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Interaction Between the Dietary Indices (DQI, DPI, HEI) and PPAR-γ Gene Variants on Cardiovascular Risk Factors in a Patient With Type 2 Diabetes Mellitus

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Abstract

Background: We investigated the interaction between PPAR-γ Pro12Ala polymorphism and Healthy Eating Index (HEI), Dietary Quality Index-International (DQI-I) and Dietary Phytochemical Index (DPI) on Cardiovascular Disease (CVD) risk factors in patients with type 2 diabetes mellitus (T2DM).

Methods: This cross-sectional study was conducted on 393 diabetic patients. PPAR-γ Pro12Ala was genotyped by PCR-RFLP method. Biochemical markers including total cholesterol (TC), low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglyceride (TG), superoxide dismutase (SOD), C-reactive protein (CRP), total antioxidant capacity (TAC), pentraxin-3 (PTX3), isoprostaneF2α (PGF2α) were measured by standard protocol. FFQ was used for dietary indices (DQI, DPI, HEI) calculation.

Results: There was no significant relationship between PPAR-γ Pro12Ala polymorphism and CVD risk factors. The rs1801282-DQI interactions were significant on WC (P= 0.01). Thus, C-allele carriers in the higher tertile of DQI had higher WC compared to GG homozygous. Further, an interaction was observed between PPAR rs1801282 polymorphism and DQI on serum IL-18 level (P = 0.03). Besides, a significant rs1801282-DPI interaction was shown on HDL concentration (P Interaction= 0.04), G allele carriers who were in the highest tertile of DPI, had lower HDL. Moreover, there were significant rs1801282-HEI interactions on ghrelin (P= 0.04) in the crude model and serum leptin (P = 0.02) in the adjusted model. Individuals with (CC, CG) genotypes in the higher tertile of HEI, had lower leptin and ghrelin concentration.

Conclusions: Higher dietary indices (DQI, DPI, HEI) may affect the relationship between PPAR-γ Pro12Ala polymorphism and waist circumference and ghrelin, leptin, HDL-c, IL-18 concentration in patients with T2DM.

Introduction

One of the most important health concerns around the world is the increasing prevalence of type 2 diabetes mellitus (T2DM). The global diabetes prevalence is estimated to be (578 million) people by 2030 [1]. Cardiovascular disease (CVD) are the main cause of death and comorbidity in patients with T2DM. According to several studies, obesity, dyslipidemia, oxidative stress, and inflammation are major risk factors for CVD [2–4]. T2DM and CVD are multifactorial disorders affected by genetics and environmental factors [5, 6]. One of the most important genes in the family of nuclear receptors (NR) is the peroxisome proliferator-activated receptor-gamma (PPAR-γ) [7]. The PPAR-γ2 Pro12 gene is highly expressed in adipose tissue, which can regulate several processes including energy hemostasis, adipogenesis, and lipid metabolism [8]. There is considerable research on the association between PPAR-γ SNP and obesity and serum lipid levels [9, 10]. The SNP of the PPAR-γ Pro12Ala gene has been reduced the activity of gamma receptor [11, 12]. Some studies showed that the Ala-allele of PPARγ Pro12Ala SNP (C/G genotype) has been associated with lower body mass index (BMI) [13]. Regarding the PPARγ considered as a lipid-sensing factor, suggested that mutations of PPAR- lead to dyslipidemia, obesity, and high level of inflammatory markers [14–16]. Thus, the hypothesis is reinforced " the PPARγ SNP may be associated with risk of T2DM and CVD. Additionally, one of the most substantial environmental factors is diet. Several investigations were studied, the usual diet contains micro and macronutrient regardless of moderation and diversity were studied as dietary intake [17]. However, currently according to the dietary pattern approach, the dietary indices are considered to show the actual image of a diet on health parameters. Thus, most studies focus on diet index-based patterns as an attractive model to evaluate the association between dietary ingredients and metabolic assessments [18, 19]. In the present study, we selected three of the most practical and main dietary indexes including Healthy Eating Index (HEI), Dietary Quality Index-International (DQI-I) and Dietary Phytochemical Index (DPI). HEI is a developed tool, which has shown us how much personal dietary near to Dietary Guidelines for Americans (DAG). Additionally, Diet Quality Index (DQI), known as a member of diet quality indexes giving a monitoring device for considering parameters of diet diversity and quality which correlated with nutrient metabolism. Only a few studies demonstrate the correlation between DQI and CVD risk factors but are now considered active field research [20, 21]. Dietary phytochemical index (DPI), as a food-based method to measure the sums of phytochemicals in dietary intake. There are inconsist results of association between DPI and cardiovascular risk factors and T2DM, which might be explained by genetic diversities [22, 23]. Therefore, gene-diet interaction as nutrigenetics approach is considered special interest to assess these associations [24, 25]. So, in some studied reported that the PPAR gamma polymorphism interact with dietary fat intake on body weight, obesity, insulin resistant, TD2M, dyslipidemia[26–28].To our knowledge to date, there was no investigation assessing the effect of interaction between special dietary patterns index and Pro12Ala polymorphism on CVD risk factors. Therefore, the present work aimed to evaluate the effect of interaction between PPAR-γ2 Pro12Ala polymorphism and HEI, DQI, and DPI on cardiovascular disease risk factors in patients with T2DM.

