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ApoA2–256T > C polymorphism interacts with Healthy Eating Index, Dietary Quality Index-International and Dietary Phytochemical Index to affect biochemical markers among type 2 diabetic patients

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Abstract

Several investigations revealed the association between ApoA2 concentration and lipid profile, inflammation and oxidative stress markers. Dietary habits also play a major role in the health status of individuals with type 2 diabetes mellitus (T2DM). This study aimed to investigate the interaction of ApoA2–256T > C with dietary indexes on ghrelin and leptin hormones together with biochemical markers among individuals with T2DM. A cross-sectional study was conducted on 726 randomly selected individuals with T2DM. A validated FFQ was used to evaluate Healthy Eating Index, Dietary Quality Index-International (DQI-I) and Dietary Phytochemical Index (DPI). ApoA2–256T > C genotypes were detected by real-time-PCR. Ghrelin, leptin and biochemical markers were also assessed. ANCOVA was used for the interaction between the polymorphism and dietary indexes. A significant interaction was observed between ApoA2–256T > C and DQI-I on high-sensitivity C-reactive protein (hs-CRP) level and superoxide dismutase (SOD) activity. Besides, the interaction of the SNP and DPI significantly affected hs-CRP and 8-isoprostane F2α (PGF2α) levels. CC in the second tertile of DPI had the lowest hs-CRP level, and it was elevated due to adhering to DQI-I ($P_{interaction} = 0{\cdot}01$ and 0·04, respectively). Moreover, T-allele (protective allele) carriers with the highest level of PGF2α and SOD activity were those in the second tertile of DPI and DQI-I, respectively ($P_{interaction} = 0{\cdot}03$ and 0·007, respectively). SOD activity, hs-CRP and PGF2α concentration may be modified in T-allele carriers and CC by the adherence to DPI and DQI-I, though additional studies are required to confirm these findings.

Key words: **ApoA2: Polymorphism: Dietary indexes: Inflammation: Oxidative Stress**

Type 2 diabetes mellitus (T2DM) is a multifactorial metabolic disorder that is known as one of the main causes of morbidity and mortality[1,2]. The International Diabetes Federation has estimated that the population of patients with T2DM will rise from 463 million in 2019 to 700 million in 2045[3]. Diabetic dyslipidaemia is the common lipid profile disorder in T2DM with high serum triglyceride, LDL and total cholesterol (TC) levels along with low HDL level[4,5]. Hence, dyslipidaemia is considered the main metabolic problem in T2DM. Furthermore, several studies demonstrated that T2DM is associated with increased inflammation and oxidative stress. Oxidative–antioxidative cycle imbalance in a patient with T2DM is due to the redundant production of reactive oxygen species and a damaging antioxidant mechanism like uric acid, superoxide dismutase (SOD) and glutathione[6]. Additionally, a high level of inflammatory markers like high-sensitivity C-reactive protein (hs-CRP), interleukin-18 and pentraxin 3 (PTX3) have an effective and reinforce role in the pathogenesis of diabetes mellitus and CVD[7,8]. Several hormones assist with the pathogenesis and aetiology of T2DM, which leptin and ghrelin are two of the most important[9]. T2DM with an

Abbreviations: DPI, Dietary Phytochemical Index; DQI-I, Dietary Quality Index-International; HEI, Healthy Eating Index; hs-CRP, high-sensitivity C-reactive protein; PGF2α, 8-isoprostane F2α; PTX3, pentraxin 3; SOD, superoxide dismutase; T2DM, type 2 diabetes mellitus; WC, waist circumference.

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interaction between genetic and lifestyle factors is considered a multifactorial disorder[10]. One of the most studied genes among T2DM patients is ApoA2 which is considered as one of the main protein components of serum HDL, synthesized in the liver and constitutes almost 20 % of HDL's protein[7,11]. It seems that ApoA2 participates in the impairment of reverse cholesterol transportation and HDL's antioxidant activity[12]. There are a few and controversial studies related to the function of ApoA2 in humans. The –256T > C is one of the most important SNP associated with plasma lipid concentration[13]. The substitution occurred at 256bp before the ApoA2 gene transcription is a common mutation which substitutes T to C and forms ApoA2–256T > C polymorphism, which leads to the incomplete and lower synthesis of ApoA2[7,14,15].

