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International Journal of Clinical Practice

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Short-Term Treatment With Myo-Inositol and D-Chiro-Inositol in 40:1 Ratio Significantly Increases the Number of Hyperandrogenic Women With PCOS Who Menstruate With Respect to 3.6:1 Ratio

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Received: 19 January 2026 | **Revised:** 7 August 2026 | **Accepted:** 8 October 2026

Academic Editor: Shweta Negi

Keywords: D-chiro-inositol | inositol ratios | menses | myo-inositol | PCOS

ABSTRACT

Background: Inositol has an established role in the management of patients with polycystic ovary syndrome (PCOS). Two stereoisomers, myo-inositol (MI) and D-chiro-inositol (DCI), are generally employed in a diversity of ratios, although the rationale for choosing one ratio over another is still highly debated. Indeed, a variety of products with different inositol ratios are currently available in the market.

Objective: We intended to compare the efficacy of two formulations, marketed in Italy, containing different inositol ratio—i.e., 40:1 and 3.6:1 MI:DCI.

Methods: We carried out a prospective, open-label, and randomized comparative evaluation of the efficacy of the two formulations in a population of overweight women with hyperandrogenic PCOS. The presence of menstrual cycle was the primary endpoint, assessed through a menstrual cycle diary. Metabolic and hormonal parameters were recorded at baseline and after 3-month treatment.

Results: The number of patients with at least one menstrual cycle significantly increased in the group treated with the 40:1 inositol ratio ($p < 0.05$), while no change was observed in the other group. The difference between the groups at the end of the study was also significant ($p < 0.01$). Free testosterone significantly decreased in patients treated with the 40:1 inositol ratio ($p < 0.001$), accompanied by significant increase in serum SHBG ($p < 0.05$—significance was however lost after conservative adjustment for multiple comparisons). We observed variations in the group treated with 3.6:1 ratio, but they failed to reach significance. Metabolic parameters, instead, significantly improved in both study groups.

Conclusions: The 40:1 inositol ratio proved superior to the 3.6:1 ratio in increasing the number of women who menstruate in the short term and should be the preferred choice when restoring menstrual cycle is the primary aim of the treatment for women with hyperandrogenic PCOS.

Trial Registration: ClinicalTrials.gov identifier: NCT06715527

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1 | Introduction

Polycystic ovary syndrome (PCOS) is a common metabolic endocrinological disorder known to affect 10%–13% of women of reproductive age [1]. The diagnosis of this condition has traditionally been achieved through use of the Rotterdam Criteria, which divides patients into four distinct phenotypes based on the combination of at least two of the following three features: (a) clinical and/or biochemical hyperandrogenism, (b) menstrual irregularity, and (c) polycystic ovarian morphology (PCOM) [2].

Moreover, most patients with PCOS regularly suffer from metabolic comorbidities such as obesity (up to 60%) [3] and insulin resistance (around 70%–75%) [4], which some researchers have lately identified as a leading cause of increased levels of hyperandrogenism, due to the established role of insulin in androgen signaling [5]. Indeed, metabolic alterations are more commonly observed in hyperandrogenic PCOS patients (phenotypes A, B, and C) than in normoandrogenic PCOS patients (phenotype D), demonstrating a crucial link between hyperandrogenism and dysmetabolism.

As a result of an intricate network of physiological alterations underlying the clinical diagnosis of PCOS, patients present higher risk of developing hormonal, reproductive, psychological, and also cardiometabolic comorbidities [6].

Due to metabolic involvement in hyperandrogenic PCOS, it is vital that therapeutic choice considers the multiple facets of the condition, primarily targeting the impaired insulin signaling. While lifestyle changes represent the first-line therapy for patients with PCOS, benefits require strict adherence to dietary restrictions, which are often easily discontinued. Insulin sensitizers, such as metformin or myo-inositol (MI), have thus become a popular alternative treatment for patients with PCOS. In particular, MI proved as effective as metformin, and devoid of gastrointestinal issues [7, 8].

Also, D-chiro-inositol (DCI), a natural stereoisomer of MI, demonstrated insulin-sensitizing effects [9], and supplementation with either isomer has been explored in the past to treat PCOS—though with conflicting results for what DCI is concerned.

However, the insulin-sensitizing characteristics that DCI exerts, even at low doses, have marked the molecule out as an attractive combination with MI for the treatment of PCOS, especially in patients characterized by hyperandrogenism and metabolic alterations. The precise ratio of these two molecules has been a matter of debate, with some authors criticizing the number of formulations available on the market, many of which lack scientific rigor to support their claims [10]. Among previous studies that compared the properties of different inositol ratios, we conducted an open randomized trial, investigating the effect of seven combinations of MI and DCI (0:1, 1:3.5, 2.5:1, 5:1, 20:1, 40:1, and 80:1) in anovulatory patients with PCOS. Following 3 months of treatment, the 40:1 combination was most effective at restoring menstrual regularity, and restoring hormonal and metabolic parameters, while increased concentrations of DCI resulted in a diminished effect [11]. Furthermore, in a recent study of hyperandrogenic women with PCOS, supplementation of 40:1 ratio between MI and DCI for 3 months resulted in significant decrease in body mass index (BMI), insulin resistance (Homeostatic Model Assessment for Insulin Resistance [HOMA-IR]), and androgenic parameters [12].

