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Inositol Improved Lipid Parameters in Women with Polycystic Ovary Syndrome

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Abstract

Introduction: Polycystic ovary syndrome (PCOS) is a prevalent endocrine disorder affecting women of reproductive age, often associated with metabolic abnormalities, including dyslipidemia, insulin resistance, and obesity. The aim of the study was to evaluate the effects of inositol supplementation on lipid profile parameters in PCOS patients.

Methods: With 100 participants, a case-control study was carried out separating a control group following a healthy diet from a case group using myo-inositol plus D-chiro-inositol (2000 mg daily). Lipid profiles were assessed at the beginning and after 8 weeks.

Result: The case group displayed considerable declines in triglycerides (14.6%, $P < 0.001$), total cholesterol (22.3%, $P < 0.001$), and low-density lipoprotein cholesterol (7.1%, $P = 0.013$). Although not statistically significant, there is a slight decrease observed in high-density lipoprotein cholesterol (HDL) levels ($p = 0.058$).

Conclusion: inositol may effectively improve lipid profiles in PCOS patients, supporting its potential as a therapeutic option for managing metabolic disturbances associated with the condition.

Keywords: Lipid profile; Inositol; Infertility; Polycystic Ovary Syndrome

Abbreviations

PCOS: Polycystic Ovary Syndrome; HDL: High-Density Lipoprotein; MI: Myo-Inositol; DCI: D-Chiro-Inositol; IPGs: Inositol-Phospho-Glycans; GPI: Glycosylphosphatidylinositol; PP1: Phosphoprotein Phosphatase 1; AMH: Anti-Mullerian Hormone; LH: Luteinizing Hormone; TG: Triglyceride; GK: Glycerol-Kinase; GPD: Glycerol-Kinase-Peroxidase; TC: Total Cholesterol: CHE: Cholesterol Esterase; CHO: Cholesterol Oxidase; LDL: Low-Density Lipoprotein; VLDL: Very Low-Density Lipoprotein; MetS: Metabolic Syndrome; CVD: Cardiovascular Disease.

Introduction

Polycystic ovary syndrome (PCOS) is a reproductive disorder with multiple metabolic derangements, affecting women worldwide, with a frequency of 8-13% [1]. It is linked to metabolic disorders including altered lipid profiles, insulin resistance, and reduced glucose tolerance. Considered the fundamental cause of infertility, PCOS is the most common endocrine disorder a woman may encounter in

her reproductive years [2]. PCOS and its expressions are identified using the Rotterdam diagnostic criteria, most often occurring phenotypes are listed in Table 1 [3]. The table below arranged from most sever phenotype A to least sever phenotype D [4].

Phenotype	Hyperandrogenism	Ovarian Dysfunction	Polycystic Ovarian Morphology
Type A	√	√	√
Type B	√	√	
Type C	√		√
Type D		√	√

Table 1: Phenotype of PCOS.

In 2003, Rotterdam Criteria were applied for diagnosis of PCOS. Therefore, extending the phenotypic expression of PCOS to encompass any two of the three primary features: oligo-amenorrhea, hyperandrogenism, and ultrasonic-appearing polycystic ovarian morphology [5]. To exclude similar conditions, a criteria were also applied to accurately define the PCOs diagnosis [6]. The PCOS is a complex ailment with hormonal imbalance, ovulatory disturbances, and a high level of androgens, particularly testosterone. This leads to symptoms such as hirsutism, acne, and ovulatory disturbances [7]. The development of these symptoms can result in anovulatory cycles, irregular menstruation, and infertility. These immature follicles develop into tiny cysts, known as “polycystic” cysts.

Inositol, a cyclic carbohydrate with six hydroxyl groups, is considered a vitamin B8. It has nine stereoisomers, including Myo-inositol and De-chiro-inositol [8]. Myo-inositol is formed from glucose and is not considered an essential nutrient. It is found in various foods such as meat, citrus fruits, corn, beans, grains, legumes, and supplements. It is necessary for the growth and development of cells in the body and can be found in various vegetables, fruits, beans, nuts, grains, and milk [9].

Inositol is a polyalcohol with nine stereoisomers, including myo-inositol (MI) and D-chiro-inositol (DCI) are mediated by inositol-phospho-glycans (IPGs), which mimic the effects of insulin by altering intracellular metabolism and enzyme activity. When insulin binds to its receptor, IPGs are generated by certain proteins found on the outer part of the cell membrane or hydrolysis of glycosylphosphatidylinositol (GPI) lipids. Two IPGs are formed: IPG-DCI and IPG-MI, which activate the glycogen synthase either directly or indirectly via the activation of phosphoprotein phosphatase 1 (PP1). IPG-MI activates PP1 by directly causing glucose absorption and blocking cAMP protein kinase A and adenylate cyclase, leading to reduced blood glucose levels [10].