Among the lifestyle factors, diet is one of the major factors in the prohibition and control of T2DM. Although to date, numerous researches have examined the relationship between particular nutrients and disorders, the assessment of dietary patterns is growing in recent studies. Assessing dietary pattern quality is one way to demonstrate a person's dietary status. Healthy Eating Index (HEI), Dietary Quality Index-International (DQI-I) and Dietary Phytochemical Index (DPI) are common indexes for evaluating dietary pattern quality and total dietary phytochemical content, respectively. HEI is developed by the USA Department of Agriculture (USDA) and formed based on Dietary Guidelines for Americans. Higher HEI scores reveal better adherence to the Dietary Guidelines for Americans[16]. DQI-I evaluates diet quality across diverse countries at every stage of nutrient transition[17]. DPI developed to assess the energy intake supplied by phytochemical foods[18]. Previous studies revealed that the interaction of ApoA2 and macronutrient intake affects several factors[19]. The high intake of MUFA and PUFA could reduce the inflammatory markers in the CC genotype of ApoA2, and subjects with this genotype tend to consume more dietary saturated fatty acids[7,19]. Moreover, obesity may inhibit the preservative role of the T allele against oxidative stress[20].

According to our knowledge, there isn't any study assessing the effect of interaction between dietary indexes and ApoA2–256T > C polymorphism; hence, this study designed to assess the interaction of ApoA2–256T > C and dietary indexes – evaluated by DQI-I, HEI and DPI – on ghrelin and leptin hormones plus biochemical markers among type 2 diabetic patients.

Methods

Data collection

In total, 726 diabetic patients (285 men and 441 women) aged 35–65 years were randomly selected during 2011–2012 from the Iranian Diabetes Society, Gabric Diabetes Association and other Health Centers for this cross-sectional study[21]. Ancestral groups that were studied consisted of 722 Iranian subjects (99·45 %). Three subjects (0·41 %) were from Afghanistan and 1 subject (0·14 %) was an Iraqi.

After taking written consent from participants, their demographic information, socio-economic and medical status were collected with a standardised questionnaire. The exclusion criteria including subjects less and more than 35 and 65, respectively, pregnancy and lactation, anti-inflammatory drug intake, multivitamin and mineral supplementation, insulin therapy and participants with a history of chronic disorders like hepatic, thyroid, renal, and coagulation disorders, stroke, inflammatory diseases and cancer. The Ethics Committee of Tehran University of Medical Sciences approved all of the stages of this study with a protocol number 91-04-161-20413-77519, and there was no potential bias in our research.

Anthropometric measurements

The anthropometric measurements include weight, height and waist circumference (WC). Weight (kg) and height (cm) were measured with standard protocols and accuracy of 100 g and 0·5 cm, respectively. WC was the mid-way between the lowest rib and the iliac crest when a participant stood firmly with an accuracy of 0·5 cm as well. The division of weight (kg) to the square of height (m) formed the BMI.

Assessment of dietary intake and physical activity

A semi-quantitative FFQ with 147 items was used for assessing dietary intake during last year which was validated by the Tehran Lipid and Glucose Study[22]. Finally, the reported amounts turned to grams per day. The scores of HEI-2015, DQI-I and DPI were calculated by FFQ. The calculation of HEI-2015 was described in detail by Smith et al.[23]. In this method, there are thirteen components for scoring which include two categories of adequacy and moderation. Reported amounts were converted to cups or ounces due to the scoring system. For converting to the ounce, we divided it by 28·35, and for converting the amounts to cup, we used Food Patterns Equivalent Database guideline[24]. We calculated this index based on the simple HEI scoring algorithm method. DQI-I[17] has four categories that evaluate variety, adequacy, moderation and overall balance. The score range of both HEI and DQI-I is 0 to 100. Thus, higher indexes scores represent better dietary quality. Furthermore, the calculation of DPI was briefly the division of the total energy of all phytochemical-rich food components to total energy intake. The scoring system has been described elsewhere[18]. The classified metabolic equivalent task questionnaire was used to assess the daily physical activity which was validated in Iran by Kelishadi et al.[25].

Biochemical and molecular analysis

Blood samples were gathered after overnight fasting (8–14 h). The serum and plasma were extracted. Commercially available kits (Pars Azmoon) were used for enzymatic measurement of the cholesterol, triglyceride, LDL-cholesterol and HDL-cholesterol. The ELISA method was used for measuring serum ghrelin and leptin concentrations (Bioassay Technology Co, and Mediagnost, respectively) and calculation of serum inflammatory markers like interleukin-18, PTX3 (Shanghai Crystal Day Biotech Co., Ltd) and hs-CRP (Diagnostic Biochem Canada Inc.) as well.

