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Association between Plasma Cholesteryl Ester Transfer Protein activity and Lipid profiles in Metabolic Syndrome in an Iranian Population

Mohammad Taghi Goodarzi[1], Mahshid Mohammadian[2], Shiva Borzouei[3] and Taghi Hassanzadeh[2]
[1]Research Center for Molecular Medicine, Hamadan University of Medical Science, Hamadan, IRAN
[2]Department of Biochemistry and Nutrition, School of Medicine, Hamadan University of Medical Science, Hamadan, IRAN
[3]Department of Internal Medicine-Endocrinology, Medical School, Hamadan University of Medical Science, Hamadan, IRAN

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Abstract

Metabolic syndrome (MS) is a predisposing factor for atherosclerosis, cardiovascular disease (CVD) and type 2 diabetes. Cholesteryl ester transfer protein (CETP) has a major role in the lipoproteins metabolism and subsequently lipid profile. This study was aimed to investigate possible relationship between plasma CETP activity and lipid profile in metabolic syndrome in a population from Iran. In this case-control study a total of 400 participants, 200 healthy individuals and 200 patients with metabolic syndrome were selected from residents of Hamadan city in western regions of Iran. A national Cholesterol Education Program guideline was used to diagnosis of MS. Blood sugar, lipid profile, and BMI were determined in all studied subjects. A fluorometric assay was used to measure the plasma CETP activity. Significant differences in lipid profile and waist circumference were observed between two studied groups (p=0.001). CETP activity was significantly higher (p<0.001) in patients compared to normolipidaemic group. Correlation analysis showed an association between CETP activity and total cholesterol, LDL cholesterol, and HDL-C. Our results suggest that individual with MS has increased CETP activity. Augmented CETP activity and its association with reduction in HDL-C and increase in LDL-C indicate the important role of CETP in alteration of lipid profile and probably pathogenesis of MS.

Keywords: CETP, metabolic syndrome, Iran

Introduction

Metabolic syndrome (MS) is a multifaceted syndrome that is very common in the general population[1]. MS is associated with changes in in blood glucose, central obesity, lipid profile, and blood pressure[2,3]. Cholesteryl ester transfer protein (CETP) has an important role in remodeling of plasma lipoproteins. This enzyme plays a central role in HDL-C metabolism by transferring cholesteryl esters (CEs) from HDL particles to apolipoprotein B (apoB) containing particles in exchange for triglycerides[4,5]. CETP facilitates the uptake of cholesterol from peripheral tissues to the liver in an antiatherogenic process known as reverse cholesterol transport. At the same time, CETP transfers esterified cholesterol from high-density lipoprotein cholesterol (HDL) to very-low-density lipoprotein (VLDL) and low-density lipoprotein (LDL) with a concurrent exchange of TGs. Hence, CETP may enhance the atherogenicity of apolipoprotein B-containing lipoproteins and negatively affect the level of HDL-C[6,7].

In humans, CETP is expressed predominantly in the liver, spleen, and adipose tissue. Lower CETP level also presents in the small intestine, adrenal glands, heart, kidneys, or skeletal muscle[8]. In reveres cholesterol transfer, a process that cholesterol is removed from peripheral tissues, HDL particles show critical roles[9,10].

Results of some prospective epidemiological studies show that increased levels of HDL-C are associated with a diminished risk of CAD[11]. High levels of HDL-C observed in patients with genetic CETP deficiency also indicate the critical role of CETP in lipoprotein metabolism[12].

Furthermore, increase in CETP activity may contribute to augmentation the risk of coronary artery disease through reducing the cholesterol content of HDL relative to LDL[13] and by promoting the formation of atherogenic small dense LDL in hyperlipidemic patients[14].

Yamashita et al. reported that CETP deficiency represents the most frequent cause of hyperalphalipoproteinemia in Asian populations and it is associated with elevated plasma levels of HDL-C to 3–6 fold above the normal rang plasma concentrations[15].

