

The Effect Myo-Inositol and D-Chiro-Inositol Co-Supplementation in Women with PCOS: A review

Ahila Meliana^a, Sarono Gayuh Wilujeng^a, Mohammad Fathul Qorib^{b*}

* mohammad-f-q@fk.unair.ac.id

^aMedical Program, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia

^bDepartment of Pharmacology, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia

Abstract

PCOS is an endocrine condition caused mostly by infertility and menstrual abnormalities. The pathophysiology of PCOS is related to the lack of hormone, reproductive and metabolic regulation which were stimulated by a variety of factors, such as insulin resistance. PCOS treatment strategies are always oral contraceptive pill (OCP) combination oral contraceptive pill, which can cause metabolism and cardiovascular side effect and is difficult to comply with consistently. Several studies stated that the combination between Myo-inositol and D-chiro-inositol (MI-DI) as therapeutics alternative to improve PCOS condition in reproductive-age women. This study investigates combination of MI-DI on PCOS in reproductive-age women. A literature review was used to conduct this investigation through PubMed, ScienceDirect, and Google Scholar databases. 1382 publications were identified in the search results, and 6 studies were relevant and matched the requirements for this investigation. MI-DI co-supplementation is effective to ameliorate metabolic and clinical abnormalities of PCOS patients.

Keywords: human & health; inositol; PCOS; supplementation; reproductive-age women

1. Introduction

PCOS is an endocrine disorder that mainly refers to infertility and menstrual irregularities [1]. 5%-10% of reproductive-age women had clinical PCOS history [2]. Another study stated that PCOS prevalence in women can reach 4%-20% [3]. PCOS is classified as a hormonal, reproductive, and metabolic disorder [4]. PCOS is characterized by clinical signs and manifestations, including menstrual cycle irregularities [5]. Long-term risks include infertility, obstetric problems, type 2 diabetes mellitus, and mental disorders [6]. Furthermore, because reproductive issues are an important and sensitive topic in many community groups, this condition can have an impact on women's quality of life. Because many people are unaware of the illness of PCOS, management is still confined to dietary and lifestyle changes, as well as drugs for insulin resistance.

PCOS is triggered by a variety of intrinsic and extrinsic causes, including impaired regulation of the primitive hypothalamus and ovarian and/or adrenal steroidogenesis [7]. Insulin resistance is associated with excessive serine phosphorylation of the insulin receptor [8] [9]. This condition can lead to elevated insulin levels, which can affect metabolic processes and a woman's menstrual cycle.

Generally, PCOS treatment strategies are always supported with exercise and proper diet [10]. However, in reality, patients are usually difficult to comply with and consistently do so. The combination oral contraceptive pill (OCP) is extensively used as a PCOS medication, however, its effects on metabolism and the cardiovascular system are still greatly biased [11]. Inositol has been extensively researched for its effectiveness to improve PCOS symptoms in reproductive-age women. Various studies have shown that combining Myo-inositol with D-chiro-inositol (MI-DI) as a therapeutic alternative is an effective treatment

for PCOS in women of reproductive age [12] [13] [14]. Both of them contribute as second messengers. Myo-inositol controls the ovulation process by influencing the follicular gonadotropin pathways. In addition, Myo-inositol is known as the one of components of the vitamin B complex. Inositol also affects insulin metabolism and plays an important role as an insulin sensitizer which is the isomer built from the epimerization pathway [15] [16].

2. Methods

This study was performed using the literature review method. The papers which were used in this investigation are based on the previous ten years' studies. A literature search was conducted through PubMed, ScienceDirect, and Google Scholar databases. The following keywords are used to find relevant articles: "Myo-inositol", "D-chiro-inositol", and "PCOS". The inclusion and exclusion criteria were used in screening the articles. The inclusion criteria were used in this study, such as the original article, investigating the combination of MI-DI supplementation in reproductive-age women, full-text available, published from 2018 to 2022, and using English. Furthermore, review articles were excluded from this investigation. Based on the search results, 1382 articles were found, and 6 studies were relevant and met the criteria for this study.

3. Result

We collected 6 papers after being screened based on intrinsic and extrinsic criteria. From these papers, we extracted data for our analysis in this study, such as first author and year of publication, title, country, study design, parameter and instrument, and result (Table 1).

