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Association between dietary atherogenic index and risk of polycystic ovary syndrome: A case-control study in Tehranian women

Parisa Navidgouei [1], Behnood Abbasi [1*], Sedigheh Hosseini [2]

[1] Department of Nutrition, Electronic Health and Statistics Surveillance Research Center, Science and Research Branch. Islamic Azad University, Tehran, Iran
[2] Preventive gynecology research center (PGRC), Shahid Beheshti University of Medical Sciences, Tehran, Iran

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ABSTRACT

Polycystic ovary syndrome is a heterogeneous disorder with various clinical manifestations, including impaired glucose metabolism, insulin resistance, and dyslipidemia. Since dietary fatty acids might have a remarkable role in the progression and development of these disorders, we conducted the present study to evaluate the association between atherogenic index and polycystic ovary syndrome. Our case-control study was performed on 494 individuals, including 203 women with polycystic ovary syndrome and 291 healthy women in Taleghani Hospital, Tehran, Iran, in July 2019. Demographic data and anthropometric indices, including height, weight, and waist circumference, were gathered by a trained expert. A valid semi-quantitative food-frequency questionnaire was used for dietary intake assessment. An empirical formula calculated the atherogenic index. In case and control groups, participants had a mean age of 28.98±5.43 and 30.15±6.21 years. There was no significant trend in total fat, cholesterol, saturated fatty acids, trans fatty acid, MUFA, linoleic, and linolenic fatty acids intake through atherogenic index quartiles ($p>0.05$). However, we observed that PUFA intake decreased through atherogenic index quartiles significantly ($p=0.034$). In addition, there was no significant association between the atherogenic index of diet and polycystic ovary syndrome risk. To sum up, we found no relationship between atherogenic index and polycystic ovary syndrome risk. More studies are needed to prove our findings.

1. Introduction

Polycystic ovarian syndrome (PCOS), as a low-grade chronic inflammation and the most prevalent endocrine abnormality, affects 5-10 percent of women worldwide of child-bearing age (1-3). PCOS is a disorder with an imbalance of sex hormones, which results in impaired menstrual cycle and blocked ovulation and is also associated with substantial metabolic defects such as obesity, metabolic syndrome, insulin resistance, and so on (4, 5). Based on Rotterdam criteria, 7 percent of Iranian women of reproductive age suffer from PCOS (6). Even though PCOS is a syndrome with an unknown etiology, genetic susceptibility, inflammatory state, and oxidative stress are explained as potential mechanisms affecting PCOS pathophysiology (7). This heterogeneous disorder has several clinical manifestations, including dermatological complications, depression, abdominal obesity, abnormal glucose metabolism, insulin resistance (IR), and dyslipidemia, which might lead to cardiovascular disease and impaired insulin sensitivity eventually (8-10). Pharmaceutical interventions and lifestyle modification strategies, such as increased physical activity and proper nutrition recommendations, are proposed to ameliorate PCOS complications (11). Diet is essential in modifying metabolic disorders, especially insulin resistance (12). Calorie restriction, low carbohydrate-ketogenic diet (LCKD), antioxidant supplementation, and desirable dietary fatty acids have been associated with improved endocrine characteristics in PCOS (12-14). The atherogenic index (AI) is an indicator of dietary fat quality and is directly related to the AI of plasma. Therefore, it might affect BMI, CVD risk, and lipid abnormalities (15). Dietary fatty acids might have a remarkable role in the progression and development of chronic disorders and metabolic diseases. To calculate diet AI,

*Corresponding author: Department of Nutrition, Electronic Health and Statistics Surveillance Research Center, Science and Research Branch. Islamic Azad University, Tehran, Iran.

