**Amy Wagner**

NTD 517: Final Project Literature Review

**Title:**Inositol Treatment for Patients with Polycystic Ovary Syndrome (PCOS)

**Background:**Polycystic ovary syndrome (PCOS) is an endocrine disorder that mainly affects women of reproductive ages but lasts throughout the lifetime1,2,3,4,5. The classic treatment of metformin combined with oral contraceptives has several unfavorable side effects such as GI upset and is not a useful treatment for women planning to conceive1,2,4. The use of inositol’s in treating PCOS is not widely practiced but may be useful in treating PCOS patients especially those who wish to conceive1,2,4.

**Research Question:** Can the treatment of a dietary supplement of myo-inositol (MI) and D-chiro-inositol (DCI) combined, help reduce and treat Polycystic Ovary Syndrome (PCOS) symptoms such as oligomenorrhea, weight gain, hirsutism, hyperandrogenism and improving insulin resistance in premenopausal women with PCOS?

**Summary of Results:**Nearly twenty research articles were initially analyzed for their inclusion into this literature review. Of the twenty, five primary research articles were ultimately selected for their inclusion in this review. The collective results from the five studies (three RCT and two case control studies) showed that the use of myo-inositol with D-chiro-inositol in a 40:1 has statistically significant positive effects on reducing insulin resistance1,4, improving endocrine profiles1, restoring ovulation and menstrual regulation1,2,3,4,5, accelerating weight loss and fat mass reduction3,5, improving BMI3,5, and decreasing hyperandrogenism1,3,4,5 in women with PCOS. Overall, the results show that a treatment of myo-inositol with D-chiro-inositol in a 40:1 ratio helps improve several symptoms associated with PCOS.

**Conclusion:**Based on the evidence found from the 5 studies evaluated in this literature review on inositol treatment in premenopausal PCOS patients, it is evident that the supplementation of myo-inositol with D-chiro-inositol, specifically in a 40:1 ratio, has statistically significant positive effects on improving symptoms and clinical presentations of PCOS.

**Conclusion Strength Table:**Overall, I graded my conclusion as being I Good/ Strong based on its strength in consistency, clinical impact and generalizability. All conclusion scores are located in the table below:

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| **Quality** | **Consistency** | **Quantity** | **Clinical Impact** | **Generalizability** |
| **Grade:**II Fair**Reason:** Not all articles were graded strong. Two articles were graded strong, the remaining three were graded neutral. | **Grade:**I Good/Strong**Reason:** Across the board it is evident that the treatment of MI:DCI in a 40:1 ratio had at least some element of positive effect in patients with PCOS. However, several studies aligned with their results in improvement in specific symptoms of PCOS, validating the consistency and effectiveness of this treatment. | **Grade:**II Fair**Reason:**A couple of the studies had a limited number of participants, however the majority of studies had a sufficient number of participants. | **Grade:**I Good/ Strong**Reason:**The results of the treatment were statistically significant for all articles reviewed and showed a positive effect in improving PCOS symptoms. | **Grade:**I Good/ Strong**Reason:**The results showed that the treatment was statistically significant in improving PCOS symptoms in both patients who were overweight/ obese and in patients who were of a normal weight. |

**References:**

1. Benelli E, Del Ghianda S, Di Cosmo C, Tonacchera M. 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*. July 2016:1-5. doi:10.1155/2016/3204083

1. Colak E, Ozcimen EE, Tohma YA, Ceran MU. May myo-inositol and d-chiro-inositol (40:1) treatment be a good option on normal-weighted polycystic ovary syndrome patients without insulin resistance? *The journal of obstetrics and gynaecology research*. September 2020. doi:10.1111/jog.14505

1. Le Donne M, Metro D, Alibrandi A, Papa M, Benvenga S. Effects of three treatment modalities (diet, myoinositol or myoinositol associated with D-chiro-inositol) on clinical and body composition outcomes in women with polycystic ovary syndrome. *European review for medical and pharmacological sciences*. 2019;23(5):2293-2301. doi:10.26355/eurrev\_201903\_17278

1. Nordio M, Basciani S, Camajani E. 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 sciences*. 2019;23(12):5512-5521. doi:10.26355/eurrev\_201906\_18223.

1. Troisi J, Cinque C, Giugliano L, et al. Metabolomic change due to combined treatment with myo-inositol, D-chiro-inositol and glucomannan in polycystic ovarian syndrome patients: a pilot study. *Journal of ovarian research*. 2019;12(1):25. doi:10.1186/s13048-019-0500-x.

**Research Question:** Can the treatment of a dietary supplement of myo-inositol and di-chiro inositol combined, help reduce and treat Polycystic Ovary Syndrome (PCOS) symptoms such as oligomenorrhea, weight gain, hirsutism, hyperandrogenism and improving insulin resistance in premenopausal women with PCOS?