Another combination, which has demonstrated potential for patients with PCOS, is the 3.6:1, respectively, of MI and DCI. In a randomized controlled trial that included women with PCOS undergoing fertility care, the 3.6:1 combination resulted in significantly higher pregnancy and live birth rates than the respective 40:1 combination, with no change in BMI, testosterone, and HOMA-IR between the two groups [13]. It should be noted this is the only study to date that has compared the two formulations, despite accumulating evidence on the efficacy of either 40:1 or 3.6:1 inositol ratios [14–17], with the latter being increasingly compared to pharmacological treatments [18]. Moreover, these two inositol ratios are frequently used in commercially available supplements that are relevant in the Italian market, causing uncertainty in both physicians and patients about their use in routine clinical practice. Therefore, to interrogate the short-term efficacy of these two supplement regimens in the management of PCOS, we conducted an open-label randomized exploratory study that compares to popular products on the Italian market, containing either 3.6:1 or 40:1 inositol ratio.

2 | Patients and Methods

2.1 | Patients

This study was a prospective, open-label, and randomized comparative evaluation. Women aged 18–45 with diagnosis of hyperandrogenic PCOS according to the Rotterdam Criteria (i.e., with biochemical hyperandrogenism or its clinical manifestations and at least one of the following: [1] oligo- or amenorrhea; [2] sonographic evidence of polycystic ovaries), and with BMI > 24.5 were enrolled at Alma Res Fertility Center, Rome (Italy), between November 2024 and March 2025, and referred to external endocrinological and nutritional consultation.

Obese women (BMI > 29.9), as well as those seeking pregnancy, were excluded. Exclusion criteria also included other conditions causing ovulatory dysfunction (e.g., hypothyroidism or hyperprolactinemia) or androgen excess (e.g., adrenal hyperplasia or Cushing's syndrome), the use of medications or supplements that could potentially influence the regularity of the menstrual cycle, and the intake of any other source of inositol at least 3 months prior to the beginning of the study. All women enrolled were informed regarding the study procedure and provided written informed consent for data collection for research purposes.

2.2 | Study Design

The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki and adhered to the guidelines set by the Committee on Publication Ethics (COPE). The research protocol was reviewed and approved by Alma Res IRB. Upon enrollment, the absence of menstrual cycle was recorded. Moreover, clinical parameters were collected including patient age, BMI, basal levels of insulin and plasma glucose, and levels of free testosterone (FT) and sex hormone-binding globulin (SHBG). Postprandial (120′) levels of insulin and plasma glucose

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were not part of the study outcomes and were collected only at baseline from patients who had these measurements from prior clinical workup.

The participants ($n = 30$) were randomly divided and assigned to one of the treatment groups, namely Group A and Group B. Women in Group A received a dietary supplement containing MI and DCI in 3.6:1 ratio, pomegranate extract, melatonin, folic acid, zinc, iodine, selenium, vitamin D, vitamin E, and vitamins B1, B2, B3, B6, and B12 (Ovosicare, Procare Health Iberia s.r.l.—Valencia, Spain); they were instructed to take two capsules in the evening every day for 3 months (daily amount of inositol = 1.4 g), preferably on an empty stomach.

Women in Group B received a dietary supplement containing MI and DCI in 40:1 ratio, α-lactalbumin and folic acid (Inofolic Combi HP, Lo.Li. Pharma s.r.l.—Rome, Italy); they were instructed to take two soft-gel capsules, one in the morning and one in the evening every day for 3 months (daily amount of inositol ca. 1.13 g), preferably on an empty stomach.

The choice of short-term intervention period is ascribed to two reasons: (1) patients easier fail treatment compliance over longer periods, leading to potential dropouts; (2) the commercially available products used in this study are routinely suggested before IVF protocols, where timing of success may be extremely relevant.

Both groups were evaluated on the day of enrollment (baseline; T0) and after 3 months of treatment (T1). The same clinical parameter recorded at baseline, with the exception of postprandial insulin and serum glucose levels, were assessed at the end of the treatment, and all patients were required to maintain a menstrual cycle diary for the entire course of the study.

The primary outcome was the restoration of the menstrual cycle, defined as the appearance of at least one menstrual cycle within the 3 months of treatment.

Secondary outcomes included the variations of BMI, metabolic parameters (HOMA-IR index, basal levels of insulin and plasma glucose), serum levels of FT and SHBG.

2.3 | Sample Size

Introducing constraints on the presence of menstrual cycle at enrollment would have drastically reduced the inclusion of patients in the study. Therefore, we were unable to anticipate a baseline situation and thus calculate a reliable sample size based on the primary outcome. We opted, instead, to consider the study as an exploratory pilot investigation. Expecting an equal number of patients in the two study arms, recruitment was stopped after planned interim evaluation of data showed statistically significant difference in the primary endpoint between groups.

