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Content

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Introduction

Experts estimate that approximately 5 – 10 % of women of reproductive age are affected by polycystic ovarian syndrome (PCOS). This syndrome is, in fact, a hormonal disorder. Women affected usually exhibit raised levels of male hormones, which are referred to as androgens. This results in male-pattern hair loss, increased facial and body hair, as well as irregular ovulation and menstruation. Therefore, PCOS is also one of the main reasons for female infertility.

As early as 1721, Italian scientist Antonio Vallisneri described women who were „obese and infertile, with two bigger-than-normal ovaries, and acne“. Even though almost 300 years have passed meanwhile, the underlying reasons are still not quite clear yet. Experts assume interactions between predisposition and environmental factors. It seems clear, however, that a couple of hormonal disturbances add up to form the vicious cycle seen in PCOS:

1. Shift in LH / FSH ratio: PCOS-patients often have a shift in the ratio of luteinising hormone (LH) and follicle-stimulating hormone (FSH). LH is important for ovulation, and FSH for oocyte maturation. Because too little FSH is there (in comparison to LH), many immature oocytes gather in the ovaries. At the same time, there is hardly any ovulation, because the oocytes do not mature properly and are therefore not ready for ovulation.

2. Hyperandrogenemia: The imbalance of LH and FSH simultaneously leads to increased androgen-production in the ovaries. These male hormones are converted to estrogen, which

happens in adipose tissue. The more overweight a woman is, the more adipose tissue she has and the more estrogen can arise. This is the reason for an association between excess weight and PCOS.

3. Elevated estrogen levels: This triggers a vicious cycle, as estrogen further enhances LH-production and inhibits FSH. As a consequence of this, more androgens are synthesized in the ovaries and even fewer oocytes reach maturity. Ultimately, this leads to infertility.

4. Hyperinsulinemia: PCOS is also closely linked to carbohydrate metabolism. This was first observed by C. Achard and J. Thiers in 1921 when they examined seven overweight women with excess facial and body hair. They described the condition as "diabetes of bearded women". Many studies have meanwhile confirmed the association of PCOS and so called insulin resistance. In affected women, the blood sugar hormone insulin cannot exert its normal effects in sugar metabolizing tissue (insulin resistance). To compensate for this, pancreatic cells produce even more insulin. A fact many people are not aware of: insulin not only stimulates sugar-uptake into cells, but also triggers synthesis of male hormones. This is how carbohydrate metabolism can contribute to PCOS symptoms.

In summary, excess estrogen, androgens and insulin together contribute to the symptoms typical for PCOS.

Diagnosis

The Rotterdam consensus is the most widely accepted across Europe, Asia and Australia.

Two of the following three criteria are required:

- oligo/anovulation
- hyperandrogenism
  - clinical (hirsutism or less commonly male pattern alopecia) or
  - biochemical (raised FAI or free testosterone)
- polycystic ovaries on ultrasound

Other aetiologies must be excluded such as congenital adrenal hyperplasia, androgen secreting tumours, Cushing syndrome, thyroid dysfunction and hyperprolactinaemia

Weight loss

Due to a close association of carbohydrate metabolism, amount of adipose tissue and PCOS), weight loss should be the first step for every PCOS patient who is overweight. Even a moderate weight loss of only 5 % can result in marked amelioration!

A typical western diet rich in highly processed carbohydrates (sugar, white flour, etc), yet only little fibre and micronutrients, is a main factor leading to insulin resistance and excess weight.

Instead, vegetables and fruits, high-quality proteins and moderate amounts of complex carbohydrates (e.g. whole-grain products, legumes, oil seeds) should make the basis of everyday nutrition.

A study from 2013 summarizes the effects of a diet like this:

"Decreasing insulin levels via a suitable diet is an attractive non-pharmaceutical therapeutic option for women with PCOS, whose elevated insulin levels stimulate testosterone synthesis, adding to PCOS symptoms."

The contraceptive pill

If the primary aim of the patient is to reduce facial hair growth and acne, taking a contraceptive pill often presents as a suitable approach.

Metformin

Metformin, a drug also used in diabetes treatment, is also effective in insulin resistance affecting an approximate 60 % of PCOS patients. It helps to optimize insulin action, thus diminishing insulin resistance and production of androgens. Lipid metabolism benefits as well.

However, in many countries metformin has not been formally recognized as treatment option for PCOS and not every patient tolerates the treatment very well.

Inositols

Due to the close association of metabolism and PCOS, nutritional interventions are frequently successful.

The micronutrient inositol has gained some attention due to many studies in recent years. Insulin needs it in order to exert its effects in target cells. According to research, inositols are as effective in treating insulin resistance as metformin, yet free from any side effects.

Inositol Treatment and ART Outcomes in Women with PCOS.

Garg D, Tal R.

Polycystic ovary syndrome (PCOS) affects 5-10% of women in reproductive age and is characterized by oligo/amenorrhea, androgen excess, insulin resistance, and typical polycystic ovarian morphology. It is the most common cause of infertility secondary to ovulatory dysfunction. The underlying etiology is still unknown but is believed to be multifactorial. Insulin-sensitizing compounds such as inositol, a B-complex vitamin, and its stereoisomers (myo-inositol and D-chiro-inositol) have been studied as an effective treatment of PCOS. Administration of inositol in PCOS has been shown to improve not only the metabolic and hormonal parameters but also ovarian function and the response to assisted-reproductive technology (ART). Accumulating evidence suggests that it is also capable of improving folliculogenesis and embryo quality and increasing the mature oocyte yield following ovarian stimulation for ART in women with PCOS. In the current review, we collate the evidence and summarize our current knowledge on ovarian stimulation and ART outcomes following inositol treatment in women with PCOS undergoing in vitro fertilization (IVF) and/or intracytoplasmic sperm injection (ICSI).

Int J Endocrinol. 2016;2016:1979654. Epub 2016 Oct 4.

Improvement in quality of oocytes in polycystic ovarian syndrome in programs of in vitro fertilization.

Vartanyan EV, Tsaturova KA, Devyatova EA, Mikhaylyukova AS, Levin VA, Petuhova NL, Markin AV, Steptsova EM.

Inositol therapy is aimed at improving the quality of oocytes during preconception care in patients with polycystic ovarian syndrome (PCOS), a cause of infertility and reproductive dysfunction. The objectives of this observational comparative multicentre study were to evaluate the effectiveness of inositol in improving the quality of oocytes/embryos and IVF cycle outcome. Group 1 patients (N = 133) received inositol 1000 mg (Inofert or Nutrilinea) + folic acid 0.1 mg. Group 2 consisted of patients with preserved ovarian reserve without PCOS (N = 137), not administered inositol prior to pregnancy. Effectiveness criteria were numbers of mature oocytes and good quality embryos, pregnancy rates per ET, 'take home baby' index and miscarriage rates. Pregnancy rates per ET (87.0% vs. 87.4%), 'take home baby' index (79.6% vs. 89.4%) and miscarriage rates (14.3% vs. 10.6%) were comparable. Use of inositol in patients with PCOS during preconception care is an effective method allowing improvement of oocytes quality and positively affecting IVF cycle prognosis. High pregnancy rates per ET

and 'take home baby' index after treatment are justifying inositol usage in patients with PCOS and infertility.

Gynecol Endocrinol. 2017;33(sup1):8-11.

Comparison of two insulin sensitizers, metformin and myo-inositol, in women with polycystic ovary syndrome (PCOS).

Fruzzetti F, Perini D, Russo M, Bucci F, Gadducci A.

Insulin resistance (IR) plays a pivotal role in PCOS. Insulin-sensitizer agents such as metformin and inositols have been shown to improve the endocrine and metabolic aspects of PCOS. The purpose of this study is to compare their effects on the clinical and metabolic features of the women with PCOS. Fifty PCOS women with IR and/or hyperinsulinemia were randomized to treatment with metformin (1500 mg/day) or myo-inositol (4 g/day). IR was defined as HOMA-IR >2.5, while hyperinsulinemia was defined as a value of AUC for insulin after a glucose load over the cutoff of our laboratory obtained in normal women. The Matsusa Index has been calculated. The women have been evaluated for insulin secretion, BMI, menstrual cycle length, acne and hirsutism, at baseline and after 6 months of therapy. The results obtained in both groups were similar. The insulin sensitivity improved in both treatment groups. The BMI significantly decreased and the menstrual cycle was normalized in about 50% of the women. No significant changes in acne and hirsutism were observed. The two insulin-sensitizers, metformin and myo-inositol, show to be useful in PCOS women in lowering BMI and ameliorating insulin sensitivity, and improving menstrual cycle without significant differences between the two treatments.

Gynecol Endocrinol. 2017 Jan;33(1):39-42. doi: 10.1080/09513590.2016.1236078. Epub 2016 Nov 3.

Myo-inositol effects in women with PCOS: a meta-analysis of randomized controlled trials.

Unfer V, Facchinetti F, Orrù B, Giordani B, Nestler J.

Myo-inositol (MI) supplementation in women with polycystic ovary syndrome (PCOS) has been evaluated over the last years. Many hormonal and reproductive impairments associated with this disorder seem relieved by the supplement. The objective of the meta-analysis was to assess the effects of MI alone or combined with d-chiro-inositol (DCI) on the endocrine and metabolic abnormalities of women with PCOS. Literature was retrieved from selected databases, MEDLINE, EMBASE, PubMed and Research Gate (up to November 2016). Only random-

ized controlled trials (RCTs) investigating the effects of MI alone or combined with DCI were reviewed. Nine RCTs involving 247 cases and 249 controls were included. Significant decreases in fasting insulin (SMD = -1.021 μU/mL, 95% CI: -1.791 to -0.251, P = 0.009) and homeostasis model assessment (HOMA) index (SMD = -0.585, 95% CI: -1.145 to -0.025, P = 0.041) were identified after MI supplementation. The trial sequential analysis of insulin meta-analysis illustrates that the cumulative z-curve crossed the monitoring boundary, providing firm evidence of the intervention effect. A slight trend toward a reduction of testosterone concentration by MI with respect to controls was found (SMD = -0.49, 95% CI: -1.072 to 0.092, P = 0.099), whereas androstenedione levels remained unaffected. Throughout a subgroup's meta-analysis, a significant increase in serum SHBG was observed only in those studies where MI was administered for at least 24 weeks (SMD = 0.425 nmol/L, 95% CI: 0.050-0.801, P = 0.026). These results highlight the beneficial effect of MI in improving the metabolic profile of women with PCOS, concomitantly reducing their hyperandrogenism.

