

# Association Between Diabetic Retinopathy, Dietary Inflammatory Index and Metabolic Syndrome in Azar Cohort Study

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## Research article

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# Abstract

**Background :** The aim of present study was to evaluate the association between diabetic retinopathy (DR), dietary inflammatory index (DII), and metabolic syndrome (MetS) in patients with type 2 diabetes in a cohort study in Iran.

**Methods:** This cross-sectional study was a part of the large Azar eye cohort study that included 1378 patients with type 2 diabetes. To diagnose DR, two mydriatic fundus photographs were captured using a digital fundus camera. The DR severity was classified as non-proliferative diabetic retinopathy (NPDR) or proliferative diabetic retinopathy (PDR). MetS was determined on the basis of the ATPIII criteria. DII was calculated according to Shivappa et al. method.

**Results:** Of 1378 diabetic patients, 185 (13.4%) had NPDR and 142 (10.3%) had PDR. The risk of NPDR and PDR increased by 2.65-fold and 2.01-fold, respectively, in patients having blood glucose levels that fell outside the recommended range. There was no statistically significant relationship between Mets, Mets components, and DII in NPDR and PDR.

**Conclusion:** The results suggest that intensive glycemic control, rather than conventional control, may help reduce the progression of DR. It seems that longitudinal studies and clinical trials for evaluating role of DII in DR are necessary.

## 1. Background

Diabetic retinopathy (DR) is the most common microvascular complication of diabetes and is a leading cause of blindness in developing countries [1]. Due to the increasing prevalence of diabetes, it is expected that the prevalence of DR also will increase. DR is commonly observed in almost all type 1 diabetic patients and in more than 60% of type 2 diabetes mellitus (T2DM) patients who have had disease for more than 20 years [2].

Considering the large burden of this disease and also the limitations of available therapies, there is great interest in developing new strategies to prevent DR [3]. Studies have investigated the potential risk factors of DR and it has been shown that increasing age, disease duration, hyperglycemia and hypertension will increase the risk of development and progression of DR [4]. Moreover, it has been reported that inflammation has a role in the pathogenesis and development of DR [5]. On the other hand, it has been documented that there is link between inflammation and metabolic syndrome, diabetes and cardiovascular diseases (CVD). In this regard, diabetic patients are susceptible to CVD and mortality rate of CVD is high among these patients. Above mentioned risk factors are known as traditional risk factors of DR, however it has been shown that, even when glycemia and hypertension are under control, the number of diabetic patients with DR is increasing. Therefore, recent investigations have aimed for the identification of new and multiple risk factors of DR and some researchers have focused on diet and its role in the development and progression of DR. The role of diet in development of diabetes has been known but its role in DR has been much less evaluated [6]. Only one study evaluated the role of whole diet as Mediterranean diet in developing DR and others assessed food groups, macro, micronutrients and individual nutrient[7]. The findings of these studies are inconclusive [8]. The findings of these studies indicated that mediterranean diet, high fruit, vegetable, reduced caloric intake may reduce risk of DR.

Although different studies have been conducted on the association of DR and diet, to the best of our knowledge, there is no published article on the association between inflammatory potential of diet as measured by the dietary inflammatory index (DII®) and DR. However, the DII has been shown to be associated with T2DM and metabolic syndrome (MetS) in several studies [9, 10]. Therefore, the aims of present study were to study the association between DR, DII and MetS components in patients with T2DM in the Azar cohort study in Iran.

## 2. Methods

Data from this cross-sectional study were obtained from the Azar cohort study (including eye cohort study), in Shabestar in East Azerbaijan province (North West of Iran) which is part of the larger Persian cohort study (Prospective Epidemiological Research Studies of Iranian Adults) [11]. Azar cohort study was explained with more details in other published article [12]. This study was approved by Ethics Committee of Tabriz University of Medical Sciences (tbzmed.rec.1393.205). Written informed consent was obtained from all participants.

A total of 11,791 subjects participated in the Azar eye cohort study. Eye examinations were performed in all participants and a questionnaire regarding eye-specific medical history was completed and a visit by a trained optometrist to assess refractive error were done. Fundus photography and slit photos also were obtained for all participants. In addition, subjects who met certain screening criteria received a complete ophthalmological examination [11]. Based on the aim of the present study, subjects who had T2DM (n = 2012; 13.4%) were selected. Participants who did not have a fundus photograph (n = 625), who had a history of gestational diabetes mellitus (n = 6) or type 1 diabetes (n = 3) were excluded. Statistical analysis was performed on the remaining 1378 patients with type 2 diabetes.

