Interaction between CETP Polymorphism and Dietary Insulin Index and Load on Cardiovascular Risk Factors: A Cross-Sectional Study of Diabetic adults

Faezeh Abaj
Tehran University of Medical Sciences

Masoumeh Raee
Isfahan University of Medical Sciences

Fariba Koohdani (fkoohdan@tums.ac.ir)
Tehran University of Medical Sciences

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Abstract

Background

The objectives were to investigate the effect of the interaction between CETP Taq1B polymorphism, Dietary Insulin Index and Insulin Load (DII and DIL) on cardiovascular risk factors among diabetic patients.

Methods

In this cross-sectional study, blood samples were collected from 220 patients. DIL and DII were obtained via validated FFQ. CETP Taq1B polymorphism was genotyped by the PCR-RFLP method.

Results

The highest BMI (P = 0.08) and WC (P = 0.01) values were observed in B2B2 genotype with the highest adherence to DII. Patients with B1B1 genotype who were in the highest DIL tertile had lower LDL/HDL (P = 0.001), TG (P = 0.03), and higher HDL (P = 0.02). The highest SOD (P = 0.01), PGF2α (P = 0.04), CRP (P = 0.02), and IL-18 (P = 0.06) was observed in B2B2 genotype carriers with the highest DIL adherence. Individuals with B2B2 genotype in the highest tertile of DII had higher CRP (P = 0.04), TAC (P = 0.01), SOD (P = 0.02), and PGF2α (P = 0.02). B1B1 homozygotes who were in the highest tertile of DII had lower lipid profile TG (P = 0.02), LDL (P = 0.08), and LDL/HDL < 0.001.

Conclusion

Based on the current study, it may be proposed that CETP Taq1B polymorphism can be associated with CVD risk factors in diabetic patients with high adherence to insulin indices, including DII and DIL.

Introduction

Type 2 diabetes mellitus (T2DM) is a metabolic disorder that occurs with high serum glucose concentrations, caused by deficiencies in insulin secretion or function (1). T2DM is a worldwide pandemic that imposes an enormous burden on public health, also being an elevated risk factor for cardiovascular disease (CVD). Patients with CVD have more than a two-to-four-fold increased risk of death versus non-CVD patients (2). As a multifactorial condition, T2DM and CVD are also determined by environmental conditions, hormonal factors, and genetic variations, which have been related to 50% of incidence (3). Recently, emerging data suggest that one of the main genetic targets is the cholesteryl ester transfer protein (CETP), which plays a crucial role in regulating lipid metabolism (4).

CETP is involved in the reverse cholesterol transport process by mediating the exchange of cholesteryl esters (CE) and triglycerides (TGs) from high-density lipoprotein cholesterol (HDL) to low-density lipoprotein (LDL) in peripheral tissues to the hepatocytes (5). The CETP gene is very polymorphic in humans, such that rs708272 (also called Taq1B) has been widely studied among CETP polymorphisms (6). According to various studies, there is a relationship between rs708272 and various CVD risk factors including T2DM, hypertension, dyslipidemia, and low HDL, although the evidence is controversial: other studies have indicated a lack of such associations (6–8). The major lifestyle factor contributing to DM and CVD, however, has been shown to be dietary pattern (9).

It seems that foods can induce postprandial insulin secretion and affect the management of hyperlipidemia, cardiac artery disease (CAD), obesity, and DM (10). Most previous studies have concentrated on dietary glycemic index (GI) and load (GL) as indices of carbohydrate quality and quantity, to demonstrate the insulinogenic effects of foods (11). Although GI and GL indicate the effect of carbohydrates on blood glucose concentrations, these indices are not always accurate in reporting insulin response (12). DII and DIL can more accurately predict insulin response to overall food consumption, determining how insulinogenic dietary properties can be mediated by various factors such as fructose, certain amino acids, and fatty acids (13). Prior studies have demonstrated that DII and DIL are more appropriate (than GI, GL, and total carbohydrate consumption) for investigating the relationship between insulin concentrations and the progress of chronic disorders (14). Relatively few studies in the literature have investigated the correlation between DII, DIL, and CVD risk factors, and the correlation remains unclear within current nutrition research (15). Several studies which showed inconsistent results may be explained by differences in genetic variations (15). Therefore, the interaction between genetics and diet (in terms of both a nutrigenetic and nutrigenomic approach) is essential in assessing these associations, which are still not well understood (16). Some findings revealed that the CETP polymorphism interacts with dietary carbohydrate intake on metabolic factors, such as hypertension, dyslipidemia, obesity, insulin resistance (IR) and DM (17).