Endocr Connect. 2017 Nov;6(8):647-658. doi: 10.1530/EC-17-0243.

Myo-inositol rather than D-chiro-inositol is able to improve oocyte quality in intracytoplasmic sperm injection cycles. A prospective, controlled, randomized trial.

Unfer V, Carlomagno G, Rizzo P, Raffone E, Roseff S.

OBJECTIVE:

Polycystic ovary syndrome (PCOS) is the most common cause of infertility due to menstrual dysfunction, and the most promising treatments for this disease are insulin sensitising agents. Myo-inositol and D-chiro-inositol are insulin sensitizing agents used in PCOS treatment. In the present paper, we aimed to compare the effects myo-inositol and D-chiro-inositol on oocyte quality in euglycemic PCOS patients.

MATERIALS AND METHODS:

Eighty-four euglycemic PCOS patients, undergoing ovulation induction for ICSI, were recruited for this study. Forty-three participants received Myo-Inositol 2 g twice a day and forty-one patients received D-chiro inositol 0.6 g twice a day.

RESULTS:

The results of our study showed that the total number of oocytes retrieved did not differ in the two treatments groups. However, the number of mature oocytes was significantly increased in the myo-inositol group compared to D-chiro-inositol. Concurrently, the number of immature

oocytes decreased in myo-inositol treated patients. Furthermore, the myo-inositol-treated group showed an increase in the mean number of top quality embryos and in the total number of pregnancies compared to the D-chiro-inositol-treated group.

CONCLUSIONS:

Our data show that, in PCOS patients having a normal insulin response, myo-inositol treatment rather than D-chiro-inositol is able to improve oocyte and embryo quality during ovarian stimulation protocols.

Eur Rev Med Pharmacol Sci. 2011 Apr;15(4):452-7.

Decreased Insulin Resistance by Myo-Inositol Is Associated With Suppressed Interleukin 6/Phospho-STAT3 Signaling in a Rat Polycystic Ovary Syndrome Model

Yulong Zhang , Changzhong Li , Wenhui Zhang , Xiangqin Zheng , Xiujuan Chen

Myo-inositol supplementation may reduce insulin resistance (IR) with few serious side effects in patients with polycystic ovary syndrome (PCOS). To explore the mechanism of this action in an animal model, a PCOS-IR rat model was generated. Enzyme-linked immunosorbent assay was used to assess changes in ovulation function during treatment with a myo-inositol supplement, and Western blotting, real-time polymerase chain reaction, and immunohistochemistry were performed to investigate the underlying molecular mechanisms. The results showed that the myo-inositol supplement decreased the homeostatic model assessment of insulin resistance (HOMA-IR) index and significantly decreased the serum levels of luteinizing hormone (LH), LH/follicle-stimulating hormone ratio, and testosterone, while increasing the serum level of estradiol. Upregulation of interleukin 6 (IL-6), phospho-STAT3 (p-STAT3), Mir-21, and Mir-155 and significant downregulation of PPAR-γ and GLUT4 were detected in the untreated PCOS-IR rat model. However, downregulation of IL-6, p-STAT3, miR-21, and miR-155 and significant upregulation of PPAR-γ and GLUT4 were detected with myo-inositol supplementation. Thus, myo-inositol supplementation may reduce Mir-21 and Mir-155 levels by downregulating IL-6 and p-STAT3 and, subsequently, reverse the expression of PPAR-γ and GLUT4, leading to a decreased HOMA-IR index. In conclusion, the identification of an IL-6/p-STAT3/Mir-155/Mir-21/PPAR-γ/GLUT4 system in the PCOS-IR rat model provides insight into the pathogenesis of PCOS and may indicate a possible therapeutic strategy. Amelioration of the basal serum glucose levels and of the HOMA/HOMA-IR index may be achieved by the reversal of the expression of PPAR-γ and GLUT4 through the downregulation of IL-6, p-STAT3, miR-21, and miR-155 with myo-inositol supplementation.

J Med Food. 2020 Apr;23(4):375-387

The Insulin-Sensitizing Mechanism of Myo-Inositol Is Associated With AMPK Activation and GLUT-4 Expression in Human Endometrial Cells Exposed to a PCOS Environment

Heidy Cabrera-Cruz, Lorena Oróstica, Francisca Plaza-Parrochia, Ignacio Torres-Pinto, Carmen Romero, Margarita Vega

Polycystic ovary syndrome (PCOS) is an endocrine-metabolic disorder characterized by hyperandrogenism and ovulatory dysfunction but also obesity and hyperinsulinemia. These characteristics induce an insulin-resistant state in tissues such as the endometrium, affecting its reproductive functions. Myo-inositol (MYO) is an insulin-sensitizing compound used in PCOS patients; however, its insulin-sensitizing mechanism is unclear. To understand the relationship of MYO with insulin action in endometrial cells, sodium/myo-inositol transporter 1 (SMIT-1) (MYO-transporter), and MYO effects on protein levels related to the insulin pathway were evaluated. SMIT-1 was assessed in endometrial tissue from women with normal weight, obesity, insulin resistance, and PCOS; additionally, using an in vitro model of human endometrial cells exposed to an environment resembling hyperinsulinemic-obese-PCOS, MYO effect was evaluated on p-AMPK and GLUT-4 levels and glucose uptake by Western blot, immunocytochemistry, and confocal microscopy, respectively. SMIT-1 was detected in endometrial tissue from all groups and decreased in PCOS and obesity ($P < 0.05$ vs. normal weight). In the in vitro model, PCOS conditions decreased p-AMPK levels, while they were restored with MYO ($P < 0.05$). The diminished GLUT-4 protein levels promoted by PCOS environment were restored by MYO through SMIT-1 and p-AMPK-dependent mechanism ($P < 0.05$). Also, MYO restored glucose uptake in cells under PCOS condition through a p-AMPK-dependent mechanism. Finally, these results were similar to those obtained with metformin treatment in the same in vitro conditions. Consequently, MYO could be a potential insulin sensitizer through its positive effects on insulin-resistant tissues as PCOS-endometrium, acting through SMIT-1, provoking AMPK activation and elevated GLUT-4 levels and, consequently, increase glucose uptake by human endometrial cells. Therefore, MYO may be used as an effective treatment option in insulin-resistant PCOS women.

Am J Physiol Endocrinol Metab. 2020 Feb 1;318(2):E237-E248.

N-acetyl-L-cysteine for PCOS patients

N-acetyl-L-cysteine is the precursor for endogenous synthesis of glutathione, thus acting as a powerful antioxidant.

Positive and negative regulation of insulin signaling by reactive oxygen and nitrogen species.

Bashan N, Kovsan J, Kachko I, Ovadia H, Rudich A.

Regulated production of reactive oxygen species (ROS)/reactive nitrogen species (RNS) adequately balanced by antioxidant systems is a prerequisite for the participation of these active substances in physiological processes, including insulin action. Yet, increasing evidence implicates ROS and RNS as negative regulators of insulin signaling, rendering them putative mediators in the development of insulin resistance, a common endocrine abnormality that accompanies obesity and is a risk factor of type 2 diabetes. This review deals with this dual, seemingly contradictory, function of ROS and RNS in regulating insulin action: the major processes for ROS and RNS generation and detoxification are presented, and a critical review of the evidence that they participate in the positive and negative regulation of insulin action is provided. The cellular and molecular mechanisms by which ROS and RNS are thought to participate in normal insulin action and in the induction of insulin resistance are then described. Finally, we explore the potential usefulness and the challenges in modulating the oxidant-antioxidant balance as a potentially promising, but currently disappointing, means of improving insulin action in insulin resistance-associated conditions, leading causes of human morbidity and mortality of our era.

Physiol Rev. 2009 Jan;89(1):27-71. doi: 10.1152/physrev.00014.2008.

Antioxidants and management of polycystic ovary syndrome in Iran: A systematic review of clinical trials.

Amini L, Tehranian N, Movahedin M, Ramezani Tehrani F, Ziaee S.

BACKGROUND:

Recently there is a focus on the antioxidants as adjuvant treatment of polycystic ovary syndrome (PCOS), the most endocrinopathy in reproductive age women.

OBJECTIVE:

The aim of this review is answer to the question whether antioxidants are effective for managing of hormonal and metabolic problems in women with PCOS based on first degree evidences from Iran.

MATERIALS AND METHODS:

A systematic review of clinical trials was done in Persian and international databases including PubMed, Scientific Information Database, Google Scholar, Iran Medex, and Magiran up to 2013. Keywords were including polycystic ovary syndrome, Iran, vitamin, antioxidant. From 440 potential studies found electronically, 11 studies; including 444 women in intervention and 390 women in control groups. Intervention in three studies was Calcium-vitamin D or calcitriol; in three studies was ω-3 fatty acids; in two studies was N-acetyl cysteine; in one study was folic acid; in one study was Zinc; and in one study was Soy.

RESULTS:

Finally, 11 studies that were relevant and met the inclusion criteria reviewed. There were 7 studies in English and 4 studies in Persian. We couldn't include all studies because all full texts were not accessible.

CONCLUSION:

The results showed that antioxidants and vitamins have positive effects on management of PCOS women. Although it seems more studies is necessary in this field.

Iran J Reprod Med. 2015 Jan;13(1):1-8.

N-acetylcysteine for polycystic ovary syndrome: a systematic review and meta-analysis of randomized controlled clinical trials.

Thakker D, Raval A, Patel I, Walia R.

OBJECTIVE:

To review the benefits and harms of N-acetylcysteine (NAC) in women with polycystic ovary syndrome (PCOS).

