Research Article

COMPARATIVE EFFECTS OF COMBINED INOSITOLS AND ALPHA-LIPOIC ACID (ALA) ON METABOLIC, HORMONAL, AND CLINICAL OUTCOMES IN OBESE HYPERINSULINEMIC WOMEN WITH POLYENDOCRINE METABOLIC OVARIAN SYNDROME (PCOS/PMOS): THE IMPACT OF FAMILY HISTORY OF DIABETES

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ABSTRACT

Background: Polyendocrine Metabolic Ovarian Syndrome (PCOS/PMOS) represents a complex metabolic-endocrine disorder in obese, hyperinsulinemic, and insulin-resistant women with a family history of diabetes. Myo-inositol (MI) and D-chiro-inositol (DCI) act as insulin-sensitizing agents, while alpha-lipoic acid (ALA) may provide additional metabolic benefits. However, comparative evidence regarding their combined effects in this high-risk population remains limited. Objective of the article is to compare the metabolic, hormonal, and clinical effects of MI, MI+DCI, and MI+DCI+ALA in obese, hyperinsulinemic women with PCOS/PMOS and a family history of diabetes.

Methods: In this randomized, double-blind, parallel-group clinical trial, 96 women aged 20–38 years with obesity (BMI ≥30 kg/m²), Rotterdam criteria-defined PCOS/PMOS, hyperinsulinemia, and insulin resistance were randomized to control, MI, MI+DCI (40:1), or MI+DCI+ALA groups. Participants were evaluated at baseline and after 12 and 24 weeks. Metabolic, hormonal, and clinical parameters, including insulin sensitivity, glucose metabolism, androgen status, lipid profile, anthropometric measures, and menstrual regularity, were assessed.

Results: After 24 weeks, all three treatment groups demonstrated improvements in metabolic and hormonal parameters compared with controls. The MI+DCI combination produced greater improvements in insulin resistance and glucose metabolism than MI alone, while the addition of ALA resulted in further improvement. Androgen levels decreased, and SHBG increased, accompanied by improved gonadotropin balance. Menstrual regularity was restored most frequently with MI+DCI+ALA, followed by MI+DCI and MI alone. Anthropometric and lipid parameters also improved, with the most pronounced overall metabolic effects observed with the triple combination. Improvements in hepatic insulin extraction and liver-related parameters were particularly evident following ALA addition.

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Conclusions: In obese women with PCOS/PMOS, hyperinsulinemia, insulin resistance and a family history of diabetes, MI+DCI supplementation was associated with greater metabolic, hormonal and clinical benefits than MI alone, while the addition of ALA provided further improvement across key metabolic outcomes. These findings support the potential role of combined inositol and ALA therapy in managing PCOS/PMOS phenotypes characterized by increased metabolic risk.

Keywords: alpha-lipoic acid; D-chiro-inositol; hyperinsulinemia; inositols; insulin resistance; metabolic risk; myo-inositol; PCOS; PMOS.

Introduction

Polyendocrine Metabolic Ovarian syndrome (PCOS/PMOS) is a significant public health issue with endocrine, reproductive, cardiometabolic, dermatologic, and psychological features. PCOS/PMOS is one of the most common conditions affecting around 10% of reproductive aged women, 1-5, with many remaining undiagnosed.[1,2]

While its causal origins remain incompletely understood, accumulating evidence suggests metabolic dysfunctions – manifested by insulin resistance, obesity, hyperglycemia, and dyslipidemia – as key contributors to the pathogenesis and progression of PCOS/PMOS.3 Hyperinsulinemia and insulin resistance affect 50 to 80% of women with Polyendocrine Metabolic Ovarian syndrome (PCOS/PMOS), depending on different populations, ethnicities, and diagnostic methods. These metabolic abnormalities are more prevalent in overweight-obese women, even if exaggerated circulating insulin levels and reduced insulin-mediated glucose metabolism are also found in up to 40% of nonobese subjects.[3,4]

Polyendocrine Metabolic Ovarian syndrome (PCOS/PMOS) is a complex metabolic-endocrine disorder in obese, hyperinsulinemic, and insulin-resistant (IR) women with a family history of diabetes.[5]

The inositol stereoisomers – Myo-inositol (MI) and D-chiro-inositol (DCI) act as insulin sensitizers.6 Inositols support the intracellular formation of insulin second messengers: phospho-myo-inositol-3-phosphate (PIP3) and inositolphosphoglycan (IPG).[7,8]