**Inclusion Criteria**

* Population Characteristics: premenopausal women with PCOS of reproductive ages up to age 46 years old
* Specifics of the Intervention: myoinositol and di chiro inositol (preferably 40:1 ratio)
* Specific Outcomes: combination of myo-inositol with di chiro inositol dietary supplement aids in reduction and treatment of common PCOS symptoms such as weight gain, oligomenorrhea, insulin resistance, hirsutism, hyperandrogenism
* Language of Articles: Limited to articles published in English
* US and or International: Both
* Types of Studies (RCTs, cohort, case-control, survey, all): Primary Sources
* Inclusive Dates of Articles: 2015-2020
* Comparison Group (yes or no): yes
* Nutrition Related Problem/ Condition: Polycystic Ovary Syndrome (PCOS)
* Limited to full text, peer reviewed academic journal articles

**Exclusion Criteria**

* Population Characteristics: postmenopausal women, pregnant women, men, children, those who are not affected by PCOS, women over the age of 46 years old
* Interventions: metformin and birth control
* Size of study groups: less than 30 participants total per study
* Year Range: Prior to 2015
* Language: Articles not published in English
* Articles without full text, are not peer reviewed, and are not academic journal articles

Table 1. Abstract Table for Article 1

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| Citation  | Benelli E, Del Ghianda S, Di Cosmo C, Tonacchera M. 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*. July 2016:1-5. doi:10.1155/2016/3204083 |
| Study design  | Randomized Controlled Trial |
| Class  | A |
| Quality rating  | **+** |
| Research purpose  | Does a combined treatment of myo-inositol (MI) and D-chiro-inositol (DCI) in a 40:1 ratio have a significant therapeutic effect on improving the endocrine profile and insulin resistance in young overweight women suffering from PCOS? |
| Inclusion criteria in the study (not your own) | Obese women with PCOS (according to the Rotterdam criteria for PCOS) who had a BMI >30 kg/m2. |
| Exclusion criteria in the study (not your own) | Patients who suffered from diabetes, who smoked, and who used alcohol were excluded from the study.  |
| Description of study protocol | Participants were randomized and separated into two groups (A & B) after providing written informed consent. Participants all started the study while being in the follicular phase of their menstrual cycles. Group A’s treatment consisted of MI + DCI in a 40:1 ratio via a soft gel capsule (550mg MI; 13.8mg DCI; 200 mcg folic acid) twice a day for 6 months. Group B was the control group and received a placebo treatment consisting of 200 mcg folic acid twice a day for 6 months. At baseline participants in groups A & B had no significant differences in the following measured lab data values: FSH, LH, 17-beta-Estradiol (E), Sex Hormone Binding Globulin (SHBG), androstenedione, free testosterone, dehydroepiandrosterone sulphate (DHEAS).All measurements of relevant data were taken at baseline and after 6 months of treatment in both groups. No significant or negative side effects were found with the use of this intervention/ treatment.  |
| Data collection summary  | Outcomes of the study show that the combined treatment of MI+DCI (40:1) helped improve the endocrine profile and insulin resistance of young overweight women with PCOS from group A (treatment group). There were no changes in sex hormones for group B (control group). Each group was treated with 200mcg of folic acid because this was the “treatment” given to the placebo / control group (group B).Measurement Detected via the following: FSH & LH serum levels measured via immune-enzymatic assay; Estradiol levels measured via competitive immunoassay; SHBG levels measured via immunoassay; androstenedione serum levels measured via conventional immune-enzymatic assay; free testosterone serum levels measured via immune-enzymatic assay; DHEAS measured via conventional immunoassay; Insulin resistance (IR) measured via homeostasis model assessment (HOMA) as well as via fasting glucose and insulin through the same measurements.Blinding was used in the form of a placebo treatment for Group B. All groups believed to be given the combined treatment of MI + DCI.  |
| Description of actual data sample  | Group A: N=21 (treatment group)Group B: N=25 (placebo group)Total participants: N=46Population: Young women with PCOS with BMI > 30kg/m2.All participants met criteria for PCOS according to the Rotterdam criteria. All patients met inclusion/ exclusion criteria in order to be a part of the study. Participants all started the study while being in the follicular phase of their menstrual cycles (both group A&B participants).No withdraw or drop out of any participants were noted. |
| Summary of results  | The results showed the following in regard to the combined treatment of MI + DCI in a 40:1 ratio: the reduction of LH was statistically significant (*p* < 0.05); reduction of free testosterone was statistically significant (*p* < 0.05); reduction of fasting insulin was statistically significant (*p* < 0.001); reduction of HOMA index was statistically significant (*p* < 0.05); the increase of 17-beta-Estradiol (E) levels was statistically significant (*p* < 0.01).The significant reduction of LH and free testosterone levels resulted in decreased hyperandrogenism in the treatment group (group A). The significant increase in E and SHBG resulted in the restoration in ovulation capability in group A.Neither group showed statistically significant alterations in BMI, FSH, androstenedione, DHEAS or fasting glucose levels from baseline to 6 months.*P* value of <0.05 was used to indicate statistical significance. A paired *t*-test was used to measure differences of the variables from baseline to 6 months.  |
| Author conclusion  | The authors concluded that the nutrition supplement and treatment of MI+DCI in a 40:1 ratio is the best “first-line” treatment for women with PCOS who experience hyperandrogenism and oligomenorrhea. This treatment is especially useful for women who plan to conceive while using this treatment, or for women who experience negative side effects from the traditional treatment option for PCOS (birth control pills combined with metformin).  |
| Your comments  | *Strengths of this study included blinding, randomization, and a control within the population that was studied. Other strengths are that the study’s intervention showed to be beneficial to the population in treating their symptoms of PCOS, the information such as the purpose, results, outcomes, and conclusions were all clearly stated, the study groups were comparable, and the study was free from conflicts of interest.**No limitations of the study were noted, however, authors recommended more studies with larger populations for stronger evidence of the results found in this study. Further limitations may be diet of the participants and if any participated in physical activity during the course of the study. Authors reported no conflict of interest or bias in this study. Funding was never noted or recorded in the study, which leaves funding bias unclear.*  |
| Funding source  | Funding for the article was not provided. Unknown funding. |