Materials And Methods

Participants and sample collection

Participants in this research project, have been part of a large study conducted previously on diabetic patients [29]. According to the inclusion and exclusion criteria, 393 adults between the ages of 35 and 65 years (218 women and 175 men), fasting blood sugar > 126mg/dl, or using oral glucose-lowering medications were included to our study from diabetes centers of Tehran city. We received written informed consent from all participant. This work was approved by the ethics committee of the Tehran University of Medical Sciences (TUMS) [no. 15061].

Dietary intake

We applied validated semi-quantitative food-frequency questionnaires (FFQ) with 147 food items [30]. The trained dietitian asked questions regarding the frequency of each food intake. Finally, the reported amount of the food frequency was converted to gram by using the Iranian food composition table (IFCT).

Assessment of (HEI-2015)

The (HEI)-2015 is an estimation overall quality of food by following the latest version of Dietary Guidelines for Americans (DGA) 2015-2020. HEI has scored a range between 0 and 100 based on 13 factors. These dietary factors including Dairy, fatty acids and whole grain with score 0-10, total fruits, greens, whole fruits, beans and vegetables, proteins, and total protein foods with score 0-5 and also the lowest and most intake for saturated fatty acid, refined grains, added sugars and sodium with score 10 and 0, respectively). Finally, all scores were summed for each factor and compute the total HEI-2015 score [31].

Assessment of (DQI-I)

Kim et al's was the first person to designed a new method for DQI-I. The index could assess diet quality as regards variety, adequacy, moderation, and overall balance. Dietary variety scored between 0-15 points for overall food group diversity and 0-5 for a protein source. The adequacy score was calculated by the amount of vegetable, grain, protein, fruit, fiber, iron, vitamin C, and calcium to get 40 points. Moderation subcategories such as saturated fat, cholesterol, total fat, sodium, and junk foods to 30 points. Eventually, the overall balance focused on fatty acid and macronutrient ratio gets 10 points. Overall, the final score of DQI-I obtained the sum up of the score in every 4 components. Thus, the more DQI-I score, the more diet quality [32].

Assessment of (DPI)

The DPI was designed by McCarty for the first time; which is calculated as this formula: DPI-I= [(daily energy derived from phytochemical-rich foods kJ (kcal)/total daily energy intake kJ (kcal))] × 100. Some foods such as vegetables and fruits, nuts, seeds, soy sources, olive and olive oil, whole grains, legumes and vegetable and natural fruit juices were included as foods with high phytochemical content[23].

CAV-1 genotyping

DNA extraction was done by the Salting out method [33]. The PPARγ2 gene Pro12Ala polymorphism (rs1801282) was genotyped by the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). The PCR products (CC: 196 bp; CG: 196, 166,30 bp; GG: 166 and 30 bp) were separated by electrophoresis, which was described in a previous study [34].

Biochemical assessment

All serum samples were collected after overnight fasting (12-14h) at the Nutrition and Genomics Laboratory of (TUMS). We stored plasma samples at −80°C. Low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), leptin, ghrelin, C-reactive protein (CRP), pentraxin, interleukin-18 (IL-18), total antioxidant capacity (TAC), superoxide dismutase (SOD), prostaglandin F2α (PGF2α), pentraxin 3(PTX3) were measured using enzymatic methods as described in a previous study [35].

