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The Relationship between Insulin Resistance and Micronutrient Intake in Polycystic Ovary Syndrome Subgroups

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ABSTRACT

Background: Polycystic ovary syndrome (PCOS) is with oxidative stress in women of reproductive age. Oxidative stress is an important factor in the development of insulin resistance. Some micronutrients are also linked to oxidative stress. The aim of this study was to determine the relationship between insulin resistance and micronutrient intake in PCOS subgroups. **Methods:** This case-control study was performed on 151 PCOS. They were divided into four groups according to the Rotterdam diagnostic criteria: D = 37, C = 40, B = 33, A = 41 and 31 women were also in the control group and did not have this syndrome. Micronutrient food intake was assessed with a 168-item FFQ feed frequency questionnaire. Insulin resistance was diagnosed with HOMA-IR index (Cut off> 2.5). The data were analyzed with SPSS 22 using Kruskal Wallis (KW), Spearman, and Chi-square tests. **Results:** The mean age of participants was 28.53 years. There was a significant relationship between the HOMA-IR and some dietary components (selenium depletion in group A, zinc depletion, vitamin D, and vitamin E in group D, and vitamin D and vitamin E depletion in control group) ($P < 0.05$). There was no relationship between subgroups B and C. **Conclusion:** Due to the significant relationship between insulin resistance indices, increasing the dietary intake of zinc, selenium, vitamin D, and vitamin E in women with PCOS, as well as increasing the dietary intake of these micronutrients in improving the physical health and fertility parameters of these people is recommended.

Keywords: *Micronutrient intake; Polycystic ovary syndrome; Insulin resistance*

Introduction

Polycystic ovary syndrome (PCOS) is a complicated endocrineopathy affecting women of reproductive age. According to the difference in the diagnostic criteria and ethnic background, the prevalence of this syndrome has been reported in the range of 11.9 +/- 2.4% (March *et al.*, 2010).

In Iran, based on the National Institute of Health (NIH) criteria, the prevalence of PCOS according

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to Rotterdam criteria is 15.2% (Mehrabian *et al.*, 2011).

PCOS is difficult to diagnose due to the heterogeneous nature and possible changes in patient's status. At present, the most commonly used criterion for diagnosis is the Rotterdam criterion based on the 2003 agreement. In this method, two out of three disorders (hyperandrogenism, chronic ovulation, and ultrasound pattern of polycystic ovaries) are necessary (Kar, 2013).

It is not a disease-specific to fertility and adolescence but can have different effects on one's life. The main complications of adolescence are prevalence of amenorrhea, oligomenorrhea, hirsutism, obesity, and acne. At the fertility age, the patient's main complaint is infertility and irregular ovulation. Complications of adolescence are still present in this period. At premenopausal and postmenopausal ages, this syndrome can increase the risk of type 2 diabetes, hypertension, dyslipidemia, cardiovascular disease, and even endometrial cancer and possibly breast cancer (Norman *et al.*, 2007) and insulin resistance (Javanmanesh *et al.*, 2016, Moran and Teede, 2009).

Insulin resistance refers to conditions in which the biological effect of insulin is diminished at any given concentration. In addition, it reduces the sensitivity of target tissues to insulin hormone, leading to insulin resistance (Yildizhan *et al.*, 2009).

Insulin resistance is also one of the pathophysiological factors in 50-80% of PCOS patients (Teede *et al.*, 2010). Among patients, 80-70% of obese patients (BMI > 30) and 20-25% of lean women (BMI < 25) showed these features (Marshall and Dunaif, 2012).

One of the mechanisms involved in insulin resistance is the presence of genetic and environmental factors such as nutrition and physical activity (Teede *et al.*, 2010). Proper diet and lifestyle modification reduce insulin resistance in PCOS patients (Salehpour, 2011).

