

Dietary Total Antioxidant Capacity and Risk of Polycystic Ovary Syndrome: A Case-Control Study

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Abstract

Background: Among multiple factors that affect the etiology of polycystic ovary syndrome (PCOS), diet has an important contribution. Chronic oxidative stress has also been implicated in the development of PCOS. The present study is an attempt to evaluate dietary total antioxidant capacity (TAC) and its relationship with odds of PCOS in Iran.

Materials and Methods: The study was carried out as a case-control study in hospital outpatient clinics, Tehran, Iran. Totally, 310 female participants with a history of PCOS and 602 age-matched controls took part in this study between June 2015 and December 2018. A reproducible and valid 168-item semi-quantitative food frequency inventory was utilized to determine the entire antioxidants of the usual diet in order to calculate dietary TAC. The relationship of dietary TAC with odds of PCOS were assessed adjusting for potential confounders through an estimation of two multivariable conditional regression models. The first tertile was presented as a reference category.

Results: In a fully adjusted model, the highest tertile of dietary TAC was associated with a reduced odds of PCOS [odds ratio (OR): 0.81, 95% confidence interval (95% CI): 0.59, 0.96, P for trend: 0.038]. In addition, PCOS odds decreased in the highest tertile of α -tocopherol intake (OR: 0.73, 95% CI: 0.56, 0.88, P for trend: 0.023). The adjusted ORs in the highest tertile of vitamin C, β -carotene and magnesium were 0.79 (95% CI: 0.83-0.97), 0.81 (95% CI: 0.67-0.98) and 0.91 (95% CI: 0.55-0.98) respectively, with a significant trend.

Conclusion: Our results provide evidence that there was a relationship between high TAC diets and lower odds of PCOS.

Keywords: Antioxidant, Diet, Oxidative Stress, Polycystic Ovarian Syndrome

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Introduction

Polycystic ovary syndrome (PCOS) is a common gynecological endocrinopathy that affects 8-13% of women in the reproductive age (1). Although, the cause of PCOS is still not fully understood, there are several possibilities. Main of them included: i. Hypothalamic/pituitary dysregulation contributes to a rise in the ovarian androgen production and ii. Hyperandrogenism leads to insulin resistance that results to PCOS (2). Due to insulin resistance, hyperinsulinemia happens and speeds up the ovarian androgen production, which can lead to the PCOS occurrence (3, 4). Recent studies have demonstrated that oxidative stress contributes to the development of PCOS, infertility and hyperandrogenism (5, 6). Important factors

that increase the oxidative stress in PCOS are insulin resistance and hyperglycemia (7).

Oxidative stress is clarified as a lack of balance among oxidants and antioxidants in the alive biological systems (8). The oxidative stress decrease is positively related to further matured oocytes in the infertile PCOS women (9). Oxidative stress causes widespread atherosclerosis lesions in the ovarian arteries (10, 11). Thus, the use of anti-oxidative agents has become an increasingly popular method in the PCOS management (12). Research works have shown that there is a relationship between PCOS and dietary intakes (13-15). The dietary antioxidants with a negative relationship with PCOS are vitamin C, vitamin E, selenium, zinc

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and beta-carotene (13). A recent study showed that plant-based dietary pattern is associated with lower odds ratio (OR) of PCOS and antioxidant-rich foods may protect the body against oxidative damage in these patients (14). Furthermore, adherence to an antioxidants-rich diet may be inversely associated with PCOS (15). There are emerging evidences that total antioxidant capacity (TAC) of dietary can be used as a measurement index that covers combined actions of dietary total antioxidants. This assay gives better predictions of dietary intake relation with chronic diseases (16). Studies demonstrate that higher dietary TAC is associated with lower weight and abdominal fat gain (17). Furthermore, higher dietary TAC is related to greater improvement in the heart disease risk factors and reduced risk of pancreatic cancer (18, 19).

Unfortunately, there is a shortage of data, especially on dietary TAC and PCOS relationship. Thus, this finding encouraged us to design a case-control study to examine the relationship of dietary TAC and the odds of PCOS.

