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ORIGINAL PAPER

Efficacy of myo-inositol in the treatment of cutaneous disorders in young women with polycystic ovary syndrome

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Abstract

Background. Polycystic ovary syndrome (PCOS) is the most common endocrine cause of hirsutism, acne and pattern alopecia, often characterised by ovulation disorders (usually manifested as oligo- or amenorrhea). In addition, 30–40% of women with PCOS have impaired glucose tolerance, and a defect in the insulin signalling pathway seems to be implicated in the pathogenesis of insulin resistance. For this reason, insulin-lowering medications represent novel approach in women with PCOS. The aim of this study was to evaluate the effects of myo-inositol (MYO), an isoform of inositol, belonging to the vitamin B complex, in the treatment of cutaneous disorders like hirsutism and acne.

Methods. Fifty patients with PCOS were enrolled in the study. BMI, LH, FSH, insulin, HOMA index, androstenedione, testosterone, free testosterone, hirsutism and acne were evaluated at the baseline and after receiving MYO therapy for 6 months.

Results. After 3 months of MYO administration, plasma LH, testosterone, free testosterone, insulin and HOMA index resulted significantly reduced; no significant changes were observed in plasma FSH and androstenedione levels. Both hirsutism and acne decreased after 6 months of therapy.

Discussion. MYO administration is a simple and safe treatment that ameliorates the metabolic profile of patients with PCOS, reducing hirsutism and acne.

Keywords: *Myo-inositol, polycystic ovary syndrome, hyperinsulinemia, hyperandrogenism, cutaneous disorders*

Introduction

Polycystic ovary syndrome (PCOS) is an endocrine-metabolic disorder affecting approximately 6–10% of women in childbearing age [1] and is characterised by anovulation and hyperandrogenism. Several factors are involved in the pathogenesis of PCOS. Presenting signs and symptoms are heterogeneous and sometimes diagnosis of PCOS may be difficult [2]. In 2003, a consensus workshop sponsored by ESHRE/ASRM in Rotterdam indicated PCOS to be present if two of three criteria are found: oligo-ovulation or anovulation (usually manifested as oligomenorrhea or amenorrhea), excess androgen activity (leading to hirsutism, acne, seborrhea) and polycystic ovaries (with typical feature at gynecologic ultrasound). Presence of polycystic ovaries is not the only finding to make a diagnosis of PCOS, and conversely, their presence alone does not establish the diagnosis [3,4].

The diagnosis requires exclusion of the other endocrine disorders that can mimic PCOS. These account for about 15% of cases of hyperandrogenemia. Causes of ovarian androgen excess include androgen-secreting ovarian tumors and hyperthecosis, while extra-ovarian causes include adrenal tumors, nonclassic adrenal hyperplasia and hyperprolactinemia. The consequences of PCOS extend beyond the reproductive axis; affected women are at significant risk for the development of metabolic and cardiovascular abnormalities as those affected by metabolic syndrome. In fact PCOS is associated with an increased risk of developing hypertension, dyslipidemia and impaired glucose tolerance or type 2

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diabetes [5,6]. Increased ovarian androgen biosynthesis in PCOS results from abnormalities at all levels of the hypothalamic-pituitary-ovarian axis. Overproduction of either testosterone or testosterone precursors leads to exaggerated testosterone action in target tissues such as the skin. The most frequent dermatologic manifestation of androgen excess is hirsurtism (60–83%). Other cutaneous manifestations of androgen excess include acne (11–43%), acanthosis nigricans and androgenic alopecia [7]. Hirsutism is defined as the presence in females of terminal, or coarse, hairs in a male-like pattern. Of the causes of hirsutism, PCOS accounts for 70–80%. It can be classified clinically as mild, moderate or severe, depending on the degree and extent of hair growth through the modified Ferriman-Gallwey scoring system [8]. Acne vulgaris typically occurs in the teenage years because of the burst of pubertal androgen activity. Persistent, severe or acne of late onset in women is suggestive of PCOS. Androgen enhance sebum production from sebaceous glands and cause abnormal follicular epithelial cell desquamation, both of which contribute to the development of a comedone. Subsequently, the comedone becomes colonised with the bacterium *Propionibacterium acnes*, leading to the formation of papules and pustules typical of acne vulgaris.

