



The association between dietary inflammatory pattern and body weight, lipid profile in Iranian diabetic adults

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ABSTRACT

Diabetes mellitus and its comorbidities which result in dyslipidemia and cardiovascular diseases (CVD) are one of the leading causes of death in the world, and diet plays a major role in those disease incidences, especially through lipid oxidation mechanisms. This, in turn, leads to tissue inflammation and the formation of atheromatous plaques. Our objective was to evaluate the association between the inflammatory potential of the diet and the incidence of dyslipidemia or its subclasses. We included 599 T2DM patients (276 men and 323 women), aged 35 to 65 years from diabetes referral centers, including Gabric Diabetes Association, Iranian Diabetes Society, and other health centers in Tehran. The lipid profiles in serum were measured by the dietary inflammatory index (DII) was computed using a validated 148-item semi-quantitative food frequency questionnaire (FFQ). The DII score ranged between - 4.85 and 5.46 and its mean and standard deviation (SD) was (-0.02±1.65). Younger individuals had higher adherence to the inflammatory diet ($p \leq 0.001$). Moreover, in the higher quartiles of DII, lower levels of physical activities were seen ($p = 0.005$). There were no significant differences in the distribution of BMI, waist circumference, or lipid profile across DII quartiles. In the overall analysis, no significant association was observed between DII and lipid profile in the crude model, but after adjusting for confounders (age, gender, BMI, physical activity, and energy intake), the DII score was found to be positively associated with total cholesterol ($\beta = 3.123$, $SE = 1.478$, $p = 0.035$) in all participants. A pro-inflammatory diet, as measured by a higher DII score, was prospectively associated with a higher level of total cholesterol in serum. This result may shed a light on the prevention of incidence dyslipidemia and CVD in diabetic patients by intervention in dietary patterns.

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1. Introduction

Chronic systemic inflammation which results in repeated tissue injuries due to higher release of pro-inflammatory cytokines has long been suggested as a key factor in the development and progression of several non-communicable diseases (NCDs), including obesity, metabolic syndrome (MetS), cardiovascular diseases (CVD), diabetes mellitus, and cancer (1, 2). In addition, the metabolic syndrome (MetS) is a multifactorial disorder characterized by a various range of metabolic abnormalities including abdominal obesity, dyslipidemia, insulin resistance, and hypertension and that is connected with a higher risk of type 2 diabetes mellitus

(T2DM), cardiovascular disease (CVD) and atherosclerosis (3, 4). Thus, MetS and its components, especially dyslipidemia represent a major public health concern. Moreover, it has been known that Low-grade, systemic inflammation is one of the main characteristics of the MetS (5, 6). Chronic inflammation processes are also influenced by environmental and individual factors such as lifestyle, smoking, diet, taking some medications, and physical activity, and genetic background (7, 8). It has been reported previously that the dietary pattern is one of the modifiable factors involved in the development of circulating inflammatory markers and inflammatory-related diseases in adults (9, 10). Then, the pro- and anti-inflammatory properties of nutrients and foods have substantially been

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noticed. It has been demonstrated that for predicting the risk of chronic diseases and mortality the overall dietary composition as an important moderator of inflammation is more important than specific nutrients (9). In recent years the Dietary Inflammatory Index (DII®) has been developed to characterize and assess the inflammatory properties of the individual's diet on a variety range from maximally anti- to pro-inflammatory (11). All of the diet components including intake of nutrient and non-nutrient, are computed and compiled into an index. The individuals who have higher adherence to the inflammatory diet have a higher score; therefore, the score has been suggested to be linked with systemic inflammation (12-14). However, the relationship between DII and intermediate biomarkers of cardiometabolic health remain largely unknown. Therefore, the main objectives of this paper were to examine whether higher DII scores, reflecting a more pro-inflammatory diet, are associated with unfavorable cardiometabolic health profiles, characterized by biomarkers of inflammation, lipoprotein metabolism in diabetic subjects (15). There is an important connection between inflammation and the development of chronic and cardiovascular diseases (16, 17). It was previously suggested that inflammation has a vital role in the disturbance of blood pressure and lipid profile (17, 18). This view was confirmed by several studies in western societies which have found that higher inflammatory properties of the diet were associated with early predictors of cardiovascular diseases such as higher plasma triglyceride and lower high-density lipoprotein (HDL) cholesterol concentrations and hypertension (19-21). Evaluation of the DII in different population settings is highly recommended because the various dietary pattern amongst cultures may have an impact on the DII value. Additionally, the role of other factors such as environments, lifestyle, and genetic background on the relationship between the DII score and metabolic health are undeniable among different population settings (22). Due to inadequate studies and limited evidence on the application of the DII in Asian countries, further research is necessary to clarify this issue. Therefore, to the best of our knowledge, this cross-sectional study was conducted to shed a light on the association between DII score and lipid profile in Iranian diabetic adults.