Moreover, we used ELISA (Shanghai Crystal Day Biotech Co., Ltd.) to measure the serum concentration of 8-isoprostane F2α (PGF2α) as well. The measurement of serum SOD activity and

the total antioxidant capacity was done by the colorimetric method (Cayman Chemical Company) and spectrophotometry, presented by Rice Evans & Miller[26], respectively. Total antioxidant capacity is a cost-effectiveness measure of the cumulative and synergistic effect of body antioxidants relative to other antioxidants measurements[27]. The intra-assay and inter-assay CV for interleukin-18, PTX3 and PGF2α were below 10 and 12 % and for hs-CRP were below 5 and 9·5 %, respectively.

Genetic analysis

Real-time PCR (TaqMan assay) was used for the determination of ApoA2 genotypes. The assessing method of genome DNA extraction has been published in the previous study[19].

Statistical analysis

The sample size was calculated by the following formula with type I error of $\alpha = 0{\cdot}05$ and type II error of $\beta = 80$ %:

$$S_p^2 = [(n_1-1)\times SD_1^2 + (n_2-1)\times SD_2^2]/[(n_1-1)+(n_2-1)-2]$$
$$= [(30-1)\times(0{\cdot}25) + (6-1)\times(0{\cdot}53)]/[(71-1)+(6-1)-2]$$
$$= 0{\cdot}042;\ S_p = 0{\cdot}208$$
$$d = (\mu_1-\mu_2)\ /\ (\sqrt{2}\times S_p) = 0{\cdot}5\ /\ (\sqrt{2}\times 0{\cdot}208) = 1{\cdot}7$$
$$N = (Z_{1-\alpha/2} + Z_{1-\beta})^2/d;\ \alpha = 0{\cdot}05,\ 1\text{-}\beta = 0{\cdot}05$$
$$= (1{\cdot}96 + 0{\cdot}84)^2\ /\ 1{\cdot}7 = 5$$

The frequency of the CC allele has not been reported yet in the Iranian population. Given that the frequency of minor allele was 1–16 % in a different population, we considered 1 % as the frequency of the CC allele in this population, so the minimum sample size for this study was 500 participants (5/0·01 = 500). With regard to the necessity of a large sample size for evaluating the gene–diet interaction, the final sample size was increased to 726 participants due to the unclear distribution of the polymorphism and further increase of statistical power.

IBM SPSS version 21 was utilised for all of the statistical analyses. Dietary indexes were divided into tertiles for assessing the adherence of subjects to indexes. The Kolmogorov–Smirnov test was performed for checking the normality of variables and variables without normal distribution were log-transformed or squared. The association of metabolic markers, ghrelin and leptin hormones, and anthropometric measurements with ApoA2–265T > C genotypes as well as dietary indexes were analysed using the independent Student's *t* tests or ANOVA. Finally, the interaction between dietary indexes and ApoA2–265T > C polymorphism on the aforementioned variables was evaluated by using the General Linear Model and ANCOVA multivariate interaction models after adjustment for confounding variables including age, gender, physical activity, smoking habits and alcohol intake. Statistical significance was tested two-sided and assigned at $P \leq 0{\cdot}05$.