Assessment of other variables

We used standard questioners for acquiring public information including age, disease history, and medications. Weight and height were measured by using a digital scale. waist circumference was measured to the nears 0.5cm. BMI was calculated by a simple formula BMI = weight/height^2 (kg/m^2). Validated International Physical Activity Questionnaire (IPAQ) was used to assess physical activity [36].

Statistical analysis

To assess the Hardy–Weinberg equilibrium deviation among allele frequency of PPARγ Pro12Ala was used Chi-squared test. The Kolmogorov-Smirnov was utilized to test of normality. Log-transformations and SQRT were used to variables with skewed distribution. To analyze the differences of variables across PPARγ Pro12Ala genotypes, we used an Independent T-test and ANCOVA in the crud and adjusted model, respectively. The means of variables across tertiles of HEI, DQI-I, and DPI were expressed as means ± SDs and compared by ANOVA and ANCOVA test in the crude and adjusted model, respectively. The interaction between PPARγ Pro12Ala polymorphism and dietary indexes (HEI.DQI-I and DPI) on cardiovascular risk factor (BMI, WC, HDL, LDL, LDL/HDL, TC, TG, leptin, ghrelin, CRP, pentraxin, IL-18, TAC, SOD, PGF2α) was performed by Generalized Linear Model (GLM) method in both crude and adjusted models. In interaction analyses, confounder variables including age, gender, physical activity, smoking, alcohol consumption were matched in the adjusted model. All statistical analyses were done using IBM SPSS Statistics (SPSS, Inc., Chicago, IL, version 25) and the significance level was considered $P < 0.05$.

Result

Association of PPAR rs1801282 and dietary indices with metabolic markers

We evaluated 393 patients with T2DM in the present study. General, biochemical and anthropometric measurements of study participants by the PPAR rs1801282 genotypes have been expressed in Table 1. There was no statistically significant difference in terms of variables except serum leptin ($P = 0.01$). Thus, higher levels of leptin were observed in CC homozygous compared with G-allele carriers. There was an inverse association between (HEI, HEUI, DQI) scores and the odds ratio of having the G allele compared to the homozygote group with CC genotype. Although, this association was not significant in crude and adjusted models ($P >0.05$) (Table 2). Besides, the general characteristics of all participants, among the tertile of (DQI-I, DPI, HEI) are shown in Table 3. In particular, subjects in the highest tertile of DQI and DPI have more likely to be older ($P<0.001$). The subjects with a higher tertile of DQI have more history of lipid-lowering medications. Besides, more compliance with the DPI index was associated with higher duration of diabetes, compared to the lowest adherence of DPI-index. Additionally, subjects in the highest tertile of (DQI-I, DPI, HEI) had less likely percent fat ($P<0.001$). Besides, participants in the lowest tertile of the DQI, have higher SOD ($P = 0.03$). Furthermore, more adherence to the DPI index was associated with lower penterexin-3 ($P = 0.03$), TG and EER. Although (TG and EER in women) was significant in the crude model, after adjusting for potential confounders including age and gender, this significance was disappeared ($p>0.05$). Finally, women with the highest compliance of HEI had lower TAC concentrations ($P = 0.04$).

The interaction between PPAR rs1801282 and dietary indices on metabolic factors

Table 4 expresses interactions between PPAR rs1801282 and HEI, DQI, DPI on anthropometric indices, and several biochemical markers. Hence, rs1801282-DQI interactions were significant only on WC (P Interaction = 0.02) in a crude model, as well as remained significant in the adjusted model (adjusted for age, gender, smoking, alcohol, physical activity) (P interaction =0.01). Further, an interaction was observed between PPAR rs1801282 polymorphism and DQI on serum IL-18 level just in the adjustment model (P interaction= 0.03). Interestingly, the highest WC and IL-18 were observed in the G-allele carriers (CG, GG) with the highest adherence to DQI. Besides, a significant rs1801282-DPI interaction was shown on HDL concentration in the adjustment model (P Interaction= 0.04), carriers of the G allele who were in the highest tertile of DPI, had lower HDL. Moreover, there were significant rs1801282-HEI interactions on ghrelin (P Interaction = 0.02) plasma concentration in the crude model. Further, an interaction was observed between PPAR rs1801282 polymorphism and HEI on the leptin plasma level, just in the adjustment model (P Interaction= 0.02). Individuals with (CC, CG) genotypes in the higher tertile of HEI, had lower leptin and ghrelin concentration (Figure 1).