2. Methods and materials

2.1. Study design and subjects

A total of 599 T2DM patients (276 men and 323 women), aged 35 to 65 years were enrolled. The participants in the present cross-sectional study were selected from diabetes referral centers, including Gabric Diabetes Association, Iranian Diabetes Society, and other health centers in Tehran. The study protocol was approved in 2018/1/3 by the Ethics Commission of Tehran University of medical sciences (IR.TUMS.VCR.1363.4128) and all participants signed written informed consent. The patients were involved based on pre-determined inclusion and exclusion criteria. To be included in the study subjects had to be diagnosed with

diabetes with the following criteria: fasting blood glucose level ≥ 126 mg/dl in the two consecutive tests; aged 35-65 years, or were under treatment with medications (oral) by a physician. Patients were excluded from the study if they were on specific diets; pregnancy or lactating; used insulin for blood glucose control; drug addiction; alcohol consumption 24 hours before blood sampling; any chronic diseases including inflammatory, heart, and liver diseases, and renal failure, cancer, acute myocardial infection, stroke, or serious injuries. The inclusion and exclusion criteria for this study were the same as a previous study on these subjects (23). In addition, the participants with missing data for biochemical measurements (n=10), incomplete food frequency questionnaire (FFQ) (n=36), individuals who had more than +3 SD for at least one of the components of lipid profile (n=22), and those above and below the reported total energy intakes (n=55) were excluded from the study.

2.2. Assessment of other variables

Weight was measured to the nearest 0.1 kg while wearing one layer of clothing and not wearing shoes by a digital scale (SECA, Hamburg, Germany). Height was recorded to the nearest 0.5 cm by a wall-mounted stadiometer whereas the shoulders were relaxed and shoes were removed. BMI was calculated based on the following equation "weight (kg)/height² (m²)". To acquire demographic characteristics, a questioner was given to all participants which contained questions comprised of age, family history of diabetes, marital condition, particular diets, education level, chronic disease background, occupation status, medicine consumption. International Physical Activity Questionnaire (IPAC) was used to acquire physical activity (PA) and was shown as metabolic equivalent hours per week (METs h/week). Activity levels were classified into low, moderate, and high groups, as described by the IPAQ scoring protocol (24).

2.3. Biochemical and serum lipid concentration assay

Blood samples were collected following overnight fasting and the serum was centrifuged, aliquoted, and stored at a temperature of -80 °C until the analysis was performed. All samples were analyzed using a single assay according to the manufacturer's protocol. All measurements were taken at the Endocrinology & Metabolism Research Institute (EMRI) Bionanotechnology laboratory of Tehran University of Medical Science. Triglyceride and total cholesterol (TC) were measured by Randox Laboratories Kit (Pars Azmoon, Iran). The serum levels of high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) were determined by turbidimetry on a Roche Hitachi analyzer (Roche, Germany).

2.4. Dietary Assessment

Usual dietary intake was evaluated by using a 148-item semi-quantitative food frequency questionnaire (FFQ) which

it's reliability and validity had been approved in Iran (25). Participants were asked by Expert dietitians during a face-to-face interview, to report their consumption frequency for each food item over the past year on a daily, weekly, or monthly basis. We used Household measures to change portion sizes to weight in grams. Due to limited data on the nutrient content of some foods and beverages of Iranian food composition tables (FCT), we had to use the US Department of Agriculture (USDA) FCT to compute nutrient and energy content of dietary intake. Nutrient intakes in micro and macro types were calculated using Nutritionist IV software (First Databank Division, the Hearst Corporation, San Bruno, CA, USA, modified for Iranian foods).

