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Cholesteryl ester transfer protein RS5833 genetic variant affect HDL-cholesterol levels and ratio total cholesterol/HDL-cholesterol in postmenopausal obese female patient

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Abstract. – OBJECTIVE: One SNP in exon 9 (r5883) has been involved with high risk of cardiovascular disease in hypertensive subjects. The goal of the present study was to test the role of this genetic variant on lipid levels and Metabolic Syndrome (MS) in menopausal obese females.

PATIENTS AND METHODS: The study enrolled a sample of 112 menopausal obese females. Measurements of adiposity parameters, blood pressure, fasting blood glucose, insulin concentration, insulin resistance (HOMA-IR), lipid profile, C reactive protein and prevalence of MS were recorded. Genotype of *CETP* gene polymorphism (rs5883) was studied.

RESULTS: The distribution of the rs5883 polymorphism in this menopausal obese population was 83.9% (n=94) (CC), 15.2% (n=17) (CT) and 0.9% (n=1) (TT). Adiposity parameters, blood pressure, fasting glucose levels, insulin levels, HOMA-IR, C reactive protein, total cholesterol, LDL-cholesterol and triglycerides were similar in both genotype groups (CC *vs.* CT+TT). Moreover, HDL cholesterol (8.5+1.2 mg/dl; *p*=0.01) and ratio total cholesterol/HDL-cholesterol (0.5±0.2; *p*=0.04) were higher in T allele carriers (dominant model). MS percentage was similar in both genotypes (37.6% *vs.* 27.2%; *p*=0.43). Logistic regression analysis showed a decreased risk of low-HDL cholesterol in T allele carriers (OR=0.18, 95% CI=0.02-0.77, *p*=0.03) after adjusting by dietary fatty acid intakes, body mass index and age.

CONCLUSIONS: The results reported here support that *CETP* variant rs5883 is related with HDL-cholesterol levels and ratio total cholesterol/HDL-cholesterol.

Key Words:
CETP gene, HDL-cholesterol, Total-cholesterol/HDL-cholesterol ratio, Metabolic syndrome, Rs5883.

Introduction

Cholesteryl Ester Transfer protein (CETP) is a hydrophobic glycoprotein (476 aminoacids) that regulates the transfer and exchange of neutral lipids and phospholipids between plasma lipoproteins[1]. This protein regulates the transfer of cholesteryl ester from High-density lipoprotein (HDL) and Low-density lipoprotein (LDL) cholesterol to other triglyceride-rich lipoproteins because of an exchange of cholesteryl ester for triglycerides. Therefore, the activity of CETP may increase efflux of cell membrane cholesterol into HDL-cholesterol and improve reverse cholesterol transport. High CETP activity produces a reduction of the HDL/total cholesterol ratio, related with increased risk for cardiovascular events[2,3]. Thus, CETP inhibitors have been investigated to evaluate their ability to increase HDL-cholesterol levels. Moreover, initial data have shown an increment of cardiovascular risk[4,5]. It is also possible that genetic *CETP* variants affect lipid levels, cardiovascular disease risk and drugs responses. Patients lacking functional *CETP* expression have a lot of cardiovascular problems[6]. Some genetic investigations of *CETP* have evaluated the promoter region of transcription start site and non-synonymous single nucleotide polymorphism (SNPs)[7]. Alternative splicing of *CETP* mRNA has been shown to produce a protein isoform lacking exon 9, which may act in a dominant-negative way by binding to full length CETP preventing its secretion[8]. One SNP in exon 9 (r5883) has been located creating a putative exonic splicing enhancer sequence[9]. This SNP has been associated with a high risk of cardiovascular disease in hypertensive patients and potential modifications on HDL cholesterol have also been described[9].

On the other hand, the epidemic of obesity has been termed "globesity" to underline the global dimension of the entity. Secondary to obe-

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sity, metabolic Syndrome (MS) is an important clustering of several factors: abdominal obesity, glucose intolerance and/or insulin resistance, low HDL-cholesterol and hypertension[10]. Menopausal females are a high-risk metabolic group of patients with a well-described lipid profile involvement[11]. Despite the potential relationship of SNP r5883 with lipid profile and cardiovascular risk, its role in postmenopausal women has not been evaluated yet[9].

