Interaction between Apo A-II –265T > C polymorphism and dietary total antioxidant capacity on some oxidative stress and inflammatory markers in patients with type 2 diabetes mellitus

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Abstract

This work aims to examine the interaction between apo A2 (Apo A-II) –265T > C SNP and dietary total antioxidant capacity (DTAC) on inflammation and oxidative stress in patients with type 2 diabetes mellitus. The present cross-sectional study included 180 patients (35–65 years) with identified Apo A-II genotype. Dietary intakes were assessed by a FFQ. DTAC was computed using the international databases. IL-18 (IL18), high-sensitivity C-reactive protein (hs-CRP), pentraxin (PTX3), serum total antioxidant capacity (TAC), superoxide dismutase (SOD) activity and 8-isoprostaneF2α (PGF2α) markers were obtained according to standard protocols. General linear model was used to evaluate the interaction. The interaction of gene and DTAC ($P_{FRAP} = 0.039$ and $P_{ORAC} = 0.042$) on PGF2α level was significant after adjusting for confounders. A significant interaction was observed on IL18 level ($P_{ORAC} = 0.018$ and $P_{FRAP} = 0.048$) and SOD ($P_{TEAC} = 0.037$) in obese patients. Among patients whose DTAC was higher than the median intake, the levels of hs-CRP and PGF2α were significantly higher only in individuals with CC genotype. Serum TAC ($P_{FRAP} = 0.030$, $P_{ORAC} = 0.049$) and SOD were significantly lower in the CC genotype. There was a favourable relationship between the high-DTAC and SOD (obese: $P_{TEAC} = 0.034$, non-obese: $P_{FRAP} = 0.001$, $P_{TRAP} < 0.0001$, $P_{TEAC} = 0.003$ and $P_{ORAC} = 0.001$) and PGF2α (non-obese: $P_{ORAC} = 0.024$) in T-allele carriers. The rs5082 SNP interacts with DTAC to influence several cardiometabolic risk factors. Also, we found dietary recommendations for antioxidant-rich foods intake might be useful in the prevention of diabetes complications in the T carrier more effectively than the CC genotype. Future large studies are required to confirm these results.

Key words: **Apo A2: Dietary total antioxidant capacity: Interaction: Polymorphism**

Type 2 diabetes mellitus (T2DM) is a complicated metabolic disorder, identified by defects in the function of insulin[1]. According to the International Diabetes Federation, the number of diabetic patients is increasing in the world. Iran is one of the countries with the highest prevalence of diabetes and is expected that by the year 2030, the diabetes population size reaches 9.2 million[2]. Oxidative stress and inflammation-related indicators have an influential role in the pathogenesis of diabetes and its complications such as CVD that are the primary cause of death in diabetic patients[3,4].

Diet is a well-known factor that can impact on plasma redox state and is the most important modifiable factor in reducing disease-related oxidative stress[5,6]. Although some researchers indicated that high intake of fruits and vegetables, which are antioxidant-rich foods decreased the risk of death from all-cause mortality and CVD by reducing inflammation and oxidative damage[7,8]. However, these food groups are not the only sources of antioxidants in the whole diet. Also, the evaluation of single antioxidants does not state the total antioxidant ability of the entire diet[9]. In this regard, dietary total antioxidant capacity (DTAC) is

an index that estimates the cumulative effect of antioxidants in the whole diet[10]. Various methods have been used to estimate DTAC[11]. To provide comprehensive and clear information, all these different indices should be applied[10]. This dietary index is a relevant tool in epidemiological studies for the investigation of diet-disease relationships and diseases associated with oxidative stress[12,13]. Some researchers have reported the beneficial effects of a high-total antioxidant capacity (TAC) diet on cardiovascular disease, systematic inflammation, oxidative stress[10].

However, individuals are not affected equally by high-dietary TAC. It means that in addition to environmental factors that are link with the risk of CVD, it can also be affected by genetic variants or interactions between genetic susceptibilities and diet. Among many SNP that have been identified in the Apo A-II gene, −265T/C (rs5082) is the most studied. It has been reported that the replacement of T with C at −265 nucleotide of the Apo A-II gene leads to reduce the transcriptional rate of the Apo A-II and its serum concentration. In this regard, Apo A-II as a major structural protein of plasma HDL which accounts for 20 % of the total protein components of this lipoprotein has a complex metabolic role[14,15]. Some researchers reported that variations in the Apo A-II −265 C > T genes differ in cardiometabolic risk factor and is associated with CVD[16,17]. In our previous study, we observed that the variants of Apo A-II − 265T/C polymorphism have various levels of oxidative stress and inflammation. In other words, diabetic patients with minor C allele are susceptible to CVD due to increased levels of inflammation and oxidative stress[18,19]. Likewise, it is suggested that a higher level of Apo A-II in carriers of the T allele is related to decreased blood leukocytes, lower serum levels of C-reactive protein (CRP), and higher activity of paraoxonase-1 (PON1)[16]. Given the above, the interaction between the variants of this polymorphism and the DTAC may affect cardiometabolic risk factors.

Since there is no report in regard to the effect of the interaction between this SNP and DTAC on cardiometabolic risk factors and also based on the relation between Apo A-II and inflammation and oxidative status, along with the effects of DTAC on oxidative stress and inflammatory markers, the objective of this study was to investigate the interactions between DTAC and Apo A-II −265T > C rs5082 on inflammation and oxidative stress markers in Iranian diabetic patients to provide evidence for genotype-based dietary recommendations, which can helpful for the delay, prevention and management of CVD in this patients.

Materials and methods

Participants and study design

Of 816 type 2 diabetic patients with identified genotype, who were randomly sampled through the diabetes referral centres in Tehran, two obese and non-obese groups were selected in this study with a ratio of 1:1. Each groups contained ninety patients with equal numbers of each genotype of Apo A-II: (30) TT, (30) CC and (30) TC. Based on the classification of previous studies and similar effects of TT and TC genotypes[19–21], we merged these two groups into one category as T allele carriers (TC + TT). In our previous study, genotype frequencies of this

polymorphism were 39·4 %, 47·7 % and 12·9 % for the TT, TC and CC genotypes, respectively[22]. BMI ≥ 30 kg/m² was considered as obesity based on the WHO criteria. All of the participants were 35–65 years old with glucose-lowering medication treatment without insulin use. Exclusion criteria including being a migrant, being pregnant, lactation, addiction, consumption of anti-inflammatory medications, clinical or inflammatory diseases such as coagulation disorders, cancers, CVD, stroke, malignant disease and patients with unexplained total energy intake (< 800 or > 4200 kcal/d)[23]. Overall, 180 T2DM patients aged 35–65 years (both genders) were subdivided into two equal groups based on (BMI ≥ 30; obese = 90) and (BMI < 30; non-obese = 90) and each group includes TT + TC (*n* 60), or CC (*n* 30) genotypes.

Demographic data and lifestyle variables (age, gender, job status, education levels, duration of diabetes and its complications, use of supplements or medication either lipid- or glucose lowering) were collected using a self-administered questionnaire. Anthropometric parameters, including weight (nearest 100 g), height and waist circumference (nearest 0·5 cm), were measured based on standard protocols[24]. BMI was computed using the 'weight (kg)/height² (m²)' equation. Also, daily physical activity was estimated in terms of metabolic equivalent × hours per day (MET h/d) using a validated physical activity questionnaire[25]. Before participating in the study, patients provided an informed written consent form. The ethics committee of Tehran University of Medical Sciences (TUMS) has approved the study protocol (identification: 97-03-161-41169).

