Impact of Myo-Inositol-Chiro Inositol Combination on the improvement of Polycystic Ovary Syndrome Condition

Zuhair Assi Hussein, Maysaa Jalal Majeed, Lubna Amer Al-Anbari[1]

Department of Biochemistry, College of Medicine, University of Baghdad, [1]High Institute for Infertility Diagnosis and ART'S, Al-Nahrain University, Baghdad, Iraq

Abstract

Background: Inositol was previously classified as a vitamin, but it is not one as it is produced by the body. It plays a role as a second messenger of insulin in several insulin-dependent processes, including polycystic ovarian syndrome (PCOS) and metabolic syndrome. **Objective:** This study aims to determine the impact of myo+ D-chiro inositol treatment on gut hormones insulin-like peptide 5 (ILP5) and phosphodiesterase 9 (PDE9) inhibitors, as well as determine if it improves the metabolic profile and the state of PCOS. **Materials and Methods:** The research conducted by the University of Baghdad's College of Medicine was authorized by the ethics committee. In the study, 50 obese women without PCOS, and 50 obese women with PCOS were enrolled, and they were then treated with 2000 mg of myo-inositol (MI) and 50 mg of D-chiro inositol (DCI) in a 40:1 ratio for 3 months while having their vital signs and laboratory tests checked both before and after the treatment. We examined fasting glucose, insulin, ILP5, PDE9 inhibitor, free testosterone, dehydroepiandrosterone, the homeostatic model assessment index, and pretreatment and posttreatment. From February 2022 to the end of August 2022, participants in the study visited the Infertility Unit at the Higher Institute for Infertility Diagnosis and Assisted Reproductive Technologies at Al-Nahrain University in Baghdad, Baghdad, Iraq. Participants in this research completed questionnaires to indicate their consent for the study to record information on women. **Results:** The results revealed that after administering the treatment to polycystic ovary patients, a significant decrease in their weight and an improvement in insulin resistance markers were observed, as well as a decrease in the levels of ILP5 (171.53 ± 22.55 vs. 83.60 ± 18.94), and an increase in the levels of phosphodiesterase9 enzyme (7.17 ± 1.58 ng/mL vs. 8.16 ± 1.37 ng/mL). **Conclusion:** This study concludes that MI–DCI could be proposed as a potential therapeutic approach for the treatment of women with polycystic ovaries, showing a positive effect on correcting PCOS symptoms and infertility.

Keywords: Chiro, D-inositol-insulin-like peptide 5, myo-PCOS, phosphodiesterase 9 inhibitors

Introduction

During their reproductive years, 5%–21% of women are affected by polycystic ovary syndrome (PCOs). Regardless of body mass index (BMI), insulin resistance is a typical finding in people with PCOS.[1] Around 15%–30% of PCOS-positive lean women and 70%–80% of PCOS-positive women with central obesity have compensatory hyperinsulinemia and insulin resistance.[2] Through enhanced luteinizing hormone production, which also impacts ovarian stimulation, hyperinsulinemia may boost ovarian androgen synthesis.[3] Inositol phosphoglycans (IPGs), which act as secondary messengers for insulin and regulate the oxidative and nonoxidative metabolisms of glucose as well as the absorption of glucose by glucose transporter type 4,[4] are used to transmit information. Additionally, IPGs serve as secondary messengers for other hormones, including thyroid stimulation hormone and follicular stimulating hormone (FSH). Myo-inositol (MI) and D-chiro inositol (DCI) are both crucial for the oxidative utilization of glucose and its storage as glycogen, as well as for the intracellular transmission of insulin's metabolic signal.[4,5] MI to DCI conversion is insulin-dependent

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Address for correspondence: Dr. Zuhair Assi Hussein, Department of Biochemistry, College of Medicine, University of Baghdad, Baghdad, Iraq.
E-mail: zuhairkirkuk2015@gmail.com

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and is slowed down in tissues with insulin resistance by the enzyme epimerase. In both people and animals with type 2 diabetes, there is a decrease in urine DCI and a rise in MI excretion.[6-9]

When performing a glucose tolerance test, individuals without PCOS produce DCI three times less than controls.[10,11] Therefore, an MI shortage or a problem with the activity or expression of the enzyme that converts MI to DCI may result in insulin resistance (which can then result in an MI deficiency because the epimerase that does the conversion is insulin-sensitive).[4] For 8 weeks, obese PCOS patients receiving DCI at 1200 mg/day had their free testosterone levels and insulin area under the curve following an oral glucose tolerance test lowered by 62% and 55%, respectively.[12]