The goal of our investigation was to test the influence of rs5883 on lipid profile and components of MS in menopausal obese females.

Patients and Methods

Subjects and Clinical Investigation

112 Caucasian obese females were enrolled in a non-probabilistic consecutive method of sampling. This sample was selected from menopausal obese females sent by the primary care physicians to our hospital. Obesity is diagnosed by a body mass index (BMI) ≥30 kg/m^2. Menopause was defined as a period of 6-12 months with amenorrhea without pregnancy and follicle stimulating hormone above 30 UI/L. The Ethics Committee of the HCUVA (HCUVA Committee 06/2017) approved the study protocol. This protocol was in accordance with the guidelines laid down in the Declaration of Helsinki. All obese females read the informed consent form and gave written informed consent.

The inclusion criteria are the following: age over 50 years, amenorrhea ≥ 6 months, body mass index ≥ 30 kg/m^2, no history of cardiovascular disease, thyroid disease, chronic renal or hepatic disorders, active alcoholism, malignant tumor. In the other hand, exclusion criteria were BMI over 45 kg/m^2, not having received drugs with influence on lipid profile during the previous 6 months (for example, hormonal therapy, glucocorticoids and anti-inflammatory drugs) or glucose levels (oral antidiabetic drugs or insulin), multivitamin complexes. Carrying out a hypocaloric diet for the previous 12 months was also an exclusion criterion.

After signed consent was obtained, blood samples from patients were collected after 10 h fasting. Glucose, insulin, HOMA-IR (Homeostasis model assessment) and lipid profile (total cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides) were determined in these blood samples. Data on blood pressure, anthropometric parameters (weight, height, body mass index (BMI), fat mass by impedance and waist circumference) were also obtained at a fasting state. Dietary intake was also recorded. To estimate the prevalence of MS, we use the criteria of ATPIII[10]. Patients have to meet at least three of the next five criteria; 1) elevated triglycerides (>150 mg/dl) or treatment for dyslipidemia, 2) elevated fasting glucose or treatment for diabetes, 3) low HDL cholesterol < 40 mg/dl (males) or <50 mg/dl (females), 4) elevated systolic or diastolic blood pressure (>130/85 mmHg or antihypertensive treatment) and 5) increased waist circumference (>94 cm (males) or >80 cm (females)). Finally, the obesity criteria were maintained at BMI> 30 kg/m^2.

Biochemical Procedures

Lipid profile (total cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides), C reactive protein (CRP), fasting glucose and insulin were determined on the same day using a clinical chemistry automated analyzer COBAS INTEGRA 400 analyser (Roche Diagnostic, Montreal, Canada). LDL cholesterol was obtained using Friedewald formula (LDL cholesterol= total cholesterol-HDL cholesterol-triglycerides/5)[12]. The homeostasis model assessment for insulin resistance (HOMA-IR) was calculated using this equation (glucose x insulin/22.5)[13].

Adiposity Parameters and Blood Pressure

Blood pressures were measured by averaging three consecutive measurements (Omron, Fremont, CA, USA). Body weight was obtained while the subjects were unclothed and not wearing shoes (Omron, Fremont, CA, USA). Height was determined with a tape measure (Omron, Fremont, CA, USA). Body mass index (BMI) was calculated with the formula: (body weight (in kg) divided by height (in m^2)). Waist circumferences (WC) were measured at the umbilical level with the use of a tape measure (Omron, Fremont, CA, USA) while the subjects were standing after normal expiration. Electrical impendanciometry was used to measure fat mass with an accuracy of 10 g[14] (EFG, Akern, Pisa, Italy).

Dietary Intakes and Physical Activity

In all subjects, records of daily dietary intake for 3 days (2 days of week and one of weekend) were recorded with a computer-based data evaluation system (Dietosource®, Gen, Switzerland).

In order to evaluate dietary intakes, a national composition food tables were used as reference[15]. A recorded self-reported questionnaire was used to obtain daily physical activity.