Discussion

According to our knowledge, this is the first attempt that investigated the interaction among PPAR-γ Pro12Ala polymorphism and dietary indices (DQI, DPI, HEI) on cardiovascular disease risk factors in a patient with T2DM. The key findings of the present study were the significant interaction between PPAR-γ2 Pro12Ala polymorphism and dietary indices (DQI, DPI, HEI) on WC, IL-18, HDL, leptin, and ghrelin in a patient with T2DM. PPAR γ was the first gene reproducibly related to CVD. Yen et al for the first time, demonstrated a significant association between the substitution of proline by alanine at codon 12 of PPARγ2 (Pro12Ala allele) and the predictors of cardiovascular diseases in patients with T2DM [37, 38]. We revealed a significant interaction among PPAR-γ2 Pro12Ala polymorphism and DQI in relation to obesity index including WC. Interestingly, PPAR-γ2 Pro12Ala polymorphism was able to change the effect of DQI-I on obesity, so that the highest WC was observed in the high-risk G-allele carriers (CG, GG) with the highest adherence to DQI. Although, several studies have shown an inverse relationship between DQI-I score and obesity. In particular, the highest adherence to DQI-I could decrease rates of obesity [39-41]. There are limited studies that evaluated the effect of gene polymorphisms and diet on obesity. PPAR-γ2 is one of the key genes of obesity, however so far findings of related research have been controversial. Our finding is consistent with the study of Mirzaei et al. that reported the Pro12Ala polymorphism in the PPARγ2 gene is related to obesity in Iranian subjects and the presence of the Ala allele could predict higher WC [42]. In the Quebec Family Study, the Ala carriers had higher WC, BMI and fat mass than non-carriers [43]. The study of Memisoglu et al. which reported there is an interaction between Pro12Ala and dietary fat intake in relation to obesity [44]. The study of Vaccaro et al. reported a various susceptibility to fat accumulation, so, WC and obesity in response to habitual high energy intake for Ala carriers versus to Pro/Pro homozygotes [45]. The underlying mechanisms associated with the effect of Ala variant on weight gain have been suggested as follows that in Ala-allele carriers decrease insulin sensitivity and lipolysis [46, 47]. So, these reasons mentioned can be responsible to elevate in body weight in those. PPAR-γ Pro12Ala is the main regulator of adipocyte differentiation that leads to promote differentiation of pre adipocytes to small adipocytes. In this way, several studies have revealed that insulin sensitivity in small adipocytes is more than large adipocytes [48]. In contrast to our study, some research shows that Pro12Ala polymorphism is not associated with anthropometric parameters [49-51]. Besides, we demonstrated a significant interaction among PPAR-γ2 Pro12Ala polymorphism and DQI in relation to IL-18. Interestingly, the highest IL-18 was observed in the high-risk G-allele carriers (CG, GG) with the highest adherence to DQI. As mentioned in the previous finding there was a significant interaction effect between PPAR-γ2 Pro12Ala polymorphism and DQI in relation to WC. Several studies indicated obesity is a chronic low-grade inflammatory condition related to the progression of T2DM and CVD [52] that human adipose tissue is able to produce and release a variety of inflammatory proteins known as adipokines such as IL-18 [53]. Moreover, we demonstrated a significant interaction among PPAR-γ2 Pro12Ala polymorphism and DPI in relation to HDL. Interestingly, PPAR-γ2 Pro12Ala polymorphism was able to change the effect of DPI on lipid profile so that the lowest HDL was observed in the high-risk G-allele carriers (CG, GG) with the highest adherence to DPI. Although, several studies have shown a relationship between DPI score and improved lipid profile [54-56], the interaction between DPI and PPAR-γ2 Pro12 polymorphism on lipid profile was not in this direction. Our finding is consistent with the study of Beamer et al. that represented subjects with the Ala allele had lower HDL and higher TG levels compared with Pro12Pro homozygous subjects [57]. In this way, Meirhaeghe et al. reported that higher levels of TC and lower levels of HDL in subjects with the Ala allele compared with Pro homozygous subjects [58]. The PPAR-γ2 gene is a key factor that is able to impact on lipid metabolism; the Pro12Ala variation leads to lipid metabolism disorder. These effects may due to the Ala isoform of PPAR-γ2 being less affective in transcriptional activity genes such as lipoprotein lipase (LPL) [59]. In contrast to our study, some research show that Pro12Ala polymorphism is not associated with lipid profiles [60]. The inconsistency seems due to the small sample size, high heterogenicity, geographically and ethnically difference and also various habitual dietary pattern and health status in studied population.