Table 2. Abstract Table for Article 2

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| Citation  | Colak E, Ozcimen EE, Tohma YA, Ceran MU. May myo-inositol and d-chiro-inositol (40:1) treatment be a good option on normal-weighted polycystic ovary syndrome patients without insulin resistance? *The journal of obstetrics and gynaecology research*. September 2020. doi:10.1111/jog.14505  |
| Study design  | Retrospective Case-Control Study |
| Class  | C |
| Quality rating  | Ø |
| Research purpose  | What is the effectiveness of myo-inositol and D-chiro-inositol (MI:DCI) (40:1) treatment in women with PCOS who are at a normal weight and do not have insulin resistance (IR)? |
| Inclusion criteria in the study (not your own) | Anovulatory women with PCOS, with oligomenorrhea, aged 16 – 40 years, with BMI of 18-40 kg/m2, who do not have insulin resistance and received 6 months of the 40:1 ratio of MI:DCI treatment were included in this study.PCOS diagnosis of all participants was done between January 2016 and October 2019 by the Gynecology and Obstetrics Clinic of Baskent University Konya Practice and Research Hospital and based off of the Rotterdam criteria. |
| Exclusion criteria in the study (not your own) | Women with PCOS who had other conditions that could interfere with ovulation (thyroid disfunction, hyperprolactinemia, Cushing’s syndrome, congenital adrenal hyperplasia, androgen-producing tumor), or took prescription medication that may affect endocrine and metabolic function were excluded from this study. |
| Description of study protocol | Women who were diagnosed with PCOS by the clinic between January 2016 and October 2019 were split into two groups based off their BMI status. Group 1 consisted of anovulatory PCOS women without insulin resistance, with oligomenorrhea, who have a BMI of 18-25 kg/m2 (normal weight group). Group 2 consisted of anovulatory PCOS women without insulin resistance, with oligomenorrhea, who have a BMI > 25 kg/m2 (obese/overweight group). Group 1’s intervention included the treatment of either a combined oral contraceptive or MI:DCI (40:1). Group 2’s intervention included the treatment of lifestyle changes (exercise and weight loss) with metformin; or participants who reused lifestyle changes, could not use metformin, or whose symptoms (such as anovulation) did not improve with lifestyle changes and metformin had the option of a treatment that consisted of a combined oral contraceptive or MI:DCI (40:1). The 40:1 ratio of MI:DCI was always 550 mg myo-inositol and 13.8 mg D-chiro-inositol. Next, menstrual cycle patterns and ovulation status were evaluated and analyzed in participants of both group 1 and group 2. Women diagnosed with PCOS by the clinic between January 2016 and October 2019 were retrospectively evaluated for inclusion into the study and only women, from either group, who were treated with at least 6 months of MI:DCI (40:1) were included in this retrospective study and kept within either Group 1 or Group 2 based on their BMI as stated above. After the 6 months of MI:DCI treatment in all participants was reached, data from group 1 and group 2 were compared for ovulation status and all data from both groups were evaluated retrospectively for this study. Insulin Resistance was measured prior to treatment in order to determine if patients were able to be included in the study or not.Ovulation status was measured prior to treatment and after 6 months of treatment.  |
| Data collection summary  | Outcomes of the study show that the 40:1 ratio of MI:DCI treatment can be considered a primary treatment for women with PCOS who are at a normal weight and do not have insulin resistance.Ovulation and menstrual cycle patterns were measured and evaluated via serum progesterone levels (ovulatory cycle; 6-25 ng/mL) and was measured on day 21 of the menstrual cycle in all participants.To rule out patients with insulin resistance, HOMA-IR was used to measure insulin resistance. A value > 2.5 indicated insulin resistance. SPSS 25.0 was used to analyze statistical data from the study. Quantitative data of group 1 and 2 was compared using Mann-Whitney *U* test with Monte Carlo simulation results. Pearson chi-square test was used for comparing categorical variables. Results of column ratios were expressed via Benjamini-Hochberg corrected *P* values. Blinding was not used. |
| Description of actual data sample  | Group 1: N=29 (anovulatory PCOS women without insulin resistance, with oligomenorrhea, who have a BMI of 18-25 kg/m2 – normal weight group).Group 2: N=17 (anovulatory PCOS women without insulin resistance, with oligomenorrhea who have a BMI > 25 kg/m2 – obese /overweight group).Groups were determined after interventions were given due to the nature of a retrospective study, therefore there was no information given on participants who withdrew from the study. There could not be any withdrawals in this study.  |
| Summary of results  | The results showed that within group 1 (normal weight group) ovulation was detected in 23 of the 29 participants. Within group 2 (overweight/ obese group) ovulation was detected in 5 of 17 participants. The difference between ovulation in group 1 to group 2 was statistically significant (*p* < 0.001). Progesterone levels showed that after 6 months of treatment, group 1 had statistically significant higher levels than group 2 (*p* < 0.001). In group 1, 6 out of 7 participants -who wanted to become pregnant-experienced spontaneous pregnancy after receiving treatment (85.7%). In group 2, 2 out of 6 participants -who wanted to become pregnant- experienced spontaneous pregnancy after receiving treatment (33.3%).Odds ratio with 95% confidence interval showed differences between group 1 and 2. Variables were analyzed at a 95% confidence level. *P* < 0.05 indicated statistically significant data. |
| Author conclusion  | The authors concluded that women with PCOS who are at a normal weight and have been treated with MI:DCI (40:1) have a statistically more successful chance at improving and correcting anovulation and inducing ovulation as opposed to women with PCOS who are overweight or obese and have undergone the same treatment. This treatment was also found to have a positive effect on pregnancy rates in women with PCOS (more effective in women at a normal weight). They also concluded that the 40:1 MI:DCI treatment should be considered a primary treatment for women with PCOS who are at a normal weight and do not have insulin resistance. |
| Your comments  | *Strengths include that the intervention showed positive statistically significant results in women with PCOS who were at a normal weight and suffering from oligomenorrhea. Other strengths were that the purpose, methods, outcomes and conclusions were clearly stated.**A Limitation to this study that was mentioned by the authors was that only patients without insulin resistance were selected for this study. This resulted in smaller populations of each group that was studied (especially the overweight/ obese group). This could be because insulin resistance in PCOS patients is so common especially in women with higher BMI’s. This study also had no randomization when splitting up participants into groups and no bias was discussed in the study. Funding was never noted or recorded in the study, which leaves funding bias unclear.* |
| Funding source  | Funding for the article was not provided. Unknown funding. |

