Original Article

The relationship between dietary patterns and lipoprotein-associated phospholipase A2 levels in adults with cardiovascular risk factors: Tehran Lipid and Glucose Study

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Background: Pathogenesis of cardiovascular diseases (CVDs) may be indicated by lipoprotein-associated phospholipase A2 (Lp-PLA2), serving as an inflammatory biomarker. However, the general dietary predictors of Lp-PLA2 have not been investigated so far. The aim of the present study is to investigate the relationship between the serum levels of Lp-PLA2 and dietary patterns in adults with cardiovascular risk factors. **Materials and Methods:** Dietary patterns extracted using factor analysis and serum levels of Lp-PAL2 in 470 adults aged 40–70 years who participated in the 5th phase of the Tehran Lipid and Glucose Study (2011–2014) were determined. Associations between the dietary patterns and serum levels of Lp-PAL2 considering some confounder factors were evaluated. **Results:** The results showed that Western and semi-Mediterranean dietary patterns had significant effects on changes in Lp-PLA2 levels in univariate analyses. In multivariate analyses, after adjusting for age, sex, total cholesterol, low-density lipoprotein cholesterol, body mass index and physical activity, energy intake, hormone therapy for women, and taking blood lipid-lowering drugs as potential confounders, the Western dietary pattern remained a significant factor influencing the Lp-PLA2 level (β value: 1.65, 95% confidence interval: 1.12, 1.89; $P < 0.05$). Moreover, after adjustment for the mentioned confounder factors, the effect of the semi-Mediterranean dietary pattern on Lp-PLA2 disappeared. **Conclusion**: It can be concluded that the Western dietary pattern is associated with higher Lp-PLA2 levels. We recommend that adults eat less carbonated drinks, fast foods, salty snacks, mayonnaise, and organ meat to counteract increased serum Lp-PLA2 levels, which are directly associated with vascular inflammation and CVDs.

Key words: Cardiovascular risk factors, dietary patterns, lipoprotein-associated phospholipase A2

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INTRODUCTION

Among several cardiovascular risk factors, hypertension, diabetes, and blood lipid play a crucial role in the plaque formation and cardiovascular disease (CVD) incidence. Atherosclerosis with inflammatory nature was developed by the vessel endothelium dysfunction and oxidative stress.[1] Pathogenesis of CVDs can be detected by the probable involvement of lipoprotein-associated phospholipase A2 (Lp-PLA2), which is known as an inflammatory biomarker. Previous studies have consistently shown a positive relationship between the concentration and activity of Lp-PLA2 in populations with or without coronary artery disease (CAD).[2-4] Some lines of evidence suggest that Lp-PLA2 may be involved in the process of atherogenesis by enhancing the inflammatory processes in the arterial intima.[5] Lp-PLA2

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attached to low-density lipoprotein cholesterol (LDL-C) enters the artery wall, and when LDL-C is oxidized, two pro-inflammatory compounds are produced through the hydrolysis of the ester bonds of oxidized phospholipids in the sn2 positions. These compounds are formed to activate inflammation by recruiting chemokines within the intima of atherosclerotic lesions in humans.[6] In this respect, previous studies have shown that Lp-PLA2 is involved in the progression of atherosclerotic lesions to rupture-prone plaques.[7,8]

Even though the probable causal role of Lp-PLA2 in atherogenesis and its plausible modification by lipid-lowering drugs have been already assumed, it is not known whether diet and food patterns can reduce the plasma levels of Lp-PLA2. One study conducted on 60 healthy controls showed that a moderate dose (2 g) of n-3 polyunsaturated fatty acid (PUFA) or a high dose (6.6 g) of n-3 PUFA had no effect on the plasma levels of Lp-PLA2.[9] Hatoum *et al*. conducted a study to determine the dietary factors, lifestyle factors, and clinical measurements associated with Lp-PLA2 activity for 853 women from the Nurse's Health Study and 878 men from the Health Professionals Follow-up Study who were free of cancer and CVD. Their results showed that substitution of 5% of energy from carbohydrates with protein was associated with reduced activity of Lp-PLA2. Moreover, smoking, taking hormones after menopause, body mass index (BMI), and alcohol consumption are the modifiable risk factors which may influence LP-PLA2 activity.[10]

To the best of our knowledge, no study has investigated the relationship between dietary patterns and LP-PLA2 in Middle Eastern population. The aim of this study is to investigate the relationship between the serum levels of LP-PLA2 and dietary factors among high-risk adults for CVD.