2.5. Dietary measurements and DII calculation

Food intake during the last year was assessed by a trained dietitian through FFQs, consisting of 148 food items (26). The respondents indicated their frequency of consumption of each food item on a daily, weekly, monthly, yearly, or a never/seldom basis according to portion sizes that were provided in the FFQs. The reported frequency of consumption for each food item was computed on daily intake and, then, portion sizes of consumed foods were converted from household measures to grams. The complete description of the DII development and validation has been published elsewhere (18, 27). The standard global mean was detracted from the actual dietary intake and the z-scores were computed. Then, the standard deviation was divided by this new value. After that, these z-scores were altered into a percentile and each percentile score was doubled up and then detracted by 1 to reduce 'right skewing' weight (27). The z-scores were calculated via, subtraction of the standard global mean from the actual dietary intake. Then, this value was divided by the standard deviation. Afterward, to reduce the 'right skewing' effect, these z-scores were changed into a percentile and each percentile score was doubled and then detracted by 1 (27). To attain a food parameter-specific individual DII score, the centered percentile score for each food parameter for each individual was then multiplied by the respective food parameter effect score (inflammatory potential for each food parameter), which was derived from the literature review (28-30). Subsequently, the overall DII score for each participant has computed through the summation of all of the food parameter-specific DII scores. Upper DII scores are an indicator of a more pro-inflammatory diet; while lower values characterize more anti-inflammatory diets (11). The FFQ was applied to attain a total of 32 food parameters and were used to compute DII (namely: energy, carbohydrate, protein, total fat, alcohol, fiber, cholesterol, saturated fatty acid, monounsaturated fatty acid, polyunsaturated fatty acid, omega 3, omega 6, vitamin A, vitamin B6, vitamin B12, vitamin C, vitamin D, vitamin E, Folic acid, Iron, Magnesium, Zinc, Selenium, Anthocyanidins, Flavan-3-ols, Flavones, Flavonols, Flavonones, Isoflavones, garlic, tea, and onion).

2.6. Statistical analysis

The normality of quantitative variables was evaluated by the Kolmogorov–Smirnov test (KS test). Categorical variables are presented as frequencies of occurrence and percentages, and continuous variables are presented as the mean and standard deviation (SD) and as the mean and (25-75 interquartile range) and percentages; differences between groups were tested using a Chi-squared test or a Student's t-test, respectively. The DII was analyzed both as a categorical (quartiles) and a continuous variable. ANOVA and Chi-square tests were applied to examine the variables across quartiles of DII. The relation between the DII and lipid profile was tested using linear regression (unadjusted) and multivariable logistic regression analysis adjusted for baseline characteristics (age, gender, BMI, and energy intake) comparing individuals grouped into quartiles. The results are reported as a percentage change (β), with 95% confidence intervals (95% CI). All reported P values were based on two-sided tests and compared to a significance level of 5%. SPSS® 21 (SPSS version 21 (SPSS Inc., Chicago, USA).) software was used for all of the statistical analyses.

3. Result

3.1. Study population characteristics

The characteristics of 599 diabetic patients were analyzed in this study. Table 1 showed the mean (\pm SD) age, BMI, height, and physical activity of participants were 54.08 (6.45) years, 29.33 (4.66) kg/m², 160.0 (9.04) cm, 69.4 (13.0) kg, 37.89 (5.45) MET/Min/week, respectively.

Table 1. Anthropometric and laboratory characteristics of the study population.