When we reached 15 participants per group, indeed, data analysis indicated significant difference in the number of women with at least one menstrual cycle between the two groups. We used the data to perform a post hoc sample size evaluation at this point. In particular, the observed difference in the percentage of women with at least one menstrual cycle after 3 months, with respect to baseline, in each group (40% vs. no change) indicated that the numerosity achieved was sufficient to ensure power analysis > 80%, with alpha set at 0.05.

2.4 | Statistical Analysis

For quantitative variables, values at different timepoints in each group were compared using Wilcoxon signed rank test, while values of the two groups at each timepoint were compared using the Mann–Whitney test.

The number of women with menstrual cycle at different timepoints within each group were compared using McNemar's test, while the different number of women who menstruate in the two groups at each timepoint was compared using the chi-square test. Variations in the number of women with menstrual cycle between T0 and T1 in each group were compared and analyzed using the Fisher's exact test.

Statistical analyses were carried out using two-sided distribution with a 0.05 significance level, using SAS (Version 9.4, SAS Institute, Inc., Cary, NC, USA) and GraphPad (GraphPad Prism 8.0.1 Software, La Jolla, CA, USA); values are indicated as mean ± standard deviation. A $p \leq 0.05$ was considered statistically significant.

Adjustment for multiple comparisons was performed for secondary outcomes using the Bonferroni and the Holm–Bonferroni corrections.

3 | Results

3.1 | Baseline Characteristics of Enrolled Patients

A total of 30 women who met the inclusion criteria were enrolled in the study and equally assigned to one of two treatment arms: Group A, formulation containing MI and DCI in 3.6:1 ratio; and Group B, formulation containing 40:1 inositol ratio. Baseline characteristics, including anthropometric data (age and BMI), serum levels of SHBG and FT, and HOMA-IR, as well as basal and 120-min postload insulin and glycemia levels, are reported in Table 1 and show no statistically significant differences between the two groups.

Postload insulin and serum glucose levels were available for 9 of 15 patients in Group B, therefore Mann–Whitney test at baseline was performed using data of 15 patients from Group A and of 9 patients from Group B. All other measurements were available for all participants.

Notably, most of the patients exhibited clinical signs of hyperandrogenism, such as hirsutism and alopecia, while having FT levels within the reference range (0.59–3.98 pg/mL).

3.2 | Number of Women With Menstrual Cycle Following MI:DCI Supplementation

Women with PCOS were evaluated for menstrual cycle following MI:DCI supplementation. At baseline (T0), both groups exhibited a similar number of women with menstrual cycle, with 33.3% ($n = 5/15$) in Group A and 40% ($n = 6/15$) in Group B, and no significant intergroup differences were observed (Figure 1A). After 3-month treatment period (T1), Group A showed no improvement in the number of women with menstrual cycle, maintaining the same percentage as observed at baseline levels (33.3%, $n = 5/15$). In contrast, Group B demonstrated a significant improvement in the number of women with menstrual cycle, with the proportion of women without menstrual cycle

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TABLE 1 | Baseline anthropometric characteristics and serum hormone profile between myo-inositol (MI) to D-chiro-inositol (DCI) ratio: a 3.6:1 (Group A) or a 40:1 (Group B) formulations.

	Group A (3.6:1)		Group B (40:1)		*p*
	Patients (*n*)	**Mean ± SD**	**Patients (*n*)**	**Mean ± SD**	
Age	15	34 ± 12	15	31.4 ± 5.6	ns, $p = 0.85$
BMI (kg/m^2)	15	27.1 ± 1.6	15	27 ± 1.2	ns, $p = 0.92$
HOMA-IR	15	5.4 ± 2.6	15	5.8 ± 1.8	ns, $p = 0.45$
Insulin (basal)	15	18.9 ± 8.7	15	19.5 ± 6.1	ns, $p = 0.62$
Insulin (120 min post-load)	15	58.4 ± 19.7	9	57,8 ± 25.0	ns, $p = 0.43$
Glycemia (basal)	15	114.5 ± 3.6	15	113.4 ± 4.1	ns, $p = 0.42$
Glycemia (120 min postload)	15	104.1 ± 16.0	9	103.8 ± 9.4	ns, $p = 0.42$
FT (pg/mL)	15	1.4 ± 0.3	15	1.2 ± 0.3	ns, $p = 0.07$
SHBG (nmol/L)	15	20.6 ± 2.9	15	25.5 ± 12.5	ns, $p = 0.35$

Note: Values are presented as mean ± standard deviation (SD). Baseline hormone profiles showed no statistically significant differences between Groups A and B. Statistical significance was evaluated using the Mann–Whitney test. HOMA-IR, Homeostatic Model Assessment for Insulin Resistance.
Abbreviations: BMI, body mass index; FT, free testosterone; ns, nonsignificant; SHBG, sex hormone-binding globulin.

decreasing from 60% ($n = 9/15$) at baseline to 20% ($n = 3/15$) at T1 (Figure 1B). Furthermore, intergroup comparison at T1 revealed a significantly lower prevalence in the number of women without menstrual cycle in Group B compared to Group A (Figure 1C). Similarly, significant difference was found by comparing the variations in the number of women with at least one menstrual cycle between T0 and T1 in each group (+40% vs. no change, $p = 0.0169$, Fisher's exact test).