MATERIALS AND METHODS

Study population

This study was conducted within the framework of the Tehran Lipid and Glucose Study (TLGS). As a community-based prospective framework, it was adopted to detect any noncommunicable diseases in a representative sample of ≥3 years old, who resided at District 13 in Tehran, the capital city of Iran. The 1st phase of TLGS was initiated in March 1999 with the ongoing data collection occurring at 3-year intervals.[11]

In the present research, 5605 men and women aged between 40 and 70 years were recruited in the 5th phase of TLGS (2011–2014). We excluded participants if there were no associated data on sex and anthropometric measurements ($n = 463$), if they were underweight ($n = 350$), no associated dietary intake information ($n = 3695$), and if they were under or over reporters of dietary intakes (<800 kcal/day or >4200 kcal/day, respectively) ($n = 1097$). After exclusions, the final analysis was conducted on the data from 470 participants.

Risk factors for CVDs were total cholesterol (TC) level >200 mg/dl, LDL-C level >100 mg/dl, high-density lipoprotein cholesterol (HDL-C) level <40 mg/dl in men and 50 mg/dl in women, triglyceride (TG) level >150 mg/dl, waist circumference upper than 102 cm in men and 88 cm in women, systolic blood pressure >140 mmHg and diastolic blood pressure >90 mmHg or on antihypertensive medication, age ≥45 for men and ≥55 for women, and cigarette smoking.[12] The participants in this study had at least five of the eight risk factors mentioned above.

Dietary assessment

A validated semi-quantitative Food-Frequency Questionnaire (FFQ) with 147 food items prepared for TLGS was used to collect the dietary data. Several trained dietitians were employed to question the participants based on their frequencies of each food intake on daily, weekly, and monthly bases during the previous year. The reliability and validity of the FFQ were found to be acceptable in the food groups after the assessment.

Food group data were standardized, and then considering ±4 standard deviation (SD), the data were truncated. The data were normalized using the logarithm. Finally, energy adjustment using the residual methods was performed. We used the factor analysis method to derive the dietary pattern from the dietary information collected from the 22 food groups [Table 1] based on the similarity of their nutrient contents. The factors were rotated by varimax rotation. The number of dietary patterns identified was based on eigenvalues >1, identification of a break point in the scree plot, and interpretability by the use of Horn's parallel analysis using the software developed by Watkins.[13] Items that had an absolute correlation ≥0.2 with a factor were considered to load on that factor and were retained in the calculation of the dietary pattern score. Food items that had absolute correlations <0.2 or cross-loaded on several factors were not included in the calculation of the dietary pattern score. Following data reduction in the factor analysis, three factors were derived. The derived dietary patterns were labeled according to the authors' data interpretations and those presented in the previous studies.[14] The food groups' intakes weighed by their factor loadings were summed up to compute the factor score of each pattern; following this, each participant received a factor score for each identified pattern,[15] and the scores were then standardized (mean = 0, SD = 1). Dietary pattern scores were

Table 1: Factor loading of three dietary patterns extracted by the factor analysis

Food groups	Healthy	Western	Semi-Mediterranean
Fruit and dried fruit	0.652[a]		
Refined grains	−0.596		
Olives	0.541		
High- and low-fat dairy products	0.462		
Poultry and fish	0.337		
Liquid oils	0.238		
Canned products	0.276		
Carbonated drinks		0.675	
Fast foods		0.613	
Salty snacks		0.563	
Mayonnaise		0.588	
Organ meats		0.315	
Legumes			0.638
Potatoes			0.649
Egg			0.515
Red meats			0.465
Tea and coffee			0.242
Percentage of variance explained[b]	11	10	7

[a]Values are factor loading of dietary patterns (*n*=470). Factor loading ≤0.2 are not shown; [b]Eigenvalue >1

categorized into quartiles. Cutoff points for quartiles of the healthy, semi-Mediterranean dietary pattern, and Western dietary pattern scores were calculated.