Parameters	Minimum	Maximum	Mean	Std. Deviation
Age (years)	35	65	54.08	6.45
Height (cm)	138	188	160	9.04
BMI (kg/m ²)	20	54	29.33	4.66
Waist Circumference (cm)	138	188	92.26	10.51
TC (mmol/L)	60.00	480	194.62	61.86
TG (mmol/L)	34	502	175.72	91.74
HDL-C (mg/dL)	17	88	53.16	0.45
LDL-C (mg/dL)	24	224	107.90	33.99
LDL/HDL	61	186	2.58	9.54
Energy (kcal)	882.73	3963.70	2613.03	751.74
Physical activity (MET h/day)	24	72.20	37.89	5.45

Data are presented as mean \pm standard deviation. n=219. BMI, Body Mass Index; WC, Waist circumference; TG, Triglyceride; HDL-C, High-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LDL-C/HDL-C, low-density lipoprotein/ High-density lipoprotein; TC, total cholesterol; DII, dietary inflammatory index. ¹Continuous variables were reported as means \pm SDs (using ANOVA test) or median (inter-quartile range) (using Kruskal-Wallis test) depending on the normality of distribution of data. ²Categorical variables were analyzed using the Chi-square test and reported as percentage (%).

The distribution of study population characteristics is shown by quartiles of DII in Table 2. The individuals who were in first quartile has lower scores and lower adherence of the inflammatory diet and it was convers in higher quartiles. The median and intra quantile rate (IQR) for age and BMI of

participants was 54 years (IQR=50-59) and 28.6 kg/m² (IQR=26.2–31.7), respectively. The DII score ranged between -4.85 and 5.46 and its mean and standard deviation (SD) was (-0.02±1.65). Individuals who had higher DII scores in higher quartile were significantly younger ($p \leq 0.001$). Moreover,

lower levels of physical activities were found in the higher quartiles of DII ($p=0.005$). There were no clear trends in the distribution of BMI, waist circumference, or lipid profile across DII quartiles. β coefficient and standard error (SE) for overall DII and lipid profile were reported in Table 3.

Table 2. Baseline characteristics of the study sample according to Dietary Inflammatory Index (DII) quartiles.

Variable	DII Quartiles				P value
	Q1 (-4.85 to -1.22)	Q2 (-1.21 to -0.02)	Q3 (-0.01 to 1.12)	Q4 (1.13 to 5.46)	
Age	55 (60-51)	56 (61-51)	54 (58-50)	53 (58-48)	0.00
Female, N (%)	106 (24)	101 (23)	129 (30)	96 (22)	0.77
Male, N (%)	69 (25)	76 (28)	48 (18)	78 (29)	0.77
BMI, kg/m ²	29.3 (26.32-7.00)	27.6 (25.33-6.90)	29.10 (26.31-8.8)	28.70 (26.31-1.90)	0.98
WC, cm	92.90±6.20	91.11 ±7.50	91.10±7.0	93.11±0.20	0.67
TG, mg/dl	138 (214-100)	155 (226-101)	169 (243-103)	155 (226-107)	0.23
HDL-C, mg/dl	11±51	12±54	12±53	11±52	0.45
LDL-C, mg/dl	100 (130-76)	106 (130-85)	104 (134-83)	107 (128-86)	0.53
LDL-C/HDL-C	1.90 (1.20-5.60)	2 (1.20-6.50)	1.20 (1.20-5.60)	2.10 (1.20-6.50)	0.58
TC, mg/dl	186 (218-148)	188 (227-156)	185 (240-150)	191 (234-148)	0.15
Physical activity, MET	38.6 (34.42-9.20)	37.6 (34.41-1.10)	36.90 (34.40-3.10)	36.70 (33.40-8.20)	0.00
DII	-2.0±11.73	-0.0±60.35	0.0±50.34	2.0±11.75	0.00

BMI, Body Mass Index; WC, Waist circumference; TG, Triglyceride; HDL-C, High-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LDL-C/HDL-C, low-density lipoprotein/ High-density lipoprotein; TC, total cholesterol; DII, dietary inflammatory index. ¹Continuous variables were reported as means ± SDs (using ANOVA test) or median (inter-quartile range) (using the Kruskal-Wallis test) depending on the normality of distribution of data. ²Categorical variables were analyzed using the Chi-square test and reported as a percentage (%).

