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Role of nutrition in polycystic ovary syndrome

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Abstract
The main purpose of the study to analyze the nutrition role in PCOS or PCOD. Macronutrients play a vital role in the development of PCOS complications. Especially macro and micro nutrient role in PCOS. Carbohydrates, high carbohydrate consumption leads to insulin resistance, Higher protein diets may result in several positive health outcomes, including lean mass preservation during weight loss and maintenance, Supplementation with omega-3 fatty acids plus vitamin E led to significant reductions in serum total testosterone and free testosterone. Micro nutrients specially folate, minerals and some antioxidants play major role in preventing the consequences of PCOS and PCOD.

Keywords: PCOS (Poly cystic ovary syndrome), nutrition, carbohydrate, fat, protein and micrnutrients

Introduction
Polycystic ovary syndrome (PCOS) is a common endocrine disorder in reproductive-aged women, which leads to reproductive, metabolic and hormonal abnormalities. It is affecting 6% to 21% women. It was identified by Stein & Leventhal in 1935, an accumulation of incompletely developed follicles in the ovaries. Highest prevalence in turkey with 19% and lowest prevalence Oman with 6.8%. India comes under medium prevalence with 6.8%. The main characteristics of PCOS include hyperandrogenism, irregular menstrual cycles, lack of ovulation, enlarged ovaries with numerous cysts and infertility. Hyperinsulinemia, insulin resistance (40%), androgen excess, ovulatory dysfunction, polycystic ovaries, gonadotropin abnormalities, obesity, adipose tissue dysfunction, difficulty to conceive and high-risk pregnancy are the most common PCOS-associated complications. The endocrinologic abnormality of PCOS begins soon after menarche. Chronically elevated luteinizing hormone (LH) and insulin resistance are 2 of the most common endocrine aberrations seen in PCOS. The genetic cause of high LH is not known. It is interesting to note that neither an elevation in LH nor insulin resistance alone is enough to explain the pathogenesis of PCOS. In vitro and in vivo evidence offer support that high LH and hyperinsulinemia work synergistically, causing ovarian growth, androgen production, and ovarian cyst formation.

Common symptoms of PCOS
Some women start seeing symptoms around the time of their first period. Others only discover they have PCOS after they've gained a lot of weight or they've had trouble getting pregnant.

Role of macronutrients in PCOS
Carbohydrate role: Carbohydrate distribution may be a significant component for glucose metabolism and IR. A high glycemic load is associated with an increased risk of diabetes and with poor glycemic control in patients with established PCOS. The glycemic load can be decreased either by decreasing the amount of carbohydrate or by consuming foods of the lower GI. The latter has been shown to improve insulin sensitivity, decrease postprandial hyperglycaemia, decrease triglycerides and increase HDL-cholesterol (Marsh and Brand-Miller, 2005) [18]. A study assessed the effects of two diets containing different carbohydrate/protein ratios on weight loss, body composition and blood lipids of adult women with excess weight. The first group consumed a diet with a 3.5 carbohydrate/protein ratio (68 g protein) and the second consumed a diet with a 1.4 ratio (125 g protein). The diets contained equal amounts of calories and fats (~50 g/day). After 10 weeks, weight loss did not differ between groups (6.96+1.36 x 7.53+1.44 kg). However, the changes in body composition, expressed by the fat loss/lean mass loss ratio, showed that the second group had a greater loss of fat than of lean mass compared to the first group (a ratio of 6.3+1.2 x 3.8+0.9 kg).

Negative energy balance and PCOS

Several studies assessing the effects of caloric restriction along with modified dietary macronutrient composition on multiple health outcomes and biochemical indices have shown that there is no optimal dietary macronutrient composition or dietary pattern for PCOS (Stamets *et al*., 2004) [42]. Overall, there is little variation in weight loss with different diets, and this variation may be due to the differences in compliance and not how the body handles different macro- or micronutrients. Negative energy balance (with a deficit of 350–1000 kcal/day) seems to be the key factor leading to successful body weight and fat loss and amelioration of menstrual cycle and insulin sensitivity, irrespectively of the adopted dietary pattern.

