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Association between Dietary Inflammatory Index (DII) and the Risk of Polycystic Ovary Syndrome: A Case-Control Study

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ABSTRACT

Background: Polycystic ovary syndrome (PCOS) is an inflammation-related condition and a common metabolic disorder in women at fertility ages. The Dietary Inflammatory Index (DII) is a validated nutritional tool for estimating the inflammatory potential of the diet. It is assumed that a high DII score (indicating a predominantly inflammatory diet) has an association with higher odds of PCOS. The current study aimed to investigate the association between DII and PCOS risk in women. **Methods:** This case-control study was conducted in 2019-2020 on 120 newly-diagnosed PCOS cases and 120 healthy controls aged 18-45 years in Khorramabad, Iran. DII was estimated based on a validated 168-item Food Frequency Questionnaire (FFQ). **Results:** The mean±SD of DII in PCOS patients was 0.40±2.09, while it was 0.45±1.92 in the control group ($P<0.001$). There was a positive association between increasing DII score and the risk of PCOS (odds ratio= 2.41; 95%CI: 1.15-5.02, P for trend =0.006) in the crude model as the fourth quartile was compared with the lowest one. This association was still significant in several models after adjusting for age and energy intake (P for trend <0.001), in the model adjusted for the physical activity level, education status, and family history of PCOS (P for trend=0.003), and also after additional adjustment for BMI (P for trend= 0.003). **Conclusions:** The present study revealed that consuming more pro-inflammatory diets with higher DII scores is related to an increased risk of PCOS.

Keywords: Insulin resistance; Polycystic ovary syndrome; Metabolic diseases; Dietary inflammatory index.

Introduction

Polycystic ovary syndrome (PCOS) is regarded as the most common endocrine and metabolic disorder in women of reproductive age (Lujan *et al.*, 2008). Various risk factors are involved in its incidence; the disease may exist as a genetic

predisposition in a person that is affected by environmental factors such as eating habits, lifestyle, and social status (Beydoun *et al.*, 2009, Fingert *et al.*, 2009, Lujan *et al.*, 2008, Merkin *et al.*, 2011, Moran *et al.*, 2012). This syndrome's

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prevalence is estimated at 4 to 12% worldwide (Meier, 2018). In Iran, however, a community-based survey reported the prevalence of 7.1% according to National Institutes of Health (NIH) (Tehrani *et al.*, 2011). In addition, a systematic review estimated the prevalence of PCOS in Iran to be up to 8.6%, 19.5%, and 41%, according to the NIH and Rotterdam criteria and the ultrasound method, respectively (Sayehmiri *et al.*, 2014). Complications of PCOS include increased risk of reproductive problems such as infertility, decreased ovulation, irregular menstrual cycles, ovarian disorders, and high levels of male hormones such as testosterone that can cause unwanted hair growth and acne, endometrial cancer, and late menopause (Lujan *et al.*, 2008). Further, it affects the quality of life by causing/co-causing depression, low self-esteem, and anxiety, as well as several metabolic disorders, including diabetes with high insulin levels or insulin resistance and cardiovascular disease (CVD) associated with high blood pressure and lipid disorders such as abnormal cholesterol level (Bu *et al.*, 2012, Gluszek *et al.*, 2012, Goodarzi *et al.*, 2012, Pastore *et al.*, 2011).

From a mechanistic point of view, PCOS is a pro-inflammatory condition, and studies manifested that chronic low-grade inflammation predisposes to metabolic abnormalities and ovarian dysfunction (Rudnicka *et al.*, 2021). In this regard, evidence indicates a strong association between hyperandrogenism and inflammation in PCOS subjects (González *et al.*, 2006). In addition, PCOS patients have a genetic predisposition for low-grade chronic inflammation and several pro-inflammatory genotypes, including those encoding tumor necrosis factor (TNF- α) and the TNF receptor type 2, as well as interleukin 6 (IL-6) and its signal transducer, which are related to this syndrome (Deepika *et al.*, 2013). Additionally, excessed serum glucose levels were observed in PCOS patients that induce an inflammatory response by increasing reactive oxygen species (ROS)-induced oxidative stress. Therefore, diet-induced inflammation in PCOS may lead to pro-inflammatory signaling, which is involved in

developing insulin resistance (González, 2012).