Materials and Methods

Study design and population

All volunteers signed informed consent before the onset of the study. The Ethics Committee of Shahid Beheshti University of Medical Sciences approved the study (IR.SBMU.RETECH.REC.1398.750). The whole procedure was conducted as per the Helsinki Declaration of 1975, as revised in 2013 and the ethical standards of the responsible committee on human experimentation.

A total of 310 patients with a PCOS history between the ages of 20-35 years and 602 age-matched healthy volunteers participated in this case-control study. This study was performed in the various hospital endocrinology clinics of Tehran, Iran. Our case group inclusion criteria comprised women with a diagnosis or a history of PCOS. Based on the international Rotterdam Criteria 2003, PCOS patients diagnosed in the past three months had to have two out of three symptoms at least (20). They were diagnosed, follow of clinical or biochemical signs of hyper-androgenism, oligo-ovulation or anovulation and polycystic ovaries by ultrasonography. Also, control group was invited from age-matched referred patients to other clinics such as orthopedic, ear, nose, throat clinics or elective surgeries were referred to the same clinics that were not suffered of ongoing or previous PCOS. They had regular menstrual cycles (26-33 day cycles) without any ovulatory abnormalities, polycystic ovary and hyper-androgenism. The rest of the inclusion criteria for the control group were similar to the case group. On the third day of their menstrual cycle, endocrine hormones serum level and full pelvic ultrasound assessment were performed. All participants, cases and controls, were free of cardiovascular diseases, cancer, diabetes, renal disease and did not follow special diets.

Socio-demographic assessment

Age, smoking, first menarche age, literacy level, history of medication, supplementation and monthly family income were recorded from the pretested baseline questionnaire. Due to participants' religious and cultural taboos, questions regarding alcohol and opium were omitted (21). Details of anthropometric and physical activity assessments have been reported previously (22).

Dietary assessment

The dietary data were collected through a valid semi-quantitative food frequency questionnaire (FFQ) (23). All participants were asked about their usual intakes over the past year, although in the case group we considered a last year before PCOS diagnosis. Nutrient Data Laboratory of United States Department of Agriculture (USDA) database was used to calculate dietary TAC for selected foods by the oxygen radical absorbance capacity method. Results were expressed as mmol of Trolox Equivalents (mmol TE/day) (24). Using residual method, dietary TAC was adjusted for total energy intake.

Statistical analysis

Data analysis was done in statistical package for the social sciences software (SPSS Inc., Chicago, IL, USA, version 20) ($P < 0.05$). Kolmogorov-Smirnov test, histogram and Q-Q plot were used for normality of continuous variables. Dietary intake variables were not normally distributed. Therefore, transformations such as logarithm, square root, reciprocal, cube root, and square were done using parametric tests. Analysis of covariance (ANCOVA) adjusting for total energy was used to examine significant differences in antioxidant intakes. OR and 95% confidence intervals (CIs) were calculated by binary conditional logistic regression models to investigate the association of odds PCOS in each tertile dietary antioxidant variables. A tertile cut-off point was used to categorize dietary TAC, Vitamin C, α -tocopherol, zinc, β -carotene, lycopene selenium and magnesium were divided into the tertiles. The first tertile was presented as a reference category. The following variables were adjusted; body mass index (BMI), sex, age, physical activity, familiar history of PCOS, smoking and total energy intake.

Results

Final analysis was conducted on 303 PCOS cases (97.7% participation rate) and 588 controls (97.7%). Twenty-one participants were initially excluded given the log scales of total energy intake, which were either >3 or <3 standard deviation (SD) from the mean.

