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Investigating the Effects of Metformin and Inositol in the Treatment of Polycystic Ovary Syndrome: A Research Protocol

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Abstract

Introduction: Polycystic Ovary Syndrome (PCOS), an androgen hormone excess and ovarian dysfunction disorder is linked to insulin resistance, metabolic disorders, and obesity. Inositol, a natural sugar compound is effective in regulating insulin levels and follicle stimulating hormones. Metformin, a biguanide drug which is used for Type 2 Diabetes treatment controls glucose levels and insulin resistance. Using inositol and metformin together for treatment of PCOS has been suggested to be beneficial for individuals with PCOS. The purpose of this study is to assess the effectiveness of metformin and inositol in improving insulin resistance, hyperandrogenism, weight, menstruation, and ovulation.

Methods: A total of 36 women between ages of 25-35 clinically diagnosed with PCOS will be recruited to participate in a six-month double- blinded controlled trial. Participants were classified to normal BMI (18.5-24.0 kg/m^2) and overweight/obese BMI (25.0-29.9 kg/m^2 and >30 kg/m^2) and were randomized into one of the following treatments: 500 mg of metformin with 4 g of inositol, 250 mg of metformin twice daily or two placebo sugar pills. Over the 6-month period, blood tests for blood sugar, insulin levels and testosterone levels, weight assessment on scale, menstruation questionnaire and ultrasound will be used to assess improvement in symptomology.

Anticipated Results: It is anticipated that in both BMI groups, there will be a decrease in insulin resistance and hyperandrogenism with metformin and inositol use. There should be a reduction of weight in both BMI groups with increased effect seen in overweight/obese BMI. Menstruation and ovulation are anticipated to become more regular in both BMI groups using metformin and inositol.

Discussion: Studies have found that metformin significantly improves insulin resistance, decrease circulating free androgens, and increases sex hormone binding globulin. Inositol has been seen to decrease insulin resistance, LH/FSH ratio and free androgen in women with PCOS. The combination of metformin and inositol is seen to improve hormonal and biochemical parameters and have a significant effect on menstrual cycle length.

Conclusion: The combination of metformin and inositol may have synergistic effects that will PCOS symptomology and improve quality of life.

Keywords: polycystic ovary syndrome; metformin; inositol; insulin resistance; hyperandrogenism; androgen excess; menstruation; ovulation; body mass index

Introduction

Polycystic ovary syndrome (PCOS) is an endocrine disorder characterized by ovarian dysfunction and is most common in women of reproductive age [1]. The prevalence of PCOS in women is approximately 4-20% worldwide [1]. Symptoms of PCOS include weight gain, acne, hirsutism, irregular menstrual cycles, pelvic pain, problems with ovulation, and can also include enlarged ovaries with cysts [1]. PCOS is diagnosed using the Rotterdam Criteria which requires the presence of two out of three criteria: oligo-ovulation or anovulation, hyperandrogenism and detection of polycystic ovaries by ultrasonography [2]. The etiology of PCOS is not well established; however, it is hypothesized to be the dysregulation in the hypothalamic-pituitary-ovarian axis with an increased level of luteinizing hormone (LH) and gonadotropin-releasing hormone (GnRH), with decreased levels of follicle-stimulating hormone (FSH) [3]. Key features of PCOS include excess androgen levels and insulin resistance impacting production of insulin and insulin-like growth factor 1 (IGF-1) that contribute to increased androgen levels [3].

Primary treatment option for PCOS is lifestyle modifications, followed by medications targeted towards specific symptoms. Lifestyle modifications include reducing caloric intake, increase in physical activity, healthier diet changes and behavioural therapy [4]. Other treatments include combined oral contraceptive pills, anti-androgens and metformin to improve ovulation, regulate

menstrual cycles and androgen levels [5]. Metformin, a biguanide has also shown to improve insulin resistance in type 2 Diabetes and in PCOS. It inhibits hepatic gluconeogenesis which decreases blood glucose levels by increasing glucose uptake in peripheral tissues [6]. Inositol, a natural sugar compound within the body and present in many foods is shown to improve insulin sensitivity in PCOS. Myo-inositol, its most abundant stereoisomer works as a secondary messenger for insulin and FSH [9]. MI has been shown to decrease LH and androgen levels while regulating ovulation and menstrual cycles in women [4].