Table 3. Abstract Table for Article 3

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| Citation  | Le Donne M, Metro D, Alibrandi A, Papa M, Benvenga S. Effects of three treatment modalities (diet, myoinositol or myoinositol associated with D-chiro-inositol) on clinical and body composition outcomes in women with polycystic ovary syndrome. *European review for medical and pharmacological sciences*. 2019;23(5):2293-2301. doi:10.26355/eurrev\_201903\_17278  |
| Study design  | Randomized Controlled Trial |
| Class  | A |
| Quality rating  | **+** |
| Research purpose  | Of three treatments for PCOS (diet, diet and myo-inositol, or diet and myo-inositol with D-chiro-inositol), which of the three provides the greatest clinical benefits in regard to clinical and body composition outcomes in overweight and obese women with PCOS? |
| Inclusion criteria in the study (not your own) | Women with PCOS (determined by Rotterdam criteria), aged 16-45 years, with a BMI > or = 25 kg/m2, who have not had hormone therapy for less than 6 months, have no other medical diseases, who have not taken medications or over-the-counter products from baseline through the 6-month duration of the study.  |
| Exclusion criteria in the study (not your own) | PCOS women with BMI < 25 kg/m2 were excluded from the study.Women who had to start taking medication due to the onset of a disease, illness, or condition, other than the supplements prescribed in this study, were removed from the study.  |
| Description of study protocol | All participants gave written informed consent in order to participate in this study. 43 Participants were randomly separated into 3 groups (1, 2 & 3). Group 1 (n = 21) was the control group and was treated with diet only (1200 Kcal). Group 2 (n= 10) was treated with the same diet of 1200 Kcal + (2000 mg MI + 200 mcg folic acid) twice a day. Group 3 (n=13) was treated with the same diet of 1200 Kcal + (550 mg MI + 13.8 mg DCI +200 mcg folic acid) twice a day. Treatments of all groups lasted over the course of 6 months.The diet given to all participants consisted of 1200 Kcal (25% fat, 15-18% protein; 57-60% low glycemic index carbohydrates). The following measurements were taken at baseline, 3 months and at 6 months of treatments: height, weight, waist circumference, hip circumference, degree of hirsutism (based off Ferriman-Gallwey score). The following measurements were taken at baseline and again at 6 months after treatment: BMI, Ferriman-Gallwey score, menstrual cycle, waist circumference, waist to hip ratio (WHR), hip circumference, and body composition via bioimpedentiometry. No women in the study participated in regular physical activity.  |
| Data collection summary  | The outcomes of the study showed that the treatment of MI:DCI in a 40:1 ratio (treatment given to group 3) along with a 1200 Kcal diet was able to accelerate weight loss and fat mas reduction, and was able to significantly improve menstrual cycle irregularities in overweight and obese patients with PCOS.Methods of measurements: age (years), height, weight (kg), BMI (based on height and weight), waist circumference (cm), hip circumference (cm), degree of hirsutism via Ferriman-Gallwey score, menstrual cycle, waist to hip ratio (WHR), body composition via bioimpedentiometry, total body water (It), fat mass (% and kg), and lean mass (% and kg).Blinding was used on all participating women. |
| Description of actual data sample  | Total Participants: N=43Group 1: N= 21Group 2: N= 10 Group 3: N=1343 women with PCOS (determined by Rotterdam criteria), aged 16-45 years, with a BMI > or = 25 kg/m2, who have not had hormone therapy for less than 6 months, have no other medical diseases, who have not taken medications or over-the-counter products from baseline through the 6-month duration of the study.At baseline there was no statistically significant difference in any of the women in this study (*p* > 0.05).Drop out criteria was mentioned, however, there was no record of women who dropped out. |
| Summary of results  | The results of the study showed that all three treatments helped participants from all groups significantly decreases body weight, BMI, waist circumference and hip circumference after 6 months. However, menstrual cycle regularity restoration was only significant in group 3 (*p* = 0.02) which was the only group where all participants experienced restoration in cycle regularity (100% success rate in group 3). Fat/Lean mass ratio decreased significantly in group 1 *(p* = 0.02), group 2 (*p* = 0.015), and group 3 (*p* = 0.005). Total body water was statistically significant between groups 2 and 3 (*p* = 0.03).Hirsutism (Ferriman-Gallwey score) was borderline statistically significant between groups 1 and 3 (*p* = 0.09).Waist to hip ratio was borderline statistically significant between groups 2 and 3 (*p* = 0.09). At 6 months, there was no statistically significant difference between the groups in regard to hirsutism (Ferriman-Gallwey score), weight, BMI, waist and hip circumferences, waist to hip ratio, and bioimpedentiometry data.Statistical significance was determined by a *p* value < 0.05. Borderline statistical significance was determined by a *p* value between 0.5 and 0.10. Normality of examined variables verified via Kolmogorov Smirnov test. Statistical analysis performed via parametric approach. Existence of statistically significant differences at baseline and at 6 months for all three groups was assessed via the ANOVA test. Trends in categorical variables were analyzed via a chi square test. All groups were compared two by two via student *t*-tests.  |
| Author conclusion  | The authors concluded that the combined treatment of MI + DCI in a 40:1 ratio along with a 1200 Kcal low glycemic index diet significantly restores menstrual cycle regularity with a 100% success rate, and significantly reduces body weight and fat mass in overweight and obese women with PCOS. |
| Your comments  | *A strength of this study was that all women participating in the study did not perform regular physical activity, therefore exercise did not affect the outcome of the study. Other strengths include that the purpose, study design, methods, and conclusion were all clearly stated.**One limitation is that all three groups should have been assigned the same number of participants. Another limitation is that obesity, insulin resistance (IR) and hyperandrogenism may contribute to higher levels of lean body mass, skewing results.* *No conflicts of interest were reported for this study.*  |
| Funding source  | Funding for the article was not provided. Unknown funding. |