The mean \pm SD for age was 29.1 ± 5.9 and 28.8 ± 6.2 in cases and controls represents the age-matched design. In comparison to the controls, BMI (33.7 ± 6.1

vs. 24.2 ± 4.9) and waist circumference (WC) (97.2 ± 8.2 vs. 80.1 ± 6.5) of the case group were higher along with the incidence of PCOS in their families ($P < 0.05$). Mean metabolic equivalent (MET) (47.3 ± 5.9 hour/day vs. 58.1 ± 7.1 hour/day) and dietary fiber intake (13 ± 3.9 vs. 16 ± 4.1) were significantly lower in cases. In addition, the mean energy intake (3009 ± 709 vs. 2139 ± 605) in the cases was significantly higher in comparison with controls ($P < 0.05$).

Table 1 lists the mean intakes of dietary antioxidant variables, both for cases and controls. Cases had lower dietary TAC, α -tocopherol, vitamin C and magnesium ($P < 0.005$). No differences were found between cases and the control group as regards lycopene, zinc, and selenium.

Table 1: Energy-adjusted antioxidant dietary variables among PCOS cases and controls

Dietary factors	PCOS women (n=303)	Control women (n=588)	P value*
Dietary TAC (mmol/day)	11.9 ± 3.9	14.1 ± 4.3	0.001
α -Tocopherol (mg/day)	5.5 ± 1.9	7.3 ± 1.5	0.035
Vitamin C (mg/day)	69.3 ± 32.3	84.1 ± 45.3	<0.001
β -Carotene (μ g/day)	1691 ± 133	1727 ± 152	0.069
Lycopene (μ g/day)	1885 ± 178	1902 ± 196	0.122
Zinc (mg/day)	11.9 ± 4.7	11.2 ± 3.9	0.234
Selenium (μ g/day)	52.3 ± 20.6	49.5 ± 22.3	0.321
Magnesium (mg/day)	189.2 ± 44.9	227.8 ± 46.7	<0.001

Data are presented as mean \pm SD. *: Based on ANCOVA, PCOS; Polycystic ovary syndrome, and TAC; Total antioxidant capacity.

Associations of dietary antioxidant variables with odds of PCOS are shown in Table 2. There was a significant relationship between the dietary TAC with an odds ratio (OR) of PCOS in the base model (OR of the highest tertile compared to lowest one: 0.77, 95% CI: 0.49-0.91). After adjusting for BMI, WC, energy intake, dietary intake of fiber, familial history of PCOS and physical activity, the highest tertile of the dietary TAC score was associated with a reduced odds ratio of PCOS (OR: 0.81, 95% CI: 0.59-0.96). There was a significant linear decrease among the dietary TAC tertiles for the odds ratio of PCOS (P trend=0.038). There was an inverse relationship between the dietary intake of α -tocopherol and the odds of PCOS in both base and fully adjusted models. The multivariable OR (95% CI) for PCOS was 0.73 (0.56-0.88) in the highest tertiles of α -tocopherol, compared to the lowest tertile. The adjusted ORs in the highest tertile of vitamin C, β -carotene and magnesium were 0.79 (95% CI: 0.83-0.97), 0.81 (95% CI: 0.67-0.98) and 0.91 (95% CI: 0.55-0.98) respectively, with a significant trend.

Table 2: ORs* of polycystic ovary syndrome by tertiles of the dietary total antioxidant capacity in Iranian population