Biochemical parameters and genotyping

Venous blood samples were collected at 08.00–10.00, after 12-h fasting. Serum lipids level (cholesterol, HDL and LDL and TAG) was measured by an enzymatic method (using kits, Pars Azmun Co.). Serum levels of oxidative stress markers, including, total antioxidant capacity (TAC), superoxide dismutase (SOD) and 8-isoprostaneF2α (8-iso-PGF2α). Serum levels of inflammatory markers, including interleukin-18 (IL-18), high-sensitivity C-reactive protein (hs-CRP) and pentraxin (PTX3). The detailed methods for measuring inflammatory factors[26], oxidative stress[20] and Apo A-II − 265T > C polymorphism (rs5082)[27] were described in our previous studies.

Dietary assessment and definition of dietary total antioxidant capacity

A validated 147-item semi-quantitative FFQ was used to obtain dietary intakes of patients through the past year[28]. Participants were asked to report the frequency of their consumption for each item of food in the questionnaire, on average, on a daily, weekly or monthly during the past year. Then the reported frequency intake converted to grams per day using household measures. Four indices were used to calculate DTAC, including the ferric reducing ability of plasma (FRAP) based on Norwegian antioxidant table that includes more than 3000 foods[29]; oxygen radical absorbance capacity (ORAC) based on the USA Department of Agriculture databases[30];

Trolox equivalent antioxidant capacity (TEAC) and total radical-trapping antioxidant potential (TRAP) that were drawn out from Italian food databases[31] that included most of the foods that are consumed by the Iranian population. For analysing similar food items (e.g. several types of bread), we used the overall mean value[32]. DTAC values were expressed: as mmol Fe^{2+}/100 g of food for FRAP method or as mmol of Trolox equivalent (mmol TE)/kg of food for TEAC, TRAP and μmol of Trolox equivalent (μmol TE)/100 g of food for ORAC methods[33,34]. For each patient, the frequencies of consumption of each food were multiplied by their related FRAP, TRAP, TEAC and ORAC values (based on published databases) and then summed to obtain DTAC[35]. Supplements with antioxidant properties were not considered in the calculation of DTAC[10,36].

Statistical methods

The sample size was defined according to type I error of $\alpha = 0.05$ and type II error of $\beta = 80\%$. Initially, participants were classified into two Apo A-II genotype groups: CC and TT + TC as T allele carriers. Also, according to the median DTAC, the participants were dichotomised into 'high' and 'low' categories ($\leq$ and < of median), FRAP ($\leq$ 15·67 and 15·77 > mmol $^{Fe2+}$/d); TRAP ($\leq$ 7·87 and 7·88 > mmol TE/d); TEAC ($\leq$ 7·27 and 7·28 > mmol TE/d) and ORAC ($\leq$ 26 854·59 and 26 854·60 > μmol TE/d). Normality distribution of data was tested by applying Kolmogorov–Smirnov's test. Variables with non-normal distributions were log-transformed for analyses. To compare general characteristics between the two groups (CC and TC + TT groups/low and high of DTAC), we used Independent Student's t test for continuous and Chi-square test for categorical variables with a normal distribution. Mann–Whitney test was used to compare the mean variables that were not normally distributed. ANCOVA test was applied to compare the mean dependents variables with adjusting for confounding variables. ANCOVA multivariate interaction models using the general linear model was tested to find the interaction between Apo A-II polymorphism (rs5082) and DTAC on oxidative stress and inflammatory markers. Additional adjustments were done for (age (years), gender (male/female), smoking (yes/no), supplement use (yes/no), physical activity (continuous), lipid-lowering medication (yes/no), coffee (continuous), fibre (continuous) and total energy intake (continuous)) as confounder factors. Based on the normally distributed, the data were expressed as mean ± SD and median (25th and 75th percentile) for normally and not normally distributed continuous variables, respectively. Categorical variables reported as frequency (%). SPSS software (SPSS Inc., version 21) was used for the statistical analysis. Variance inflation factor > 2 was not used in the models. Also, P-value < 0·05 was considered significant.

Result

Study population characteristics

The 180 diabetic patients were evaluated in this comparative study. General characteristics based on each participant's genotype are reported in (Table 1). According to our findings, genotype frequency among study participants was as follows CC (33·3 %) and TC + TT (66·7 %). Sex distribution of T2DM population was (male = 36·7 % – female = 63·3 %) in CC genotype and (male = 35·8 % – female = 64·2 %) in T-allele carriers. The mean age was higher in the CC genotype group ($P = 0.004$). No significant difference was found in the other variables studied (e.g. lipid profiles, physical activity, dietary intake, glucose and lipid-lowering medication) between the two genotype groups. Out of 147 FFQ items, the total antioxidant capacity of the diet in the FRAP, ORAC, TEAC and TRAP methods was estimated from 117(80 %), 72(49 %), 68(46 %) and 61(41 %) food items, respectively. In other studies, the percentage of compliance of the FFQ with international data of DTAC has been reported from 44·8 %[37] to 100 %[38].

Associations between the apo a-II _265T/C SNP and oxidative stress markers

The interaction between Apo A-II –265T > C polymorphism and DTAC (FRAP, TRAP, TEAC and ORAC) on oxidative stress variables (SOD activity, TAC and PGF2α concentration) in the whole population and the obese subgroup are reported in Tables 2, 3, 4, 5, 6, 7, respectively.

SOD activity is higher in T-allele carriers in individuals with higher DTAC ($P_{TEAC} = 0.038$ and $P_{ORAC} = 0.008$) (Table 2). And, this positive relationship between DTAC and SOD level was also observed in obese and non-obese patients with TT + TC genotype than genotype CC (obese: $P_{obese\ TEAC} = 0.034$; non-obese: $P_{FRAP} = 0.001$, $P_{TRAP} < 0.0001$, $P_{TEAC} = 0.003$ and $P_{ORAC} = 0.001$) (Table 5). A significant interaction was observed in obese patients in crude and also adjusted model 1 ($P_{crude\ TEAC} = 0.037$, $P_{1\ TEAC} = 0.042$) (Table 5).

Serum TAC is also higher in T-allele carriers in individuals with higher DTAC in the whole population ($P_{FRAP} = 0.030$ and $P_{ORAC} = 0.049$) (Table 3). However, there was no significant interaction between this SNP and DTAC on the level of serum TAC in the obese subgroup (Table 6).

PGF2α is lower in T-allele carriers only in individuals with higher indices both in obese and non-obese patients (obese: $P_{FRAP} = 0.043$; non-obese: $P_{FRAP} < 0.0001$, $P_{TRAP} = 0.007$, $P_{TEAC} = 0.001$ and $P_{ORAC} < 0.0001$). A genotype–DTAC interaction on serum PGF2α was seen in non-obese patients in crude and also adjusted model ($P_{crude\ ORAC} = 0.006$, $P_{1\ ORAC} = 0.007$ and $P_{2\ ORAC} = 0.008$), ($P_{1\ FRAP} = 0.047$ and $P_{2\ FRAP} = 0.043$) and ($P_{1\ TEAC} = 0.038$ and $P_{2\ TEAC} = 0.042$) (Table 7).

Associations between the apo a-II _265T/C SNP and inflammatory factors

The interaction between APOA-II –265T > C SNP and DTAC (FRAP, TRAP, TEAC and ORAC) on inflammatory variables (PTX3, hs-CRP and IL18 concentration) in the whole population, and the obese subgroups are reported in Tables 8, 9, 10, 11, 12, 13, respectively.