Research studies have evaluated the efficacy of metformin and inositol in PCOS [5]. However, there is a lack of research consisting of the combined use of metformin and inositol for symptom management in PCOS. The purpose of this study was to investigate the effects of metformin and inositol on symptoms of PCOS particularly, insulin resistance and hyperandrogenism. Furthermore, secondary outcomes including weight loss, menstruation, and ovulation will also be investigated.

Methods

PCOS Participants

Females between the ages of 25-35 will be recruited for this study. The women must be clinically diagnosed with PCOS using the Rotterdam criteria that includes the presence of two out of three clinical features of: oligo-ovulation or anovulation, hyperandrogenism and detection of polycystic ovaries by ultrasonography [7]. The Body Mass Index (BMI) is assessed, and participants will be grouped based on BMI range: normal BMI (18.5-24.0 kg/m^2) and overweight/obese (25.0-29.99 kg/m^2 and $\geq$ than 30 kg/m^2). Participants previously diagnosed with Type 1 and 2 Diabetes, Cushing's syndrome, hypothyroidism, and pituitary gland or hypothalamus disorders will be excluded from the study. Participants being treated for other clinically diagnosed diseases or taking any prescribed medication for PCOS within the last 12 months will also be excluded from the study.

Study Protocol

This study is a 6-month randomized blinded control trial that investigates the improvement of insulin resistance, hyperandrogenism, weight gain, menstrual irregularities, and ovulation of 36 women between the ages of 25-35 diagnosed with PCOS. Group A consists of 18 women with PCOS with a normal BMI and group B consists of 18 females with overweight/obese BMI. Participants in each group will be further randomized into three different intervention groups. One to receive 500 mg of metformin (brand name Glucophage produced by Merck) taken once daily with their evening meal [8] and a 4 g of inositol supplement once daily in the morning or evening with food (MET and INO) (n=6), another to receive 250 mg of metformin (brand name Glucophage produced by Merck) twice daily taken with or after evening meal (MET) (n=6) and lastly to receive two placebo sugar pill (control) (n= 6). Over the 6-month period, blood tests for blood sugar, insulin levels and testosterone levels, weight assessment on scale, menstruation questionnaire and ultrasound will be assessed at baseline, midpoint (3 months) and endpoint. The mentstration questionnaire will be an investigator developed scale based on cycle duration, menstrual flow and heaviness and associated symptoms.

Outcome Measurement

Clinical outcomes of PCOS including insulin resistance, hyperandrogenism, and metabolic symptoms of weight gain, and menstruation and ovulation irregularity were evaluated. Insulin resistance is assessed using the Glycated Hemoglobin Test (HbA1c) and Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) test. HbA1c measures the amount glucose attached to hemoglobin (blood sugar) levels over the past 2-3 months [9] while HOMA-IR measures beta-cell function and insulin resistance by multiplying fasting glucose levels and fasting insulin levels [10]. Hyperandrogenism is evaluated using a blood test to measure testosterone levels and calculated free androgen index (FAI) ratio. Body weight is measured using kilogram or pounds scale. In addition, menstruation and ovulation changes will assessed using a questionnaire that assesses cycle length, bleeding days and a follicle tracking ultrasound scan.

Statistical Analysis

To compare the effect of MET and INO on the improvement of clinical symptoms of PCOS, one-way analysis of variance (ANOVA) was used. Intention to treat (ITT) principle was used for adjustment. Probability values (p-values) of <0.5 were considered statistically significant. Statistical analysis was done using "R Studio" programming.