Dietary antioxidant variables	Tertiles of energy-adjusted intake			P for trend
	1 st	2 nd	3 rd	
Dietary TAC (mmol/day)				
No. cases/No. controls	131/196	93/196	79/196	
Base model [†]	1.00 (Ref.)	0.87 (0.53-1.07)	0.77 (0.49-0.91)	0.015
Full model [‡]	1.00 (Ref.)	0.89 (0.48-1.03)	0.81 (0.59-0.96)	0.038
α-Tocopherol (mg/day)				
No. cases/No. controls	138/196	89/196	76/196	
Base model [†]	1.00 (Ref.)	0.73 (0.53-1.03)	0.69 (0.50-0.83)	<0.001
Full model [‡]	1.00 (Ref.)	0.77 (1.23-1.02)	0.73 (0.56-0.88)	0.003
Vitamin C (mg/day)				
No. cases/No. controls	143/196	83/196	77/196	
Base model [†]	1.00 (Ref.)	0.75 (0.43-1.08)	0.74 (0.73-1.05)	0.069
Full model [‡]	1.00 (Ref.)	0.82 (0.83-1.03)	0.79 (0.83-0.97)	0.039
β-Carotene (μg/day)				
No. cases/No. controls	124/196	90/196	89/196	
Base model [†]	1.00 (Ref.)	0.80 (0.49-1.19)	0.77 (0.65-1.08)	0.105
Full model [‡]	1.00 (Ref.)	0.84 (0.60-1.18)	0.81 (0.67-0.98)	0.046
Lycopene (μg/day)				
No. cases/No. controls	122/196	93/196	88/196	
Base model [†]	1.00 (Ref.)	0.96 (0.69-1.22)	0.99 (0.73-1.18)	0.112
Full model [‡]	1.00 (Ref.)	0.94 (0.79-1.03)	0.93 (0.63-1.07)	0.059
Zinc (mg/day)				
No. cases/No. controls	100/196	88/196	115/196	
Base model [†]	1.00 (Ref.)	1.13 (0.71-1.29)	0.99 (0.72-1.39)	0.305
Full model [‡]	1.00 (Ref.)	1.05 (0.83-1.15)	1.02 (0.95-1.19)	0.114
Selenium (μg/day)				
No. cases/No. controls	130/196	98/196	75/196	
Base model [†]	1.00 (Ref.)	1.09 (0.78-1.24)	1.27 (0.62-1.33)	0.286
Full model [‡]	1.00 (Ref.)	1.11 (0.72-1.21)	1.25 (0.65-1.39)	0.273
Magnesium (mg/day)				
No. cases/No. controls	128/196	90/196	85/196	
Base model [†]	1.00 (Ref.)	0.91 (0.59-1.03)	0.89 (0.50-1.04)	0.062
Full model [‡]	1.00 (Ref.)	0.93 (0.53-0.98)	0.91 (0.55-0.98)	0.047

Adjusted odds ratio (OR) estimates and 95% confidence intervals (CIs) for polycystic ovary syndrome (PCOS), according to the tertile of each dietary antioxidant variables. *: A conditional logistic regression model, †; Adjusted for age (5-year categories), ‡; Adjusted for age (5-year categories), body mass index (BMI, Kg/m²), waist circumference (WC, cm) intake (Kcal/d), dietary intake of fiber (g/d), familial history of PCOS (yes/no) and physical activity (MET/h/d).

Discussion

To be best of our knowledge, the association of dietary TAC with PCOS was assessed for the first time in a

developing country in the present study. Higher intake of dietary TAC, α -tocopherol, vitamin C, β -carotene and magnesium were inversely associated with lower odds of PCOS, even after adjusting for confounding factors. Intake of the α -tocopherol, vitamin C and β -carotene were significantly associated with reducing the odds of PCOS. Our data are consistent with Shahrokhi and Naeini (13) study that demonstrated relationship between the higher intakes of vitamin C, vitamin E, and β -carotene and the reduced odds of PCOS. Barrea et al. (25) reported a relationship between the Mediterranean diet (rich in antioxidants) and decreased odds of PCOS that consistent with our findings these data show a relationship between a diet high in the TAC and decreased odds of PCOS. Similarly with the current study, we previously found a significant negative association between adherence to the antioxidant nutrient pattern and odds of PCOS (15). Furthermore, clinical trials demonstrated the beneficial effects of dietary antioxidants on the PCOS management (26). It was interesting that, Shahrokhi and Naeini (13) and present study are contradictory about the relationship of the zinc and selenium intakes with PCOS. In the present study, we found no significant association between zinc and selenium with the odds of PCOS, while Shahrokhi and Naeini (13) showed dietary selenium and zinc were inversely associated with PCOS at a significant level.

