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Comparing Metformin, Inositol, and Lifestyle Modifications to Improve Symptomatology of Polycystic Ovary Syndrome (PCOS): A Research Protocol

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Abstract

Introduction: Polycystic ovary syndrome (PCOS), a common endocrinological disorder of women of reproductive age, affects about 5-20% of women globally. It is diagnosed through the Rotterdam criteria with the presence of two out of three clinical features of oligo-anovulation, hyperandrogenism, and/or polycystic ovaries. Hyperinsulinemia and insulin resistance are central features of PCOS , along with obesity. This study aims to compare three treatment interventions: metformin, inositol, and lifestyle modifications to improve symptoms of PCOS.

Methods: In this four-arm randomized study, 48 women of reproductive age (25-36 years) will be recruited over a 12-week period. Impacts of treatment types (metformin, inositol and lifestyle modifications) will be determined in improving symptoms of PCOS. Control group, "Group A" (N=12) will not be going through any treatment; "Group B" (N=12) will be taking 500 mg of metformin daily, with close assessment of side effects; "Group C" will take 2 g of inositol supplements twice daily with a 40:1 myo-inositol and D-chiro-inositol ratio; and "Group D" will undergo lifestyle modifications, closely monitored by personal trainers, nutritionists, and dietitians, to facilitate weight loss. ANOVA, Pearson's correlation, and Kruskal-Wallis H test will be conducted to determine significance.

Anticipated Results: PCOS patients of group C, inositol intake, may be seen to have greatest improvements in PCOS symptomatology due to its insulin sensitizing, metabolic, and hormonal influences, with minimal adverse effects.

Discussion: Previous studies have shown inositol consumption to result in significant improvements in insulin resistance, menstrual cycle regularity, Acne score, Ferriman-Gallwey score, endocrine and metabolic parameters, reduced serum levels of total testosterone, and elevated sex hormone binding globulin in women with PCOS. Metformin may yield similar effects to inositol, but greater adverse effects may be present. Through a reduced BMI, lifestyle modifications have shown to significantly reduce total androgen profile, waist circumference, and lipid profile while increasing clinical pregnancy rate by 20%.

Conclusion: The comparison of three treatment modalities may be beneficial for PCOS patients to provide optimal treatment. It may be beneficial to compare a combination of treatment interventions in the future for additive or synergistic effects.

Keywords: polycystic ovary syndrome; hyperandrogenism; ovulation; polycystic ovaries; hyperinsulinemia

Introduction

Polycystic ovary syndrome (PCOS) is an endocrine disorder that affects 5-20% of reproductive aged women globally [1,2,3]. The common characteristics of PCOS include menstrual cycle disturbance, hyperandrogenism (hirsutism, alopecia, and acne), infertility, and obesity [4]. PCOS is diagnosed based on Rotterdam criteria and requires two out of the three clinical features of oligo-anovulation, hyperandrogenism, and/or polycystic ovaries to be present [5]. The pathogenesis of PCOS remains unclear but has been hypothesized to result from functional ovarian hyperandrogenism (FOH) through the dysregulation of androgen secretion distinguished by 17-hydroxyprogesterone hyperresponsiveness to gonadotropin stimulation [6]. Others may present with FOH detectable by testosterone elevation upon suppression of adrenal and androgen production [6]. Many studies have also displayed an association between PCOS and low-grade chronic inflammation, with increased inflammatory markers or representative gene markers in PCOS patients [2]. Development of PCOS may result in increased risk of developing cardiovascular disease, atherosclerosis, high blood pressure, and infertility [2].

Insulin resistance and hyperinsulinemia are central features of PCOS [7], with 44% of PCOS patients also presenting with obesity [8]. The clinical presentation of PCOS is worsened with the presence of obesity, increasing insulin resistance, further elevating ovarian and adrenal androgens of unbound testosterone [8]. Although there is no consensus of a PCOS treatment regimen, lifestyle

management and other drugs/supplements have been explored for symptom management [9].

