Metabolic Effects of D-Chiro-Insitol and Myo-Insitol in Polycystic Ovary Syndrome

Abstract

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women of reproductive age. The pathogenesis has not been fully deciphered. PCOS is associated with insulin resistance (IR), menstrual irregularities, cardiovascular disease, obesity, hirsutism, infertility, and endometrial cancer. The use of D-chiro-inositol (DCI) for the treatment of IR in PCOS has been controversial with contradictory data being published. Our objective is to evaluate the effect of DCI combined with myo-inositol (MI), and metformin on the metabolic outcomes of PCOS in a Lebanese women cohort.

This is a prospective study of 150 Lebanese women diagnosed with PCOS and treated with Ovacure® (DCI+MI+folic acid), or a combination of Ovacure® and metformin. Patients aged 13 to 55 years were randomly selected from different clinics in Beirut and Mount Lebanon. A questionnaire covering the personal and health status, physical activity, medications and anthropometrics was completed before enrolment.

The prevalence of obesity in our population was 35.3%. Although IR was more prevalent among obese women with PCOS, non-obese subjects were also found to have a significant incidence of IR. After a 6 months course of treatment with Ovacure®, a significant decrease in fasting glucose, HOMA-IR, Glycated Hemoglobin (HbA1c), Low Density Lipoprotein (LDL), Triglycerides (TG), weight and Body mass index (BMI) levels were noted. Furthermore, adding metformin to Ovacure®, lowered weight and BMI further but not IR.

In this study, we show that the combination of MI and DCI may improve the metabolic profile in PCOS. The addition of metformin may help control overweight further but not IR.

Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women of reproductive age, it occurs in 6 to 18% of this group. It is characterized by hyperandrogenism, chronic non-ovulation, polycystic ovaries, hirsutism, endometrial cancer, and frequently, insulin resistance (IR) and the metabolic syndrome [1–3].

Inositol or vitamin B 8 is one of the B complex vitamins shown to have beneficial effects on insulin sensitization in PCOS [4]. D-chiro-inositol (DCI) is synthesized from myo-inositol (MI) when needed. Every tissue in the body has its own ratio of MI to DCI. However, PCOS ovaries appear to have an enhanced conversion to DCI, depleting MI levels and resulting in poor egg quality [5]. New research has shown that a combination of MI and DCI is an effective approach to treat PCOS and is better than MI or DCI given alone [6]. One limitation to study this effect are the exogenous sources of inositol that may affect the outcomes like the interaction between MI and coffee that may affect the absorption in the gastrointestinal tract [7].

Ovacure® is a dietary supplement with MI (1000 mg/capsule), DCI (25 mg/capsule) and folic acid (200 mcg/capsule), reproducing the plasma physiological ratio of MI to DCI of 40:1. DCI and MI combination, have been shown to improve insulin sensitivity and promote ovulation [8]. It has been hypothesized that defects in inositol synthesis and use may have etiologic implications in PCOS patients.
We conducted this prospective study on 150 women aged 13 to 55 years with the objective of assessing the effects of Ovacure® given alone, or in combination with another insulin sensitizer, metformin.

Material and Methods

This is a prospective study of 150 subjects diagnosed with PCOS according to the Rotterdam criteria [9]. Patients were considered to have PCOS if they had two of the following:

1. Hyperandrogenism: elevated serum androgen levels and/or ovarian androgen concentration and/or hirsutism, acne or androgenic alopecia
2. Chronic oligo-anovulation
3. Polycystic ovaries by ultrasonography

Our objective was to explore the relationship between the combination of MI and DCI in a 40:1 ratio and its effects on the PCOS metabolic outcomes (insulin resistance, diabetes, dyslipidemia, weight and BMI) as well as the effect of adding metformin to this combination. The study design was approved by the committee of ethics in the Department of Human Nutrition and Dietetics of the Faculty of Agricultural and Food Sciences – the Holy Spirit University, Lebanon.

A group of 150 Lebanese women chosen randomly, from 4 endocrinology clinics, were enrolled in the study. The women were aged 13 to 55 years, having PCOS according to Rotterdam criteria. Initially, screening questions and laboratory tests were collected including weight, insulin, glucose, lipid profile (LDL, HDL, TG), and glycated hemoglobin (HbA1c) prior to treatment. Fifty one patients were excluded from the study for not meeting the inclusion criteria. The exclusion criteria included taking any hormonal treatment for the last six months, the presence of diabetes mellitus, Cushing syndrome, thyroid disease, androgen producing tumors, or adrenal hyperplasia.