3.3 | MI:DCI in 40:1 Ratio Improves SHBG and FT Levels in Women With Hyperandrogenic PCOS

A significant increase in serum SHBG levels, along with a significant decrease in FT levels, were observed after treatment with 40:1 inositol ratio, but not after treatment with 3.6:1 inositol ratio (Figure 2).

Moreover, significant differences in serum SHBG and FT levels were observed between the two groups after treatment (Figure 3).

3.4 | Adjustment for Multiple Comparisons

Given the number of statistical comparisons performed for the secondary outcomes, we assessed the robustness of findings by applying post hoc corrections for multiple testing. The primary outcome was not subjected to correction, as it represented a single defined endpoint. For the six comparisons involving hormonal parameters (SHBG and FT, within-group and between groups), we applied both the Bonferroni correction ($\alpha = 0.0083$) and the less conservative, sequential Holm–Bonferroni method. The differences in SHBG and FT between groups at T1 (both $p < 0.00001$), as well as within-group increase in FT in Group B ($p = 0.00152$), remained highly significant under both correction methods. Within-group increase in SHBG in Group B ($p = 0.0147$) remained significant under the Holm correction (threshold = 0.0167) but not under the more conservative Bonferroni correction (threshold = 0.0083), indicating that this specific finding should be interpreted with caution, likely considering the limited sample size of this study.

3.5 | Improvement of Metabolic Outcomes Following MI:DCI Supplementation

The effects of combined supplementation with MI and DCI were evaluated after 3-month treatment (T1) in both groups. As reported in Tables 2 and 3, both formulations significantly improved the metabolic outcomes under investigation, without significant difference between the two groups at the end of the treatment period (T1).

4 | Discussion

In this study, we compared the effects of two commercially available supplements containing different ratios of MI and DCI, demonstrating that only the 40:1 ratio restores menstrual cycle in women with PCOS in the short term, while the 3.6:1 ratio fails to do so.

MI and DCI are essential to the physiological processes that take place in the ovaries, and both are popular among dietary supplements for managing PCOS. MI, for instance, has been used for almost two decades to restore ovulation in women with PCOS [19, 20], and its clinical effects—especially in counteracting metabolic alterations [21]—are comparable to those of metformin [7, 22], which is commonly used as off-label treatment for PCOS [23].

Such effects depend on the pivotal role that MI exerts in ovarian physiology, serving as an intracellular second messenger of FSH [24]. Its signaling ensures follicle growth and maturation by promoting the expression of aromatase enzyme in the granulosa cells [25], thus supporting the biosynthesis of estradiol and the physiological selection of the dominant follicle.

On the contrary, specific applications of DCI were until recently far less investigated [26], and its clinical effects perceived comparable to those of MI. The understanding of individual properties of both isomers is only of more recent knowledge, driven by the discovery of defined MI:DCI ratios in organs and tissues with different metabolic activities [27], which suggested specific and well-defined roles for the two. Further evidence came when researchers found lower MI:DCI ratios in thecal cells

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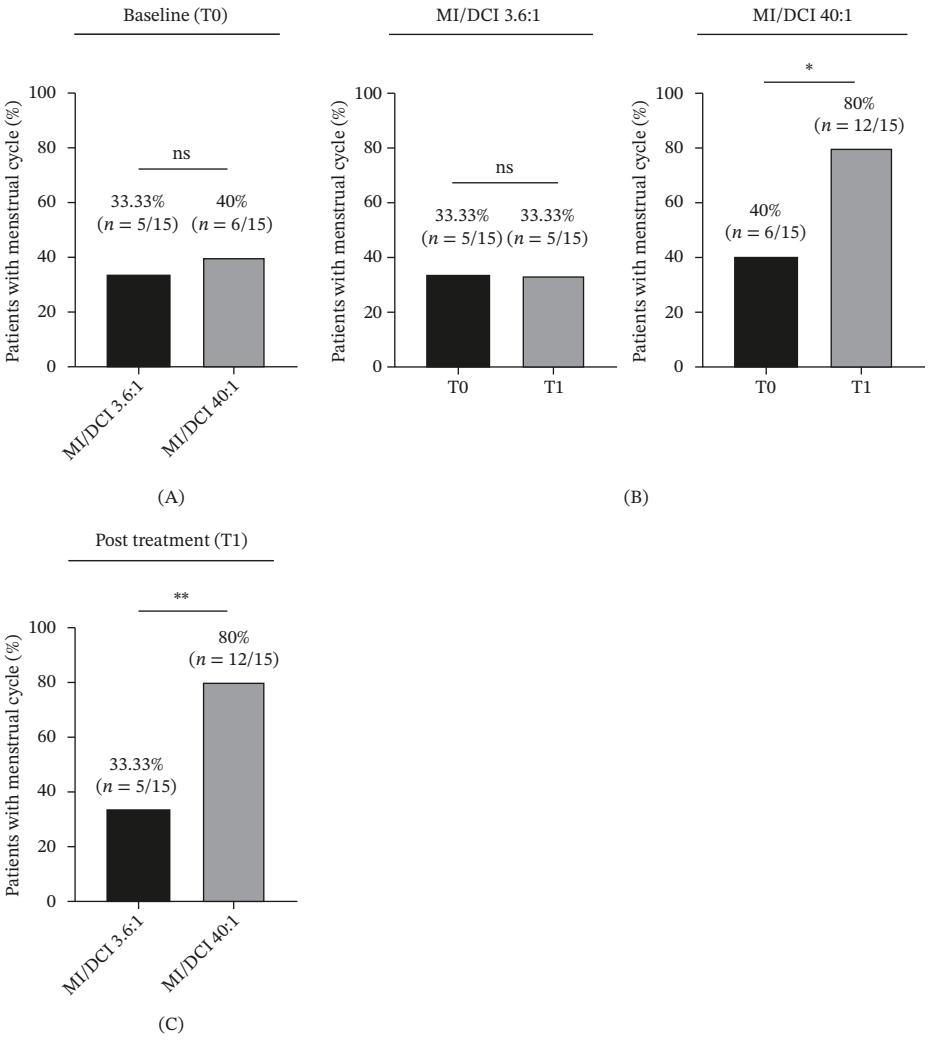