Female androgenic alopecia refers to slowly progressive hair loss that is characterised by diffuse reduction in the volume and density of hair. It can be a progressive thinning of hair at the crown with preservation of the frontal hairline or balding with bitemporal recession. Minoxidil is the most commonly used and only Food and Drug Administration approved drug to treat androgenic alopecia in women.

Acanthosis nigricans, that is mostly a cutaneous marker of insulin resistance, is a skin condition characterised by velvet grey-brown, poorly marginated plaques with thickened skin and accentuation of skin markings that tipically develop in areas of flexures, including the neck, axillae, groin and under the breasts [9].

The pathogenesis of PCOS is still poorly understood.

Recently, it has become clear that a frequent feature of women with PCOS is impaired glucose tolerance and insulin resistance accompanied by compensatory hyperinsulinemia, and increasing evidence suggests that hyperinsulinemia plays an important role in the pathogenesis of PCOS [10,11]. There is plenty evidence that hyperinsulinemia results in increased ovarian androgen biosynthesis *in vivo* and *in vitro* [12,13] and decreased sex hormone-binding globulin (SHBG) synthesis from the liver [14], leading to increased bioavailability of free androgens.

Hence, lowering of insulin levels may be useful in restoring normal endocrinological and clinical parameters of this condition. Lifestyle modification programs with an emphasis on behavioral management, dietary and exercise interventions have been successful in reducing the risk of diabetes and the metabolic syndrome in the general population and improving reproductive and metabolic features in PCOS [15]. Insulin-sensitising drugs have recently been advocated as possibly safe and more effective long-term treatment than the oral contraceptive pill or anti-androgen drugs (cyproterone acetate, flutamide). Metformin is the most experienced insulin-sensitising drug in the treatment of PCOS [16]. It enhances insulin sensitivity both in the liver, where it inhibits hepatic glucose production, and the peripheral tissue, where it increases glucose uptake and utilisation in muscle tissue. By increasing insulin sensitivity, metformin reduces insulin resistance, insulin secretion and hyperinsulinemia [17]. However, recent studies suggest that some abnormal action of insulin might be dependent from inositolphosphoglycan (IPG) mediators of insulin action [18,19], and evidence suggests that a deficiency in a specific D-chiro-inositol-containing IPG (DCI-IPG) may contribute to insulin resistance in individuals with impaired glucose tolerance, type 2 diabetes [20]. Furthermore, it has been shown that metformin may improve the action of insulin in obese women with PCOS in part by improving insulin-mediated release of DCI-IPG mediator [21]. Indeed, a defect in tissue availability or altered metabolism of DCI or inositol phosphoglycan mediators has been found in PCOS women and may contribute to their insulin resistance [22]. DCI administration has been demonstrated to reduce insulin resistance both in lean and obese patients with PCOS improving ovarian function and decreasing hyperandrogenism [23,24]. Besides DCI, another inositol, myo-inositol (MYO) has been reported to be greatly correlated to ovarian function [25]. MYO is an isomer of a C_6 sugar alcohol that belongs to the vitamin B complex group. Epimerisation of the six hydroxyl groups of inositol results in the formation of up to nine stereoisomers, including MYO and DCI. MYO is widely distribuited in nature whereas DCI, the product of epimerisation of the C1 hydroxyl group of MYO, is relatively rare [26]. Recent studies reported that MYO supplementation, similarly to DCI administration, reduces serum insulin, decreases serum testosterone and enhances ovulation [27,28].

Administration of oral MYO significantly reduced hyperandrogenism and ameliorated the abnormal metabolic profile of women with hirsutism [29].

The aim of this study was to evaluate the efficacy of MYO in the treatment of different cutaneous conditions associated with androgen excess in patients with PCOS, evaluating also changes in hormonal parameters and insulin sensitivity.

Materials and methods

From May 2007 to August 2008, 50 young patients with PCOS (mean age ± SD, 25.4 ± 3.3 years) were enrolled in the study. These patients were selected among a population attending our Gynecological Department. Other condition causing ovulatory disorders or androgen excess as hyperprolactinaemia, hypothyroidism, adrenal hyperplasia and Cushing's syndrome, were excluded by hormonal tests.

Exclusion criteria were BMI > 30 kg/m^2 or hormonal medications, including contraceptive pills, for the past 6 months.

Every woman presented signs of hyperandrogenism (hirsutism and/or acne) and we assessed its severity. On the basis of the number of lesions on the face/chest/back, we distinguished moderate (<20) from severe (>20) acne. Moreover using a modification of the Ferriman-Gallwey score, that quantifies hairs in nine body areas, we classified hirsutism in mild (FG score = 8–9), moderate (FG score = 10–14), severe (FG score = 15–21).