Table 1. Summary of included literature

First author (Year)	Country	Study design	Parameter and instrument	Participant	Result
Colak (2020) [12]	Turkey	Retrospective case-control study	Ovulation status; MI-DI supplementation (40:1) for six months	46 anovulatory women without insulin resistance; 21 women were normal-weight and the others were overweight	23 patients were ovulated which were only 5 overweight women. The result was statistically significant.
Khan (2022) [13]	Pakistan	Prospective cohort study	MI-DI co-supplementation (40:1) for six months	106 of 13-19 years adolescents with PCOS	The co-supplementation ameliorates the clinical features, laboratory parameters, and ultrasound imaging.
Nordio (2019) [14]	Italy	Randomize, Interventional, Open-label	MI-DI combination with the different ratios for three months	49 women aged 18-45 years with PCOS	40:1 is the best ratio for PCOS treatment

Januszewski (2019) [15]	Poland	A prospective clinical study.	MI-DI (10:1) co-supplementation for six months	70 PCOS women were included	The co-supplementation improved the decrease in weight, FT, LH, FSH, insulin, and also glucose levels.
Vyas (2022) [16]	India	Retrospective, multi-center, real-world study	The supplementation of tablet that contained MI-DI (11:3) supplementation for three months	29 women aged 12-45 years with PCOS	The combination ameliorates the participant's menstruation and spontaneous ovulation.
Mendoza (2019) [17]	Spain	Double-blind, multi-center RCT with quadruple masking	The study group received soft capsules of MI-DI (3.6: 1) and the control group received MI-DI (40:1) twice daily twice daily for 3 months	60 women aged 18-40 years with PCOS with BMI<30	The combination improves PCOS women's reproductive performance and OHSS possibility.

4. Discussion

Myo-inositol and D-chiro-inositol (MI-DI) co-supplementation improve PCOS in reproductive-age women. This supplementation has been proven to enhance clinical features and laboratory parameters in women with PCOS.

PCOS raises inflammatory mediators, such as adipokine and free fatty acid levels [18]. However, insulin resistance is a major contributor to PCOS pathophysiology [19]. Insulin resistance is associated with PCOS in 65-70% of cases. Insulin sensitivity reduction affects compensatory hyperinsulinemia and increases LH stimulation. In addition, it creates androgen-dependent ovulation. Interference with the mediator inositolphosphoglycan (IPG), which is involved in the activating enzymes that are involved in glucose metabolism, may result in the incorrect insulin pathway. Insulin resistance is caused by an inositol deficit in IPG [22]. Therefore, the combination between lifestyle, dietary changes, and medical therapy may be more effective, including inositol supplementation [12]. Cell membrane synthesis, cell growth, intracellular signaling, peripheral nerve development and function, osteogenesis, and reproduction are all activities involving inositol, which is particularly included as PCOS pathological mechanism [13] [15].

The benefits of inositol are lowering insulin resistance as a blood sugar controller. The important role of inositol is in regulating many metabolic pathways and hormonal signaling. D-chiro-inositol helps maintain glycemic control of insulin by preventing damage caused by a synaptic accumulation of β -amyloid oligomers. Inositol has been proven to PCOS as an insulin sensitizer agent [20]. In addition, structurally almost all intracellular components in oocytes are composed of Myo-inositol. This May be one of the important factors behind the effect of Myo-inositol on PCOS [14]. MI-DI combination improves insulin sensitivity, ameliorates the ovulation process, and reduces oxidative stress. Enhancing the D-chiro-inositol dosage impaired oocyte maturation. This condition leads to fertility decline [21].

MI and DI are highly excellent at managing glucose through the body's synthesis and consumption of glucose. Both are involved in androgen production and FSH signaling in the ovary. Lowering LH by both inositols can reduce the LH/FSH ratio. This is due to the fact that inositol works as a second messenger, namely inositol 3 phosphate (IP3), which is vital in the control of intracellular calcium homeostasis. Increased inositol levels can boost IP3 levels and speed up the previously aberrant maturation process [12].

MI is the most typical isoform of inositol, followed by DI since it has a very good therapeutic impact. Many studies have shown that MI and DCI can be utilized as PCOS treatment by functioning as distinct insulin mediators due to their good potential to improve insulin resistance [14]. Insulin resistance is the primary target of inositol treatment since it is thought that IPG destruction has a role in metabolic disorders and causes PCOS [15]. The combination of these two types of inositol can be an alternative treatment for sub-fertile conditions in women with PCOS [13]. Patients with normal weight who have PCOS conditions have a tendency to be more successful with inositol combination therapy in improving conditions of infertility and spontaneous pregnancy. In addition, the combination of other vitamins and antioxidants with inositol is also effective for reducing BMI in obese patients [12]. In addition, DI also affects the quality of oocytes and embryos with various mechanisms involved, but a significant increase in DI doses can adversely affect oocyte maturation [17].

