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Association of dietary phytochemical index with metabolic markers, serum asymmetric dimethylarginine and atherogenic indices in patients with polycystic ovary syndrome

Farshad Amirkhizi[1], Mahdiyeh Taghizadeh[2], Soudabeh Hamedi-Shahraki[3*†] and Somayyeh Asghari[2*†]

Abstract

Background Polycystic ovary syndrome (PCOS) is associated with an increased risk of cardiovascular diseases (CVD). Plant-based diets are associated with reduced CVD risk factors. This study aimed to explore the associations between dietary phytochemical index (DPI) and asymmetric dimethylarginine (ADMA), lipid profile, atherogenic indices, and other metabolic biomarkers in women with PCOS.

Methods In this cross-sectional study, 150 females aged 18–45 years diagnosed with PCOS were recruited. An interviewer-administered questionnaire was applied to gather the relevant demographic characteristics, detailed clinical information, and lifestyle habits of participants. A validated semi-quantitative food frequency questionnaire was used to assess dietary intake, and DPI was calculated accordingly. We used multiple linear regression to determine the association between serum concentrations of ADMA, total testosterone, sex hormone-binding globulin (SHBG), fasting serum glucose (FSG), insulin, and lipid profile, as well as atherogenic indices across quartiles of DPI.

Results There was a negative correlation between the DPI and serum levels of ADMA (p-trend = 0.022), triglycerides (TG) (p-trend = 0.003), oxidized low-density lipoprotein cholesterol (ox-LDL) (p-trend = 0.001), insulin (p-trend = 0.045) and Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) (p-trend = 0.018). Moreover, there was a tendency for visceral adiposity index (VAI) (p-trend = 0.005) and atherogenic index of plasma (AIP) (p-trend = 0.001) to decrease as the quartile categories of DPI increased. No significant regular trend was found for serum levels of FSG, SHBG, total testosterone, other lipid profiles, and lipid accumulation product (LAP).

Conclusions These findings suggest that adherence to a phytochemical-rich diet decrease the CVD risk factors in PCOS patients.

†Somayyeh Asghari and Soudabeh Hamedi-Shahraki contributed equally to this work and were the co-corresponding authors.

*Correspondence:
Soudabeh Hamedi-Shahraki
s.hamedy1@gmail.com
Somayyeh Asghari
asghari.nut@gmail.com; sasghari@sina.tums.ac.ir

Full list of author information is available at the end of the article

Keywords Polycystic ovary syndrome, Dietary phytochemical index, Atherogenic indices, Asymmetric dimethylarginine

Introduction

Polycystic ovary syndrome (PCOS) is a multifaceted hormonal and metabolic disorder that affects 5–20% of women of reproductive age [1, 2]. This condition presents with various clinical and metabolic manifestations including hyperandrogenism, obesity, glucose intolerance, hirsutism, acne, and raised androgens with irregular menses and infertility [3].

Although the precise mechanisms remain largely unknown, insulin resistance and hyperandrogenism are the key contributors to its pathogenesis [4]. The presence of insulin resistance, coupled with the high prevalence of abnormal fat distribution, known as visceral adiposity in women with PCOS, increases the risk for atherogenic dyslipidemia, inflammation, oxidative stress, type 2 diabetes, hypertension, and ultimately cardiovascular disease (CVD) [5–8]. Given the challenges associated with the accessibility and expense of scanning methods, novel measurements like the visceral adiposity index (VAI) and lipid accumulation product (LAP) have emerged as promising tools for predicting PCOS-related subclinical atherosclerosis and insulin resistance [7]. On the other hand, atherogenic dyslipidemia, characterized by high triglycerides (TG) and a high low-density lipoprotein cholesterol to high-density lipoprotein cholesterol (LDL-C/HDL-C) ratio, is linked to increased CVD risk [9, 10]. The atherogenic index of plasma (AIP), derived from the logarithm of the ratio of TG to HDL-C, serves as a useful tool in evaluating CVD risk factors [10].

Most cardiovascular risk factors have been suggested to negatively affect endothelial function through common pathogenic pathways that result in increased asymmetric dimethylarginine (ADMA) accumulation [11]. As a competitive endogenous inhibitor of nitric oxide (NO) synthase isoforms, ADMA reduces the production of NO [12]. Consequently, it impairs endothelial function and promotes atherosclerosis [13]. Multiple studies have identified ADMA as a novel and powerful risk predictor of CVD, surpassing traditional risk factors [14, 15]. Studies have demonstrated that individuals with atherosclerosis, chronic heart failure [16, 17], hypertension [18], hypercholesterolemia [19], and diabetes mellitus [20], as well as women with PCOS [21], exhibit elevated levels of ADMA [22]. Notably, oxidative stress is linked to increased ADMA production and decreased ADMA metabolism [18].