Serum PTX3 level is significantly higher in T-allele carriers only in non-obese diabetic patients with lower DTAC, than the CC genotype ($P_{TRAP} = 0.031$), while other measures did

Table 1. Characteristics of patients with type 2 diabetes mellitus*

| Variables | APOA2 genotype | | | | |
| | CC | | TT + TC | | |
	Mean	SD	Mean	SD	*P*-value†
Number of participants					
n	60		120		
%	33·3		66·7		
Age, year	56	6	53	7	0·004
Male/female					0·913
n	22/38		43/77		
%	36·7/63·3		35·8/64·2		
Smoking, Yes/No					0·292
n	4/56		14/106		
%	6·7/93·3		11·7/88·3		
Physical activity, MET h/d	37·33	1·12	38·47	1·16	0·093
Weight (kg)	74·1	12·8	75·9	13·4	0·384
BMI (kg/m²)	29	4	30	5	0·749
Waist circumference (cm)	91·7	10·4	92·4	10·9	0·675
Lipid profile					
TC (mg/dl)	192·79	99·50	199·16	73·54	0·333
TAG (mg/dl)	166·55	110·01	190·38	120·59	0·143
HDL (mg/dl)	54·45	14·21	52·85	11·29	0·721
LDL (mg/dl)	108·50	36·93	109·68	38·28	0·682
Medical history					
Diabetes duration					0·460
≤ 5 years					
n	26		59		
%	43·3		49·2		
> 5 years					
n	34		61		
%	56·7		50·8		
History of CVD, Yes/No					0·912
n	21/39		41/79		
%	35/65		34·2/65·8		
Supplement use, Yes/No‡					0·751
n	29/31		55/65		
%	48·3/51·7		45·8/54·2		
Lipid-lowering medication, Yes/No§					0·342
n	50/5		111/9		
%	91·7/8·3		92·5/7·5		
Glucose-lowering medication, Yes/No‖					0·844
n	35/25		61/59		
%	(58·3/41·7)		(50·8/49·2)		
Food intake					
Energy, kcal/d	2416·31	2·84	2392·27	2·82	0·648
Carbohydrate, g/d	327·01	1·46	317·03	1·45	0·518
Protein, g/d	84·01	1·46	84·69	1·40	0·891
Fat, g/d	92·38	2·97	91·56	2·96	0·839
Fiber, g/d	38·47	3·05	36·23	3·06	0·381
Dietary total antioxidant capacity					
FRAP (mmol Fe²⁺/100 g)	15·81	3·25	14·65	3·27	0·326
TRAP (mmol TE/kg)	8·24	1·55	8·36	1·57	0·897
TEAC (mmol TE/kg)	7·50	1·52	7·47	1·56	0·950
ORAC (μmol TE/100 g)	28 566·78	2·83	26 502·65	2·82	0·159

APOA2, apolipoprotein A2; CC, C allele homozygotes; TT/TC, T allele carriers ;TC, Total cholesterol; FRAP, ferric reducing ability of plasma; TRAP, total reactive antioxidant potential; TEAC, trolox equivalent antioxidant capacity and ORAC, oxygen radical absorbance capacity.
* All data are means ± standard deviations unless indicated.
† Obtained using the independent *t* test for continuous variables and Chi-square test for the categorical variable.
‡ Supplements of vitamins and minerals.
§ Statins, gemfibrozil andnicotinamide.
‖ Metformin, glibenclamide and thiazolidinedione.

not illustrate this relationship (Table 11). Also, no significant genotype–DTAC interaction was observed in the serum level of PTX3 (Tables 8 and 11).

Serum hs-CRP level was significantly lower in T-allele carriers in individuals with higher DTAC (P_{FRAP} = 0·010, P_{TRAP} = 0·002, P_{TEAC} = 0·003 and P_{ORAC} = 0·020) (Table 9). This association between DTAC and the hs-CRP level was also observed in non-obese patients carrying the T allele (P_{FRAP} = 0·002, P_{TRAP} = 0002, P_{TEAC} = 0·005 and P_{ORAC} = 0·018) (Table 12).

Serum IL18 was lower in T carrier groups who consumed high-DTAC. But no gene–diet interaction was found in the whole population (Table 10). On the other hand, obese individuals with

Table 2. Interaction between apo a-II –265T > C polymorphism and the dietary total antioxidant capacity (TAC): ferric reducing ability of plasma (FARP), total reactive antioxidant potential (TRAP), trolox equivalent antioxidant capacity (TEAC) and oxygen radical absorbance capacity (ORAC) intake on the superoxide dismutase activity (SOD) activity level

SOD	CC		TT ± TC		$P\ddagger$	P^*	P_1 Model 1	P_2 Model 2
	Mean	SD	Mean	SD				
FRAP						0·154	0·129	0·312
≤ 15·76	0·12	1·25	0·14	1·33	0·002			
<15·77	0·11	1·32	0·16	1·43	< 0·0001			
$P\dagger$	0·440		0·148					
TRAP					$P\ddagger$	0·113	0·073	0·211
≤ 7·87	0·12	1·27	0·14	1·43	0·013			
<7·88	0·11	1·33	0·15	1·30	< 0·0001			
$P\dagger$	0·165		0·338					
TEAC					$P\ddagger$	0·070	0·058	0·151
≤ 7·27	0·12	1·25	0·14	1·34	0·003			
<7·28	0·11	1·34	0·16	1·40	< 0·0001			
$P\dagger$	0·444		0·038					
ORAC					$P\ddagger$	0·086	0·111	0·258
≤ 26 854·59	0·12	1·24	0·14	1·33	0·002			
< 26 854·60	0·11	1·34	0·16	1·40	< 0·0001			
$P\dagger$	0·868		0·008					

For variables that did not have a normal distribution, the log transformation method was used before analysis.
* P; P interactions are obtained with the general linear model (two-way ANOVA). P_1; the P_1 value of the interaction (model 1) is adjusted for sex (as categorical), smoking (as categorical), coffee and PUFA-w3 intake (as continuous) using ANCOVA test. P_2; the P_2 value of the interaction (model 2) further adjusted for age (as continuous), WC (as continuous), supplement use (as categorical) and total energy intake (as continuous) using ANCOVA test.
Independent samples t test was used to compare the SOD activity level in the two categories of antioxidant intake (†P) or between two genotypic groups (‡P).

Table 3. Interaction between apo a-II –265T > C polymorphism and the dietary total antioxidant capacity (TAC): ferric reducing ability of plasma (FRAP), total reactive antioxidant potential (TRAP), trolox equivalent antioxidant capacity (TEAC) and oxygen radical absorbance capacity (ORAC) intake on the serum TAC level

Serum TAC	CC		TT ± TC		$P\ddagger$	P^*	P_1 Model 1	P_2 Model 2
	Mean	SD	Mean	SD				
FRAP						0·432	0·442	0·551
≤ 15·76	2·28	3·56	2·37	3·63	0·446			
> 15·77	2·25	3·57	2·47	3·38	0·030			
$P\dagger$	0·803		0·302					
TRAP					$P\ddagger$	0·885	0·918	0·681
≤ 7·87	2·25	3·49	2·42	3·63	0·176			
> 7·88	2·27	3·59	2·41	3·42	0·168			
$P\dagger$	0·881		0·969					
TEAC					$P\ddagger$	0·960	0·995	0·823
≤ 7·27	2·26	3·59	2·41	3·63	0·203			
> 7·28	2·27	3·49	2·41	3·45	0·140			
$P\dagger$	0·950		0·998					
ORAC					$P\ddagger$	0·471	0·540	0·618
≤ 26 854·59	2·28	3·52	2·37	3·56	0·412			
> 26 854·60	2·25	3·56	2·46	3·49	0·049			
$P\dagger$	0·840		0·332					

For variables that did not have a normal distribution, the log transformation method was used before analysis.
* P; P interactions are obtained with the general linear model (two-way ANOVA). P_1; the P_1 value of the interaction (model 1) is adjusted for age (as continuous), smoking (as categorical), supplement use (as categorical) and coffee intake (as continuous) using ANCOVA test. P_2; the P_2 value of the interaction (model 2) further adjusted for sex (as categorical), WC (as continuous), PUFA-w3 and total energy intake (as continuous) using ANCOVA test.
Independent samples t test was used to compare serum TAC level in the two categories of antioxidant intake (†P) or between two genotypic groups (‡P).