E-mail address: abbasi.b@srbiau.ac.ir (Behnood Abbasi).

different fatty acids should be evaluated. In this regard, it should be noted that omega-6 polyunsaturated fatty acids (PUFA), such as linoleic acid (LA) (18:2n – 6) are appreciated for their anti-atherogenic properties (16). Numerous studies have confirmed the anti-thrombogenic action of omega-3 PUFA, including eicosatetraenoic acid (EPA) and docosahexaenoic acid (DHA), which regulate platelet adhesion, improve endothelial function, modify dyslipidemia, decrease inflammation, and reduce insulin resistance (16, 17, 18, 19). In addition, monounsaturated fatty acid (MUFA) has been recommended due to its role in managing body weight and attenuating pancreatic inflammation and cardiovascular disease risk (16, 20, 21). On the other hand, evidence has shown that saturated fatty acids (SFA) trigger the toll-like receptor 4 (TLR4) signaling pathway and promote inflammation by increasing the expression of cyclooxygenase 2 (COX2) and nuclear factor kappa B (NF-κB) (22, 23). Since dietary fatty acids may have an essential role in the pathogenesis of PCOS by affecting inflammation and insulin resistance, and there is limited evidence around this issue, in this context, we aimed to evaluate AI of diet in PCOS and healthy volunteers in a case-control design.

2. Materials and methods

2.1. Study design

This study was conducted in Taleghani Hospital, Tehran, Iran, between July 2019 and December 2019. To increase study power, the number of participants in the control group was considered 1.5 times more than the case group, and finally, 494 women, including 203 women with PCOS and 291 healthy women, participated in this case-control study. The study protocol was approved by the Islamic Azad University, Tehran, Iran's ethical committee (IR.IAU.SRB.REC. 13988.028), and all participants filled out the written informed consent. Patients were selected based on having 2 out of 3 indicators of Rotterdam criteria, including oligomenorrhea and/or anovulation, biochemical and/or clinical signs of hyperandrogenism and polycystic ovaries, by a gynecologist (24). Women outpatients with PCOS aged 18 to 45 years were recruited in the study, and those with hyperprolactinemia, hypothyroidism, Cushing's syndrome, liver and adrenal malignancies, hormone therapy, birth control drug intake, smoking and alcohol abuse were not qualified to enter the study. The criteria for selecting participants in the control group were healthy subjects with a Freeman-Galloway score < 8 and regular menstruation period.

2.2. Participant's characteristics

A trained nutritionist prepared a detailed questionnaire to obtain demographic data about age, marital status, educational degree, family history of PCOS and other diseases, and anthropometric indices, including height, weight, and waist circumference. Height was measured with an inelastic tape with an accuracy of 0.1 cm, and weight measurement was done using the SECA scale made in Germany with an accuracy of 100 grams (25). Waist circumference was measured with a flexible tape meter with an accuracy of 0.1 cm above the iliac crest in the narrowest area (25). To calculate body mass index (BMI), weight (kg) was divided by the square of the height (m) (25). The physical activity assessment was done using an IPAQ questionnaire; on this basis, physical activity was reported as MET minutes per day (26).

2.3. Assessment of dietary fatty acid index

A valid semi-quantitative food-frequency questionnaire (FFQ) that included 147 food items was used for dietary intake assessment during the past 12 months on a daily, weekly, and monthly basis (27). After recording food frequency, values were converted to grams by Nutritionist IV software (First Databank, San Bruno, CA, USA). An empirical formula calculated the fat quality index. The atherogenic index formula was a correlation between the saturated and unsaturated fatty acids. Total saturated fatty acids were the sum of Lauric acid (C12:0), Myristic acid (C14:0), and Palmitic acid (C16:0), which were divided by unsaturated fatty acids, including total amounts of MUFA, Omega-6 and Omega-3 polyunsaturated fatty acids (15).

$$AI = [(4\times C14:0) + C16:0+C18:0] / [\sum MUFA + \sum PUFA – n6 + \sum PUFA – n3]$$

2.4. Statistical analysis

Statistical analysis was performed using SPSS version 21.0 (SPSS Inc., USA). Quantitative variables were expressed as mean ± standard deviation (SD), while categorical variables were presented as percentages. Independent sample t-tests and chi-square tests were used for comparing quantitative and qualitative data, respectively. Analysis of Variance (ANOVA) was employed to assess differences among quartile means. Logistic regression models were utilized to calculate odds ratios (ORs) with corresponding 95% confidence intervals (CIs), using the first quartile of the Atherogenic Index (AI) as the reference in multivariate models. Two regression models were constructed, adjusting for various confounding factors: Model 1 included age (years), BMI (kg/m²), energy intake (kcal), body weight (kg), and waist circumference (cm); Model 2 further adjusted for educational status, marital status, physical activity, and intake of multivitamin-mineral, folic acid, omega-3, and vitamin D supplements. Statistical significance was set at $p<0.05$.

