

ORIGINAL ARTICLE

Combined treatment with L-Glutathione, D-Chiro-Inositol, Myo-inositol and N-Acetylcysteine reduces insulin resistance in overweight/obese patients with polycystic ovary syndrome

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Abstract

Background

Polycystic ovary syndrome (PCOS) is a common endocrine-metabolic disorder frequently associated with insulin resistance and increased cardiometabolic risk.

Objective

To evaluate the effects of combined supplementation with L-glutathione, D-chiro-inositol, Myo-inositol, and N-acetylcysteine on metabolic and hepatic insulin-related parameters in overweight/obese women with PCOS.

Methods

Over 12 weeks, a total of 32 overweight/obese women with PCOS (mean BMI 30.72 ± 0.96 kg/m²) received daily oral integrative therapy comprising reduced L-glutathione (50 mg), D-chiro-inositol (500 mg), Myo-inositol (100 mg), and N-acetylcysteine (150 mg). The patients had received no hormonal or insulin-sensitizing treatments during the prior six months. Clinical and laboratory assessments were conducted before and after treatment, evaluating hormonal parameters during the follicular phase, as well as fasting glucose, insulin, C-peptide, Homeostatic Model Assessment for Insulin Resistance (HOMA-IR), and the Hepatic Insulin Extraction index (calculated as insulin/C-peptide).

Results

After 12 weeks, significant reductions were observed in fasting glucose, fasting insulin, Homeostatic Model Assessment for Insulin Resistance (from 3.24 ± 0.31 to 2.23 ± 0.32 ; $p=0.02$), and the Hepatic Insulin Extraction index (from 5.78 ± 0.35 to 4.94 ± 0.44 ; $p=0.006$). No changes were observed in C-peptide levels. Subgroup analysis showed that these improvements remained significant in patients with a first-degree family history of type 2 diabetes mellitus, but not in patients without such a history.

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Conclusions

Combined supplementation with L-glutathione, D-chiro-inositol, Myo-inositol, and N-acetylcysteine was associated with reductions in insulin resistance markers in overweight/obese women with PCOS, especially among those with a family history of diabetes. L-glutathione and N-acetylcysteine, through their antioxidant effects, may improve insulin-degrading enzyme expression and activity in the liver, thereby increasing hepatic insulin clearance and reducing compensatory hyperinsulinemia and insulin resistance.

Keywords: Polycystic ovary syndrome, insulin resistance, combined treatment, hepatic insulin clearance, oxidative stress, obesity.

Introduction

Polycystic ovary syndrome (PCOS) is a condition affecting 6% to 20% of women of reproductive age [1-2]. Insulin resistance, although not included among the diagnostic criteria, has been identified as strongly associated with PCOS [3-5]. Clinically, insulin resistance is characterized by compensatory hyperinsulinemia, as the body requires disproportionately high insulin concentrations to elicit an appropriate metabolic response to a glucose load [3,6]. This can be due to reduced sensitivity of peripheral tissues and/or altered receptor signaling caused, for example, by impaired epimerase expression, which converts myo-inositol to D-chiro-inositol, thus affecting glucose internalization in cells, typically in PCOS patients with familial diabetes [7-9]. This condition contributes to metabolic dysfunction, increases androgen secretion, and consequently exacerbates the syndrome [3]. Moreover, it is closely linked to overweight and obesity and confers an elevated risk of developing type 2 diabetes, hypertension, and dyslipidemia [10]. Being present in up to 50-70% of obese women with PCOS and in 15-30% of women with PCOS of normal weight [5], insulin resistance has become an important factor to assess, not only because of its association with metabolic syndrome [11] but also because of its link to other diseases, such as metabolic dysfunction-associated steatotic liver disease, which includes steatohepatitis and its more severe inflammatory form, metabolic dysfunction-associated steatohepatitis [12-14]. Metabolic dysfunction-associated steatotic liver disease is strongly related to insulin resistance and predisposes individuals to severe liver diseases [13-15]. The prevalence of metabolic dysfunction-associated steatotic liver disease is between 34% and 70% in patients with a concomitant diagnosis of PCOS, which is higher than that in the general population (14-34%) [15-16].

