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Comparison between effects of myo-inositol and D-chiro-inositol on ovarian function and metabolic factors in women with PCOS

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Abstract

Myo-inositol and D-chiro-inositol are capable of improving the ovarian function and metabolism of polycystic ovary syndrome (PCOS) patients. The aim of this work is to compare the effects of myo-inositol and D-chiro-inositol in PCOS. We enrolled 50 patients, with homogeneous biophysical features, affected by PCOS and menstrual irregularities, and we randomly divided them into two groups: 25 were treated with 4 g of myo-inositol/die plus 400 mcg of folic acid/die orally for six months, 25 with 1 g of D-chiro-inositol/die plus 400 mcg of folic acid/die orally for six months. We analyzed in both groups pre-treatment and post-treatment BMI, systolic and diastolic blood pressure, Ferriman–Gallwey score, Cremoncini score, serum LH, LH/FSH ratio, total and free testosterone, dehydroepiandrosterone sulfate (DHEA-S), Δ-4-androstenedione, SHBG, prolactin, glucose/immunoreactive insulin (IRI) ratio, homeostatic model assessment (HOMA) index, and the resumption of regular menstrual cycles. Both the isoforms of inositol were effective in improving ovarian function and metabolism in patients with PCOS, although myo-inositol showed the most marked effect on the metabolic profile, whereas D-chiro-inositol reduced hyperandrogenism better.

Keywords

D-Chiro-inositol, metabolic factors, myo-inositol, ovarian function, polycystic ovary syndrome

History

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Introduction

Polycystic ovary syndrome (PCOS) is one of the most common endocrinological diseases of women in reproductive age, occurring in about 4–8% of this population [1,2]. About 74% of PCOS patients have anovulatory cycles, 42% of them have insulin-resistance, and 48% have hyperandrogenism [3]. This syndrome could be considered as the result of concurrent endocrinological alterations, which influence each other. Hyperandrogenism could be due to the local inflammatory response of the ovarian theca cells by reactive oxygen species (ROS) [4] or by specific cytokines and chemokines secreted by the fatty tissue [5–7]. Furthermore, obesity interferes with the hypothalamus–hypophisis–gonads regulation system, and so inhibits the physiological process of ovarian follicular maturation [8]. Moreover, in PCOS patients, insulin-resistance is commonly associated with hyperinsulinemia, and the latter enhances androgen production by theca cells [9–11] and reduces the circulating levels of sex hormone binding globulin (SHBG), leading to increased levels of free testosterone [12]. For this reason, researchers tried to use insulin-sensitizing drugs to stem the symptoms of this pathology: therefore, they decided to use different inositol isoforms [13], with the aim of increasing insulin action on various tissues and, by doing so, improving the ovulatory function and inhibiting or limiting testosterone production. It turned out that, actually, the use of inositol may improve the possibility of spontaneous ovulation and regular menstrual cycles, as well as increasing progesterone production in the luteal phase of female infertile patients with PCOS [14]. However, studies with wide cohorts and adequate statistic power that may clarify which of the inositol isoforms is more active to improve symptoms and biochemical rates of female patients suffering from PCOS, and how different isoforms may act in different way on them (even considering the patient's pre-treatment biometric parameters) are still missing in the literature. The main aim of the current study is to compare myo-inositol and D-chiro-inositol effects on ovarian function and on metabolic factors of patients suffering from PCOS.

Methods

Between August 2011 and January 2013, 50 female patients were recruited in the Department of Pediatric, Gynecological, Microbiological and Biomedical Sciences of AOU ''Gaetano Martino'' (University of Messina). Counseling was requested by all of them due to menstrual irregularities (Figure 1). The unique adopted criterion of inclusion was the diagnosis of PCOS, according to Rotterdam's criteria [15]. Patients who were suffering of other associated diseases such as hyperprolactinemia, hypo and hypertiroidism, adrenal cortex hyperplasia and Cushing Syndrome, hypoadrenocorticalism, and Addison syndrome, non-classical deficiency of 21-hydroxylase were excluded from this study. We randomized and divided the patients into two groups: 25 were treated with 4 g of myo-inositol/die plus 400 mcg of folic acid/die orally for six months, 25 with 1 g of D-chiro-inositol/die plus 400 mcg of folic acid/die orally for six months. Neither the enrolled patients nor the researchers knew which patient belonged to the myo-inositol group or to the D-chiro-Inositol group (double blind). In order to eliminate possible bias, both the pre-treatment