Low HDL-C in association with an elevated triglyceride concentration is characteristics of MS. These alterations can be a result of an increased triglyceride load in the HDL particle. Hepatic lipase which hydrolyzes the triglyceride has a role in this process. The reduction in triglyceride content of these particles leads to formation of a small HDL particle which can be filtered by the kidney, resulting in a decrease in apolipoprotein (apo A) and HDL concentrations[16,17]. CETP activity was significantly increased in human with MS and this

increase might be responsible for the reduced HDL-C and increased TGs and LDL-C levels observed in MS [18]. Our aim of this investigation was to study the relationship between plasma lipid levels and CETP activity in Iranian subjects with and without metabolic syndrome.

Material and Methods

A total of 400 participants (unrelated subjects), 200 healthy individuals and 200 patients with metabolic syndrome (102 males; 98 females) were selected from residents of Hamadan, a city located in the west of Iran. The study protocol was approved by the Ethics Committee of the Hamadan University of Medical Sciences and written consent was obtained from all participants.

MS were identified when 3 out of the 5 criteria of the National Cholesterol Education Program (ATP III) were met[16,17]. All individuals with metabolic syndrome did not have any other disease that could affect lipid levels, such as thyroid disorder, liver disease, renal failure and diabetes mellitus. These patients were not on any lipid lowering treatment. All the control subjects were healthy individuals. Body weight and height were measured and the body mass index (BMI) calculated. Written informed consent was obtained from all those enrolled, according to the criteria of the Ethical Committee of Hamadan University of Medical Sciences.

Biochemical measurements: Weight, height and waist circumference were measured. Body mass index (BMI) was calculated as weight divided by height squared (kg/m^2). Fasting blood samples (10 ml) were collected after an overnight fasting for the determination of blood TC, TG, HDL-C and VLDL cholesterol (VLDL-C) levels and fasting blood sugar (FBS), which were measured by routine biochemical assays. All kits used for this study were obtained from Pars Azmoon Company (Tehran, Iran). LDL-C was calculated according to the Friedewald formula. The plasma CETP activity was measured by Roar Biomedical kit (USA), in a Perkin Elmer LS55 fluorescence spectrometer (UK). The assay was read at excitation wavelength of 465 nm and emission wavelength of 535 nm. A standard curve was prepared, according to the manufacturer's guidelines, to calculate the CETP activity.

Statistical analysis: Continuous variable were shown as mean ± standard deviation (SD). Students T-test was used for the comparison of lipid parameters between two studied groups. Correlations between CETP activity and lipid parameters were determined using Pearson test. All statistical analysis was performed using SPSS software (Version 21, USA) and $P<0.05$ was considered significant.

Results and Discussion

Demographic and biochemical characteristics of the studied subjects are presented in table-1. Age and sex were similar in two groups. Frequencies of obesity and high waist circumference were higher in MS group compared to healthy subjects. Also more atherogenic lipid profile with higher TGs and lower HDL-C (p =0.001) (Table-1) was observed in MS subjects. Furthermore, comparing to healthy group, MS subjects had lower HDL-C levels (48.4 ± 14.1 mg/dL vs. 53.6 ± 10.9 mg/dL p =0.001), higher LDL-C (144.6 ± 40.4 vs. 104.6 ± 25.9 p=0.001), higher triglyceride (282.9 ± 121.3 vs. 131.1 ± 51.1 p=0.001) and higher total cholesterol (248.9 ± 45.3 vs. 184.8 ± 31.5 mg/dL, p =0.001). Analyzing the obtained results indicated significant differences in blood sugar, total cholesterol, TGs, HDL-C, LDL-C levels as well as BMI, waist circumference, systolic and diastolic blood pressures between two studied groups. CETP activity was also significantly higher (p=0.001) in subjects with MS as compared to healthy individuals (151.6± 32.3 and 109.1 ± 16.2 pmol/µl.h respectively).