FIGURE 1 | Percentage of women with menstrual cycle following MI:DCI supplementation. (A) Baseline (T0) comparison between groups; (B) comparison between T0 and T1 for each group; (C) comparison at T1 between groups. Percentage of women with menstrual cycle is relative to the total number of participants in each group at both timepoints. Changes within groups from T0 to T1 were analyzed using McNemar's test, while differences between groups at T0 and T1 were analyzed using the chi-square test. Statistically significant differences are indicated as $^{*}p < 0.05$; $^{**}p < 0.01$.

from the ovaries of patients with PCOS [28], and higher DCI content in the follicular fluid of lower quality oocytes, retrieved during IVF protocols [29].

As originally suggested by the work of Larner, the role of DCI in ovarian physiology is likely related to insulin signaling [9]. Indeed, by enhancing insulin sensitivity, DCI promotes the production of androgens from thecal cells in the ovaries [30], thus becoming central to ovarian physiology.

However, subsequent research proved that DCI also reduces the gene expression of aromatase in a dose-dependent manner [31, 32], regulating ovarian steroidogenesis in a more complex fashion.

Understanding what MI and DCI do at the molecular level in the ovaries was crucial to determine their therapeutic usage, and this is particularly relevant in the case of DCI, which exhibits dual behavior depending on the specific case and conditions.

Earlier reports by the group of Nestler, indeed, described that DCI supplementation to insulin-resistant women with PCOS was able to restore ovulation in 6 to 8 weeks [33]. Response to treatment was associated with a reduction in blood testosterone levels, due to decreased insulin stimulus, independently of BMI [34]. However, supplementation with higher dosages seems to favor the downregulation of aromatase, drowning out the metabolic effect on insulin sensitivity [35, 36].

On these bases, a specific MI:DCI ratio should be selected according to the desired clinical outcome, and considering the characteristics of patients and the pathological alterations. Our findings reinforced previous evidence that in the case of PCOS [11, 37], especially if insulin resistance is present, combinations of MI and DCI that reflect the average plasma ratio of 40:1 are more effective than the others.

This study also confirms that the 40:1 ratio significantly increased SHBG values with respect to ratios with higher content of DCI, resulting in a significant decrease of FT levels in the serum. Both MI alone and the 40:1 MI:DCI ratio already proved effective in ameliorating androgen status in patients with PCOS, but only after 6-month treatment [18, 38, 39]. To the best of our knowledge, besides our previous study [11], only one more recent clinical trial reported that 40:1 inositol ratio significantly reduces

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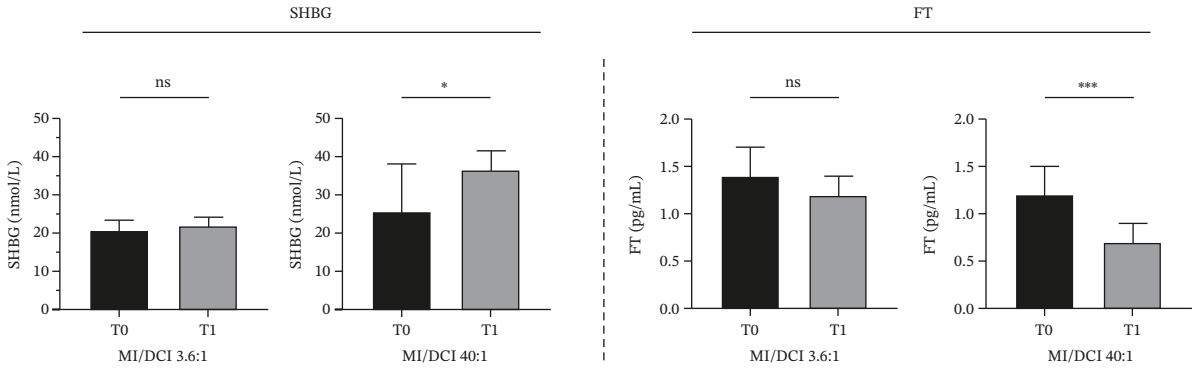