2 copies of the minor allele (CC) who consumed greater amounts of DTAC tended to have greater serum IL18 compared with individuals with low intake of DTAC ($P_{FRAP} = 0·047$ and $P_{ORAC} = 0·008$). Also, this interaction was significant in obese patients both in crude ($P_{FRAP} = 0·048$ and $P_{ORAC} = 0·018$), adjusted model 1 ($P_{1\ FRAP} = 0·036$ and $P_{1\ ORAC} = 0·012$) and also adjusted model 2 ($P_{2\ FRAP} = 0·027$ and $P_{2\ ORAC} = 0·007$) (Table 13).

Discussion

According to our knowledge, this study is the first attempt to examine the interaction between Apo A-II –265T > C polymorphism and DTAC intake on some oxidative stress and inflammatory markers in diabetic patients. In this regard, we have previously reported that the Apo A-II –265T/C SNP was associated with oxidative stress and inflammatory markers. Such that,

Table 4. Interaction between apo a-II –265T > C polymorphism and the dietary total antioxidant capacity (TAC): ferric reducing ability of plasma (FRAP), total reactive antioxidant potential (TRAP), trolox equivalent antioxidant capacity (TEAC) and oxygen radical absorbance capacity (ORAC) intake on the PGF2α level

	CC		TT ± TC					
PGF2α	Mean	SD	Mean	SD	$P\ddagger$	P^*	P_1 Model 1	P_2 Model 2
FRAP						0·097	0·028	0·039
≤ 15·76	73·70	8·05	71·74	5·90	0·278			
> 15·77	75·54	5·14	70·42	5·00	< 0·0001			
$P\dagger$	0·323		0·197					
TRAP					$P\ddagger$	0·571	0·299	0·525
≤ 7·87	74·22	8·08	71·15	5·53	0·091			
> 7·88	75·23	5·16	71·10	5·49	0·001			
$P\dagger$	0·585		0·956					
TEAC					$P\ddagger$	0·135	0·070	0·170
≤ 7·27	73·32	8·07	71·20	5·50	0·228			
> 7·28	75·96	4·77	71·04	5·54	>0·0001			
$P\dagger$	0·148		0·874					
ORAC					$P\ddagger$	0·066	0·020	0·042
≤ 26 854·59	73·85	7·52	71·97	5·65	0·209			
> 26 854·60	75·45	5·74	70·11	5·16	< 0·0001			
$P\dagger$	0·358		0·065					

* P; P interactions are obtained with the general linear model (two-way ANOVA). P_1; the P_1 value of the interaction (model 1) is adjusted for sex (as categorical), supplement use (as categorical), coffee and PUFA-w3 intake (as continuous) using ANCOVA test. P_2; the P_2 value of the interaction (model 2) further adjusted for age (as continuous), smoking (as categorical), WC (as continuous) and total energy intake (as continuous) using ANCOVA test. Independent samples t test was used to compare the PGF2α level in the two categories of antioxidant intake ($\dagger P$) or between two genotypic groups ($\ddagger P$).

we observed that the diabetic patients with CC genotype had lower SOD activity. Also, in the T-carrier group, the serum levels of PGF2α and hs-CRP were significantly higher in the obese *v.* non-obese subjects. Besides, we previously observed that obesity is a risk factor for increased oxidative stress and inflammation in the T carriers group[18,19].

In this present study, we found that the levels of oxidative stress and inflammatory factors were still higher in the CC genotype group in individuals with higher DTAC. In another word, high-DTAC could not modify the adverse effects of being in the CC genotype. Moreover, we observed that the presence of the T allele in diabetic patients with an antioxidant-included diet is a protective agent against inflammation and oxidative stress. These results could reflect the anti-atherogenic properties of Apo A-II. Also, we founded that following a diet with high contents of antioxidant can prevent or delay the complications of diabetes in the T carrier genotype more effectively than the CC genotype.

In general agreement with our study, Moradi *et al.* have pointed out that losing weight through calorie restriction could increase the Paraoxonase-3 enzyme more efficiently in T allele carriers compared to C allele carriers.[39] In this regard, it has been reported that Paraoxonase-3 is an enzyme that plays an important role in the antioxidant properties of HDL and consequently protects against atherosclerosis[40]. In addition, energy restriction exerts anti-oxidative effects in animals and humans through maintaining a proper cellular redox status and modulation of pro-inflammatory genes such as TNFα, IL-6 and CRP[41]. Also, one intervention study has reported that energy restriction for six week in twenty-eight diabetic patients resulted in a shift to smaller HDL sub-fractions in patients carriers of the –265 T allele compared to the CC genotype[42]. In this regard, Kontush *et al.* indicated that small and dense HDL has an important role in protecting LDL from oxidation[43]. Therefore, it seems that improved

nutrition may be considered as an effective way to reduce the risk of CVD in the T carrier group.

In the current survey, we also observed a significant gene–diet interaction on the inflammatory factors only in obese diabetic patients. It has been reported that the phenotypic response to diet is determined partly by the baseline value of the phenotype that is itself affected by genetic factors[44]. In this regard, obesity is known to increase inflammation. Also, researchers stated that obesity is an important risk factor for elevated levels of inflammation and consequently CVD in the T allele carrier group[18,19]. Our findings suggest that diabetic patients with obese status may express a more effective response to lifestyle modification and antioxidant-rich foods intake. The possible mechanism may be due to the association of the Apo A-II with human appetite and satiety signals[45]. However, further studies are needed to get a better understanding of the genes–DTAC interactions, and their effect on inflammatory parameters in obese patients.

Regarding gene–DTAC interaction, some nutritional genomics studies illustrated interactions between Apo A-II gene polymorphism and a Mediterranean diet as an antioxidant-rich dietary pattern[46,47]. Besides, Keramat *et al.* reported that there is a significant interaction between genetic variations at this locus with environmental factors such as dietary intake of anti-inflammatory fatty acids (e.g. *n*-3 PUFA and MUFA) and pro-inflammatory FA (e.g. SFA) on inflammatory markers[26]. Also, they found that a higher intake of *n*-3 PUFA and MUFA was associated with decreased serum levels of IL-18 and hs-CRP in the CC genotype. Moreover, Zamani *et al.* indicated that there is a positive association between *n*-3 PUFA intake and serum SOD activity in the CC genotype, which is inconsistent with our results[20]. In this regard, some studies have shown that *n*-3 PUFA, like dietary antioxidants, have anti-inflammatory properties. The anti-inflammatory mechanism of *n*-3 PUFA is