In women with polycystic ovary syndrome (PCOS), impeded inositol and/or GPI metabolism can lead to insulin resistance. However, obesity plays a role in abnormal IPG-DCI synthesis independently of PCOS. MI reduces body weight, leptin secretion, and elevates HDL cholesterol. Myo-inositol is the most prevalent inositol isomer in the human body, which is converted into DCI by an insulin-dependent enzyme. The MI/DCI ratio is impacted by dysregulation of enzyme activity [10,11].

In the ovary, DCI causes excess insulin-dependent testosterone production, while MI increases the effects of FSH via anti-Mullerian hormone (AMH). MI has been detected in follicular fibroblasts and seems to enhance the quality of oocytes and embryos. The MI/DCI ratio is typically 100:1, while it is just 0.2:1 in PCOS [12]. Hyperinsulinemia augments ovarian androgen production by boost luteinizing hormone (LH) secretion, impacting ovarian stimulation. Insulin uses inositol phosphoglycans (IPGs) as secondary messengers, regulating oxidative and non-oxidative glucose metabolisms and its uptake by GLUT4 [13].

The epimerase enzyme responsible for converting myo-inositol into DCI is insulin dependent, and this conversion is diminished in insulin resistance tissues. A reduction in myo-inositol or a defect in the function/expression of epimerase enzyme that converts MI to DCI can lead to insulin resistance. DCI at 1200mg/day takes by obese PCOS patients for 8 weeks significantly reduced insulin area under the curve after an oral glucose tolerance test by 62% and free testosterone levels by 55%, triglyceride concentrations diminish from 184 mg/dL to 110mg/dL, and ovulation was repaired in 86% of patients taking DCI [14].

Material and Methods

Study Settings

From November 1, 2023, until February 1, 2024, case-control study comprising 100 people was undertaken. The study received ethical approval from the University of Mosul’s College of Pharmacy and the Mosul Health Directorate. Participants split apart. Group used myoinositol plus de-

chiro-inositol (2000 mg once daily) (case group), and the control group followed a healthy diet.

Ethical Approval: The study was approved by the scientific council of the Academy of Clinical Pharmacy and the Nineveh Health Directorate's central ethical committee. Every participant signed an informed consent. Patient questionnaires, abdominal imaging, and thorough tests were used in data collection. Two hundred PCOS patients between the ages of fifteen and thirty-five underwent anthropometry, hormonal, and biochemical testing. Along with specifics on symptoms, drugs, and laboratory findings before and after therapy, the questionnaire gathered personal, familial, and demographic information.

Women with PCOS between the ages of 15 and 35 who met the Rotterdam criteria-2003 were included in the study. These criteria require at least two of the following: high androgen levels, ovarian dysfunction, and certain ultrasonic results from the ovaries. Exclusions covered women with autoimmune diseases, diabetes, cardiovascular disease, hypertension, chronic renal failure, malignant diseases, or a history of specific drugs. We also excluded women who were unable to reduce their weight and those who were older than fifty years. Using disposable syringes, blood samples (5mL) were taken from women with PCOS on the second or third day of their cycle. After centrifugation, the serum was used for lipid profile analysis.

Materials

The study measured lipid profiles using BS-230-MINDARY equipment.

Lab Techniques for Lipid Profile: Sample collection and preparation are the first steps in determining triglyceride (TG) concentration. Human serum is the preferred sample, as whole blood, hemolysis, and urine are not recommended. Freshly drawn serum should be collected in a suitable gel tube and then centrifuged. The plan involves a series of steps involving lipase, glycerol-kinase (GK), and glycerol-kinase-peroxidase (GPD) that change TG into hydrogen peroxide (H_2O_2). The H2O2 then breaks down 4-Aminoantipyrine to make quinone-imine, a colorful dye whose absorbance rise is exactly equal to the concentration of TG. 10 µL of human plasma or serum are needed for the operation; this is gathered in a gel tube, centrifuged, and then transferred to a HITACHI CUP. This cup is placed in the machine, and through specific programming, the result is obtained. Before usage, the LH (CLIA) reagent kit has to be gently inverted to resuspend settled microparticles. With the analyzer automatically computing the TG concentration in mg/dL, the findings show up on the screen and are noted on laboratory paper.

Human serum is once again the recommended sample for measurement of total cholesterol (TC), collected and centrifuged as with TG. Cholesterol esterase (CHE) breaks down cholesterol ester to produce free cholesterol, which, along with endogenous cholesterol, generates H2O2 through cholesterol oxidase (CHO). Then, using phenol, H2O2 oxidizes 4-Aminoantipyrine to produce quinone-imine, a colorful dye. The increase in absorbance is directly proportional to cholesterol levels. The procedure mirrors that for TG, with 10 µL of serum required, centrifugation, and application to a HITACHI CUP. Before usage, the reagent kit is gently inverted; the sample is run through the machine, and results show on the screen. Following calibration, the analyzer uses an automatic TC concentration calculation in mg/dL.