Results

In the present study, among 726 diabetic patients, 39·3 % were men and 60·7 % were women. The interaction effects of the polymorphism with dietary indices were evaluated in two ways. First, analyses were performed into three genotyping groups of TT, TC and CC, which were represented in Supplementary Tables S1 to S3 of Supplementary material. Second, interactions were evaluated in two groups of T-allele carriers and homozygous for C allele due to resembling effects of TT & TC genotypes, which have been considered along with regard to consistency with our previous studies[7,11,19,28–30]. The T-allele carriers and CC genotype of ApoA2–256T > C had a frequency of 88·2 and 11·8 %, respectively. The allelic distribution complied with the Hardy–Weinberg equilibrium[19]. The CC homozygous was significantly older than the T-allele carriers ($P = 0{\cdot}04$). None of the other general characteristics were significantly different in the two groups of genotypes (Table 1). Table 2 shows a comparison of the dietary indexes scores, anthropometric and biochemical measurements according to ApoA2–256T > C genotypes. CC homozygous had significantly higher serum hs-CRP ($P = 0{\cdot}02$), PGF2α levels ($P = 0{\cdot}01$) and DQI-I score ($P = 0{\cdot}02$). Moreover, there was a higher HEI-2015 score near to significant in CC genotype as opposed to T-allele carriers ($P = 0{\cdot}06$). On the other hand, T-allele carriers had significantly higher serum TC ($P = 0{\cdot}03$), TG ($P = 0{\cdot}01$), PTX3 ($P = 0{\cdot}05$), total antioxidant capacity ($P = 0{\cdot}05$) and SOD activity ($P < 0{\cdot}0001$) compared with CC homozygous. Besides, a significant reduction in WC, BMI and LDL-cholesterol level and a significant elevation in HDL-cholesterol concentration were observed through the tertiles of HEI-2015, and there was not any other significant difference in laboratory parameters according to the dietary indexes (Table 3). We found a gene–diet interaction between DQI-I and ApoA2–256T > C in associations with hs-CRP serum concentration and SOD activity ($P_{interaction} = 0{\cdot}02$ and $P_{interaction} = 0{\cdot}01$, respectively) in crud model. This interaction remained statistically significant in adjusted model ($P_{Interaction} = 0{\cdot}04$ and $P_{interaction} = 0{\cdot}007$, respectively). In particular, the CC homozygous who placed in the last tertile of DQI-I had the highest hs-CRP level contrary to T-allele carriers ($P = 0{\cdot}008$). Plus, T-allele carriers in the second tertile had the highest SOD activity than CC homozygous. Furthermore, a significant interaction was detected between DPI and ApoA2–256T > C for hs-CRP and PGF2α in both crude ($P_{Interaction} = 0{\cdot}009$ and $P_{Interaction} = 0{\cdot}03$, respectively) and adjusted models ($P_{Interaction} = 0{\cdot}01$ and $P_{Interaction} = 0{\cdot}03$, respectively). The highest mean of hs-CRP and PGF2α was observed in CC homozygous and T-allele carriers, respectively, in the first and third tertiles of DPI. No significant interaction was found between ApoA2–256T > C polymorphisms and dietary indexes (HEI, DQI-I and DPI-I) on other parameters.

Discussion

As far as we are aware, this is the first study attempt to investigate the interactions of ApoA2–256T > C and dietary indexes on ghrelin and leptin hormones and biochemical markers among patients with type 2 diabetes. Based on our findings, CC homozygous had better DQI-I and HEI-2015 scores, lower TC, triglyceride, PTX3, total antioxidant capacity and SOD activity and higher hs-CRP and PGF2α than T-allele carriers. These findings were in line with the results of our previous works[7,11,14,19,20,31,32]. A gene–diet interaction showed that adherence to DQI-I and DPI modifies the effect of ApoA2–

Table 1. Comparison of general and anthropometric characteristics between CC genotype and T allele carrying group (TT/TC)
(Mean values and standard deviations; number and percentages)

	TT/TC ($n = 640$)				CC ($n = 86$)				
Variables	Mean	SD	*n*	%	Mean	SD	*n*	%	*P*-value
Age (year)	53·89	6·7			55·42	5·65			0·04
Physical activity (MET.h/d)	37·87	5·57			37·23	4·58			0·31
Weight (kg)	76·45	13·99			74·88	12·42			0·32
Height (cm)	161·28	9·17			160·1	9·05			0·26
Body Mass Index (kg/m^2)	29·37	4·76			29·25	4·54			0·83
Waist circumference (cm)	92·22	10·41			92·69	11·75			0·21
Diabetes duration (year)	1·88	1·25			1·99	1·24			0·45
Gender			252	39·4					0·48
Male			388	60·6			33	38·4	
Female			118	18·4			53	61·6	
Smoking			17	2·7			8	9·3	0·1
Alcohol intake							4	4·7	0·23
Disease history			518	80·8					
Diabetes			241	37·7			73	84·9	0·23
Coronary artery disorder			113	17·7			35	40·7	0·33
Renal			107	16·7			13	15·1	0·61
Liver							15	17·4	0·48
Lipid-lowering medications			45	7					0·74
Without medications			192	30			5	5·8	
Atorvastatin			32	5			29	33·7	
Simvastatin			316	49·3			2	2·3	
Gemfibrozil			56	8·7			41	47·7	
Other medications							9	10·5	
Anti-diabetic agents			278	43·4					0·53
Without medications			298	46·5			36	41·9	
Metformin			6	0·9			44	51·2	
Glibenclamide			22	3·4			–		
Metformin + Glibenclamide			37	5·8			4	4·7	
Other medications							2	2·3	

$P \leq 0{\cdot}05$; Student's *t* test was used for comparing mean differences of quantitative variables, χ^2 test was used for qualitative variables.

