



The Relationship between Macronutrient Intake and Insulin Resistance in Polycystic Ovary Syndrome

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ABSTRACT

Background: Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women of reproductive age. It is linked to genetic and environmental factors such as nutrition. Insulin resistance (IR) is one of the major pathological changes in PCOS. This study aimed to determine the relationship between IR and macronutrient intake in PCOS subgroups. **Methods:** This case-control study was performed on 151 women with PCOS and were divided into four groups according to the Rotterdam diagnostic criteria: A=41, B=33, C=40, and D=37, and 31 women were also in the control group and did not have this syndrome. All macronutrients were assessed with a 168-item food frequency questionnaire (FFQ). **Results:** There was a significant relationship between HOMA-IR and some dietary components (Increased calorie in group A, increased total fat intake in group C, lower intake of unsaturated fats (PUFA and MUFA) in group D and higher intake of saturated fat (SFA) and protein intake in the control group). There was no correlation in subgroup B (ovulatory phenotype). **Conclusion:** Due to the significant relationship between IR and some dietary components in PCOS subtypes, it is recommended to maintain a balance in carbohydrate and fatty acids intake, and increase dietary fiber to improve health parameters in PCOS subjects.

Keywords: *Macronutrient; PCOS; Insulin resistance*

Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women (Legro *et al.*, 2013). One of the most commonly used definitions for PCOS is the presence of at least two of the three clinical-biochemical criteria of Rotterdam. The symptoms include hyperandrogenemia, oligomenorrhea or ovulation, and macroscopic ultrasound evidence

that the size of the ovaries in these women is 2 to 5 times the normal range and the ovaries contain numerous cysts that are typically less than one centimeter in diameter (Azziz *et al.*, 2005, ESHRE and ASRM-Sponsored PCOS Consensus Workshop Group, 2004). The syndrome may occur with some or all of the symptoms, menstrual disorders, infertility, hirsutism, acne, and alopecia

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(Aali and Naderi, 2004).

The prevalence of PCOS due to different clinical features and biochemical characteristics of these patients has been reported differently in several studies according to race, ethnicity, and study population (Kauffman *et al.*, 2002). In a study by Gabrielli *et al.* in Brazil, the prevalence of PCOS was estimated to be 32% among 859 women between the ages of 18 and 45 years (Gabrielli and Aquino, 2012). In a study by Ramazan *et al.* in Iran, its prevalence was estimated at 14.6% according to the Rotterdam criteria (Ramezani *et al.*, 2011).

This syndrome is associated with a wide range of reproductive, metabolic, and psychological disorders (Moran *et al.*, 2013). In 2004, the cost of treatment in the US health care system was estimated to be approximately \$ 4 billion; 40% of which was for women with insulin resistance (IR) PCOS and type 2 diabetic women, and its management, especially in people with IR PCOS, is very important (Conway *et al.*, 2014).

The most well-known cause of the pathogenesis of PCOS is IR (Berek, 2012). IR is a central pathogenic factor that occurs during the development of hyperinsulinemia and is a cardiometabolic disorder stimulating all tissues and increasing the abnormality in the process of ovarian steroidogenesis. Therefore, IR in patients with polycystic ovaries compared to healthy women may increase the risk of diabetes mellitus, dyslipidemia, atherosclerosis, and cardiovascular disease (Hernández-Valencia *et al.*, 2010, Zangeneh *et al.*, 2017).

Its pathophysiology is not fully understood, although several hypotheses have been proposed, malformations in four endocrine active components including the ovary, renal gland, hypothalamic-pituitary axis, and insulin-sensitive tissues such as the insulin (Abu-Wasel *et al.*, 2013). Both lean and obese women with PCOS are susceptible to IR, but obese women are more susceptible (Ehsani *et al.*, 2015). Obesity can act as a gonadotropin due to IR, impaired synthesis of androgens or adipocytokines, and direct or indirect effects on adipose tissue. It can also affect the

peripheral metabolism of steroids (Blüher, 2013). Therefore, changes in lifestyle and weight loss through exercise and nutrition are recommended for these patients (Conway *et al.*, 2014).