Lifestyle modifications are a treatment intervention often studied due to the impact of obesity accompanying PCOS on conception, influencing fertility in women with PCOS. Thus, weight loss can lead to improvements in endocrine profiles and reproductive outcomes in PCOS patients [11]. Losing about 5-10% of total body weight through lifestyle modifications can cause up to 30% central fat reduction, improving insulin sensitivity and ovulation [11].

Among exploration of PCOS treatment interventions, metformin is a drug often prescribed to many women with PCOS. Metformin is an insulin sensitizing agent proven to reduce blood glucose concentrations and is effective in inducing weight loss [10]. However, persistent use of metformin has shown to cause acute gastrointestinal adverse effects including nausea, vomiting, diarrhea, gas, and rarely lactic acidosis [12]. Another insulin sensitizer is inositol, a natural sugar compound with eight isomers which has demonstrated to improve insulin sensitivity. Myo-inositol and D-chiro inositol are the most abundant inositol isomers studied in improving insulin sensitivity and reproductive outcomes in PCOS [13], and act as insulin second messengers [14]. Although well-tolerated inositol supplementation may potentially cause mild side effects, including nausea, tiredness, dizziness, headaches, and stomach pain. Through improvements in metabolic and hormonal states, restoring spontaneous ovulation, and improving ovarian stimulation in assisted reproductive technology, inositol's may be an effective treatment choice for PCOS [14].

The of lack regulated treatment for PCOS has caused exploration of various drugs, supplements, and modifications throughout literature to investigate and propose potential treatment options. This study aims to compare and analyze three different potential treatment regimens for women with PCOS: metformin (a drug), inositol (a natural vitamin supplement), and lifestyle modifications (exercise and nutrition). Although various studies have examined the influence of these interventions upon improving PCOS symptoms individually, this study aims to compare all three interventions to aid the lack of consensus of optimal PCOS treatment. Previously throughout literature, all three interventions have not been compared individually to test for improvements in PCOS symptoms. This emphasizes the importance of testing for the degree of change for each parameter by comparing the baseline and post-test values. This will provide an isolated assessment of the impact each intervention has upon parameters, providing clinicians and patients with insight on best course of treatment and potential combinatory treatment options.

It is hypothesized that inositol may have greatest benefits in improving PCOS related symptoms including hyperandrogenism and hyperinsulinemia, metabolic, and hormonal influences, with minimal adverse effects.

Methods

Study Protocol

This prospective single centre, randomized study will recruit 48 women with PCOS between the ages of 25-36 years of age. The impact of treatments will be determined over a 12-week period, assessing improvements in the clinical features of PCOS. Participants must've been diagnosed within the last 12 months and no previous PCOS treatment (i.e., consumption of metformin or inositol) was ensured prior to study conduction. This is conducted to minimize differing outcomes based upon interactions or pre-developed resistances to treatment types.

At baseline, upon an overnight fast (minimum 8-hours), blood of participants will be obtained to measure fasting serum insulin and glucose, and serum sex hormones, through testing. This will be done through the homeostasis model assessment-estimated insulin resistance (HOMA-IR) and beta cell function, due to its straightforward and cost-efficient applications [17]. BMI testing will be done to measure baseline profiles of body fat based upon height and weight. polycystic ovaries will also be assessed at baseline through ultrasound. The Ferriman-Gallwey score will be used to evaluate hirsutism and the Acne Score will be used to evaluate acne. Pre-treatment testing will be continued throughout study with monthly follow-ups (every 4 weeks) measuring fasted serum insulin and glucose, and serum sex hormones, HOMA-IR, BMI Ferriman-Gallwey score, and ultrasound for polycystic ovaries.

Participants are matched for baseline characteristics and are randomized into one of the four interventions. Control group, group A (N=12) will proceed with their regular lifestyle and diet, apart from any treatment intervention. Group B (N=12) will be receiving 500 mg of metformin daily (dapagliflozin-metformin, brand name XigDuo manufactured by AstraZeneca Canada Inc.) with their evening meal [18], with close assessment of side effects. Group C (N=12) will be taking 2 g of inositol supplements (Myo + D-Chiro inositol manufactured by Fairhaven Health) twice a day (before breakfast and before bedtime), with 40:1 myo-inositol and D-chiro-inositol ratio. Group D (N=12) will be closely monitored by personal trainers, nutritionists, and dietitians, recruited from a certified and licensed organization, to facilitate weight loss. This will be done through 1 hour of HIIT training daily (30 sec of work at 100% maximal aerobic velocity, followed by 30 sec of active recovery at 50% of maximal aerobic velocity, with 15 repetitions to begin and adding a repetition each week to reach 27 repetitions by end of the program [19]). Participants will also remain in a 500-calorie caloric deficit from daily requirements (with nutrition distribution of 50-60% carbohydrates, 25-30% fat, and 15-20% proteins [20]). Treatment groups B-D will be compared to control group, A, to assess efficacy between treatment types on improving