3. Results

Table 1 illustrates case and control groups' demographic, anthropometric, and dietary assessments. Participants had a mean age of 28.98 ± 5.43 and 30.15 ± 6.21 in case and control groups, respectively. Comparing marital and educational status, 26 and 52.6 percent of participants in the case and control groups were single, and 54 and 83 percent of individuals in case and control groups had university degrees. As shown in Table 1, all anthropometric indices, including

body weight, BMI, and WC, were significantly higher in the case group compared to controls (p<0.001, p<0.001, and p=+0.006, respectively). However, the control group subjects had higher physical activity levels (1996.65 ± 1258.03 MET-min/d, p<0.001). Comparable differences were found between case and control groups in carbohydrate and fiber intake, with higher gram per day intake in the case group (p=0.038 and p<0.001). No remarkable difference was seen in multivitamin-mineral and NSAID intake between both groups, although a higher percentage of individuals in the control group had omega-3 supplement consumption (p=0.03). As Table 2 presents, there is no significant trend in total fat between AI quartiles (p=0.061). Also, no significant difference was seen in cholesterol, saturated fatty acids, trans fatty acids, MUFA, linoleic, and linolenic fatty acids intake by grams when comparing the first quartile to the fourth quartile (p>0.05). However, we observed that PUFA intake decreased significantly through AI quartiles (p=0.034). According to the findings of Table 3 and reported odds ratios and 95% confidence intervals, no significant association was seen between AI score and PCOS risk (p>0.05). Also, no significant relationship was seen in regression models 1 and 2 (p=0.408 and p=0.380), after adjustment for age, BMI, energy, weight, WC, educational status, marital status, physical activity, taking the multivitamin-mineral supplement, folic acid, omega-3, and vitamin D supplement consumption.

Table 1. General characteristics of study participants.

Variable	Case (n=203)	Control (n=291)	P-value
Age (years)	28.98 ± 5.43	30.15 ± 6.21	0.029*
Marital status (single), n (%)	53 (26.1)	153 (52.6)	<0.001*
Educational status (university degree), n (%)	110 (54.1)	242 (83.2)	<0.001*
Body weight (kg)	67.91 ± 13.14	63.79 ± 10.51	<0.001*
BMI (kg/m^2)	25.74 ± 5.44	23.65 ± 3.90	<0.001*
WC (cm)	87.21 ± 43.38	79.92 ± 9.68	0.006*
Physical activity (MET-min/d)	1638.97 ± 572.95	1996.65 ± 1258.03	<0.001*
Total energy (kcal/d)	2500.07 ± 696.19	2388.03 ± 657.88	0.070
Carbohydrate (g/d)	344.10 ± 95.78	326.06 ± 93.83	0.038*
Protein (g/d)	86.17 ± 28.89	88.26 ± 27.96	0.421
Fat (g/d)	92.49 ± 36.18	86.98 ± 33.15	0.081
Dietary fiber (g/d)	44.73 ± 23.47	38.01 ± 18.21	<0.001*
Multi vitamin-mineral intake, n (%)	34 (16.7)	70 (24.1)	0.050
Omega 3 supplement intake, n (%)	7 (3.4)	24 (8.2)	0.030*
NSAID intake, n (%)	71 (35.1)	108 (37.2)	0.635

BMI: body mass index, WC: waist circumferences. Values reported as a mean ± standard deviation for quantitative variables and as number (percentage) for qualitative variables. p<0.05 considered significant.

Table 2. Dietary intake of fatty acids based on AI quartiles.