METHOD:

Literature search was conducted using the bibliographic databases, MEDLINE (Ovid), CINAHL, EMBASE, Scopus, PsyInfo, and PROQUEST (from inception to September 2013) for the studies on women with PCOS receiving NAC.

RESULTS:

Eight studies with a total of 910 women with PCOS were randomized to NAC or other treatments/placebo. There were high risk of selection, performance, and attrition bias in two studies and high risk of reporting bias in four studies. Women with NAC had higher odds of having a live birth, getting pregnant, and ovulation as compared to placebo. However, women with NAC were less likely to have pregnancy or ovulation as compared to metformin. There was no significant difference in rates of the miscarriage, menstrual regulation, acne, hirsutism, and adverse events, or change in body mass index, testosterone, and insulin levels with NAC as compared to placebo.

CONCLUSIONS:

NAC showed significant improvement in pregnancy and ovulation rate as compared to placebo. The findings need further confirmation in well-designed randomized controlled trials to examine clinical outcomes such as live birth rate in longer follow-up periods. Systematic review registration number is CRD42012001902.

Obstet Gynecol Int. 2015;2015:817849. doi: 10.1155/2015/817849. Epub 2015 Jan 8.

N-Acetylcysteine improves oocyte and embryo quality in polycystic ovary syndrome patients undergoing intracytoplasmic sperm injection: an alternative to metformin.

Cheraghi E, Mehranjani MS, Shariatzadeh MA, Esfahani MH, Ebrahimi Z.

Polycystic ovary syndrome (PCOS) is associated with low-quality oocytes. The aim of the present study was to investigate the effects of metformin (MET), N-acetylcysteine (NAC) and their combination on follicular fluid parameters, oocytes and embryo quality in PCOS patients. A prospective randomised placebo-controlled pilot study on 60 Iranian women with PCOS (aged 25-35 years) undergoing intracytoplasmic sperm injection (ICSI) was designed. Women were divided into four groups (n=15 in each): (1) an MET, administered 1500mg day(-1) MET; (2) an NAC group, administered 1800mg day(-1) NAC; (3) an NAC + MET group; and (4) a placebo group. Drugs were administered from the 3rd day of previous cycle until the day of oocyte aspiration (6 weeks treatment in total). Data were analysed by one-way ANOVA, with significance set at $P<0.05$. The number of immature and abnormal oocytes decreased significantly in the NAC compared with placebo group, with a concomitant increase in the number of good-quality embryos in the NAC group ($P<0.05$). Malondialdehyde levels decreased significantly in the NAC and NAC + MET groups compared with the place-

bo-treated group (P<0.02). In addition, there were significant decreases in leptin levels in the NAC, MET and NAC + MET groups compared with the placebo group (P<0.001). Insulin and LH levels were significantly lower in the MET and NAC groups compared with the placebo-treated group (P<0.02). We concluded that NAC improves oocyte and embryo quality and could be administered as an alternative to MET.

Reprod Fertil Dev. 2016 Apr;28(6):723-31. doi: 10.1071/RD14182.

A comparison between the effects of metformin and N-acetyl cysteine (NAC) on some metabolic and endocrine characteristics of women with polycystic ovary syndrome.

Javanmanesh F, Kashanian M, Rahimi M, Sheikhansari N.

OBJECTIVE:

To compare N-acetyl cysteine (NAC) and metformin on polycystic ovary syndrome (PCOS).

METHOD:

Study was performed as a randomized double-blind clinical trial on women with diagnosis of PCOS without additional complications. In one group, oral NAC 600 mg, three times a day and in the other group, 500 mg oral metformin, three times a day were prescribed. Duration of treatment was 24 weeks, and after finishing this period of treatment, fasting blood glucose (FBS) and insulin, lipid profile and Homeostasis Model Assessment (HOMA) index were measured (all the blood samples were taken while fasting) and were compared in the two groups.

RESULTS:

Forty-six women in NAC group and 48 women in metformin group finished the study. The two groups did not show significant difference according to age, body mass index (BMI) of more than 30; mean BMI, AUB, FBS, fasting blood insulin, lipid profile and HOMA index before treatment. After 24 weeks of treatment; BMI >30 [17 (35.4%) versus 7 (15.2%), p = 0.033], mean BMI [(28.36 ± 2.27) versus (27.11 ± 3.55), p = 0.44], number of women with the complain of abnormal uterine bleeding (AUB) [24 (50%) versus 13 (28.3%), p = 0.037], FBS [(90.02 ± 6.24) versus (86.61 ± 7.81), p = 0.021], fasting insulin (10.40 ± 2.64 versus 8.89 ± 2.20, p = 0.004), HOMA Index (2.09 ± 0.69 versus 1.71 ± 0.45, p = 0.001), low density lipoprotein (LDL) (141.83 ± 26.98 versus 127.89 ± 28.70, p = 0.017) were less in NAC group. Triglyceride (TG) and total cholesterol did not show significant difference between the two groups after treatment. High-density lipoprotein (HDL) was higher in NAC group.

CONCLUSION:

NAC can improve lipid profile and fasting blood sugar (FBS) and fasting blood insulin better than metformin.

Gynecol Endocrinol. 2016;32(4):285-9. doi: 10.3109/09513590.2015.1115974. Epub 2015 Dec 10.

Comparison of metformin and N-acetyl cysteine, as an adjuvant to clomiphene citrate, in clomiphene-resistant women with polycystic ovary syndrome.

Nemati M, Nemati S, Taheri AM, Heidari B.

OBJECTIVE:

To evaluate the effects of short- and long-term treatment with metformin and NAC, in an adjuvant to clomiphene citrate (CC), on the improvement of hormonal profile (SHBG, total testosterone, FBS, and fasting insulin) and fertility status in CC-resistant women with PCOS.

MATERIALS AND METHODS:

One hundred and eight CC-resistant PCOS patients participated in the study and received either metformin (1500mg/day) or NAC (1800mg/day) with 100mg/day of CC for 8 and 12 weeks. Mean BMI, hirsutism score, LH/FSH ratio, endometrial thickness, mature follicle number, and serum concentrations of LH, FSH, E2, fasting insulin, total testosterone and FBS were evaluated before and after short- and long-term treatment. Furthermore, ovulation and pregnancy rates in the first and second cycles were also determined in treated patients.

RESULTS:

There was no significant difference in all variables before and 8 weeks after treatment with metformin and NAC. The BMI- and insulin-lowering effects of metformin were significantly higher than NAC after long-term treatment. However, the reducing-effect of NAC on hirsutism score and FBS levels was significantly more than metformin after 12 weeks. Treatment with metformin and NAC significantly increased ovulation and pregnancy rates in CC-resistant PCOS patients. In the first and second cycles, ovulation and pregnancy rates in patients treated with NAC were slightly higher than those received metformin.

CONCLUSIONS:

Compared with metformin, administration of NAC in an adjuvant to CC is recommended for improving of hormonal profile and treatment of anovulatory infertility in hyperinsulinemic patients especially women with PCOS who are CC-resistant.

J Gynecol Obstet Hum Reprod. 2017 Sep;46(7):579-585. doi: 10.1016/j.jogoh.2017.07.004. Epub 2017 Jul 8.

N-Acetylcysteine Compared to Metformin, Improves The Expression Profile of Growth Differentiation Factor-9 and Receptor Tyrosine Kinase c-Kit in The Oocytes of Patients with Polycystic Ovarian Syndrome.

Cheraghi E, Soleimani Mehranjani M, Shariatzadeh SMA, Nasr Esfahani MH, Alani B.

BACKGROUND:

Paracrine disruption of growth factors in women with polycystic ovarian syndrome (PCOS) results in production of low quality oocyte, especially following ovulation induction. The aim of this study was to investigate the effects of metformin(MET), N-acetylcysteine (NAC) and their combination on the hormonal levels and expression profile of GDF-9, BMP-15 and c-kit, as hallmarks of oocyte quality, in PCOS patients.

MATERIALS AND METHODS:

This prospective randomized, double-blind, placebo controlled trial aims to study the effects of MET, NAC and their combination (MET+NAC) on expression of GDF-9, BMP-15 and c-kit mRNA in oocytes [10 at the germinal vesicle (GV) stage, 10 at the MI stage, and 10 at the MII stage from per group] derived following ovulation induction in PCOS. Treatment was carried out for six weeks, starting on the third day of previous cycle until oocyte aspiration. The expression of GDF9, BMP15 and c-kit were determined by quantitative real time polymerase chain reaction (RT-qPCR) and western blot analysis. Data were analyzed with one-way ANOVA.

RESULTS:

The follicular fluid (FF) level of c-kit protein significantly decreased in the NAC group compared to the other groups. Significant correlations were observed between the FF soluble c-kit protein with FF volume, androstenedione and estradiol. The GDF-9 expression in unfertilized mature oocytes were significantly higher in the NAC group compared to the other groups ($P<0.001$). Similar difference was not observed between the MET, NAC+MET and control groups. The c-kit expression in unfertilized mature oocytes were significantly lower in the NAC group compared to the other groups ($P<0.001$). Similar difference was not observed between the MET, NAC+MET and control groups (Registration number: IRCT201204159476N1).

CONCLUSION:

We concluded that NAC can improve the quality of oocytes in PCOS.

Int J Fertil Steril. 2018 Jan;11(4):270-278. doi: 10.22074/ijfs.2018.5142. Epub 2017 Oct 12.

Omega-3-fatty acids

Lipids play an important role in the orthomolecular therapy of PCOS. They modulate the activity of hormone receptors and expression of certain genes involved in excessive weight gain and insulin resistance. As modulators of anti-inflammatory mediators, they are of interest for lean patients with PCOS, too.

Nutrient-Induced Inflammation in Polycystic Ovary Syndrome: Role in the Development of Metabolic Aberration and Ovarian Dysfunction.

González F.