The combination of these two inositol isomers can increase ovulation rates and promote oocyte development to maturity [12]. In fact, the combination MI-DI when administered to adolescent girls may well prevent PCOS symptoms by increasing insulin sensitization and ovarian steroidogenesis. This combination has so far had no side effects [13]. Therefore, combining MI-DI at a 40:1 ratio provided a higher effect than either of the treatments alone. The 40:1 ratio is based on the two molecules' normal blood ratios [12] [14] [17]. This ratio combination helps to reduce oxidative stress and normalize the menstrual cycle, ovulatory physiology, and metabolic syndrome [15]. Although metformin is the main treatment for PCOS with insulin resistance, but it is not recommended for long-term use [23]. This ratio might be considered first-line treatment because it can be used to decrease the risk of metabolic syndrome and improve PCOS clinical manifestation [24].

5. Conclusion

According to this study, current treatment for PCOS using oral contraceptive pills, glucose-lowering, and lifestyle and diet modification was not effective. MI-DI co-supplementation in a 40:1 ratio has proven to ameliorate PCOS clinical manifestations while lowering the risk of metabolic and cardiovascular syndrome.

Acknowledgments

None

References

- [1] Shi, Y., Wang, Y., Zhu, X., Yin, R., Ma, Y., Han, H., Han, Y., Zhang, Y., 2022. The Application of Complementary and Alternative Medicine in Polycystic Ovary Syndrome Infertility, Evidence-Based Complementary and Alternative Medicine, p. 1.
- [2] Sadeeqa, S., Mustafa, T., Latif, S., 2018. Polycystic Ovarian Syndrome-Related Depression in Adolescent Girls: A Review, Journal of Pharmacy & Bioallied Sciences 10, p. 55-59.
- [3] Deswal, R., Norwal, V., Dang, A., Pindir, C. S., 2020. The Prevalence of Polycystic Ovary Syndrome: A Brief Systematic Review, Journal of Human Reproductive Science 13, p. 261-271.