	AI				
Variable	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P-value
Total fat (gr)	93.81 ± 33.89	90.79 ± 27.57	91.05 ± 36.91	92.37 ± 37.07	0.061
Cholesterol (mg)	314.90 ± 121.68	321.63 ± 134.70	298.63 ± 149.53	312.50 ± 123.13	0.815
Saturated fat (g)	25.79 ± 9.18	26.02 ± 11.85	26.82 ± 10.41	26.08 ± 14.50	0.112
Trans fatty acid (g)	0.0003 ± 0.0007	0.0007 ± 0.0002	0.0004 ± 0.001	0.0005 ± 0.001	0.332
MUFA (g)	31.23 ± 14.66	30.58 ± 13.95	30.60 ± 9.66	31.80 ± 11.91	0.539
PUFA(g)	25.58 ± 11.81	22.30 ± 8.11	18.92 ± 5.35	16.56 ± 4.79	0.034*
Linoleic fatty acid (g)	22.47 ± 10.85	22.31 ± 7.30	21.18 ± 4.65	23.89 ± 4.22	0.083
Linolenic fatty acid (g)	1.46 ± 0.90	1.28 ± 0.65	1.25 ± 0.52	1.41 ± 0.49	0.093

AI: atherogenic index. MUFA: mono-unsaturated fatty acids. PUFA: poly-unsaturated fatty acids. Values reported as a mean ± standard deviation. p<0.05 considered significant.

Table 3. The association of AI score with the risk of polycystic ovary syndrome.

AI	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P-value
Crude	1	2.83 (1.69- 4.75)	2.74 (1.75- 4.93)	2.95 (2.13- 5.13)	0.129
Model 1	1	2.81 (1.64- 4.79)	2.98 (1.74- 5.11)	2.97 (2.03- 5.18)	0.408
Model 2	1	2.35 (1.29- 4.30)	2.45 (1.37- 4.75)	2.37 (1.54- 5.33)	0.380

AI: atherogenic index. Data are odds ratio and 95% confidence interval. Logistic regression models were used: Model 1: Adjusted for age (yr) and BMI (Kg/m2) and energy (kcal). Model 2: Additional adjustment for weight, waist circumferences, educational status, marital status, physical activity, taking multivitamin-mineral supplement, folic acid supplement, omega-3 supplement and vitamin D supplement. P< 0.05 considered significant.

4. Discussion

There is a lack of literature about AI assessment of diet in PCOS women. In this regard, we conducted the present study to determine if AI poses an independent risk factor for PCOS. Our case-control study demonstrates that more PUFA is associated with lower AI. However, we didn't find a significant relationship between AI and PCOS risk. Based on evidence, women with PCOS had a higher risk of cardiovascular diseases and, on average, had lower levels of HDL cholesterol, higher non-HDL cholesterol, and triglyceride levels (28). As Patel et al. indicate in their animal study, a high-fat diet results in metabolic complications and hormone disturbances similar to changes in PCOS patients, including glucose intolerance,