The tissue-specific MI/DCI ratio depends on the activity of epimerase, the enzyme deputed to transform MI into DCI. Epimerase activity is stimulated by insulin and is reduced in the presence of insulin resistance. In the ovaries, which are insulin-sensitive, the physiologic MI/DCI ratio should be 100:1. In hyperinsulinemic women with PCOS/PMOS, the enzymatic epimerase activity is enhanced in the gonad, thus leading to a lower MI/DCI ratio at this level.[8]

The imbalance in the inositol pathway inside the ovary is believed to play a role in the ovulatory dysfunction of PCOS/PMOS. Therefore, during the past decades, oral nutritional supplementation with MI has been proposed as a novel therapy in these women. The treatment was reported to enhance insulin sensitivity and improve the clinical and hormonal characteristics of patients with PCOS/PMOS.[7,8]

The Cochrane review found evidence that DCI may improve ovulation rate in the syndrome. There was no conclusive evidence that DCI affected BMI, WHR, or blood pressure, or hormonal parameters, except for serum SHBG levels, fasting glucose, fasting insulin, and lipids (total cholesterol and triglycerides). Given the lack of strong evidence, the new international guideline

offers cautious recommendations regarding the use of inositols: inositol (in any form) should currently be considered an experimental therapy for PCOS/PMOS, with emerging evidence of efficacy that highlights the need for further research.[7-9]

Recently, attention has also been focused on the role of Alpha-lipoic Acid (ALA), which shows additional benefits on glucose metabolism and oxidative balance. Alpha-lipoic acid (ALA), a biological antioxidant and a natural cofactor of mitochondrial dehydrogenase complexes, was originally investigated in patients with type 2 diabetes because of the close relationship between oxidative stress and insulin resistance.[10]

There is a growing body of evidence that ALA may act indirectly to maintain cellular antioxidant status by either inducing the uptake or enhancing the synthesis of endogenous low-molecular-weight antioxidants or antioxidant enzymes. Several studies have suggested that oral supplementation with ALA may improve insulin sensitivity in peripheral tissues and help maintain glycemic control in patients with diabetes mellitus.10 The hypothesized mechanism of action relies on stimulation of glucose uptake via intracellular redistribution of GLUT1 and GLUT4 transporters.[11]

Oxidative stress is now recognized to play a central role in the pathophysiology of many different disorders;[12] among them is increased in women with Polyendocrine Metabolic Ovarian Syndrome, because of an increased production of free radicals associated with impaired plasma total antioxidant capacity (TAC) in both obese and normal-weight PCOS/PMOS women.[13-15]

The increased oxidant status could participate in the onset and maintenance of insulin resistance in these patients.[16]

However, evidence directly comparing the relative effectiveness of MI alone versus MI+DCI and MI+DCI+ALA combinations in these high-risk groups has remained limited.[17-21]

Our study aimed to evaluate the comparative effects of myo-inositol (MI) and D-chiro-inositol (DCI), combined with alpha-lipoic acid (ALA), on metabolic, hormonal, and clinical outcomes in obese women with Polyendocrine Metabolic Ovarian Syndrome (PCOS/PMOS), focusing on the impact of a family history of diabetes.

Methods

A randomized, double-blind, parallel-group clinical trial involving 96 obese patients (BMI≥30 kg/m², age: 20- 38 years) with confirmed PCOS/PMOS according to the Rotterdam criteria, who had hyperinsulinemia and insulin resistance (IR) and a family history of diabetes (type 1 or type 2 diabetes). Subjects participating in the study, after informed consent, were randomly assigned to four main groups: (1) control (n=22), (2) MI 4 g/day (n=25), (3) MI + DCI (40:1 ratio; n=25), and (4) MI + DCI (40:1 ratio) + ALA 600 mg/day (n=24). Patients were assessed at baseline and at 12 and 24 weeks after the start of treatment.

Study participants underwent ultrasound scanning on days 3- 6 of menstrual bleeding. Target parameters for evaluation included the hormonal profile, OGTT, HOMA-IR, hepatic insulin extraction (HIE) index, lipid profile, BMI, hip circumference, and assessment of menstrual cycle regularity.

Results

After 24 weeks, all three study groups, in addition to the control group, showed significant metabolic and hormonal improvements. However, the MI+DCI group showed a significant decrease in HOMA-IR and 2-hour OGTT glucose levels, with further improvement in the MI+DCI+ALA combination group.