To the authors’ knowledge, there has been no previous evaluating the interaction between the DII, DIL, and CETP polymorphism towards CVD risk factors. Therefore, the present study aimed to evaluate the effects of interaction between CETP Taq1B polymorphism and the DII and DIL insulin indices on CVD risk factors in T2DM patients.

Results

In the current study, 220 patients with T2DM were evaluated. The genotype distributions were within HWE (P-value > 0.05). A statistical analysis of the basic information of patients, among DII and DIL tertiles, are presented in Table 1. An individual with higher adherence to DIL (P = 0.001) and DII (P = 0.006) was...
more likely to be male. Subjects with a higher DIL tertile presented greater energy intake values ($P = 0.001$). Patients in the highest tertile of DIL ($P = 0.01$) and DII ($P = 0.01$) were more likely to have lower ghrelin concentrations.

Figure 1 and Fig. 2 show the interactions between CETP TaqB1 polymorphism and DII and DII on anthropometric indices and several biochemical markers.

CETP TaqB1 polymorphism and DIL interactions were significant in terms of LDL/HDL ($P = 0.001$), TG ($P = 0.03$), and HDL ($P = 0.02$): carriers of the B1B1 genotype who were in the highest tertile of DIL had lower LDL/HDL, TG, and higher HDL.

Interactions between CETP TaqB1 polymorphism and DIL were significant in terms of WC ($P = 0.005$): carriers of B2B2 genotype who were in the last tertile of DIL had higher WC. Also, CETP TaqB1 polymorphism and DIL interactions were significant in terms of SOD ($P = 0.01$), PGF2a ($P = 0.04$), CRP ($P = 0.02$), and IL-18 ($P = 0.06$): higher SOD, PGF2a, CRP, and IL-18 values were observed in B2B2 genotype carriers with the highest adherence to DII.

Further, a significant interaction between CETP TaqB1 and DII was shown in terms of BMI ($P = 0.08$) and WC ($P = 0.01$), where the highest BMI and WC were observed in B2B2 genotype carriers with the highest adherence to DII. Also, a significant interaction between CETP TaqB1 and DII was shown in terms of CRP ($P = 0.04$), TAC ($P = 0.01$), SOD ($P = 0.02$), and PGF2a ($P = 0.02$): individuals with B2B2 genotype in the last tertile of DII had higher CRP, TAC, SOD, and PGF2a.

A significant interaction between CETP rs708272 and DII was shown in terms of TG ($P = 0.02$, LDL/HDL ($P < 0.001$), and LDL ($P = 0.08$): B1B1 homozygotes in the highest tertile of DII had lower lipid profiles.

**Discussion**

To the authors’ knowledge, this was the first study investigating the interaction between CETP TaqB1 polymorphism and DII and DII on CVD risk factors in T2DM patients. The key findings of the current study were the significant interaction effect of CETP rs708272 polymorphism with DII and DII on obesity indices (WC and BMI), lipid profiles (TG, HDL, LDL/HDL), inflammatory markers (IL-18, CRP, and PGF2a), and antioxidant markers (TAC and SOD) in T2DM patients.

T2DM patients have an elevated risk of CVD. Additionally, CETP is a key gene related to CVD pathogenesis (18). The relation between the CETP TaqB1 polymorphism and the risk factors of CVD in patients with T2DM has been evaluated in previous studies. A significant interaction between CETP TaqB1 polymorphism and DIL was demonstrated in relation to obesity indices, including WC and BMI. CETP TaqB1 polymorphism was found to be able to increase the effects of DII and DII on obesity. In the present study, B2B2 genotype carriers in the last tertile of DII and DII were more obese. Although several studies have reported an association between DII and DII scores and obesity (19, 20), the interaction between DII and DII with CETP polymorphism on obesity was not evaluated in previous reports.