## **2.1. Demographic characteristics of participants**

The demographic characteristics of the participants; i.e., age, gender, marital status and educational level, were collected by questionnaire. Individual habits such as smoking, drug use, hookah, and alcohol consumption and being passive smokers were evaluated by questionnaire. Socio-economic status was defined based on job category, educational level and family assets using principal component analysis. Socioeconomic status was classified as very high, high, middle, low or very low based on a quintuple of obtained scores [13].

## **2.2. Anthropometric and blood pressure measurements**

Weight, height and waist circumference were measured and the body mass index (BMI) was calculated by dividing the weight (kg) by the height (m) squared. The anthropometric measurements are described in detail elsewhere [11]. Blood pressure was measured twice on one day with an interval of two minutes and twice in each arm in a sitting position after 10 minutes of rest by a trained nurse using a mercury sphygmomanometer (Rudolf Richter, DE-72417; Germany). The averages of these two measurements were considered as the systolic and diastolic blood pressure.

## **2.3. Biochemical Factors**

Blood samples were collected after an overnight fast of  $\geq 12$  hours. Fasting blood sugar (FBS), serum triglyceride (TG), high density lipoprotein (HDL) were determined by enzymatic methods. Low density lipoprotein (LDL) was calculated by Friedewald's formula.

## **2.4. Definition of diabetes and MetS**

Participants were considered to have diabetes if they were currently using glucose-lowering medications or if they had FBS  $\geq 126$  mg/dl or Hb1AC  $\geq 6.5\%$  [14]. Type 1 diabetes was determined on the basis of medical history, age at onset of diabetes and treatment type for glycemic control. Any diabetic that did not have Type 1 diabetes was classified as having T2DM.

MetS was defined according to the National Cholesterol Education Program Adult Treatment Panel III report criteria (ATP III) [15]. Subjects with three or more of the following conditions were defined as having MetS: waist circumference  $\geq 102$  cm in men and  $\geq 88$  cm in women, TG  $\geq 150$  mg/dl (drug treatment for elevated triglycerides is an alternate indicator), HDL-C values of  $< 40$  mg/dl in men and  $< 50$  mg/dl in women. Hypertension was defined as elevated systolic blood pressure ( $\geq 130$ ) and/or diastolic ( $\geq 85$ ) mmHg or the use of antihypertensive medication. Elevated fasting glucose was considered to be  $\geq 100$  mg/dl or the use of glucose-lowering medication.

## **2.5. Dietary inflammatory index (DII®)**

Dietary intake of subjects was evaluated by food frequency questionnaire which was completed by trained nutritionist. Each food item was converted to gr/day and then analyzed by Nutritionist IV. The energy-adjusted DII (E-DII) score was calculated on the basis of Shivappa et al. method which is described in detail elsewhere [16]. The food parameters included in calculation of the E-DII in this study were vitamin B12, vitamin B6, -carotene, caffeine, carbohydrate, cholesterol, energy, total fat, fiber, vitamin B9, iron, magnesium, mono-unsaturated fatty acid, vitamin B3, -3 fatty acids, -6 fatty acids, protein, poly unsaturated fatty acids, vitamin B2, saturated fatty acid, selenium, vitamin B1, vitamin A, vitamin C, vitamin D, vitamin E and zinc, tea, garlic and onion. All food items were adjusted for energy using the energy density method.

More negative DII scores are correlated with anti-inflammatory diet and more positive scores indicate more pro-inflammatory diet [16].

## 2.6. Diabetic retinopathy assessment

According to Azar cohort protocol, after maximal dilation of the pupils using mydrax 1% to each eye, two photographs were captured by a digital fundus camera (TRC-NW6S; Topcon; Japan) equipped with a Nikon D-80 digital camera (Nikon; Japan). All patients underwent 45°, two-field macula-centered fundus imaging. For determining risk factors of DR, DR severity was classified as non-proliferative diabetic retinopathy (NPDR) or proliferative diabetic retinopathy (PDR). If DR was diagnosed in both eyes and the severity was different in each eye, the highest stage of DR was considered for statistical analysis.