To prevent the progression of metabolic disturbances associated with PCOS into more severe conditions, it is crucial to implement a comprehensive management plan that starts with lifestyle modification, encompassing a balanced diet, regular physical activity, and weight management. When lifestyle interventions are insufficient, additional pharmacological approaches may be warranted. The 2023 recommendations have introduced additional drugs for the management of PCOS, with a focus on weight loss and metabolic improvement. These include medications such as metformin or anti-obesity drugs such as liraglutide, semaglutide, and orlistat. However, common adverse effects of these drugs, often gastrointestinal in nature (such as nausea, vomiting, and diarrhoea), can lead to poor treatment compliance [17]. To avoid these adverse symptoms, many integrative therapies such as Myo-inositol, D-chiro-inositol [7-8,18-20], L-glutathione, and N-Acetylcysteine [21], used alone or in various combinations, have been studied and have shown excellent results in managing insulin resistance and improving the metabolic profile in PCOS patients [18,22-23]. This study aimed to investigate the effects of an integrative oral combination of L-glutathione (50 mg), D-chiro-inositol (500 mg), Myo-inositol (100 mg), and N-Acetylcysteine (150 mg) in a population of overweight or obese women with PCOS.

Methods

Study design and participants

From the records of the Gynecological Endocrinology outpatient clinic at the University of Modena and Reggio Emilia (Modena, Italy), we identified 32 overweight or obese women with a diagnosis of PCOS who had been evaluated between January 2022 and April 2024 and did not require hormonal therapy. Among these, we included only patients who had initiated and completed a 12-week supplementation period with an integrative treatment consisting of L-glutathione (50 mg), D-chiro-inositol (500 mg), Myo-inositol (100 mg), and N-acetylcysteine (150 mg). All PCOS patients were selected according to the diagnostic criteria established by the Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome [4].

In addition, patients had to fulfill the following criteria: absence of enzymatic adrenal deficiency and/or other endocrine diseases (including diabetes), normal prolactin levels (range, 5-25 ng/mL), no hormonal treatment during the 6 months prior to the study, and a body mass index >25.

As a routine procedure, our center screens PCOS subjects before and after at least 3 months (12 weeks) of treatment as follows: on days 3-6 of the menstrual cycle and on days 3-6 of the first bleeding occurring after the 12th week of treatment. The following parameters were evaluated: luteinizing hormone, folli-

cle-stimulating hormone, thyroid-stimulating hormone, estradiol, progesterone, prolactin, androstenedione, 17-hydroxyprogesterone, dehydroepiandrosterone sulfate, insulin, glutamic-oxaloacetic transaminase, and alanine aminotransferase. Total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglyceride plasma levels were also evaluated. Based on the presence of familial diabetes, the entire cohort was divided into patients with familial diabetes (n=26) and those without (n=6). Insulin resistance was assessed using the Homeostatic Model Assessment for Insulin Resistance index, which was calculated according to the following formula: $[\text{fasting insulin } (\mu\text{U/mL}) \times \text{fasting glucose } (\text{mg/dL})] / 405$. A higher Homeostatic Model Assessment for Insulin Resistance value indicates lower insulin sensitivity [24]. In accordance with the standard procedures of the Gynecological Endocrinology outpatient clinic at the University of Modena and Reggio Emilia (Modena, Italy), written informed consent was obtained for retrospective analysis and publication of de-identified clinical and biochemical data collected from PCOS patients included in this study.

The present investigation was conducted as a retrospective observational study and received approval from the local Institutional Ethics Committee (#72/2025/OSS/AOUMO).

Measurement of blood hormones and metabolic parameters

All laboratory analyses for each participant, both at baseline and after supplementation, were performed within the same assay run to reduce analytical variability. Plasma luteinizing hormone and follicle-stimulating hormone levels were measured using a highly sensitive immunofluorometric method, with a lower detection limit of 0.1 mIU/mL. The intra-assay and inter-assay coefficients of variation were 4.0% and 6.0%, respectively.