Glycemic index, glycemic load (GL) and PCO

Five available clinical trials examined the effects of low GI on glucose or energy metabolism and hormonal responses in women with PCOS and reported successful weight loss, irrespective of GI. Out of the five trials, two showed increased insulin sensitivity and one showed decreased insulin levels, IR, DHEAS and high-sensitivity C-reactive protein (hsCRP) with the adoption of the low-GI diet. Results from one trial showed that a high-protein, moderately low-carbohydrate with low and medium GL resulted in significant reductions in blood insulin (–4 mIU/L), IR (homeostatic model assessment for IR [HOMA-IR], –0.8) and hsCRP (–0.9 mg/L) levels compared to a conventional diet. Similarly, results from a 12-month dietary intervention with two similar macronutrient composition, energy-reduced, low-fat, low-saturated fat, moderate-to-high fiber diets (23% protein, 50% carbohydrates, 27% fat), low or high GI, showed that the low-GI diet provided a threefold greater improvement in whole-body insulin sensitivity and improved menstrual regularity and better emotional scores, compared to a conventional hypocaloric, low-fat diet (Papavasiliou K and Papakonstantinou, 2017) [44].

Protein in PCOS

High-protein, moderately low-carbohydrate with low and medium GL resulted in significant reductions in blood insulin (–4 mIU/L), IR (homeostatic model assessment for IR [HOMA-IR], –0.8) and hsCRP (–0.9 mg/L) levels compared to a conventional diet. Higher protein diets may result in several positive health outcomes, including lean mass preservation during weight loss and maintenance, better glycemic control and amelioration of other cardiovascular disease risk factors, such as blood pressure, it is not clear yet whether these effects are due to the higher protein or lower carbohydrate intake, and no recommendations can be made currently (Toscani *et al*. 2011) [39].

Sorensen *et al*., 2012 [35] demonstrated that a high-protein, low-carbohydrate diet (~40% protein, 30% carbohydrate, 30% fat) decreased significantly more body weight (–4.4 kg), fat mass (–4.3 kg), WC (–3.7 cm) and glucose concentrations (–0.2 mmol/L) compared to a low-protein, high-carbohydrate diet (~15% protein, 55% carbohydrate, 30% fat). However, no differences between diets were found for SHBG, total and free testosterone and C-peptide. Polyunsaturated fatty acids, PUFA: 17% diet, led to a greater decrease in fasting insulin concentrations and the acute insulin to glucose response compared to the control diet. Gower *et al*., 2013 [12] reported high-fat and moderately low-carbohydrate (~41% carbohydrate, 19% protein and 40% fat) diet-induced significant glucose metabolism improvements (decreased basal β-cell response, fasting insulin, fasting glucose and IR), hormonal responses (lower testosterone) and decreased blood lipids and adipose tissue (intra-abdominal adipose tissue [–7.1%], subcutaneous abdominal adipose tissue [–4.6%] and intramuscular adipose tissue [–11.5%])

Protein decrease of the concentration of insulin-like growth factor 1 (IGF-1), which is involved in the development of PCOS (Desse *et al*. 1999) [45]. Sidika *et al*. 2007 [34] reported that protein intake suppressed ghrelin significantly longer than did glucose, which suggested a prolonged satietogenic effect. High-protein diets are being promoted because of their beneficial effects on satiety lean body mass, weight maintenance, and lipid markers.

Farshchi *et al*., 2009 [6] and Sorensen *et al*., 2012 [35] reported that high protein and low carbohydrate diet (40% protein and 30% carbohydrate effect on fat loss (6.3 to 3.8 kg), reduced body weight (4-4kg) triglycerides reduced (23%) and HDL increased (23%) in diet to the Second group had a greater loss of fat than of lean mass compared to the first group (a ratio of 6.3 to 3.8 kg) in the duration of 6 months.