A pathophysiology paradigm shift has emerged with the discovery that polycystic ovary syndrome (PCOS) is a proinflammatory state. Despite the dogma that the compensatory hyperinsulinemia of insulin resistance is the promoter of hyperandrogenism, physiological insulin infusion has no effect on androgen levels in PCOS. The dogma also does not explain the cause of hyperandrogenism and ovarian dysfunction in the 30 to 50% of women with PCOS who are of normal weight and lack insulin resistance. Inflammation is the underpinning of insulin resistance in obesity and type 2 diabetes, and may also be the cause of insulin resistance when present in PCOS. The origin of inflammation in PCOS has been ascribed to excess abdominal adiposity or frank obesity. However, nutrients such as glucose and saturated fat can incite inflammation from circulating mononuclear cells (MNC) of women with PCOS independent of excess adiposity and insulin resistance, and can also promote atherogenesis. Hyperandrogenism activates MNC in the fasting state to increase MNC sensitivity to nutrients, and is a potential mechanism for initiating inflammation in PCOS. However, chronic ovarian androgen suppression does not reduce inflammation in normal-weight women with PCOS. Direct exposure of ovarian theca cells to proinflammatory stimuli in vitro increases androgen production. These findings may be corroborated in vivo with anti-inflammatory therapy to normal-weight insulin-sensitive women with PCOS without abdominal adiposity to observe for amelioration of ovarian dysfunction.

Semin Reprod Med. 2015 Jul;33(4):276-86. doi: 10.1055/s-0035-1554918. Epub 2015 Jul 1.

The influences of vitamin D and omega-3 co-supplementation on clinical, metabolic and genetic parameters in women with polycystic ovary syndrome.

Jamilian M, Samimi M, Mirhosseini N, Afshar Ebrahimi F, Aghadavod E, Talaee R, Jafarnejad S, Hashemi Dizaji S, Asemi Z.

OBJECTIVE:

The aim of this study was to evaluate the effect of the co-administration of vitamin D and omega-3 fatty acid on clinical, metabolic and genetic parameters in women with polycystic ovary syndrome (PCOS).

METHODS:

This randomized, double-blinded, placebo-controlled clinical trial was conducted on 60 subjects, aged 18-40 years old with PCOS. Subjects were randomly allocated to take either 50,000 IU vitamin D every 2 weeks plus 2000 mg/day omega-3fatty acid from fish oil (n = 30) or placebo (n = 30) for 12 weeks. Gene expression analysis of inflammatory cytokines was conducted on peripheral blood mononuclear cells (PBMCs) of PCOS women using RT-PCR method.

RESULTS:

Vitamin D and omega -3 fatty acid co-supplementation significantly decreased serum total testosterone levels (-0.2 ± 0.5 vs. + 0.1 ± 0.4 ng/mL, P = 0.02) compared with the placebo. In addition, vitamin D and omega-3 fatty acid co-supplementation resulted in a significant improvement in beck depression inventory (-1.4 ± 1.6 vs. -0.5 ± 0.6, P = 0.01), general health questionnaire scores (-4.5 ± 4.3 vs. -1.9 ± 2.3, P = 0.005) and depression anxiety and stress scale scores (-5.0 ± 5.1 vs. -2.3 ± 3.5, P = 0.01) compared with the placebo. Additionally, vitamin D and omega-3 fatty acid co-administration significantly decreased serum high-sensitivity C-reactive protein (hs-CRP) (-1.2 ± 1.9 vs. + 0.1 ± 0.7 mg/L, P = 0.001) and malondialdehyde (MDA) levels (-0.4 ± 0.4 vs. + 0.2 ± 0.6 μmol/L, P < 0.001), and significantly increased plasma total antioxidant capacity (TAC) levels (+ 114.6 ± 122.2 vs. -2.4 ± 168.2 mmol/L, P = 0.003) compared with the placebo. Results of RT-PCR demonstrated that vitamin D and omega-3 fatty acid co-supplementation significantly downregulated gene expression of interleukin-1 (IL-1) (P = 0.03), and upregulated vascular endothelial growth factor (VEGF) (P = 0.004) in PBMCs of subjects with PCOS, when compared with placebo.

CONCLUSIONS:

Overall, the co-administration of vitamin D and omega-3 fatty acid for 12 weeks had beneficial effects on mental health parameters, serum total testosterone, hs-CRP, plasma TAC and MDA levels, and gene expression of IL-1 and VEGF among women with PCOS.

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J Affect Disord. 2018 May 26;238:32-38. doi: 10.1016/j.jad.2018.05.027. [Epub ahead of print]

Effectiveness of Omega-3 fatty acid for polycystic ovary syndrome: a systematic review and meta-analysis.

Yang K, Zeng L, Bao T, Ge J.

OBJECTIVE:

To assess the effectiveness and safety of omega-3 fatty acid for patients with PCOS.

METHODS:

In this meta-analysis, data from randomized controlled trials were obtained to assess the effects of omega-3 fatty acid versus placebo or western medicine in women with PCOS. The study's registration number is CRD42017065859. The primary outcomes included the change of homeostatic model assessment (HOMA) of insulin resistance, total cholesterol (TC), triglyceride (TG) and adiponectin.

RESULT:

Nine trials involving 591 patients were included. Comparing with the control group, omega-3 fatty acid may improve HOMA index (WMD -0.80; 95% CI -0.89, - 0.71; P<0. 00001), decrease TC and TG level [TC: (WMD -9.43; 95% CI -11.90, - 6.95; P<0. 00001); TG: (WMD -29.21; 95% CI -48.08, - 10.34; P = 0. 002)], and increase adiponectin level (WMD 1.34; 95% CI 0.51, 2.17; P = 0. 002).

CONCLUSION:

Based on current evidence, omega-3 fatty acid may be recommended for the treatment of PCOS with insulin resistance as well as high TC (especially LDL-C) and TG.

Reprod Biol Endocrinol. 2018 Mar 27;16(1):27. doi: 10.1186/s12958-018-0346-x.

Effect of Omega-3 Supplementation on Visfatin, Adiponectin, and Anthropometric Indices in Women with Polycystic Ovarian Syndrome.

Nadjarzadeh A, Dehghani-Firouzabadi R Daneshbodi H, Lotfi MH, Vaziri N, Mozaffari-Khosravi H.

BACKGROUND:

Polycystic ovary syndrome (PCOS) is a multifactorial, metabolic disorder. Characteristics are chronic anovulation, polycystic ovaries and hyperandrogenism. The aim of this study was to determine the effect of omega-3supplementation on visfatin, adiponectin, and anthropometric indices in PCOS women.

METHODS:

The study was a randomized double blind placebo-controlled clinical trial. It was conducted on 84 women with polycystic ovary syndrome (26.92±5.05 years, BMI=31.69 Kg/m (2)) who referred to the fertility and infertility research center and Shahid Sadoughi hospital in Yazd. After the examination, evaluation and para-medical assessment by obstetrician, they were recruited. They took 3 capsules of omega-3 (each one contained 180 mg EPA and 120 mg DHA) or placebo (each contained 1 g paraffin) daily for 8 weeks. Statistical analysis was paired T-test and student T-test, and a $p<0.05$ was considered statistically significant.

RESULTS:

After the intervention, visfatin concentration did not change in neither groups. But, at the end of the study, the mean of adiponectin concentration increased ($p<0.001$) in omega-3 group. Moreover, the mean of changes in this factor was significantly different between groups ($p<0.005$). FSH did not change in two groups of the study. However, the mean of LH decreased about 1.74 mIU/ml in omega-3 group ($p<0.005$). The mean of change of LH/FSH ratio between groups was significant ($p<0.05$). After the intervention, prolactin did not meaningfully change in both groups.

CONCLUSION:

Our results showed that 8 weeks of supplementation of omega-3 may have some beneficial effects on PCOS biochemical characteristics such as LH, LH/FSH, and adiponectin.

J Reprod Infertil. 2015 Oct-Dec;16(4):212-20.

The effect of omega-3 supplementation on androgen profile and menstrual status in women with polycystic ovary syndrome: A randomized clinical trial.

Nadjarzadeh A, Dehghani Firouzabadi R, Vaziri N, Daneshbodi H, Lotfi MH, Mozaffari-Khosravi H.

BACKGROUND:

There is some evidence regarding the effect of poly unsaturated fatty acid intake on androgen levels and gonadal function in polycystic ovary syndrome (PCOS).

OBJECTIVE:

This study was conducted to determine the effect of omega-3 supplementation on sex hormone-binding protein (SHBG), testosterone, free androgen index (FAI) and menstrual status in women with PCOS.

MATERIALS AND METHODS:

This double-blind randomized clinical trial was conducted on 78 overweight/obese women with PCOS. Participants were randomized to receive omega-3 (3gr/day) or placebo for 8 weeks. Data about weight, height and nutrient intake as well as blood samples were collected before and after intervention. Serum concentrations of testosterone (nmol/L) and SHBG (nmol/L) were measured. FAI was also calculated as the ratio of testosterone to SHBG.

RESULTS:

Seventy eight patients (age: 26.92±5.46 yrs, Body Mass Index: 31.69±4.84 Kg/m(2)) completed the study. There was no significant difference in mean age, weight, height, Body Mass Index and intake of energy, and macronutrients between 2 study groups before and after treatment. All the participants had irregular periods. After the trial the percentage of regular menstruation in the omega-3 group was more than the placebo group (47.2% vs. 22.9%, p=0.049). Furthermore, testosterone concentration was significantly lower in the omega-3 group compared with placebo, after supplementation (p=0.04). SHBG and FAI did not change in either group.

CONCLUSION:

Omega-3 supplementation could reduce serum concentrations of testosterone and regulate menstrual cycle without significant effect on SHBG and FAI. Future studies with longer period of supplementation are warranted. This article extracted from M.Sc. thesis. (Niloufar Vaziri) Registration ID in IRCT: IRCT201112318564N1.

Iran J Reprod Med. 2013 Aug;11(8):665-72.

Efficacy of omega-3 in the treatment of polycystic ovary syndrome.

Oner G, Muderris II.