In the study of Thomson *et al.*, weight loss of 9 kg over 20 weeks in overweight and obese individuals with PCOS led to a significant decrease in fasting insulin, IR-HOMA, testosterone, free androgen specificity (FAI), increased sex hormone-binding globulin (SHBG), and improved fertility (FAI = Total Testosterone (TT) (nmol/l)/SHBG (nmol/l) * 100) (Thomson *et al.*, 2009).

In nutrition science, macronutrients are divided into three broad categories, including protein, carbohydrate, and fat. The major role of macronutrients is to provide energy in calorie units (Williams, 1995). Some studies have shown that protein, carbohydrate, and fat intake can exacerbate IR (Kasim-Karakas *et al.*, 2004, Panagiotakos *et al.*, 2005, Pehlivanov and Orbetzova, 2007, Zivkovic *et al.*, 2007). Some studies also reported that high protein, high carbohydrate, and fat-rich diets reduced IR or had no effect on IR (Sjaarda *et al.*, 2015, Stender and Dyerberg, 2004, XIA and ZHANG, 2012, Zhang *et al.*, 2015).

Since nutritional behaviors play a major role in human health or disease, it is important to examine the relationship between nutrition and PCOS. On the other hand, due to the inconsistencies in previous studies, this study aims to determine the relationship between IR and macronutrient intake in four subgroups of the PCOS phenotype based on Rotterdam criteria.

Materials and Methods

Design and participants: The present case-control study investigated dietary intake of macronutrients in four subgroups of PCOS and a control group with IR in Tehran during 2015-2016. The sample size based on the results of the pilot study and the correlation between the IR index and dietary component showed that the minimum correlation between these indices was 0.50. Therefore, with 95% confidence and 80% test

power, the number of samples required based on the following formula for each subgroup with approximately 27 samples was 26.2. Taking into account a drop-out rate of 20%, the final volume per phenotype was estimated at 31 individuals.

The samples were referrals to the gynecology ward, endocrinology ward of Arash Hospital, and private clinic using a convenience sampling method if they were eligible to enter the study after filling informed consent form.

The inclusion criteria in the case group were Iranian race and age of 18-40 years. The exclusion criteria were chronic metabolic and non-metabolic diseases affecting diet such as diabetes mellitus, hyperthyroidism, hypothyroidism, and hyperlipidemia, taking medicines that affect appetite and diets, specific diet, pregnancy, and hormone use for three months before starting the study. The criteria in the control group were age of 18-40 years and without any diagnostic criteria for PCOS (non-hirsute: without excessive hair growth, with regular ovulation cycles), and those who referred to women's clinic for other reasons. Then the two groups were matched for education, body mass index (BMI), economic status, and physical activity and exercise status.

Initially, the disease was diagnosed after excluding other abnormalities that mimic the PCOS phenotype (ovarian or adrenal neoplasm, Cushing's syndrome, hyperprolactinemia, thyroid disease and congenital adrenal hyperplasia starting in adulthood by assessing 17-Hydroxyprogesterone (17-OHP), dehydroepiandrosterone sulfate (DHEAS), cortisol, thyroid hormones, and prolactin levels (Berek, 2012) .

Then based on the Rotterdam diagnostic criteria, two of the following three disorders are necessary:

1- Clinical hyperandrogenism (Hirsutism or H). Clinical hyperandrogenism: The Ferriman-Gallwey score of 8 (Tehrani *et al.*, 2014), and above or biochemical hyperandrogenism: elevated serum TT levels or free androgen index (FAI): hyperandrogenic TT, greater than 0.68 ng/ml and FAI more than 5.36% (Hashemi *et al.*, 2014). TT and sex hormone-binding globulin (SHBG) assay methods were measured by electro quantitative luminescence using a Roche German kit by Cobas

E411. $FAI = TT \text{ (nmol/l)}/SHBG \text{ (nmol / l)} * 100$ (Goodarzi *et al.*, 2011).

2-Ovulation disorder (Oligo/anovulation or O).

The menstrual cycle of more than 35 days (oligomenorrhea) or more than 3 months (amenorrhea) (Schorge *et al.*, 2008).