All patients were evaluated for LH, FSH, basal insulin, androstenedione, testosterone, free testosterone within the first 5 days of the, eventually induced, menstrual cycle. Insulin resistance was measured using homeostasis model assessment (HOMA index) [30].

After informed consent was obtained , patients were treated orally with MYO 2 g plus folic acid 200 μg (Inofolic®; Loli Pharma, Rome, Italy) as soluble powder, twice daily, continuously for 6 months. No changes of life style or diet was required.

Serum samples were obtained after 3 months of treatment and compaired to the baseline measurements. Clinical evaluation was performed before and after 3 and 6 months of treatment.

Statistical analysis

Paired *t*-tests were used to identify the differences between variables at baseline and after 3 and 6 months of treatment with MYO. A p-value < 0.05 was considered statistically significant.

Results

Basal and after-treatment parameters are reported in Table I.

Significant changes were observed in biochemical features of patients with PCOS because several hormonal parameters changed during the treatment interval of just 3 months, as shown in Table I. Indeed, mean plasma LH (14.1 ± 5.7 vs. 8.4 ± 2.2 mIU/ml; $p < 0.005$), testosterone (92 ± 38 vs. 64 ± 31 ng/dl; $p < 0.001$) and free testosterone (1.2 ± 0.2 vs. 0.7 ± 0.3 ng/dl; $p < 0.001$) significantly decreased as well as basal insulin levels (12.2 ± 2.2 vs. 6.7 ± 1.1 mcIU/ml; $p < 0.005$) and consequently the HOMA index (2.9 ± 0.8 vs. 1.4 ± 0.5; $p < 0.01$). Serum FSH (6.0 ± 1.6 vs. 4.4 ± 2.3 mIU/ml) and androstenedione (2.6 ± 0.6 vs. 2.2 ± 0.5 ng/ml) concentrations decreased after MYO therapy but not in a statistically significant way.

Also clinical features improved after MYO treatment of 3 and 6 months (Tables II and III). All patients of our study presented hirsutism before getting MYO (mild in 40%, moderate in 42% and severe in 18% of patients). During the observational period the hirsutism score decreased after 3 months (disappearance in 16%, mild in 34%, moderate in 36% and severe in 14% of patients) and after 6 months of MYO treatment (disappearance in 30%, mild in 32%, moderate in 30%, severe in 8% of patients). FG score was significantly reduced (11.4 ± 3.2 vs. 8.1 ± 2.6; $p = 0.003$) if compared baseline and 6 months follow-up observations.

Table I. Hormonal and metabolic profile at baseline and after 3 months of myo-inositol treatment (T1 = 3 months).

	Baseline	T1	*p*
LH (mIU/ml)	14.1 ± 5.7	8.4 ± 2.2	0.005
FSH (mIU/ml)	6.0 ± 1.6	4.4 ± 2.3	NS
Androstenedione (ng/ml)	2.6 ± 0.6	2.2 ± 0.5	NS
Testosterone (ng/dl)	92 ± 38	64 ± 31	0.001
Free testosterone (ng/dl)	1.2 ± 0.2	0.7 ± 0.3	0.001
Basal insulin (mcIU/ml)	12.2 ± 2.2	6.7 ± 1.1	0.005
HOMA index	2.9 ± 0.8	1.4 ± 0.5	0.01

NS, non-significance.

Table II. Number of cases and severity of hirsutism at baseline, after 3 months and 6 months of treatment with myo-inositol (T1 = 3 months; T2 = 6 months).

	Baseline	T1	T2
Mild	20 (40%)	17 (34%)	16 (32%)
Moderate	21 (42%)	18 (36%)	15 (30%)
Severe	9 (18%)	7 (14%)	4 (8%)
Disappearance	–	8 (16%)	15 (30%)
Mean mFG score	11.4 ± 3.2	9.9 ± 2.8	8.1 ± 2.6*

mFG, modified Ferriman-Gallwey score.
*$p = 0.03$.

Table III. Number of cases and severity of acne at baseline and after 3 and 6 months of treatment with myo-inositol (T1 = 3 months; T2 = 6 months).