High-density lipoprotein (HDL) concentration measurement uses the same steps for collecting and preparing the sample. Human serum that has been freshly drawn and centrifuged is preferred. The principle involves directly determining serum HDL levels without pre-treatment or centrifugation. Cholesterol esters are converted to free cholesterol and then to H2O2, which oxidizes 4-Aminoantipyrine with phenol to form a colored dye. The increase in absorbance is directly proportional to HDL concentration. The process calls for gathering 10 µL of serum, centrifuging, and then putting it in a HITACHI CUP. Before usage, the reagent kit is gently inverted; the sample is run in the machine, and results show up on the screen. The analyzer automatically calculates HDL concentration in mg/dL.

The measurement of low-density lipoprotein (LDL) concentration typically uses the Friedewald equation, which estimates LDL based on the concentrations of TC, HDL, and TG. Measuring TC, HDL, and TG; calculating very low-density lipoprotein (VLDL) cholesterol by dividing the TG value by 5; and finally, estimating LDL using the equation LDL = TC - HDL - VLDL. In a clinical environment, this method enables a precise and quick estimate of LDL content.

Results

After an 8-week Inositol supplementation in the case group as opposed to the control group, the study shows notable changes in lipid profile parameters. Particularly, triglycerides (TG) by 14.6% (P-value 0.001) and total cholesterol (TC) levels by 22.3% (P-value 0.001) showed rather considerable declines. Additionally, low-density lipoprotein cholesterol (LDL) decreased significantly by 7.1% (P-value 0.013) (Figure 1).

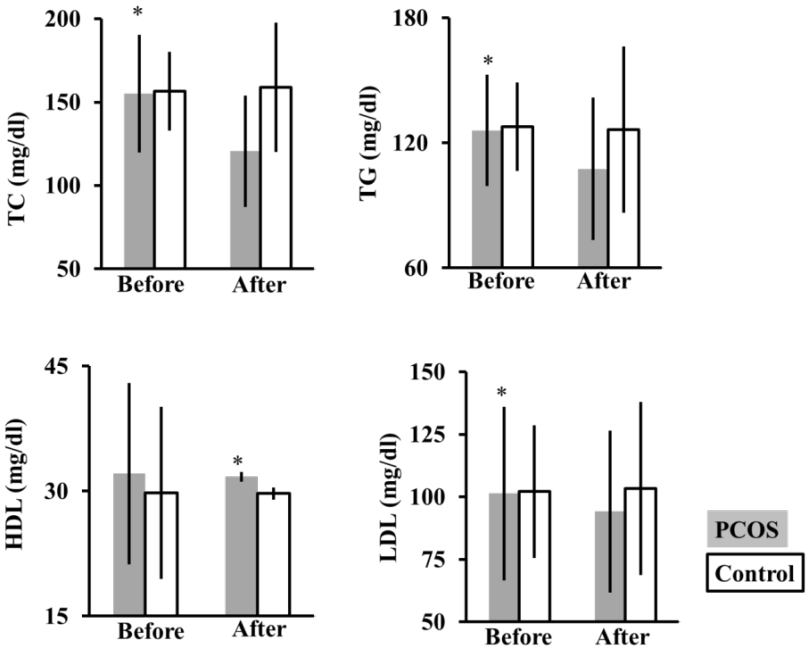

Figure 1: Lipid profile measured in control and PCOS patients before and after 2 months of inositol therapy. Data expressed as mean±SD (n=50 per group). * indicates significant differences between before and after 8 months in the same group at p value less than 0.05 using two sample t-test.

Discussion

The present study confirmed that inositol improved lipid profile via reduction of TC, TG, and LDL, alongside elevated HDL. These results line up with research done by Costantino, et al. [15] though not statistically significant; a small drop in high-density lipoprotein cholesterol (HDL) (P-value 0.058) also was noted [15]. This remark supports the research carried out by Ravn, et al. [16].

In contrast to our findings, Carvalho, et al. [17] meta-analysis revealed that myo-inositol administration had no significant impact on cholesterol and triglyceride levels, underscoring a divergence in outcomes that merits further investigation [17]. Similarly, folate supplementation at 5 mg/d for four weeks failed to alter lipid profiles in individuals with familial hypercholesterolemia, as evidenced by previous studies [18]. These discrepancies highlight the complexity of metabolic responses to nutrient interventions and suggest that factors such as dosage, duration of treatment, and individual metabolic differences might play crucial roles. Notably, our research aligns with emerging data supporting the role of inositol as a modulator of insulin-mediated metabolic parameters. This finding is consistent with previous evidence emphasizing the relationship between insulin resistance and inositol-phosphoglycan intracellular balance. The modulation effect observed in our study suggests potential therapeutic avenues for leveraging inositol derivatives to manage metabolic disorders linked to insulin resistance. Therefore, the integration of these conflicting results into a cohesive framework necessitates additional targeted research to elucidate the precise mechanisms and conditions under which inositol exhibits its modulatory effects on lipid metabolism [19].