Table 5. Interaction between apo a-II −265T > C polymorphism and the dietary total antioxidant capacity (TAC) on the superoxide dismutase activity (SOD) activity level in obese and non-obese patients

| | Obese§ | | | | | | | | Non-Obese | | | | | | | |
| | CC(30) | | TT ± TC(60) | | | | | | CC(30) | | TT ± TC(60) | | | | | |
SOD	Mean	SD	Mean	SD	P‡	P*	P_1 Model 1‖	P_2 Model 2¶	Mean	SD	Mean	SD	P‡	P*	P_1 Model 1**	P_2 Model 2††
FRAP						0·202	0·256	0·277						0·203	0·190	0·225
≤ 15·76	0·10	1·19	0·13	1·28	0·002				0·13	1·20	0·15	1·35	0·193			
> 15·77	0·09	1·18	0·14	1·60	0·003				0·12	1·32	0·16	1·32	0·001			
P†	0·141		0·402						0·326		0·355					
TRAP					P‡	0·434	0·470	0·516						0·090	0·089	0·101
≤ 7·87	0·10	1·18	0·13	1·53	0·021				0·14	1·20	0·15	1·35	0·281			
> 7·88	0·09	1·14	0·14	1·25	< 0·0001				0·12	1·30	0·16	1·33	< 0·0001			
P†	0·223		0·848						0·125		0·341					
TEAC					P‡	0·037	0·042	0·057						0·500	0·502	0·532
≤ 7·27	0·10	1·18	0·12	1·28	0·007				0·13	1·22	0·15	1·36	0·063			
> 7·28	0·09	1·14	0·16	1·54	< 0·0001				0·12	1·32	0·16	1·32	0·003			
P†	0·223		0·034						0·663		0·554					
ORAC					P‡	0·092	0·123	0·126						0·287	0·306	0·304
≤ 26 854·59	0·10	1·23	0·13	1·30	0·004				0·13	1·17	0·15	1·35	0·040			
> 26 854·60	0·09	1·22	0·15	1·56	< 0·0001				0·13	1·33	0·17	1·32	0·001			
P†	0·355		0·081						0·874		0·097					

FRAP, ferric reducing ability of plasma; TRAP, total reactive antioxidant potential; TEAC, trolox equivalent antioxidant capacity and ORAC, oxygen radical absorbance capacity. For variables that did not have a normal distribution, the log transformation method was used before analysis.

* P; P interactions are obtained with the general linear model (two-way ANOVA).

Independent samples t test was used to compare the SOD activity level in the two categories of antioxidant intake (†P) or between two genotypic groups (‡P).

§ Obesity was defined as BMI ≥ 25 kg/m².

‖ The P_1 value of the interaction (model 1) is adjusted for age (as continuous), supplement use (as categorical), smoking (as categorical), coffee, PUFA-w3 and total energy intake (as continuous)using ANCOVA test.

¶ The P_2 value of the interaction (model 2) further adjusted for sex (as categorical) using ANCOVA test.

** The P_1 value of the interaction (model 1) is adjusted for age (as continuous), sex (as categorical), smoking (as categorical), coffee, PUFA-w3 and total energy intake (as continuous)using ANCOVA test.

†† The P_2 value of the interaction (model 2) further adjusted for supplement use (as categorical) using ANCOVA test.

Table 6. Interaction between apo a-II −265T > C polymorphism and the dietary total antioxidant capacity (TAC) on the serum TAC level in obese and non-obese patients

| | Obese¶ | | | | | | | | Non-Obese | | | | | | | |
| | CC(30) | | TT ± TC(60) | | | | | | CC(30) | | TT ± TC(60) | | | | | |
SerumTAC	Mean	SD	Mean	SD	P‡	P*	P_1 Model 1§	P_2 Model 2‖	Mean	SD	Mean	SD	P‡	P*	P_1 Model 1§	P_2 Model 2‖
FRAP						0·438	0·133	0·139						0·740	0·746	0·717
≤ 15·76	2·28	3·18	2·29	3·55	0·983				2·30	3·89	2·46	3·75	0·387			
> 15·77	2·17	3·32	2·32	3·38	0·264				2·32	3·66	2·57	3·38	0·059			
P†	0·365		0·807						0·911		0·410					
TRAP						0·500	0·309	0·361						0·445	0·328	0·330
≤ 7·87	2·30	3·22	2·29	3·45	0·973				2·22	3·74	2·53	3·74	0·102			
> 7·88	2·17	3·25	2·28	3·52	0·368				2·36	3·74	2·50	3·38	0·320			
P†	0·302		0·980						0·493		0·800					
TEAC						0·629	0·386	0·469						0·578	0·784	0·837
≤ 7·27	2·30	3·22	2·30	3·52	0·938				2·24	3·89	2·51	3·70	0·139			
> 7·28	2·17	3·25	2·26	3·45	0·435				2·36	3·63	2·51	3·42	0·250			
P†	0·302		0·744						0·547		0·992					
ORAC						0·450	0·201	0·208						0·861	0·921	0·860
≤ 26 854·59	2·28	3·18	2·27	3·42	0·955				2·28	3·78	2·47	3·68	0·311			
> 26 854·60	2·19	3·28	2·31	3·59	0·353				2·32	3·66	2·56	3·45	0·097			
P†	3·99		0·764						0·868		0·530					

FRAP, ferric reducing ability of plasma; TRAP, total reactive antioxidant potential; TEAC, trolox equivalent antioxidant capacity and ORAC, oxygen radical absorbance capacity. For variables that did not have a normal distribution, the log transformation method was used before analysis.

* P; P interactions are obtained with the general linear model (two-way ANOVA). Independent samples *t* test was used to compare serum TAC levels in the two categories of antioxidant intake (P†) or between two genotypic groups (P‡).

§ The P_1 value of the interaction (model 1) is adjusted for age (as continuous), sex (as categorical), supplement use (as categorical), smoking (as categorical), coffee and PUFA-w3 intake (as continuous) using ANCOVA test.

‖ The P_2 value of the interaction (model 2) further adjusted for total energy intake (as continuous)using ANCOVA test.

¶ Obesity was defined as BMI ≥ 25 kg/m².

Table 7. Interaction between apo a-II –265T > C polymorphism and the dietary total antioxidant capacity (TAC) the PGF2α level in obese and non-obese patients

PGF2α	Obese§ CC(30) Mean	SD	TT ± TC(60) Mean	SD	P‡	P*	P$_1$ Model 1‖	P$_2$ Model 2¶	Non-Obese CC(30) Mean	SD	TT ± TC(60) Mean	SD	P‡	P*	P$_1$ Model 1**	P$_2$ Model 2††
FRAP						0·619	0·185	0·162						0·078	0·047	0·043
≤ 15·76	74·73	8·55	72·12	4·73	0·318				72·58	7·69	71·42	6·80	0·627			
> 15·77	76·33	4·97	72·30	5·34	0·043				75·09	5·30	69·35	4·53	< 0·0001			
P†	0·577		0·902						0·276		0·141					
TRAP						0·948	0·614	0·560						0·517	0·365	0·314
≤ 7·87	75·12	8·80	71·87	5·11	0·251				73·38	7·61	70·55	5·87	0·178			
> 7·88	76·00	4·91	72·57	4·66	0·045				74·70	5·39	70·19	5·83	0·007			
P†	0·764		0·626						0·565		0·796					
TEAC						0·955	0·569	0·505						0·061	0·038	0·042
≤ 7·27	75·12	8·80	71·81	5·21	0·243				71·78	7·37	70·69	5·76	0·584			
> 7·28	76·00	4·91	72·66	4·48	0·046				75·94	4·80	70·07	5·93	0·001			
P†	0·746		0·547						0·058		0·661					
ORAC						0·638	0·832	0·819						0·006	0·007	0·006
≤ 26 854·59	76·04	7·84	71·98	5·08	0·118				71·66	6·81	71·97	6·21	0·888			
> 26 854·60	75·21	6·14	72·47	4·67	0·155				75·61	5·61	68·82	5·01	< 0·0001			
P†	0·766		0·735						0·082		0·024					

FRAP, ferric reducing ability of plasma; TRAP, total reactive antioxidant potential; TEAC, trolox equivalent antioxidant capacity and ORAC, oxygen radical absorbance capacity.
* P; P interactions are obtained with the general linear model (two-way ANOVA). Independent samples *t* test was used to compare thePGF2α level in the two categories of antioxidant intake (†P) or between two genotypic groups (‡P).
§ Obesity was defined as BMI $\geq$ 25 kg/m^2.
‖ The P$_1$ value of the interaction (model 1) is adjusted for age (as continuous), sex (as categorical), supplement use (as categorical), smoking (as categorical), coffee and PUFA-w3 intake (as continuous) using ANCOVA test.
¶ The P$_2$ value of the interaction (model 2) further adjusted for total energy intake (as continuous) using the ANCOVA test.
** The P$_1$ value of the interaction (model 1) is adjusted for age (as continuous), supplement use (as categorical), smoking (as categorical), coffee and PUFA-w3 total energy intake (as continuous) using ANCOVA test.
†† The P$_2$ value of the interaction (model 2) further adjusted for sex (as categorical) using ANCOVA test.