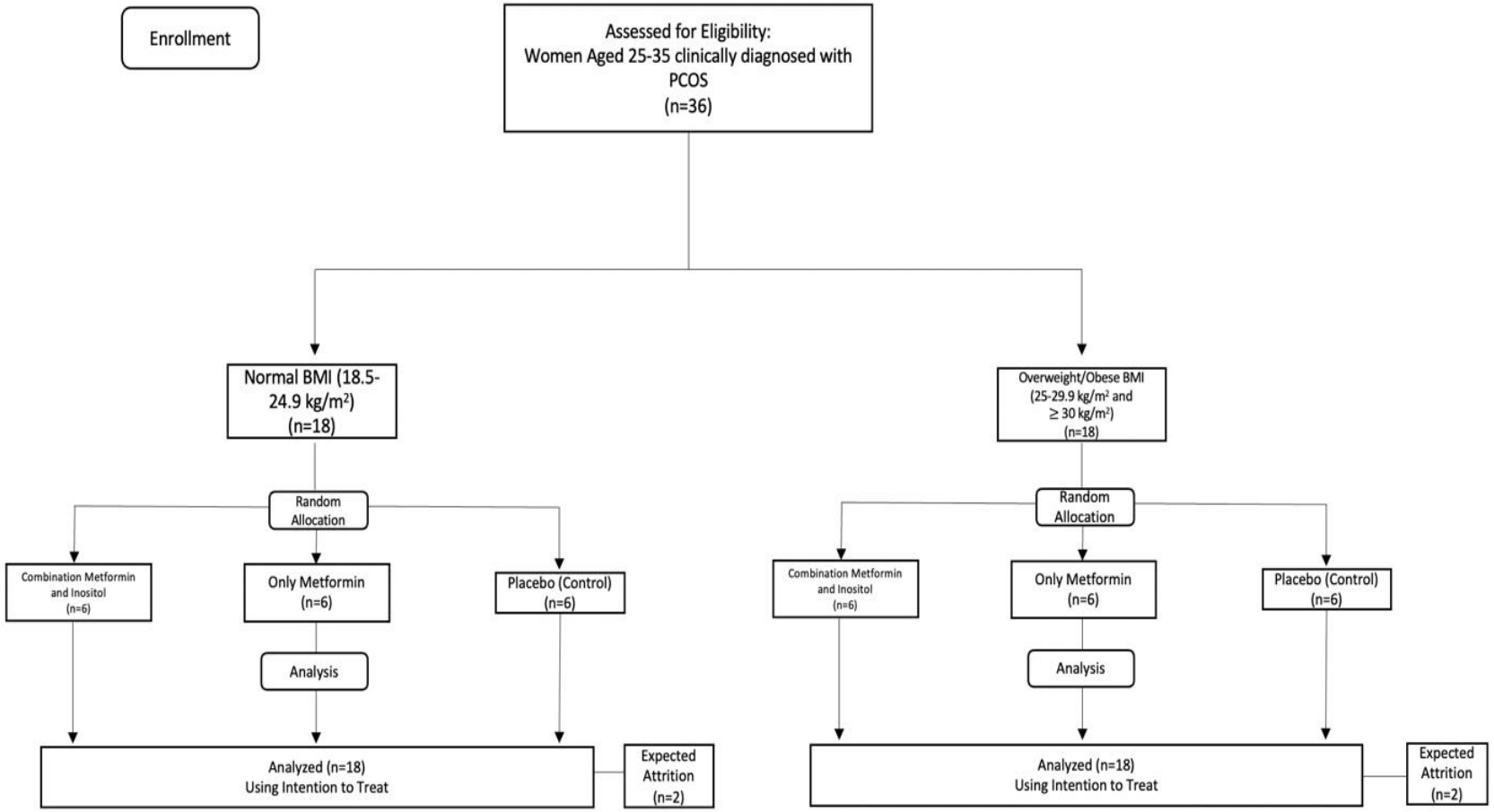

Figure 1. Flowchart of study protocol. Abbreviation used: BMI; body mass index. Created using Microsoft PowerPoint software.