Blood collection and laboratory measurements

Participants were asked to take fast for 12 h, and TC, HDL-C, and TG levels were measured using with a Hitachi 911 Analyzer using reagents and calibrators from Roche Diagnostics (Indianapolis, IN, USA); coefficient of variation (CV) were 1.8%. The concentration of LDL-C was measured with a homogeneous direct method from Genzyme (Cambridge, MA, USA); CVs were 3.1%.

The quantitative determination of Lp-PLA2 was measured with a commercial enzyme-linked immunosorbent assay kit (Abcam, USA). Blood pressure was taken on the right arm by a qualified physician after 15-min rest, using a standardized mercury sphygmomanometer, twice in a sitting position; the mean of two measurements was considered as participant blood pressure.

Anthropometrics and lifestyle measurements

A questionnaire was utilized by the trained interviewers to assess the participants' demographic characteristics of age, educational level, smoking status, and level of physical activity expressed as metabolic Equivalent hours per week. The current smokers and nonsmokers were grouped as those smoking daily or occasionally and those having stopped smoking or never smoking, respectively. Physical activity level was determined using a Modifiable Activity Questionnaire (MAQ) translated in Persian. This questionnaire is based on the times and frequencies of performing light-, moderate-, high-, and very high-intensity common activities during the previous year. The high reliability and relatively moderate validity of the mentioned MAQ were reported among the studied Tehranian adults.[16] The minimally clothed participants with no shoes were weighed to the nearest 100 g using a digital scale. A tape meter was utilized to measure the participants' heights to the nearest 0.5 cm while keeping them in a standing position with no shoes. The obtained weights (kg) were divided by the squares of the heights (m^2) to calculate BMI. Using a soft tape meter, waist circumference measurement at the widest part over light clothing was done to the nearest 0.1 cm without exerting any pressure against the body based on anatomical landmarks.

Statistical analysis

Based on the hypothesis specified for the effects of dietary patterns on Lp-PLA2, we applied linear regressions to the influencing factors for exposure to a dietary pattern. *B* values with 95% confidence intervals (CI) were estimated for the effects of predicting factors. Separately, Lp-PLA2 was treated as a dependent variable in univariate and multivariate analyses. In multivariate analyses, age, sex, TC, LDL-C, BMI and physical activity, energy intake, hormone therapy for women, and taking blood lipid-lowering drugs were considered as potential confounders. When healthy pattern considered as reference, the association between Western and semi-Mediterranean pattern with Lp-PLA2 levels was compared with the healthy pattern. All statistical analyses were conducted using SPSS (Version 20; Chicago, IL, USA), and $P < 0.05$ was considered statistically significant.

RESULTS

Following data reduction in the factor analysis, three factors were derived. The derived factors (dietary patterns) were labeled on the basis of the authors' interpretation of the data and on prior studies.[14] The factor loading of food groups in the three extracted dietary patterns is presented in Table 1. The three dietary patterns were named healthy dietary pattern, Western dietary pattern, and semi-Mediterranean dietary pattern. The healthy dietary pattern was high in fruits and dried fruits, olives, high- and low-fat dairy products, poultry and fish, liquid oils, and canned products. The Western dietary pattern was dominated by carbonated drinks, fast foods, salty snacks, mayonnaise, and organ meats. Finally, the semi-Mediterranean dietary pattern contained legumes, potatoes, eggs, red meats, tea, and coffee. Overall, these dietary patterns explained 27.6% of the total variance.

The characteristics of the study participants across the quartiles of Lp-PLA2 are presented in Table 2. Participants with the highest Lp-PLA2 levels were more likely to be men. Participants in the third quartile of Lp-PLA2 had the highest BMI, although this finding was not significant. For any increase in Lp-PLA2 level, TC and LDL-C levels in the participants also increased. The more active individuals had the lowest levels of Lp-PLA2.

The results of linear regressions on Lp-PLA2 indicated that the Western and semi-Mediterranean dietary patterns had significant effects on changes in Lp-PLA2 levels in univariate analyses [Table 3]. The trend of results showed that when healthy pattern considered as a reference pattern, the Western pattern associated with 0.35 ng/ml increased in Lp-PLA2 levels, whereas 0.12 ng/ml reduction in Lp-PLA2 levels related to semi-Mediterranean pattern.