Table 4. Abstract Table for Article 4

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| Citation  | Nordio M, Basciani S, Camajani E. 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 sciences*. 2019;23(12):5512-5521. doi:10.26355/eurrev\_201906\_18223. |
| Study design  | Randomized Controlled Trial |
| Class  | A |
| Quality rating  | Ø |
| Research purpose  | Which ratio of myo-inositol (MI) to D-chiro-inositol (DCI) has the greatest effect on treating symptoms of PCOS? |
| Inclusion criteria in the study (not your own) | Women with PCOS (according to Rotterdam criteria), aged 18- 45 years.  |
| Exclusion criteria in the study (not your own) | Exclusion criteria: Women who suffer from other pathologic or age-related conditions resulting in defunction and irregularity in ovulation; women who have excessive androgens (adrenal hyperplasia or Cushing’s syndrome); women who have poor ovarian reserve; women who take other drugs which may affect ovulation; obese women with BMI >29.9 kg/m2; women whose partners have sperm abnormalities.  |
| Description of study protocol | All participants signed informed consent prior to the start of the study. 56 women with PCOS, aged 18-45 years were randomly and equally assigned to 7 different groups (8 participants per group). Treatments consisting 2g inositol’s were given twice a day to participants of all groups over the course of 3 months. Treatment ratios were given to the groups as followed: Group 1: N=8 (treated with MI:DCI ratio of 0:1)Group 2: N=8 (treated with MI:DCI ratio of 1:3.5)Group 3: N=8 (treated with MI:DCI ratio of 2.5:1)Group 4: N=8 (treated with MI:DCI ratio of 5:1)Group 5: N=8 (treated with MI:DCI ratio of 20:1)Group 6: N=8 (treated with MI:DCI ratio of 40:1)Group 7: N=8 (treated with MI:DCI ratio of 80:1)Measurements taken at baseline and at 3 months: FSH, LH, Sex Hormone Binding Globulin (SHBG), 17-beta-Estradiol (E2), free testosterone, HOMA index, basal and postprandial insulin, BMI, menses. Ovulation was measured every month.  |
| Data collection summary  | The outcomes showed that the 40:1 ratio of MI:DCI had the best and greatest effect on treating and restoring ovulation in women with PCOS. The primary outcome followed ovulation regulation. The secondary outcome followed levels of FSH, LH, Sex Hormone Binding Globulin (SHBG), 17-beta-Estradiol (E2), free testosterone, HOMA index, basal and postprandial insulin, BMI, menses. Methods of measurements: ovulation regulation (measured every month for 3 months via progesterone assay performed during the medium luteal phase of the menstrual cycle), and progesterone was measured via assay at month 1, month 2 and month 3 (post-treatment).Differences between times were measured via ANOVA. Chi-square tests were used to measure differences in quantitative variables between two treatment groups at a time (all treatments were compared to each other). The use of blinding was not mentioned in the study. |
| Description of actual data sample  | 55 women with PCOS (according to Rotterdam criteria), aged 18-45 years. All participants had a BMI < 30 kg/m2. Group 1: N=8 (treated with MI:DCI ratio of 0:1)Group 2: N=8 (treated with MI:DCI ratio of 1:3.5)Group 3: N=7 (treated with MI:DCI ratio of 2.5:1)Group 4: N=8 (treated with MI:DCI ratio of 5:1)Group 5: N=8 (treated with MI:DCI ratio of 20:1)Group 6: N=8 (treated with MI:DCI ratio of 40:1)Group 7: N=8 (treated with MI:DCI ratio of 80:1)One participant, from group 3, dropped out from the study. The participant’s reason for withdrawing from the study was not related to the study. Averages of BMI and age of all participants at baseline did not show a significant difference.  |
| Summary of results  | The results of the study showed that the 40:1 ratio of MI:DCI had the best and greatest effect on treating and restoring ovulation in women with PCOS. Treatments of the following ratios were shown to restore ovulation (20:1, 40:1, 80:1). Treatments of MI:DCI given in a 40:1 ratio showed the greatest success in treating PCOS symptoms. Treatment of MI:DCI given in a 20:1 ratio showed the second best success. Treatments of MI:DCI in a 80:1 ratio showed the third best success. Other treatment ratios did not have successful outcomes. FSH changes were not significant in any group after 3 moths. LH decreased with all treatments but was only significantly decreased in the groups who received either a 40:1 ratio of MI:DCI or an 80:1 ratio treatment.All treatment ratios resulted in an increase in SHBG and E2 levels but were only significantly increased in the group who received a 40:1 ratio of MI:DCI treatment. HOMA index was significantly reduced from baseline in all treatments.The best result for improving basal and postprandial insulin was shown in the treatment of MI:DCI in a 40:1 ratio.All treatment groups showed no significant changes in BMI between baseline and at 3 months. Statistical significance was determined by a *p* value < or = 0.05.\*P values were not mentioned specifically or numerically, they were only mentioned as a treatment being statistically significant or not for a given variable based on the *p* value which determined statistical significance (*p* value < or = 0.05). Statistical information was given in graphs with no exact number for each statistic.  |
| Author conclusion  | The authors of this study concluded that the 40:1 ratio of MI:DCI had the greatest effect on treating and restoring ovulation in PCOS patients. |
| Your comments  | *Strengths of this study include that the purpose, methods and conclusions, inclusion and exclusion criteria were all clearly stated. Another strength was that each group had the same number of participants and that participants were randomly assigned to each treatment group.* *One limitation is that the study could have benefitted from a larger number of participants per group. Eight participants per group isn’t a large enough sample to determine success of the various treatments. Another limitation is that three months is too short a time period to determine success of the treatments on BMI status. Another limitation was that p values were not mentioned specifically or numerically, they were only mentioned as a treatment being statistically significant or not for a given variable based on the p value which determined statistical significance (p value < or = 0.05).* *A major limitation and conflict is that this study was terminated due to ethical reasons because of significance found in primary and secondary outcomes.* *No conflicts of interest were reported for this study.* |
| Funding source  | Funding for the article was not provided. Unknown funding. |

