 0.05$ vs baseline; **$p < 0.01$; ***$p < 0.005$.

*$p < 0.05$ vs Group A; **$p < 0.01$ vs Group A; ***$p < 0.005$ vs Group A.

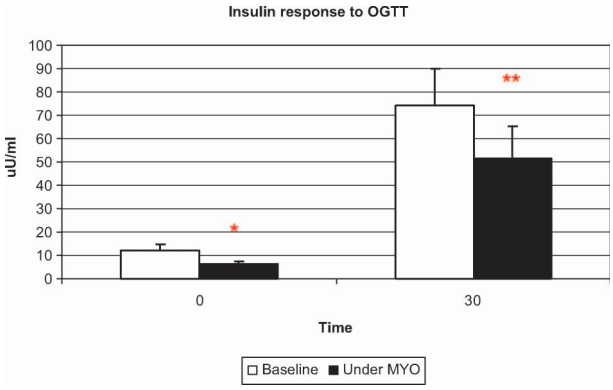

Figure 1. Patients under MYO administration showed a reduction of both insulin plasma levels before and 30 minutes after oral glucose load. (mean ± SEM) $*p < 0.05$, $**p < 0.01$.

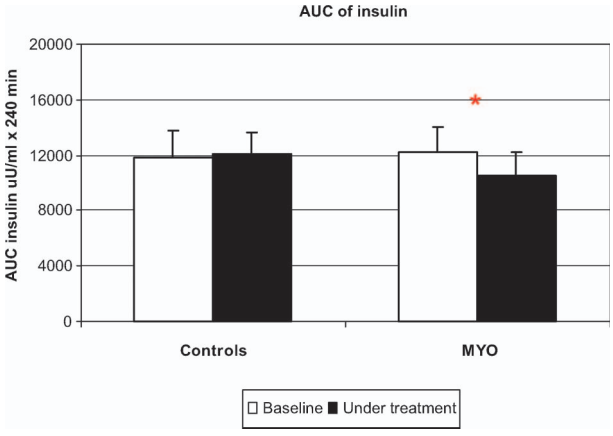

Figure 2. AUC of insulin (suntracted af baseline) after oral glucose load (OGTT). MYO administration significantly reduced the AUC of insulin after 12 weeks of treatment (Group A). Control subjects (Group B) did not show changes. (mean ± SEM) $*p < 0.05$.

absence of diabetes [5–8,29], probably due to (especially in lean/normal-weight PCOS subjects) a genetic/familiar predisposition [29,30]. Such an observation is of great relevance since many PCOS patients are overweight or obese and. The combination of a genetic predisposition to insulin resistance and that due to excess weight creates the basis of severe disease risk. Indeed PCOS-induced insulin resistance determines a higher risk for the development of type 2 diabetes, hypertension, dyslipidemia, all elements of the so called ''syndrome X'' or dysmetabolic syndrome [29,31].

In these last years the recognition that a metabolic dysfunction, that is peripheral insulin resistance, might be at the basis and/or one of the main triggers of polycystic ovary syndrome, has induced clinicians to use compounds to improve insulin sensitivity such as metformin [5,6,8] and troglitazone [8,29,32–35] to treat PCOS patients. Since hyperinsulinemia stimulates ovarian androgens production in PCOS patients [5,8,36] attention has been given to inositolphosphoglycan (IPG) mediators as post-receptor mediators or second messenger of insulin signaling [37,38].

Our data support the hypothesis of a primary role of IPG as second messenger of insulin signal and are in agreement with previous studies [14,16,17,18,19,25] and demonstrate that MYO administration significantly affect the hormonal milieu in PCOS patients. Nestler et al. [14] reported that d-chiro-inositol (DCI) administration, a member of the phosphoglycan family, was effective in ameliorating PCOS hormonal disturbances after 6–8 weeks of treatment by reducing insulin resistance, and LH, T and DHEAS plasma levels. Our present study has demonstrated that MYO is also effective on PCOS similarly to DCI. Our data confirm what has been previously reported by Gerli et al. [17] in terms of recovery of menstrual cyclicity and demonstrates specific positive effects on insulin plasma levels and on insulin response to oral glucose load. Indeed, in our study, MYO decreased insulin plasma levels, glucose-to-insulin ratio, HOMA index as well as other hormonal parameters such as LH, LH/FSH, testosterone and PRL, typically elevated in PCOS patients and determined the occurrence of normal menstrual cycles in all patients under study similarly to DCI [14,16] or to insulin sensitizers [8] such as metformin [5,6]. Indeed MYO administration reduced insulin response to glucose load similarly to the widely used metformin [5,6].