Materials and Methods

The Ethical Committee approved the study of the College of Medicine/University of Baghdad. In the study, 50 obese women without PCOS. A total of 50 samples of polycystic ovary patients were selected and followed up by giving MI treatment at a dose of 2000 and 50 mg of DCI in the 40:1 ratio for 3 months, monitoring vital signs and laboratory tests before and after giving the treatment to women with polycystic ovaries (PCOs). The study was conducted on those who attended the Infertility Unit at the Higher Institute for Infertility Diagnosis and Assisted Reproductive Technologies, Al-Nahrain University in Baghdad City, Iraq, from February 2022 to the end of August 2022. Questionnaires were filled out by participants to get the agreement of participants in this study to record the information on healthy subjects and patient groups.

Exclusion criteria

Women with PCOs due to genetic affected, which are diagnosed by gynecology. All patients with metabolic or endocrinology disorders were excluded from this study, including diabetes mellitus, hypertension, liver disease, chronic renal disease, and premature ovarian failure (ovarian tumors and virilizing adrenal).

Inclusion criteria

Women who matched the study specification, which was mentioned in subjects.

Collection of blood samples for biochemical and hormonal studies

For the biochemical and hormonal examinations, fasting blood samples (5 mL) from each participant in this research were taken. The samples were then centrifuged for 10 min at 3000 rpm to separate the serum.

Dehydroepiandrosterone (DHEA), insulin, and free testosterone levels in serum were assessed using the Magnum-800 Chemiluminescence Immunoassay System. Insulin-like peptide (ILP-5) and phosphodiesterase 9 (PDE9) serum levels were assessed using enzyme-linked immunosorbent equipment. All kits from Biobase (Shandong, China) were used to test the serum levels of glucose, total cholesterol, triglycerides, and high-density lipoprotein cholesterol (HDL-C) using a BK-500 Auto Chemistry Analyzer (Shandong, China) following the manufacturer's recommendations. Using the formulas provided by the manufacturer, the levels of low-density lipoprotein cholesterol (LDL-C) and very low-density lipoprotein cholesterol (VLDL-C) were determined. The High Institute of Infertility Diagnosis and Assisted Reproductive Technologies at Al-Nahrain University conducted the biochemical investigation.

Twenty-five obese women from a total of 50 women with PCOs, were selected by the gynecologist, and subjected to MI–DCI supplement (amount of 2000 mg MI and 50 mg of DCI in the 40:1 ratio), for 3 months, and they were followed along the length of this period to see it, effect on PCOs resulting from insulin resistance. Student's *t* test to determine the significant differences between two groups.

Ethical approval

The study was conducted following the ethical principles that have their origin in the Declaration of Helsinki. It was carried out with patients' verbal and analytical approval before samples were taken. The study protocol, the subject information, and the consent form were reviewed and approved by a local ethics committee No. 336 on February 1, 2022.

Results

The matching ages of the study's population are confirmed by the nonsignificant results when the comparison is done. The choice of the group's BMI is also proven by the results, which show a nonsignificant difference ($P > 0.05$) among groups and there is a nonsignificant ($P > 0.05$) difference between obese women with PCOs and without PCOs in their BMI shown in Table 1.

Table 1: General distribution of the study's population expressed as mean ± SD

Parameters	Groups	*N*	Mean ± SD	*P* value
Age (years)	Obese women with PCOs	50	26.57 ± 5.46	0.95 (n.s)
	Obese women without PCOs	50	27.04 ± 5.86	
BMI (kg/m^2)	Obese women with PCOs	50	35.27 ± 2.48	0.32 (n.s)
	Obese women without PCOs	50	34.70 ± 3.24	

(s): significant $P \leq 0.05$, (n.s): nonsignificant $P > 0.05$

Obese women with PCOs show significant ($P < 0.05$) elevation in the level of serum ILP5 in comparison with healthy women, whereas it shows significant ($P < 0.05$) reduction in serum level of serum phosphodiesterase 9A (PDE9A) in the comparison. Elevated serum-free testosterone confirms PCOs associated with insulin resistance leading to hyperandrogenism excess presented with elevation in serum testosterone and DHEA shown in Table 2.