PCOS symptomatology. This will be assessed through measuring degree of change across parameters (BMI, menstrual cycle length, insulin sensitivity, acne/hirsutism, hyperandrogenism, and polycystic ovaries) through specific testing, to improve the clinical presentation of PCOS. Any adverse effects, such as persistent gastric issues should result in immediate discontinuation of the drug.

Table 1. Parameters which will be tested are displayed alongside the baseline testing used. Changes across parameters will be measured through comparison between baseline testing and measurements upon enrolment. Each parameter will be measured for each arm of the study. Clinical features of PCOS anticipated to be influenced by each parameter are listed. All simulations were performed using the software Microsoft Word.

Parameter	Baseline Testing	Impacted Clinical Feature of PCOS	Frequency of Measurement Upon Enrolment
BMI	Measure profiles of body fat based upon height and weight	Ovulation	Every 4 – weeks (3 time points after baseline)
Menstrual Cycle Length	Tracking cycle length	Ovulation	
Insulin Sensitivity	Fasted (minimum 8 hours) blood testing of serum insulin and glucose levels HOMA-IR and beta cell function	Hyperandrogenism, ovulation, polycystic ovaries	
Acne/Hirsutism	Ferriman-Gallwey score (Hirsutism) and Acne Score (Acne)	Hyperandrogenism	
Hyperandrogenism	Fasted (minimum 8 hours) blood testing of serum sex hormones (free testosterone) and sex hormone binding globulin	Hyperandrogenism	
Polycystic Ovaries	Ultrasound assessing polycystic ovaries (follicle size and volume)	Polycystic ovaries and ovulation	

PCOS Patients

Obese women between the ages of 25-36 diagnosed with PCOS will be recruited for eligibility in the study by contacting local fertility clinics. Diagnosis of PCOS is confirmed using the Rotterdam criteria, which requires two out of three clinical features of oligo-anovulation (infrequent menstruation), clinical hyperandrogenism (hirsutism, acne, alopecia) or biochemical hyperandrogenism (elevated levels of total or free testosterone), and polycystic ovaries (≥ 12 follicles with a diameter of 2-9mm, with potential ovarian volume >10mL in at least one of the ovaries) to be present [5]. To verify obesity, Body Mass Index (BMI) is assessed and would require to be greater than or equal to 30 kg/m^2 [15]. Participants are excluded from the study if diagnosed with types 1 and 2 diabetes, pituitary insufficiency, persistent hyperprolactinaemia, congenital adrenal hyperplasia, and serum creatinine >1.5mg/dl [16]. PCOS patients undergoing fertility treatment are also excluded from the study. Eligible participants are aware of study protocol and give consent to participate in the study.

Outcome Measures

Benefits of metformin, inositol, and lifestyle modifications to improve PCOS symptomatology will be measured through restoration or improvements in clinical features of PCOS (i.e., oligo-anovulation, hyperandrogenism, and polycystic ovaries (follicle size and ovary volume)). Changes observed across test parameters may influence improvements in these features, conducted through parameter specific testing. Improvements in insulin sensitivity will be assessed through blood testing for fasting serum insulin and glucose levels, alongside the HOMA model for insulin resistance; indicative of improvements in hyperandrogenism and ovulation. Moreover, hyperandrogenism will be assessed through blood testing for fasting serum sex hormones and the Ferriman-Gallwey score measuring hirsutism. BMI testing

will be continually conducted to assess changes over the course of the treatment interventions which may influence improvements in ovulation. Polycystic ovaries and ovulation will be examined and measured through ultrasound. Ovulation and menstrual cycle abnormalities will be tested through tracking of cycle length and bleeding days. Outcome measures will be assessed every 4-weeks to analyze influence of different treatment interventions.