Table 2. Comparison of subjects' indexes scores, anthropometric measurements and laboratory parameters according to ApoA2–256T > C genotypes
(Mean values and standard deviations)

	TT/TC, ($n = 640$)		CC, ($n = 86$)		
Variables	Mean	SD	Mean	SD	*P*-value*
HEI-2015	54·62	9·19	56·62	9·92	0·06
DQI-I	59·65	8·29	60·99	7·96	0·02
DPI	41·13	12·21	44·38	13·21	0·2
BMI	29·37	4·8	29·25	4·5	0·8
WC	92·2	10·4	92·7	11·7	0·7
HDL-C	53·32	12·59	52·98	12·96	0·8
LDL-C	108·04	35·4	105·98	36·01	0·6
LDL/HDL	2·64	10·01	2·07	0·72	0·6
Cholesterol	200·83	72·14	186·51	85·97	0·03
Triglyceride	187·69	196·65	165·8	111·74	0·01
Leptin	24·88	14·98	25·12	13·5	0·9
Ghrelin	2·29	1·05	2·47	1·68	0·5
PTX 3	2·67	32·17	2·52	0·46	0·05
IL-18	247·38	32·17	251·57	27·57	0·4
hs-CRP	1·95	1·31	2·87	1·67	0·002
TAC	2·54	0·57	2·36	0·53	0·06
SOD	0·16	0·05	0·12	0·03	<0·0001
PGF2α	71·37	5·57	74·78	6·58	0·01

WC, waist circumferences; hs-CRP , high-sensitivity C-reactive protein; PTX3, pentraxin 3; IL-18 , Interleukin 18; TAC, total antioxidant capacity; SOD, superoxide dismutase; PGF2α, prostaglandin F2α.
* $P \leq 0{\cdot}05$; Student's *t* test.

Table 3. Comparison of subjects' anthropometric measurements, clinical and laboratory parameters according to tertile (T) of indexes (Mean values and standard deviations)