As expected, as a result of selecting patients, indicators of diagnostic insulin resistance showed a significant increase, which results in the selection of patients who have PCOs as a result of insulin resistance. Obese women with PCOS have as expected (they were diagnosed by a gynecologist), the significantly highest level of serum insulin ($P \leq 0.05$), when compared with healthy women (obese) with the same diagnostic line for insulin resistance, the serum glucose level is shown in Table 3 with the highest level in obese women with PCOS. To confirm the diagnosis of insulin resistance in women, homeostatic model assessment for insulin resistance (HOMA-IR) is dependent, which documented that women with PCOs have insulin resistance (significantly highest $P \leq 0.05$ level of HOMA-IR) in comparison with healthy women.

Table 2: Mean ± SD of serum ILP-5, serum PDE-9A, free testosterone, and serum DHEA in healthy women with PCOs and obese women with PCOs

Parameter	Healthy women without PCOs $N = 50$	Obese women with PCOs $N = 50$	*P* value
	Mean ± SD	Mean ± SD	
Serum ILP5 (ng/mL)	95.6 ± 27.7	137.3 ± 48.0	0.02(s)
Serum PDE9A (ng/mL)	7.44 ± 1.86	6.41 ± 1.46	0.04(s)
Serum-free testosterone (Pg/dl)	1.62 ± 1.12	1.92 ± 0.85	0.15(n.s)
Serum DHEA	167.7 ± 80.9	214.5 ± 89.2	0.01(s)

(s): significant $P \leq 0.05$, (n.s): nonsignificant $P > 0.05$

Table 3: Insulin resistance guide markers (serum FG, serum insulin, and HOMA-IR) expressed as mean ± SD

Parameter	Healthy women without PCOs $N = 50$	Obese women with PCOS $N = 50$	*P* value
	Mean ± SD	Mean ± SD	
Serum FG (mmol/L)	5.18 ± 0.79	6.0 ± 1.4	0.01(s)
Serum insulin (μIU/mL)	13.74 ± 4.52	37.2 ± 16.8	0.03(s)
HOMA-IR	3.17 ± 1.9	10.58 ± 7.38	0.01(s)

(s): significant $P \leq 0.05$, (n.s): nonsignificant $P > 0.05$

Women were showing significant ($P \leq 0.05$) reduction in their weight represented by BMI, and insulin resistance marker [serum fasting glucose (FG), serum insulin, and HOMA-IR], which improved to normal reference ranges, but serum lipid profile did not show a significant ($P > 0.05$) difference during this period expect serum LDL, which highly significant decrease in its level shown in Table 4.

Serum ILP5 shows a significant decrease ($P \leq 0.05$) in its level in women with PCOs after MI–DCI supplementation, whereas serum PDE9A shows a significant increase ($P \leq 0.05$) in its level after MI–DCI supplementation. Each serum-free testosterone and serum DHEA show no significant ($P > 0.05$) difference, before and after supplementation as shown in Table 5.

Discussion

Approximately 30%–40% of people with PCOS have insulin resistance and hyperandrogenism. MI enhances the menstrual cycle, lowers hyperandrogenism, and improves insulin sensitivity. Numerous writers have researched its impact on assisted reproductive technologies.[13,14]

People with PCOS who orally consume inositol report decreased triglyceride levels, lower blood pressure, and improved blood sugar, ovulation, and conception rates. The metabolic and hormonal parameters of the participants significantly improved after 3 months of inositol medication, and after 6 months, the clinical pregnancy rate of the inositol treatment group was 45.5%.[15,16]

MI increases insulin sensitivity, decreases hyperandrogenism, and improves the menstrual cycle MI modulates the activation of glucose transporters and glucose utilization, and glycogen synthesis takes place under the control of DCI. This molecule on the ovary regulates the insulin-induced androgen synthesis, whereas MI regulates glucose uptake and FSH signaling, this is the possible effect of MI on polycystic ovary through its action on glucose homeostasis.[17-19]

In other words, inositol reduces glycemia levels and hyperinsulinemia, while buffering the negative effects of sustained insulin stimulation upon the adipose tissue and the endocrine system. As such, MI has become a reliable treatment option for insulin-resistant PCOS patients.[20-24]

It is worth noting that two of the women who were given instead had a pregnancy after the period of administration, also we note that most of the patients had an improvement in their lipid profile and improved their insulin resistance as well as improved some symptoms like acne, hirsutism, and menstruation regulation.