These studies demonstrate the benefits of a protein-rich diet regarding body composition, blood lipids, glucose homeostasis, as well as satiety in overweight women during the weight loss process. Similar results were obtained in a study conducted on hyperinsulinemic and normoglycemic obese men. Two groups of subjects consumed different low-energy diets that provided 80% of resting energy expenditure. One received a high-protein (45%) and low-carbohydrate (25%) diet and the other a higher-carbohydrate (58%) and lower-protein (12%) diet, with both diets containing the same amount of fat (30%). The results showed a greater weight loss in the group receiving more dietary protein (8.3+0.7 x 6.0+0.6 kg, $p<0.05$). Serum levels of total cholesterol, triglycerides and LDL-c were significantly reduced in both groups, but a significant reduction in HDL-c occurred only in the group receiving more protein. Fasting serum insulin levels were reduced in both groups but reached normal levels only in the group receiving the high-protein diet.

Fat role in PCOS

The body has a virtually infinite capacity to store fat, particularly in hyperinsulinaemic individuals. Experiments with fat overfeeding suggest that fat excess decreases carbohydrate oxidation with no apparent change in fat oxidation. When carbohydrate is present in excess or is inadequately oxidised, fat deposition is increased through the process of de novo lipogenesis. Moderately low-carbohydrate, high-fat diets have been shown to decrease fasting insulin and AUC for insulin and to increase insulin sensitivity in three trials in women with PCOS. (Perelman D *et al*., 2017: Gower *et al*., 2013 [26, 12] and Douglas *et al*., 2006) [3].

Metabolic and hormonal parameters in the group of women with PCOS are improved by cis fatty acids, in comparison to Trans fatty acids, which was proved in the study of Kasim-Karakas *et al*. (2004) [17]. Trans isomers of fatty acids lower the activity of peroxisome proliferator-activated receptors γ (PPAR), leading to increased ovulation disorders. The results showed that fat intake and total cholesterol were not related to ovulatory infertility but that there was a positive association between the intake of trans fatty acids and the risk of infertility. Total daily energy intake above 2% in the form of unsaturated trans fatty acids was associated with a 94% risk of the occurrence of ovulatory infertility (CI 22-208%). The

isocaloric replacement of monounsaturated fatty acids (MUFA) with trans fatty acids significantly increased the risk of infertility (RR = 2.32;)

Metabolic and hormonal effects of PUFA in PCOS: 1) PUFA rich in the diet significantly increased the fasting glucose and AUC for glucose. (76 +/- 3 to 95 +/- 3 mg/dl), the fasting serum insulin and AUC for insulin did not change significantly during the study. After 3 months PUFA – rich diet ingestion did not alter FSH, LH, testosterone, free testosterone. Ingestion of omega n-3 fatty acid significantly increased serum HDL (43.5 to 45.86mg/dl) and decreased total cholesterol(186 to 170), LDL cholesterol(117 to 112), TG(126 to 119mg/dl), glucose, insulin and HOMA compared with placebo (Mohammadi *et al*. (2012) [22-23, 27]. Soybean oil reduced (testestosteron 3.33 to3.05 nmol/l,) and tended to reduce SHBG (from 18.4±2.4 to 16.2±2.5 nmol/l), without affecting DHEAS. Fish and flaxseed oils did not affect testosterone, SHBG or DHEAS. Serum fasting glucose, insulin levels did not alter in either group during the study. Supplementation with omega-3 fatty acids plus vitamin E led to significant reductions in serum total testosterone (-0.5±0.7 vs. -0.1±0.5 ng/mL,) and free testosterone (Ebrahimi *et al*., 2017.) [4]

ω-3 fatty acids

ω-3 fatty acids, at first was found in fatty fish. Fish oil that is the main source of dietary ω-3 fatty acids; have several healthy effects including anti-inflammatory, antithrombotic, antiarrhythmic and antiatherogenic effects. While insulin resistance is an important component in the pathogenesis of PCOS and on the other hand, this syndrome is associated with inflammatory factors, so polyunsaturated fatty acids (PUFA) may treat PCOS with the help to decrease insulin resistance and androgen excess. Oner and muderris showed ω-3 also may be effective in decreasing hirsutism, BMI, LH, testosterone, insulin, Homeostatic model assessment (HOMA) levels, and increasing Sex hormone-binding globulin (SHBG) and TNF-α in women with PCOS. Mohammadi *et al* also found 8 weeks supplementation with ω-3 fatty acids can reduce TC/HDL-C and LDL-C/HDL-C ratios and increase paraoxonase-1(PON1) activity in comparison with placebo. They believe using the ω-3 fatty acids is an appropriate approach to decrease cardiometabolic risks. Besides, Rafraf *et al*., 2012 [22-23, 27] reported ω-3 fatty acid supplementation could make lower levels of glucose, insulin and insulin resistance but no significant changes in serum levels of high sensitive C-reactive protein in PCOS women. They concluded that ω-3 fatty acid supplementation is a helpful approach for PCOS metabolic disturbances although this needs more studies.