In the overall analysis, no significant association was observed between DII and lipid profile in the crude model, but after adjusting for confounders (age, gender, BMI, physical activity, and energy intake), the DII score was found to be positively associated with total cholesterol ($\beta=3.123$, $SE=1.478$,

$p=0.035$) in all participants. Therefore, participants who had higher DII score had higher TC levels. As shown in Table 3, TC increased by 3.123 in the higher dietary inflammatory diet score, with adjusted confounders.

Table 3. Associating of the dietary inflammatory index and lipid profile.

Variable	Model 1			Model 2		
	B	SE	P-value	β	SE	P-value
HDL-C	0.20	0.27	0.45	0.28	0.28	0.23
LDL-C	0.57	0.77	0.46	0.79	0.81	0.32
LDL-C/HDL-C	-0.03	0.21	0.87	-0.05	0.23	0.81
Total Cholesterol	2.33	1.41	0.10	3.12	1.47	0.03
Triglyceride	3.15	3.47	0.13	3.86	2.21	0.19

Linear regression.

Model 1: Crude Model.

Model 2: Adjusted for age (year), sex (in the category of the total population), body mass index (kg/m²), and standardized energy intake (kcal), physical activity.

4. Discussion

The final effect of a certain dietary component on both inflammatory responses and health outcomes can be modified by interactions among nutrients (31). The inflammatory marker might be regulated by adherence to a healthy dietary pattern as a determinant factor and based on last research, the pro- and anti-inflammatory status of many specific foods and nutrients have been recognized and presented as the Dietary inflammatory index (DII) which result in chronic systemic inflammation and related diseases (9). No previous study had investigated the association between the DII score and different subtypes of CVD and lipid profile, to the best of the author's knowledge this cross-sectional study was conducted to assess the association between the DII and lipid profile for the first time among Iranian diabetic patients. We found that

the DII score was not correlated with any of the anthropometric measures, LDL, HDL, TG, and LDL/HDL. Interestingly, our data demonstrate that the DII was positively and significantly correlated with higher TC concentration after correction for age, sex and BMI, energy intake, and physical activity. With regard to conventional cardiovascular risk factors, we observed that an inflammatory diet was related to higher total cholesterol. Furthermore, correlation analysis identified that an increased inflammatory potential of the diet was positively associated with plasma TC levels. Thus, our findings also should be interpreted in the light of studies that have found a preventive role of diets with an overall high-quality concerning dyslipidemia and CVD incidence. Limited data exist regarding the associations between dietary inflammatory potential, circulating biomarkers of lipid profile. So far, several studies showed the association between DII and

C-reactive protein (CRP) (11), interleukin 6 (IL-6) (28), tumor necrosis factor (TNF) (28), fibrinogen (13), and more recently with white blood cell (WBC) counts (32). To date, studies have examined the association between the DII and MetS risk, with inconsistent relationships identified. A recent meta-analysis confirmed that individuals with the highest DII scores and thus the most pro-inflammatory diet showed a 36% increased risk of CVD incidence and mortality, relative to those with the lowest DII scores (33). These effects on lipid profiles are almost in line with data from the Supplémentation en Vitamines et Minéraux Antioxydants (SU.VI.MAX) study conducted in a cohort of 3726 subjects, which confirmed that the individual with lower HDL-C and higher triglyceride had higher adherence to a pro-inflammatory diet (34). Sokol et al. illustrated that the DII is inversely associated with HDL-C in a Polish population of 3862 contributors (35). Taking into account our association findings and the above lines of evidence, a pro-inflammatory diet might have a negative effect on the cardiometabolic risk profile across different populations (20). Moreover, a cohort of French adults was done by Neufcourt et al. (19) showed in a large study population (n=3726) that at baseline, the DII score was positively connected with triglyceride level, but not with HDL cholesterol level. After a follow up of 13 years, it was shown that there is a significant association between the DII score and higher triglyceride and lower HDL cholesterol levels. This relation has also been confirmed by a small-scale study (n=90) in Colombia (20). Our intermediate size study in Iranian diabetic adults could not confirm these findings. On the other hand, research among 447 police officers in the U.S showed no significant relationship between increasing DII score and increased risk for low HDL cholesterol or elevated triglyceride concentrations (35). Thus, the contradictory results may be explained by the different dietary patterns, population, genetic and sample size, differences in the prevalence of inflammation-related diseases such as dyslipidemia, CVD, and diabetes. Cardiovascular diseases have been diagnosed by dyslipidemia or disturbance of lipid profile including triglyceride and cholesterol which are known as early biomarkers. Though, this concept is a controversial issue. In recent years, it is suggested that the Inflammation may be a more important biomarker of cardiovascular diseases (35). This new hypothesis is vital due to the possible prevention of dietary approaches for cardiovascular disease prevention. Therefore, it may be more valuable to consider lowering the inflammatory properties of the diet as a key factor in the prevention of cardiovascular disease, instead of aiming to lower cholesterol and triglycerides. There are not exact and certain mechanisms underlying the regulatory role of an anti-inflammatory diet in low-grade inflammation in cardiometabolic diseases and lipid profile. However, it has been hypothesized that pro-inflammatory properties of unhealthy dietary patterns could generate an intrinsic immune response which results in an increased production of pro-inflammatory cytokines and reduced production of anti-inflammatory cytokines, stimulating states of chronic inflammation and as the consequence, it induces a higher risk