Phytochemicals are chemical compounds found abundantly in plant-based foods, have garnered significant attention in recent years for their potential health benefits [23]. Regular consumption of phytochemicals has been linked to a reduced risk of various chronic inflammatory diseases, attributed to their powerful antioxidant and anti-inflammatory properties [24]. A practical tool to measure the phytochemical content of a diet is the dietary phytochemical index (DPI), developed by McCarty et al.., which calculates the proportion of daily energy intake derived from phytochemical-rich foods [25]. Multiple studies have demonstrated that higher DPI scores are associated with a reduced risk of chronic illnesses, including but not limited to obesity, metabolic syndrome, type 2 diabetes mellitus, cancers, and CVD [26–29]. Early detection and management of atherosclerosis risk factors in patients with PCOS can help protect these patients from CVD. To the best of our knowledge, no study has been conducted previously to investigate the association of DPI with metabolic markers, serum ADMA, and atherogenic indices in patients with PCOS. Therefore, our study aims to fill this gap in the literature by examining the potential relationship between DPI and these metabolic markers in patients with PCOS.

Methods

Study design and participants

This cross-sectional study was conducted from October 2022 to June 2023 on a population of 150 women, aged 18 to 45, living in the city of Zabol, Iran, who suffered from PCOS. Serum levels of total cholesterol (TC) obtained from the study by Aghdam et al. [30]. were considered as the key dependent variable for estimating the sample size. Considering standard deviation (s.d.) of 37, a degree of precision of 6 (d = 6), and type 1 error of 5%, a total number of 150 subjects were estimated to be needed for the present study.

The Rotterdam Consensus Criteria [31] were utilized to diagnose women with PCOS. Accordingly, PCOS was diagnosed when at least two of the following criteria were met: chronic amenorrhea or oligomenorrhea, clinical and laboratory evidence of hyperandrogenism, and polycystic ovaries.

Subjects who have experienced CVD or endocrine disorders, like diabetes and hyperthyroidism, cancer, renal or liver dysfunction were excluded from this study. Those who had taken antioxidant supplements or medications that could induce metabolic or hormonal changes, such as estrogens, metformin, corticosteroids, and lipid-lowering medications within three months before the enrollment in the study were also excluded. In addition, smoking, adhering to a specific diet, utilizing fish oil supplements, and taking anti-inflammatory medications in the past three months were all exclusion criteria.

The study was carried out in accordance with the ethical standards laid down in the Declaration of Helsinki and the ethical committee of Zabol University of Medical Sciences confirmed the study protocol (ethics code number: IR.ZBMU.REC.1401.031). The study protocol was explained to participants and they were then asked to sign a written informed consent.

Demographic and anthropometric assessment

All participants were required to complete a general questionnaire and have their anthropometric measurements taken. The trained personnel interviewed all participants who were enrolled in the study. The relevant demographic characteristics, detailed clinical information, and lifestyle habits of the participants were collected through a questionnaire.

The weight of the participant was measured using an electronic weighing scale (Hamburg, Germany) with as few clothing items as possible, while their height was measured in upright position using a fixed wall scale. By dividing weight (kg) by height squared (m^2), body mass index (BMI) was established. The waist circumference (WC) was measured with a tape measure that was unstretched and had an accuracy of 0.1 cm. Prior to each measurement, all measuring tools were calibrated to minimize errors.

A bioelectrical impedance analysis (BIA) system (InBody S10, JMW140, Korea) was employed to measure the percentage of body fat mass (%FM) and visceral fat level (%VF).

Dietary intake assessment

A validated semi-quantitative food frequency questionnaire (FFQ) with 168 food items was employed for the evaluation of dietary intakes [32]. A trained nutritionist recorded how many times the subject consumed food in the previous year on a daily (e.g. bread), weekly (e.g. rice, meat) or monthly (e.g. fish) basis through face-to-face interviews. The assistants assisted subjects in estimating food quantities using household measurements (e.g. spoon, bowl, ladles) that were calibrated. After that, the portion sizes were converted to grams. The intake of calorie and nutrients were calculated using Nutritionist IV software (First Databank; Hearst, San Bruno, CA, USA) based on the Iranian foods-modified US Department of Agriculture food composition. Nearly all foods on the participant list were coded, and those that were not available were coded to a similar item.

Dietary phytochemical index calculation

DPI was calculated using the method developed by McCarty as follows: PI = [daily energy derived from phytochemical-rich foods (kcal)/total daily energy intake (kcal) × 100 [25]. Fruits, vegetables, legumes (including soy), whole grains, nuts, olives, olive oil, tea, and coffee were the food items used for DPI calculations. Potatoes were not considered as vegetables because they are usually eaten as starch components instead of as vegetables. Natural fruit and vegetable juices as well as tomato sauces were included in the fruit and vegetable groups because these are also considered as rich sources of phytochemicals.

Biochemical measurements

After fasting for 10–12 h, blood samples were collected from each study subject and centrifuged at 3500 rpm (~2000 g) to separate the sera. Fasting serum glucose (FSG), total cholesterol (TC), HDL-C, LDL-C, and TG concentrations were evaluated enzymatically at the day of sample collection by commercial kits (Pars-Azmoon Co., Tehran, Iran). The remaining sera were kept in -80°C until the assays were carried out. The enzyme-linked immunosorbent assay (ELISA) kit (DiaMetra, Milan, Italy) was utilized for measuring serum insulin levels. To calculate the non–HDL-C level, the HDL-C level was subtracted from the TC level.