	Baseline	T1	T2
Moderate	26 (68%)	22 (58%)	13 (34%)
Severe	12 (32%)	8 (21%)	5 (13%)
Disappearance	–	8 (21%)	20 (53%)

Thirty-eight of the 50 patients were affected by acne (moderate in 68%, severe in 32%). Also this clinical feature improved after treatment for 3 months (disappearance in 21%, moderate in 58%, severe in 21%) and 6 months (disappearance in 53%, moderate in 34%, severe in 13%).

Discussion

PCOS is characterised by chronic anovulation and is the most common cause of excess androgen production [31]. It is also the most common hormonal disturbance that can underlie hirsutism (over half of cases), acne, seborrhea and pattern alopecia [32]. On the other hand, each of these symptoms is a variably expressed skin manifestation of androgen excess, so any or all may be absent in patients with the moderate degree of hyperandrogenemia that typifies PCOS [33].

It is the prevalent endocrinopathy in women in childbearing age and by far the mainly cause of anovulatory infertility.

Patients affected by PCOS have been demonstrated to present peripheral insulin resistance with compensatory hyperinsulinemia, which is a prominent feature of the syndrome and appears to have a pathophysiologic role in the hyperandrogenism of the disorder [34].

Management of PCOS is determined by symptomatology. The treatment of PCOS is directed at the patient's main complaints, which typically consist of various combinations of hirsutism, menstrual irregularity or obesity-related metabolic problems [35]. The primary goal of pharmacologic therapy for cutaneous disorders of hyperandrogenism is the reduction of androgen production and action. Hence, many medications that reduce androgen excess are useful in the treatment of both hirsutism and acne. Combination oral contraceptives are one such class of medications. Some progestins may have potential added advantages because of possessing specific antiandrogen effects. For example, cyproterone acetate competes with dihydrotestosterone for binding to the androgen receptor and it has been demonstrated to be useful in the treatment of hirsutism, acne and seborrhea in women with PCOS [36].

This approach is effective in achieving the traditional treatment goals in the PCOS, which include ameliorating the effects of androgen excess (e.g., hirsutism, male pattern baldness and acne) and restoring regular menses, thereby preventing endometrial hyperplasia.

Insulin appears to have a direct effect on the severity of hirsutism in PCOS and appears to have a synergistic interaction with total testosterone [37].

As consequence, diet and exercise counseling are the cornerstone of therapy for obesity and insulin resistance and their complications, i.e., acanthosis nigricans, metabolic syndrome and diabetes mellitus, which are risk factors for cardiovascular disorders. Screening and monitoring for glucose intolerance is recommended for patients with PCOS, particularly in those who are obese [38].

For this reason, insulin-sensitising agents have been reported could play an important role in the treatment of the disorders PCOS-related. Metformin, a biguanide, is the most commonly used insulin sensitiser for the approach of PCOS [39] but is associated with a higher incidence of side-effects such as nausea, vomiting and other gastrointestinal disturbances [40].

A position statement of the American Association of Clinical Endocrinologists recommends that metformin be considered the initial intervention in most women with the PCOS, particularly those who are overweight or obese [41].

Because recognition that insulin resistance might be dependent from a receptorial defect of IPG, attention has been given to different isoforms of inositol [42,43]. DCI and MYO administration increases the action of insulin in patients with PCOS thereby improving ovulatory function and decreasing testosterone concentration. Moreover these modifications of hormonal milieu, associated to a direct ovarian activity, restore spontaneous ovulation and menstrual cycles, and increases progesterone secretion in the luteal phase in most infertile patients with PCOS [27,28].

In our study, MYO treatment improves insulin sensitivity, decreasing circulating androgen levels. As a consequence, MYO supplementation benefits cutaneous disorders of hyperandrogenism, reducing hirsutism score and acne.

Endocrine, metabolic and dermatological results achieved by MYO administration, a novel compound with insulin-sensitiser effects, are comparable with those presented recently in literature [29].

Nevertheless, known the metabolic derangements associated with the PCOS, it seems practical and appropriate to plan long-term therapy that addresses not only management of the consequences of androgen excess and anovulation but also the new goals of ameliorating insulin resistance and reducing the risks of type 2 diabetes and cardiovascular disease.

For these reasons, insulin-lowering medications represent novel therapies for cutaneous disorders in patients with PCOS, who do not need or desire contraception. MYO, ameliorating the performances of insulin signal and consequently reducing insulin levels, represent a simple and safe treatment.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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