## 2.7. Statistical Analysis

Data was presented using mean (SD) and frequency (percentage) for the numeric and categorical variables, respectively. To investigate the association between the levels of DR and systemic factors, univariable and multivariable logistic regression modeling were used. In multivariable analysis, the models were adjusted for age, gender, marital status, and socioeconomic status, place of residence, cigarette smoking, hookah smoking, and drug use and alcohol consumption. In the analysis, the odds ratios (ORs) and 95% confidence interval (CI) were presented. To compute the p-value for trend, categorical variables were entered into logistic model quantitatively. All analyses were conducted in SPSS® 17 (SPSS; USA) and statistical significance was set at  $p < 0.05$ .

## 3. Results

Of 1378 diabetic patients, 185 (13.4%) had NPDR and 142 (10.3%) had PDR. The characteristics of the patients stratified by level of DR are presented in Table 1. A rate of patients with obesity, MetS, abdominal obesity, hypo-HDL cholesterolemia and hypertriglyceridemia was higher in diabetic patients without DR than in those with NPDR and PDR. Moreover, the percentage of patients with uncontrolled blood glucose and blood pressure was higher in the PDR group than in the other study groups. According to E-DII quartile, 25.2%, 23.5%, and 24.8% of patients without DR, with NPDR, and PDR were in the most pro-inflammatory E-DII quartile (4th).

Table 1

Baseline characteristics according to level of diabetic retinopathy (DR) in patients with type 2 diabetes from the Azar cohort study.

Variables	Level of DR					
	No DR (n*=1051)		Non proliferative DR (n*=185)		Proliferative DR (n*=142)	
	N	%	N	%	N	%
<b>Age (years)</b>						
< 50	302	28.7	44	23.8	16	11.3
≥ 50	749	71.3	141	76.2	126	88.7
<b>Gender</b>						
Male	429	40.8	86	46.2	73	51
Female	622	59.1	99	53.5	69	48.5
<b>Marital status</b>						
Single	86	8.2	18	9.7	14	9.8
Married	965	91.8	167	90.3	128	90.2
<b>Place of living</b>						
Urban	793	75.5	148	80.0	105	73.9
Rural	258	24.5	37	20.0	37	26.10
<b>Socioeconomic status</b>						
Very low	225	21.7	43	23.4	39	27.9
Low	235	22.6	38	20.7	28	20.0
Middle	226	21.8	46	25.0	26	18.6
High	190	18.3	35	19.0	25	17.9
Very high	162	15.6	22	12.0	22	15.7
<b>BMI (kg/m<sup>2</sup>)</b>						
Normal (18.5–24.9)	119	11.3	21	11.4	29	20.4
Overweight (25–29.9)	396	37.7	81	43.8	53	37.3
Obese (≥ 30)	536	51	83	44.9	60	42.3
<b>Metabolic syndrome</b>						
Yes	822	78.3	141	76.2	104	74.8
No	228	21.7	44	23.8	35	25.2
<b>Metabolic syndrome components</b>						
Abdominal obesity*	736	70.0	118	63.8	89	62.7

\* abdominal obesity: waist circumference in men ≥ 102 cm, in women ≥ 88 cm; § Hypo HDL-cholesterolemia: HDL-C < 40 mg/dl in men and < 50 mg/dl in women; # Glycemic control : Fasting blood sugar (FBS) = 80–130 mg/dL, ; ## hypertension: blood pressure < 140/90

	Level of DR					
	No DR (n*=1051)		Non proliferative DR (n*=185)		Proliferative DR (n*=142)	
Hypertension	557	53.2	109	59.2	87	62.6
Hypo HDL-cholesterolemia <sup>§</sup>	666	63.4	112	60.5	81	57.0
Hypertriglyceremia <sup>§§</sup>	557	53.0	91	49.2	70	49.3
<b>Glycemic control #</b>						
Not controlled	448	42.6	131	70.8	93	65.5
Newly diagnosed diabetes	156	14.8	5	2.7	4	2.8
Controlled	447	42.5	49	26.5	45	31.7
<b>Hypertension ##</b>						
Not controlled	167	16	29	15.8	34	24.5
Controlled	880	84.0	155	84.2	105	75.5
<b>Cholesterol</b>						
≥ 200 mg/dl	427	40.6	63	34.1	53	37.3
< 200 mg/dl	624	59.4	122	65.9	89	62.7
<b>LDL-cholesterol</b>						
≥ 100(mg/dl)	648	62.0	102	56.0	78	54.9
< 100(mg/dl)	398	38.0	80	44.0	64	45.1
* abdominal obesity: waist circumference in men ≥ 102 cm, in women ≥ 88 cm; § Hypo HDL-cholesterolemia: HDL-C < 40 mg/dl in men and < 50 mg/dl in women; # Glycemic control : Fasting blood sugar (FBS) = 80–130 mg/dL, ; ## hypertension: blood pressure < 140/90						