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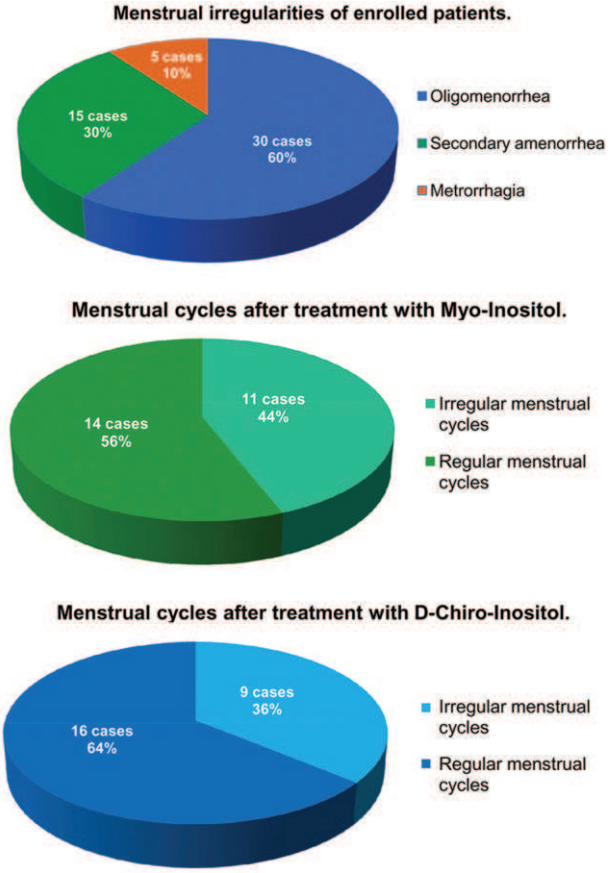

Figure 1. Menstrual irregularities of enrolled patients (pre-treatment) and evaluation of resumption of regular menstrual cycles after treatment with Myo-Inositol or D-Chiro-Inositol.

and the post-treatment evaluations of all the patients were performed by the same physician. The following pre-treatment and post-treatment parameters were analyzed in both groups: BMI, systolic, and diastolic arterial pressure (expressed in Hg mm); Ferriman–Gallwey score for the evaluation of hirsutism; Cremoncini score for the acne evaluation; Plasmatic LH (expressed in mIU/mL); LH/FSH ratio; total testosterone (expressed in ng/dL); free testosterone (expressed in pg/mL); dehydroepiandrosterone sulfate (DHEA-S) (expressed in μg/dL); Δ-4-androstenedione (expressed in ng/mL); SHBG (expressed in nmol/L); prolactin (expressed in mIU/L); glycemia/immunoreactive insulin (IRI) ratio; and homeostasis model assessment (HOMA) to check the insulin resistance. Furthermore, the resumption of regular menstrual cycles was evaluated after the treatment in both groups. Enrolled patients did not take any drug (as insulin sensitizers, oral contraceptives, anti-androgens, glucocorticoids, and corticosteroids) which could have modified the analyzed parameters during the previous six months or during the treatment. As far as the statistical analysis of the tested parameters is concerned, quantitative modalities were expressed by means and standard deviations, while qualitative modalities through frequencies. To analyze the statistical significance of our results, we used the *t* test for matched data to check our hypothesis, in two different moments of the survey, in the two different experimental branches (pre and post-treatment with myo-inositol; pre- and post-treatment with D-chiro-inositol), whereas we used Student's *t* test for independent groups to check the hypothesis of comparison between the two experimental branches before and after the treatment (myo-inositol versus D-chiro-inositol pre- and post-treatment). For the analysis of the recovery of regular menstrual cycles (qualitative variable expressed by frequencies), we used the χ^2 test to verify the hypothesis on the two experimental branches. All values of $p < 0.05$ were considered statistically significant. A first pre-treatment analysis was made to check whether in the two experimental branches the enrolled patients did not have statistically significant differences in the analyzed parameters, which may invalidate the subsequent analysis. Afterwards, for each analyzed parameter, the increased or decreased percentage (Δ%) between pre and post-treatment in the two groups was estimated. Finally, those parameters, which had shown a statistically significant increased or decreased percentage (Δ%) between pre- and post-treatment in both groups were selected, and we made a comparison between the post-treatment values of these parameters.