Patients were considered hyperinsulinemic or insulin resistant if their Homeostasis Model Assessment (HOMA-IR) level exceeded 2.5.

In a prospective design, we monitored the effects of Ovacure® intake on the metabolic consequences of PCOS. All 99 patients were treated with 2 tablets of Ovacure® per day over a period of six months. In addition, 82 patients out of the 99 were given metformin. The method of randomization was numerical, not double blinded due to the method of recruitment. The metabolic tests were performed before and 6 months following therapy (Figure 1).

PCOS outcomes after Ovacure® supplementation were analyzed using the ANOVA and McNemar tests, the independent and the paired sample t-tests.

All statistical analysis were performed using the Statistical Package for Social Sciences (SPSS) version 21.0. The confidence interval (CI) was set at 95% and significance was considered at a p-value <0.05. Results were presented as percentages for qualitative variables and as minimum, maximum, mean and standard deviation (SD) for quantitative variables

Results

Among the 99 participants, 17 were treated with Ovacure® alone, while the other 82 patients were treated with Ovacure® and metformin.

Among the 99 participants, 48.5% were overweight at baseline with a BMI between 25 kg/m² and 29.99 kg/m² and 35.3% were obese with a BMI above 30 kg/m².

Before treatment, among the underweight patients (N=5), 40% had IR. For those who had a normal BMI (N=35), 28.6% had IR. Among the overweight patients (N=24), 70.8% had IR while 82.9% of the obese women (N=35), had IR (Table 1).

Following therapy with Ovacure®, paired sample t-test, showed a very significant decrease among the 99 participants of the mean fasting glucose by an average of 4 mg/dL (p<0.001), the mean HOMA-IR decreased by 1.2, and HbA1c levels decreased by 0.21%. A significant weight loss (p<0.001) and a drop in BMI (p<0.001) were also noted.

The lipid panel displayed a positive effect as the total cholesterol decreased by 14.63 mg/dL (p<0.001), LDL decreased by 7.74 mg/dL on the average (p<0.001), TG decreased by 14.15 mg/dL (p<0.05). On the other hand we found a significant increase in HDL of 1.15 mg/dL (p<0.05).

Before the treatment, 58 participants (58.6%) had IR and after 6 months of treatment, the number decreased to 31 with 31.3% improvement (p<0.001) (Figure 2).

We studied the prevalence of IR in patients with normal BMI compared to patients having a BMI >25 kg/m², before and after the treatment. IR decreased in both obese and non-obese patients. After the treatment, the number of insulin resistant patients having a normal BMI decreased from 30% to 13.3% (p<0.001), while the prevalence decreased among overweight and obese patients from 78% to 46.3% (p<0.001) (Table 2).

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<th>Table 1: Association between obesity and IR in PCOS patients.</th>
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<td>Percentage of IR at baseline</td>
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In an independent sample t-test, we studied the difference in HOMA-IR levels, between two types of therapy, Ovacure® alone (Group A) versus Ovacure® combined to an insulin sensitizer, metformin (Group B). We found that those in group A showed a decrease of 0.97 in the mean HOMA-IR, while those in group B showed a decrease of 1.24 of the mean of HOMA-IR, the difference was not statistically significant (p=0.62).

We found a significant drop in weight in group B with an average weight loss of 4.64 kg, compared to the group receiving Ovacure® alone 2.7 kg, (p <0.05).

BMI dropped significantly more in group B (1.77±1.45 kg/m²) as compared to group A (1±0.62 kg/m²) (p < 0.05) (Table 3).

**Discussion**

Inositol is a naturally occurring vitamin in fruits, nuts, beans, and grains and is synthesized as well by the body. While there are nine known isomers of inositol, MI and DCI have been the most studied in PCOS.

Sixty percent of our cohort with PCOS was overweight or obese. Our results are similar to those reported in the literature. Among others, Messinis et al., found that obesity incidence varies between 35 and 80% among women with PCOS [10].

A significant improvement in weight loss and BMI was reported by Nordio & Proietti using a combination of MI and DCI [11]. In addition, we found that the combination of DCI and MI with metformin can lead to even more significant weight loss and BMI drop.