Table 8. Interaction between apo a-II –265T > C polymorphism and the dietary total antioxidant capacity (TAC): ferric reducing ability of plasma (FRAP), total reactive antioxidant potential (TRAP), trolox equivalent antioxidant capacity (TEAC) and oxygen radical absorbance capacity (ORAC) intake on the PTX3 level

| PTX3 | CC | | TT ± TC | | | | | |
	Mean	SD	Mean	SD	P‡	P*	P_1 Model 1	P_2 Model 2
FRAP						0·777	0·558	0·742
≤ 15·76	2·53	0·45	2·70	0·42	0·107			
> 15·77	2·45	0·45	2·66	0·52	0·267			
P†	0·955		0·681					
TRAP					P‡	0·459	0·226	0·377
≤ 7·87	2·52	0·43	2·73	0·40	0·050			
> 7·88	2·52	0·47	2·63	0·52	0·396			
P†	0·993		0·196					
TEAC					P‡	0·821	0·479	0·666
≤ 7·27	2·54	0·44	2·71	0·41	0·094			
> 7·28	2·51	0·46	2·65	0·52	0·299			
P†	0·830		0·490					
ORAC					P‡	0·565	0·277	0·374
≤ 26 854·59	2·50	0·46	2·70	0·40	0·051			
> 26 854·60	2·54	0·45	2·65	0·53	0·311			
P†	0·744		0·588					

* P; P interactions are obtained with the general linear model (two-way ANOVA). P_1; the P_1 value of the interaction (model 1) is adjusted for age (as continuous), sex (as categorical) and WC (as continuous) using ANCOVA test. P_2; the P_2 value of the interaction (model 2) further adjusted for supplement use (as categorical), smoking (as categorical), coffee, PUFA-w3 and total energy intake (as continuous) using ANCOVA test.
Independent samples t test was used to compare the PTX3 level in the two categories of antioxidant intake (†P) or between two genotypic groups (‡P).

Table 9. Interaction between apo a-II –265T > C polymorphism and the dietary total antioxidant capacity (TAC): ferric reducing ability of plasma (FRAP), total reactive antioxidant potential (TRAP), trolox equivalent antioxidant capacity (TEAC) and oxygen radical absorbance capacity (ORAC) intake on the hs-CRP level

| hs-CRP | CC | | TT ± TC | | | | | |
	Median	IQR	Median	IQR	P‡	P*	P_1 Model l	P_2 Model 2
FRAP						0·706	0·748	0·954
≤ 15·76	3·23	3·31	1·49	1·97	0·066			
> 15·77	3·32	2·76	2·18	2·53	0·010			
P†	0·379		0·507					
TRAP					P‡	0·330	0·375	0·594
≤ 7·87	3·23	3·39	1·80	2·02	0·137			
> 7·88	3·32	2·76	1·43	2·44	0·002			
P†	0·253		0·953					
TEAC					P‡	0·560	0·635	0·856
≤ 7·27	3·23	3·56	1·80	1·94	0·067			
> 7·28	3·32	2·76	1·52	2·51	0·003			
P†	0·445		0·881					
ORAC					P‡	0·751	0·745	0·530
≤ 26 854·59	3·58	3·51	1·49	2·01	0·020			
> 26 854·60	3·32	2·98	1·97	2·39	0·020			
P†	0·938		0·476					

* P; P interactions are obtained with the general linear model (two-way ANOVA). P_1; the P_1 value of the interaction (model 1) is adjusted for age (as continuous), sex (as categorical), smoking (as categorical) and total energy intake (as continuous). P_2; the P_2 value of the interaction (model 2) further adjusted for supplement use (as categorical), and WC (as continuous), coffee and PUFA-w3 intake (as continuous) using ANCOVA test. Mann–Whitney test was used to compare the hs-CRP level in the two categories of antioxidant intake (†P) or between two genotypic groups (‡P).

related to inhibition of the toll-like receptors. Whereas antioxidants exert this anti-inflammatory impact through inhibiting nuclear factor-κB[48]. According to our finding, two studies indicated that C homozygote carriers diabetic patients appeared to be less modifiable with less the inflammatory potential of the diet[49] and high antioxidants capacity[50]. Based on the recent studies in this area of research, it seems that anti-inflammatory fatty acids and antioxidant-rich diets can be effective in the prevention of the progression of diabetes complications in T allele carriers and C-allele homozygotes, respectively.

The mechanisms behind these novel observed interactions are not still clearly understood; however, multiple lines of evidence support our findings. Apo A-II is the second apolipoprotein in HDL and plays a complex and unknown role in lipoprotein metabolism and atherosclerosis susceptibility. The −265T/C polymorphism can be applied to examine the physiological role of Apo A-II in humans. It has been suggested that −265T/C SNP is found in the middle of element D on chromosome 1 and affects binding nuclear factors (such as AIID1, AIID4 and AIID2) to the promoter of the Apo A-II gene. Such

Table 10. Interaction between apo a-II −265T > C polymorphism and the dietary TAC: FRAP, TRAP, TEAC and ORAC intake on the PGF2α level

PGF2α	CC		TT ± TC					
	Median	IQR	Median	IQR	P‡	P*	P Model 1*	P Model 2
FRAP						0.413	0.358	0.483
≤ 15·76	245·60	41·27	245·54	51·05	0.842			
> 15·77	253·37	38·60	235·65	50·46	0.307			
P†	0·388		0·686					
TRAP					P‡	0.868	0.773	0.991
≤ 7·87	254·60	41·13	239·47	54·88	0.739			
> 7·88	250·52	40·24	237·00	46·60	0.586			
P†	0·724		0·674					
TEAC					P‡	0.329	0.262	0.415
≤ 7·27	236·07	50·35	239·67	51·00	0.626			
> 7·28	253·40	38·10	236·03	59·18	0.288			
P†	0·153		0·951					
ORAC					P‡	0.220	0.189	0.278
≤ 26 854·59	245·68	44·71	245·65	47·00	0.608			
> 26 854·60	253·37	39·92	236·03	49·40	0.193			
P†	0·238		0·597					

FRAP, ferric reducing ability of plasma; TRAP, total reactive antioxidant potential; TEAC, trolox equivalent antioxidant capacity and ORAC, oxygen radical absorbance capacity.
* P; P interactions are obtained with the general linear model (two-way ANOVA). P_1; the P_1 value of the interaction (model 1) is adjusted for sex (as categorical) smoking (as categorical) coffee and PUFA-w3 intake (as continuous) using ANCOVA test. P_2; the P_2 value of the interaction (model 2) further adjusted for age (as continuous), supplement use (as categorical), WC (as continuous) and total energy intake (as continuous) using ANCOVA test. Mann–Whitney test was used to compare the IL18 level in the two categories of antioxidant intake (†P) or between two genotypic groups (‡P).

that, this SNP probably interrupts the delicate balance of binding of the nuclear factors. The corollary is that the transcription rate of the Apo A-II gene and its plasma concentration are reduced in constructs containing the −265C site compared with constructs containing the −265T site[14,51].