The dietary inflammatory index (DII) is a scoring algorithm based on a thorough review of articles published between 1950 and 2010 by Shivappa (Shivappa *et al.*, 2014). This index estimates the capacity of various dietary items on the levels of inflammatory factors such as IL-1 β , IL-4, IL-6, IL-10, TNF- α , and c-reactive protein (CRP) (Vahid *et al.*, 2020). Shivappa *et al.* reported the inflammatory potential of 45 food items (Shivappa *et al.*, 2014). The pro-inflammatory, anti-inflammatory, and neutral food items with scores of 1, -1, and -1, respectively, are regarded as having no impact on the above-mentioned inflammatory factors (Shivappa *et al.*, 2014). This index has been expanding since 2009 and has updated in 2014 (Shivappa *et al.*, 2014). The purpose of creating it was to provide a nutritional tool to evaluate the inflammatory potential of the diet based on the pro-inflammatory and anti-inflammatory properties of various dietary components, including macronutrients, vitamins, minerals, flavonoids, and specific nutrients based on the previous studies on cell culture as well as animal and human studies (Neufcourt *et al.*, 2015, Ruiz-Canela *et al.*, 2015). A high score of DII indicates a pro-inflammatory diet, while a low score indicates an anti-inflammatory diet. This index, whose validity and two dietary evaluation methods have recently evaluated reliability, could predict High-sensitivity (hs)-CRP values greater than 3 mg/l (Shivappa *et al.*, 2014, Vahid *et al.*, 2020).

With regard to the previous studies, a diet with high DII is strongly associated with metabolic syndrome (MetS), hypertension, elevated triglycerides, decreased high-density lipoproteins (HDL), CVD, and increased inflammatory factors (Neufcourt *et al.*, 2015, Neufcourt *et al.*, 2016, Shivappa *et al.*, 2015, Tabung *et al.*, 2015). To our knowledge, no study has been performed on the association between DII and PCOS odds. Therefore, the present study aimed to investigate the association between DII and PCOS in Iranian women. A high DII score (indicating a predominantly inflammatory diet) is associated with

a higher risk of PCOS according to our hypothesis.

Materials and Methods

Study design and Participants: The present incidence-based case-control study investigated 120 newly diagnosed cases of PCOS and 120 healthy controls aged between 18-45 years in Khorramabad, Iran, in 2019-2020. Participants were selected using a consecutive random sampling method. Rotterdam criteria were applied for the diagnosis of PCOS patients (Franks, 2006) and healthy females referring to the same center, hospital or clinics with regular menstruation were considered eligible to be included in the study as control group. The inclusions criteria for both groups were age ranges of 18-45 years, no history of chronic diseases including diabetes, liver, thyroid, CVD, and kidney diseases, not following a special diet, no use of appetite suppressants or anti-obesity drugs, having PCOS with no more than 6 months after its diagnosis for case group (or having PCOS for control group) and no use of insulin and metformin. Individuals with nutrition disorders, following a special diet or exercise for weight loss, smoking, alcohol, and using any multivitamin and mineral supplements were not included in the study. In order to increase the comparability between the study groups, the case and control groups in terms of age (18-30, 31-35, and 36-45 years) and marital status were matched. The effects of other confounding variables, including body mass index (BMI), educational level, physical activity and family history of PCOS were adjusted by including them in the various statistical models.