Genotyping CETP Gene

DNA was isolated from buccal swabs using QIAamp®. Genotyping (rs5583) was realized with customized assays with the TaqMan® OpenArray™ Genotyping platform (Thermo Fisher, Pittsburg, PA, USA). All samples were loaded using the AccuFill system, and amplification realized on the QuantStudio 12K Flex Real-Time qPCR instrument (Thermo Fisher, Pittsburg, PA, USA). A total volume of 10 µl with 2.5 µl TaqMan OpenArray Master Mix (Applied Biosystems, Foster City, CA, USA) and 2.5 µl human DNA sample were mixed on arrays following the manufacturer's instructions (Thermocycler Life Technologies, Carlsbad, CA, USA). Genotype calling and sample clustering for Open Array assays were performed in TaqMan Genotyper (Life Technologies, Carlsbad, CA, USA).

Statistical Analysis

All the parameters were evaluated using SPSS for Windows, version 23.0 software package (SPSS Inc, IBM, Armonk, NY, USA). Hardy Weinberg equilibrium was checked with a statistical test (Chi-square) to compare our expected and observed counts. Sample size was calculated to detect differences over 4 mg/dl in HDL cholesterol levels between genotype groups (90% power and 5% significance). The analysis was performed under a dominant model with rs5883 T- allele as the risk allele (CC *vs.* CT+TT). The results were showed as average±standard deviation. Variables were analyzed with Student's *t*-test for independent samples. Logistic regression analyses adjusted by age and weight were realized to obtain odds ratio (OR) and 95% confidence interval (CI). With this model, the association of the rs5883 SNP with the risk of Metabolic syndrome and components of MS was evaluated. A *p*-value under 0.05 was considered statistically significant.

Results

We recruited 112 menopausal obese females. The average age was 62.0±5.4 years (range: 57-69) and the mean body mass index (BMI) was 39.5±3.2 kg/m^2 (range: 36.1-42.1). This genetic variant was in Hardy Weinberg equilibrium (p=0.32). The distribution of the rs5883 polymorphism in this sample was 83.9% (n=94) (CC), 15.2% (n=17) (CT) and 0.9% (n=1) (TT). The allele frequency was C (0.91) and T (0.09).

Table I shows adiposity parameters and blood pressure. We did not detect differences in the age of the selected menopausal obese women. Applying the dominant genetic model (CC *vs.* CT+TT), we did not detect statistical differences between both genotype groups in adiposity parameters and blood pressure.

Biochemical characteristics according to genotype are showed in Table II. Fasting glucose levels, insulin levels, HOMA-IR, C reactive protein, total cholesterol, LDL-cholesterol and triglycerides were similar in both genotypes. Moreover, HDL cholesterol (8.5±1.2 mg/dl; p=0.01) and ratio total cholesterol/HDL-cholesterol (0.5±0.2; p=0.04) were higher in T allele carriers (dominant model) than non-T allele carriers.

Table III shows dietary intakes and physical activity. We did not detect statistical differences between both genotype groups. Physical activity was also similar in both groups.

Table I. Adiposity parameters and blood pressure.

Parameters	CC n = 94	CT+TT n = 18	*p*
Age (years)	62.1 ± 3.8	61.1 ± 3.7	0.54
BMI (kg/m^2)	39.3 ± 3.1	39.6 ± 2.1	0.28
Weight (kg)	97.3 ± 11.1	98.3 ± 10.3	0,41
Fat mass (kg)	51.2 ± .2	59.8 ± 3.3	0.37
WC (cm)	117.1 ± .2	119.9 ± .1	0.29
SBP (mmHg)	130.0 ± 11.8	126.1 ± 9.1	0.31
DBP (mmHg)	80.4 ± 5.3	79.4 ± 4.2	0.45

BMI: body mass index DBP, diastolic blood pressure; SBP, systolic blood pressure; WC, waist circumference. NO statistical differences between genotype groups.

Table II. Biochemical parameters (mean ± SD).