The purpose of this study was to evaluate the efficacy and safety of omega-3 in the treatment of polycystic ovary syndrome and to compare the clinical, hormonal, TNF-a and resistin levels in the patients treated with omega-3. A total of 45 non-obese PCOSwomen were studied. Women were treated with daily oral 1,500 mg of omega-3 for 6 months. Body mass index (BMI), hirsutism score, fasting glucose and insulin levels were noted for each case. Hirsutism was assessed at 6-month intervals using the Ferriman-Gallwey (F-G) scoring system. Hormonal,

TNF-a and resistin levels at 6 months of therapy were compared with baseline values. BMI, F-G scoring, insulin and HOMA levels decreased significantly during treatment, but glucose levels did not change. In the hormonal profile, serum LH and testosterone levels decreased and sex hormone-binding globulin levels increased significantly after the 6 months of therapy. On the other hand, TNF-a levels showed a significant increase, whereas resistin levels showed no change. Omega-3 may be also effective in improving hirsutism and insulin resistance in patients with PCOS.

J Obstet Gynaecol. 2013 Apr;33(3):289-91. doi: 10.3109/01443615.2012.751365.

Hormonal and metabolic effects of polyunsaturated fatty acids in young women with polycystic ovary syndrome: results from a cross-sectional analysis and a randomized, placebo-controlled, crossover trial.

Phelan N, O'Connor A, Kyaw Tun T, Correia N, Boran G, Roche HM, Gibney J.

BACKGROUND:

Polycystic ovary syndrome (PCOS) is characterized by an adverse metabolic profile. Although dietary changes are advocated, optimal nutritional management remains uncertain. Polyunsaturated fatty acids (PUFAs), particularly long-chain (LC) n-3 (omega-3) PUFAs, improve metabolic health, but their therapeutic potential in PCOS is unknown.

OBJECTIVES:

We aimed to determine the associations between plasma PUFAs and metabolic and hormonal aspects of PCOS to investigate the efficacy of LC n-3 PUFA supplementation and to support the findings with mechanistic cellular studies.

DESIGN:

We selected a cross-sectional PCOS cohort (n = 104) and conducted a principal component analysis on plasma fatty acid profiles. Effects of LC n-3 PUFA supplementation on fasting and postprandial metabolic and hormonal markers were determined in PCOS subjects (n = 22) by a randomized, crossover, placebo-controlled intervention. Direct effects of n-6 (omega-6) compared with n-3 PUFAs on steroidogenesis were investigated in primary bovine theca cells.

RESULTS:

Cross-sectional data showed that a greater plasma n-6 PUFA concentration and n-6:n-3 PUFA ratio were associated with higher circulating androgens and that plasma LC n-3 PUFA status was associated with a less atherogenic lipid profile. LC n-3 PUFA supplementation reduced plasma bioavailable testosterone concentrations ($P < 0.05$), with the greatest reductions in subjects who exhibited greater reductions in plasma n-6:n-3 PUFA ratios. The treatment of bovine theca cells with n-6 rather than with n-3 PUFAs up-regulated androstenedione secretion ($P < 0.05$).

CONCLUSIONS:

Cross-sectional data suggest that PUFAs modulated hormonal and lipid profiles and that supplementation with LC n-3 PUFAs improves androgenic profiles in PCOS. In bovine theca cells, arachidonic acid modulated androstenedione secretion, which suggests an indirect effect of n-3 PUFAs through the displacement of or increased competition with n-6 PUFAs. This trial was registered at clinicaltrials.gov as NCT01189669.

Am J Clin Nutr. 2011 Mar;93(3):652-62. doi: 10.3945/ajcn.110.005538. Epub 2011 Jan 26.

Chromium

Chromium is well known for its positive effects on blood sugar and insulin levels. Unfortunately, stress and high carbohydrate consumption can increase its demand considerably, which is why supplementation in PCOS can be helpful.

Chromium supplementation and polycystic ovary syndrome: A systematic review and meta-analysis.

Fazelian S, Rouhani MH, Bank SS, Amani R.

INTRODUCTION:

polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women. Some vitamins and mineral can play role in improvement of PCOS. Chromium (Cr) is an essential element in glucose and insulin homeostasis. However, findings are not consistent regarding PCOS improvement. Therefore, the purpose of this paper was to assess the effect of Cr supplementation in PCOS that have not yet fully been elucidated.

METHODS:

We searched ISI Web of Science, MEDLINE (1966 to June 2016), Google Scholar databases and Proquest and identified eligible papers and extracted the following terms: total testosterone, DHEAS, insulin sensitivity, fasting glucose, fasting insulin, OGTT 1h glucose, OGTT 2h glucose (mg/dL), LH (mIU/mL), FSH, DHEAS, ferriman-Galwey score (FG score). We calculated overall effect size with random effects model, between-study heterogeneity with I square (I2) statistic. Publication bias was assessed using Begg's test regression.

RESULT:

Totally, 7 RCTs were selected. Results indicated that Cr supplementation had a beneficial effect on BMI with effect size: -2.37 (kg/m2), 95% CI: -2.99, -1.76, p=0.001 and free testosterone concentration with effect size=-0.52 (pg/mL), 95% CI: -0.83, -0.23, p=0.001. Cr reduced fasting insulin in subgroup of studies with >10 participants with effect size: -0.86mIU/ml, 95% CI: -0.67, -0.17; p=0.001. Cr supplementation had no beneficial effects on reducing total testosterone, FG score, DHEA, FSH and LH.

CONCLUSION:

This systematic review and meta-analysis shows that using Cr picolinate supplementation has beneficial effects on decreasing BMI, fasting insulin and free testosterone in PCOS patients.

J Trace Elem Med Biol. 2017 Jul;42:92-96. doi: 10.1016/j.jtemb.2017.04.008. Epub 2017 Apr 21.

The Influences of Chromium Supplementation on Glycemic Control, Markers of Cardio-Metabolic Risk, and Oxidative Stress in Infertile Polycystic ovary Syndrome Women Candidate for In vitro Fertilization: a Randomized, Double-Blind, Placebo-Controlled Trial.

Jamilian M, Zadeh Modarres S, Amiri Siavashani M, Karimi M, Mafi A, Ostadmohammadi V, Asemi Z.

This study was carried out to investigate the effects of chromium intake on glycemic control, markers of cardio-metabolic risk, and oxidative stress in infertile polycystic ovary syndrome (PCOS) women candidate for in vitro fertilization (IVF). This randomized double-blind, placebo-controlled trial was done among 40 subjects with infertile PCOS candidate for IVF, aged 18-40 years old. Individuals were randomly allocated into two groups to take either

200 µg/day of chromium (n = 20) or placebo (n = 20) for 8 weeks. Biochemical parameters were assessed at baseline and at end-of-trial. Compared with the placebo, taking chromium supplements led to significant reductions in fasting plasma glucose (- 2.3 ± 5.7 vs. + 0.9 ± 3.1 mg/dL, P = 0.03), insulin levels (- 1.4 ± 2.1 vs. + 0.4 ± 1.7 µIU/mL, P = 0.004), homeostatic model of assessment for insulin resistance (- 0.3 ± 0.5 vs. + 0.1 ± 0.4, P = 0.005), and a significant increase in quantitative insulin sensitivity check index (+ 0.004 ± 0.008 vs. - 0.001 ± 0.008, P = 0.03). In addition, chromium supplementation significantly decreased serum triglycerides (- 19.2 ± 33.8 vs. + 8.3 ± 21.7 mg/dL, P = 0.004), VLDL- (- 3.8 ± 6.8 vs. + 1.7 ± 4.3 mg/dL, P = 0.004) and total cholesterol concentrations (- 15.3 ± 26.2 vs. - 0.6 ± 15.9 mg/dL, P = 0.03) compared with the placebo. Additionally, taking chromium supplements was associated with a significant increase in plasma total antioxidant capacity (+ 153.9 ± 46.1 vs. - 7.8 ± 43.9 mmol/L, P < 0.001) and a significant reduction in malondialdehyde values (-0.3 ± 0.3 vs. + 0.1 ± 0.2 µmol/L, P = 0.001) compared with the placebo. Overall, our study supported that chromium administration for 8 weeks to infertile PCOS women candidate for IVF had beneficial impacts on glycemic control, few variables of cardio-metabolic risk, and oxidative stress.

Biol Trace Elem Res. 2018 Jan 6. doi: 10.1007/s12011-017-1236-3. [Epub ahead of print]

The Effects of Chromium Supplementation on Endocrine Profiles, Biomarkers of Inflammation, and Oxidative Stress in Women with Polycystic Ovary Syndrome: a Randomized, Double-Blind, Placebo-Controlled Trial.

Jamilian M, Bahmani F, Siavashani MA, Mazloomi M, Asemi Z, Esmaillzadeh A.

Limited data are available indicating the effects of chromium administration on endocrine profiles, biomarkers of inflammation, and oxidative stress among women with polycystic ovary syndrome (PCOS). This study was done to assess the effects of chromium administration on endocrine profiles, biomarkers of inflammation, and oxidative stress in women with PCOS. Participants of this randomized, double-blind, placebo-controlled trial consisted of 60 patients with PCOS who received either 200 µg chromium supplements (n = 30) or placebo daily (n = 30) for 8 weeks. Endocrine profiles, inflammatory factors, and biomarkers of oxidative stress were assessed at study baseline and at the end of intervention. After 8 weeks of intervention, pregnancy rate in chromium group was higher than that in the placebo group: 16.7 % (5/30) vs. 3.3 % (1/30), P = 0.08. In addition, prevalence of acne (20.0 vs. 3.3 %, P = 0.04)

decreased following the administration of chromium supplements compared with the placebo. Taking chromium led to a significant reduction in hirsutism (-1.8 ± 2.5 vs. -0.2 ± 0.8, P = 0.002), serum high-sensitivity C-reactive protein (hs-CRP) (-717.0 ± 1496.1 vs. +227.1 ± 1669.6 ng/mL, P = 0.02), plasma malondialdehyde (MDA) (-0.1 ± 0.7 vs. +1.1 ± 1.5 μmol/L, P < 0.001), and a significant increase in plasma total antioxidant capacity (TAC) concentrations (+250.7 ± 265.2 vs. +13.0 ± 201.6 mmol/L, P < 0.001). We failed to find any significant effect of chromium administration on endocrine profiles and nitric oxide (NO) and glutathione (GSH) levels. Overall, taking chromium for 8 weeks among women with PCOS had beneficial effects on acne, hirsutism, hs-CRP, TAC, and MDA levels, but it did not affect endocrine profiles, NO, and GSH.