FIGURE 2 | Effects of MI:DCI supplementation on sex hormone-binding globulin (SHBG) and free testosterone (FT) levels in both study groups. Serum hormone levels were assessed at baseline (T0) and after 3 months of treatment (T1) in both Groups A and B. Data are presented as mean ± standard deviation (SD). Differences between T0 and T1 within each group were analyzed using the Wilcoxon signed rank test. Significant changes are indicated as $^{*}p < 0.05$; $^{***}p < 0.001$. Abbreviations: SHBG, sex hormone-binding globulin; FT, free testosterone, MI, myo-inositol; DCI, D-chiro-inositol.

Free Androgen Index—defined as FAI (%): [total testosterone/SHBG] ∗ 100—after 3-month supplementation [11]. In both cases, most of the included patients exhibited biochemical hyperandrogenism, with either an average value of FT > 1.5 ng/dL or FAI > 4.5.

The observation that 40:1 inositol ratio reduces testosterone levels also in our study, where most of patients had FT levels within the reference range, is particularly relevant, also given the short time of treatment.

In general, fast response to treatments is crucial because compliance decreases with increasing therapy duration [40]; this is even more important in the case of PCOS, where most patients search for medical support after unsuccessfully seeking pregnancy.

In line with our previous results, we found that the formulation containing the 40:1 inositol ratio significantly improved the number of women who menstruate after 3 months, while the other inositol ratio fails to exert appreciable efficacy in such short time, strengthening the idea that the choice of proper inositol ratio is paramount to restore the correct ovarian physiology.

To fully rationalize the observed superiority of the 40:1 inositol ratio with respect to the other ratio under investigation, some more comprehensive aspects should be considered, including other ingredients and the pharmaceutical form of the two commercially available formulations.

The product with 40:1 inositol ratio also contains α-lactalbumin, which is known to increase the passive absorption of both MI and DCI in the intestine. Indeed, in vitro experiments with Caco-2 cells, mimicking gut epithelium, demonstrated that active peptides from α-lactalbumin acidic digestion can regulate the opening kinetics of the tight junctions between intestinal cells, increasing their permeability to inositol. The study also confirmed such effect in vivo with the concomitant administration of MI and α-lactalbumin to healthy volunteers, which resulted in higher plasma concentration of inositol with respect to the administration of the sole inositol [41]. MI, as well as DCI, has specific intestinal transporters called sodium/MI cotransporters (SMIT), which seem to be downregulated in certain individuals, causing the so-called phenomenon of *inositol resistance*. Montanino and coworkers later demonstrated that the association with α-lactalbumin also overcomes inositol resistance. In their study, the investigators reported that 86% of women that were unresponsive to MI ovulated after 3-month treatment with the combination of MI and α-lactalbumin [42], raising the global efficacy to 95% of women included in the study. It is important to notice that the results reported in this article do not reflect precisely the different effects of two inositol ratios, rather those of two structured formulations, including ancillary components that potentially affect the outcomes under investigation.

On the other hand, the product containing the 3.6:1 inositol ratio has a complex formulation, including melatonin, botanical extracts, and several vitamins and minerals. All these components concur to counteract local and systemic oxidative stress, which is known to be involved in the etiopathogenesis of PCOS [43], and their contribution must also be considered when evaluating the clinical effect of the supplementation. Among them, melatonin exerts specific roles in regulating ovarian physiology and is being investigated within assisted reproduction protocols to improve in vitro fertilization outcomes [44]. From a mechanistic perspective, melatonin indeed proved to promote communication between developing oocytes and somatic granulosa cells and helps favoring intracellular antioxidant environment [45]; moreover, the activity of melatonin in stabilizing circadian rhythms has direct effect on the well-being of female reproductive organs [46].