In the current study, we found a significant interaction between PPAR-γ2 Pro12Ala polymorphism and HEI in relation to leptin and ghrelin concentration. In particular, the lowest leptin and ghrelin level was observed in the G-allele carriers (CG, GG) with highest adherence to HEI. In line with our study, the animal and cell culture studies have shown the pharmacological activation of PPARγ by thiazolidinedione (TZD) leads to the down-regulation of leptin gene expression [61, 62]. Several studies reported higher leptin and ghrelin levels with the G-allele carriers than those with CC genotype, which conflicted with our results [63-65]. Although, the limited number of studies and various diseases have makes it hard to propose a precious mechanism. Hence, we need to design large studies regarding diabetic medication used especially TZD which can act as high-affinity ligands for binding PPARγ, and also decreases expression or levels of adipocyte-derived factors including leptin and ghrelin [66-68]. There are some limitations of the present study as mentioned follow; firstly, because of the cross-sectional nature, causality cannot be concluded; secondly, a small sample size of studied participants; thirdly, the FFQ used for evaluating dietary intakes was a self-reported tool which may be under and over-estimation of some food items and as a memory potential bias; fourthly, we did not have data regarding other dietary components such as eating patterns and dietary habits that may be effective on our results; fifthly, due to limited budget and time, we cannot replicate of present analysis; finally, this study was performed in Iranian diabetic patient, so results may not be generalizable to all subjects in the world. Nevertheless, we need to well-designed large prospective studies in various populations. Despite all limitations mentioned, this current study is the first attempt to survey the interaction between PPAR-γ Pro12Ala (rs1801282) polymorphisms and dietary indices (DQI, DPI, HEI) on cardiovascular disease risk factors. Importing, discovering gene-diet interactions has the potential to provide personal dietary recommendations on the basis of genetic makeup.

Conclusion

Therefore, based on the present findings, it could be hypothesized that PPAR-γ Pro12Ala (rs1801282) may be associated with increased cardiovascular disease risk factors in patients with T2DM even with high adherence to dietary indices including DQI and DPI. This could be critical for clinical diagnosis and gene therapy. Due to the limited study about the Pro12Ala polymorphism of the PPAR-gamma 2 gene, more researches are warranted to evaluate the impacts on other populations.

Abbreviations

T2DM, type 2 diabetes mellitus; PPAR-γ, Peroxisome proliferator-activated receptor gamma; HDL-c, high density lipoprotein cholesterol; LDL-c, low density lipoprotein cholesterol; VLDL, very low density lipoprotein; TG, triglyceride; TC, total cholesterol; SNP, single nucleotide polymorphism; PCR-RFLP, polymerase chain reaction- restriction fragment length polymorphism; DQI, Diet Quality Index; HEI, Healthy Eating Index; DPI, Dietary Phytochemical Index; ANOVA, analysis of variance; ANCOVA, analysis of covariance; MI, body mass index; WC, waist circumference

Declarations

Ethics approval and consent to participate: The protocol of the study was approved by the ethics committee of TUMS (Ethics number: 15061). All participants completed a written informed consent

Consent for publication: 'Not applicable'

Availability of data and material: The authors confirm that the data supporting the findings of this study are available within the article (Figure1, Table 1 and Table 2)

Figure 1. The interaction between PPARγ rs1801282 and tertile of dietary index (DQI, DPI, HEIB) on; (a): Waist circumference (WC), (b): Interlukin-18 (IL-18), (C): HDL, (d): Ghrelin, (e): Leptin

Table 1. Comparison of the clinical characteristics in the recessive genetic according to PPAR-γ rs1801282genotyp

Table2. OR and CI for association between dietary quality indices and PPAR-γ(rs1801282)

Table3: Comparison of general characteristics of participant anthropometric and biochemical data between tertile of (DQI-I, DPI, HEI)

Table4: Interactions between PPAR-γ (rs1801282) and dietary indexes on CVDs risk factors

Competing interests: The authors declare no conflict of interest

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Tables

Table1: Comparison of the clinical characteristics in the recessive genetic according to PPAR-γ rs1801282genotyp