	Healthy Eating Index-2015						
	T1 ($n = 239$)		T2 ($n = 241$)		T3 ($n = 244$)		
Variables	Mean	SD	Mean	SD	Mean	SD	*P*-value*
BMI, kg/m^2	29·9	4·8	29·3	4·8	28·9	4·5	0·03
WC, cm	93·8	11·4a	92	11·4	91	9·8	0·01
HDL, mg/dl	51·4	12·7a	53·6	11·9	54·8	13·2	0·01
LDL, mg/dl	103·7	33·9	106·7	33·07	112·9	38·6	0·02
LDL/HDL	2·8	11·2	2·04	0·7	2·9	11·9	0·56
Cholesterol, mg/dl	196·2	69·2	201·9	85·6	199·4	65·7	0·6
Triglyceride, mg/dl	184·7	114·8	187·6	99	182·9	108·4	0·57
Leptin, ng/ml	23·5	12·5	23·9	14·8	26·9	15·4	0·24
Ghrelin, ng/ml	2·3	1·3	2·4	1·4	2·4	1·3	0·96
PTX 3, ng/ml	2·6	0·4	2·7	0·5	2·6	0·5	0·37
IL-18, pg/ml	252·9	34·3	246·9	27·8	246·9	30·03	0·5
hs-CRP, mg/l	2·1	1·5	2·3	1·6	2·3	1·2	0·65
TAC, g/dl	2·5	0·5	2·5	0·6	2·4	0·6	0·59
SOD, U/ml	0·2	0·5	0·1	0·04	0·1	0·1	0·92
PGF2α, pg/ml	72·5	6·3	71·7	6·3	73·3	5·8	0·38
	Dietary Quality Index-International						
	T1 ($n = 275$)		T2 ($n = 217$)		T3 ($n = 230$)		*P*-value*
BMI, kg/m^2	29·7	5·01	29·3	4·5	28·9	4·5	0·19
WC, cm	92·5	11·1	92·6	9·9	91·8	10·5	0·67
HDL, mg/dl	53·9	13·5	52·7	12·2	53·05	12·04	0·62
LDL, mg/dl	107·6	33·2	106·1	33·4	109·03	39·1	0·83
LDL/HDL	2·1	0·7	2·9	11·65	2·9	12·2	0·7
Cholesterol, mg/dl	201·3	69·6	194·6	60·1	200·7	89·6	0·64
Triglyceride, mg/dl	191·5	111·04	180·8	102·2	181·9	108·1	0·55
Leptin, ng/ml	24·4	12·1	26·4	16·5	24·3	14·7	0·6
Ghrelin, ng/ml	2·3	1·2	2·2	1·2	2·5	1·5	0·59
PTX 3, ng/ml	2·6	0·4	2·6	0·5	2·6	0·5	0·91
IL-18, pg/ml	255·2	29·2	247·2	35·2	245·2	27·3	0·19
hs-CRP, mg/l	1·9	1·5	2·3	1·5	2·4	1·5	0·2
TAC, g/dl	2·5	0·6	2·4	0·6	2·5	0·5	0·77
SOD, U/ml	0·2	0·05	0·1	0·05	0·1	0·04	0·46
PGF2α, pg/ml	72·4	5·3	72	7·2	73·02	5·9	0·66
	Dietary Phytochemical Index						
	T1 ($n = 240$)		T2 ($n = 241$)		T3 ($n = 243$)		*P*-value*
BMI, kg/m^2	29·6	5·01	29·4	4·7	29·1	4·5	0·44
WC, cm	93·01	10·5	92·2	10·2	91·6	11·01	0·33
HDL, mg/dl	54·3	14·4	53·2	11·8	52·4	11·4	0·41
LDL, mg/dl	109·8	34·3	104·9	35·7	108·8	36·3	0·24
LDL/HDL	2·1	0·65	2·7	11·1	2·9	11·9	0·45
Cholesterol, mg/dl	201·9	82·7	199·4	70·8	196·6	67·8	0·93
Triglyceride, mg/dl	198·1	124·6	179·2	93·2	178·7	101·9	0·21
Leptin, ng/ml	23·4	13·2	25·9	16·6	25·2	13·5	0·55
Ghrelin, ng/ml	2·4	1·5	2·2	1·2	2·4	1·3	0·42
PTX 3, ng/ml	2·6	0·4	2·7	0·4	2·6	0·5	0·45
IL-18, pg/ml	247·8	34·5	249·9	28	248·6	28	0·94
hs-CRP, mg/l	2·2	1·4	2·3	1·6	2·3	1·5	0·94
TAC, g/dl	2·4	0·5	2·4	0·5	2·6	0·6	0·3
SOD, U/ml	0·2	0·05	0·1	0·05	0·1	0·04	0·84
PGF2α, pg/ml	72·02	5·8	73·3	6·05	72·2	6·5	0·5

WC, waist circumferences; PTX3, pentraxin 3; IL-18 , Interleukin 18; hs-CRP , high-sensitivity C-reactive protein; TAC, total antioxidant capacity; SOD, superoxide dismutase; PGF2α, prostaglandin F2α.
* One-way Anova test.
[a] Post-hoc; Tukey test.

256T > C polymorphisms on hs-CRP, PGF2α and SOD activity. The SOD activity and level of PGF2α in T-allele carriers increased in the second tertile of DQI-I and DPI and reduced in the third tertile. On the other hand, CC homozygous showed an increase of hs-CRP level by the adherence to DQI-I, and it was the lowest in the second tertile of DPI. The –256T > C is the most studied SNP among the various SNP of the ApoA2 gene, which is related to reduced serum ApoA2 concentration[33]. Determining the risk allele of the aforementioned SNP is a point of contention. The findings of the present study were consistent with the results