Parameters	CC n = 94	CT+TT n = 18	*p*
Fasting Glucose (mg/dl)	107.0 ± 5.2	104.8 ± 4.3	0.34
Total cholesterol (mg/dl)	208.5 ± 25.1	211.7 ± 21.2	0.45
LDL-cholesterol (mg/dl)	111.2 ± 12.3	114.3 ± 10.1	0.32
HDL-cholesterol (mg/dl)	54.1 ± 3.4	62.6 ± 3.2*	0.01
Triglycerides (mg/dl)	132.1 ± 33.9	138.9 ± 35.9	0.45
Ratio total colesterol/HDL cholesterol	3.8 ±0.2	3.3 ± 0.2*	0.04
Insulin (mUI/l)	18.4 ±3.0	18.1 ± 3.2	0,43
HOMA-IR	4.8 ± 3.1	4.7 ± 3.2	0.65
CRP (mg/dl)	9.8 ± 1.1	9.7 ± 0.8	0.41

CRP: C reactive protein. HOMA-IR (homeostasis model assessment of insulin resistance). *$p < 0.05$, in CC *vs*. CT+TT genotypes.

The frequency of metabolic syndrome and different components of MS (central obesity, hypertriglyceridemia, hypertension or hyperglycemia) have been reported in Table IV. We did not observe statistical differences. According to the results of metabolic characteristics, the percentage of individuals who had low HDL-cholesterol was lower in T allele carriers than non-T allele carriers (OR= 0.21, 95% CI=0.05-0.73; p=0.015). Logistic regression analysis reported a low risk of low-HDL cholesterol in T allele carriers (OR=0.18, 95% CI=0.02-0.77, p=0.03) after adjusting by dietary fatty acid intakes, BMI and age.

Discussion

This study shows that *CETP* SNP (rs5883) was associated with HDL-cholesterol levels and ratio total-cholesterol/HDL-cholesterol regardless of dietary intakes and other cardiovascular risk factors in obese menopausal patients.

As far as we know, this is the first investigation to evaluate the effect of this genetic variant of *CETP* on lipid profile in obese menopausal women. This is an interesting area of investigation since *in vitro* research has reported that CETP is associated with high-density lipoprotein (HDL) metabolism and atherosclerosis[16]. CETP is responsible for the modification of HDL-cholesterol to LDL-cholesterol and therefore, it is a well-known atherosclerosis factor[16]. Genetic investigations have reported that mutated or deficient *CETP* gene subjects have high HDL-cholesterol levels[17].

CETP is a glycoprotein synthesized by adipocytes and hepatocytes[18]. Eventually, it may be important to evaluate genetic variables in obese patients. This protein decreases HDL levels by playing a role in conversion of cholesteryl esters to smaller non-HDL cholesterol, like LDL cholesterol. Investigations examining the association of CETP genetic variants with HDL cholesterol and atherosclerosis events have shown conflicting results. Genetic background of populations may influence these results. For example, in a Turkish population[19], the genotypes of the rs5883 CETP gene SNPs did not differ between healthy

Table III. Dietary Intakes and physical activity (mean ± SD).

Parameters	CC n = 94	CT+TT n = 18	*p*
Calories (cal/day)	1688.3 ± 304.2	1731.5 ± 250.5	0.28
Carbohydrates (g/day)	186.3 ± 33.1	203.2 ± 5.1	0.34
Proteins (g/day)	77.5 ± 9.2	89.6 ± .4	0.49
Lipids (g/day)	64.6 ± 8.1	66.7 ± 7.1	0,53
Fiber (g/day)	14.8± 3.2	14.1 ± 3.1	0.45
Cholesterol (mg/day)	347.6 ± 220.9	418.7 ± 197.8	0.25
Saturated fatty acids (g/day)	17.7 ± 7.2	15.8± 2.1	0,39
MonounSaturated fatty acids (g/day)	29.1 ± 4.1	29.2 ± .8	0.45
PolyunSaturated fatty acids (g/day)	6.2 ± 4.2	7.7 ± .9	0.23
Physical activity (minutes/week)	97.9 ± 12.7	101.3 ±12.1	0.33

No statistical differences detected.

Table IV. Metabolic syndrome (MS), components of MS.