Table 5. Abstract Table for Article 5

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| Citation  | Troisi J, Cinque C, Giugliano L, et al. Metabolomic change due to combined treatment with myo-inositol, D-chiro-inositol and glucomannan in polycystic ovarian syndrome patients: a pilot study. *Journal of ovarian research*. 2019;12(1):25. doi:10.1186/s13048-019-0500-x. |
| Study design  | Prospective Case-Control Study; Pilot Study |
| Class  | C |
| Quality rating  | Ø |
| Research purpose  | What effect does the combined treatment of myo-inositol (MI), D-chiro-inositol (DCI), and glucomannan have on the metabolic profiles of women with PCOS? |
| Inclusion criteria in the study (not your own) | 15 Overweight/ obese women with PCOS (according to Rotterdam criteria), aged 18 to 35 years, with a BMI > 25 kg/m2, who do not have any other acute intercurrent or chronic illnesses. 15 Healthy control participants (non-PCOS patients) were aged 18- 35 years, who did not have any other acute intercurrent or chronic illnesses.  |
| Exclusion criteria in the study (not your own) | Women taking hormonal medications which affect insulin sensitivity (inositol’s or metformin) were excluded. |
| Description of study protocol | Participants gave written informed consent prior to the start of the study. Participants who received treatment received a total of 1.75 g MI, 0.25g DCI, and 4g glucomannan (a water-soluble polysaccharide; a dietary fiber) per day (this dosage was split in half and taken twice a day by participants). Treatment lasted over the course of 3 months. Neither the treated group nor the control group were allowed to change their lifestyle regimen during the course of the study. BMI and characteristics/ frequency of menstrual cycle were measured/ collected at enrollment. Glucose, insulin, triglycerides and cholesterol were measured at baseline and after 3 months of treatment.  |
| Data collection summary  | Outcomes of this study showed that the treatment of MI, DCI and glucomannan resulted in a statistically significant decrease in BMI and body mass, as well as a statistically significant increase in menstrual cycle regulation after 3 months of treatment in overweight and obese women with PCOS.Degree of hirsutism was measured via the Ferriman-Gallwey score, degree of acne was measured via the Global evaluation scales of 2002 from the FDA, menstrual loss was measured via the menstrual pictogram by Magnay et al., ovary volume/ size and antral follicle count was measured via a transvaginal ultrasound by a gynecologist. The following labs were collected via blood tests: glucose, insulin, triglycerides, cholesterol, Homeostatic Model Assessment for Insulin Resistance (HOMA-IR).Statistical analysis was measured via Statistica software and Minitab. Normal data distribution was measured via the Shapiro-Wilks test. *T*-tests were used to measure inter-group and intra-group comparisons. Categorical variable differences among groups were determined via a Pearson chi-squared test. The significance of class discrimination was measured via a permutation test. Variable Importance in Projection (VIP) scores were calculated for metabolites. Alpha value = 0.05. Blinding was not recorded. |
| Description of actual data sample  | Treatment group:15 Overweight/ obese women with PCOS (according to Rotterdam criteria), aged 18 to 35 years, with a BMI > 25 kg/m2, who do not have any other acute intercurrent or chronic illnesses. Control group: 15 Healthy control participants (non-PCOS patients) were aged 18- 35 years, who did not have any other acute intercurrent or chronic illnesses.Minimum sample size was included in order to have 80% statistical power based on the sample size. Treatment participants and Control participants were drastically different at baseline and continued to be different after 3 months. The control group was based off “health women” who do not suffer from PCOS. The treatment group consisted of overweight and obese women with PCOS. There was no record of any participants who dropped out of this study.  |
| Summary of results  | Results of the study showed that the treatment group of women who were overweight/ obese had a statistically significant decrease in BMI and body mass after 3 months of treatment (*p* < 0.05). Glucose levels, insulin levels, and HOMA-IR values did not significantly change after 3 months of treatment.Menstrual cycle regulation improved significantly after 3 months of treatment (*p* < 0.05).Antral follicle count and ovary volume decreased after 3 months of treatment (*p* < 0.05). Hirsutism and acne decreased after 3 months of treatment. \* No *p* value was noted.A *p* value < 0.05 determined statistical significance.  |
| Author conclusion  | Authors concluded that many serum molecules are associated with PCOS and can be manipulated by the combined treatment of MI, DCI and glucomannan. This treatment resulted in statistically significant decrease in BMI and body mass, as well as a statistically significant increase in menstrual cycle regulation after 3 months of treatment. |
| Your comments  | *Strengths: Results, conclusion, and purpose of the study were clearly stated. The focus on one treatment made the study easy to follow and understand. Methods were detailed and clearly stated.* *Limitations: The control group was different than the population being studied. To get a better understanding if the treatment worked it would have been better to have a control group that was also obese/ overweight and had PCOS (matching the treatment groups criteria) in order to have an accurate understanding of the treatment’s effect on PCOS patients.* *Two personal conflicts of interest that were noted were that two of the authors work for companies that develop and market diagnostic tests based on metabolomics.* |
| Funding source  | Funding for this study was provided by POR CAMPANIA FESR 2014/2020.  |