Anticipated Results

Participants will be assessed for baseline characteristics and presence of metabolic symptoms including insulin resistance, hyperandrogenism, weight gain, menstrual irregularities, and ovulation caused by PCOS. A total of 36 participants with normal BMI (18.5-24.0 kg/m^2) and overweight/obese (25.0-29.99 kg/m^2 and $\geq$ than 30 kg/m^2) were enrolled into the study and placed into three intervention groups: MET and INO, only MET and control. There is an expected attrition rate of 11.1% based on the total number of participants and expected attrition of 4 participants. Participant attribution is possibly due to side effects from the combined regiment, or loss to follow-up. Participants who did not complete the study are included in the analysis using intention to treat principle.

Metabolic Parameters

It is anticipated that metabolic symptoms including insulin resistance and weight gain are significantly improved in participants that received MET and INO compared to MET and the control group. It is anticipated that insulin resistance will improve in both the normal BMI group and overweight BMI group using MET and INO. Participants with overweight/obese BMI may have significant higher weight loss compared to normal BMI group using MET and INO intervention. Participants with normal BMI are anticipated not to have significant changes in weight for MET and INO. It is anticipated that participants in the MET and INO group will have HbA1c values between 4.0-5.6 % (20-38 mmol/mol) [11]. The HOMA-IR calculation for both BMI participant groups is anticipated to be between 0.5-1.4 [12].

Hormonal Parameters

MET and INO treatment of PCOS will improve hyperandrogenism, menstrual and ovulation irregularities compared to MET and control. MET and INO have a more significant impact on hormonal parameters compared to receiving MET and control groups. With the normal BMI and overweight/obese BMI groups, it is anticipated that the free androgen index will have values between 15-70 (ng/dL) with MET and INO as treatment for PCOS [13]. Menstruation and ovulation are anticipated to significantly improve for both BMI groups while receiving MET and INO.

Discussion

This 6-month study investigates the effects of using metformin and inositol to improve metabolic and hormonal symptoms in women between the ages of 25-35 with normal or overweight/obese BMI clinically diagnosed with PCOS.

It was anticipated that the MET and INO intervention would have the most significant results in improving insulin resistance and hyperandrogenism compared to MET or placebo groups. These results are anticipated to be consistent regardless of BMI groups. Weight loss is anticipated to be more significant in the overweight/BMI group using MET and INO. In the normal BMI group, it is anticipated that using MET and INO, BMI will not change or will slightly decrease. Menstrual cycle and ovulation are anticipated to become more frequent and regular with MET and INO groups. The metabolic and hormonal parameters are anticipated to significantly improve with MET and INO, but some degree of improvement can be seen using only MET.

Metformin: Metabolic and Hormonal Parameters

Insulin resistance (IR), a common metabolic symptom found in 60-100% of women with PCOS [14], results in increased circulating insulin and IGF-1 stimulating the ovary to release excess testosterone and decrease levels of circulating sex hormone binding globulin (SHBG) [15]. Metformin acts by reducing cellular energy stores of adenosine triphosphate (ATP) which increases the activity of adenosine monophosphate (AMP)-activated protein kinase resulting in increased glycogen storage in skeletal muscle, increased insulin sensitivity, decreased hepatic glucose production and decreased blood glucose levels [16]. The maximum recommended daily dosage of metformin is 2000 mg a day and can be given in standard or slow-release tablets [17]. It is recommended to start with 500 mg daily dose to build tolerance and limit side effects [18], including diarrhea, weakness, gastrointestinal intolerance, nausea, and vomiting [19].

Metformin improves the insulin sensitivity in peripheral tissues contributing to the reduction of circulating insulin levels [18]. There is an increased prevalence of insulin resistance in overweight/obese BMI women as compared to lean counterparts [20]. Consistent to the anticipated findings of the study, it has been suggested that normal and lean BMI should respond to insulin resistance pharmacological treatments such as metformin [21]. It is anticipated that both BMI groups taking metformin will show HbA1c normal/ baseline values between 4.0-5.6 % (20-38 mmol/mol) [11]. The HOMA-IR calculation for both BMI participant groups is anticipated to be between 0.5-1.4 which signifies optimal insulin sensitivity [22]. Studies have found that metformin treatment has decreased PCOS participants' HOMA-IR by 22% [23]. Compared to other studies, it was found that metformin decreases BMI when given a higher dose for a longer duration however, it should be an adjuvant therapy in combination with lifestyle modifications [24]. BMI was seen to decline 1.25 kg/m^2 using MET in overweight/obese BMI groups [25]. This is consistent with the anticipated results of increased reduction of BMI in overweight/obese BMI groups as compared to normal BMI.