DII and DII may represent insulin concentrations in response to consuming certain foods, and are perhaps more appropriate than dietary GI and GL in assessing the relation between insulin exposure and metabolic disorders (21). It is proposed that DII and DII have a direct and indirect effect on obesity. A high score of DII and DII may lead to greater body fat formation by promoting pre-adipocytes differentiation and proliferation to adipocytes (19, 20). Besides, a high score may cause reductions in insulin sensitivity and lipolysis, while increasing insulin growth factor-1 (IGF-1) and insulin secretion levels (22, 23). Experimental studies have shown that a high stimulation of IGF-1 on pre-adipocytes proliferation could be associated with body fat accumulation (24). IGF-1 increased glucose uptake and glucose oxidation in adipocytes, elevated lipogenesis, and inhibited lipolysis in cells (25). According to some studies, insulinogenic foods result in a higher risk of insulin resistance and DII/DII, independent from potential risk factors (26). Dietary pattern interventions, such as restricting insulinoenic foods, have a key role in the management of IR and its metabolic disorders (27). CETP is a protein synthesized by various tissues, especially adipose tissue in humans, which leads to the storing of CE in adipocytes, resulting in the formation of fatty deposits (28). Results have suggested a potential pathway relating CETP polymorphisms with an elevated risk of obesity and obesity-related diseases (29). Additionally, there is a linear association between CETP activity and insulin resistance in obese T2DM patients; high CETP activity also contributes to high insulin secretion (30). Therefore, high DII/DII score and CETP polymorphism may act synergistically to elevate a patient’s susceptibility to insulinemic spikes, which relate to obesity.

The present findings are consistent with previous studies that have reported elevated plasma CETP activity in obese participants. Dullaart et al. demonstrated that plasma CETP activity was increased in obese subjects. Also, CETP activity was related to BMI and plasma C-peptide (31). Arai et al. revealed that CETP activity and protein levels were elevated in obese participants (32). In contrast to the present study, however, Heilbronn et al. reported that BMI was higher in obese B1B2 participants, compared to obese subjects with B1B1 and B2B2 (33). Maroufi et al. reported that Taq1B polymorphisms had no effect on related metabolic syndrome parameters, including WC (34). Also, some studies have shown that CETP polymorphism is not associated with anthropometric parameters (35, 36). These inconsistencies seem due to an important role of gene-diet interactions. It has been shown that relations between CETP TaqB1 and anthropometric indices can be population-specific, and consequently are regulated by environmental factors, especially dietary factors (37).

The present results also demonstrated a significant interaction among CETP TaqB1 polymorphism and DII/DII in relation to inflammatory factors. The highest IL-18, CRP, and PGF2a were observed in the B2B2 genotype carriers with the highest adherence to DII and DII. As indicated in the findings, there was a significant interaction effect between Taq1B CETP polymorphism and DII/DII in association with anthropometric indices. Numerous findings have reported obesity as causing chronic low-grade inflammatory disorder, contributing to the progression of T2DM and CVD (38). In these conditions, human adipose tissue secretes a high level of inflammatory markers, including IL-18, CRP and PGF2a (39).

A further novel finding is the significant interaction between CETP TaqB1 polymorphism and DII/DII towards antioxidant markers, including TAC and SOD. CETP Taq1B polymorphism was able to inverse the effect of DII and DII on oxidant status, so that the highest TAC and SOD was observed in the B2B2 genotype with the highest adherence to DII and DII. However, while there is no available study about the relation between DII/DII with antioxidant status, several studies have reported that insulin concentrations and insulin resistance lead to an imbalance between oxidant and antioxidant systems, a condition...
known as oxidative stress (40). In recent years, oxidative stress has been implicated in T2DM pathogenesis by producing excessive free radicals, decreasing glutathione, vitamin E, vitamin C, and via reduced antioxidant enzyme activity, such as SOD and TAC (41). SOD and TAC lead to the conversion of superoxide radicals into hydrogen peroxide, and decrease oxygen toxicity (41). It seems that CETP Taq1B polymorphism can invert the effect produced by insulin. However, the reason for this difference is not apparent, and further studies are warranted to evaluate the mechanism of action.