In multivariate analyses, after adjusting for age, sex, TC, LDL-C, BMI and physical activity, energy intake, hormone therapy for women, and taking blood lipid-lowering drugs as potential confounders, the Western dietary pattern remained a significant factor influencing the Lp-PLA2 level (β value: 1.32, 95% CI: 1.05, 1.64; $P = 0.035$); in other words, the Western dietary pattern caused a marked increase in Lp-PLA2 levels [Table 4]. Meanwhile, after adjustment for the mentioned confounder factors, the effect of the semi-Mediterranean dietary pattern on Lp-PLA2 disappeared. As seen in univariate analysis, the trend of association between dietary patterns and Lp-PLA2 levels remained unchanged. Although after adjustment for confounders, the association between Western pattern with Lp-PLA2 levels became stronger and 1.32 ng/ml increase in Lp-PLA2 levels compared to reference (healthy pattern) can be seen.

DISCUSSION

The present study was conducted to determine the relationship between dietary patterns and Lp-PLA2 levels in adults with cardiovascular risk factors. A total of 470 adults participated in this study.

The most important finding of this cross-sectional study was the relationship between the Western dietary pattern and increased levels of Lp-PLA2, and even after adjusting for confounding factors, the association remained strong. This is the first study to examine associations between dietary patterns and Lp-PLA2 levels in a large cross-sectional study on adults with cardiovascular risk factors.

Men relative to women had higher levels of Lp-PLA2, a finding that has been consistently observed in other studies.[3,10,17] This finding is probably due to the effects of estrogen on reducing the level of Lp-PLA2.[18] Another possible reason for this difference between men and women could be the lower concentrations of LDL-C among the women. There are two ways in which high levels of LDL-C are associated with increased levels of lipase. First, LDL-C is the primary carrier of Lp-PLA2, and approximately 80% of Lp-PLA2 circulates bound to LDL-C, up to an additional 15% circulates with HDL-C, and the rest circulates with very-low-density-lipoprotein;[19] second, LDL-C is oxidized as a substrate used for Lp-PLA2 activity.[10] This fact can also explain another finding of the present study regarding the relationship between higher levels of LDL-C and Lp-PLA2.

The results of the present investigation showed that Lp-PLA2 levels were significantly lower in more active adults than in other participants. In line with our results,

Table 2: Basic characteristics of the participants according to the lipoprotein-associated phospholipase A2 (ng/ml) quartiles

Basic characteristics	Q1 (<13.1 ng/ml) (*n*=114)	Q2 (13.2–17.5 ng/ml) (*n*=113)	Q3 (17.6–25.5 ng/ml) (*n*=113)	Q4 (>25.6 ng/ml) (*n*=113)	*P*
Age (years)	43.3±12.8	45.2±13.1	42.2±11.5	48.4±13.1	0.25
Sex (%)					
Men	18.5	23.5	29.0	29.0	0.01
BMI (kg/m^2)	25.6±10.2	25.8±11.5	28.5±13.2	26.8±14.3	0.056
Total cholesterol (mg/dl)	212±36	225±42	264±51	270±49	0.02
LDL-C (mg/dl)	124±29	124±34	139±32	178±40	0.01
HDL-C (mg/dl)	41±18	50±22	51±21	31±19	0.06
TG (mg/dl)	159±35	168±40	156±29	172±32	0.07
Systolic BP (mmHg)	126±26	125±29	135±36	142±41	0.12
Diastolic BP (mmHg)	81±19	83±22	91±36	90±29	0.26
Cigarette smoking (%)					
Yes	23.8	27.2	21.8	27.2	0.16
No	26.6	24.8	24.8	23.8	0.06
Waist circumference (cm)	98±28	100±32	109±38	105±29	0.13
Physical activity (MET/h/week)	18.2	17.9	16.9	14.0	0.02

All values expressed as mean±SD, but the values of physical activity are median. SD=Standard deviation; MET=Metabolic equivalent; BMI=Body mass index; LDL-C=Low-density lipoprotein cholesterol; HDL-C=High-density lipoprotein cholesterol; TG=Triglyceride; BP=Blood pressure

Table 3: Univariate analysis for the association between dietary patterns and lipoprotein-associated phospholipase A2 (ng/ml)

Dietary patterns	β	95% CI	*P*
Healthy pattern	Reference	-	-
Western pattern	0.35	0.11, 0.78	0.026*
Semi-Mediterranean pattern	−0.12	−3.52, −0.16	0.043*