Dietary intakes: A valid 168-item food frequency questionnaire (FFQ) (Mirmiran *et al.*, 2010) was used to assess the dietary intakes of the study participants. FFQ presents a list of food items and a standard serving size/portion size for each item. Participants reported the frequency of their food consumption during the previous year (frequency of food items on daily, weekly, or monthly intake). Additionally, in order to calculate the DII, it was necessary to have information about the intake of several foods such as spices, including saffron, ginger, turmeric, black pepper,

rosemary, and thyme, which are not available in FFQ. As a result, the interviewees asked additional questions regarding these foods' intake. The questionnaire was completed by face-to-face interview. During the interview, the average size of each food item in the FFQ was explained to participants. Daily intakes (units per day) of total energy, protein, carbohydrates, fiber, total fat, polyunsaturated fatty acids (PUFA), monounsaturated fatty acids (MUFA), and saturated fatty acids (SFA), and food groups were determined. The Nutritionist IV software modified for Iranian foods items was utilized for macro-micronutrient analyses (extractions from the FFQs).

Calculation of DII: The DII was calculated based on the intakes of 45 food parameters obtained from the FFQ. The inflammatory scores, global means, and standard deviations (SD) of the global intake of each nutritional parameter were extracted (Shivappa *et al.*, 2014). To calculate the DII score, these items' energy-adjusted values were first calculated. Then, the values obtained for each variable were subtracted from the corresponding mean global intake and divided by the global SD to obtain the z-score. The acquired z-score was then converted to a centered percentile score in order to reduce skewness, and this percentage score for each food parameter was multiplied by 2 and subtracted from 1. The numbers for each food parameter were multiplied by the corresponding inflammatory score in the next step. Then the inflammatory score of all food parameters was summed to obtain the total DII score for each participant. A higher DII score (more positive) indicates a pro-inflammatory diet, whereas a lower score (more negative) displays an anti-inflammatory diet. The minimum DII score is -8.87, while the maximum score is +7.98 (Shivappa *et al.*, 2014).

In this study, from a total of 45 nutrients, 36 dietary parameters were applied to calculate the DII, containing energy, carbohydrates, protein, total fat, MUFA, PUFA, SFA, cholesterol, omega 3, omega 6, fiber, thiamine, riboflavin, niacin, vitamin B6, folic acid, vitamin B12, vitamin A,

vitamin C, vitamin E, vitamin D, beta-carotene, iron, selenium, zinc, magnesium, caffeine, tea, onion, garlic, turmeric, saffron, pepper, ginger, thyme, and rosemary.

Anthropometric measures: Anthropometric parameters of participating women, including weight, height, waist circumference (WC), hip circumference, and BMI, were measured. Measurements were performed according to standard protocols. Height, without wearing shoes in a standing position, determined using a measuring tape and recorded with an accuracy of 0.1 cm. Weight was measured while the subjects were light clothed and without shoes, using a Seka scale (made in Germany) with an accuracy of 100 g. WC was evaluated using a flexible anthropometric tape the midway between the lowest ribs margin and the iliac crest at the level of the umbilicus with the least possible coverage, and an accuracy of 0.1 cm. The hip circumference was measured using a flexible anthropometric tape in the widest part of the pelvis with the least possible coverage. In addition, BMI was calculated by dividing weight by height squared (kg/m^2).

Measurements of other variables: A general questionnaire was used to collect additional variables such as socioeconomic status, including age, education, occupation, monthly income, marital status, drug use (any types of drugs), and intake of nutritional supplements (minerals, vitamins). The data related to physical activity were collected using the International Physical Activity Questionnaire (IPAQ) (Moghaddam *et al.*, 2012, Vasheghani-Farahani *et al.*, 2011).

Ethical considerations: All participants signed a written informed consent before data collection. The ethics committee of Lorestan University of Medical Sciences approved the protocol and design

of the study with the ethics code of IR.LUMS.REC.1398.058.