Role of micronutrients in PCOS

Vitamin D: Vitamin D, often called the sunshine vitamin, is recognized as being important in controlling blood sugar and improving insulin sensitivity. Low levels of vitamin D is also associated with insulin resistance and obesity in women with PCOS (Nicole Galan., 2018.) [24]

Vitamin D insufficiency could contribute to the development of insulin resistance and obesity as the major features of PCOS (Wehr *et al*., 2009) [41]. Besides, it has been reported that gene polymorphism is linked with PCOS (at least partially) through the role of this gene on insulin blood levels and insulin resistance (Mahmoudi *et al*., 2009) [21]. Yet, the mechanism(s) by which low vitamin D levels can cause insulin resistance is unclear (Lerchbaum and Obermayer-Pietsch, 2012) [20]. In human study, Tarcin *et al*. (2009) [38] suggested that vitamin D could act as a potent antioxidant through the inhibition of oxidative stress and lipid peroxidation. Given that chronic inflammation and oxidative stress play causative roles in the pathogenesis of insulin resistance (Ceriello and Motz, 2004) [43] and on the other hand, vitamin D has effects on insulin levels and expression of the insulin receptor and also inhibits inflammation.

Role of micronutrients in PCOS

A recent meta-analysis of eight clinical trials with a total of 298 females with PCOS showed a slight reduction in serum total testosterone levels following n-3 PUFA supplementation among females with PCOS, without significant impact on SHBG and DHEAS levels (Mohammadi *et al*.2012) [22-23, 27].

Foroozanfard *et al*., 2015 [8] study showed that 220 mg zinc sulfate supplementation per day for 8 weeks among PCOS had beneficial effects on fasting glucose, insulin, IR and TG. Jamilian *et al*., 2015 [8] reported that 200 mg/day selenium supplementation for 8 weeks among PCOS had beneficial effects on fasting insulin, IR, insulin sensitivity, TG and VLDL levels, without affecting fasting glucose and other lipid profiles. Another study found that 200 mg/day chromium supplementation for 8 weeks among PCOS had favourable effects on fasting insulin, IR and insulin sensitivity. (Jamilian *et al*., 2015) [8] Moreover, 5 mg/day folate supplementation for 8 weeks among PCOS had beneficial effects on inflammatory factors and biomarkers of oxidative stress (Bahmani *et al*., 2014) [1]. Some of the nutrients paly major therapeutic role in PCOS women those are inositol, reservatol and isoflavonoids.

Unfer *et al.* (2012) [40] performed a meta-analysis of 6 randomized placebo-controlled trials which used a range of 0.2-4 g/day Myo-inositol in PCOS patients and concluded that myo-inositol supplementation can decrease the levels of various hormones such as LH, LH/follicle stimulating hormone (FSH), PRL, and testosterone and improve dyslipidemia by reducing insulin concentrations.

The administration of resveratrol lowered serum superoxide dismutase (SOD) activity and elevated glutathione peroxides (GPx) level. Moreover, a reduction in the levels of plasma anti-Mullerian hormone and insulin-like growth factor 1, besides in the number of antral follicles was observed in PCOS rats. Vitamin D insufficiency could contribute to the development of insulin resistance and obesity (Rashidi *et al*., 2009) [28] determined that combined consumption of metformin 1500 mg/d plus calcium 1000 mg/d and vitamin D 400IU/d was more effective in the treatment of PCOS, as indicated by the maturation of follicles than either compound alone. Firouzabadi *et al*. (2012) [7] reported that in 100 infertile PCOS women, following the intake of metformin1500 mg/d plus calcium 1000 mg/d and vitamin D 100000 IU/month for 6 months, body mass index (BMI) was significantly reduced and follicle maturation and hyperandrogenism was improved in comparison with those treated with metformin 1500 mg/d alone. In conclusion, there is insufficient evidence to recommend micronutrient supplements for women with PCOS at this time.