Table 6. Worksheet overview table

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| **Author****Year****Study Design****Class rating (from table 2)** | **Study type and purpose** | **Study populations** | **Intervention** | **Measurable Outcome** | **Limitations** |
| Benelli E, Del Ghianda S, Di Cosmo C, Tonacchera M, 2016**Study Design:** Randomized Controlled Trial**Class:** A**Rating: +** | Randomized Controlled Trial**Purpose:** To evaluate if the combined treatment of myo-inositol MI) and D-chiro-inositol (DCI) in a 40:1 ratio has a significant therapeutic effect on improving the endocrine profile and insulin resistance in young overweight women suffering from PCOS. | 46 obese women with PCOS who had a BMI >30 kg/m2. PCOS determined by Rotterdam criteria.Group A: N=21Group B: N=25 | Participants were randomized and separated into two groups (A & B). Group A’s treatment consisted of MI + DCI in a 40:1 ratio via a soft gel capsule (550mg MI; 13.8mg DCI; 200 mcg folic acid) twice a day over the course of 6 months. Group B, the control group received a placebo treatment consisting of 200mcg of folic acid twice a day over the course of 6 months. | Outcomes of the study show that the combined treatment of MI+DCI (40:1) helped improve the endocrine profile and insulin resistance of young overweight women with PCOS from group A (treatment group). There were no changes in sex hormones for group B (control group). Measurements were taken at baseline and at 6 months. The results showed the following in regard to the combined treatment of MI + DCI in a 40:1 ratio: the reduction of LH was statistically significant (*p* < 0.05); reduction of free testosterone was statistically significant (*p* < 0.05); reduction of fasting insulin was statistically significant (*p* < 0.001); reduction of HOMA index was statistically significant (*p* < 0.05); the increase of 17-beta-Estradiol (E) levels was statistically significant (*p* < 0.01). | *No limitations of the study were noted, however, authors recommended more studies with larger populations for stronger evidence of the results found in this study. Further limitations may be diet of the participants and if any participated in physical activity during the course of the study. Authors reported no conflict of interest or bias in this study. Funding was never noted or recorded in the study, which leaves funding bias unclear.*  |
| Colak E, Ozcimen EE, Tohma YA, Ceran MU, 2020**Study Design:** Case-Control Study**Class:** C**Rating:** Ø | Retrospective Case-Control Study**Purpose:** To analyze the effectiveness of myo-inositol and D-chiro-inositol (MI:DCI) (40:1) treatment in women with PCOS who are at a normal weight and do not have insulin resistance (IR). | Group 1: N=29 (anovulatory PCOS women without insulin resistance, with oligomenorrhea, who have a BMI of 18-25 kg/m2 – normal weight group).Group 2: N=17 (anovulatory PCOS women without insulin resistance, with oligomenorrhea who have a BMI > 25 kg/m2 – obese /overweight group).PCOS determined by Rotterdam criteria. | The women in group 1 and group 2 who were included in the retrospective study received 6 months treatment of MI:DCI (40:1) (550mg MI; and 13.8mg DCI).  | Outcomes of the study show that the 40:1 ratio of MI:DCI treatment can be considered a primary treatment for women with PCOS who are at a normal weight and do not have insulin resistance.The difference between ovulation in group 1 to group 2 was statistically significant (*p* < 0.001). Progesterone levels showed that after 6 months of treatment, group 1 had statistically significant higher levels than group 2 (*p* < 0.001). In group 1, 6 out of 7 participants -who wanted to become pregnant-experienced spontaneous pregnancy after receiving treatment (85.7%). In group 2, 2 out of 6 participants -who wanted to become pregnant- experienced spontaneous pregnancy after receiving treatment (33.3%). | *A Limitation to this study that was mentioned by the authors was that only patients without insulin resistance were selected for this study. This resulted in smaller groups to be studied (especially the overweight/ obese group) because insulin resistance in PCOS patients is so common especially in women with higher BMI’s. This study also had no randomization when splitting up participants into groups and no bias was discussed in the study. Funding was never noted or recorded in the study, which leaves funding bias unclear.* |
| Le Donne M, Metro D, Alibrandi A, Papa M, Benvenga S, 2019**Study Design:** Randomized Controlled Trial**Class:** A**Rating: +** | Randomized Controlled Trial**Purpose:** To determine which of the three treatments for PCOS (diet, diet and myo-inositol, or diet and myo-inositol with D-chiro-inositol), provides the greatest clinical benefits in regard to clinical and body composition outcomes in overweight and obese women with PCOS. | 43 women with PCOS (determined by Rotterdam criteria), aged 16-45 years, with a BMI > or = 25 kg/m2, who have not had hormone therapy for less than 6 months, have no other medical diseases, who have not taken medications or over-the-counter products from baseline through the 6-month duration of the study.Group 1: N= 21Group 2: N= 10 Group 3: N=13  | 43 Participants were randomly separated into 3 groups (1,2 & 3). Group 1 (n = 21) was the control group and was treated with diet only (1200 Kcal). Group 2 (n= 10) was treated with the same diet of 1200 Kcal + (2000 