Hyperandrogenism (HA) affects 70-80% of women with PCOS and is due to an imbalance in LH and FSH leading to increased steroidogenesis [26]. Metformin has been seen to reduce HA by suppressing androgen

production in adrenal gland and ovary, increasing the production of SHBG and reducing pituitary LH [27]. This supports the anticipated result that metformin intervention will significantly decrease hyperandrogenism in normal BMI and overweight/obese BMI in PCOS. However, a study conducted by Harbone *et al.,* found that improvement in hyperandrogenism using metformin was caused by the reduction of circulating insulin and there were no significant changes found in SHBG and androgen levels [28]. This suggests that metformin's primary mechanism of action is its insulin sensitizing properties that subsequently affect regulation of androgen levels. Metformin is seen to reduce serum testosterone levels by 25-50% in women with PCOS [29].

Women with PCOS have an increased LH/FSH ratio causing a direct effect on the ovulation and menstruation cycles [30]. It is anticipated that using metformin in the treatment of PCOS will help regulate menstrual and ovarian cycles. Findings from Velazquez *et al.,* observed that metformin decreased androgen levels that resulted in the menstrual regularity [18]. A study by Creanga *et al.,* found metformin to increase the likelihood of ovulation in women with PCOS when compared to placebo [31].

Inositol: Metabolic and Hormonal Parameters

Inositol acts as a second messenger and regulates the signalling of hormones such as insulin, thyroid-stimulating hormone (TSH) and follicle-stimulating hormone [32]. Stereoisomer myo-inositol (MI) has an increased effect on metabolic symptoms such as high fasting insulin levels while D-chiro-inositol (DCI) has been shown to have an increase effect on hormonal symptoms such as hyperandrogenism [33]. Inositol is effective dose is 4g a day to see improvement in clinical symptoms of PCOS. Inositol is a generally recognized as safe (GRAS) supplement by FDA that is found over the counter [34]. MI is better tolerated for the treatment of PCOS due to its limited gastrointestinal side effects seen only in the dose higher than 12 g/day [35].

Inositol counteracts the insulin resistance exhibited by PCOS and can help to decrease hyperglycemia and increase insulin sensitivity of cells [33]. A study conducted by Benelli *et al.,* found that a combination of MI and DCI had a statistically significant reduction in HOMA index and fasting glucose in obese BMI women with PCOS [36]. In a meta-analysis conducted by Unfer *et al.,* it was seen that treatment in 247 women treated with MI or MI combined with DCI and folic acid (FA), MI alone significantly decreased fasting insulin and HOMA index [37]. These studies support the anticipated result that inositol will decrease insulin resistance in women regardless of BMI.

Inositol has beneficial effects on BMI and weight reduction through its improvement of insulin sensitivity and its involvement in the insulin signalling pathway [25]. In a meta-analysis conducted by Zarezadeh *et al.,* it found that inositol significantly decreased BMI scores in individuals with overweight or obese BMI and that MI had the strongest effect on reducing BMI when compared to other inositol stereoisomers [22]. These results support the anticipated results that MI supplementation will significantly decrease BMI in both normal and overweight/obese BMI. HA is characterized by an increased free androgen index, and increased serum total of testosterone and androstenedione [38]. A meta-analysis conducted by Unfer *et al.,* found that MI supplementation reduced testosterone concentration and increases serum SHBG when administered for at least 24 weeks [37]. MI is seen to improve hyperandrogenemia in obese and lean women with PCOS [28]. These finding show that the anticipated result that inositol will lower hyperandrogenism in both BMI groups as the mechanism of MI remains the same regardless of weight. It has been seen that administration of 2g MI twice daily for 6 months significantly decreased levels of total androgens, testosterone, and the severity of hirsutism and increased SHBG levels [38]. The use of 4g of inositol for 6 months is the same in the proposed study suggesting that similar results will be found leading to an overall decrease of hyperandrogenism in women with PCOS.