of endothelial dysfunction, metabolic syndrome, and CVD (36). Another possible explanation could be that inflammation is more strongly linked to MI or dyslipidemia. An inflammatory response in the artery wall would be initiated by the infiltration and retention of low-density lipoprotein cholesterol in the arterial intima (37). It involves the binding of blood cells, especially monocytes, which then differentiate into macrophages and internalize a broad range of molecules including oxidized low-density lipoprotein particles. Ultimately, the macrophages are transformed into foam cells, the prototypical cells in atherosclerosis (38). Several endogenous and microbial molecules can ligate pattern-recognition receptors (Toll-like receptors) on these cells, leading to the release of pro-inflammatory cytokines and ultimately to tissue damage and the chronic disease such as diabetes and CVD will be occurred (39, 40). Furthermore, we have found any correlation between DII and body mass index (BMI). Several studies were conducted to assess the relation between DII and body composition, in a cross-sectional analysis of the Spanish PREDIMED trial, the DII score was related with BMI only in women but not in men which is not in line with Shivappa et al. study (13). In Myanmar, a small cross-sectional study among overweight and non-overweight female school teachers showed that the DII score was not associated with overweight (41). A role for DII in the development of obesity was indicated by Ramallal et al. (42). They showed that in a non-overweight adult Spanish cohort the DII score was not associated with BMI at baseline, but a higher DII score was associated with a higher body weight increment after 8 years of follow up and a higher risk of developing overweight or obesity. Based on these studies and our findings, the effect of the DII on body weight remains inconclusive. Well-controlled longer-term intervention studies are required to shed more light on the role of DII in body weight regulation. Those convincing evidence showed that there is an important association between obesity and its cardiovascular co-morbidities (16, 43-45). Previously it was suggested that low-grade inflammation was associated with the development of dyslipidemia (16). Therefore, the dietary patterns which increase the inflammation in the body may have a vital role in the incidence of dyslipidemia and CVD especially in diabetic patients who are at a higher risk of those diseases. Some limitations of this study should be acknowledged. The main one might be the number of enlisted subjects that were relatively low. The cross-sectional design of the study is another important limitation as it prevented us from inferring causality. One of the inevitable limitations of this type of study is those questionnaire responses are subjectively based on participants' memory and their perception of pain.

5. Conclusion

Because of the potential importance of diet in the development of inflammation, intervention studies that investigate the effect of manipulation of the inflammatory properties of the diet on the inflammatory process are

warranted. In summary, our results suggest that an increased anti-inflammatory potential of diet, as measured by the DII, was associated with improved total cholesterol. These findings underline the importance of promoting anti-inflammatory nutrition as an effective strategy for preventing CVD in diabetic patients who are at higher risk. Moreover, results from this study provide a practical implication that can help reduce the inflammatory properties of the diet of individuals in the study population. This can be done by reducing the consumption of carbohydrate-rich foods (e.g., rice, sugar, and wheat-based products) and increasing consumption of unsaturated fat and protein-rich foods (such as eggs and fatty fish).

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