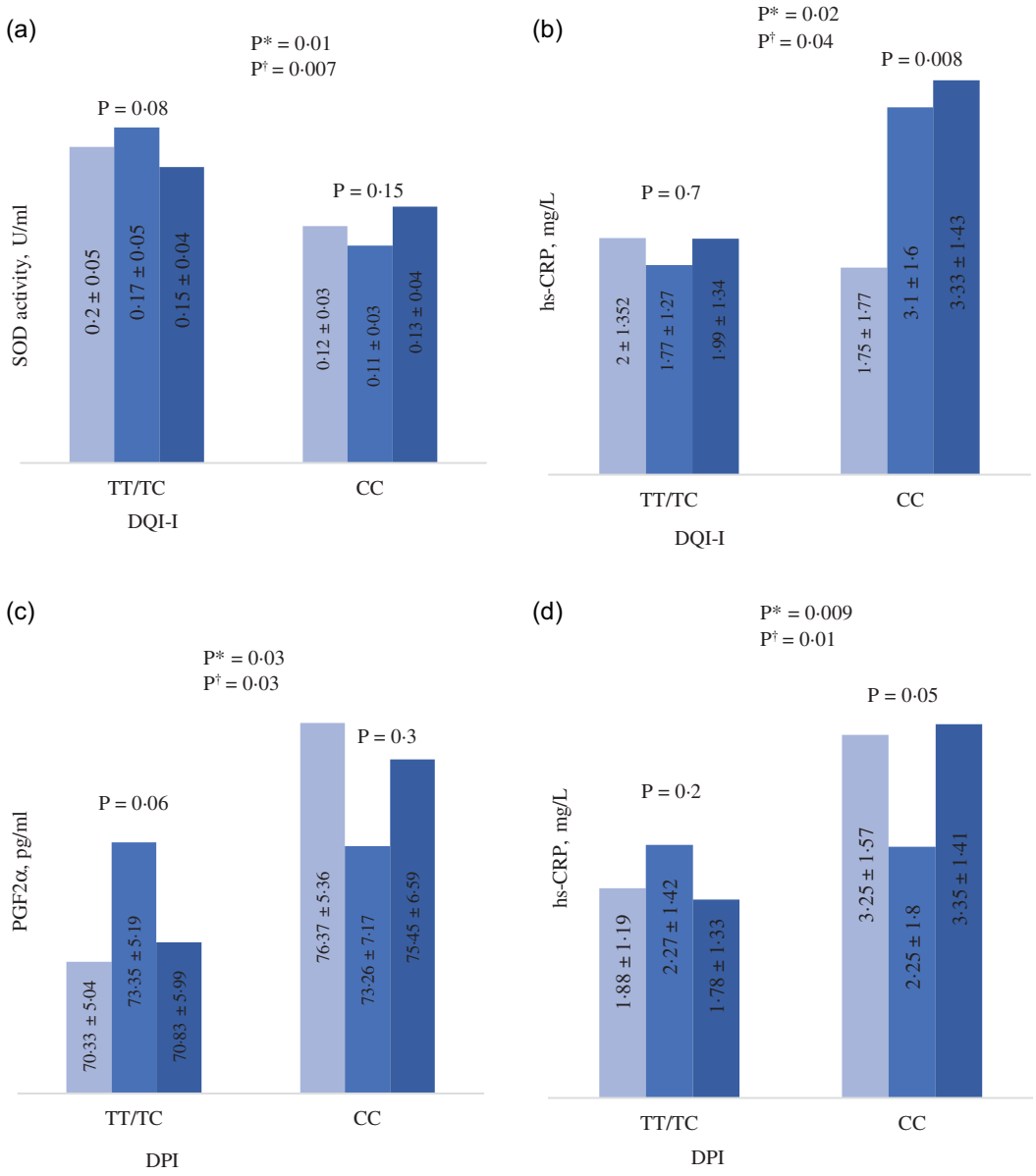

Fig. 1. Interaction between APOA2−265T > C polymorphism and the indices on laboratory parameters. The bars indicate mean ± SD. , T1; , T2; , T3. *P for unadjusted interaction that obtained from multivariate models using ANCOVA †P for adjusted interaction obtained from multivariate models using ANCOVA. Adjusted for age, gender, physical activity, smoking, and alcohol intake

of studies that described CC homozygous as a risk allele[29–32]; nevertheless, several studies reported the CC homozygous as a protective allele of cardiovascular disorders[34,35]. It has been remarked that the reduced serum ApoA2 concentration might be the main cause of higher hs-CRP levels in CC homozygous which is directly associated with oxidative stress factors[36–38]. According to a study conducted on transgenic rabbits with the human ApoA2 gene, lower plasma levels of hs-CRP and higher paraoxonase-1 (PON1) activity were significantly observed in these rabbits which leads to low odds of atherosclerosis[39,40]. Nevertheless, a lower activity of PON1 was reported in several transgenic mice studies with human ApoA2[34]. It should be noted that, unlike transgenic mice, transgenic rabbits represent a better animal model for human ApoA2 metabolism[41]. There is a controversy in findings of lipid profile. Consistent with our findings, subjects with lower serum ApoA2 concentration had significantly lower TC and triglyceride in Birjmohun et al. study[36], whereas a conflicted relationship was reported between ApoA2 and lipid profile in some other studies[15,42]. In this study, a significant reduction in WC, BMI and LDL-cholesterol level and a significant elevation in HDL-cholesterol concentration were observed through the tertiles of HEI-2015. With consideration to Al-Ibrahim et al. study, anthropometric measurements like WC and BMI were decreased by increasing the adherence to HEI which is in line with the results of this study. Dialectical findings have been reported about lipid profiles as well. HDL-cholesterol and LDL-cholesterol levels were increased and decreased, respectively, through the