Data analysis: Mean values were compared according to the Student's t-test, and the means of more than two groups' values were assessed using analysis of variance (ANOVA). The chi-square test was utilized for comparing the distribution of categorical variables. Multivariable regression models were applied to estimate odds ratios (ORs) and 95% confidence intervals (CIs) which were adjusted for multiple covariates in various models. DII scores were analyzed as quartiles. Statistical tests were performed using SPSS software (SPSS 21). The P-values <0.05 were considered statistically significant.

Results

In the current study, the DII ranged between -4.66 (most anti-inflammatory diet) and +5.6 (most pro-inflammatory diet). The characteristics of 240 participants, consisting of 120 cases with PCOS and 120 controls, are demonstrated in **Table 1**. The mean age of the participants was 31.9 ± 6.9 years, and for women in the control group was 32.9 ± 6.1 years. Significant differences were observed in physical activity level (cases 1097.6 ± 256.0 vs. controls 1503.8 ± 484.0 , $P=0.001$), energy intake (cases 3220.1 ± 856.0 vs. controls 2933.6 ± 873.0 , $P=0.01$), and DII scores (cases 0.40 ± 2.00 vs. controls -0.45 ± 1.92 , $P=0.001$) between case and control groups, respectively. Patients were more likely to have a positive family history of PCOS compared to controls ($P \leq 0.001$). Participants' characteristics among categories of DII are illustrated in **Table 2**. There were significant differences across DII categories in energy intake and education level, and participants in the fourth quartile of DII have more energy intake.

Table 1. Characteristics of study participants in term of study groups.

Variables	Case (n=120)	Control (n=120)	P-value ^b
Age (years)	31.9±6.9 ^a	32.9±6.1	0.23
Energy intake (kcal)	3220.1±856.0	2933.6±873.0	0.01
Body mass index (kg/m ²)	25.7±3.6	25.3±4.1	0.48
Dietary Inflammatory Index (DII)	0.40±2.09	-0.45±1.92	0.001
Physical activity (Met-Min/Week)	1097.6±256.	1503.8±484.0	0.001
Family history of polycystic ovary syndrome	n(%)	n(%)	
Yes	27(22.5)	2(1.7)	< 0.001
No	93(77.5)	118(98.3)	
Education level			0.26
No formal education	1(66.7)	2(33.3)	
Under Diploma	18(45.0)	22(55)	
Diploma	55(57.3)	41(42.7)	
Post Diploma	45(44.6)	56(55.4)	
Marital status			1.00
Married	107(50.0)	107(50.0)	
Single	13(50.0)	13(50.0)	

PCOS: Polycystic ovary syndrome; ^a: Mean±SD; ^b: Continuous variables were evaluated using t-tests. Categorical variables were evaluated using Chi-square tests.

Table 2. Participant characteristics by the level of the dietary inflammatory index (DII).

Variables	Q1	Q2	Q3	Q4	P-value ^b
	DII≤-1.68	-1.68<DII<-0.2	-0.2≤DII<1.5	DII≥1.5	
Case/Control participants	23/37	26/34	35/25	36/24	0.03
Age (years)	31.9±6.9 ^a	33.6±5.8	32.7±6.1	31.4±7.1	0.27
Energy intake (kcal)	3047.8±1113.6	2738.3±712.8	3060.8±927.0	3460.6±813.0	<0.001
Body mass index (kg/m ²)	25.4±3.3	26.0±4.0	25.3±3.7	25.2±3.9	0.69
Family history of PCOS	n(%)	n(%)	n(%)	n(%)	
Yes	4(13.8)	7(24.1)	6(20.7)	12(41.4)	0.14
No	56(26.5)	53(25.1)	54(25.6)	48(22.7)	
Education level					0.007
No formal education	0(0.0)	0(0.0)	0(0.0)	3(100)	
Under Diploma	9(22.5)	9(22.5)	7(17.5)	15(37.5)	
Diploma	18(18.8)	22(22.9)	32(33.3)	24(25.0)	
Post Diploma	33(32.7)	29(28.7)	21(20.8)	18(17.8)	
Marital status					0.67
Married	52(24.3)	55(25.7)	55(25.7)	52(24.3)	
Single	8(30.8)	5(19.2)	5(19.2)	8(30.8)	

PCOS: Polycystic ovary syndrome; DII: Dietary inflammatory index; ^a: Mean±SD; ^b: ANOVA was used for continuous variables, and Chi-square was used for categorical variables.