Our data enforce previous findings of Chiu et al. [18,19] that described a correlation between oocyte quality and follicular fluid concentrations of MYO both in in-vitro models and in IVF programs. Such a report sustained the hypothesis that MYO is required to enhance the developmental competence of maturing oocytes [18] probably through other concomitant effects. Our data support the hypothesis that the improved sensitivity to insulin signal induced by myo-inositol administration allows a better cellular performance in response to insulin (i.e. induced a higher sensitivity). In addition the reduction of plasma insulin levels, especially of the exaggerated insulin levels in response to glucose load, probably lessens the negative effect of insulin on citP450, gonadotropin secretion, androgen production, thus allowing restoration of normal gonadotropin secretion, improved follicular recruitment and growth and improved ovulation [5–9,29,30].

Our PCOS patients showed a significant amelioration of typical hormonal parameters. In fact high LH levels, high LH/FSH ratio, high T and HOMA index all decreased as well as the AUC of insulin under glucose load, the latter being a clear signal of the improved peripheral sensitivity to insulin action. Interestingly PRL plasma levels also resulted significantly lower under MYO administration, although baseline PRL levels were within the normal range. Such data sustain the hypothesis of a clear positive effect induced by both the reduction of androgen plasma levels and/or the reduction of psychological

stress, often present in PCOS patients, especially in patients deeply concerned by their health problems.

The present study supports the hypothesis that MYO supplementation, similarly to DCI administration, induces the reduction of insulin levels probably acting on the higher availability of such precursors of IPG and, thus, ameliorating the performances of this second messenger of the insulin signal. Our data support what recently reported by Papaleo et al. [39] who demonstrated the efficacy of MYO in emeliorating the response of a group of PCOS patients to ovulation induction, and demonstrated what hormonal changes took place under MYO administration. Our data together with those of Papaleo [39] suggest that a deficiency in the precursors of IPG such as myo-inositol (MYO) and/or d-chiro-inositol (DCI) might be an additional cofactor contributing to the pathophysiology of the insulin resistance of PCOS patients. Indeed recent data have demonstrated that PCOS patients have lower levels of plasma and higher urinary levels of DCI in comparison to healthy eumenorrheic subjects [16]. Our study demonstrated that MYO administration, besides DCI, has a modulatory role on insulin sensitivity, gonadotropin and androgen secretion, though no significant differences for plasma or urinary MYO concentrations have been previously reported in PCOS patients [16]. However it cannot be excluded that a minimal part of such positive effects observed under MYO administration might be related also to a minimal MYO-DCI conversion.

Though the present study did not evaluate the waist circumference and the waist-to-hip ratio, no significant changes in BMI were observed patients thus suggesting that the hormonal changes observed were related to specific metabolic effect of MYO. Improvement of insulin sensitivity participated to the modulation of gonadotropin and androgen secretion and induced their significant reduction, similarly to that observed under insulin sensitizers administration [4–8]. Since no changes in life style and diet occurred in both groups of patients, our data suggest that MYO supplementation induces direct and/or indirect changes so to modulate metabolism, insulin sensitivity and endocrine milieu, similarly to previous reports [14].

This study, together with all data published recently on PCOS and on the use of insulin-sensitizers [4–8], sustain the hypothesis that PCOS is probably more than a ''syndrome'' and that specific genetic/familiar factors might be at the basis of some of the many hormonal disturbances described up to now for PCOS. Insulin resistance (or the reduced insulin sensitivity) described in obese but mainly in normal weight/lean PCOS and the compensatory hyperinsulinemia might be considered as simple sign of intrinsic/constitutional genetically based defect of the insulin signal transduction partly and/or greatly related to a defect of the synthesis and/or function of inositolphosphoglycan (IPG) mediators [14,16]. Although a renal defect might also explain the altered urinary clearance of inositol compounds, as recently reported [16], certainly an endocellular defect of the IPG might trigger the compensatory hyperinsulinemia in most, though not all, PCOS subjects. Since only small amounts of inositol are introduced with the diet [16], the supplementation with inositol in PCOS patients seems to be potentially beneficial especially in improving metabolic pathways under insulin control.

In conclusion though the number of patients studied is small, our data support the hypothesis that a defect of insulin signal transduction has to be considered as part of the physiopathological factors that participate to the triggering of the PCO ''syndrome''. In fact myo-inositol supplementation is efficient in changing many of the hormonal disturbances of PCOS, improving insulin sensitivity of target tissues and positively affecting the reproductive axis and hormonal functions through the reduction of insulin plasma levels.

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Disclosure

This study and the data presented in the present manuscript have no conflict of interest that would prejudice its impartiality; or a potential conflict of interest that is fully declared within the text of the article.

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