3-Polycystic ovary view in ultrasound (P)

An ovarian volume greater than 10 cubic centimeters in at least one ovary or observation of more than 5 to 8 multiple fine follicles (Schorge *et al.*, 2008).

After entering the study, they were divided into the following four phenotypes:

1) Complete phenotype or A (H + P + O)

2) Ovulatory phenotype or B (H + P)

3) Normoandrogenic phenotype or C (P + O)

4) Normosonography phenotype or D (H + O) (Kar, 2013).

Finally, 182 participants were included in the study (31 people in the control group, 41 people in group A, 33 people in group B, 40 people in group C, and 37 people in group D).

Measurements: The researcher assessed physical activity by asking research units about whether or not they exercise. The groups became homogeneous in terms of physical activity (Kim *et al.*, 2007). For all samples, the 168-item Food Frequency Questionnaire (FFQ) was completed. Validity and reliability have been evaluated by others (Asghari *et al.*, 2012, Mirmiran *et al.*, 2010). This questionnaire was used to obtain a person's usual diet during the past year. For analyze the nutritional information of the FFQ questionnaire, Excel-based software was used. Thus, by entering the amount of each food consumed items in the cell, the amount of nutrients was calculated. Finally, the total amount of nutrients consumed by each individual was obtained from the sum of all the nutrients in each food item consumed (Hosseini-Esfahani *et al.*, 2015).

Given the different daily calorie intakes of each individual, it is obvious that the ratio of each nutrient to the total daily calorie intakes and consequently the contribution of one nutrient to the total calorie intakes may also be different. Therefore, to make an accurate comparison

between the information obtained from each individual with the other participants, after obtaining the daily caloric intake of each of these macronutrients, they were calibrated for energy adjusting. Finally, the whole analysis was performed on the energy-regulated data.

Anthropometric evaluations (height, weight, and BMI), ovarian sonography, hirsutism as a clinical symptom of hyperandrogenism, and hormonal tests were performed to determine serum androgens. Questions were raised about menstruation. Fat [total fat, saturated fatty acids (SFA), polyunsaturated fatty acid (PUFA), monounsaturated fatty acid (MUFA)], Calories, protein and fiber (total and soluble) were measured.

IR was assessed using the HOMA-IR index. The original HOMA-IR model was described in 1985 with a formula for approximate estimation by Mathew *et al.* (Matthews *et al.*, 1985). The cut-off point for defining IR was considered based on the HOMA-IR > 2.5 (Wallace *et al.*, 2004).

Five milliliters of venous blood for checking the fasting blood glucose and insulin levels was obtained from all research units in the laboratory in the fasting state. Glucose was measured by glucose oxidase assay and insulin was measured by immunoradiometric method. Beck Man's immunotech kit was used to check the cases, with an extra-test accuracy of 3.4% and an intra-test accuracy of 4.3%.

Ethical considerations: In this study, it has been tried to include all ethical considerations. The ethics code by the Ethics Committee is D52/5503.

Data analysis: SPSS software was used for data analysis and statistical tests. At first, the Kolmogorov-Smirnov test was used for data normality. Parametric tests (for normal data) and non-parametric tests (for non-normal data) were used to analyze the data. Kruskal Wallis test (for non-normal data) and one-way ANOVA test (for

normal data) were used to compare the variables. The Spearman correlation test (because data were not normal) was used to investigate the relationship between quantitative variables. The Chi-square test was also used to investigate some underlying variables. $P\text{-value} \leq 0.05$ was considered the level of significance.

Results

The results showed (**Table 1**) that there were no significant differences between the four subgroups of PCOS women and the control group in terms of age ($P=0.09$), BMI ($P=0.99$), an education level ($P=0.30$), economic status ($P=0.27$), and physical activity status ($P=0.87$).

There was a significant difference in the index of insulin. The number of women with PCOS who also had IR was higher in phenotype A than in other groups (61%). In phenotype B, 51.5%, phenotype C, 37.5% and phenotype D, 48.6% had PCOS and IR at the same time. In the control group, although they had no symptoms of PCOS, two (6.5%) patients had the syndrome (**Table 2**).