In nutrition, micronutrients play an important role in human health, including the prevention and treatment of diseases, as well as the optimization of physical and mental performance (Woodside *et al.*, 2005). The antioxidant effects of several micronutrients, such as zinc, selenium, chromium, and carotenoids (Zeng, 2009) were considered as contributing factors to the development of insulin resistance (González *et al.*, 2006).

There is limited data investigating the diet composition of PCOS women (Douglas *et al.*, 2006). There are inconsistent results from studies mostly conducted in western countries. Some studies have not reported any difference in nutrient intake in women with or without PCOS (Douglas *et al.*, 2006, Wright *et al.*, 2004) .

Previous studies have also shown an inverse association between carotenoid intake and fasting glucose and insulin concentrations due to their antioxidant effects (Sugiura *et al.*, 2006). In some studies, the inverse relationship of insulin resistance to HOMA-IR with vitamins E and D due to inhibition of oxidative stress and inflammation has been reported (Chiu *et al.*, 2004, Gabrielli and Aquino, 2012, Isharwal *et al.*, 2009). There is also a negative association of insulin resistance with zinc, assuming that alpha-zinc glycoprotein may act as an adipokine that interferes with insulin resistance (Hashemipour *et al.*, 2009). However, results regarding zinc levels in patients with PCOS are highly contradictory and some studies have not found zinc administration to be beneficial in these patients (Hashemipour *et al.*, 2009, Kim *et al.*, 2007). Evidence suggests that chromium plays a role in controlling blood sugar and improving insulin activity and enhancing insulin sensitivity, appetite regulation, and weight control (Vincent, 2018). Studies have shown that chromium has been shown to affect insulin function and increase insulin sensitivity in patients with PCOS (Lydic *et al.*, 2006). It has also been suggested that high selenium intake reduces the risk of diseases due to oxidative stress and inflammation. The antioxidant and anti-inflammatory effects of selenium can have a protective effect on insulin resistance and diabetes (Rayman, 2012).

Accordingly, PCOS is a common, heterogeneous, and inherited disorder that affects women throughout their lives (Sirmans and Pate, 2014). The disease affects several systems. Early diagnosis and

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long-term management can help control this syndrome as well as prevent its long-term consequences, such as insulin resistance (Brady *et al.*, 2009). There have been few studies investigating the association between insulin resistance and dietary intake, and there are many inconsistencies in their results. Eating habits are rooted in the culture of every region in the world (Shishehgar *et al.*, 2016). Therefore, the researchers designed and conducted a study to determine the relationship between insulin resistance and micronutrient intake (chromium, selenium, zinc, carotenoids, vitamins D and E) in women with PCOS in four phenotypes based on Rotterdam criteria.

Materials and Methods

Study design and participants: The present study is a case-control study to investigating dietary intake of micronutrients in four subgroups of PCOS and control group with insulin resistance in Tehran, Iran during 2015-2016. The sample size based on the results of the pilot study and the correlation between insulin resistance 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 was 26.2 based on the following formula for each subgroup (approximately 27 samples). Considering 20% of sample loss, the final volume per phenotype was estimated at 31 samples.

$$n = \frac{\left(z_{1-\frac{\alpha}{2}} + z_{1-\beta}\right)^2}{\left(c(r)\right)^2} + 3$$

$$C(r) = \frac{1}{2}\log_e \frac{1+r}{1-r} = \frac{1}{2}\log_e \frac{1+0.5}{1-0.5} = 0.55$$

$$n = \frac{(1.96 + 0.84)^2}{(0.55)^2} + 3 = 26.2 \cong 27$$

$$27 + 0.2(27) = 31$$

The participants were selected from referrals to gynecology and endocrinology ward of Arash hospital, and selected private clinic if they were eligible to enter the study after filling informed consent form. The inclusion criteria in the case group consisted of Iranian nationality, age of 18-40 years, lack of chronic metabolic and non-metabolic diseases affecting diet (such as diabetes mellitus, hyperthyroidism, hypothyroidism, and hyperlipidemia), not taking medicines that affect appetite and diet, no specific diet, no pregnancy, no hormone use for three months before starting the study. In the event of any problems, including pregnancy and illness requiring specific drug use, they were excluded. The inclusion 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), referring 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 (AOAH)) by assessing 17OHP, DHEAS, cortisol, thyroid hormones, and prolactin levels (Berek and Brerek, 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 (Ramezani Tehrani *et al.*, 2014), and above or biochemical hyperandrogenism: elevated serum total testosterone levels or free androgen index (FAI)): hyperandrogenic serum total testosterone (TT), greater than 0.68 ng/ml and free androgen index (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 (nmol/l)/SHBG (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).