*Statistically significant. CI=Confidence interval

Table 4: Multivariate analysis for the association between the dietary patterns and lipoprotein-associated phospholipase A2 (ng/ml)

Dietary patterns	β	95% CI	*P*
Healthy pattern	Reference	-	-
Western pattern	1.32	1.05, 1.64	0.035*
Semi-Mediterranean pattern	−0.01	−0.16, 0.43	0.75

*Statistically significant. Age, BMI and physical activity, energy intake, fasting blood glucose, hormone therapy for women, and taking blood lipid-lowering drugs were adjusted. BMI=Body mass index; CI=Confidence interval

Rana *et al*.[20] in a study designed to evaluate the contribution of physical activity and abdominal obesity to the variation in inflammatory biomarkers, and the incidence of coronary heart disease (CHD) in a European population showed that circulating levels of Lp-PLA2 (women only) were linearly associated with increased waist circumference and decreased physical activity levels. Several studies have shown that physical activity might reduce plasma levels of pro-inflammatory cytokines and upregulate the expression of anti-inflammatory factors in the vascular wall, which may directly inhibit the development of atherosclerosis.[21-23] Our results showed that after adjusting for age, sex, TC, LDL-C, BMI and physical activity, energy intake, hormone therapy for women, and taking blood lipid-lowering drugs as potential confounders, the Western dietary pattern remained a significant factor influencing the Lp-PLA2 level; in other words, the Western dietary pattern caused a marked increase in Lp-PLA2 levels. The main feature of the Western dietary pattern is the high use of fast foods and foods containing high amounts of saturated fat, and in this dietary pattern, vegetable use and fruit use are very low. A study conducted in Taiwan[24] reported that serum Lp-PLA2 activity was lower in healthy Taiwanese participants who followed a vegetarian diet than in omnivores. There are several possible reasons for lower Lp-PLA2 in individuals who consume more vegetables and fruits. First, Lp-PLA2 is a specific marker of vascular inflammation. Previous studies have shown that the consumption of a high-fat meal increases plasma TGs, and nonesterified fatty acids serve as important mediators of the vascular inflammation effect.[25-27] PUFAs are classified as omega-3 (n-3) and omega-6 (n-6), and both are precursors of eicosanoids that serve as signaling molecules, although the major eicosanoid metabolites and their functional effects differ. Eicosanoids derived from n-6 PUFAs increase vascular inflammation and the development of atherosclerosis, whereas those from n-3 PUFAs decrease inflammation and protect against atherosclerosis.[28] Dietary fatty acids derived from vegetables are mostly n-3 PUFAs, and most dietary n-6 PUFAs are obtained from foods of animal origin such as red meat. Second, cooking patterns such as deep frying, grilling, and roasting used for meat dishes are associated with increased inflammation markers.[29,30] Third, the intake of foods containing high levels of trans-fatty acids will increase serum inflammation markers and adhesion molecules and promote CVD.

There are several limitations of this study. First, the analysis was based on cross-sectional data, and thus, causality could not be inferred. Second, the collection of data by the FFQ relies on an individual's memory, and this method is susceptible to recall bias. Moreover, some individuals cannot accurately estimate the portion size of the food they consume. However, the use of highly trained interviewers in this study reduced this type of error. Third, residual confounding effects could not be avoided. Fourth, there are some limitations of the factor analysis method, namely there are several subjective or arbitrary decisions regarding the use of factor analysis, including consolidation of food items into a food group, number of factors extracted in the rotation method, and interpretability of factors. However, eigenvalues and scree plots are tools that can help extract the best factors. Fifth, questions about physical activity are fully subjective, and their answers are difficult to verify.

Employment of an adequately large population, which was demographically representative of Tehran population, was the greatest strength of this investigation. In this study, we used multivariate analysis to show a relationship between dietary patterns and serum Lp-PLA2 level, and the strength of this method was taking into account the confounding variables.

CONCLUSION

The "Western" dietary pattern was concluded to be associated with higher levels of Lp-PLA2. To counteract their enhanced serum levels, which are directly associated with vascular inflammation and CVDs, we recommend adults to eat more fruits and vegetables.

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Conflicts of interest

There are no conflicts of interest.

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