Spearman test results showed that IR in different PCOS subgroups and control groups correlated with the oral intake frequency of macronutrients. In subgroup A, the HOMA-IR was significantly correlated with daily calorie intake ($P=0.03$). In subgroup B, there was no significant relationship between the HOMA-IR and any of the dietary components ($P>0.05$). In subgroup C, there was a significant positive relationship between HOMA-IR and total fat ($P=0.03$). In subgroup D, there was a significant negative relationship between the HOMA-IR with PUFA ($P=0.01$), MUFA ($P=0.003$), and SFA ($P=0.004$). In the control group, there was a significant positive correlation between HOMA-IR, SFA ($P=0.04$), and protein intake ($P=0.01$, Table 3).

Table 1. Comparison of demographic variables at baseline between groups.

Variables	Phenotype A N=41	Phenotype B N=33	Phenotype C N=40	Phenotype D N=37	Control N=31	P-value
Age (y)	28.07 ± 4.70	27.00 ± 5.44	29.70 ± 6.44	29.83 ± 5.93	28.07 ± 4.70	0.09 ^a
Body mass index (kg/m ²)	25.48 ± 5.23	25.06 ± 4.28	25.08 ± 3.93	24.98 ± 4.80	25.48 ± 5.23	0.99 ^a
Educational status						
Under diploma	4 (9.8)	3 (9.1)	4 (10.0)	2 (5.4)	2 (6.5)	0.30 ^b
Diploma	9 (22.0)	5 (15.2)	10 (25.0)	15 (43.2)	14 (45.2)	
Bachelor	19 (46.3)	16 (48.5)	20 (50.0)	16 (40.5)	10 (32.3)	
Master's degree and higher	9 (22.0)	9 (27.3)	6 (15.0)	4 (10.8)	5 (16.1)	
The economic situation						
Poor	16 (39.0)	23 (69.7)	23 (57.5)	21 (56.8)	17 (54.8)	0.27 ^b
Medium	16 (39.0)	5 (15.2)	11 (27.5)	7 (18.9)	7 (22.6)	
Good	9 (22.0)	5 (15.2)	6 (15.0)	9 (24.3)	7 (22.6)	
Physical activity status						
Level 1	23 (56.1)	20 (60.6)	25 (62.5)	25 (67.6)	20 (67.6)	0.87 ^b
Level 2	6 (14.6)	6 (18.2)	7 (17.5)	5 (13.5)	5 (13.5)	
Level 3	12 (29.3)	7 (21.2)	8 (20.0)	7 (18.9)	6 (18.9)	

^a: Kruskal Wallis test; ^b: Chi-square test; **Level 1**: Normal daily activities without exercise. **Level 2**: Moderate physical activity: (1 to 2 times a week, each time for at least 20 minutes). **Level 3**: High physical activity: (3 or more 3 times a week, Each time for at least 20 minutes).

Table 2. Comparison of insulin resistance status in PCOS subgroups and control group.

Insulin resistance status ^a	Phenotype A		Phenotype B		Phenotype C		Phenotype D		Control group	
	n	%	n	%	n	%	n	%	n	%
NO	16	39.5	16	48.5	25	62.5	19	51.4	29	93.5
Yes	25	61.0	17	51.5	15	37.5	18	48.6	2	6.5
Total	41	100	33	100	40	100	37	100	31	100

^a: Yes is HOMA-IR >2.5 and No is less than 2.5; P<0.001 Chi-square test.

Table 3. Correlation between dietary components and HOMA IR index in four subgroups of PCOS and control group

Phenotype A	Total fiber	Soluble fiber	Total fat	PUFA	MUFA	SFA	Protein
Calories							
0.334 ^a	-0.188	-0.139	0.195	0.181	-0.151	0.010	0.017
0.033 ^b	0.240	0.385	0.227	0.264	0.352	0.952	0.916
Phenotype B							
0.019	0.309	0.288	-0.173	0.094	-0.069	-0.051	-0.037
0.915	0.080	0.104	0.337	0.604	0.705	0.776	0.836
Phenotype C							
0.074	0.036	-0.035	0.341	0.226	0.256	0.053	-0.063
0.649	0.824	0.830	0.031	0.161	0.110	0.747	0.697
Phenotype D							
-0.028	-0.288	-0.132	0.124	-0.404	-0.473	0.062	-0.311
0.033	0.240	0.385	0.227	0.013	0.003	0.004	0.061
Control group							
0.139	0.247	0.522	0.202	0.482	0.512	0.366	0.443
0.455	0.181	0.066	0.275	0.067	0.052	0.043	0.012