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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) Phenotype or D (H + O) (Kar, 2013).

Finally, 182 participants were included in the study (31 people in 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 to exercise. The participants' physical activity was measured at three levels based on their responses. Level 1: Normal daily activities without exercise, Level 2: Moderate physical activity: (1 to 2 times a week, each time for at least 20 min). High physical activity: (3 or more 3 times a week, each time for at least 20 min) (Kim *et al.*, 2007).

For all samples, a 168-item FFQ (Food Frequency Questionnaire) was completed. Validity and reliability have been evaluated by Asghari and Mirmiran (Asghari *et al.*, 2012, Mirmiran *et al.*, 2010). This questionnaire was used to obtain a person's usual diet during the past year. This questionnaire includes all food groups breads, rice, pasta, cereals, dairy (milk, yogurt, buttermilk, cheese, whey, and ice cream), meat group (minced and sliced lamb and beef, Fish, and poultry), group of vegetables (leafy and non-leafy vegetables), group of fruits (all kinds of fruits and juices), group of oils, all kinds of sweets, nuts, noodles, canned foods, beans, tea and coffee, soda, and eggs.

In order to analyze the nutritional information of the FFQ questionnaire, Excel software was used to analyze nutrient intakes (including formulas programmed in Excel in which the nutrients of the food frequency questionnaire are broken down into micronutrients). In the program above, for each micronutrient of each nutrient, a function is defined based on the amount of nutrients in one gram of each nutrient. Thus, by entering the consumption amount (gram) of each food item in its respective cell, Excel calculated the number of nutrients in the germ consumed in that nutrient. 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 intake of each individual, it is obvious that the ratio of each nutrient to the total daily calorie intake and consequently the contribution of one nutrient to the total calorie intake may also be different. Therefore, in order to make an accurate comparison between the information obtained from each individual with the other participants, after daily calorie 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, hormonal tests were performed to determine serum androgens. Questions were raised about menstruation. Menstrual disorder was evaluated.

The studied micronutrients included zinc, selenium, carotenoids, chromium, vitamin D, and vitamin E.

In this study, insulin resistance was assessed using HOMA-IR index. The original HOMA-IR model was described in 1985 with a formula for approximate estimation by Mathews (Matthews *et al.*, 1985). The formula of the HOMA-IR index was calculated by multiplying the fasting blood glucose concentration (mmol/l) and the fasting insulin concentration (mmol/ml) divided by a fixed number of 22.5. The cut-off point for defining insulin resistance was considered based on the HOMA-IR criterion (cut off > 2.5) (Wallace *et al.*, 2004).

Five milliliters of venous blood (to check fasting blood glucose and insulin levels) were obtained from all research units in the laboratory and 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

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analysis and statistical tests. First, Kolmogorov-Smirnov test was used for data normality. Spearman correlation test (in case of non-normal data) was used to investigate the relationship between quantitative variables. Chi-square test was also used to investigate some underlying variables. Significance level was considered P-value ≤ 0.05.

Results

The results of Kruskal Wallis and Chi-square tests showed 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), education level (P = 0.30), economic status (P = 0.27), and physical activity status (P = 0.87). The two groups were homogeneous (**Table 1**).

Insulin resistance status was compared with the HOMA-IR index (Cut off > 2.5) in PCOS and control groups with the Chi-square test. There was a significant difference in the insulin resistance. The number of women with PCOS who also had insulin resistance was higher in phenotype A compared to other groups (61%).