Recent studies illustrate the potential benefits of inositol supplementation on lipid profiles in patients with various metabolic conditions, though results remain mixed and call for further scrutiny. Kim, et al. [20] reported that a 13-week regimen of inositol supplementation significantly reduced total cholesterol, LDL cholesterol, and the LDL/HDL cholesterol ratio while elevating HDL cholesterol in patients with T2DM, although it did not affect triglyceride levels. Contrastingly, among obese women with PCOS, a daily intake of 1200 mg of inositol over six to eight weeks improved insulin action, ovulatory function, androgen levels, blood pressure, and TG levels [21]. Moreover, postmenopausal women with metabolic syndrome (MetS) who took inositol for six months experienced significant decreases in triglycerides by 43.2% and increases in HDL cholesterol by 48.6%, but no changes were observed in other lipid parameters [22]. Supporting these findings, Pundir, et al.'s meta-analysis demonstrated

that inositols could effectively regulate menstrual cycles and ovulation while also making positive metabolic adjustments in PCOS patients [23]. Notwithstanding these encouraging outcomes concerning triglycerides and HDL-cholesterol enhancement, it is widely acknowledged that elevated concentrations of TG, TC, and LDL cholesterol—alongside reduced HDL cholesterol—pose significant cardiovascular disease (CVD) risks [24,25]. Nutraceuticals like inositol have shown promise not only for their lipid-modulating effects but also for their broader impact on human dyslipidemia; they potentially reduce atherosclerosis progression and CVD burden by mechanisms such as upregulating hepatic LDL receptors or decreasing intestinal cholesterol absorption [26-30]. The synthesis of this evidence underscores the therapeutic relevance of nutraceutical interventions but also highlights the necessity for continued research to clarify their efficacy fully.

The meta-analysis conducted by Tabrizi, et al. [19] in 2018 highlights the differential impact of inositol supplementation on HDL-cholesterol levels between patients with polycystic ovary syndrome (PCOS) and those without. Specifically, the study found that inositol supplementation had a positive effect on elevating HDL-cholesterol levels in PCOS patients, whereas no significant effect was observed in non-PCOS individuals. The duration of the trials included in the analysis ranged from 6 weeks to 12 months, allowing for an examination of how varying lengths of supplementation influence outcomes. In a subgroup analysis, it was revealed that trials with duration of less than 14 weeks did not show significant changes; however, those with durations equal to or exceeding 14 weeks demonstrated a significantly beneficial effect on increasing circulating HDL-cholesterol levels [19]. This finding underscores the importance of sustained treatment periods when assessing the efficacy of nutritional supplements like inositol in modulating lipid profiles, particularly among specific patient populations such as those with PCOS. By distinguishing between different lengths of intervention and their respective outcomes, the study provides valuable insights into optimizing treatment protocols for achieving desired health benefits.

Recent studies indicate that the binding of insulin to specific receptors facilitates the intracellular transport of inositol phosphoglycan, suggesting its pivotal role as a mediator in the insulin signaling cascade [31]. This mechanism potentially elucidates how decreasing insulin resistance, following inositol intake, may enhance peripheral insulin sensitivity [32], which is crucial for improving overall metabolic health. Enhanced insulin sensitivity can subsequently ameliorate lipid profiles by reducing visceral fat weight, hepatic lipid accumulation, and insulin secretion while elevating adiponectin concentrations [33].

Adiponectin is particularly significant because it enhances insulin sensitivity and counteracts factors such as leptin, resistin, and C-reactive protein—molecules associated with increased insulin resistance [34,35]. In clinical trials, myo-inositol (MI) supplementation at a dose of 4 g/day for 8 weeks significantly elevated adiponectin levels among patients with gestational diabetes [12], underscoring the effectiveness of MI in regulating glycemic control. Furthermore, co-supplementation involving MI, soy isoflavones, and cocoa polyphenols over six months markedly decreased resistin levels among postmenopausal women with Metabolic Syndrome (MetS) [36], highlighting a multifaceted approach to managing metabolic disorders. Additionally, significant weight loss and reductions in leptin levels observed after MI administration are indicative of improved lipid profiles [37], demonstrating MI's potential utility in comprehensive metabolic management strategies. These findings collectively underscore the therapeutic promise of inositol and related compounds in combating insulin resistance and optimizing lipid metabolism.

Conclusion

The study found significant changes in lipid profile parameters after 8 weeks of Inositol supplementation, including significant declines in triglycerides and total cholesterol, and a significant decrease in low-density lipoprotein cholesterol.

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