Insulin resistance was evaluated by calculating Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) according to the formula developed by Matthews et al. as following formula: fasting insulin (U/l) × fasting glucose (mg/dl)/405 [33].

The measurement of total testosterone, sex hormone-binding globulin (SHBG), and ox-LDL levels was carried out using an ELISA kit (Bioassay Technology Laboratory, Shanghai Biotech, Shanghai City, China). Serum ADMA levels were also evaluated by using a commercial ELISA kit according to the manufacturer's instructions.

The plasma atherogenic index (AIP) was determined using log (TG/HLD-C) [34]. The visceral adiposity index (VAI) and the lipid accumulation product (LAP) were estimated according to following formulas [35].

VAI= [WC (cm) / (36.58 + 1.89 × BMI)] × (TG/0.81) × (1.52/HDL-C)

LAP= [WC (cm) -58] × [TG (mmol/l)]

Statistical analysis

Data are displayed as mean ± standard deviation (SD) for continuous variables and absolute numbers (%) for categorical variables. Energy-adjusted DPI was calculated as [(DPI×1000)/energy intake], and was assigned as quartiles based on their 25th -50th -75th percentile values. Participants were classified based on cut-points of DPI in quartile categories as follows: first quartile, < 23.71; second quartile, 23.71 to 28.44; third quartile, 28.45 to 33.53; and fourth quartile, >33.53. To assess the normal distribution of variables, the Kolmogorov-Smirnov test was utilized.

Differences in general characteristics across quartile of DPI were compared using the analysis of variance (ANOVA) for continuous variables and the chi-square test for categorical variables. Energy-adjusted means for dietary intakes across DPI quartiles were compared by analysis of covariance (ANCOVA). Comparison of biochemical parameters and atherogenic indices across DPI categories were also done using ANCOVA test with adjustment for age, BMI, and disease duration. To determine the association between DPI with biochemical parameters and atherogenic indices, multiple linear regression was utilized by adjusting age, sex, BMI, and disease duration.

All statistical analyses were performed with the Statistical Package for the Social Sciences software version 27 (IBM Corp., Armonk, NY, USA). In all analyses, a p-value < 0.05 was considered statistically significant.

Results

The study comprised of 150 women with PCOS who had a mean age and BMI of 33.7 ± 5.8 years and 28.1 ± 2.8 kg/m^2, respectively. The mean duration of the disease diagnosis among the participants was 5.0 ± 2.4 years. General characteristics of the participants are provided in Table 1. There were no significant differences in age, anthropometric measures, fat mass, visceral fat, disease duration, and the proportion of women with obesity across quartile categories of DPI.

Energy-adjusted dietary intakes of the participants across quartile categories of DPI are illustrated in Table 2. The mean of DPI was 19.9 ± 3.0, 26.4 ± 1.2, 31.1 ± 1.6, and 37.9 ± 4.1 in the first, second, third, and fourth quartiles, respectively. Energy, carbohydrates, vitamin C, vitamin A, and folate intakes significantly increased across increasing DPI quartiles (for all P-trend < 0.001). A significant increasing trend across DPI quartiles were found for dietary intakes of fruits (P-trend = 0.002), vegetables (P-trend = 0.023), and olive sources (P-trend = 0.001). However, no significant regular trend was observed for other investigated food items.

Table 3 indicates the mean serum levels of biochemical parameters in the participants across quartile categories of DPI. Serum levels of insulin (P-trend = 0.045), TG (P-trend = 0.003), ox-LDL (P-trend = 0.001), ADMA (P-trend = 0.022), and HOMA-IR (P-trend = 0.018) significantly decreased across increasing DPI quartiles. No significant regular trend was found for serum levels of FBG, TC, LDL-C, HDL-C, non-HDL, SHBG, and total testosterone.

Regarding atherogenic indices, there was a trend towards decreasing in VAI (P-trend = 0.005) and AIP (P-trend = 0.001) with increasing quartile categories of DPI (Fig. 1). No significant association was found between DPI and LAP in the participants.

The results of multiple linear regression analysis investigating the association between DPI with biochemical parameters and atherogenic indices are shown in Table 4. DPI score indicated a significant inverse correlation with the serum levels of ADMA (P = 0.002), ox-LDL (P < 0.001), insulin (P = 0.008), TG (P < 0.001), and HOMA-IR (P = 0.001) after adjusting for age, BMI, and disease duration. Likewise, a significant inverse correlation was found between DPI score and atherogenic indices including VAI (P = 0.001) and AIP (P < 0.001).