In phenotype B, (51.5%), in phenotype D, (48.6%) and in phenotype C, (37.5%) had PCOS and HOMA-IR at the same time. In the control group, although they had no symptoms of PCOS, two participants (6.5%) had the syndrome (**Table 2**).

Spearman test results showed that insulin resistance in different PCOS subgroups and control group correlated with the frequency of oral consumption of micronutrients. In subgroup A, there was a significant negative relationship between the insulin resistance and selenium micronutrient intake (P = 0.01). In groups B and C, no significant relationship was found between the insulin resistance and any of the micronutrients. In subgroup D, a significant negative correlation was found between insulin resistance and micronutrient zinc (P = 0.02), vitamin D (P = 0.05), and vitamin E (P = 0.001). In the control group, there was a significant negative relationship between insulin resistance and vitamin D (P = 0.02) and vitamin E (P = 0.001, **Table 3**)

Table 1. Comparison of demographic variable between groups.

Variables	Phenotype A N=41	Phenotype B N=33	Phenotype C N=40	Phenotype D N=37	Control group N=31	P-value
Quantitative variables						
Age (y)	28.07 ± 4.70[a]	27.00 ± 5.44	29.70 ± 6.44	29.83 ± 5.93	28.07 ± 4.70	0.09[b]
BMI (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[b]
Qualitative variables						
Educational status	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	
Under Diploma	4 (9.8)	3 (9.1)	4 (10.0)	2 (5.4)	2 (6.5)	0.30[c]
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)	
Economic situation						
Poor	16 (39.0)	23 (69.7)	23 (57.5)	21 (56.8)	17 (54.8)	0.27[c]
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[c]
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]: Mean ± SD, [b]: Kruskal Wallis test, [c]: Chi-square test, BMI: Body mass index, 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).

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

Insulin resistance	Phenotype A	Phenotype B	Phenotype C	Phenotype D	Control Group
No	16 (39.5)[a]	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]: N (%), Chi-square; P <0.001

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

Variables		Selenium	Zinc	Carotenoids	Chromium	Vitamin D	Vitamin E
Phenotype A	R	-0.37	-0.02	-0.13	-0.07	0.25	-0.01
	P-value	0.01	0.86	0.38	0.63	0.10	0.90
Phenotype B	R	0.06	-0.06	-0.13	0.15	-0.01	0.03
	P-value	0.70	0.70	0.38	0.40	0.95	0.86
Phenotype C	R	-0.11	-0.12	-0.13	0.09	-0.12	0.08
	P-value	0.49	0.46	0.38	0.56	0.45	0.61
Phenotype D	R	-0.31	-0.37	-0.32	0.13	-0.32	-0.51
	P-value	0.06	0.02	0.05	0.41	0.04	0.001
Control group	R	0.12	0.27	-0.13	0.12	-0.40	-0.57
	P-value	0.48	0.14	0.38	0.45	0.02	0.001

Discussion

Many studies have investigated and compared insulin resistance with nutritional factors, but so far no study has investigated the association between insulin resistance and micronutrient intake in four phenotypes of women with PCOS. Also, due to different dietary patterns in different countries, this study investigates the relationship between insulin resistance and micronutrient intake in Iran. In the present study, micronutrients were evaluated in two broad categories, including minerals and vitamins with the insulin resistance. The results showed that insulin resistance in different PCOS subgroups and the control groups was correlated with the frequency of oral micronutrient intake.

In subgroup A, there was a significant negative relationship between the insulin resistance and selenium intake. There was no significant relationship between insulin resistance and any of the micronutrients in groups B and C. In subgroup D, there was a significant negative relationship between insulin resistance and zinc, vitamin D, and vitamin E. In the control group there was a significant negative correlation between insulin resistance with vitamin D and vitamin E intake.