Biol Trace Elem Res. 2016 Jul;172(1):72-8. doi: 10.1007/s12011-015-0570-6. Epub 2015 Nov 28.

Selenium

Selenium Supplementation and the Effects on Reproductive Outcomes, Biomarkers of Inflammation, and Oxidative Stress in Women with Polycystic Ovary Syndrome.

Razavi M, Jamilian M, Kashan ZF, Heidar Z, Mohseni M, Ghandi Y, Bagherian T, Asemi Z.

Selenium supplementation could be effective on reproductive outcomes, biomarkers of inflammation, and oxidative stress among women with polycystic ovary syndrome (PCOS). The aim of the study was to determine the effects of selenium supplementation on reproductive outcomes, biomarkers of inflammation, and oxidative stress in PCOS patients. The present randomized double-blind, placebo-controlled trial was conducted on 64 women aged 18-40 years old with PCOS at the clinic affiliated to Ardabil University of Medical Sciences, Ardabil, Iran. The participants were randomly assigned to 2 groups receiving either 200 μg selenium daily (n=32) or placebo (n=32) for 8 weeks. Hormonal profiles, biomarkers of inflammation, and oxidative stress were measured and compared both before and after the treatment. After 8 weeks of intervention, pregnancy rate in the selenium group was higher than in the placebo group: 18.8 (6/32) vs. 3.1% (1/32), p=0.04. In addition, alopecia (40.6 vs. 9.4%, p=0.004) and acne (46.9 vs. 12.5 %, p=0.003) decreased following the consumption of selenium supplements compared with placebo. Additionally, patients who received selenium supplements had significantly decreased serum dehydroepiandrosterone (DHEA) levels (p=0.02), hirsutism (modified Ferriman-Gallwey scores) (p<0.001), serum high sensitivity C-reactive protein (hs-CRP) (p=0.02), and plasma malondialdehyde (MDA) levels (p=0.01) compared with

placebo. We did not observe any significant effects of taking selenium supplements on other hormonal profiles, nitric oxide (NO), and other biomarkers of oxidative stress. Taken together, selenium supplementation for 8 weeks among PCOS women had beneficial effects on reproductive outcomes, DHEA, hs-CRP, and MDA levels. Supporting Information for this article is available online at http://www.thieme-connect.de/products.

Horm Metab Res. 2016 Mar;48(3):185-90. doi: 10.1055/s-0035-1559604. Epub 2015 Aug 12.

Magnesium

Low intakes of dietary fiber and magnesium are associated with insulin resistance and hyperandrogenism in polycystic ovary syndrome: A cohort study.

Cutler DA, Pride SM, Cheung AP.

BACKGROUND:

Women with polycystic ovary syndrome (PCOS) often have insulin resistance (IR) which may be worsened by obesity. The roles of dietary intake and activity are unclear. Our objectives were to determine whether (a) high caloric intake or inactivity explains obesity in PCOS, and (b) dietary composition is associated with PCOS phenotypes.

METHODS:

Eighty-seven women with PCOS and 50 women without PCOS participated in this cohort study at a reproductive medicine center. Data collected included 3-day food and physical activity records, anthropometrics, and metabolic and hormonal assays.

RESULTS:

Women with PCOS had increased body mass index (BMI) but similar caloric intake and activity to women without PCOS. There were no differences in protein, carbohydrates, fat, or glycemic load consumption, but women with PCOS consumed less fiber (medians: 19.6 vs. 24.7 g) and less magnesium (medians: 238.9 vs. 273.9 mg). In women with PCOS, those with IR consumed less fiber, less magnesium, and greater glycemic load than those without IR (medians: 18.2 vs. 22.1 g, 208.4 vs. 264.5 mg, 89.6 vs. 83.5). Fiber intake of women with PCOS was negatively correlated with IR, fasting insulin, glucose tolerance, testosterone, and dehydroepiandrosterone sulfate. Magnesium intake was negatively correlated with IR, C-reactive pro-

tein, and testosterone, but positively correlated with HDL cholesterol. Fiber intake and BMI accounted for 54.0% of the variance observed in IR.

CONCLUSIONS:

Obesity in women with PCOS could not be explained by overeating or inactivity. Increasing dietary fiber and magnesium intakes may assist in reducing IR and hyperandrogenemia in women with PCOS.

Food Sci Nutr. 2019 Feb 27;7(4):1426-1437. doi: 10.1002/fsn3.977. eCollection 2019 Apr.

The Effects of Magnesium and Zinc Co-Supplementation on Biomarkers of Inflammation and Oxidative Stress, and Gene Expression Related to Inflammation in Polycystic Ovary Syndrome: a Randomized Controlled Clinical Trial.

Afshar Ebrahimi F, Foroozanfard F, Aghadavod E, Bahmani F, Asemi Z.

zinc are known to exert multiple beneficial effects including anti-inflammatory and antioxidant actions. To our knowledge, data on the effects of magnesium and zinc co-supplementation on biomarkers of inflammation and oxidative stress and gene expression related to inflammation in subjects of polycystic ovary syndrome (PCOS) are scarce. This study was conducted to evaluate the effects of magnesium and zinc co-supplementation on biomarkers of inflammation and oxidative stress and gene expression related to inflammation in subjects with PCOS. This randomized double-blind, placebo-controlled trial was conducted among 60 subjects with PCOS diagnosed according to the Rotterdam criteria, aged 18-40 years old. Participants were randomly assigned into two groups to take either 250 mg of magnesium oxide plus 220 mg of zinc sulfate (containing 50 mg zinc) supplements (n = 30) or placebo (n = 30) twice a day for 12 weeks. Biomarkers of inflammation and oxidative stress were assessed at baseline and at end of treatment. Gene expression related to inflammatory cytokines was assessed in peripheral blood mononuclear cells (PBMCs) of PCOS women with RT-PCR method. After the 12-week intervention, compared with the placebo, magnesium and zinc co-supplementation significantly decreased serum high-sensitivity C-reactive protein (hs-CRP) (- 1.6 ± 2.4 vs. + 0.1 ± 0.7 mg/L, P = 0.001) and protein carbonyl (PCO) (- 0.14 ± 0.28 vs. + 0.02 ± 0.07 mmol/mg protein, P = 0.002) and significantly increased plasma total antioxidant capacity (TAC) levels (+ 60.7 ± 69.4 vs. - 1.5 ± 141.5 mmol/L, P = 0.03). Results of RT-PCR demonstrated that compared with the placebo, magnesium and zinc co-supplementation downregulated gene expression of interleukin-1 (IL-1) (P = 0.007) and tumor necrosis factor alpha (TNF-a) (P = 0.03) in PBMCs of subjects with PCOS. Over-

all, magnesium and zinc co-supplementation, compared with the placebo, for 12 weeks among PCOS women had beneficial effects on serum hs-CRP, plasma PCO, TAC, and gene expression of IL-1 and TNF-a.

Biol Trace Elem Res. 2018 Aug;184(2):300-307. doi: 10.1007/s12011-017-1198-5. Epub 2017 Nov 10.

Vitamin D

According to a German nutritional survey from 2008, up to 91 % of women do not reach the nutritional reference values for vitamin D. Obviously, this is a problem for PCOS patients, as vitamin D is well known to impact insulin resistance.

Vitamin D Status Relates to Reproductive Outcome in Women With Polycystic Ovary Syndrome: Secondary Analysis of a Multicenter Randomized Controlled Trial.

Pal L, Zhang H, Williams J, Santoro NF, Diamond MP, Schlaff WD, Coutifaris C, Carson SA, Steinkampf MP, Carr BR, McGovern PG, Cataldo NA, Gosman GG, Nestler JE, Myers E, Legro RS; Reproductive Medicine Network.

CONTEXT:

Experimental evidence supports a relevance of vitamin D (VitD) for reproduction; however, data in humans are sparse and inconsistent.

OBJECTIVE:

To assess the relationship of Vit D status with ovulation induction (OI) outcomes in women with polycystic ovary syndrome (PCOS).

DESIGN:

A retrospective cohort.

SETTING:

Secondary analysis of randomized controlled trial data.

PARTICIPANTS:

Participants in the Pregnancy in PCOS I (PPCOS I) randomized controlled trial (n = 540) met the National Institutes of Health diagnostic criteria for PCOS.

INTERVENTIONS:

Serum 25OHD levels were measured in stored sera.

MAIN OUTCOME MEASURES:

Primary, live birth (LB); secondary, ovulation and pregnancy loss after OI.

RESULTS:

Likelihood for LB was reduced by 44% for women if the 25OHD level was < 30 ng/mL (<75 nmol/L; odds ratio [OR], 0.58 [0.35-0.92]). Progressive improvement in the odds for LB was noted at thresholds of ≥38 ng/mL (≥95 nmol/L; OR, 1.42 [1.08-1.8]), ≥40 ng/mL (≥100 nmol/L; OR, 1.51 [1.05-2.17]), and ≥45 ng/mL (≥112.5 nmol/L; OR, 4.46 [1.27-15.72]). On adjusted analyses, Vit D status was an independent predictor of LB and ovulation after OI.

CONCLUSIONS:

In women with PCOS, serum 25OHD was an independent predictor of measures of reproductive success after OI. Our data identify reproductive thresholds for serum 25OHD that are higher than recommended for the non-pregnant population.

J Clin Endocrinol Metab. 2016 Aug;101(8):3027-35. doi: 10.1210/jc.2015-4352. Epub 2016 May 17.

The Effects of Vitamin D Supplementation on Biomarkers of Inflammation and Oxidative Stress Among Women with Polycystic Ovary Syndrome: A Systematic Review and Meta-Analysis of Randomized Controlled Trials.