	PPAR-γ (rs1801282)		Pvalue*
	CC	(CG+GG)	
Age(year)	52.97± 6.37	52.81±7.45	0.88
Weight	76.82±13.79	79.35±14.94	0.29
BMI	29.09±4.48	30.05±5.06	0.29
WC	92.21±10.68	93.76±11.92	0.41
TC	202.4±80.5	205.11±72.29	0.84
HDL-C	52.67±11.02	53.77±13.72	0.56
LDL-C	111.6±34.64	109.61±27.54	0.73
LDL/HDL	3.17±13.37	2.14±0.64	0.64
TC/HDL	3.97±1.77	4.08±1.77	0.71
TG	180.3. ±107.71	158.36±78.10	0.23
Ghrelin	2.14±1.18	2.83±1.63	0.1
Leptin	23.78±14.07	12.57±8.47	**0.01**
CRP	2.43±1.52	3.05±1.50	0.38
TAC	2.52±0.52	2.32±0.4	0.4
SOD	0.14±0.04	0.130.03	0.43
IL-18	244.84±31.91	251.03±41.16	0.67
PGF2α	72.37±**6.75**	72±6.2	0.9
Pentrexin3	2.68±0.44	2.65±0.48	0.88

Values are means ± SD Independent T.test (Pvalue*)

BMI, body mass index; ***WC***, waist circumference; ***TG***, triglyceride; ***TC***, total cholesterol; ***CRP***, c-reactive protein; ***TAC***, Total antioxidant capacity; ***SOD***, Superoxide Dismutase; ***IL18***, interleukin 18; ***PGF2α***, Prostaglandin F2α

Table2: OR and CI for association between dietary quality indices and PPAR-γ(rs1801282)

	PPAR-γ (rs1801282)	
	CC	(CG+GG) OR (95%CI)
HEI.Total score	1(Ref)	
Crude	1(Ref)	0.99(0.95,1.03)
Adjust	1(Ref)	0.99(0.95,1.03)
DQI-I. Total score		
Crude	1(Ref)	0.97(0.93,1.02)
Adjust	1(Ref)	0.97(0.93,1.02)
DPI.Total score		
Crude	1(Ref)	1.04(0.98,1.04)
Adjust	1(Ref)	1.01(0.99,1.04)

Table3: Comparison of general characteristics of participant anthropometric and biochemical data between tertile of (DQI-I, DPI, HEI)

	DQI-I					DPI				
	T_1	T_2	T_3	P*	P$	T1	T2	T3	P*	P$
Age	52.03±6.37	52.05±6.89	54.96±5.65	**<0.001**		51.05±6.28	52.76±6.64	55.02±5.89	**<0.001**	
Family history of diabetes (%)	37.2	34.5	28.4	0.81		31.8	31.8	36.5	0.2	
Duration of disease2 (%)	34.9	31.4	33.7	0.28		20.9	34.9	44.2	**0.04**	
Weight	76.28±14.8	77.7±13.83	77.22±12.97	0.69	0.62	79.17±14.21	75.08±13.44	76.93±13.84	**0.05**	0.36
BMI	29.03±4.83	29.27±4.47	29.24±4.3	0.89	0.46	29.37±4.62	28.65±4.17	29.51±4.79	0.26	0.34
WC	90.95±11.17	92.69±10.16	93.55±10.93	0.13	0.59	93.17±10.14	90.95±10.57	92.93±11.54	0.19	0.84
Percent fat	39.33±7.11	35.56±5.18	29.38±5.22	**<0.001**	**<0.001**	37.62±8.21	35.21±6.21	32.04±5.89	**<0.001**	**<0.001**
EER. women	2042.27±204	2045.14±171	2024.59±153	0.77	0.91	2082.71±190	2017.29±161	2017.46±179	**0.04**	0.14
Physical activity (METs)	38.08±6.42	38.03±4.78	38.51±5.52	0.75	0.86	37.0±6.09	38.84±5.64	38.46±5.01	0.07	0.09
HDL	54.31±11.39	51.76±12.02	52.08±10.22	0.13	0.72	54.05±11.96	51.74±11.10	52.48±10.74	0.24	0.89
LDL	112.55±29.94	111.56±32.99	110.03±39.15	0.83	0.93	115.59±34.61	106.43±31.16	112.32±35.76	0.09	0.69
LDL/HDL	2.14±0.65	3.53±14.99	3.62±16.59	0.57	0.92	2.21±0.64	3.42±15	3.58±16.07	0.64	0.67
T. CHOL	203.87±65.91	196.6±54.81	20.33±110.13	0.46	0.86	204.23±87.7	206.46±72.88	197.41±78.18	0.63	0.73
TG	184.49±117.4	173.36±100.2	176.63±96.95	0.67	0.9	199.07±127.3	174.46±88.25	162.07±94.48	**0.01**	0.47
Leptin	21.91±13.07	24.7±15.39	21.61±13.3	0.47	0.53	20.85±13.27	21.54±14.40	25.92±14.12	0.17	0.05
Ghrelin	1.94±0.85	2.27±1.37	2.34±1.33	0.29	0.15	2.28±1.48	2.04±1.09	2.25±1.1	0.64	0.21
CRP	2.34±1.53	2.54±1.48	2.48±1.61	0.88	0.51	2.53±1.5	2.44±1.6	2.41±1.52	0.94	0.63
Penterein3	2.65±0.38	2.68±0.53	2.7±0.39	0.89	0.93	2.68±0.43	2.78±0.46	2.58±0.43	0.23	**0.03**
IL-18	250.51±31.07	244.76±36.6	241.17±27.84	0.55	0.8	245.28±36.69	241.98±32.49	248.13±26.9	0.76	0.2
TAC	2.58±0.56	2.47±0.57	2.48±0.42	0.67	0.34	2.49±0.53	2.57±0.6	2.46±0.42	0.68	0.39
SOD	0.16±0.05	0.13±0.04	0.14±0.04	0.15	**0.03**	0.14±0.04	0.15±0.05	0.13±0.05	0.48	0.06