Zinc is an essential micronutrient that enhances the ability of insulin to bind to its receptors (Marreiro *et al.*, 2004). Zinc deficiency reduces the response of tissues to insulin, possibly due to its similarity to insulin function (Miranda and Dey, 2004). Possible mechanisms of the effect of zinc deficiency on insulin resistance include impaired insulin secretion from the pancreas, impaired insulin binding to its receptors, impaired insulin receptor synthesis, impaired glucose carrier structure, and impaired glucose entry into the cell (Taghdir *et al.*, 2009). There have been several studies on the relationship between insulin resistance and zinc. The study by Guler *et al.* is in line with the present study, this prospective study was performed on 53 women with PCOS and 33 healthy women without PCOS. Serum zinc levels in patients with PCOS were compared with insulin resistance. The results showed that serum zinc levels in women with PCOS with insulin resistance were significantly lower than women with PCOS and without insulin resistance (Guler *et al.*, 2014). Also, a clinical trial study by Foroozanfard *et al.* on 52 patients with PCOS reported that administration of 220 mg/day of zinc sulfate

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supplementation after 12 weeks reduced insulin resistance (Foroozanfard *et al.*, 2015).

The clinical trial study of Jamilian *et al.* contradicts the results of the present study. The results of this study showed that the administration of 8 weeks of zinc supplementation at 220 mg/day had no effect on insulin resistance. The reason for contradiction with the present study may be due to the small sample size and differences in method (Jamilian *et al.*, 2016).

It has been suggested that high selenium intake reduces the risk of oxidative stress and inflammatory diseases. The antioxidant and anti-inflammatory effects of selenium can have a protective effect on insulin resistance and diabetes (Rayman, 2012). But there have been controversial studies on the association between insulin resistance and selenium intake. Consistent with the present study is the study of Wang *et al* (Wang *et al.*, 2017). In a study by Wang, the results showed that insulin resistance increased when dietary intake of selenium was lower than 1.6 µg/day. In the present study, selenium intake was lower in all PCOS phenotypes, and this micronutrient deficiency was associated with insulin resistance.

The results of the clinical trial study of Hosseinzadeh (Hosseinzadeh *et al.*, 2016) were inconsistent with the results of the present study. Hosseinzadeh conducted a study on 53 patients with PCOS. After 12 weeks of intervention, in 26 patients (200 µg/day of selenium supplement) and 27 patients placebo group, despite the theoretical effects of selenium, the results showed that selenium supplementation in PCOS patients worsened insulin resistance status. Jamilian *et al.* aimed to determine the effect of selenium supplementation on the status of 70 patients with PCOS. Results showed that administration of 200 µg of selenium daily for 8 weeks did not have beneficial effects on insulin resistance. Perhaps the reason for the differences in the results of this study with the present study is the small sample size (Jamilian *et al.*, 2015).

Chromium is one of the essential micronutrients in the body. Evidence suggests that it plays an important role in the natural metabolism of carbohydrates. In the 1950s, scientists found that chromium is essential for maintaining normal glucose tolerance and blood sugar control in rats. Chromium plays a role in controlling blood sugar and improving insulin activity and increasing insulin sensitivity, appetite regulation, and weight control (Vincent, 2018). Most studies have shown that chromium affects insulin function and increased insulin sensitivity in patients with PCOS (Lydic *et al.*, 2006). In a study by Lydic *et al.*, the administration of 1000 µg of chromium picolinate in women with PCOS for 2 months improved glucose levels and insulin sensitivity (Lydic *et al.*, 2006). In a clinical trial of Amooee, which included 92 women with PCOS, receiving 200 micrograms of chromium picolinate reduced insulin sensitivity to the control group. These two studies are inconsistent with the present study. This may be due to differences in the type and method of study (Amooee *et al.*, 2013).