hyperinsulinemia, hyperandrogenism, increased thickness of the follicular wall, and number of cystic follicles (29). Although we didn't find significant results, several studies have demonstrated an association of plasma AI with metabolic disturbances. A meta-analysis by Zhu et al. (30) explores the relationship between lipid parameters and the risk of type 2 diabetes mellitus (T2DM). Moreover, two cross-sectional studies by Cai et al. (31) and Fernández-Macías et al., (32) report a strong relationship between AI and coronary artery disease and CVD events. Also, Wang et al. believed that AI can be used as an auxiliary tool for non-alcoholic fatty liver disease diagnosis in obese individuals (33). In addition, Qin et al. (34) express AI of plasma as a comprehensive indicator for managing dyslipidemia in patients with T2DM. Although various studies are available assessing the AI of plasma, there is a limited number of studies regarding the AI of diet concerning different aspects of health. We failed to find an association between dietary AI and fatty acid intake, except for PUFA. Although the relationship between cardiovascular diseases and cholesterol intake is controversial, some evidence revealed that higher cholesterol intake increases serum cholesterol levels in susceptible responders. However, dietary cholesterol did not affect normal individuals (35, 36). In a study by Zhu et al. (37), dietary cholesterol was reported as an indicator of dyslipidemia and remarkably increased serum cholesterol levels. Women with PCOS have heightened cardiovascular risks, and a decrease in SFA intake ameliorates cardiovascular complications (38). In addition, there is a novel mechanism by which SFA causes insulin signaling impairments due to the expression of miRNAs (39). Furthermore, SFAs contribute to de novo lipogenesis in the liver and cause insulin resistance (40). Sekar et al. indicate that SFA develops metabolic syndrome (41). It was previously reported by Kasim-Karakas et al. (42) that cis fatty acids, compared to trans fatty acids, had improved hormonal and metabolic indicators in women with PCOS. In line with this finding, trans fatty acids had detrimental effects on ovulation by lowering peroxisome proliferator-activated receptors γ (PPAR) activity (43, 44). Since we failed to find a significant relationship between fatty acids intake and AI, future well-designed studies with larger sample sizes are recommended. Our study has shown an inverse association between PUFA and AI. In a survey by Barrea et al., adherence to the Mediterranean diet was evaluated in women with PCOS, and based on their results, individuals with PCOS had a higher quantity intake of SFA and lower intake of PUFA and MUFA compared to controls (45). PUFAs have been proven to be effective in lowering both triglyceride and VLDL concentrations through suppression of sterol regulatory element binding protein 1 (SREBP-1) expression and elevation of fatty acid oxidation by activating peroxisome proliferator-activated receptor (PPARa) (46). Gonza´lez-Pe´riz's (47) findings in an animal study showed that omega-3 PUFAs had beneficial effects in ameliorating hepatic steatosis and obesity-induced insulin resistance. Also, Derosa et al. (48) indicate that 3 grams of omega-3 consumption in overweight and obese participants with impaired fasting glucose reduced hyperglycemia and might have an effect in preventing the progression of type 2 diabetes. Furthermore, Yahay et al. (49) investigated the effect of canola and olive oil consumption compared to sunflower oil in PCOS women. Based on the results, canola oil consumption improves liver function, lipid profile, and HOMA-IR compared to olive and sunflower oils. The possible explanation for canola oil's beneficial effects includes high MUFAs, ALA, and lower n6/n3 PUFA (50). Moreover, a study by Maki et al. showed that corn oil, as a rich source of linoleic acid, improves lipoprotein profile vs olive oil (51). Some available data claimed that dietary intake and circulating status of LA negatively correlate with cardiovascular risk factors, mainly based on cholesterol-lowering effect and improving glucose metabolism (52). In total, the composition of the macronutrients in the diet, especially fatty acids, may play an essential role in modifying several aspects of life, so evaluating fatty acids indices, including AI, should be of interest. As Moussavi Javardi et al. (15) propose, there is a direct association between dietary AI and AI of plasma in overweight/obese volunteers compared to normal participants. Clinicians should be aware of these associations and consider them in further studies. The current study is the first to explore the association between AI of diet and PCOS, with a relatively large sample size. In addition, we used multiple logistic regression models with adjustment of several confounding factors, which are considered strengths of our study. However, the present study has potential limitations. We were unable to assess the lipid profiles of participants due to financial constraints. Moreover, we were unable to find a causal relationship due to the design of our study, and the risk of recall bias is always probable due to using FFQ.

5. Conclusion

Our findings indicated no significant association between dietary AI and PCOS risk. However, more studies are needed to help make nutritional recommendations for alleviating this disease's complications. In conclusion, our study found no significant association between dietary atherogenic index (AI) and the risk of polycystic ovary syndrome (PCOS). However, we observed an inverse relationship between polyunsaturated fatty acid (PUFA) intake and AI, suggesting the potential benefits of PUFA consumption. While our findings do not support the use of AI as an independent risk factor for PCOS, they highlight the complex relationship between dietary fat composition and metabolic health in women with PCOS.

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