Measurements of prolactin, estradiol, progesterone, androstenedione, thyroid-stimulating hormone, 17-hydroxyprogesterone, dehydroepiandrosterone sulfate, insulin, glutamic-oxaloacetic transaminase, alanine aminotransferase, glucose, triglycerides, total cholesterol, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol were carried out using standard automated clinical chemistry procedures at the Central Laboratory of Modena Hospital. Analysis of two quality-control samples showed that the average coefficients of variation were 4.2% within assays and 10.4% between assays.

Statistical analysis

Statistical analyses were conducted using QuickStatCalculations (<https://www.socscistatistics.com/>). The normality of data distribution was pre-verified using the Shapiro-Wilk test. Data are expressed as mean $\pm$ standard error of the mean to reflect the precision of the mean estimates. Since the metabolic parameters followed a normal distribution, longitudinal changes within the same cohort (baseline vs. 12 weeks) were assessed using the paired Student's t-test. A p-value of <0.05 was considered statistically significant. Given the exploratory nature of the study and the limited number of predefined outcomes, adjustments for multiple comparisons were not applied.

Results

Table 1 summarizes hormonal and metabolic parameters before and after 12 weeks of integrative supplementation. A significant reduction in glucose and insulin plasma levels, as well as in the Homeostatic Model Assessment for Insulin Resistance and Hepatic Insulin Extraction index, was observed. A 23% reduction in insulin levels was observed. No changes were observed in reproductive hormone parameters or in the lipid profile.

Table 2 shows the differences in outcomes between PCOS patients with (n=26) and without (n=6) a history of familial diabetes. PCOS patients with a family history of diabetes showed significant improvements in blood glucose and insulin levels, as well as in the Homeostatic Model Assessment for Insulin Resistance and Hepatic Insulin Extraction index after 12 weeks of treatment. PCOS patients without a family history of diabetes showed a reduction, although not significant, in Homeostatic Model Assessment for Insulin Resistance, Hepatic Insulin Extraction index values, and plasma insulin and glucose levels. The small sample size of this group may have limited the statistical power to detect significant differences. Therefore, no comparison between the two groups was performed. Nevertheless, a consistent trend toward improvement in metabolic parameters was also observed in the subgroup without a family history of diabetes, although

without reaching statistical significance, likely due to the limited sample size and reduced statistical power.

Discussion

Our study shows that administering Myo-inositol, D-chiro-inositol, L-glutathione, and N-acetylcysteine improves specific metabolic parameters in patients with PCOS. In fact, this supplementation induced a significant decrease in fasting glucose, insulin levels, and the Homeostatic Model Assessment for Insulin Resistance. Improvements in insulin resistance markers such as the Homeostatic Model Assessment for Insulin Resistance and circulating insulin levels could be significant for women with PCOS, since insulin resistance is linked to reproductive and metabolic issues in this group [25]. Improved insulin sensitivity might lead to better metabolic risk profiles and could affect long-term health outcomes, including the likelihood of developing type 2 diabetes and liver disease [9-10].

Additionally, liver function improved, as reflected by a decrease in the Hepatic Insulin Extraction index. These findings are consistent with previous studies reporting improvements in metabolic parameters in women with PCOS following supplementation with Myo-inositol and D-chiro-inositol, or D-chiro-inositol alone [9,26-27]. A key difference of the present study lies in the supplementation strategy adopted: rather than the conventional 40:1 Myo-inositol/D-chiro-inositol ratio [29-30], we used a 1:4 ratio [26]. The choice of a 1:4 Myo-inositol/D-chiro-inositol ratio was based on the aim of exploring a higher relative contribution of D-chiro-inositol in a population characterized by insulin resistance and altered hepatic insulin handling, in which D-chiro-inositol may play a more relevant role in insulin signaling pathways [8]. Although the optimal Myo-inositol/D-chiro-inositol ratio remains a matter of debate, different ratios may exert distinct metabolic effects, and the present findings suggest that alternative formulations may also be clinically relevant [18]. Further studies are needed to directly compare different ratios and their metabolic and clinical outcomes in women with PCOS. To the best of our knowledge, this is the first study to combine N-acetylcysteine and L-Glutathione, two compounds with well-established antioxidant properties, with Myo-inositol and D-chiro-inositol.