Table 1 General characteristics of patients with PCOS across quartiles of DPI

Variables	Quartiles of DPI				*P*
	1 (< 23.71)	2 (23.71 to 28.44)	3 (28.45 to 33.53)	4 (> 33.53)	
N	37	38	38	37	
Age (years)	32.1 ± 6.6	34.7 ± 5.3	34.0 ± 6.3	33.8 ± 4.9	0.280[a]
Weight (kg)	71.4 ± 9.1	73.8 ± 9.6	73.3 ± 8.0	74.8 ± 6.7	0.366[a]
Height (cm)	162.3 ± 6.2	161.9 ± 7.6	160.7 ± 5.7	161.4 ± 6.5	0.758[a]
BMI (kg/m^2)	27.1 ± 2.9	28.1 ± 3.2	28.3 ± 2.2	28.7 ± 2.6	0.063[a]
WC (cm)	91.0 ± 7.8	92.0 ± 11.0	93.7 ± 8.0	93.5 ± 9.5	0.545[a]
Fat mass (%)	23.8 ± 6.4	25.4 ± 6.8	26.0 ± 5.0	25.8 ± 5.9	0.393[a]
Visceral fat (%)	11.9 ± 3.4	12.2 ± 3.2	13.0 ± 3.6	12.6 ± 3.5	0.559[a]
Obesity, n (%)[c]	8 (21.6)	12 (31.6)	8 (21.1)	15 (40.5)	0.196[b]
Duration of PCOS (years)	4.6 ± 2.4	5.5 ± 2.6	4.5 ± 2.2	5.3 ± 2.4	0.159[a]

PCOS, polycystic ovary syndrome; DPI, dietary phytochemical index; BMI, body mass index; WC, waist circumference

Data are reported as mean ± standard deviation for continuous variables and number (%) for categorical variables.

[a]One-way analysis of variance (ANOVA)

[b]Chi-square test

[c]Obesity was defined as BMI ≥ 30 kg/m^2

Discussion

Earlier research has shown an association between the DPI and the risk of chronic diseases [36–39], however, there have been limited studies on this relationship specifically in individuals with PCOS. This study is among the first to explore the relationship between DPI and cardiovascular risk factors in the PCOS population. The results of the present study indicated a positive correlation between DPI and consuming fruits, vegetables, and olive sources. DPI showed a negative correlation with the serum levels of insulin, TG, ox-LDL, ADMA and, HOMA-IR. Moreover, in relation to atherogenic indices, there was a tendency for VAI and AIP to decrease as the quartile categories of DPI increased. No significant regular trend was found for serum levels of FBG, TC, LDL-C, HDL-C, non-HDL, SHBG, total testosterone, and LAP.

ADMA, being an eNOS inhibitor, can elevate the risk of CVD by decreasing endothelial NO levels, as NO is crucial for blood vessel function [40]. A decrease in NO levels can result in blood vessels becoming constricted,

Table 2 Energy-adjusted dietary intakes of patients with PCOS across quartiles of DPIa

Variables	Quartiles of DPI				*P*-trend[b]
	1 (< 23.71)	2 (23.71 to 28.44)	3 (28.45 to 33.53)	4 (> 33.53)	
N	37	38	38	37	
DPI	19.9 ± 3.0	26.4 ± 1.2	31.1 ± 1.6	37.9 ± 4.1	< 0.001
Total Energy (kcal/d)[d]	2119 ± 280	2117 ± 196	2312 ± 160	2380 ± 279	< 0.001
Nutrients					
Carbohydrate (g/d)	278.8 ± 52.6	303.0 ± 22.9	320.6 ± 70.6	340.7 ± 58.6	< 0.001
Protein (g/d)	73.1 ± 13.2	69.2 ± 12.5	75.5 ± 10.2	74.2 ± 12.3	0.125
Total fat (g/d)	93.4 ± 12.6	89.9 ± 14.0	95.8 ± 14.9	91.5 ± 13.4	0.287
SFA (g/d)	28.8 ± 7.3	31.8 ± 8,5	30.6 ± 7.1	33.1 ± 10.4	0.149
MUFA (g/d)	26.9 ± 9.3	27.4 ± 8.0	26.0 ± 9.3	25.7 ± 7.4	0.815
PUFA (g/d)	18.9 ± 7.9	21.8 ± 9.8	23.8 ± 9.4	23.1 ± 9.8	0.109
Vitamin C (mg/d)	129.8 ± 12.1	136.3 ± 8.3	138.3 ± 8.4	141.3 ± 12.0	< 0.001
Vitamin A (RAE/d)	712.7 ± 247.0	704.5 ± 256.0	843.4 ± 285.3	941.6 ± 292.4	< 0.001
Vitamin E (mg/d)	15.3 ± 5.9	14.7 ± 4.7	15.5 ± 6.1	17.3 ± 8.1	0.325
Folate (mcg/d)	243.9 ± 20.2	253.1 ± 15.5	255.6 ± 13.7	262.6 ± 11.2	< 0.001
Food groups					
Whole grains (g/d)	31.5 ± 16,7	28.7 ± 18.8	25.7 ± 14.3	35.3 ± 20.2	0.115
Fruits (g/d)	215.4 ± 92.6	199.7 ± 93.8	236.2 ± 96.6	280.8 ± 88.9	0.002
Vegetables (g/d)	224.9 ± 83.0	247.7 ± 65.5	268.9 ± 79.4	276.0 ± 81.8	0.023
Legumes (g/d)	12.9 ± 5.7	15.1 ± 4.9	14.2 ± 6.7	15.2 ± 4.2	0.264
Nuts (g/d)	4.89 ± 0.87	5.05 ± 1.18	4.76 ± 0.93	5.44 ± 1.34	0.048
Seeds (g/d)	2.94 ± 1.12	2.66 ± 1.29	3.14 ± 1.22	3.37 ± 1.39	0.102
Meats (g/d)	85.8 ± 40.4	81.3 ± 29.4	82.6 ± 32.7	92.8 ± 31.1	0.587
Dairy products (g/d)	177.9 ± 51.3	188.1 ± 53.8	193.8 ± 60.6	175.5 ± 54.2	0.434
Soy sources (g/d)	3.72 ± 1.56	4.20 ± 1.39	4.07 ± 1.47	4.41 ± 1.63	0.262
Olive sources (g/d)	1.24 ± 0.51	1.52 ± 0.53	1.58 ± 0.45	1.73 ± 0.62	0.001