In a study authored by Nestler in 1999, 1,200mg of DCI was given to a group of women with PCOS for 6 to 8 weeks while another group received placebo. DCI increased the effects of insulin, decreased androgens, triglycerides, blood pressure and improved ovulation in 86% of women. However, when Nestler repeated this study in 2008, using double the amount of DCI (2,400mg), the authors were unable to confirm their previous findings [12,13].

It has been suggested that MI can prevent gestational diabetes in women with PCOS. D’Anna et al. showed the prevalence of gestational diabetes in patients on MI to be 17.4% compared to 54% in those not receiving it [14].

MI has been well documented to be superior to DCI in improving insulin resistance, ovulation quality and reducing the risk for gestational diabetes in women with PCOS. However, when MI is combined with DCI in an optimal ratio, better results were reported [15].

Sacchinelli et al., has shown that 30% to 40% of women with PCOS are insulin resistant [16]. In our study, the prevalence of insulin resistance among PCOS women was higher, reaching 58.6%. Similar to our report, King et al. showed that IR is present in both obese and non-obese patients [17]. Insulin resistance was more prevalent in overweight and obese patients.

After 6 months of treatment, glucose fasting, HOMA-IR and HbA1c decreased significantly when the patients were treated with Ovacure®. In addition, we saw a significant decrease in the LDL and TG, while HDL increased significantly.

When comparing the metabolic outcomes according to the treatment strategy (Ovacure® alone versus Ovacure® and metformin), the combination didn’t offer any advantage on the insulin levels compared to the treatment with Ovacure® alone. However, there was a significant decrease in both weight and BMI in the group treated with Ovacure® and metformin combination.

Both MI and DCI have been studied in infertile women with PCOS, with MI showing the most promise in improving ovulation and egg quality. In a study published in 2007, 25 women received MI (4g/day) for six months. The results showed 88% of the patients had one spontaneous menstrual cycle during treatment, of whom 72% maintained normal ovulation activity. A total of 10 pregnancies (40% of patients) were obtained [18].

Raffone et al., compared the effects of metformin and MI in women with PCOS. Sixty women received 1,500 mg/day of metformin, while 60 women received 4 g/day of MI plus 400 mcg of folic acid. Ovulation was restored in 65% of women treated with MI vs. 50% in the metformin group. More pregnancies occurred in the MI group vs. metformin (18% vs. 11%) [19].
A study published in the European Review Medical Pharmacology PCOS patient received either 2g of MI twice daily or 600 mg of DCI twice daily. Women who received MI had better, more mature eggs and more pregnancies than those who took DCI [20].

While DCI has been shown to improve insulin and androgen abnormalities in PCOS, Isabella et al showed that DCI alone, administered at high dosages (6000-2400 mg daily) negatively affected oocyte quality and ovarian response. What’s more, the higher the dose of DCI, the worse the oocyte quality and ovulation response [21].

**Conclusion**

MI and DCI work differently and probably through different signal pathways as their supplementation leads to different effects. One of their mechanisms of action may involve an effect on the insulin receptor rendering the cells more insulin responsive and allowing glucose entry. This may explain the improvement seen in IR, the lipid profile, HbA1C and weight control.

Our data clearly shows that the physiologic combination of MI and DCI improves the metabolic factors in PCOS. Other studies showed in a randomized, double-blind, placebo-controlled design that MI (4 g/day) for 14 weeks, increased HDL levels and resulted in significant weight loss and decreased leptin levels in women with PCOS, although no change in insulin was detected [22]. In a double-blind placebo controlled trial, Minozzi et al showed that MI (4 g/day) decreased insulin, triglycerides, testosterone, and blood pressure in women with PCOS [23]. Venturella et al. showed that 2 g/day of MI for six months resulted in significant weight loss and improved HDL and LDL levels. While MI at 1,200 mg/day for 12 weeks have been shown to significantly decrease androgens and insulin in non-obese women with PCOS [24]. Based on these and other data, we join the many authors in recommending he use of MI and DCI in a ratio of 40:1 as a first line approach in PCOS [11]. Furthermore, we recommend the addition of metformin for those who need additional weight loss and sugar control. We hope future trials will strengthen this data by using a double blind, randomized design.

**Aknowledgements**

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**References**


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