^a: Correlation coefficient; ^b: P-value; PUFA: Polyunsaturated fatty acid; MUFA: Monounsaturated fatty acid; SFA: Saturated fatty acid

Discussion

Many studies have investigated and compared IR with nutritional factors, but so far no study has investigated the association between IR and macronutrient intake in four phenotypes of women with PCOS. Due to differences in dietary patterns in different countries, this study investigates the relationship between IR and nutritional patterns in the consumption of macronutrients in Iran. In the present study, macronutrients were evaluated in three broad categories including protein, carbohydrate, and fat with HOMA-IR. The results showed that IR in different PCOS subgroups and the control group correlated with oral intake frequency of macronutrients.

In subgroup A, the HOMA-IR was correlated with daily calorie intake. In subgroup B, there was no relationship between the HOMA-IR and any of the dietary components. In subgroup C, there was a positive relationship between HOMA-IR and total fat. In subgroup D, there was a negative relationship between the HOMA-IR with PUFA, and MUFA. In the control group, there was a positive correlation between HOMA-IR, SFA, and protein intake.

So far, no study has been found on the intake of macronutrients individually in insulin-resistant PCOS phenotypes. Therefore, the present study compared the results of studies evaluating the association between different dietary components and IR in these patients. Graff reported a correlation between dietary glycemic index and IR in people with the classic PCOS phenotype (phenotypes A and B) (Graff *et al.*, 2013). In Pehlivanov's study, people with PCOS in subgroups A and B received more calories and had a higher HOMA-IR index (Pehlivanov and Orbetzova, 2007), and these two studies were in line with the present study.

A case-control study was conducted by Zhang in China on 169 PCOS women and 338 control and non-PCOS women who were homogeneous in age. The results showed that women with PCOS had lower carbohydrate and calorie intake than controls (Zhang *et al.*, 2015), which was contrary to the results of the present study due to differences in

culture, nutrition, and taste between different races. Douglas studied 30 women with PCOS and 27 healthy women who were matched for age, race, and BMI and reported that people with PCOS tend to consume high glycemic index foods, but there was no significant positive association between food and IR (Douglas *et al.*, 2006). The difference in the results of this study may be due to the lower sample size than the present study.

Sjaarda *et al.* also conducted a study on 259 women with PCOS and reported that there was no association between a high carbohydrate diet and high calorie intake or any macronutrients with IR (Sjaarda *et al.*, 2015), which was due to the type of research examples. The study was performed on 259 women without a history of infertility and PCOS. The only examples in this study were women with amenorrhea. The results of this study are contrary to the results of the present study. Ebbeling *et al.* considered the type of carbohydrate intake more important than its total amount to maintain the metabolic health of women with PCOS. Low glycemic diets improved IR (Ebbeling *et al.*, 2005). Brynes *et al.* also showed that high glycemic foods had the opposite effect (Brynes *et al.*, 2003).

IR is the physiological condition during which the insulin hormone is less able to lower blood sugar. The subsequent rise in blood sugar can be so high that it goes beyond the normal range of blood sugar and can be detrimental to health. Some cells, such as fat and muscle cells, require insulin to enter glucose. If these cells do not respond to the circulating insulin, their blood sugar will rise. IR has several effects, including a decrease in the ability of adipocytes to harvest blood lipids and increased hydrolysis of peripheral triglycerides.