The observed reduction in plasma insulin levels in PCOS patients with familial diabetes, with no changes in plasma C-peptide levels, is consistent with a possible increase in hepatic insulin clearance, as indicated by the decreased Hepatic Insulin Extraction index. However, this reduction in insulin levels might be ascribed, at least in part, to increased peripheral insulin sensitivity due to the action of inositol, as already described in the literature [28]. The Hepatic Insulin Extraction index reflects the proportion of insulin secreted by the pancreas that is extracted by the liver before reaching the systemic circulation and is commonly calculated as the ratio between plasma insulin and C-peptide concentrations [9].

The Hepatic Insulin Extraction index represents an indirect marker of hepatic insulin clearance and liver insulin handling, and although it is not routinely used in clinical practice, it provides useful insights into hepatic insulin metabolism. However, its interpretation should be considered indirect and context-dependent. Assessment of the Hepatic Insulin Extraction index is clinically relevant because it provides information not only on hepatic insulin clearance but also on liver functional integrity, with higher Hepatic Insulin Extraction index values associated with reduced hepatocyte function [29].

Furthermore, as demonstrated by Genazzani et al. [9], Hepatic Insulin Extraction index values are higher in women with PCOS who have a family history of diabetes compared with those without such a history, indicating altered hepatic insulin clearance. Such impairment may reflect an underlying dysfunction in hepatic insulin-degradation mechanisms, potentially involving reduced expression or activity of the insulin-degrading enzyme, as previously suggested [9,30-31]. Impaired insulin-degrading enzyme expression or function would result in decreased insulin extraction and persistently elevated fasting circulating insulin levels, thereby sustaining hyperinsulinemia. Such liver dysfunction is also supported by the previously reported increases in plasma transaminase levels [9,32]. Accordingly, women with PCOS with familial diabetes exhibit higher plasma transaminase levels [9] and may be more susceptible to developing liver diseases such as metabolic dysfunction-associated steatotic liver disease [16,33].

The notable reduction of the Hepatic Insulin Extraction index observed after the 12-week treatment interval, especially in overweight/obese PCOS patients with a family history of diabetes, supports the idea

that our intervention may have had a meaningful effect on hepatic metabolic function. Since no changes were observed in C-peptide levels, this reduction in circulating insulin is likely attributable to increased hepatic clearance rather than reduced pancreatic secretion, as previously demonstrated in our studies [9,22,34-35]. We hypothesize that this enhancement in clearance may be linked to the restoration of insulin-degrading enzyme activity. Insulin-degrading enzyme is a key protease responsible for hepatic insulin degradation, and its function is known to be impaired by oxidative stress. The redox-modulating properties of L-glutathione and N-acetylcysteine could theoretically preserve or upregulate insulin-degrading enzyme expression, thereby mitigating compensatory hyperinsulinemia. However, as insulin-degrading enzyme activity was not directly measured in this cohort, this mechanism remains speculative [35].

Strengths and limitations

The present study is characterized by several limitations that must be acknowledged. First, the retrospective, non-controlled design does not allow for direct comparison with a placebo or a standard pharmacological intervention. Moreover, this study design implies inherent limitations, primarily selection bias, since only patients who successfully completed the 12-week supplementation period were considered. Consequently, the metabolic improvements observed must be interpreted as exploratory. The absence of a control group means that the potential influence of time-dependent variables or undisclosed lifestyle changes cannot be entirely ruled out, despite the patients' stable clinical histories. Secondly, the sample size (n=32) is relatively small, particularly within the subgroup of patients without a family history of diabetes (n=6), which likely limited the statistical power to detect significant changes in that specific population.