Statistical Analysis

ANOVA will be used to compare outcome significance including fasted serum glucose and insulin, and serum sex hormones (free testosterone and sex hormone binding globulin) between three treatment types and control group.

Pearson's correlation coefficient will be used to measure statistical significance of weight loss in improving PCOS symptomatology.

Kruskal-Wallis H test will be used to determine significant differences between the 4 arms across tested parameters.

Anticipated Results

Upon testing various PCOS parameters across treatment groups to measure the degree of change over the intervention period, it can be anticipated that inositol may be most effective in improving PCOS symptomatology, followed by metformin. This can be anticipated as their insulin sensitizing properties and hormonal effects should improve at-least 2 of the 3 diagnostic features of PCOS, specifically oligo-anovulation and hyperandrogenism. Effects of metformin and inositol would likely be largely seen upon improving insulin sensitivity, menstrual cycle length, polycystic ovaries, and hyperandrogenism with substantial influence on improving BMI and acne/hirsutism. Participant dropout may also be observed due to potential side effects experienced because of metformin or inositol use, including persistent gastric issues or resistance. Furthermore, lifestyle modifications should improve insulin sensitivity, ovulation, and specifically BMI. Despite the anticipated improvement across parameters through lifestyle modifications, this variability may suggest greater improvements to be seen across parameters (including insulin sensitivity, menstrual cycle length, and acne/hirsutism) when a weight loss regimen is prescribed in conjunction with metformin or Inositol.

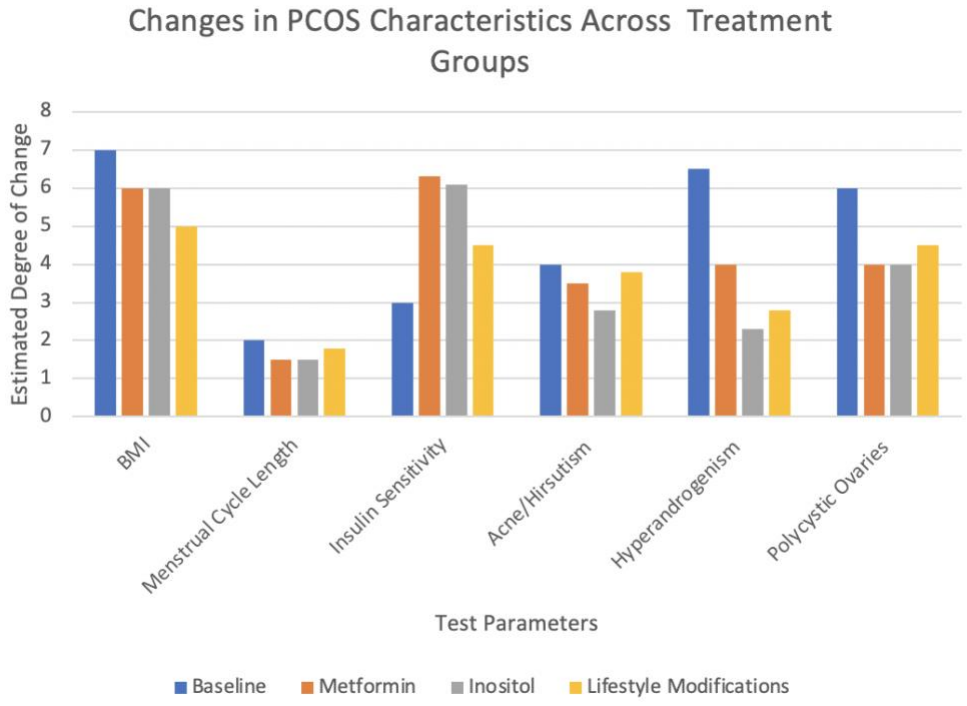

Figure 1. Anticipated changes in test parameters across treatment groups, comparative to baseline scores. All simulations were performed using the software Microsoft Excel.