Finally, another promising finding was the significant interaction between CETP Taq1B polymorphism and DII/DIL with lipid profile markers, including TG, HDL, and LDL/HDL. The lowest TG and LDL/HDL, and the highest HDL, were observed in the B1B1 genotype carriers with the highest adherence to DII and DIL. Although several studies have shown a relationship between DII/DIL scores and lipid profiles, the interaction between DII/DIL and CETP polymorphism on lipid profiles had not been evaluated in previous studies.

Additionally, prior research has shown that the B1B1 genotype is associated with a better response to nutritional interventions, compared with carriers of B2 alleles. Previous research showed a significant interaction, where B1/B1 homozygotes had a lower TG/HDL ratio after a kiwifruit intervention, compared to a control diet, while B2 carriers were not affected (42). Nahid Ramezani-Jolfaie et al. revealed that, for diabetic patients, dietary oil treatments would be more helpful (lower LDL; HDL, TG; HDL, TC; HDL, Insulin, and HOMA-IR) among subjects with B1B1 alleles than among B2 allele carriers (43).

Some authors have also suggested that subjects with B1B1 allele of CETP polymorphism showed a better response in regards to high carbohydrate dietary interventions. Overall these findings are in accordance with findings reported by Juan Dua et al., demonstrating that males with CETP Taq1B B1B1 allele have higher apo A-I and HDL concentrations after following a high carbohydrate and low fat (HC/LF) diet for 6 days (44). Perez et al. reported that carriers of B2 alleles who consumed sucrose as more than 5% of total kcal/day had higher TC and LDL serum levels, compared to B1B1 homozygotes (45).

A series of recent studies have indicated that plasma CETP activity decreased by hyperinsulinemia condition in healthy subjects, but not in diabetic patients (46). Siewert et al. suggested that insulin has a direct influence on CETP; but in IR conditions, this particular insulin action may be diminished (47). Therefore, it is suggested that diabetic patients with B1B1 allele may be counteracted with CETP activity and HDL plasma reduction.

Several studies have been shown that CETP is able to transfer HDL cholesterol esters to Apolipoprotein B (ApoB), including VLDL, remnants of VLDL, and LDL. Due to an important role of CETP polymorphisms in lipids metabolism, it is considered that genetic polymorphism in the CETP gene is related to CVD risk factors by changing serum lipid profiles (48, 49). The inconsistency may be due to distinct populations; the studies were conducted among different gender, ethnic, and geographic populations, with a variety of habitual dietary patterns and various underlying diseases.

**Conclusion**

Based on the current study, it could be proposed that CETP polymorphism may be associated with CVD risk factors in T2DM patients with high adherence to insulin indices, including DII and DIL. This conclusion illustrates that the CETP Taq1B B1 allele could counteract the CVD risk induced by high DII and DIL. This could be critical for clinical diagnosis and gene-based therapy. Due to the limited nature of the study, further research is warranted to assess the effects on other populations.

**Methods**

**Study Population**

A cross-sectional study was designed with 220 diabetic patients in Tehran, Iran, who had participated in a large study conducted previously (50). All criteria including inclusion and exclusion criteria, demographic data, dietary intake (147-item FFQ), physical activity questionnaire (METs), and anthropometric variables in the current study were extracted from the authors’ previous research. All study subjects gave their written informed consent and the study was conducted based on the Declaration of Helsinki, and Ethics Committee of the Tehran University of Medical Sciences approved the protocol (no. 15060).

**General, Anthropometric and Physical Activity Assessments**

Information such as age, disease history, and medication was collected from each participant by questionnaire. Anthropometric measurements, including height (m) and weight (kg) were evaluated without shoes, and using a digital scale; waist circumference (WC) was evaluated at the narrowest part of the abdomen. Finally, body mass index (BMI) was computed by dividing weight (kg) by height squared (meters). Physical activity was measured by the short-form International Physical Activity Questionnaire (IPAQ) (51).

**Biochemical Assessments**

All blood samples were collected after 12-14 hours of fasting at the Nutrition and Genomics Laboratory at TUMS. All samples were centrifuged and stored at -80°C until analysis. Inflammation markers, including IL-1β, PGF2, and CRP concentrations, were measured by using an enzyme-linked immunosorbent assay (ELISA). TG, HDL, total cholesterol, and LDL serum levels were determined by enzymatic method (Pars Azmun Co., Tehran, Iran). Superoxide dismutase (SOD) enzymatic activity was measured using the colorimetry method (Cayman Chemical Company, USA). Spectrophotometry was used to detect total antioxidant capacity (TAC).