Akbari M, Ostadmohammadi V, Lankarani KB, Tabrizi R, Kolahdooz F, Heydari ST, Kavari SH, Mirhosseini N, Mafi A, Dastorani M, Asemi Z.

The current systematic review and meta-analysis of randomized controlled trials (RCTs) was conducted to summarize the effect of vitamin D supplementation on biomarkers of inflammation and oxidative stress among women with polycystic ovary syndrome (PCOS). Cochrane library, Embase, PubMed, and Web of Science database were searched to identify related randomized-controlled articles (RCTs) published up to November 2017. Two researchers assessed study eligibility, extracted data, and evaluated risk of bias of included RCTs, independently. To check heterogeneity Q-test and I2 statistics were used. Data were pooled by using the random-effect model and standardized mean difference (SMD) was considered as summary effect size. Seven RCTs were included into our meta-analysis. The findings showed that vitamin D supplementation in women with PCOS significantly decreased high-sensitivity C-reactive protein (hs-CRP) (SMD -1.03; 95% CI, -1.58, -0.49; p <0.001) and malondialdehyde (MDA) (SMD -1.64, 95% CI -2.26 to -1.02, p <0.001), and significantly increased total antioxidant capacity (TAC) levels (SMD 0.86, 95% CI 0.08 to 1.64, p=0.03). Vitamin D supplementation had no significant effect on nitric oxide (NO) (SMD 0.11, 95% CI -0.44 to 0.66, p=0.69) and total glutathione (GSH) levels (SMD 0.54, 95% CI -0.20 to 1.28, p=0.15). Overall, the current meta-analysis demonstrated that vitamin D supplementation to

women with PCOS resulted in an improvement in hs-CRP, MDA and TAC, but did not affect NO and GSH levels.

Horm Metab Res. 2018 Apr;50(4):271-279. doi: 10.1055/s-0044-101355. Epub 2018 Feb 23.

Vitamin D, PCOS and androgens in men: a systematic review.

Trummer C, Pilz S, Schwetz V, Obermayer-Pietsch B, Lerchbaum E.

BACKGROUND:

Accumulating evidence from animal and human studies suggests that vitamin D is involved in many functions of the reproductive system in both genders.

AIM:

The aim of this review was to provide an overview on the effects of vitamin D on polycystic ovary syndrome (PCOS) in women and androgen metabolism in men.

METHODS:

We performed a systematic literature search in PubMed for relevant English language publications published from January 2012 until September 2017.

RESULTS AND DISCUSSION:

The vitamin D receptor and vitamin D-metabolizing enzymes are found in reproductive tissues of women and men. In women, vitamin D status has been associated with several features of PCOS. In detail, cross-sectional data suggest a regulatory role of vitamin D in PCOS-related aspects such as ovulatory dysfunction, insulin resistance as well as hyperandrogenism. Moreover, results from randomized controlled trials (RCTs) suggest that vitamin D supplementation may be beneficial for metabolic, endocrine and fertility aspects in PCOS. In men, vitamin D status has been associated with androgen levels and hypogonadism. Further, there is some evidence for a favorable effect of vitamin D supplementation on testosterone concentrations, although others failed to show a significant effect on testosterone levels.

CONCLUSION:

In summary, vitamin D deficiency is associated with adverse fertility outcomes including PCOS and hypogonadism, but the evidence is insufficient to establish causality. High-quality RCTs are needed to further evaluate the effects of vitamin D supplementation in PCOS women as well as on androgen levels in men.

Endocr Connect. 2018 Mar;7(3):R95-R113. doi: 10.1530/EC-18-0009. Epub 2018 Feb 15.

Magnesium deficit ? overlooked cause of low vitamin D status?

Zittermann A.

Like vitamin D deficit, magnesium deficit is considered to be a risk factor for cardiovascular disease. Several steps in the vitamin D metabolism, such as vitamin D binding to its transport protein and the conversion of vitamin D into the hormonal form 1,25-dihydroxyvitamin D by hepatic and renal hydroxylation, depend on magnesium as a cofactor. A new analysis of two National Health and Nutrition Examination Surveys data sets, published in BMC Medicine, investigated potential interactions between magnesium intake, circulating 25-hydroxyvitamin D, which is the generally accepted indicator of vitamin D status, and mortality. Data indicate a reduced risk of insufficient/deficient vitamin D status at high magnesium intake and an inverse association between circulating 25-hydroxyvitamin D and mortality, particularly cardiovascular mortality, among those with magnesiumintake above the median. The study provides important findings concerning potential metabolic interactions between magnesium and vitamin D and its clinical relevance. However, results should be considered preliminary since biochemical data on individual magnesium status were lacking, confounding cannot be excluded and questions on the dose response relationship still remain to be answered. Please see related research article: http://www.biomedcentral.com/1741-7015/11/187.

BMC Med. 2013 Oct 24;11:229. doi: 10.1186/1741-7015-11-229.

The Role of Vitamin D Oral Supplementation in Insulin Resistance in Women with Polycystic Ovary Syndrome: A Systematic Review and Meta-Analysis of Randomized Controlled Trials.

Łagowska K, Bajerska J, Jamka M.

OBJECTIVE:

To evaluate the effect of vitamin D supplementation (alone or with co-supplementation) on insulin resistance in patients with polycystic ovary syndrome (PCOS).

METHODS:

We performed a literature search of databases (Medline, Scopus, Web of Knowledge, Cochrane Library) and identified all reports of randomized controlled trials (RCTs) published prior to April 2018. We compared the effects of supplementation with vitamin D alone (dose

from 1000 IU/d to 60,000 IU/week) or with co-supplements to the administration of placebos in women diagnosed with PCOS. The systematic review and meta-analysis protocol was registered in the International Prospective Register of Systematic Reviews (Prospero) as number CRD42018090572.

MAIN RESULTS:

Eleven of 345 identified studies were included in the analysis; these involved 601women diagnosed with PCOS. Vitamin D as a co-supplement was found to significantly decrease fasting glucose concentrations and the HOMA-IR value. HOMA-IR also declined significantly when vitamin D was supplemented with a dose lower than 4000 IU/d.

CONCLUSIONS:

Evidence from RCTs suggests that the supplementation of PCOS patients with continuous low doses of vitamin D (<4000 IU/d) or supplementation with vitamin D as a co-supplement may improve insulin sensitivity in terms of the fasting glucose concentration (supplementation with vitamin D in combination with other micronutrients) and HOMA-IR (supplementation with vitamin D in continuous low daily doses or as co-supplement).

Nutrients. 2018 Nov 2;10(11). pii: E1637. doi: 10.3390/nu10111637.

Carnitine and PCOS

Plasma L-carnitine levels of obese and non-obese polycystic ovary syndrome patients.

Celik F, Kose M, Yilmazer M, Köken GN, Arioz DT, Kanat Pektas M.

It is well-known that plasma L-carnitine concentrations are significantly decreased in obese individuals. A study showed that L-carnitine concentrations are significantly lower in lean PCOS patients than in lean healthy women. Thus, it has been suggested that lowered L-carnitine is associated with PCOS. This study also showed that the women with PCOS had significantly lower L-carnitine levels than those of the healthy controls. In addition, this study hypothesised that low L-carnitine levels in PCOS patients were associated with obesity and/or insulin resistance. Moreover, plasma L-carnitine concentrations were found to be statistically similar in PCOS patients and healthy controls, when controlled for obesity. This study implied that L-carnitine could be used as an adjunctive therapy in the management of insulin re-

sistance or obesity in women who have PCOS. Further research might be planned to clarify the clinical effects of L-carnitine administration in PCOS patients with insulin resistance and/or obesity.

J Obstet Gynaecol. 2017 May;37(4):476-479. doi: 10.1080/01443615.2016.1264375. Epub 2017 Jan 31.

Adding L-carnitine to clomiphene resistant PCOS women improves the quality of ovulation and the pregnancy rate. A randomized clinical trial.

Ismail AM, Hamed AH, Saso S, Thabet HH.

OBJECTIVE:

To evaluate the effectiveness of L-carnitine on improving the ovulation and pregnancy rates as well as adverse metabolic indices in clomiphene-resistant PCOS.

DESIGN:

Single center, double blinded, superiority, randomized controlled clinical trial.

SETTING:

Women's Health Hospital, Assiut University.

METHODS:

One hundred and seventy women diagnosed with PCOS were found to be clomiphene resistant. The women were randomly allocated into two groups: Group A (n=85), where patients received 250 mg clomiphene citrate from day three until day seven of the cycle plus L-carnitine (LC) 3g daily; and Group B (n=85) received 250 mg clomiphene citrate with placebo.

OUTCOME:

Primary outcome is cumulative clinical pregnancy rate. Secondary outcomes are changes in serum glucose level and lipid profile.

RESULTS:

The combination of L-carnitine and CC significantly improve both the ovulation and the cumulative pregnancy rates in clomiphene resistant PCOS (55 (64.4%) vs. 15 (17.4%) and 44 (51.5) % vs. 5 (5.8) %). The number of stimulated follicles reaching ≥17 mm diameter was significantly more in Group A to Group B (2.2 ± 0.77 vs. 0.16 ± 0.79; p<0.0001). Group A needed significantly fewer days for adequate follicular maturation, had a thicker endometrium and higher oestradiol concentration at the time of human chorionic gonadotrophin injection (10.1 ± 0.1mm vs. 6.8 ± 0.4mm; p<0.0001). The same group had a higher mean luteal-phase serum

progesterone compared with the control group (13.55 ± 0.99 vs. 10.6 ± 0.98 ng; p<0.0001). A significant difference was found regarding the clinical pregnancy rates (42 (49.4%) vs. (1) 1.1% respectively p value <0.0001).

CONCLUSION:

Adding L-carnitine when treating clomiphene-resistant PCOS patients not only improved the quality of ovulation and the pregnancy rate with an acceptable patient tolerability, but also enhanced the patient lipid profile and body mass index.

Eur J Obstet Gynecol Reprod Biol. 2014 Sep;180:148-52. doi: 10.1016/j.ejogrb.2014.06.008. Epub 2014 Jun 23.