PCOS, polycystic ovary syndrome; DPI, dietary phytochemical index; SFA, saturated fatty acids; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid; RAE, retinol activity equivalents

Data are reported as mean ± standard deviation

[a]All values are adjusted for energy intake, except for total energy

[b]Obtained from ANCOVA

which in turn can lead to elevated blood pressure and diminished blood flow. This decrease can also elevate the risk of blood clot formation and inflammation within the blood vessels [41]. The present study's results indicated an inverse correlation between DPI and serum ADMA levels. Several in-vivo and in-vitro studies have indicated that specific phytochemicals such as salvianolic acid [42], kaempferol [43], piceatannol, and resveratrol [44] can help reduce ADMA levels. Furthermore, consuming olive oil polyphenols has been demonstrated to reduce plasma ADMA levels [45]. However, there is a lack of research that comprehensively evaluate all phytochemicals. Dietary studies suggest that consuming food patterns rich in fruits and vegetables, the primary sources of phytochemicals, may be associated with lower ADMA levels. For instance, a study carried out in patients with coronary artery disease found that ADMA levels were lower in patients in the highest quartile of Dietary Approaches to Stop Hypertension (DASH) score compared to those in the lowest quartile score [46]. However, in contrast to the DASH score, no association was found between the Alternative Healthy Eating Index (AHEI) score and ADMA levels in the same study [46]. Some studies have also examined the link between specific food groups rich in phytochemicals and ADMA. Increased intake of tea and vegetables was strongly linked to the lower plasma ADMA levels in healthy individuals [47]. However, no such correlation was found for fruit consumption [47].

Reduced dimethylarginine dimethylaminohydrolase (DDAH) function is likely the primary mechanism for higher ADMA levels, as DDAH is a hydrolytic enzyme responsible for the clearance of ADMA and plays a crucial role in adjusting ADMA levels. Increased oxidative stress leads to a decrease in DDAH activity [48]. Additionally, oxidative stress can also enhance the activity of enzymes involved in ADMA production, such as protein arginine methyltransferase (PRMT) [18, 48]. Therefore, the inhibition of oxidative stress by antioxidants, such as phytochemicals, may increase DDAH activity and decrease PRMT activity, thereby preventing the increase in ADMA levels.

Table 3 Biochemical parameters in patients with PCOS across quartiles of DPI

Variables	Quartiles of DPI				*P*-trend[a]
	1 (< 23.71)	2 (23.71 to 28.44)	3 (28.45 to 33.53)	4 (> 33.53)	
n	37	38	38	37	
FBG (mg/dl)	101.8 ± 15.0	105.3 ± 16.3	97.6 ± 12.2	100.4 ± 15.2	0.268
Insulin (μU/ml)	18.1 ± 4.7	16.2 ± 5.3	15.6 ± 5.7	15.8 ± 5.1	0.045
HOMA-IR	4.5 ± 1.5	4.0 ± 1.6	3.8 ± 1.5	3.7 ± 1.4	0.018
TC (mg/dl)	189.1 ± 26.4	186.7 ± 23.9	184.0 ± 18.0	191.9 ± 25.2	0.742
LDL-c (mg/dl)	137.2 ± 19.1	133.0 ± 26.5	133.7 ± 23.9	129.8 ± 28.4	0.243
HDL-c (mg/dl)	50.7 ± 5.3	47.5 ± 5,9	51.6 ± 4.9	50.9 ± 5.8	0.259
TG (mg/dl)	172.8 ± 26.7	169.9 ± 27.4	167.6 ± 23.1	155.7 ± 15.8	0.003
Non-HDL-C	138.4 ± 26.1	139.2 ± 23.9	132.4 ± 18.8	141.0 ± 25.2	0.949
SHBG (nmol/l)	71.7 ± 36.1	62.7 ± 31.7	66.1 ± 31.4	73.1 ± 35.3	0.761
Total testosterone (ng/ml)	1.14 ± 0.54	1.11 ± 0.63	1.05 ± 0.55	1.04 ± 0.64	0.440
ADMA (μmol/l)	0.96 ± 0.31	0.82 ± 0.39	0.83 ± 0.34	0.75 ± 0.38	0.022
Ox-LDL (U/l)	114.9 ± 39.5	102.4 ± 29.6	95.2 ± 33.0	88.9 ± 32.3	0.001