Results

Student's *t* test for matched data in relation to pre-treatment analyzed parameters (Table 1) did not show statistically significant differences in the two groups. The analysis of pre- and post-treatment parameters for the group of patients who took the myo-inositol or D-chiro-inositol showed the values reported in Table 1. In the group treated with myo-inositol, we evidenced a statistically significant reduction of diastolic and systolic arterial pressure, of LH, of LH/FS ratio, of total testosterone, of free testosterone, of the Δ-4-androstenedione, and of prolactin and HOMA Index. In the same patients, there was a statistically significant increase of SHBG and of glycemia/IRI ratio. Conversely, in the group treated with D-Chiro-Inositol we noticed a statistically significant reduction of systolic arterial pressure (but not of the diastolic), of Gallwey–Ferriman Score, of LH, of LH/FSH ratio, of total Testosterone, of free Testosterone, of Δ-4-androstenedione, of Prolactin, and of HOMA Index. In the same patients, we noticed a statistically significant increase of SHBG and glycemia/IRI ratio. Finally, we selected parameters that had shown a statistically significant increased or decreased percentage value (Δ%) between pre- and post-treatment in both groups, and we compared those values in the two groups, after the treatment (Table 2). Furthermore, we showed that the myo-inositol compared to D-chiro-inositol decreased mostly:

- systolic arterial pressure (1.06%), but not in a statistically significant way;
- LH/FSH ratio (40.05%);
- total testosterone (6.84%)
- Δ-4-androstenedione (0.01%), but not in a statistically significant way;
- prolactin (0.24%), but not in a statistically significant way;
- HOMA Index (5.54%);

and, at the same time, SHBG considerably rises (2.68%).

Conversely, D-chiro-inositol compared to myo-inositol decreased more, but not in a statistically significant way:

- LH (0.88%);
- free testosterone (1.26%)

at the same time, glycemia/IRI ratio (1.58%) increased more, but not in a statistically significant way.

As far as the features of post-treatment menstrual cycles are concerned (Figure 1), in the group treated with myo-inositol we found:

- Eleven cases (44%) of persistency of irregular menstrual cycles.
- Fourteen cases (56%) of menstrual cycle regularization.

In the group treated with D-chiro-inositol, we found:

- Nine cases (36%) of persistency of persistency of irregular menstrual cycles.
- Sixteen cases (64%) of menstrual cycle regularization.

The χ^2 test, in this case, did not evidence statistically significant differences between the two experimental branches ($\chi^2 = 0.083\%$; $p = 0.773$).

Table 1. Analysis of the effects of myo-inositol and Dchiro-inositol on ovarian function and metabolic factors in women with PCOS.

	Pre-treatment analysis of parameters of endocrine and metabolic function			Analysis of the effects of myo-inositol on metabolic and endocrine function				Analysis of the effects of D-chiro-inositol on metabolic and endocrine function			
	Myo-inositol pre-treatment	D-Chiro-inositol pre-treatment	*p* Value	Myo-inositol pre-treatment	Myo-inositol post-treatment	*p* Value	Δ%	D-Chiro-inositol pre-treatment	D-Chiro-inositol post-treatment	*p* Value	Δ%
Age	20.25 ± 4.47	19.25 ± 3.47	0.077	–	–	–	–	19.25 ± 3.47	–	–	–
BMI	25.1 ± 5.2	24.37 ± 5.31	0.087	25.1 ± 5.2	24.7 ± 4.6	0.183	–	24.37 ± 5.31	23.87 ± 4.45	0.090	–
Systolic PA (mm Hg)	104.5 ± 14.03	103.75 ± 14.33	0.095	104.5 ± 14.03	96 ± 6.58	0.020	−8.85	103.75 ± 14.33	96.25 ± 6.94	0.040	−7.79
Diastolic PA (mm Hg)	68.5 ± 8.18	68.12 ± 9.28	0.096	68.5 ± 8.18	64.5 ± 5.98	0.040	−6.20	68.12 ± 9.28	64.37 ± 6.23	0.059	–
Ferriman–Gallwey Score	10.1 ± 1.5	10.05 ± 1.41	0.096	10.1 ± 1.5	9.3 ± 1.0	0.055	–	10.05 ± 1.41	9.36 ± 0.91	0.020	−12.18
Cremoncini Score	1.1 ± 0.7	1 ± 0.7	0.086	1.1 ± 0.7	0.9 ± 0.8	0.210	–	1 ± 0.7	0.75 ± 0.9	0.072	–
LH (mIU/mL)	13.24 ± 2.93	12.99 ± 3.14	0.092	13.24 ± 2.93	8.60 ± 1.05	0.001	−53.95	12.99 ± 3.14	8.39 ± 1.07	0.002	−54.83
LH/FSH ratio	2.93 ± 0.49	2.25 ± 0.53	0.170	2.93 ± 0.49	1.59 ± 0.22	0.001	−84.28	2.25 ± 0.53	1.56 ± 0.21	0.003	−44.23
Total testosterone (ng/dL)	77.76 ± 14.19	75.28 ± 13.61	0.083	77.76 ± 14.19	49.60 ± 10.64	0.001	−56.77	75.28 ± 13.61	50.21 ± 11.98	0.005	−49.93
Free testosterone (pg/mL)	2.14 ± 0.61	2.20 ± 0.66	0.091	2.14 ± 0.61	1.66 ± 0.32	0.008	−28.92	2.20 ± 0.66	1.69 ± 0.28	0.020	−30.18
DHEA-S (μg/dL)	309.88 ± 113.52	286.25 ± 105.70	0.080	309.88 ± 113.52	287.2 ± 73.49	0.214	–	286.25 ± 105.70	288.93 ± 82.55	0.097	–
Δ-4-Androstenedione (ng/mL)	3.71 ± 0.58	3.45 ± 0.49	0.058	3.71 ± 0.58	3.50 ± 0.54	0.001	−6.00	3.45 ± 0.49	3.34 ± 0.44	0.008	−5.99
SHBG (nmol/L)	21.54 ± 5.45	21.2 ± 3.93	0.093	21.54 ± 5.45	26.02 ± 5.90	0.002	+17.22	21.2 ± 3.93	24.87 ± 3.55	0.010	+14.76
Prolactin (mIU/L)	408.39 ± 99.75	382.55 ± 75.65	0.073	408.39 ± 99.75	370.77 ± 78.52	0.008	−10.15	382.55 ± 75.65	348.07 ± 54.74	0.030	−9.91
Glic/IRI ratio	5.52 ± 1.69	5.83 ± 1.45	0.082	5.52 ± 1.69	9.72 ± 3.84	0.005	+43.21	5.83 ± 1.45	10.56 ± 3.74	0.010	+44.79
HOMA	3.51 ± 1.65	3.14 ± 1.08	0.076	3.51 ± 1.65	1.75 ± 0.84	0.001	−100.57	3.14 ± 1.08	1.61 ± 0.70	0.001	−95.03