Some of the important nutrient's role in PCOS

- Isoflavonoids
- Resveratrol

Isoflavonoids and PCOS

The isoflavonoids such as genistein and daidzein, which are mostly found in legumes such as soybeans and chickpeas, have received considerable attention in recent 2 decades (Eden, 2012) [46]. A number of studies have shown improvement in insulin resistance and/or glycemic control in response to isoflavone genistein consumption, a response that appears to be, at least partially, due to the positive effects of this agent on β- cells function through the promotion of proliferation and the inhibition of apoptosis in such cells (Gilbert and Liu, 2013) [10]. A quasi-randomized trial performed in 146 subjects with PCOS revealed that 18 mg of genistein (twice a day) for 3 months compared with cellulose as a placebo could significantly decrease the serum concentrations of low-density lipoprotein cholesterol (LDL-C). Also, according to these results, LH, dehydroepiandrosterone sulfate (DHEAS), testosterone,
and triglyceride levels were lower in patients after genistein consumption comparing with before the supplementation indicating that genistein could be a useful tool for nutrition therapy of POCS patients due to the beneficial effects on reproductive hormonal levels and also the improvement of lipid profiles (Khani *et al*., 2011) [19]. These data are in line with the observation of Kamel (2013) [16] who found significantly favourable changes in LH level and FSH/LH ratio after ten days of treatment with phytoestrogen in women with PCOS.

Resveratrol

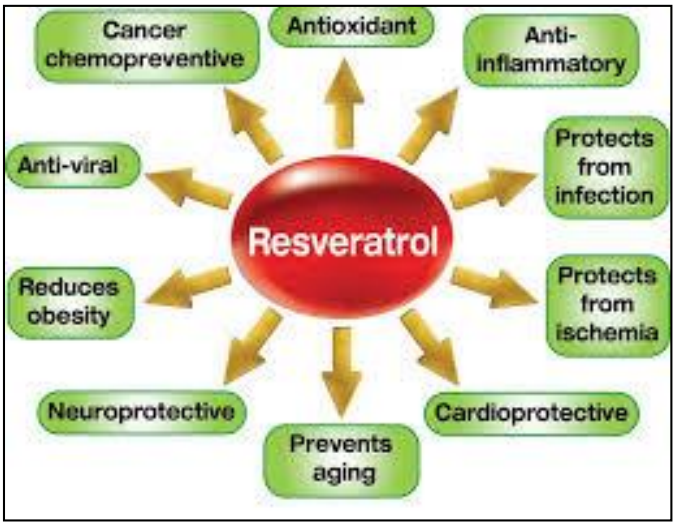

Fig 1: Resveratrol

Resveratrol (trans-3,5,4'-trihydroxystilbene) is a naturally occurring phytoalexin that is produced by some plants such as grapes, nuts and berries in response to injury or fungal infection. Resveratrol is thought to have a number of incredible health benefits, including antioxidant, anti-inflammatory, anti-cancer, antiaging and cardioprotection. Resveratrol (trans-3,5,4'-trihydroxystilbene) is a naturally occurring phytoalexin that is produced by some plants such as grapes, nuts and berries in response to injury or fungal infection. Due to Antioxidant properties resveratrol supplementation had a therapeutic effect on experimental PCOS induced by dihydrotestosterone (Ergenoglu *et al*., 2015) [5].