Discussion

This study investigates the effects of three interventions including metformin, inositol, and lifestyle modifications in improving clinical features and symptoms of PCOS. It is anticipated that all three interventions would improve symptoms of PCOS with the most profound effect observed in inositol intake. Greatest improvements in ovulation, hyperandrogenism and polycystic ovaries may be anticipated

through inositol usage, through changes in insulin sensitivity, menstrual cycle length, acne/hirsutism, hyperandrogenism (serum sex hormone levels), and polycystic ovaries observed on ultrasound. These improvements would be closely anticipated through the intake of metformin as well, but greater adverse effects may be present. While BMI would significantly decrease following lifestyle modifications due to the pronounced effect across metabolic and reproductive processes, a greater intervention duration may make these effects more prominent. Substantial improvements may be seen when using a combination of potential treatment types.

Improved PCOS symptoms may be anticipated with a significant decrease in BMI due to the pronounced effect of a reduced BMI on improving insulin sensitivity and ovulation [11]. However, such effects may require a longer period to observe as this mechanism of action secondarily influences the symptoms of PCOS. Initially it targets changes in BMI through regulating lipid profiles. Increased BMI, presenting as obesity can often lead to long term complications including cardiovascular risk and diabetes, alongside compromised reproductive function in PCOS patients, but can be significantly improved through lifestyle modifications [21]. Lifestyle modifications have displayed a 20% increase in clinical pregnancy rate (6-8% greater than other interventions) and a significant reduction in total androgen profile, waist circumference, and lipid profile [20]. Although, metformin and inositol do not primarily target weight loss, BMI may be substantially reduced in PCOS patients [22]. Studies have predicted that the intake of metformin alongside a caloric deficit may be associated with greater weight-loss than a low-calorie diet alone [23], which may be further examined if significant effect is observed.

Insulin sensitivity may also be significantly influenced by inositol and metformin as they are both insulin sensitizing agents which have comparable effects in ameliorating insulin sensitivity [22]. Improving insulin sensitivity would also allow for improvements in elevated ovarian and adrenal androgens of unbound testosterone [8]. The severity of insulin resistance in PCOS patients can be notably influenced by weight gain [24]. Hence, substantial improvements may be seen in insulin sensitivity with weight loss through lifestyle modifications. However, metformin and inositol may result in greater improvements in insulin sensitivity in comparison to lifestyle modifications, as their primary influence and composition targets improvements in insulin sensitivity. PCOS patients which consumed Myo-inositol or D-chiro inositol for six months, displayed significant improvements in insulin-resistance, regularity of the menstrual cycle, the Acne Score, and endocrine and metabolic parameters in PCOS patients [25].

Likewise, improvements in menstrual cycles and polycystic ovaries can be primarily anticipated through inositol and metformin intake. Studies assessing improvements in menstrual cycles of PCOS patients, did not display significant differences between lifestyle modification or metformin groups alone, or combined [26]. Moreover, comparisons between metformin and inositol have shown to result in significant reductions in BMI and menstrual cycle normalization in about 50% of patients, with no significant change in acne and hirsutism [22]. Metformin has been found to be effective in restoring normal menstruation and in inducing ovulatory cycles in oligomenorrheic PCOS patients [27]. PCOS patients often face complications in pregnancy or fertility, however metformin administration did not show any significant advantage [27]. Additionally, the combination of metformin and myo-inositol was compared to metformin alone in improving menstrual cycle, hormonal and biochemical parameters, live birth rate, spontaneous conception, abortions, multiple pregnancy, and ovarian hyperstimulation syndrome [28]. It was found that the group which received metformin (500mg) with Myo-inositol (600mg) three times a day, had a significant improvement in menstrual cycles (cycle length and bleeding days) and live birth rate compared to the group with metformin alone, while improvements in biochemical and hormonal parameters in both groups were comparable [28].

Similarly, hyperandrogenism can be anticipated to significantly improve after inositol and metformin treatment due to the influences upon sex hormone binding globulin (SHBG). SHBG have binding properties with sex hormones to decrease levels of free testosterone circulating in the blood of PCOS patients. Hence, it can be anticipated that PCOS patients have reduced levels of SHBG, with the prevalence of hyperandrogenism and elevated free testosterone [5]. Inositol has been found to significantly increase serum SHBG, upon inositol administration for a minimum of 24-weeks [31]. In addition, SHBG may be significantly increased across patients following lifestyle modifications, with substantial improvements in patients taking metformin [26].