Table 2. Comparative analysis of the parameters that showed statistically significant post-treatment reduction or increase with myo-inositol or D-chiro-inositol.

	Δ% post treatment with myo-inositol	Δ% post treatment with D-Chiro-Inositol	Δ% between the two treatments	*p* Value
Systolic PA (mm Hg)	−8.85	−7.79	1.06	0.204
LH (mIU/mL)	−53.95	−54.83	0.88	0.256
LH/FSH ratio	−84.28	−44.23	40.05	0.003
Total testosterone (ng/dL)	−56.77	−49.93	6.84	0.026
Free testosterone (pg/mL)	−28.92	−30.18	1.26	0.201
Δ-4-Androstenedione (ng/mL)	−6.00	−5.99	0.01	0.361
SHBG (nmol/L)	+17.22	+14.76	2.68	0.042
Prolactin (mIU/L)	−10.15	−9.91	0.24	0.298
Glic/IRI ratio	+43.21	+44.79	1.58	0.174
HOMA	−100.57	−95.03	5.54	0.032

Discussion and conclusions

The aim of our work was to compare myo-inositol and D-chiro-inositol effects on ovarian function and on metabolic factors in PCOS. In full agreement with other studies in the literature [16–20], our data showed that the treatment of PCOS patients with myo-inositol or with D-chiro-inositol improves the metabolic and endocrine function indexes, re-addressing them to the homeostasis. In particular, both the inositol isoforms are likely to reduce the systolic arterial pressure, LH, LH/FSH ratio, circulating androgens levels, prolactin, and to increase the action of insulin (increased glycemia/IRI ratio, decreased HOMA index) and of SHBG. Moreover, our data points out that myo-inositol compared to D-chiro-inositol may decrease more and in a statistically significant way LH/FSH ratio, total testosterone, and HOMA index, and in a not statistically significant way, even the values of systolic arterial pressure, Δ-4-androstenedione, and prolactin, and at the same time, the treatment may increase more and in a statistically significant way SHBG levels. Conversely, D-chiro-inositol compared to myo-inositol is likely to reduce mostly (but not in a statistically significant way) LH and free testosterone levels, and at the same time, it may increase more (but not in a statistically significant way) glycemia/IRI ratio. From our data, we may deduce that both the Inositol isoforms proved to be effective in improving the ovarian function and metabolism of PCOS patients, although myo-inositol showed the most marked action on the metabolic profile, whereas D-chiro-inositol affected positively mostly hyperandrogenism indexes. As far as the features of post-treatment menstrual cycles are concerned, we noticed a higher regularization of cycles in patients treated with D-chiro-inositol compared to those treated with myo-inositol, although the statistical significance was not gained. Despite our data, there is the need of further studies on larger cohorts and with greater statistical power which may accurately clarify the post-treatment outcomes with the different inositol isoforms in PCOS, establishing the most suitable therapeutic strategies in relation to the pre-treatment conditions of the patient, to the possibility of a ''personal dosage'' based on patients' features, and evaluating the variability of the long-term outcomes on the basis of these parameters.