There are some dialectical findings regarding the relation between serum Apo A-II level, oxidative stress and inflammation status. Some researchers indicated an inverse relationship between Apo A-II level and the risk of CVD in type 2 diabetic patients[17] and healthy people[52]. Also, it has been reported that the serum level of Apo A-II is negatively correlated with hs-CRP as an inflammatory marker which is directly related to oxidative stress[53]. In contrast, some researchers indicated that serum Apo A-II concentration may be a powerful risk marker of CAD in T2DM patients[54]. Also, Xiao et al. revealed that Apo A-II rs5082 SNP appears to be cardioprotective[55]. Apo A-II may be effective on anti-atherogenic pathways through the amphipathic α-helices as structural domains of this apolipoprotein, which are related to anti-atherogenic functions[56]. Also, Apo A-II interacts with heat shock proteins that are related to repair damaged proteins induced by various stresses. In this regard, it has been reported that among the heat shock proteins family, HSP60 is a high-affinity HDL-binding protein particularly via binding of the Apo A-II[57].

The findings of animal studies are also inconsistent. Some studies have shown that overexpression of human Apo A-II in transgenic mice is associated with decreased PON1 activity and increased the size of atherosclerotic lesions[58,59]. However, one animal study reported that human Apo A-II transgenic rabbits exhibited lower levels of serum CRP and blood leukocytes as an inflammatory marker and higher PON1 activity compared with non-transgenic rabbits[16]. Our results are consistent with animal studies that have been performed in rabbits. The reason for the discrepancy in the results of animal studies is probably due to the difference in the amount and type of Apo A-IIs expressed[16]. Also, studies have been conducted in mice that are not the best animal model for examining human Apo A-II metabolism[52,60]. Human Apo A-II in transgenic mice is higher than plasma human Apo A-II concentration, which could lead to malfunction of the HDL antioxidant system[58]. However, one animal study performed in the transgenic mice indicated that human Apo A-II protected VLDL from oxidation more efficiently than the HDL of controls[61].

On the other hand, a diet rich in antioxidants may be effective in the prevention of CVD. The possible mechanism may be due to the NF-κB-regulated pathway which is be involved in the production of parameters related to inflammation[33]. Also, antioxidants may regulate adiponectin expression via peroxisome proliferator-activated receptor-g[62]. Moreover, the observed associations in the current study may be due to the fibre content of foods with high DTAC. The typical antioxidant-rich foods are high in fibre and provide a synergistic effect on the level, function and bioaccessibility of the antioxidant substances present in the diet[63]. Fibre and short-chain fatty acids from their fermentation in the intestine are another factor that could also contribute to the relation between dietary TAC and CVD-related risk factors through inhibit NF-κB and stimulate the peroxisome proliferator-activated receptor-a pathway[64]. However, in one study has been stated that the inverse association between high-DTAC and mortality remained significant even after adjusting for fibre intake[65]. Other studies found no relationship between DTAC and cardiometabolic risk factors[66,67]. Did not capture the usual dietary intake and use only one method to estimate DTAC may be the reasons for the lack of association observed in some studies[3]. Some documents revealed that the antioxidant-rich diets are associated with the serum TAC[68,69]. However, we did not find any significant association between DTAC and rs5082 variants on this factor. This finding is in agreement with other studies, which suggest that DTAC may not be related to serum

Table 11. Interaction between apo a-II −265T > C polymorphism and the dietary TAC on the PTX3 level in obese and non-obese patients

PTX3	Obese§ CC(30) Mean	SD	TT ± TC(60) Mean	SD	P‡	P*	P₁ Model 1‖	P₂ Model 2¶	Non-obese CC(30) Mean	SD	TT ± TC(60) Mean	SD	P‡	P*	P₁ Model 1**	P₂ Model 2††
FRAP						0·588	0·706	0·845						0·444	0·483	0·679
≤ 15·76	2·51	0·52	2·58	0·43	0·680				2·55	0·37	2·80	0·39	0·062			
> 15·77	2·46	0·53	2·65	0·28	0·275				2·58	0·41	2·67	0·62	0·579			
P†	0·791		0·545						0·810		0·315					
TRAP						0·969	0·885	0·768						0·322	0·456	0·608
≤ 7·87	2·48	0·54	2·61	0·42	0·423				2·56	0·33	2·83	0·37	0·031			
> 7·88	2·45	0·52	2·59	0·30	0·366				2·57	0·43	2·63	0·63	0·718			
P†	0·866		0·852						0·921		0·127					
TEAC						0·963	0·998	0·723						0·692	0·803	0·854
≤ 7·27	2·48	0·54	2·61	0·41	0·421				2·58	0·36	2·79	0·40	0·112			
> 7·28	2·45	0·52	2·59	0·31	0·366				2·56	0·42	2·68	0·62	0·459			
P†	0·866		0·864						0·860		0·395					
ORAC						0·6 54	0·523	0·249						0·716	0·664	0·691
≤ 26 854·59	2·39	0·52	2·58	0·42	0·213				2·61	0·37	2·80	0·36	0·124			
> 26 854·60	2·53	0·52	2·64	0·26	0·502				2·54	0·41	2·66	0·64	0·466			
P†	0·489		0·617						0·642		0·250					

FRAP, ferric reducing ability of plasma; TRAP, total reactive antioxidant potential; TEAC, trolox equivalent antioxidant capacity and ORAC, oxygen radical absorbance capacity.

* P; P interactions are obtained with the general linear model (two-way ANOVA). Independent samples t test was used to compare the PTX3 level in the two categories of antioxidant intake (†P) or between two genotypic groups (‡P).

§ Obesity was defined as BMI ≥ 25 kg/m².

‖ The P₁ value of the interaction (model 1) is adjusted for age (as continuous), supplement use (as categorical), coffee and PUFA-w3 and total energy intake (as continuous) using ANCOVA test.

¶ The P₂ value of the interaction (model 2) further adjusted for sex (as categorical) and smoking (as categorical) using ANCOVA test.

** The P₁ value of the interaction (model 1) is adjusted for age (as continuous), smoking (as categorical), coffee and PUFA-w3 and total energy intake (as continuous) using ANCOVA test.

†† The P₂ value of the interaction (model 2) further adjusted for sex (as categorical) and supplement use (as categorical) using ANCOVA test.