Multivariable regression models (ORs and 95% CIs) for the odds of PCOS are presented in **Table 3**. When the energy-adjusted DII (E-DII) score was fit as a continuous variable, the crude model results uncovered a positive association between increasing DII score and odds of PCOS (OR= 1.23, 95% CI: 1.08-1.41; *P* for trend=0.006). Moreover, identical results were observed when modeling the

DII as quartiles. After adjusting for age and energy intake in model 1, the OR for the highest quartile in comparison with the lowest quartile was 3.05 (95% CI: 1.4-6.63; *P* for trend<0.001). Moreover, in the second model and after adjusting for the physical activity level, education, and family history of PCOS along with the first model, the results were identical to the model 1 (OR quartile 4

vs. quartile 1=2.79, 95% CI: 1.23-6.3; *P* for trend=0.003). Further, additional adjustment for BMI in model 3 manifested the same results (OR

quartile 4 vs. quartile 1=2.81, 95% CI:1.25-6.4; *P* for trend=0.003).

Table 3. Odds Ratios and 95% Confidence Intervals for the association between DII and polycystic ovary syndrome.

Model	Dietary inflammatory index (quartiles)				P-value for trend	DII (Continuous)
	Q1	Q2	Q3	Q4		
	DII≤-1.68	-1.68<DII≤-0.2	-0.2≤DII≤1.5	DII≥1.5		
Crude	1.0	1.23(0.59,2.55) ^a	2.25(1.08,4.67)	2.41(1.15,5.02)	0.006	1.23(1.08,1.41)
Model I	1.0	1.13(0.53,2.41)	2.42(1.14,5.10)	3.05(1.40,6.63)	0.001	1.3(1.14,1.51)
Model II	1.0	1.02(0.47,2.10)	2.16(0.99,4.70)	2.79(1.23,6.30)	0.003	1.27(1.09,1.47)
Model III	1.0	1.01(0.47,2.10)	2.1(1.0, 4.70)	2.8(1.25,6.40)	0.003	1.28(1.09,1.49)

DII: Dietary inflammatory index; Model I: Adjusted for energy intake and age. Model II: Model I plus physical activity, education level, and family history of PCOS. Model III: Model II plus body mass index; ^a: Odds ratio (95% confidence interval).

Discussion

This case-control study evaluated the association between dietary-induced inflammation, measured by the DII, and odds of PCOS. Based on the results, PCOS patients had more pro-inflammatory diets (with higher DII scores) than the control group. With regard to the reports, the odds of PCOS in participants who consume a predominantly inflammatory diet (higher DII score) are approximately 2.8 times higher than ones who consume a mainly anti-inflammatory diet (lower DII score). This result is consistent with several studies assessing the association between DII and other inflammatory diseases. For instance, Kim *et al.* concluded that higher DII scores are positively related to the increased odds of hyperglycemia and central obesity in men and post-menopausal women (Kim *et al.*, 2018). Another study on type 2 diabetic patients revealed that the odds of diabetes were tripled in patients with the highest quintile of DII compared to the lowest one (Denova-Gutiérrez *et al.*, 2018). However, in a study in Iran, although the CRP level was significantly more in the higher DII tertiles, it was not associated with DII scores after adjusting for confounding factors such as BMI and physical activity level (Vatandoost *et al.*, 2020). One of the most common manifestations of PCOS is insulin resistance and resulting hyperinsulinemia, affecting nearly 50-70% of these patients. This situation can trigger hyperandrogenism and lead to