Parameters	CC n = 94	CT+TT n = 18	*p*
Percentage of MS	37.6%	27.2%	0.43
Percentage of central obesity	44.7%	38.9%	0.55
Percentage of Hypertriglyceridemia	33.3%	22.2%	0.23
Low HDL cholesterol	50.0%	16.6%*	0.01
Percentage of Hypertension	73.1%	55.5%	0.49
Percentage of hyperglycaemia	28.0%	22.2%	0.38

The cutoff points for the criteria of; central obesity (waist circumference > 88 cm in female and > 102 in male), hypertension (systolic BP >130 mmHg or diastolic BP > 85 mmHg or specific treatment), hypertriglyceridemia (triglycerides > 150 mg/dl or specific treatment) or hyperglycaemia (fasting plasma glucose >110 mg/dl or drug treatment for elevated blood glucose). *$p <$ 0.05, in CC *vs*. CT+TT genotypes.

controls and coronary artery diseases patients. This SNP did not show a relationship with HDL cholesterol levels[19]. However, this study has a low sample size (45 subjects in each group) and some patients were taking statins. In addition, both groups showed a significant difference in weight, male/female ratio and age. Moreover, Hsu et al[20] reported an association of genetic variations in the *CETP* gene and HDL-cholesterol (Chinese population). Papp et al[9] reported in the Whitehall II study of 4745 subjects (Caucasian subjects), that rs5883 SNP was independently associated with increased HDL-cholesterol. This last study reported that every unit of increase in HDL levels is associated with 53% increase of myocardial infarction risk[21]. In our present investigation, we also detected differences in the total cholesterol/HDL-cholesterol ratio, and this ratio is known as an atherogenic index. This index is considered a cardiovascular risk predictor, with higher predictions than other risk factors, such as LDL-cholesterol[21]. In this context, Papp et al[9] reported in a multiethnic cohort of hypertensive subjects with coronary disease that T allele was associated with increased myocardial infarction, stroke and all-cause of mortality. Moreover, *CETP* polymorphisms appear to affect cardiovascular risk in a sex-dependent manner, showing different metabolism in females and males[22-24]. In our investigation we decided to evaluate a homogeneous group of obese menopausal females. Although, elevated HDL cholesterol levels associated with T allele would normally be considered protective, the high cardiovascular risk[9] reported in this previous study could be secondary to different causes that are not related to lipids. In addition, CETP may have different biological effects not reflected in overall HDL cholesterol levels, for example anti-inflammatory properties[25].

From a pathophysiological point of view, the genetic variant rs5883 on exon 9 is associated with an increased formation of the isoform delta 9 protein. This protein dimerizes with the full-length form preventing its efflux from the liver[26]. This fact modifies the HDL cholesterol levels. In our study, the relationship between T allele and high HDL-cholesterol levels was maintained by adjusting the analysis also for the intake of nutrients. This fact is important because an influence on the production of delta splice by the diet has been reported[27,28]. Mechanism of regulation of *CETP* gene expression are only partially understood and it is known that diet induced transcription of *CETP* gene, through a factor known as CCAAT/enhancer binding protein[27,28].

Limitations of our study are as follows: one is that the study has been designed in menopausal obese females, so the data are not generalizable to males or non-obese females. The second, the design as a cross-sectional design does not allow to extract causality. The third is that dietary intake was determined with a diet questionnaire, which would lead to biases in the estimation of the intake. The fourth, we have evaluated only Caucasian subjects. As we have commented, studies in other ethnic groups have shown contradictory data. Finally, we have not determined the CETP expression in tissues or blood.

Conclusions

The results reported here support *CETP* variant rs5883 is related with HDL-cholesterol levels and ratio total cholesterol/HDL-cholesterol. Thus, this SNP is a potential cardiovascular disease marker. Follow-up studies are necessary to evaluate the relationship of this SNP and other

genetic variants[29] with new cardiovascular events and the response of treatments. Recently, a SNP statin interaction has been described for this genetic variant on strokes[30].

Conflict of Interest
The Authors declare that they have no conflict of interests.

Ethical Approval
All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (HCU-VA Committee 06/2017) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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Informed Consent
Informed consent was obtained from all individual participants included in the study.

Authors' Contribution
Daniel Antonio de Luis designed the study and wrote the article. Olatz Izaola, JJ Lopez, E Gomez realized nutritional evaluation. D Primo realized biochemical evaluation.

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