The resveratrol exerts suppressive action on insulin release in both *in vitro* and *in vivo (*Szkudelski, 2006, 2008) [37]. Resveratrol increased the apoptosis of ovarian theca-interstitial (T-l) cells and prevented the cell proliferation *in vitro* at concentration 30–100 μM. The antiproliferative actions of resveratrol might be more pronounced among PCOS patients, whose ovarian function is disturbed as a result of excessive T-l cells production. In contrast with this data, Ortega *et al*. (2012) [25] observed minimal effects of resveratrol on the apoptosis of rat granulosa cells. Additionally, resveratrol showed the *in vitro* it could inhibit the secretion of estrogen and vascular endothelial growth factor (VEGF) in rat granulosa cells (Ortega *et al*., 2012) [25]. Thence, biological effects of resveratrol on ovarian cells that may result in in changes of the balance between relative ratios of such cells and a decrease of VEGF expression have pervasive consequences in PCOS condition.

Antioxidants and PCOS

The use of antioxidants in the management of women with PCOS has attracted lots of interests. Some characteristics of PCOS such as obesity and abdominal adiposity, androgen excess, and insulin resistance can develop oxidative stress in these patients. Indeed, PCOS is a condition with a significant decrease in serum antioxidant and vitamins levels and these women are in an increased risk of oxidative status.

Oxidative stress and antioxidant decrease may lead these women to increased risk of cardiovascular disease, insulin resistance, hypertension, central obesity, and dyslipidemia Antioxidant supplementation have been shown to improve insulin sensitivity and other health threating conditions in women with PCOS. Despite the important role of alternative medicine especially antioxidants in the management of PCOS women, there are not many well-designed papers or detailed literature reviews report in this field, especially in Iran. On the other hand, the available studies addressing antioxidant use in PCOS women yielded controversial results, because of their sample sizes or the diversity in the prescribed antioxidant or outcomes assessed in them. For overcoming these limitations, updating our knowledge on this field and a critical appraisal of all available studies might be helpful to guide clinical practice.

N-Acetyl cysteine (NAC)

NAC (N-acetyl-cysteine) is an antioxidant that derivative from the amino acid L-cysteine. NAC can have effects on insulin receptor activity as well as insulin secretion and subsequently increase glucose utility. Besides, NAC has antiapoptotic activity and decreasing effects on homocysteine (Hcy) levels. Diet cannot provide NAC, but its nutritional supplement is available. Fulghesu *et al.* (2002) [9] study showed NAC can have an effect on levels of circulating insulin and insulin sensitivity in PCOS women with hyperinsulinemia. NAC is an appropriate choice for induction ovulation or augmentation in PCOS women and can be used as an adjuvant to Clomiphene Citrate.The study of Saleh pour *et al.* (2009) [31] through a prospective double-blind clinical trial on 46 PCOS women showed 6 weeks use of NAC can increase ovulation rate and HDL levels and decrease weight, body mass index (BMI), and waist/hip ratio, fast blood sugar (FBS), serum insulin, total cholesterol, LDL levels, and HOMA-IR index while luteinizing hormone (LH), 61 T Follicle-stimulating hormone 61T (FSH), prolactin, LH/FSH levels and glucose/insulin ratio were the same with no significant changes. Another study of Saleh pour *et al.* showed that using of NAC as an adjuvant in Clomiphene

citrate cause an increase in the number of follicles >18 mm, mean endometrial thickness on the day of hCG administration, ovulation and pregnancy rates with no adverse side-effects and no cases of ovarian hyper stimulation syndrome.

Conclusion

Insulin resistance and sex hormonal imbalance are the major causes of PCOS. Macronutrients play a vital role in the development of PCOS complications, carbohydrates, glycemic index and load effect on health risks. Its associated with – infertility, DM, Obesity, CVD, and multiple syndrome. Low carbohydrate, high protein and high PUFA or MUFA (fat) diet helps in weight loss, controlling symptoms and prevent from diabetes. Macronutrients play a vital role in the of PCOS, carbohydrates, glycemic index and load effect health risks. Its associated with – infertility, DM, Obesity, CVD, and multiple syndrome. Low carbohydrate, high protein and high PUFA or MUFA (fat) diet helps in weight loss, controlling diabetes. Nutrients are- myoinositol, resveratrol, is flavones, flaxseed act as a novel therapeutic treatment for PCOS complications. Diet, lifestyle modification and exercise important to prevent the complications of PCOS.

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