ADMA, asymmetric dimethylarginine; ox-LDL, oxidized low density lipoprotein; FBG, fasting blood glucose; HOMA-IR, homeostasis model assessment of insulin resistance; TC, total cholesterol; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; TG, triglyceride; SHBG, sex hormone binding globulin

Data are reported as mean ± standard deviation

[a]One-way analysis of covariance (ANCOVA) with adjustment for age, BMI, and disease duration

Dyslipidemia is a prevalent metabolic issue in PCOS patients [49], often manifesting in various patterns such as low HDL-C levels, elevated TG, TC, and LDL-C levels [50], potentially influenced by factors like IR, hyperandrogenism, diet, exercise, and genetics [51]. In our study, among serum lipids, only serum TG levels decreased with increasing DPI quartile. While HDL-C, LDL-C, non-HDL, and TC did not show this trend. It is consistent with our previous research in obese patients, where higher DPI scores were only linked to a lower risk of hypertriglyceridemia among lipid-related cardiovascular risk factors [52]. This finding is also in line with the recent meta-analysis in which it was shown that adherence to the higher DPI is associated with lower serum TG levels in adults [53]. Besides, in the aforementioned meta-analysis, no significant relationship between low HDL-C levels and DPI was found [53]. In an Iranian study, results indicated no significant correlation between DPI and LDL-C, TC, and TG in patients with type 2 diabetes mellitus [54]. However, in another cross-sectional study in adults with type 1 diabetes mellitus, participants in the higher tertile of DPI, had significantly lower LDL-C compared with those in the lower tertile [30]. A longitudinal study among Iranian adults observed that after three years of follow-up, the levels of TC, TG, HDL-C, and non-HDL-C in the highest quartile of DPI, significantly decreased in healthy men but not in women [27].

Phytochemicals can lower lipid levels through various pathways. For instance, phytosterols can compete with cholesterol for absorption in the intestines, potentially reducing cholesterol levels [55]. Quercetin can hinder TG synthesis in human intestinal CaCo-2 cells by inhibiting the secretion of apoB-100 and apoB-48 [56]. Some phytochemicals act as potent ligands for regulatory receptors in lipid metabolism, such as peroxisome proliferator-activated receptors [57]. By enhancing the expression of genes involved in fatty acid transport and oxidation in peroxisomes and mitochondria, these receptors can regulate lipid metabolism [57]. Additionally, the synergistic interplay between phytochemicals offers a promising strategy for achieving lipid-lowering effects in humans [58]. Nevertheless, further research is necessary to fully comprehend their impact on overall lipid profiles.

Ox-LDL is a form of LDL that has been altered through oxidation [59]. It is considered more atherogenic and inflammatory compared to the native LDL, and is believed to play a significant role in the development of atherosclerosis [60, 61]. In agreement with the results of the present study, a cross-sectional study in healthy adults showed that DPI was inversely associated with ox-LDL as a marker of lipid peroxidation [62]. Moreover, adherence to the Mediterranean diet resulted in lower ox-LDL levels in a cohort study [63]. Additionally, in the same cohort study, ox-LDL concentrations were inversely associated with the consumption of fruit, vegetables, and olive oil, which are the main sources of phytochemicals [63]. Apart from the observational studies, several intervention trials in different populations have shown that consumption of certain phytochemicals such as quercetin [64, 65] and curcumin [66] also resulted in reduction of ox-LDL levels. Although no significant regular trend was observed in the serum levels of LDL-C across quartiles of DPI in the present study, ox-LDL decreased as DPI quartile increased. Phytochemicals can act as antioxidants by scavenging free radicals and preventing LDL oxidation. They help protect LDL from oxidation and lower ox-LDL levels.

AIP is associated with coronary disease and may predict atherosclerosis, making it a useful screening tool for heart disease even when all lipid levels are normal. It can provide early clues about CVD in PCOS patients due to its simplicity and effectiveness [67]. Our study is among the limited number of studies which has evaluated the association of diet with AIP. A significant inverse correlation was found between DPI score and AIP. In consistent