**Dietary Assessment**
A validated 147-item food-frequency questionnaire (FFQ) was used to obtain a common dietary intake for patients (52). The FFQ contained 147 food items with standard portion sizes commonly used by Iranians, based upon measurements widely used in the community (e.g. number of slices for bread, glasses for drinks, plates for rice, etc.) (53). The portion sizes in the FFQ were converted into amounts of foods consumed. An expert interviewer carried out the FFQ and recorded participant responses. All reported consumption frequencies were converted to grams per day using household measures. The daily consumption of nutrients and total energy were calculated for each subject by using the Iranian food composition table (FCT) and the United States Department of Agriculture (USDA) guidelines.

**Assessment of DIL and DII**

DII was based on prior studies conducted by Brand-Miller (54). DII calculates the incremental insulin area under the curve over 2h, in response to the consumption of a 1000-KJ portion of the test food, then divided by the area under the curve after ingestion of a 1000-KJ portion of the reference food (54-56). In the current study, food items in the FFQ and the Brand-Miller study were matched in terms of energy content, carbohydrates, fiber, protein, and fat. To evaluate the average DIL, the insulin load from each food over the past year was calculated by the formula:

\[
\text{Insulin load of food} = \text{Insulin index of food} \times \text{energy content of food (kcal/d)}
\]

By summing up the insulin load from each food, DIL was determined. The DII of each food was computed by dividing DIL by total energy intake.

**Genotyping**

DNA genotyping was carried out by the salting-out extraction method, as previously published (57). CETP polymorphism (rs708272) was genotyped by the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method. The PCR technique was employed by using primer (F:50-CACTAGCCAGAGAGGAGTG-30; R: 50-TGAGCCCAGCCGCACTAAC-30). 2% agarose gel electrophoresis was used to analyze the product.

**Statistical Analysis**

All data were analyzed using IBM SPSS Statistics (version 25; SPSS Inc., IL). Significance level was considered P<0.1 for interaction analysis, and normality was analyzed by Kolmogorov Smirnov test.

Adherence to Hardy-Weinberg equilibrium (HWE) was determined by using the chi-square test. The means of variables across the tertiles of DII and DIL were expressed as means ± SDs. Crude means between three genotypes (B1B1, B1B2, and B2B2) groups were compared using a one-way ANOVA test. The interaction between CETP rs708272 polymorphism and insulin indices (DII and DIL) on CVD factor (BMI, WC, HDL, LDL, LDL/HDL, T. Chol, TG, CRP, IL-18, TAC, SOD, PGF2α) was performed by a generalized linear regression model (GLM) in both the crude and adjusted models. In all interaction analyses, age, gender, physical activity, smoking, alcohol consumption, and familial history of diabetes were matched in the adjusted model.

**Declarations**

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**Author contributions**

FA contributed to conception, design, data analyses, data interpretation, and manuscript drafting. FK and MR supervised the study. All authors approved the final manuscript for submission.

**Conflicts of interest**

None of the authors declared any personal or financial conflicts of interest.