Other micronutrients studied are carotenoids. Carotenoids are a group of pigments that play an important role in the absorption of light in plants. Carotenoids are not made in the vertebrate body and must be made available through the diet of these animals. Carotenoids perform various physiological functions in the body, including light absorption, antioxidant properties, and the strengthening of the immune system against various diseases (Dorfman, 2012). Consistent with the present study is a descriptive-analytical study by Gol Afroozi *et al.*. In this study, carotenoids were measured in the subjects with intake and there was no statistically significant difference between carotenoid intake and insulin resistance (Gol Afroozi and Koushak, 2006). The study by Ylonen was not in line with the results of the present study. The study by Ylonen on 81 individuals at risk for type II diabetes, reported that dietary carotenoids were inversely correlated with fasting blood glucose and insulin resistance. Thus, free radicals appear to impair insulin action by altering the physical status of the target cell membrane. Carotenoids, by neutralizing free radicals, improve the secretion and function of insulin in regulating blood sugar (Ylönen *et al.*,

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2003). Perhaps the reason for the difference between the results of this study and the present study is the difference in the type of research units.

Vitamin D, called calciferol, is one of the essential vitamins and fat-soluble vitamins that help bone growth and health by controlling calcium and phosphorus balance. It helps in bone metabolism by increasing phosphorus and calcium uptake by the intestines and by reducing the excretion of the kidneys, as well as by helping to translate nucleus genes into cell growth (Chung *et al.*, 2009). A review by Thomson *et al.* suggests that there is a relationship between vitamin D status and hormonal and metabolic disorders in PCOS (Thomson *et al.*, 2012). The mechanism of this effect is unknown, but a possible reason is the disruption of the mechanisms regulating ovarian apoptosis. Also due to its immune-modulating role, vitamin D deficiency may induce inflammatory responses and consequently insulin resistance (Bikle, 2009). Studies by Yildizhan, Hahn, and Krul-Poel reported lower levels of vitamin D in women with PCOS (Hahn *et al.*, 2006, Krul-Poel *et al.*, 2018, Yildizhan *et al.*, 2009).

The results of the study by Ardabili were not consistent with the results of the present study. This clinical trial study was performed on 50 patients with PCOS. The results showed that vitamin D supplementation containing 50,000 units every 20 days for two months did not affect HOMA-IR. Perhaps the reason for this difference in the results with the present study is the small sample size and short interval of intervention (Ardabili *et al.*, 2012)

Vitamin E is one of the fat-soluble vitamins. Vitamin E was discovered in 1920 and was isolated from the wheat germ in 1936 and is called alpha-tocopherol. It is contained in the fat layer of the cell wall and inside the cell and prevents cell wall damage (Dorfman, 2012). Limited studies have been conducted on the effect of vitamin E on PCOS. The favorable effects of vitamin E on insulin resistance have been observed due to the inhibition of oxidative stress and inflammation. The effects of plasma alpha-tocopherol-induced partial improvement on insulin resistance have been observed in studies of Manning and Caballero (Caballero, 1993, Manning *et al.*, 2004). In Manning's study, 800 IU of vitamin E was used and there was a significant decrease in serum insulin and insulin resistance compared to the control group. Vitamin E appears to decrease insulin action, decrease insulin and fasting serum glucose by decreasing cellular oxidative stress, altering membrane properties, and decreasing inflammatory activity. Vitamin E administration can improve insulin action by improving the Physico-chemical status of the plasma membrane due to reduced oxidative stress (Manning *et al.*, 2004).

Given the association of insulin resistance with micronutrient deficiencies of zinc, selenium, vitamin D, and vitamin E levels in the diet of people with PCOS, it is recommended that clinical trials with a larger sample size be designed and performed to evaluate the administration of micronutrient supplements to these patients.

The limitations of this study include the lack of cooperation of many physicians in requesting appropriate tests and also some research units did not perform the requested tests.

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Authors' contributions

Kamali Z: Article writing and idea generation. Ziaei S: performed research plan, and supervised the study. Kazemnezhad A: analyzed the data. Movahedinejad M: designed the research and had primary responsibility for final content.

Conflict of interest

The authors declare that there is no conflict of interest in this study.

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