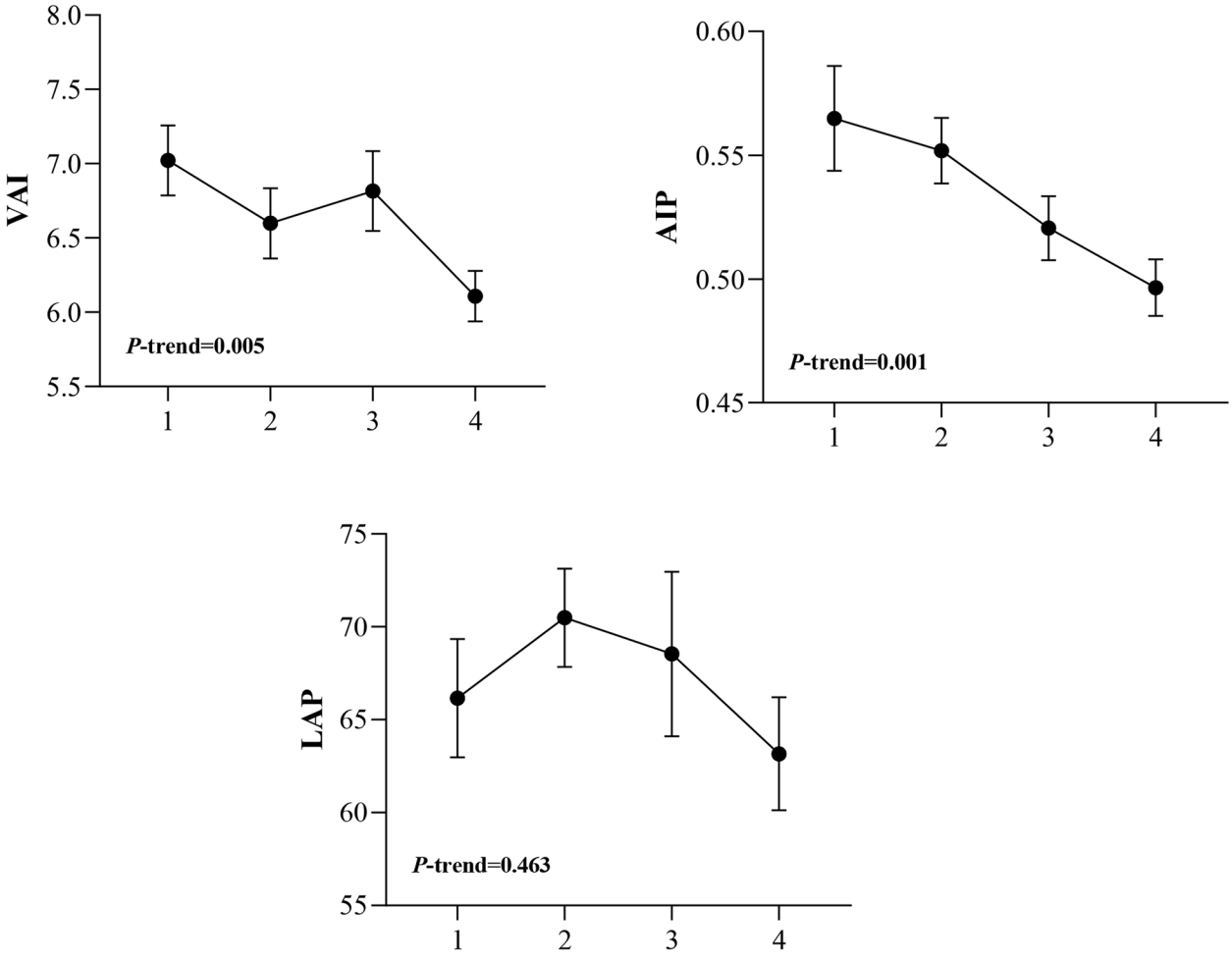

Fig. 1 Atherogenic indices of patients with PCOS across quartiles of dietary phytochemical index (DPI). Data are illustrated as mean ± S.E. (S.E.; shown by vertical bars). The number of patients was 37–38 in each quartile. *P*-trend values were obtained from analysis of covariance (ANCOVA) with adjustment for age, BMI, and disease duration. Quartile cut-points of dietary DPI are as follows: first quartile, < 23.71; second quartile, 23.71 to 28.44; third quartile, 28.45 to 33.53; fourth quartile, > 33.53. $P < 0.05$ was considered significant. AIP, atherogenic index of plasma; LAP, lipid accumulation product; VAI, visceral adiposity index

with our findings, in an Iranian population-based cross-sectional study higher adherence to plant-based diet index (PDI) and moderate adherence to healthful plant-based diet index (hPDI) were associated with decreased odds of high-risk AIP [68]. An earlier study also demonstrated that incorporating both the Mediterranean Diet (MD) and regular physical activity was effective in reducing AIP levels, indicating a positive impact on cardiovascular health [69]. In contrary, another study reported that adherence to a healthy diet guideline was not significantly associated with AIP levels [70]. In our study, higher adherence to DPI resulted in reduced TG levels, potentially contributing to a decrease in AIP.

VAI and LAP as indicators of visceral adiposity and visceral adipose tissue function, are also useful tools for early detection of metabolic dysfunction and cardiovascular risks before it develops into an overt metabolic syndrome [7, 8]. They are both strongly related to the severity of insulin resistance [7]. In the present study, there was a trend towards decreasing in VAI with increasing quartile categories of DPI but no significant association was found between DPI and LAP in the participants. In a recent study researchers have identified a dietary pattern positively correlated with VAI. Low consumption of cruciferous vegetables and high consumption of fried vegetables were among the 13 food groups of dietary patterns that were associated with an increase in VAI [71]. Phytochemicals found in cruciferous vegetables may have positive impacts on the function of adipose tissue [72]. Moreover, frying vegetables can potentially result in a decrease in the content of some beneficial bioactive components [73]. In another study, despite a high diet diversity score, PCOS subjects also exhibited high VAI and LAP values [74]. A randomized clinical trial carried out

Table 4 Results of multiple linear regression analysis that evaluated the association between DPI with biochemical parameters and atherogenic indices ($n = 150$)a