The findings of multivariable logistic regression indicated that age > 50 years old (OR 3.21; 95% CI 1.87–5.49) and of female gender (OR 1.51; 95% CI 1.06–2.14) were significantly associated with PDR (Table 2). The results of the present study indicated that the risk of NPDR and PDR increased 2.65-fold and 2.01-fold, respectively, in patients with high blood glucose levels outside the recommended range (Tables 2). As shown in Table 3, there was no significant relationship between MetS in NPDR and PDR as compared to no DR. Among MetS components, only hypertension increased risk of PDR by 1.49(1.03–2.14). In this regard, we observed that patients within the normal range of BMI were more likely to have PDR (OR 2.14; 95% CI 1.32–3.48) (Table 3). As shown in Table 4, we did not find any significant association between different quartiles of DII and NPDR and PDR.

Table 2

The association of demographic and baseline characteristics of study subjects with non-proliferative and proliferative diabetic retinopathy

variables	Non proliferative DR (n = 185)	P	proliferative DR (n = 142)	P
	OR (95%CI)		OR (95%CI)	
<b>Age (Year)</b>				
< 50	Reference			
≥ 50	1.26(0.88–1.81)	0.19	3.21(1.87–5.49)	< 0.001
<b>Gender</b>				
Male	1.24(0.91–1.70)	0.16	1.51(1.06–2.14)	0.02
Female	Reference			
<b>Socioeconomic status</b>				
Very low	1.40(0.81–2.44)	0.22	1.22(0.70–2.12)	0.48
Low	1.19(0.67–2.08)	0.54	0.87(0.48–1.58)	0.66
Middle	1.49(0.86–2.57)	0.15	0.84(0.46–1.54)	0.58
High	1.39(0.78–2.46)	0.25	0.96(0.52–1.78)	0.91
Very High	Reference			
<b>Glycemic control<sup>#</sup></b>				
Not controlled	2.08(1.42–3.03)	< 0.001	2.01(1.36–2.97)	< 0.001
Newly diagnosed	0.25(0.09–0.72)	< 0.001	0.25(0.08–0.72)	< 0.001
Controlled	Reference			
<sup>#</sup> Glycemic control: if Fasting blood sugar (FBS) = 80–130 mg/dL, it was considered as glycemic control				

Table 3

Association of metabolic syndrome and its components with non-proliferative and proliferative diabetic retinopathy

Variables	Non proliferative DR			proliferative DR				
	Unadjusted OR (95%CI)	P	adjusted OR (95%CI)	P	Unadjusted OR (95%CI)	P	adjusted OR (95%CI)	P
<b>BMI (kg/m<sup>2</sup>)</b>								
Normal (18.5–24.9)	1.12(0.67–1.89)	0.64	1.02(0.6–1.76)	0.91	2.14(1.32–3.48)	0.002	1.12(0.67–1.89)	0.64
Over weight (25–29.9)	1.30(0.93–1.82)	0.11	1.21(0.8–1.70)	0.26	1.17(0.79–1.74)	0.41	1.30(0.93–1.82)	0.11
Obese (≥ 30)	Reference							
<b>Metabolic syndrome</b>	0.88(0.61–1.28)	0.53	0.88(0.60–1.28)	0.52	0.82(0.54–1.24)	0.35	0.78(0.51–1.18)	0.24
<b>Metabolic syndrome components</b>								
Abdominal obesity**	1.37(0.95–1.82)	0.09	1.19(0.82–1.72)	0.35	1.37(0.95–1.98)	0.08	1.18(0.77–1.79)	0.35
Hypertension	1.29(0.94–1.77)	0.11	1.32(0.94–1.84)	0.10	1.49(1.03–2.14)	0.03	1.34(0.91–1.97)	0.13
Hypertriglyceremia <sup>€</sup>	0.85(0.62–1.16)	0.31	0.88(0.64–1.21)	0.43	0.85(0.6–1.20)	0.37	0.95(0.66–1.36)	0.78
Hypo-HDL-cholesterolemia <sup>§</sup>	0.87(0.63–1.20)	0.40	0.92(0.66–1.27)	0.61	0.77(0.54–1.10)	0.16	0.83(0.58–1.20)	0.34
Total cholesterol ≥ 200 mg/dl	0.74(0.53–1.03)	0.08	0.77(0.55–1.08)	0.13	0.85(0.59–1.23)	0.40	0.93(0.64–1.36)	0.73
Total cholesterol < 200 mg/dl	Reference							
LDL-cholesterol ≥ 100 mg/dl	0.77(0.56–1.01)	0.11	0.79(0.57–1.09)	0.16	0.73(0.51–1.04)	0.08	0.75(0.52–1.07)	0.12
LDL-cholesterol < 100 mg/dl	Reference							
*n = number; ** abdominal obesity: waist circumference in men ≥ 102 cm, in women ≥ 88 cm; <sup>§</sup> Hypo HDL-cholesterolemia: HDL-C < 40 mg/dl in men and < 50 mg/dl in women ; <sup>€</sup> Hypertriglyceridemia: triglyceride ≥ 150 mg/dl; <sup>¥</sup> adjusted for age, gender, marital status, socioeconomic status, place of living, cigarette smoking, hookah smoking use of drugs, drinking alcohol								