- [4] Reyes-Mun˜oz, E., Sathyapalan, T., Rosetti, P., Shah, M., Long, M., Gaetano, V., La Rosa, V. L., Clanci, S., Vitale, S.G., 2018. Polycystic Ovary Syndrome: Implication for Drug Metabolism on Assisted Reproductive Techniques—A Literature Review, *Advances in Therapy* 35, p. 1805-1815.
- [5] Jahan, H., Wing, K., 2020. Polycystic Ovary Syndrome and its Relationship with Infertility and its Management 39, p. 53-59.
- [6] Balen, A. H., 2017. Polycystic Ovary Syndrome (PCOS), *The Obstetrician & Gynaecologist* 19, p. 29
- [7] De Leo, V., Musacchio, M. C., Capelli, M. G., Massaro, G., Morgante, Petraglia, F., 2016. Genetic, Hormonal and Metabolic Aspects of PCOS: An Update, *Reproductive Biology and Endocrinology* 14, p. 1-17.
- [8] Ilias, I., Rizzo, M., Zubulienė, L., 2022. Metformin: Sex/Gender Differences in Its Uses and Effects—Narrative Review, *Medicina* 58, p. 1-14.
- [9] Zeng, X., Xie, Y., Liu, Y., Long, S., Mo, Z., 2017. Polycystic Ovarian Syndrome: Correlation Between Hyperandrogenism, Insulin Resistance and Obesity, *Clinica Chimica Acta* 502, p. 2014-221.
- [10] Lim, S., Smith, C. A., Costello, M. F., MacMillan, F., Moran, L., Ee, C., 2019. Barriers and Facilitators to Weight Management in Overweight and Obese Women Living in Australia with PCOS: A Qualitative Study, *BMC Endocrine Disorders* 19, p. 1-9.
- [11] Bozdag, G., Yildiz, B. O., 2013. Combined Oral Contraceptives in Polycystic Ovary Syndrome—Indications and Cautions, *Polycystic Ovary Syndrome* 40, p. 115-127.
- [12] Colak, E., Ozcimen, E. E., Tohma, Y. A., Ceran, M. U., 2020. May Myo-inositol and D-chiro-inositol (40:1) Treatment be a Good Option on Normal-weighted Polycystic Ovary Syndrome Patients without Insulin Resistance?, *Obstetric and Gynaecology Research* 46, p. 2605-2611.
- [13] Khan, R. B., Sarosh, M., Anwer, S., 2022. Role of Myo-inositol and D-Chiro-Inositol in Improvement of Endocrine and Clinical Parameters in Teenage Girls affected by PCOS: A Prospective Cohort Study, *Pakistan Journal of Medical & Health Sciences* 16, p. 21-24.
- [14] Nordio, M., Basciani, S., Camajani, E., 2019. The 40:1 Myo-inositol/D-chiro-inositol Plasma Ratio is Able to Restore Ovulation in PCOS Patients: Comparison with Other Ratios, *European Review for Medical and Pharmacological Science* 23, p. 5512-5521.
- [15] Januszewski, M., Issat, T., Jakimiuk, A. A., Malgorzata, S. Z., Jakimiuk, A. J., 2019. Metabolic and Hormonal Effects of A Combined Myo-Inositol and D-Chiro-Inositol Therapy on Patients with Polycystic Ovary Syndrome (PCOS), *Ginekologia Polska* 90, p. 7-10.
- [16] Vyas, L., Raiturker, A. P., Sud, S., Poonam, G., Abhyankar, M., Revankar, S., Walia, S., 2022. Management of Polycystic Ovary Syndrome Among Indian Women Using Myo-Inositol and D-Chiro-Inositol, *Bioinformation* 18, p. 103-110.
- [17] Mendoza, N., Diaz-Rpoero, M. P., Aragon, M., Maldonado, V., Llaneza, P., Lorente, J., Medoza-Tesarik, R., Maldonado-Lobon, J., Olivares, M., Fonolla, J., 2019. Comparison of the Effect of Two Combinations of Myo-Inositol and D-Chiro-Inositol in Women with Polycystic Ovary Syndrome Undergoing ICSI: a Randomized Controlled Trial, *Gynecological Endocrinology* 35, p. 695-700.
- [18] Veterini, V., Santoso, B., Widjiati, 2015. Oxygen Hyperbaric Exposure Induces GLUT4 Expression Reduction and No Folliculogenesis Alterations in Rat PCOS with Insulin Resistance Model, *Majalah Obstetri & Ginekologi* 23, p. 112-117.
- [19] Puspita, I. M., Santoso, B., Utomo, B., 2019. Green Tea Extract Reduces Insulin Level and Folliculogenesis in Insulin-resistant PCOS Rats Model, *Majalah Obstetri & Ginekologi* 27, p. 103-107.
- [20] Benelli, E., Ghiada, S. D., Di Cosmo, C., Tonacchera, M., 2016. A Combined Therapy with Myo-Inositol and D-Chiro-Inositol Improves Endocrine Parameters and Insulin Resistance in PCOS Young Overweight Women, *International Journal of Endocrinology* 2016.
- [21] Kumari, A. A. R., I'thisom, R., Hendarto, H., Dwiningsih, S. R., 2021. The Relationship of Antral Follicle Count (AFC) with Levels of Estradiol Serum and Mature Ovarian Follicles in Women

- Undergoing the IVF Program at the Graha Amerta Fertility Clinic of General Hospital of Dr. Soetomo in the Period 2018, Indian Journal of Forensic Medicine & Toxicology 15, p. 1997-2003.
- [22] Bizzari, M., Carlomagno, G., 2014. Inositol: History of an Effective Therapy for Polycystic Ovary Syndrome, European Review for Medical and Pharmacological Science 2014, p. 1896-1903.
- [23] Wulandari, L. P., Santoso, B., Purwanto, B., Miftahussurur, M., Annas, J. Y., Budiono, 2021. Effect of Moringa Oleifera Leaf Extract on Oxidative Stress and Theca Cell in Polycystic Ovary Syndrome Model with Insulin Resistance, Medico-legal Update 21, p. 744-749.
- [24] Laganà, A. S., Garzon, S., Casarin, J., Frachi, M., Ghezzi, F., 2018. Inositol in Polycystic Ovary Syndrome: Restoring Fertility through a PathophysiologyBased Approach, Trends in Endocrinology & Metabolism 29, p. 768-780.