Group:	HOMA – IR (Baseline)	HOMA-IR (12 weeks)	HOMA-IR (24 weeks)
Control	5.8	5.7	5.6
MI	5.9	4.9	4.5
MI+DCI	6.0	4.3	3.6
MI+DCI+ALA	6.1	3.9	2.9

Group:	2-hour OGTT glucose mg/dL – baseline	HOMA-IR (12 weeks)	HOMA-IR (24 weeks)
Control	168	166	165
MI	170	162	150
MI+DCI	172	150	135
MI+DCI+ALA	175	135	122

After 24 weeks, Hepatic insulin metabolism is significantly improved only in the triple combination. (MI+DCI+ALA) group.

Group:	HIE Baseline	HIE 12 weeks	HIE 24 weeks
Control	0.42	0.41	0.43
MI	0.41	0.45	0.48
MI+DCI	0.40	0.48	0.52
MI+DCI+ALA	0.40	0.52	0.60

In these groups, levels of common testosterone, androstenedione, and DHEAs decreased, while SHBG increased, leading to greater normalization of the LH/FSH ratio.

Parameters at Baseline and after 24 weeks:	Control	MI	MI+DCI	MI+DCI+ALA
TT (ng/dL)	78 → 76	80 → 65	82 → 54	84 → 48
Androstenedione (mg/mL)	3.9 → 3.8	4.0 → 3.2	4.1 → 2.7	4.2 → 2.3
DHEAs (µg/dL)	360 → 355	370 → 320	375 → 290	370 → 260
SHBG (nmol/L)	28 → 29	27 → 38	26 →46	25 → 55

Group:	LH/FSH Ratio (Baseline)	LH/FSH Ratio (24 weeks)
Control	2.4	2.3
MI	2.5	1.9
MI+DCI	2.6	1.4
MI+DCI+ALA	2.7	1.2

The menstrual cycle was restored in 68% of the triple combination patients, in 64% of the inositols combination recipients, in 42% of the recipients of Myo-inositol, and in 18% of the control group.

Group:	The menstrual cycle restoration rate (%): 24 weeks
Control	18%
MI	42%
MI+DCI	64%
MI+DCI+ALA	68%

BMI, hip circumference, and lipid parameters improved with the same level of compliance in both the MI-only and MI+DCI combination groups, with no changes in liver enzymes or HIE; the latter parameters improved significantly in recipients of the triple combination. The dynamics of BMI and hip circumference also decreased accordingly.

Group:	BMI Baseline	BMI 12 weeks	BMI 24 weeks
Control	33.8	33.6	33.6
MI	33.9	33.1	32.9
MI+DCI	34.1	32.7	31.6
MI+DCI+ALA	34.2	31.9	30.3

Group:	hip circumference (cm) Baseline	hip circumference (cm) at 24 weeks
Control	112	111
MI	113	108
MI+DCI	114	105
MI+DCI+ALA	114	102

Key Findings

The combination of MI + DCI + ALA showed the strongest and most comprehensive effect in PCOS patients with obesity, insulin resistance, and familial diabetes risk, because it simultaneously improves Insulin sensitivity – Maximal reduction in HOMA-IR and 2-hour OGTT glucose; hepatic insulin metabolism – Significant improvement in hepatic insulin extraction (HIE); an-

drogen profile – Sharp decrease in androgens (TT, A4, DHEAS) and increase in SHBG; normalization of the LH/ FSH ratio; reduction in BMI and central adiposity; menstrual function - Highest frequency of menstrual cycle restoration.

Conclusions

Our study results support the evidence that the combined use of myo-inositol, D-chiro-inositol (40:1 ratio) and alpha-lipoic acid provides better metabolic, hormonal and clinical outcomes in obese PCOS/PMOS patients with hyperinsulinemia and insulin resistance (IR) and familial risk for diabetes, suggesting a preferential role for combination therapy in PCOS/PMOS phenotypes with high metabolic risk.

In the polyendocrine metabolic ovarian syndrome phenotype with high metabolic risk (family history of diabetes), the triple combination is the preferred therapeutic choice. However, further long-term and large-scale clinical studies are necessary to obtain more precise results, which will significantly improve therapeutic care strategies in high-risk PCOS/PMOS patients.

Declarations

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Conflict of Interest: The authors declare no competing interests.

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