PGF2α	72±5.4	72.04±7.95	73.01±6.14	0.8	0.44	71.66±6.68	71.79±6.42	73.66±6.97	0.43

WC = waist circumferences, BMI = body mass index, HDL-c high density lipoprotein cholesterol, LDL-c = low density lipoprotein cholesterol, CH = cholesterol, TG =
triglyceride, CRP = C-reactive protein, PTX3 = Pentraxin 3, IL18 = interleukin 18, TAC = total antioxidant capacity, SOD = superoxide dismutase, PGF2α = prostaglandin
F2α. The normalized log-transformed were utilized, values are means±SD

Table4: Interactions between PPAR-γ (rs1801282) and dietary indexes on CVDs risk factors

	DQI-I*(rs1801282)			DPI*(rs1801282)			HEIB*(rs1801282)		
	β (95%CI) (CG+GG) 1(Ref) CC	P*	P†	β (95%CI) (CG+GG) 1(Ref) CC	P*	P†	β (95%CI) (CG+GG) 1(Ref) CC	P*	P†
BMI	0.05 (-0.008,0.11)	0.08	0.06	0.04(-0.01,0.09)	0.14	0.17	-0.02(-0.08,0.02)	0.32	0.36
WC	0.05 (-0.006,0.09)	**0.02**	**0.01**	0.01(-0.02,0.05)	0.46	0.28	-0.02(-0.07,0.01)	0.25	0.23
%Fat	-0.3 (-5.7,5.1)	0.91	0.97	3.74(-1.96,9.45)	0.19	0.18	-2.82(-8.24,2.6)	0.3	0.36
HDL	-0.5 (-0.13,0,01)	0.13	0.16	-9.82(19.78,0.12)	0.05	**0.04**	0.03(-0.03,0.11)	0.32	0.31
LDL	0.08(-0.04,.21)	0.22	0.23	0.03(-0.08,0.15)	0.56	0.66	-0.01(-0.14,0.1)	0.78	0.78
LDL/HDL	0.05(-0.1,0.2)	0.5	0.5	0.07(-0.09,0.25)	0.37	0.4	-0.03(-0.19,0.12)	0.65	0.72
TC	-72.61(-146,0.78)	0.05	0.05	0.06(-0.06,0.18)	0.32	0.33	-0.06(-0.18,0.04)	0.24	0.3
TG	0.17 (-0.03,0.38)	0.1	0.06	0.12(-0.06,0.31)	0.18	0.27	0.13(-0.04,0.31)	0.14	0.14
Leptin	-0.28(-0.73,0.15)	0.2	0.36	-0.19(-0.77,0.38)	0.5	0.25	-0.37(-0.93,0.17)	0.18	**0.02**
Ghrelin	0.11(-0.22,0.44)	0.5	0.55	0.16(-0.33,0.67)	0.5	0.67	-0.42(-0.83, -0.004)	**0.04**	0.07
CRP	-0.38(-1.92,1.16)	0.62	0.54	-2.36(5.14,0.41)	0.09	0.07	-0.06(-1.38,1.26)	0.92	0.83
Penterein-3	-0.12(-0.5,0.26)	0.52	0.37	-0.16(-0.41,0.08)	0.18	0.09	-0.22(-0.55,0.11)	0.19	0.17
IL-18	2.52(-0.6,4.12)	0.08	**0.03**	-0.75(-2.7,1.18)	0.44	0.4	-2.26(-4.78,0.26)	0.07	0.07
TAC	0.27(-0.09,0.63)	0.14	0.11	0.06(-0.22,0.36)	0.65	0.9	0.14(-0.23,0.51)	0.45	0.54
SOD	0.02(-0.15,0.19)	0.81	0.75	0.1(-0.009,0.21)	0.07	0.07	0.1(-0.04,0.25)	0.17	0.08
PGF2α	10.32(-8.14,28.79)	0.27	0.16	0.64(-11.65,12.94)	0.91	0.74	2.44(-13.68,18.57)	0.76	0.95