However, a key strength of this investigation lies in its focus on a highly specific and clinically challenging phenotype: overweight/obese PCOS patients. By utilizing the Hepatic Insulin Extraction index, we provide novel mechanistic insight into how antioxidant-inositol synergy may specifically target hepatic insulin clearance rather than solely pancreatic secretion. This real-world observation identifies a specific metabolic endotype (those with familial diabetes) that may benefit from targeted integrative strategies, providing a foundation for future randomized controlled trials.

Conclusions

In conclusion, this exploratory study suggests that a combined oral supplementation of reduced L-glutathione, N-acetylcysteine, Myo-inositol, and D-chiro-inositol is associated with significant metabolic improvements in overweight/obese women with PCOS. Our findings indicate a reduction in insulin resistance and improved hepatic insulin clearance, particularly in the subset of patients with a first-degree family history of type 2 diabetes. The observed changes in the Hepatic Insulin Extraction index provide a preliminary clinical signal that antioxidant-inositol synergy may influence hepatic insulin-degradation pathways, potentially involving modulation of the insulin-degrading enzyme. These findings should be considered hypothesis-generating, and future large-scale, double-blind, placebo-controlled trials are warranted to confirm these observations and further elucidate the role of hepatic insulin clearance as a therapeutic target in PCOS management.

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Conflicts of interest

The authors declare having no conflicts of interest.

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Table 1. Hormonal and metabolic parameters of all patients under study (n=32) before and after 12 weeks of integrative treatment.

	LH mIU/ mL	FSH mIU/ mL	TSH μIU/mL	E2 pg/mL	PRL ng/mL	Andro- stenedione pg/mL	17OHP pg/mL	Glucose mg/dL	Insulin μIU/mL	C-peptide ng/mL	Total cholesterol mg/dL	HDL-C mg/dL	LDL-C mg/dL	TG mg/dL	AST IU/L	ALT IU/L	DHEA-S μg/mL	BMI Kg/m²	HOMA- IR index	HIE index
Baseline																				
Mean ± SEM	6.93 ± 0.65	5.36 ± 0.46	2.65 ± 0.21	66.75 ± 11.58	14.55 ± 11.58	2.30 ± 0.23	1.68 ± 0.17	85.31 ± 1.25	15.27 ± 1.50	2.39 ± 0.11	178.32 ± 5.90	50.86 ± 1.91	110.41 ± 4.52	88.41 ± 6.55	21.81 ± 1.76	20.33 ± 3.42	2.46 ± 0.19	30.72 ± 0.96	3.24 ± 0.31	5.78 ± 0.35
After treatment																				
Mean ± SEM	8.83 ± 1.71	4.93 ± 0.62	3.11 ± 0.49	102.79 ± 25.38	14.03 ± 1.76	2.27 ± 0.32	1.72 ± 0.29	82.74 ± 2.65	11.72 ± 1.55	2.35 ± 0.2	172.32 ± 9.49	49.79 ± 2.67	102.79 ± 8.04	89.32 ± 15.43	23.11 ± 1.50	18.95 ± 2.28	2.40 ± 0.33	29.30 ± 1.61	2.24 ± 0.32	4.95 ± 0.45
p value vs Baseline	NS	NS	NS	NS	NS	NS	NS	0.0497	0.0173	NS	NS	NS	NS	NS	NS	NS	NS	NS	0.0255	0.0059

Data are expressed as mean ± standard error of the mean (SEM).
LH, luteinizing hormone; FSH, follicle stimulating hormone; TSH, thyroid stimulating hormone; E2, estradiol; PRL, prolactin; 17OHP, 17-hydroxyprogesterone; DHEA-S, Dehydroepiandrosterone sulphate; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; TG, triglyceride; AST, aspartate amino transferase; ALT, alanine amino transferase; HOMA-IR, homeostatic model assessment for insulin resistance; BMI, body mass index; HIE, hepatic insulin extraction; NS, non-significant.

Table 2. Hormonal and metabolic parameters of patients before and after 12 weeks of integrative treatment, stratified by presence of history of familial diabetes.