The therapy of Myo+ D-chiro inositol, which has been successfully used to treat insulin resistance, was

Table 4: Mean ± SD of BMI, serum FBG, insulin, serum cholesterol, TG, HDL-C, LDL-C, VLDL, TG/HDL ratio, and HOMO-IR of obese women with PCOs before and after MI–DCI treatment

Parameters	*N*	Obese women with PCOs before inositol treatment	Obese women with PCOs on inositol treatment	*P* value
		Mean ± SD	Mean ± SD	
BMI (kg/m^2)	25	33.79 ± 12.34	30.74 ± 2.12	0.04(s)
Serum FG (mmol/L)	25	6.27 ± 1.45	5.36 ± 0.95	0.01(s)
Serum insulin (μIU/mL)	25	26.97 ± 12.38	15.32 ± 5.25	0.01(s)
HOMA-IR	25	9.66 ± 4.55	3.78 ± 1.83	0.02(s)
Serum cholesterol (mg/dL)	25	156.90 ± 32.07	174.70 ± 45.59	0.20(n.s)
Serum TG (mg/dL)	25	120.80 ± 89.95	125.50 ± 84.0±	0.86(n.s)
Serum HDL-C (mg/dL)	25	27.65 ± 2.87	30.35 ± 3.86	0.02(s)
Serum LDL-C (mg/dL)	25	105.09 ± 26.04	30.35 ± 3.86	0.01(s)
Serum VLDL-C (mg/dL)	25	24.16 ± 17.99	25.10 ± 16.81	0.86(n.s)

(s): significant $P \leq 0.05$, (n.s): nonsignificant $P > 0.05$

Table 5: Mean ± SD of serum ILP-5, PDE9, testosterone, DHEA of obese women with PCOs before and after MI–DCI

Parameters	*N*	Obese women with PCOs before MI–DCI supplementation *N* = 20	Obese women with PCOs on MI–DCI supplementation *N* = 20	*P* value
		Mean ± SD	Mean ± SD	
Serum ILP5 (ng/mL)	25	171.53 ± 22.55	83.60 ± 18.94	0.05(s)
Serum PDE9A (ng/mL)	25	7.17 ± 1.58	8.16 ± 1.37	0.02(s)
Serum fasting testosterone (pg/dL)	25	1.97 ± 0.65	1.78 ± 0.78	0.43(n.s)
Serum DHEA (μg/dL)	25	193.72 ± 42.96	209.21 ± 56.37	0.33(n.s)

(s): significant $P \leq 0.05$, (n.s): nonsignificant $P > 0.05$

a key component of the research because of its impact on ILP5 and PDE9A. In polycystic patients, it can be shown that ILP5 is impacted in the direction of reduction and PDE9A is affected in the direction of rise following therapy, demonstrating its connection to PCOs caused by insulin resistance via weight loss. When incubated with intact fat cells, insulin, in a time- and dose-dependent way, inhibits isoproterenol-induced cellular cyclic adenosine monophosphate generation and lipolysis and activates the phosphodiesterase.[25] Key steps in insulin's antilipolytic activity include the serine phosphorylation and activation of PDE9A and the activation of a kinase that phosphorylates PDE *in vitro*.[26]

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Conflicts of interest
There are no conflicts of interest.

References

1. Zhang J, Xing C, Cheng X, He B. Canagliflozin combined with metformin versus metformin monotherapy for endocrine and metabolic profiles in overweight and obese women with polycystic ovary syndrome: A single-center, open-labeled prospective randomized controlled trial. Front Endocrinol 2022;13:1003238.
2. Ding H, Zhang J, Zhang F, Zhang S, Chen X, Liang W, *et al*. Resistance to the insulin and elevated level of androgen: A major cause of polycystic ovary syndrome. Front Endocrinol 2021;12:741764.
3. Cadagan D, Khan R, Amer S. Thecal cell sensitivity to luteinizing hormone and insulin in polycystic ovarian syndrome. Reprod Biol 2016;16:53-60.
4. Al-yasiry RZ, Jwad MA, Hasan MF, Alsayigh HA. How obesity affects female fertility. Med J Babylon 2022;19:111-4.
5. Larner J, Brautigan DL, Thorner MO. D-chiro-inositol glycans in insulin signaling and insulin resistance. Mol Med 2010;16:543-52.
6. Kennington AS, Hill CR, Craig J, Bogardus C, Raz I, Ortmeyer HK, *et al*. Low urinary chiro-inositol excretion in non-insulin-dependent diabetes mellitus. N Engl J Med 1990;323:373-8.
7. Al Kadhi MM, Mahmood HG, Jwad MA. The evaluation of serum prostate specific antigen level in women with polycystic ovarian syndrome with insulin resistance. Biochem Cell Arch 2022;22.
8. Ortmeyer HK, Bodkin NL, Lilley K, Larner J, Hansen BC. Chiroinositol deficiency and insulin resistance. I. Urinary excretion rate of chiroinositol is directly associated with insulin resistance in spontaneously diabetic rhesus monkeys. Endocrinology 1993;132:640-5.
9. Majeed MJ, Razak Al-Sharifi ZA, Ibrahim SJ. Role of betatrophin and irisin on diabetes mellitus type 1 management (experimental study). Indian J Public Health Res Dev 2019;10:1135-38.
10. Baillargeon J-P, Diamanti-Kandarakis E, Ostlund RE, Apridonidze T, Iuorno MJ, Nestler JE. Altered D-chiro-inositol urinary