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Declaration of interest

All authors have no proprietary, financial, professional, or other personal interest of any nature in any product, service or company.

References

1. Azziz R, Woods KS, Reyna R, et al. The prevalence and features of the polycystic ovary syndrome in an unselected population. J Clin Endocrinol Metab 2004;89:2745–9.
2. Norman RJ, Dewailly D, Legro RS, Hickey TE. Polycystic ovary syndrome. Lancet 2007;370:685–97.
3. Kurdoglu Z, Ozkol H, Tuluce Y, Koyuncu I. Oxidative status and its relation with insulin resistance in young non-obese women with polycystic ovary syndrome. J Endocrinol Invest 2012;35: 317–21.
4. González F, Rote NS, Minium J, Kirwan JP. Reactive oxygen species-induced oxidative stress in the development of insulin resistance and hyperandrogenism in polycystic ovary syndrome. J Clin Endocrinol Metab 2006;91:336–40.
5. Franks S. Polycystic ovary syndrome: a changing perspective. Clin Endocrinol (Oxf) 1989;31:87–120.
6. James RG, Krakower GR, Kissebah AH. Influence of androgenicity on adipocytes and precursor cells in female rats. Obes Res 1996;4: 463–70.
7. Schuring AN, Schulte N, Sonntag B, Kiesel L. Androgens and insulin – two key players in polycystic ovary syndrome. Recent concepts in the pathophysiology and genetics of polycystic ovary syndrome. Gynakol Geburtshilfliche Rundsch 2008;48:9–15.
8. Norman RJ, Clark AM. Lifestyle factors in the aetioloy and management of polycystic ovary syndrome. In: Kovacs GT, ed, Polycystic ovary syndrome. 1st ed. Cambridge: Cambridge University Press; 2000, pp. 98–116.
9. Kuşçu NK, Var A. Oxidative stress but not endothelial dysfunction exists in non-obese, young group of patients with polycystic ovary syndrome. Acta Obstet Gynecol Scand 2009;88:612–7.
10. Azziz R. Androgen excess is the key element in polycystic ovary syndrome. Fertil Steril 2003;80:252–4.
11. Ehrmann DA, Barnes RB, Rosenfield RL, et al. Prevalence of impaired glucose tolerance and diabetes in women with polycystic ovary syndrome. Diabetes Care 1999;22:141–6.
12. Landay M, Huang A, Azziz R. Degree of hyperinsulinemia, independent of androgen levels, is an important determinant of the severity of hirsutism in PCOS. Fertil Steril 2009;92:643–7.
13. Cheang KI, Baillargeon JP, Essah PA, et al. Insulin-stimulated release of D-chiro-inositol-containing inositolphosphoglycan mediator correlates with insulin sensitivity in women with polycystic ovary syndrome. Metabolism 2008;57:1390–7.
14. Genazzani AD, Lanzoni C, Ricchieri F, Jasonni VM. Myoinositol administration positively affects hyperinsulinemia and hormonal parameters in overweight patients with polycystic ovary syndrome. Gynecol Endocrinol 2008;24:139–44.
15. Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). Hum Reprod 2004;19:41–7.
16. Costantino D, Minozzi G, Minozzi E, Guaraldi C. Metabolic and hormonal effects of myo-inositol in women with polycystic ovary syndrome: a double-blind trial. Eur Rev Med Pharmacol Sci 2009; 13:105–10.
17. Papaleo E, Unfer V, Baillargeon JP, Chiu TT. Contribution of myo-inositol to reproduction. Eur J Obstet Gynecol Reprod Biol 2009; 147:120–3.
18. Nordio M, Proietti E. The combined therapy with myo-inositol and D-chiro-inositol reduces the risk of metabolic disease in PCOS overweight patients compared to myo-inositol supplementation alone. Eur Rev Med Pharmacol Sci 2012;16:575–81.
19. Nestler JE, Jakubowicz DJ, Reamer P, et al. Ovulatory and metabolic effects of D-chiro-inositol in the polycystic ovary syndrome. N Engl J Med 1999;340:1314–20.
20. Iuorno MJ, Jakubowicz DJ, Baillargeon JP, et al. Effects of D-chiroinositol in lean women with the polycystic ovary syndrome. Endocr Pract 2002;8:417–23.