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Tables

Table 1: The association between baseline characteristic and metabolic markers with Dietary Insulin Load (DIL) and Dietary Insulin Index (DII) in T2DM patients.
| Tertiles of DIL | T1 | T2 | T3 | p* | T1 | T2 | T3 |
|----------------|----|----|----|----|----|----|----|
| N             | 73 | 74 | 72 |    | 72 | 74 | 73 |
| Sex (Male/ Female) | 19(22.1)/54(40.3) | 26(30.2)/48(35.8) | 41(47.7)/32(23.9) | 0.001 | 18(20.9)/54(40.3) | 31(36)/44(32.8) | 37(43)/36(26.9) |
| Cigarette smoking (yes/no)% | 13(32.5)/56(32) | 13(32.5)/60(34.3) | 14(35)/59(33.7) | 0.24 | 16(40)/55(31.4) | 9(22.5)/62(35.4) | 15(37.5)/58(33.1) |
| Alcohol consumption (yes/no)% | 1(25)/72(25) | 2(50)/72(33.3) | 1(25)/72(25) | 0.78 | 1(25)/71(32.9) | 2(50)/73(33.8) | 1(25)/72(33.3) |
| Familial History of Diabetes (yes/no)% | 65(89.04)/8(25) | 63(86.3)/10(31.3) | 59(80.82)/14(19.17) | 0.48 | 62(86.11)/10(31.3) | 63(84)/12(37.5) | 63(86.3)/10(31.3) |
| Age (year) | 52.41±6.13 | 52.76±6.7 | 51.53±6.94 | 0.49 | 52.72±5.96 | 51.76±6.95 | 52.25±6.39 |
| BMI (kg/m²) | 28.74±5.3 | 29.96±4.58 | 28.86±5.06 | 0.15 | 29.03±4.55 | 29.86±6.07 | 28.67±4.12 |
| WC (cm) | 90.37±14.04 | 92.77±10.44 | 91.74±11.37 | 0.33 | 90.81±10.63 | 93.49±14.4 | 90.54±10.53 |
| Physical activity (Met.wk) | 38.65±6.01 | 38.39±4.6 | 37.38±5.16 | 0.31 | 38.59±6.2 | 38.12±4.82 | 37.73±4.78 |
| Energy intake (kcal/day) | 1890.67±399.49 | 2481.65±497.49 | 3288.51±1010.12 | <0.001 | 2547.45±879.53 | 2389.18±744.25 | 2736.63±1018.57 |
| HDL-c(mg/dl) | 53.95±10.15 | 52.5±12.17 | 53.5±11.78 | 0.54 | 53.43±11.48 | 53.06±10.69 | 53.4±12.08 |
| LDL-c(mg/dl) | 120.46±31.6 | 117.62±32.11 | 117.53±38.52 | 0.82 | 119.51±33.64 | 115.37±29.29 | 120.81±38.97 |
| CH(mg/dl) | 215.2±99 | 204.04±59.71 | 213.36±67.77 | 0.44 | 211.01±62.89 | 218.98±99.1 | 202.36±63.4 |
| LDL/HDL | 2.28±0.65 | 2.30±0.64 | 4.79±21.51 | 0.69 | 2.27±0.6 | 2.24±0.63 | 4.87±21.50 |
| TG(mg/dl) | 159.88±104.47 | 203.56±139.36 | 187.45±110.36 | 0.09 | 176.71±105.3 | 204.61±142.42 | 168.7±105.63 |
| Leptin(ng/ml) | 24.18±15.03 | 22.55±15.55 | 24.89±16.8 | 0.93 | 22.33±14.01 | 25.4±17.03 | 23.64±16.04 |
| Ghrelin(ng/ml) | 2.22±1.08 | 2.55±1.29 | 1.88±0.73 | 0.01 | 1.99±0.43 | 2.68±1.4 | 1.86±0.87 |
| hs.CRP (mg/L) | 2.24±1.36 | 2.5±1.66 | 3.26±1.46 | 0.14 | 2.18±1.49 | 2.66±1.44 | 2.9±1.53 |
| PTX3(ng/ml) | 2.67±0.39 | 2.74±0.44 | 2.81±0.55 | 0.65 | 2.67±0.39 | 2.68±0.42 | 2.83±0.52 |
| IL18(pg/ml) | 244.24±20.83 | 248.75±28.03 | 252.56±28.70 | 0.64 | 247.20±32.45 | 244.87±27.71 | 250.15±28.71 |
| TAC(g/dl) | 2.55±0.63 | 2.33±0.46 | 2.34±0.34 | 0.34 | 2.51±0.58 | 2.4±0.6 | 2.44±0.41 |
| SOD(U/ml) | 0.14±0.04 | 0.13±0.03 | 0.15±0.06 | 0.5 | 0.14±0.03 | 0.13±0.04 | 0.15±0.05 |
| PGF2α(pg/ml) | 72.77±6.32 | 75.73±6.15 | 71.53±8.09 | 0.25 | 73.61±6.93 | 73.21±5.87 | 72.38±7.88 |

Data are presented as mean ± standard deviation (SD) or percent. Abbreviation: DIL: dietary insulin load, DII: dietary insulin index, 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 = prosta glandin F2α. Obtained from ANOVA or Chi-square test, where appropriate.