quartiles of HEI but unlike a significant decrease of LDL-cholesterol level in Alternate Healthy Eating Index-2010 (AHEI-2010), it was not significant in HEI-2010[43]. Likewise, a significant association of HEI with BMI, WC and LDL-cholesterol was exhibited in Haghighatdoost et al. study[44]. Shivappa et al. showed a significant increase for HDL-cholesterol level and a significant decrease for BMI in tertiles of AHEI-2010[45]. In contrast to our results, no significant relationships were reported between WC, BMI and HDL-cholesterol concentration and quartiles of HEI-2015 by Khodarahmi et al.[46]. There is not any study for evaluating the interaction of the genotypes with dietary patterns, and the gene–diet interaction studies were only focused on the interplay of ApoA2–256T > C and dietary fatty acid intake. The association between high intake of SFA and higher BMI and WC in CC genotype has been figured out in several studies[11,29,47,48]; however, there was not any significant interplay between genotypes and SFA intake on WC in Basiri et al. study[11]. Keramt et al. showed higher median consumption of *n*-3 PUFA and MUFA and decreased hs-CRP and interleukin-18 serum concentration in CC homozygous, whereas an elevation in serum concentration of hs-CRP was seen with a higher median intake of SFA in T-allele carriers[7]. The interplay of ApoA2–256T > C and SFA consumption increased the levels of LDL-cholesterol and LDL/HDL in CC homozygous in the Noorshahi et al. study[19]. No precious mechanism has been revealed yet, but some probable explanation might be available for the interaction of the polymorphism and dietary indexes on some laboratory parameters. As it was illustrated in Fig. 1, despite the adherence to DQI-I, hs-CRP increased in CC homozygous. The intake of MUFA and added sugars was also decreased and increased, respectively, in tertiles of DQI-I in CC homozygous. Considering PPAR as regulator factors of lipid and glucose hemostasis, activated by MUFA, they might reduce inflammation by downregulating pro-inflammatory genes in adipose tissue. Therefore, decreased MUFA and increased added sugars intake were likely to elevate hs-CRP amount; however, some confounding variables might be ignored in this relationship. Furthermore, SOD activity and linolenic acid were highest in the second tertile of DQI-I among T-allele carriers. Studies suggested that *n*-3 PUFA like linolenic acid can inhibit the production of reactive oxygen species or may interfere in modulating the enzymes responsible for reactive oxygen species production[49]. Likewise, hs-CRP decreased in the second tertile of DPI in minor allele and elevated after that. Consistent with this study, Edalati et al. exhibited the same trend of hs-CRP in tertile of DPI, despite the insignificant relationship between them[50]. Oxidative stress and inflammation reduction were suggested as potential protective effects of phytochemical-rich diets. It has been suggested that oxidative stress is associated inversely with the DPI score[18]. We saw that T-allele carriers in the second tertile of DPI had the highest amount of PGF2α. Higher consumption of vegetables and fruits is associated with a higher intake of phytochemicals and some other antioxidant components. In the current study, it was observed that, in contrary to high vegetables and fruits consumption, the intake of antioxidants like vitamin E, selenium and fibres is reduced in individuals of DQI-I's second tertile; therefore, PGF2α increased in these people; however, more investigations needed to determine the actual mechanism of these relationships. Though these findings were novel in this concept, this study has some limitations. This is a cross-sectional study without measurement of ApoA2 serum concentration. As we used FFQ for evaluating the dietary intakes, we cannot ignore the recall bias and over-report or under-report of participants. In conclusion, adherence to DPI and DQI-I interacts with ApoA2 genotypes and could significantly impact on inflammation and oxidative stress. These results emphasise the consideration of gene–diet interaction in health status of diabetic patients.

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Supplementary material

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