Further mechanistic implications can be inferred from recent evidence correlating increased oxidative stress within the follicular microenvironment with higher concentrations of anti-Müllerian hormone (AMH) [47], which is frequently elevated in women with PCOS and endocrine-metabolic alterations [48, 49], and suggested as diagnostic biomarker of the syndrome [50]. Because interventions in both study groups significantly improved metabolic parameters, increased insulin sensitivity is unlikely to rationalize the difference observed in the number of women who menstruated. Direct effect of the two inositol ratios —or, rather, of the two formulations tested in this study—on local AMH levels that improves ovarian physiology in a different manner is an interesting hypothesis, and future investigations should include measurement of circulating AMH levels. Trials

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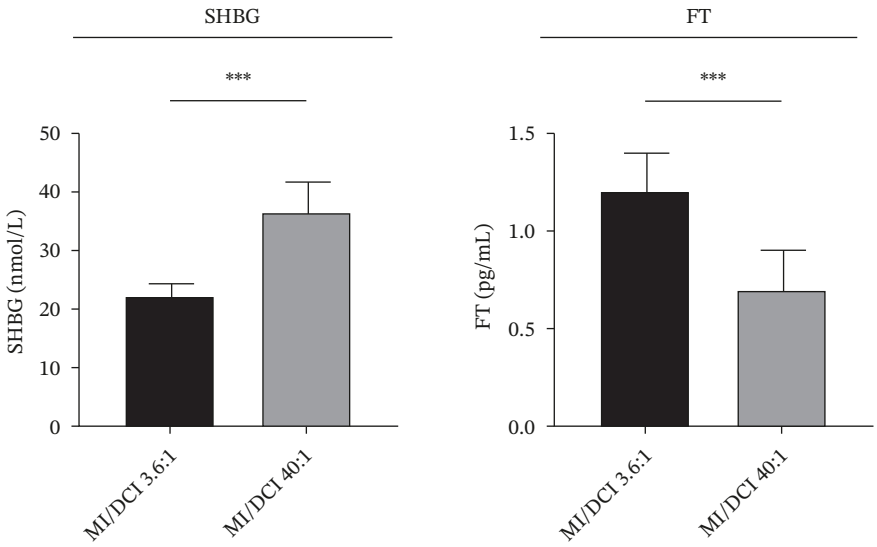


FIGURE 3 | Comparison of serum SHBG and FT levels between the study groups at the end of the treatment period (T1). Serum hormone levels were assessed after 3 months of treatment (T1) in both groups. Data are presented as mean ± standard deviation (SD). Differences between groups were analyzed using the Mann–Whitney test. Statistically significant differences are indicated as $^{***}p < 0.001$. Abbreviations: SHBG, sex hormone-binding globulin; FT, free testosterone; MI, myo-inositol; DCI, D-chiro-inositol.

TABLE 2 | Improvement of the metabolic outcomes after treatment with myo-inositol (MI) and D-chiro-inositol (DCI) in 3.6:1 ratio (Group A).

Group A (3.6:1)	Patients (*n*)	Baseline (T0) Mean ± SD	Patients (*n*)	Post treatment (T1) Mean ± SD	*p*
BMI (kg/m^2)	15	27.1 ± 1.6	15	25.8 ± 1.7	***0.00064
HOMA-IR	15	5.4 ± 2.6	15	2.7 ± 1.1	***0.00064
Basal insulin	15	18.9 ± 8.7	15	10.5 ± 3.9	***0.00064
Basal glycemia	15	114.5 ± 3.6	15	103.5 ± 7.2	***0.00096

Note: All values are reported as mean ± standard deviation (SD). Statistical significance was evaluated using Wilcoxon signed rank test. Significant differences between baseline (T0) and the end of treatment (T1) are indicated as $^{***}p < 0.001$. HOMA-IR, Homeostatic Model Assessment for Insulin Resistance.
Abbreviations: BMI, body mass index; ns, nonsignificant.

TABLE 3 | Improvement of the metabolic outcomes after treatment with myo-inositol (MI) and D-chiro-inositol (DCI) in 40:1 ratio (Group B).

Group B (40:1)	Patients (*n*)	Baseline (T0) Mean ± SD	Patients (*n*)	Post treatment (T1) Mean ± SD	*p*
BMI (kg/m^2)	15	27.0 ± 1.2	15	25.1 ± 1.3	***0.00064
HOMA-IR	15	5.8 ± 1.8	15	3.1 ± 1.3	***0.00064
Basal insulin	15	19.5 ± 6.1	15	12.5 ± 5.0	***0.001
Basal glycemia	15	113.4 ± 4.1	15	100.7 ± 4.5	***0.00064

Note: All values are reported as mean ± standard deviation (SD). Statistical significance was evaluated using Wilcoxon signed rank test. Significant differences between baseline (T0) and the end of treatment (T1) are indicated as $^{***}p < 0.001$. HOMA-IR, Homeostatic Model Assessment for Insulin Resistance.
Abbreviations: BMI, body mass index; ns, nonsignificant.

including women with PCOS undergoing in vitro fertilization procedures would allow evaluation of follicular concentration of AMH and be even more informative.

The different pharmaceutical forms of the two supplements that we tested may also play a role. While the commercial product containing the 3.6:1 inositol ratio comes in tablets, the product with the 40:1 ratio comes as soft-gel capsules. Such technology enhances the bioavailability of certain active molecules [51], including melatonin and inositol [52, 53]. In particular, delivery in soft-gel capsules proved to elevate the plasma concentration of inositol of about three times with respect to powder intake [53], with administration of 1.2 g as soft-gel exhibiting comparable absorption profile to 4 g in powder form over 24 h. Pharmacokinetic data indicates the absence of significant differences in maximum plasma concentration (C_{max}), time to peak concentration (T_{max}), and area under the curve (AUC), suggesting that bioavailability of the formulation in soft-gel capsules in this study

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is much greater than the other formulation, despite similar amounts of inositol.