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Table 12. Interaction between apo a-II −265T > C polymorphism and the dietary TAC on the CRP level in obese and non-obese patients

CRP	Obese¶ CC(30) Median	IQR	TT ± TC(60) Median	IQR	P‡	P*	P₁ Model 1§	P₂ Model 2‖	Non-Obese CC(30) Median	IQR	TT ± TC(60) Median	IQR	P‡	P*	P₁ Model 1§	P₂ Model 2‖
FRAP						0·190	0·124	0·145						0·110	0·195	0·208
≤ 15·76	3·84	1·11	2·5	1·94	0·017				1·01	2·70	0·975	1·69	0·754			
> 15·77	2·97	3·11	3·27	1·13	0·876				3·32	2·53	1·09	2·00	0·002			
P†	0·567		0·166						0·043		0·737					
TRAP						0·823	0·686	0·727						0·140	0·182	0·205
≤ 7·87	3·74	1·96	2·54	1·69	0·057				0·77	2·91	0·93	1·86	0·602			
> 7·88	3·48	3·02	2·79	2·31	0·206				3·27	2·71	1·15	1·89	0·002			
P†	0·738		0·961						0·062		0·449					
TEAC						0·764	0·779	0·858						0·383	0·489	0·467
≤ 7·27	3·74	1·96	2·54	1·69	0·053				2·05	2·91	1·06	1·69	0·318			
> 7·28	3·48	3·02	2·79	2·31	0·232				3·32	2·76	0·98	2·00	0·005			
P†	0·738		0·929						0·155		0·848					
ORAC						0·547	0·467	0·473						0·927	0·928	0·883
≤ 26 854·59	3·86	1·60	2·54	2·14	0·022				2·08	3·64	0·90	1·29	0·189			
> 26 854·60	3·33	3·15	2·79	1·57	0·466				3·08	1·89	1·21	2·56	0·018			
P†	0·699		0·682						0·574		0·183					

FRAP, ferric reducing ability of plasma; TRAP, total reactive antioxidant potential; TEAC, trolox equivalent antioxidant capacity and ORAC, oxygen radical absorbance capacity.

* P; P interactions are obtained with the general linear model (two-way ANOVA). Test Mann–Whitney test was used to compare the CRP level in the two categories of antioxidant intake (†P) or between two genotypic groups (‡P).

§ The P₁ value of the interaction (model 1) is adjusted for age (as continuous), supplement use (as categorical), smoking (as categorical), coffee and PUFA-w3 and total energy intake (as continuous) using ANCOVA test.

‖ The P₂ value of the interaction (Model 2) further adjusted for sex (as categorical) using ANCOVA test.

¶ Obesity was defined as BMI ≥ 25 kg/m².

Table 13. Interaction between apo a-II −265T > C polymorphism and the dietary TAC on the IL18 level in obese and non-obese patients

IL18	Obese§ CC(30) Median	IQR	TT ± TC(60) Median	IQR	P‡	P*	P_1 Model 1‖	P_2 Model 2¶	Non-obese CC(30) Median	IQR	TT ± TC(60) Median	IQR	P‡	P*	P_1 Model 1**	P_2 Model 2††
FRAP						0·048	0·036	0·027						0·450	0·361	0·401
≤ 15·76	245·76	30·17	264·70	37·62	0·206				236·02	55·79	235·15	35·35	0·565			
> 15·77	271·09	35·18	244·95	74·43	0·199				246·00	20·84	235·30	50·26	0·906			
P†	0·047		0·398						0·925		0·614					
TRAP						0·051	0·052	0·060						0·069	0·058	0·094
≤ 7·87	250·24	46·05	265·30	37·62	0·202				254·60	40·91	234·50	30·27	0·129			
> 7·88	266·26	34·33	246·50	45·60	0·130				236·67	33·45	235·47	44·60	0·507			
P†	0·095		0·258						0·376		0·079					
TEAC						0·068	0·054	0·070						0·583	0·662	0·845
≤ 7·27	250·24	46·05	264·7	37·62	0·270				230·07	50·13	235·10	27·40	0·856			
> 7·28	266·26	34·33	253·30	73·95	0·239				246·34	22·84	235·30	49·40	0·800			
P†	0·095		0·426						0·455		0·277					
ORAC						0·018	0·012	0·007						0·456	0·512	0·542
≤ 26 854·59	245·68	35·16	263·19	41·00	0·116				244·50	55·79	235·15	47·20	0·499			
> 26 854·60	275·66	34·19	246·50	73·95	0·155				236·90	20·84	235·30	49·05	0·761			
P†	0·008		0·542						0·708		0·683					

FRAP, ferric reducing ability of plasma; TRAP, total reactive antioxidant potential; TEAC, trolox equivalent antioxidant capacity and ORAC, oxygen radical absorbance capacity.

* P; P interactions are obtained with the general linear model (two-way ANOVA). Mann–Whitney test was used to compare the IL18 level in the two categories of antioxidant intake (†P) or between two genotypic groups (‡P).

‖ The P_1 value of the interaction (model 1) is adjusted for sex (as categorical), supplement use (as categorical), smoking (as categorical), coffee and PUFA-w3 and total energy intake (as continuous) using ANCOVA test.

¶ The P_2 value of the interaction (model 2) further adjusted for age (as continuous) using ANCOVA test.

** The P_1 value of the interaction (model 1) is adjusted for age (as continuous), sex (as categorical), supplement use (as categorical), smoking (as categorical), PUFA-w3 and total energy intake (as continuous)using ANCOVA test.

†† The P_2 value of the interaction (model 2) further adjusted for coffee intake (as continuous) using ANCOVA test.

§ Obesity was defined as BMI ≥ 25 kg/m^2.

TAC[70,71]. It seems that serum TAC reaches its peak plasma concentration 2 h after consuming antioxidant-rich foods[72]. On the effect of diet on the genome, two human studies have shown that adherence to a healthy lifestyle[73] and higher DTAC[74] have favourable effects on telomere length, which are highly sensitive to the hydroxyl radical.

As mentioned before, a gold standard or specific method for measuring the DTAC is not available yet. Generally, there are two principal mechanisms that antioxidants can neutralise radicals: single electron transfer mechanism, which is the base of FRAP and TEAC methods, and hydrogen atom transfer mechanism, which is the base of ORAC and TRAP methods[75]. Redox-related status is multifactorial, and every single method provides specific information[76]. In our study, the most significant interactions were observed in single electron transfer-based methods, particularly in the TEAC method.

Limitation

The strength of this study is that it is the first attempt to investigate the interaction between rs5082 genotypes and DTAC on some oxidative stress and inflammatory marker in the Middle East and that it was a community-based study. This research conducted in Tehran. Tehran, as the third most populous metropolis in the Middle East, is always faced with migration from other cities and therefore in terms of population distribution includes almost all ethnicities. Thus, cross-sectional studies with a genetic approach can be the best choice. To calculate the antioxidant potential, four methods to estimate DTAC (FARP, TRAP, TEAC and ORAC) were used. In addition, this gene–diet interaction was also investigated in terms of patients' weight status (obese/non-obese). Also, identification of these gene–diet interactions could be useful in recommendations or proper planning for personal nutrition to the prevention and management of CVD in diabetic patients.

It is essential consideration some limitations in this study. First, the cross-sectional design of the study prevented us from inferring causation. Second, DTAC indexes were calculated based on international databases. Since the antioxidant content may vary according to geographic location, this may lead to underestimation of DTAC, attenuation or invalidity of the assessed association. Third, subjects with high-DTAC may also have healthier eating behaviours that may affect our findings. To reduce these errors, the findings were adjusted for several confounding factors, including smoking, physical activity, obesity and supplement use. Fourth, the FFQ that used for the evaluation of the usual intake of participants was not particularly validated for the estimation of diet's TAC. With regard to DTAC estimation, when no data were available regarding cooked foods (typically have higher DTAC values), the value of raw foods was substituted. Fifth, metabolism and bioavailability of antioxidants are not considered in the DTAC. Sixth, we lacked data on socio-economic status, anxiety status, sleep status, body composition, alcohol consumption and blood glucose as a potential moderator of CVD. Seventh, dietary supplements did not consider for calculating DTAC. Eighth, it is possible that observed associations affected by functional polymorphisms in other genes.

Conclusion

This study indicates that this could be a novel link between DTAC and Apo A-II rs5082 polymorphism in diabetic patients. Based on these results, dietary recommendations for antioxidant-rich foods intake might be useful in the delay or prevention of diabetes complications in the T carrier genotype more effectively than the CC genotype. Future researches are needed to confirm these results, by replicating the same study in different populations and preferably with a bigger sample size.

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