As to the important role of diet in the chronic diseases, examine the general dietary antioxidant intake seems essential, particularly, the different antioxidants proportion of diet in combination with synergistic effects that prevent diseases via several mechanisms. Dietary TAC considers the synergistic interactions of antioxidant nutrients and can be used to assess the relationship between dietary intake and several chronic disorders. Verit et al. (27) found that TAC was the most important prediction element to PCOS. Kanafchian et al. (28) concluded TAC is decreased in the PCOS patients, which may be due to increased oxidative stress. Enechukwu et al. (29) showed that decreased TAC correlates with the cause of PCOS in these patients. However, Ghowsi et al. (30) and Shahrokhi and Naeini (13) found that there were not any significant differences in the serum TAC in the PCOS patients and the healthy control group.

An imbalance between the antioxidant and free radical production in the ovaries can cause negative effects on the oocyte quality, productivity, development, and growth of the placenta (31, 32). Lowered oxidative stress is related to better prognosis of PCOS (33). PCOS can lead to a decrease in the quality of life, especially if it is accompanied by chronic diseases like type 2 diabetes mellitus, obesity, dyslipidemia, hypertension, heart disease in which oxidative stress may intensify complications of these diseases (34). Antioxidants have a relationship with apoptosis in the ovarian tissue via different mechanisms. These are

connected with proper growth and action of interstitial cells (35). Antioxidants, which impede or restrict, the harmful results of oxygen radicals have a vital role in the reproductive system functional and fertility process in the female (36). The dietary approaches to stop hypertension (DASH) diet is featured with using of the high amount of fruit, vegetables and legumes (37). A review study showed that the DASH diet and lower levels of oxidative stress biomarkers are related to each other (38). Obese women with the DASH eating plan are at the risk of the improvement of insulin resistance and inflammatory factors (37). Also, a dietary trigger like glucose can induce oxidative stress and cause an inflammatory response even without excess of adiposity in the PCOS patients. Based on a previous study, Mediterranean-inspired low glycemic load anti-inflammatory diet can improve hormones, body composition, and menstrual cyclicality, metabolic status, and inflammatory factors (39).

Our study has several limitations. Although, the validity and reproducibility of FFQ among Iranians has been well supported, our data may suffer from measurement error. However, we excluded participants that under/over reported their energy intakes. The nature of case-control design with its inherent biases would not allow establishing causation. Since cases were chosen out of a newly-diagnosed PCOS patients, there is less concern about recall bias. Since control group were recruited from the same hospital, similar socioeconomic status, a great element in the developing countries that influence nutritional status/intake can be greatly controlled. In order to control selection bias, we selected our control group of the same clinical center because their participation rate were higher. Residual confounding may not be completely ruled out because of imprecise measurements of covariates. However, there is a small risk that measurement errors in confounders were extreme since the crude and multivariable results were basically similar. Moreover, studies have reported that clinic PCOS patients tend to be more overweight than community PCOS patients, which can significantly affect the severity of PCOS (40). Similarly, the women in our study were more severely affected. We did not match cases and controls for BMI due to overmatching as it could narrow the exposure range.

One of the strengths present study was the high participation rate. When dietary information is obtained at onset of disease, it may not always reflect a typical eating pattern, thus cases may have altered their diet according to their disease symptoms. Therefore, to reduce the possibility of changing the habitual dietary intake, cases were included in the study 3 months prior to the interview. Controls were also free of any major risk factors for PCOS. Another strength was the use of FFQ along with a detailed assessment with adjustment for potential confounders. Compared to a single 24-h dietary recall, the FFQ allowed us to collect rarely consumed food items as well as seasonal variations.

Conclusion

Our results indicated that a high TAC diet plays a role in lowering the odds ratio of developing PCOS, although large prospective studies are needed to expand on these findings.

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Authors' Contributions

G.E., N.S.; Conceptualized and designed the study and wrote the manuscript. G.E., N.S., S.R., M.N.; Analyzed data, interpreted the data, provided professional comments. N.S., S.R., M.N., S.N.M.; Collected data. S.M., S.R., M.N., S.N.M.; Critically revised the manuscript for intellectual content and data accuracy. G.E.; Had responsibility for final content. All of the authors read and approved the final manuscript.

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