Table 4  
Relationships between dietary Inflammatory Index score and non-proliferative and proliferative diabetic retinopathy

	Non proliferative DR				Proliferative DR			
	Unadjusted OR(95%CI)	P	Adjusted <sup>‡</sup> OR (95%CI)	P	Unadjusted OR(95%CI)	P	Adjusted OR <sup>‡</sup> (95%CI)	P
<b>Dietary inflammatory index</b>								
Q1:-3.57-1.084	0.82(0.53–1.28)	0.82	0.83(0.53–1.30)	0.43	1.00 (0.60–1.66)	0.98	1.05(0.63–1.77)	0.83
Q2:-2.10-1.51	0.84(0.54–1.31)	0.45	0.84(0.53–1.3)	0.44	1.03(0.63–1.71)	0.88	1.03(0.61–1.73)	0.91
Q3:-1.60-2.39	0.86(0.56–1.34)	0.52	0.86(0.55–1.34)	0.52	1.04(0.63–1.71)	0.87	1.13(0.68–1.89)	0.62
Q4:-1.31-5.45	<b>Reference</b>				<b>Reference</b>			
<sup>‡</sup> adjusted for age, gender, marital status, socioeconomic status, place of living, cigarette smoking, hookah smoking use of drugs, drinking alcohol								

## 4. Discussion

The results of this study indicated that the duration of diabetes, high blood glucose, and high blood pressure were associated with DR and, in particular, PDR. In this study of 1378 diabetic patients, 185 (13.4%) had NPDR and 142 (10.3%) had PDR. The prevalence of DR varies by country from 9.6% in India to 43.1% in Indonesia. The prevalence of DR in different provinces of Iran have been reported to be 30.5% in Tehran to 76.4% in Isfahan [17]. It should be noted that, in most studies, a prevalence of DR of 30%-40% has been reported [17]. The wide range of prevalence in various regions can be ascribed to the type and duration of diabetes, ethnicity [18], method of DR determination (fundus photograph or ophthalmoscopy) and level of awareness and self-management of diabetes [19]. In the terms of systemic factors, the current results are similar to those of previous studies which reported the duration of diabetes, poor glycemic control and high blood pressure as important determinants of the risk of incidence and progression of DR [20–22].

No significant relationship was found between DR and MetS. In line with these findings, Chen et al. [23] reported that the prevalence of MetS was high in diabetic patients, but there was no significant association with the incidence and severity of DR. The results of the Korean National Health and Nutrition Examination Surveys also showed that MetS and its components did not increase the risk of DR [24]. On the other hand, some studies have reported a positive relationship between MetS and DR [25–27]. In this regard, Bonadonna et al. [25] noted that the risk of DR increased 1.49-fold in diabetic patients as compared with patients without MetS. The discrepancy between the results of different studies may be due to the use of different criteria for defining MetS and DR.

In the current study, diabetic patients with normal BMI values had 83% higher odds of DR compared with obese patients. This association has been supported by previous studies in Asia which have reported no significant or inverse relationship between BMI and DR [28–31]. The results of Asian and Western studies differ in this respect. In Australian diabetic patients, a higher BMI increased the risk of DR [32], which is the opposite of the results of the aforementioned Asian studies [28, 30, 31]. We have no explanation for the relationship between normal BMI and DR; it was assumed that BMI might not be as good indicator of obesity as percentage of body fat.