chronic oligo- or anovulation via elevating pro-inflammatory markers (Rosenfield and Ehrmann, 2016). Pro-inflammatory cytokines secreted from adipose tissue can induce insulin resistance by increasing the phosphorylation of serine/threonine residues in the docking protein insulin receptor substrate-1 (Shoelson *et al.*, 2006). On the other hand, inflammatory markers such as TNF- α can cause insulin resistance in visceral tissues by activating c-Jun N-terminal kinase 1 and 2 (Vázquez-Carballo *et al.*, 2013). Epidemiological studies have proved that insulin resistance could increase the risk of cardiovascular diseases (Chen *et al.*, 2011, Saboori *et al.*, 2016). Furthermore, it is related to an increased incidence of some neoplasms, including breast, colorectal, and prostate cancers (Cowey and Hardy, 2006, Saboori *et al.*, 2019). PCOS is a low-grade inflammatory disease, and pro-inflammatory markers, including IL-6 and TNF- α , are increased in these patients, which can induce hyperandrogenism observed in the PCOS patients (Kaya *et al.*, 2010, Repaci *et al.*, 2011).

The evidence recommends that diet can influence inflammation by its diverse effects on the secretion of pro-inflammatory and anti-inflammatory markers. For instance, the western diet, characterized by high levels of red meat and refined grains consumption, has pro-inflammatory effects, while adopting a Mediterranean dietary pattern with levels of fruit, vegetables, and whole

grains could reduce inflammation (Schwingshackl and Hoffmann, 2014). In addition, the current study exhibited that choosing a more inflammatory diet characterized by a high DII score had a close relationship with an increased risk of PCOS disease. This association remained significant after adjusting for several confounding factors, including energy intake, physical activity, BMI, and family history of PCOS, which uncovers the profound effects of diet on the incidence of inflammation-related diseases.

To the best of our knowledge, this is the first study that assesses the association between DII and PCOS. Another benefit of this study was utilizing a authenticated FFQ to thoroughly examine the participants' dietary intakes. However, it should be mentioned that using FFQ might increase recall bias, as its results depend on the respondents' memory. Another limitation of this study was the number of participants, which was relatively low for these types of studies. Although, the promising results of this small study can be beneficial and strategic for future studies. Therefore, studies with high sample size and prospective designs seem to be essential to confirm our results.

While this study provides valuable insights into the association between DII and polycystic ovary syndrome, several limitations should be acknowledged. The relatively small sample size and cross-sectional design limit the generalizability and ability to establish causality. Additionally, the use of self-reported data and potential recall bias in dietary assessment pose challenges to the validity of the findings. However, the study's strengths lie in its novelty as the first investigation of its kind, validated dietary assessment methods and adjustment for relevant confounders. Overall, while these limitations warrant cautious interpretation, the study contributes valuable insights into the role of dietary inflammation in PCOS development, suggesting avenues for further research and potential dietary interventions.

Conclusions

The results of the present study illustrated that consuming more pro-inflammatory diets with

higher DII scores is associated with an increased risk of PCOS. The results continued to be significant after adjusting for confounding factors, including BMI and physical activity level, indicating the use of more dietary-related anti-inflammatory food items such as fatty fish, turmeric, green tea and limiting dietary intake of pro-inflammatory food items such as sugars, trans fats, fried foods, for prevention and/or control of PCOS.

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Conflict of interests

The authors declare no conflict of interest concerning this manuscript.

Authors' contributions

Saboori S: designing the study and Supervision; Kavei P: sampling and data collection; Birjandi M, Saboori S, and Yousefi Rad E: Data analysis and/or interpretation; Kavei P, Akbari S, and Saboori S: drafting the manuscript; Falahi E, Vahid F, and Hebert J: revising the article for important intellectual content. All authors have approved the final manuscript.

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