Variables	DPI		
	B (S.E.)	β	P^a
ADMA (µmol/l)	-4.88 (1.54)	-0.25	0.002
Ox-LDL (U/l)	-0.06 (0.02)	-0.30	< 0.001
FBG (mg/dl)	-0.07 (0.04)	-0.15	0.070
Insulin (µU/ml)	-0.29 (0.11)	-0.21	0.008
HOMA-IR	-1.24 (0.37)	-0.27	0.001
TC (mg/dl)	-0.02 (0.03)	-0.08	0.400
LDL-C (mg/dl)	-0.04 (0.02)	-0.14	0.103
HDL-C (mg/dl)	0.11 (0.10)	0.09	0.279
TG (mg/dl)	-0.09 (0.02)	-0.32	< 0.001
Non-HDL-C	-0.03 (0.02)	-0.09	0.270
SHBG (nmol/l)	-0.01 (0.02)	-0.06	0.442
Total testosterone (ng/ml)	-1.17 (0.98)	-0.10	0.236
VAI	-1.36 (0.38)	-0.28	0.001
AIP	-24.22 (5.78)	-0.33	< 0.001
LAP	-0.05 (0.03)	-0.14	0.113

DPI, dietary phytochemical index; ADMA, asymmetric dimethylarginine; ox-LDL, oxidized low density lipoprotein; FBG, fasting blood glucose; HOMA-IR, homeostasis model assessment of insulin resistance; TC, total cholesterol; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; TG, triglyceride; SHBG, sex hormone binding globulin; VAI, visceral adiposity index; AIP, atherogenic index of plasma; LAP, lipid accumulation product; B, unstandardized coefficient; S.E., standard error

[a]Adjusted for age (continuous), BMI (kg/m^2), disease duration (continuous)

$P < 0.05$ was considered significant

among women with PCOS, revealed that CoQ10, vitamin E (alone or in combination) had beneficial effects on LAP, but only the combination of supplements was able to significantly reduce VAI [75]. As mentioned, the LAP and VAI indices are strongly associated with IR. Accordingly, in the present study, higher quartiles of DPI were associated with lower serum levels of insulin and HOMA-IR in women with PCOS. Similar to our results, a study conducted among Iranian populations found that adhering to a high-PI diet was linked to a reduced likelihood of developing hyperinsulinemia and insulin resistance over time [76]. Phytochemicals may sensitize insulin receptors due to their antioxidant and anti-inflammatory properties [77]. They can trigger AMPK to boost GLUT4 translocation for better glucose uptake and activate the PI3K/Akt pathway to enhance insulin sensitivity [77]. Additionally, they can improve insulin sensitivity by modulating insulin production, secretion, and protecting pancreatic β-cells [53].

Strengths and limitations

This study had both strengths and limitations. It is the first to explore the link between DPI and metabolic markers, ADMA levels, and atherogenic indices in PCOS patients. We adjusted for potential confounders like age, BMI, and disease duration. However, there may be biases from unknown confounders, common in observational studies. The study took a holistic approach, looking at overall diet rather than single nutrients, using a validated FFQ for data collection. Yet, measurement errors could affect categorizations of phytochemical intake. DPI composition varies by region, limiting generalizability. The cross-sectional design prevents establishing cause-and-effect relationships. Future research, especially prospective or longitudinal studies, is crucial for confirming these findings.

Conclusions

In conclusion, the findings of this study demonstrated a significant inverse association between DPI and atherogenic indices, hypertriglyceridemia, ox-LDL, ADMA, and insulin resistance as CVD risk factors in PCOS population. Further investigation, especially prospective studies, are required to validate the current findings. If confirmed by additional studies, these results suggest that increasing the consumption of phytochemical-rich foods like fruits, vegetables, and olive sources could be an effective strategy for preventing CVD in individuals with PCOS.

Abbreviations

PCOS	Polycystic ovary syndrome
CVD	Cardiovascular diseases
DPI	Dietary phytochemical index
ADMA	Asymmetric dimethylarginine
SHBG	Sex hormone-binding globulin
FSG	Fasting serum glucose
HOMA-IR	Homeostatic model assessment for insulin resistance
VAI	Visceral adiposity index
AIP	Atherogenic index of plasma

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Author contributions

F.A. We're involved in the study designing, interpretation of the data, and development of the manuscript. M.T. prepared the first draft of the manuscript and coordinated in the data collection. S.H.S. performed the statistical analysis, and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Data availability

The datasets generated and/or analyzed during the current study are not publicly available due to university data ownership policies, but are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

All experiments were performed in accordance with the declaration of Helsinki and Zabol University of Medical Sciences ethical guidelines and regulations. The research protocol was approved by the Zabol University of Medical Sciences (ethics code number: IR.ZBMU.REC.1401.031). All participants signed a written inform consent before participating in the study.

Competing interests
The authors declare no competing interests.

Author details
[1]Department of Nutrition, School of Public Health, Zabol University of Medical Sciences, Zabol, Iran
[2]Department of Clinical Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences, No#44, Hojjatdoust St., Naderi St., Keshavarz Blvd, Tehran 141556117, Iran
[3]Department of Epidemiology and Biostatistics, Faculty of Public Health, Zabol University of Medical Sciences, Bagheri St., Shahid Rajaei St, Zabol 9861615881, Iran

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