As for metabolic alterations, we found that inositol intervention is generally beneficial for the management of patients with PCOS, regardless of the ratio. Specifically, both formulations used in this study proved to ameliorate the metabolic profile of the participants included. Indeed, with respect to baseline values, supplementation of inositol led to reduced HOMA-IR index, basal glycemia, and insulin levels. This is in accordance with our previous findings that different inositol ratios give positive response on the metabolic profile of patients with PCOS [11].

The observation that BMI significantly decreases in both study groups after 3 months of inositol treatment was less expected, instead, and in contrast with previous evidence.

One likely explanation may reside in the baseline values of BMI. While in our previous studies they were in the normal range, in this case, patients in both groups were overweight, with an average BMI > 27 (Table 1). Support to this hypothesis comes from a recent study that investigated the clinical benefits of supplementation with MI:DCI in 40:1 ratio to patients with PCOS of phenotype A. The authors observed a significant reduction in BMI after 3 months, but the majority of patients were either overweight or obese, with an average baseline BMI > 33 [12].

We need to point out that all patients were advised to adopt healthy lifestyle habits, such as balanced diet and moderate physical activity, but they were not prescribed any calorie-restrictive plan to follow. Although patients reported no relevant changes in their lifestyle habits during the observation period, the absence of controlled dietary routine is a limitation of this study, and in general, for studies that investigate treatments for PCOS. Despite lifestyle adjustments being recommended as first-line approach to treat PCOS [50, 54], tight control over life habits of patients is quite complicated to achieve, leaving this type of studies with a certain degree of bias that might be only mitigated by increasing the sample size.

Even though we cannot rule out that uncontrolled lifestyle habits influence the observed reduction of BMI, concealing differences between different inositol ratios, the known effect of inositol combinations on glucose metabolism, and insulin sensitivity unquestionably leads to reduced energy storage as adipose tissue [55] and thus helps to counteract weight gain.

4.1 | Study Limitations and Future Directions

Given its design and lack of sufficient background information, the study remains of exploratory nature, and the findings should be cautiously interpreted considering the limited sample size before deriving any general conclusion. The presented results, however, do provide preliminary evidence to devise future studies with more precise power calculation and more rigorous architecture. Indeed, even though we deem that placebo effect is negligible considering the outcomes investigated, double-blinded studies controlled with placebo would avoid potential biases that an open-label study brings about. Moreover, we need to point out that the results of this study pertain to short-term effects of supplementation, as discussed previously, and no information regarding long-term outcomes can be inferred unless dedicated studies are carried out.

5 | Conclusion

The results of this study support the beneficial role of inositol supplementation in improving the metabolic profile of overweight women with hyperandrogenic PCOS, especially when the treatment is associated with lifestyle adjustments.

The choice of the correct inositol ratio seems, however, paramount to restore menstrual cycle in a timely manner. This aspect is a critical factor for certain types of patients, including infertile women who are trying to conceive without resorting to IVF programs.

By comparing the efficacy of two different inositol-based formulations available on the Italian market, our investigation highlights that the 40:1 MI:DCI ratio significantly increases the number of patients with menstrual cycle within 3-month treatment; on the contrary, the 3.6:1 ratio exhibits no effect. Such difference is likely ascribed to concurring factors. While the 3.6:1 ratio lacks rationale, the 40:1 ratio corresponds to the average ratio found in human blood. Moreover, pharmaceutical forms and the presence of other ingredients influenced the clinical results observed. The commercial supplement with the 40:1 ratio comes as soft gelatin capsules and contains α-lactalbumin, which are known to increase bioavailability, and thus efficacy, of inositol.

Given the multitude of marketed products containing a diversity of inositol ratios, guided choices are necessary. Our results lay the basis for designing adequately powered comparative studies, possibly including placebo control, to confirm these preliminary findings, and add scientific evidence that may help doctors to better tailor the treatment for patients with PCOS.

Author Contributions

Conceptualization and writing–original draft preparation: Maurizio Nordio and Cesare Aragona. Methodology, formal analysis, investigation, and writing–review and editing: Maurizio Nordio, Sabrina Basciani, Gabriele Bilotta, and Cesare Aragona. Supervision: Maurizio Nordio.

Acknowledgments

We thank Dr. Orietta Picconi for the priceless support with statistical analysis.

Funding

This research received no external funding. The APC is covered by Lo.Li. Pharma s.r.l.

Ethics Statement

The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki and adhered to the guidelines set by the Committee on Publication Ethics (COPE). The research protocol was reviewed and approved by Alma Res IRB.

Consent

All participants were informed regarding the study procedure and provided written informed consent for data collection for research purposes.

Conflicts of Interest

The authors declare no conflicts of interest.

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Data Availability Statement

The data presented in this study are available upon reasonable request from the corresponding author due to privacy protection and patient confidentiality.

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