clearance in women with polycystic ovary syndrome. Diabetes Care 2006;29:300-5.
11. Behayaa HR, Juda TM, Mohammed SB. The effect of androgen hormones in acne pathogenesis: A review. Med J Babylon 2022;19:345-9.
12. Nestler JE, Jakubowicz DJ, Reamer P, Gunn RD, Allan G. Ovulatory and metabolic effects of D-chiro-inositol in the polycystic ovary syndrome. N Engl J Med 1999;340:1314-20.
13. Johns Hopkins Medicine. A 'Cousin' of Viagra Reduces Obesity by Stimulating Cells to Burn Fat. ScienceDaily; 2021.
14. Merviel P, James P, Bouée S, Le Guillou M, Rince C, Nachtergaele C, *et al*. Impact of myo-inositol treatment in women with polycystic ovary syndrome in assisted reproductive technologies. Reprod Health 2021;18:1-8.
15. Jain M, Singh M. Assisted Reproductive Technology (ART) Techniques. Treasure Island, FL: StatPearls Publishing; 2022.
16. Kalra B, Kalra S, Sharma JB. The inositols and polycystic ovary syndrome. Indian J Endocrinol Metab 2016;20:720-4.
17. Unfer V, Facchinetti F, Orrù B, Giordani B, Nestler J. Myo-inositol effects in women with PCOS: A meta-analysis of randomized controlled trials. Endocr Connect 2017;6:647-58.
18. Bevilacqua A, Bizzarri M. Inositols in insulin signaling and glucose metabolism. Int J Endocrinol 2018;2018:1-8.
19. DiNicolantonio JJ, O'Keefe JH. Myo-inositol for insulin resistance, metabolic syndrome, polycystic ovary syndrome and gestational diabetes. Open Heart 2022;9:e001989.
20. Montt-Guevara MM, Finiguerra M, Marzi I, Fidecicchi T, Ferrari A, Genazzani AD, *et al*. D-chiro-inositol regulates insulin signaling in human adipocytes. Front Endocrinol 2021;12:660815.
21. Abdulhussein AJ, Mutlag SH. The effect of N-butanol fraction of Iraqi Cressa cretica species on sex hormones and ovary morphology in vivo female PCOs rat-model. NeuroQuantology 2022;20:320-8.
22. Laganà AS, Garzon S, Casarin J, Franchi M, Ghezzi F. Inositol in polycystic ovary syndrome: Restoring fertility through a pathophysiology-based approach. Trends Endocrinol Metabol 2018;29:768-80.
23. Laganà AS, Forte G, Bizzarri M, Kamenov ZA, Bianco B, Kaya C, *et al*. Inositols in the ovaries: Activities and potential therapeutic applications. Expert Opin Drug Metab Toxicol 2022;18:123-33.
24. Matshar AS, Majeed MJ, Mohson MS. The correlation between serum inositol 1, 4, 5 triphosphate level and primary hypothyroidism. Al-Kindy Coll Med J 2022;18:228-32.
25. Pintaudi B, Di Vieste G, Bonomo M. The effectiveness of myo-inositol and D-chiro inositol treatment in type 2 diabetes. Int J Endocrinol 2016;2016:9132052.
26. Kitamura T, Kitamura Y, Kuroda S, Hino Y, Ando M, Kotani K, *et al*. Insulin-induced phosphorylation and activation of cyclic nucleotide phosphodiesterase 3B by the serine-threonine kinase Akt. Mol Cell Biol 1999;19:6286-96.