mg MI + 200 mcg folic acid) twice a day. Group 3 (n=13) was treated with the same diet of 1200 Kcal + (550 mg MI + 13.8 mg DCI +200 mcg folic acid) twice a day. Treatments of all groups lasted over the course of 6 months. | The outcomes of the study showed that the treatment of MI:DCI in a 40:1 ratio (treatment given to group 3) along with a 1200 Kcal diet was able to accelerate weight loss and fat mas reduction, and was able to significantly improve menstrual cycle irregularities in overweight and obese patients with PCOS. Fat/Lean mass ratio decreased significantly in group 1 *(p* = 0.02), group 2 (*p* = 0.015), and group 3 (*p* = 0.005). Total body water was statistically significant between groups 2 and 3 (*p* = 0.03).Hirsutism (Ferriman-Gallwey score) was borderline statistically significant between groups 1 and 3 (*p* = 0.09).Waist to hip ratio was borderline statistically significant between groups 2 and 3 (*p* = 0.09).  | *One limitation is that all three groups should have been assigned the same number of participants. Another limitation is that obesity, insulin resistance (IR) and hyperandrogenism may contribute to higher levels of lean body mass, skewing results.*  |
| Nordio M, Basciani S, Camajani E, 2019**Study Design:** Randomized Controlled Trial**Class:** A**Rating:** Ø | Randomized Controlled Trial; Clinical Trial; Randomized; Interventional; Open-Label**Purpose:** To determine which of 7 different ratios of MI: DCI treatment had the greatest effect on treating symptoms of PCOS? | 55 women with PCOS (according to Rotterdam criteria), aged 18-45 years. All participants had a BMI < 30 kg/m2. Group 1: N=8 (treated with MI:DCI ratio of 0:1)Group 2: N=8 (treated with MI:DCI ratio of 1:3.5)Group 3: N=7 (treated with MI:DCI ratio of 2.5:1)Group 4: N=8 (treated with MI:DCI ratio of 5:1)Group 5: N=8 (treated with MI:DCI ratio of 20:1)Group 6: N=8 (treated with MI:DCI ratio of 40:1)Group 7: N=8 (treated with MI:DCI ratio of 80:1)One participant, from group 3, dropped out from the study. | Participants were randomly and equally assigned to 7 different groups. Treatments consisting 2g inositol’s were given twice a day to participants of all groups over the course of 3 months. Treatment ratios were given to the groups as followed: Group 1: MI:DCI ratio of 0:1;Group 2: MI:DCI ratio of 1:3.5;Group 3: MI:DCI ratio of 2.5:1;Group 4: MI:DCI ratio of 5:1;Group 5: MI:DCI ratio of 20:1;Group 6: MI:DCI ratio of 40:1;Group 7: MI:DCI ratio of 80:1. | The outcomes showed that the 40:1 ratio of MI:DCI had the best and greatest effect on treating and restoring ovulation in women with PCOS. Treatments of MI:DCI given in a 40:1 ratio showed the greatest success in treating PCOS symptoms. Treatment of MI:DCI given in a 20:1 ratio showed the second best success. Treatments of MI:DCI in a 80:1 ratio showed the third best success. Other treatment ratios did not have successful outcomes. | *One limitation is that the study could have benefitted from a larger number of participants per group. Eight participants per group isn’t a large enough sample to determine success of the various treatments. Another limitation is that three months is too short a time period to determine success of the treatments on BMI status. Another limitation was that p values were not mentioned specifically or numerically, they were only mentioned as a treatment being statistically significant or not for a given variable based on the p value which determined statistical significance (p value < or = 0.05).* *A major limitation and conflict is that this study was terminated due to ethical reasons because of significance found in primary and secondary outcomes.*  |
| Troisi J, Cinque C, Giugliano L, et al, 2019**Study Design:** Case-Control Study**Class:** C**Rating:** Ø | Prospective Case-Control Study; Pilot Study**Purpose:** To analyze the effect that the combined treatment of myo-inositol, D-chiro-inositol and glucomannan has on the metabolic profile of women with PCOS.  | Treatment group: 15 Overweight/ obese women with PCOS (according to Rotterdam criteria), aged 18 to 35 years, with a BMI > 25 kg/m2, who do not have any other acute intercurrent or chronic illnesses. Control group: 15 Healthy control participants (non-PCOS patients) were aged 18- 35 years, who did not have any other acute intercurrent or chronic illnesses. | Participants who received treatment received a total of 1.75 g MI, 0.25g DCI, and 4g glucomannan (a water-soluble polysaccharide; a dietary fiber) per day (this dosage was split in half and taken twice a day by participants). Treatment lasted over the course of 3 months.  | Outcomes of this study showed that the treatment of MI, DCI and glucomannan resulted in a statistically significant decrease in BMI and body mass, as well as a statistically significant increase in menstrual cycle regulation after 3 months of treatment in overweight and obese women with PCOS. | *Limitations: The control group was different than the population being studied. To get a better understanding if the treatment worked it would have been better to have a control group that was also obese/ overweight and had PCOS (matching the treatment groups criteria) in order to have an accurate understanding of the treatment’s effect on PCOS patients.* *Two personal conflicts of interest that were noted were that two of the authors work for companies that develop and market diagnostic tests based on metabolomics.* |