Table-1
Demographic and biochemical characteristics of the participants

Parameters	MS	Controls	P Value
Number of participants	200	200	_
Age (year)	50.6 ± 11.9	49.4 ± 12.9	NS
BMI ($kg/m^{2)}$	25.8 ± 6.6	22.1 ± 5.9	0.001
WC (cm)	107.5±9.1	91.5 ± 10.7	0.001
TC (mg/dl)	248.9 ± 45.3	184.8 ± 31.5	0.001
HDL-C (mg/d)	48.4 ± 14.1	53.6 ± 10.9	0.001
TG (mg/dl)	282.9 ± 121.3	131.1 ± 51.1	0.001
FBS (mg/dl)	98.1±31.1	83.5±35.8	0.001
SBP (mmHg)	139.1 ± 10.6	128.1 ± 10.2	0.001
DBP (mmHg)	85.2±5.9	76.8 ± 6.2	0.001
Smoking % (n)	40.5(81)	39(78)	_

Data are expressed as mean ± standard deviation. BMI: body mass index, WC: Waist circumference; SBPs: systolic blood pressure; DBP: diastolic blood pressure; TC: total cholesterol; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; TG: triglyceride; MS: metabolic syndrome, NS: non significant

CETP activity was significantly related to plasma levels of total cholesterol (r=0.63 p<0.001), LDL cholesterol (r=0.57, p<0.01), and TG (r=0.38, p<0.01). Also there was a negative correlation between HDL-C and CETP activity (r=-0.85, p<0.01).

Furthermore patients with high plasma CETP activity had significantly higher total cholesterol, LDL cholesterol and triglycerides compared to those with lower CETP levels. Patients with high CETP had also higher systolic and diastolic blood pressure, whereas HDL cholesterol levels were inversely correlated to CETP activity.

This investigation was aimed to study the possible association between plasma lipid levels and CETP activity in Iranian

subjects with and without metabolic syndrome. Since MS is accompanied by several physiologic and metabolic changes including: visceral obesity, hypertension, high TGs and low HDL-C, and insulin resistance, it is considered as a major health problem and risk factor for cardiovascular events[17,18]. Obesity is considered to play a central role in the development of MS[19]; low HDL-C and high TG levels are also core components of this disorder. Also the previous studies demonstrated a role of small dense-LDL particles in MS[20,21].

It is believed that increase in cholesterol in patients with the MS is secondary change to TG elevation. In the presence of increased plasma TG levels, the cholesteryl ester transfer protein mediates TG-cholesteryl ester exchange between LDL and VLDL[22]. Sandhofer A. et al. showed that CETP activity significantly increases in human with MS and this increase might be responsible for the reduced HDL-C and LDL-C particle diameters in these subjects[23].

Lipids and lipoproteins metabolism in humans may be controlled by enzymes, including cholesteryl ester transfer protein, because of their central position in the lipids metabolism regulation[24,25]. It has been documented that variation in lipid and lipoprotein concentrations was associated with the CETP activity, in both metabolic syndrome subjects and normolipidaemic individuals. HDL is a key component of transfer of excess cholesterol to liver; moreover HDL prevents LDL oxidation and may diminish the expression of endothelial cell adhesion molecules[23]. The recent effect and also the role of HDL particles in efflux of cholesterol from peripheral cholesterol-loaded cells[26,27], can present the fact that low HDL-C is associated with increase in CVD risk. Peroxidation of fatty acids content of lipoprotein particle can be a health hazard[28].

Increased activity of CETP has been observed in subjects with high levels of LDL cholesterol, triglycerides, and increased blood pressure. Our obtained results confirms the previous studies findings showing an association between higher CETP activity with faster progression of MS components and increased activity of this enzyme in subjects with MS. Furthermore, CETP activity correlated positively with LDL-C level and negatively with HDL-C level in both studied groups. Several studies suggested that only in hypertriglyceridemia (≥400 mg/dL), CETP activity is the rate-limiting factor for lipid exchange, whereas in normolipidaemia, TG levels determine the rate of CE transfer[23]. Increased CETP activity can be expected to result in increased LDL cholesterol with concomitant decreased HDL cholesterol levels[29].

Our study reports that CETP activity was significantly increased in human with MS and this increase might be responsible for the reduced HDL-C levels and leads to increase LDL-C observed in MS. Small number of studied subjects can be mentioned as limitation of our study. The study population was not on any lipid lowering treatment that may limit the extrapolation of our results to patients using lipid lowering medication.

Conclusion

Our results suggest that the components of lipid profiles are related with MS-associated variables. Also our findings showed higher CETP activity in MS subjects is associated with low HDL-C levels and high LDL-C. This observation indicates that CETP might have a proatherogenic role in metabolic syndrome.

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