Oral carnitine supplementation reduces body weight and insulin resistance in women with polycystic ovary syndrome: a randomized, double-blind, placebo-controlled trial.

Samimi M, Jamilian M, Ebrahimi FA, Rahimi M, Tajbakhsh B, Asemi Z.

OBJECTIVE:

Limited data are available for evaluating the effects of oral carnitine supplementation on weight loss and metabolic profiles of women with polycystic ovary syndrome (PCOS). This study was designed to determine the effects of oral carnitinesupplementation on weight loss, and glycaemic and lipid profiles in women with PCOS.

DESIGN, PATIENTS AND MEASUREMENTS:

In a prospective, randomized, double-blind, placebo-controlled trial, 60 overweight patients diagnosed with PCOS were randomized to receive either 250 mg carnitine supplements (n = 30) or placebo (n = 30) for 12 weeks. Fasting blood samples were obtained at the beginning and the end of the study to quantify parameters of glucose homoeostasis and lipid concentrations.

RESULTS:

At the end of the 12 weeks, taking carnitine supplements resulted in a significant reduction in weight (-2·7 ± 1·5 vs +0·1 ± 1·8 kg, P < 0·001), BMI (-1·1 ± 0·6 vs +0·1 ± 0·7 kg/m(2) , P < 0·001), waist circumference (WC) (-2·0 ± 1·3 vs -0·3 ± 2·0 cm, P < 0·001) and hip circumference (HC) (-2·5 ± 1·5 vs -0·3 ± 1·8 cm, P < 0·001) compared with placebo. In addition, compared with placebo, carnitine administration in women with PCOS led to a significant reduction in fasting plasma glucose (-0·38 ± 0·36 vs +0·11 ± 0·97 mmol/l, P = 0·01), serum insulin levels (-14·39 ±

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25·80 vs +3·01 ± 37·25 pmol/l, P = 0·04), homoeostasis model of assessment-insulin resistance (-0·61 ± 1·03 vs +0·11 ± 1·43, P = 0·04) and dehydroepiandrosterone sulphate (-3·64 ± 7·00 vs -0·59 ± 3·20 μmol/l, P = 0·03).

CONCLUSIONS:

Overall, 12 weeks of carnitine administration in PCOS women resulted in reductions in weight, BMI, WC and HC, and beneficial effects on glycaemic control; however, it did not affect lipid profiles or free testosterone.

Clin Endocrinol (Oxf). 2016 Jun;84(6):851-7. doi: 10.1111/cen.13003. Epub 2016 Jan 29.

Oral carnitine supplementation influences mental health parameters and biomarkers of oxidative stress in women with polycystic ovary syndrome: a randomized, double-blind, placebo-controlled trial.

Jamilian H, Jamilian M, Samimi M, Afshar Ebrahimi F, Rahimi M, Bahmani F, Aghababayan S, Kouhi M, Shahabbaspour S, Asemi Z.

INTRODUCTION:

Limited data are available assessing the effects of oral carnitine supplementation on mental health parameters and biomarkers of oxidative stress of women with polycystic ovary syndrome (PCOS).This study was designed to determine the effects of oral carnitine supplementation on mental health parameters and biomarkers of oxidative stress in women with PCOS.

METHODS:

In the current randomized, double-blind, placebo-controlled trial, 60 patients diagnosed with PCOS were randomized to take either 250 mg carnitine supplements (n = 30) or placebo (n = 30) for 12 weeks.

RESULTS:

After 12 weeks' intervention, compared with the placebo, carnitine supplementation resulted in a significant improvement in Beck Depression Inventory total score (-2.7 ± 2.3 versus -0.2 ± 0.7, p < 0.001), General Health Questionnaire scores (-6.9 ± 4.9 versus -0.9 ± 1.5, p < 0.001) and Depression Anxiety and Stress Scale scores (-8.7 ± 5.9 versus -1.2 ± 2.9, p = 0.001). In addition, changes in plasma total antioxidant capacity (TAC) (+84.1 ± 151.8 versus +4.6 ± 64.5 mmol/L, p = 0.01), malondialdehyde (MDA) (-0.4 ± 1.0 versus +0.5 ± 1.5 μmol/L, p = 0.01) and MDA/TAC ratio (-0.0005 ± 0.0010 versus +0.0006 ± 0.0019, p = 0.003) in the sup-

plemented group were significantly different from the changes in these indicators in the placebo group.

CONCLUSIONS:

Overall, our study demonstrated that carnitine supplementation for 12 weeks among patients with PCOS had favorable effects on parameters of mental health and biomarkers of oxidative stress.

Gynecol Endocrinol. 2017 Jun;33(6):442-447. doi: 10.1080/09513590.2017.1290071. Epub 2017 Feb 21.

L-Carnitine improves endocrine function and folliculogenesis by reducing inflammation, oxidative stress and apoptosis in mice following induction of polycystic ovary syndrome.

Kalhori Z, Mehranjani MS, Azadbakht M, Shariatzadeh MA.

Polycystic ovary syndrome (PCOS) is related to low levels of serum l-carnitine, which has antioxidant, anti-inflammatory and antiapoptotic properties. The aim of this study was to investigate the effect of l-carnitine on folliculogenesis in mice following induction of PCOS. PCOS was induced by daily injections of testosterone enanthate (1mg per 100g, s.c., for 35 days). NMRI mice (21 days old) were divided into four groups (n=6 per group): Control, Control+l-carnitine, PCOS and PCOS+l-carnitine. Mice were treated with 500mgkg-1, i.p., l-carnitine every second day for 28 days. Ovaries were studied stereologically and serum concentrations of FSH, LH, testosterone, interleukin (IL)-6 and tumour necrosis factor (TNF)-a were determined using ELISA kits. Serum concentrations of malondialdehyde (MDA) and the ferric ion reducing antioxidant power (FRAP) were also analysed. Apoptosis of follicles was evaluated by terminal deoxyribonucleotidyl transferase-mediated dUTP-digoxigenin nick end-labelling (TUNEL). CD31 was assessed immunohistochemically. Data were analysed using one-way analysis of variance (ANOVA) and Tukey's test, differences considered significant at $P<0.05$.The total volume of the ovary, cortex volume, oocyte volume, zona pellucida thickness and the number of antral follicles increased significantly, whereas the number of primary and preantral follicles decreased significantly, in the PCOS+l-carnitine versus PCOS group. In the PCOS+l-carnitine group, serum concentrations of FSH and FRAP increased significantly, whereas there were significant decreases in serum concentrations of testosterone, LH, MDA, IL-6 and TNF-a, as well as in the percentage of TUNEL-positive apoptotic cells, compared with the PCOS group. l-Carnitine improves folliculogenesis and is therefore suggested as a therapeutic supplement in the treatment of PCOS.

Reprod Fertil Dev. 2019 Jan;31(2):282-293. doi: 10.1071/RD18131.

Effects of L-carnitine on Polycystic Ovary Syndrome

Saghar Salehpour, Leila Nazari, Sedighe Hoseini, Parya Bameni Moghaddam, Latif Gachkar

OBJECTIVE:
Polycystic ovary syndrome (PCOS) is a common disorder in women of reproductive age. This study investigated the effects of L-carnitine on the clinical and laboratory findings of women with PCOS.
METHODS:
Eighty women diagnosed with PCOS between 2017 and 2018 by the Rotterdam Criteria were enrolled in the study; six were lost during the study. The participants were given L-carnitine 3 g daily (Pursinapharma, Iran) for three months. Blood samples were taken after overnight fasting at baseline and three months into the study to assess the levels of fasting glucose, insulin, triglycerides, high-density lipoprotein (HDL), low-density lipoprotein (LDL), free testosterone, dehydroepiandrosterone (DHEA), and the insulin resistance index (HOMA-IR). The patients were weighed before and after treatment and had their body mass index (BMI) calculated. Menstrual cycles and manifestations of hirsutism were also assessed.
RESULTS:
The data showed a significant improvement in insulin sensitivity and decreases in serum LDL levels and the BMI after three months of treatment. There was a significant increase in serum HDL levels. More regular menstrual cycles and decreased hirsutism were also observed.
CONCLUSION:
It appears that treatment with L-carnitine might decrease the risk of cardiovascular events by normalizing metabolic profiles and the BMI.
JBRA Assisted Reproduction 2019;23(4):392-395 doi: 10.5935/1518-0557.20190033

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Insulin resistance

Inositol treatments are able to significantly improve the regularity of the menstrual cycle, the Acne Score, endocrine as well as metabolic parameters, and insulin-resistance in young, overweight, PCOS patients (Formuso et al, 2015). Research underlines the importance of a healthy balance of D-chiro- and myo-inositols (Garg and Tal, 2016).

Deficient vitamin D status

Metabolic disturbances in PCOS are often associated with vitamin D - deficiency (Krul-Poel et al, 2013).

Unfavourable omega-6/omega-3-PUFA ratio

Omega-3 fatty acids reduce serum concentrations of testosterone and LH (Oner et al, 2013) and regulate menstrual cycle (Nadjarzadeh et al, 2013).

Hyperhomocysteinemia

Homocysteine levels are frequently elevated in PCOS patients (Cerqueira et al, 2010). Vitamins B6, B12 and folic acid contribute to normal homocysteine metabolism.

Oxidative stress

N-acetyl-L-cysteine can improve pregnancy and ovulation rates (Thakker et al, 2015).

Ineffective glucose metabolism

Coenzyme Q10 can support aerobic glucose metabolism, contributing to improved insulin levels (Samimi et al, 2017).

High BMI

L-carnitine is involved in mitochondrial function and can effectively support weight-loss programs for PCOS patients (Samimi et al, 2016).

Ideal for PCOS patients trying for pregnancy due to high content of folic acid, coenzyme Q10 and NAC, supporting oocyte quality (Cheraghi et al, 2016, Burstein et al, 2009).

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- Omega-3-PUFAs
- Vitamin C with sustained release
- Patent lodged
- Free from gluten and lactose

Indications

- PCOS
- Insulin resistance
- Fertility patient with oligomenorrhoea and obesity

Dosage

2 capsules and 1 sachet daily

-

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