Irregular or longer menstrual cycles have been associated with increased androgen and decreased SHBG in women with PCOS [39]. In a study conducted by Gerli *et al.,* it was found that the effect of MI increased follicular maturation through increased estradiol and inositol has a significantly higher ovulation frequency when compared to placebo [40]. Similarly, other studies have seen that MI supplementation reduces LH and free androgens in normal/lean BMI PCOS women helping to restore ovulation [21]. A study conducted by Zacché *et al.,* found that MI decreased LH levels and reduced the increased LH/FSH ratio that is normally found in women with PCOS [41]. These studies support the anticipated result that MI can re-establish and induce menstrual and ovulation cycles to become more frequent and regular in both normal and overweight/obese BMI groups.

Metformin and Inositol for PCOS

The combination of metformin and myo-inositol has been seen to have an increased effect on improving hormonal and biochemical parameters and improving menstrual cycles [42]. MET and INO have an increased effect on menstrual cycle when compared to MET and both treatments had a similar effect on weight and BMI [40]. It has been seen that MET and INO have decreased cycle length by 3 days as compared to MET only [25]. Using MET and INO will both decrease insulin resistance, hyperandrogenism, weight and regulate menstrual and ovarian cycles through their mechanisms of action. Metformin and inositol have positive synergic effects on metabolic and hormonal symptoms of PCOS and will increase the quality of life in women with PCOS [43].

Strengths and Limitations of the Study

The strengths of this proposed study include studying multiple metabolic and hormonal outcomes, focusing on the additive effects of using MET and INO for the treatment of PCOS, using a blinded randomized study design to limit bias, and having a longitudinal follow-up. However, this proposed study is limited to small sample size, does not consider genetic and racial differences, lack of different geographical representation, limitations of intention to treat principle and does not consider underweight BMI.

Conclusions

This proposed study assessed the efficacy of metformin and inositol in the improvement of metabolic and hormonal symptoms of women diagnosed with PCOS. Previous meta-analyses and studies have found the beneficial effect of metformin and inositol separately however, there are limited studies reviewing the combination on symptomology of PCOS. It can be anticipated that the similar effects of metformin and inositol may have a synergistic effect on improving insulin resistance, hyperandrogenism, weight, menstrual cycle, and ovulation. Future studies should examine the effects of metformin and inositol on different ethnic groups and adding an underweight BMI category would be beneficial in observing the extent of improvement in symptoms of PCOS and the long-term effects of metformin and inositol treatment.

List of Abbreviations Used

PCOS: polycystic ovary syndrome
LH: luteinizing hormone
GnRH: gonadotropin-releasing hormone
FSH: follicle-stimulating hormone
IGF-1: insulin-like growth factor 1
MI: myo-inositol
BMI: body mass index
MET and INO: metformin and inositol
MET: metformin
HbA1c: glycated hemoglobin test
HOMA-IR: homeostatic model assessment of insulin resistance
FAI: free androgen index
ANOVA: one-way analysis of variance
ITT: intention to treat
P-values: probability values
IR: insulin resistance
SHBG: sex hormone binding globulin
ATP: adenosine triphosphate
AMP: adenosine monophosphate
HA: hyperandrogenism
TSH: thyroid-stimulating hormone
DCI: D-chiro-inositol
GRAS: generally recognized as safe

Conflicts of Interest

The author declares that they have no conflicts of interest.

Ethics Approval and/or Participant Consent

This research protocol did not require ethical approval or participant consent as it is a proposed study. This research protocol provides a potential study design and anticipated results based on peer-reviewed scientific articles.

Authors' Contributions

MA: Designed the study, collected, and analysed data, drafted the manuscript, and gave final approval of the version to be published.

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