The results of regression analysis indicated that there was no significant association between a high level of TG, total cholesterol, LDL-C and lower level of HDL-C and DR. These results are in agreement with the results of earlier large population-based studies [33, 34]. In contrast, in other studies, dyslipidemia in diabetic patients has been reported to be a risk factor for DR [35, 36]. The contradictory results can be attributed to differences in ethnicity, race, genetics, geographical area and life style.

In this study, we could not confirm an association between the DII and DR. It has been reported that inflammation plays important role in the development of DR. In this regard, findings of previous studies indicated that using anti-inflammatory agent such as salicylates or minocycline had positive effects in preventing the progression of DR[37, 38]. According to these results, recently researchers noted the DII may influence the development of DR. As far as we know this is the first study which examine the association between DII and DR. Previous studies evaluated the role of whole diet or individual nutrient in incidence and development of DR. The result of systematic review study by Wong et al indicated that dietary fibre, oily fish, a Mediterranean diet and a reduced caloric intake can reduce the risk of DR[8]. The role of antioxidants, fatty acids, proteins and alcohol are not well described [8]. Because there is no study about DII and DR we have to compare our results with studies that evaluate dietary factors that have anti-inflammatory role such as vitamin C, carotenoids, vitamin E, etc.

Tanka et al noted vitamin C decreased risk of DR[39], while findings of other cross-sectional studies did not report this inverse association [40, 41]. Dow et al reported that results of various studies showed there was no association between vitamin E, carotenoids, and vitamin D [42]. The findings of the present study are similar to these other studies. It is conceivable that no significant association between DII and DR may be due to recall bias involved in completing the FFQ. Most patients in our study had diabetes when they participated in the cohort study. Thus, they may have changed their diets on the basis of physician advice factors. Also, they may have been embarrassed to report a bad (i.e., pro-inflammatory diet). For example we know that dietary self-reports are often biased by response sets such as social desirability and social approval[43, 44]. These could be explanations for the absence of an observed association between DII and DR.

The present study had some limitations, including its cross-sectional design and the fact that HbA1C could not be measured in all study participants. As noted, there are potential information biases that result from self-report of dietary intake. Despite its weaknesses, the present study has several strengths. DR was identified on the basis of fundus photography with pupil dilation, which is the best method of determining DR [45]. Moreover, the very large sample of diabetic patients improves statistical power. Other strength of present study is the assessment of dietary inflammatory index as a possible risk factor for the development of DR. however, this also may be limited by the self-reported nature of the dietary data.

In conclusion, the results showed that poor glycemic control, and high blood pressure was associated with advanced levels of DR. Therefore, in confirmation of previous studies, intensive glycemic control rather than conventional control can be helpful in the prevention of the incidence and progression of DR [46, 47]. Moreover, there is a need to increase self-care awareness of diabetic patients about achieving the goal of glycemic and blood pressure control. We could not confirm the association between DII and DR. It seems that longitudinal studies and clinical trials for evaluating role of dietary-associated inflammation in DR are necessary.

## Abbreviation List

Diabetic retinopathy: DR

Dietary inflammatory index : DII

Metabolic syndrome : MetS

Non-proliferative diabetic retinopathy: NPDR

Proliferative diabetic retinopathy: PDR

Type 2 Diabetes Mellitus : T2DM

Cardiovascular Diseases :CVD

Fasting blood sugar : FBS

Triglyceride :TG

High density lipoprotein : HDL

Low density lipoprotein: LDL

Body mass index: BMI

energy-adjusted DII : E-DII

## Declarations

### Ethics approval and consent to participate

This study was approved by the ethic committee of Tabriz University of medical sciences (tbzmed.rec.1393.205).

### Consent for publication

Not Applicable

### Availability of data and materials

The data that support the findings of this study are available from [Vice Chancellor for Research] but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of [Vice Chancellor for Research]

### Competing interests

The authors declare that they have no competing interests

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### Authors' contributions

-The conception or design of the work: MHS,ARO,ZN,EF

-The acquisition, analysis:ZN,EF ,NS,JRH

OR interpretation of data:EF,ZN,MAJ

Drafted the work or substantively revised:EF,NF,SZ,UH,JG,MM

All authors have read and approved the manuscript

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