Other parameters including acne and hirsutism, indicative of hyperandrogenism, would not be anticipated to differ drastically among treatment interventions, but improvements have previously been analyzed from the usage of inositol. Myo-inositol intake was found to significantly decrease serum total testosterone, the Ferriman-Gallwey score (evaluating hirsutism), serum high-sensitivity C-reactive protein levels (measuring inflammation levels in the body) in women with PCOS with hyperinsulinism and normoinsulinism when compared with metformin [29].

Treatment duration may have considerable influence on the efficacy of treatment interventions. Pronounced effects upon test parameters may be scrutinized through greater treatment durations. This may specifically be seen in lifestyle modifications to allow adequate weight loss in a healthy manner to see a pronounced effect on BMI, further improving insulin sensitivity and ovulation [11]. Inositol intake may also benefit from a greater treatment duration, as hyperandrogenism was significantly improved over a minimum 24-week period [31]. Lengthening study durations

may necessitate greater funding and increased participant availability. Continued observance of adverse effects to treatment interventions, including gastric issues may be critical to exclude patients from further assessment. Moreover, resistance to supplements may require future additions of an enzyme to increase efficacy of the treatment.

Although, inositol has been proven to be effective in improving metabolic and reproductive functions in PCOS patients, a substantial number of patients have been found to be resistant to the supplement in turn decreasing its efficacy in desired treatment outcomes. However, clinical benefits of inositol in PCOS patients can be sustained in resistant women through the addition of the enzyme alpha-lactalbumin, providing inositol resistant PCOS patients with significant progress in treatment and re-establishing ovulation [30].

Improvements in hyperinsulinemia, lipid profiles, hyperandrogenism, and polycystic ovaries through treatment types may be interpreted as beneficial for women with PCOS. If inositol is determined as a beneficial treatment option, it would aid women with limited ability to partake in other treatments. Consumption of inositol may aid patients who cannot participate in lifestyle modifications due to limited mobility or dietary restrictions, and those facing varying degrees of side effects by consuming metformin. Although lifestyle modifications and weight loss are often found as the first course of treatment, the conjunction of metformin or inositol with such modifications may provide better prognosis of PCOS. This study provides an isolated comparison for improvements in each parameter upon participation in the three interventions.

Conclusions

This study assessed the influence of three treatment interventions in improving symptoms of PCOS, an endocrinological disorder characterized by oligo-anovulation, hyperandrogenism, and/or polycystic ovaries. Metformin, inositol, and lifestyle modifications were compared to determine the extent of symptom improvement in PCOS. It can be anticipated that inositol may yield greatest improvements, while lifestyle modifications may result in pronounced effects over a longer intervention period. Inositol and metformin can be anticipated to result in substantial improvements in hyperandrogenism, insulin sensitivity, menstrual cycle length, polycystic ovaries, and hirsutism. Lifestyle modifications may be most effective in reducing BMI, secondarily improving other parameters. Comparing effectiveness of these three interventions may be beneficial for women with PCOS who may face adverse effects to drugs, resistance to supplements, or experience mobility or dietary restrictions. Further extending this comparison with combined treatment interventions (i.e., inositol alone vs. inositol and lifestyle modifications) to observe additive or synergistic effects, may provide better indications for future PCOS treatments to optimize improvements in symptomatology.

List of Abbreviations Used

PCOS: polycystic ovary syndrome
FOH: functional ovarian hyperandrogenism
HOMA – IR: homeostasis model assessment-estimated insulin resistance
BMI: body mass index
SHBG: sex hormone binding globulin

Conflicts of Interest

The author(s) declare that they have no conflict of interests.

Ethics Approval and/or Participant Consent

This research protocol did not require ethics approval. This study will require ethics approval before it is conducted which may be done through registration in clinicaltrials.gov.

Authors' Contributions

JD: Designed this study, collected, and analyzed data, drafted the manuscript, and gave final approval for this version to be published.

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