Familial diabetes (n=26)	LH mIU/mL	FSH mIU/mL	TSH µIU/mL	E2 pg/mL	PRL ng/mL	Andro-stenedione ng/mL	17OHP ng/mL	Glucose mg/dL	Insulin µIU/mL	C-peptide ng/mL	Total cholesterol mg/dL	HDL-C mg/dL	LDL-C mg/dL	TG mg/dL	AST IU/L	ALT IU/L	DHEA-S µg/mL	BMI Kg/m²	HOMA-IR index	HIE index
Baseline																				
Mean ± SEM	6.67 ± 0.78	5.24 ± 0.5	2.7 ± 0.25	70.76 ± 14.32	14.94 ± 2.03	2.17 ± 0.26	1.63 ± 0.19	86.08 ± 1.55	14.95 ± 1.8	2.4 ± 0.13	181.04 ± 6.41	52.57 ± 1.91	110.28 ± 4.77	91.00 ± 7.33	21.23 ± 2.15	21.09 ± 4.16	2.50 ± 0.24	31.70 ± 1.06	3.21 ± 0.38	5.62 ± 0.41
After treatment																				
Mean ± SEM	9.69 ± 1.78	5.38 ± 0.59	2.72 ± 0.38	88.21 ± 21.96	14.02 ± 1.57	2.29 ± 0.34	1.65 ± 0.30	84.21 ± 2.34	10.59 ± 0.88	2.37 ± 0.19	176.07 ± 9.3	52.64 ± 2.46	102.79 ± 7.93	90.50 ± 16.95	21.64 ± 1.15	19.29 ± 2.31	2.39 ± 0.32	30.65 ± 1.46	2.12 ± 0.19	4.59 ± 0.29
p value vs Baseline	NS	NS	NS	NS	NS	NS	NS	0.0425	0.0347	NS	NS	NS	NS	NS	NS	NS	NS	NS	0.0236	0.0049

No familial diabetes (n=6)	LH mIU/mL	FSH mIU/mL	TSH µIU/mL	E2 pg/mL	PRL ng/mL	Andro-stenedione ng/mL	17OHP ng/mL	Glucose mg/dL	Insulin µIU/mL	C-peptide ng/mL	Total cholesterol mg/dL	HDL-C mg/dL	LDL-C mg/dL	TG mg/dL	AST IU/L	ALT IU/L	DHEA-S µg/mL	BMI Kg/m²	HOMA-IR index	HIE index
Baseline																				
Mean ± SEM	7.73 ± 1.47	5.24 ± 0.28	2.79 ± 0.53	38.8 ± 7.88	12.8 ± 3.36	12.8 ± 0.78	1.65 ± 0.5	83.8 ± 1.56	18.92 ± 3.14	2.64 ± 0.34	161.00 ± 32.87	37.33 ± 6.98	111.6 ± 31.29	90.5 ± 19.09	25.67 ± 1.08	17.33 ± 4.32	2.35 ± 0.32	27.54 ± 2.14	3.87 ± 0.58	6.85 ± 0.88
After treatment																				
Mean ± SEM	6.00 ± 3.61	2.60 ± 1.07	3.85 ± 1.43	200.33 ± 71.79	14.53 ± 6.33	2.16 ± 0.18	2.00 ± 0.63	81.00 ± 3.08	11.47 ± 7.13	1.97 ± 0.45	147.00 ± 20.5	43.67 ± 2.16	115.67 ± 18.95	73.33 ± 16.39	24.00 ± 3.94	14.67 ± 2.94	2.09 ± 0.6	24.77 ± 1.33	2.32 ± 1.48	5.19 ± 2.06
p value vs Baseline	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS

Data are expressed as mean ± standard error of the mean (SEM).

LH, luteinizing hormone; FSH, follicle stimulating hormone; TSH, thyroid stimulating hormone; PRL, Prolactin; 17OHP, 17-hydroxyprogesterone; DHEA-S, Dehydroepiandrosterone sulphate, E2, estradiol; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; TG, triglyceride; AST, aspartate amino transferase; ALT, alanine amino transferase; HOMA-IR, homeostatic model assessment for insulin resistance; BMI, body mass index; HIE, hepatic insulin extraction; NS, non-significant.