This hydrolysis can increase the free fatty acids in the bloodstream. Since the human genotype has not changed over the centuries, environmental factors have been considered a major contributor to the increase in IR in recent years. One of the most important issues in this regard is the energy balance between the number of calories consumed through food and the number of calories consumed during physical activity. In addition to energy

balance, the type of food consumed is also important. From an evolutionary perspective, it has been suggested that being overweight and other related diseases are the natural results of high-calorie intake (Homayounfar *et al.*, 2013). Being Overweight (as IR) can act as a gonadotropin and thereby impair the synthesis of androgens. Overweight can also affect the hypothalamus and ovaries through adipocytokines, indirectly or indirectly, and ultimately affect the peripheral metabolism of steroids. Therefore, as the first line of treatment for women with PCOS, the amount of calorie intake and weight management should be considered (Ehsani *et al.*, 2015). High-calorie intake was associated with IR in patients with complete PCOS phenotype (lack of ovulation, hirsutism, and abnormality in the ultrasound view).

Kasim-Karakas examined the effects of dietary PUFA in 17 patients with PCOS, which is consistent with the results of the present study. During a 3-month diet period, dietary fats were replaced with PUFAs, which reported that PUFAs significantly increased diol 3-glucuronide progeny, thereby reducing IR and ovulation (Kasim-Karakas *et al.*, 2004). Zivkovic reported that diets containing MUFA in women with PCOS decrease IR (Zivkovic *et al.*, 2007). In a study by McLaughlin, diets containing MUFA and PUFA lipids reduced IR in patients with PCOS (McLaughlin *et al.*, 2016). In the present study, in subgroup D, an inverse relationship was observed between daily intake of PUFA and MUFA with HOMA-IR.

Tierney stated that diets rich in MUFA increased IR (Tierney and Roche, 2007), which is not consistent with the present study. In the study by XIA, there was a positive correlation between saturated fat intake and HOMA-IR in women with PCOS. This study was in line with the present study (XIA and ZHANG, 2012). Stender conducted a study to determine the effect of trans-fatty acids on health. Their results showed that high-fat diets, especially saturated fats and trans-fatty acids, were associated with decreased IR. The results of this study were contrary to the results of the present study. In the current study, an increase

in saturated fat intake in subgroups D and control was associated with increased IR (Stender and Dyerberg, 2004). Perhaps the reason for this contradiction, in the quality and quantity of fats is that diet composition plays an important role in homeostasis and insulin sensitivity in animals and humans. Some studies have shown that high-fat diets can cause hyperglycemia and IR. Fatty acids with varying degrees of saturation may not be able to induce fat-induced IR. It seems that the combination of fatty acids or types of fatty may have an independent effect on insulin function and alter insulin sensitivity (Saidpour *et al.*, 2011). In the present study, total fat increased in subgroup C and subgroups D, decreased MUFA and PUFA consumption, and increased SFA led to increased IR. In the control group, increased SFA intake and increased protein led to increased IR.

Another finding of the present study was the effect of macronutrients such as protein on IR. High protein intake increased IR that consistent with the study of Panagiotakos, which had a positive correlation between protein intake and IR (Panagiotakos *et al.*, 2005). One of the studies that are inconsistent with the present study is the XIA study, which was conducted to compare diet composition in women with and without PCOS. Eighty-six women (47 with PCOS and 39 without PCOS) participated in this study. The results showed a negative correlation between protein intake and HOMA-IR (XIA and ZHANG, 2012).

The limitations of this study include the lack of cooperation of many physicians in requesting appropriate tests. On the other hand, some research units did not perform the requested tests.

Conclusion

In the present study, considering the relationship between some dietary components and IR, it is important to study the dietary pattern and its modification in the management of people with PCOS. Even in the control group (without clinical or laboratory evidence of a diagnosis of PCOS), some nutritional factors (more SFA saturated fat intake and high protein intake) were associated with IR. Therefore, modifying the dietary pattern

can improve the status of PCOS and prevent the potential risks of IR in different PCOS subtypes. In general, the results of this study suggest that balance carbohydrate and fatty acids intake and dietary fiber intake improve health parameters in PCOS patients.

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Authors' contributions

Gholami M: Manuscript writing and idea generation. Ziaei S: performed research plan, and supervised the study. Kazemnejad A: analyzed the data. Movahedinejad M: designed the research and had primary responsibility for final content.

Conflicts of interest

There is no conflict of interest.

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