BMI, body mass index; ***WC***, waist circumference; ***TG***, triglyceride; ***TC***, total cholesterol; ***CRP***, c-reactive protein; ***TAC***, Total antioxidant capacity; ***SOD***, Superoxide Dismutase; ***IL18***, interleukin 18; ***PGF2α***, Prostaglandin F2α

P value* with unadjusted (crude)

P value† with adjustments for potential confounding factors including (Age, Sexuality, Smoking, Alcohol, Physical activity)

Figures

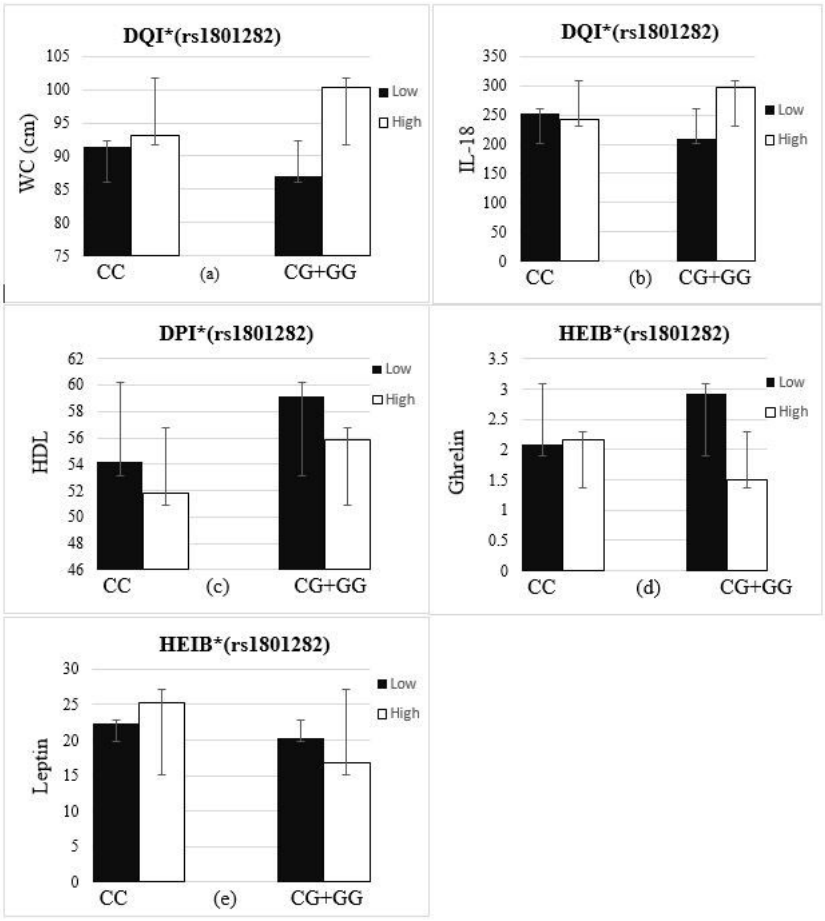

Figure 1

The interaction between PPARγ rs1801282 and tertile of dietary index (DQI, DPI, HEIB) on; (a): Waist circumference (WC), (b): Interlukin-18 (IL-18), (C): HDL, (d): Ghrelin, (e): Leptin.