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CETP Gene and Its Role in Diabetes Mellitus Type II - A Review

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Abstract

Plasma lipoproteins are continuously remodelled through the actions of enzymes and lipid transfer proteins. In particular, the transfers of cholesteryl esters (CE) and triglycerides (TG) are facilitated by a specialized protein known as the cholesteryl ester transfer protein (CETP).

Genetic polymorphisms of the enzymes and proteins involved in lipid metabolism like cholesteryl ester transfer protein CETP have been shown to affect plasma lipid concentrations. CETP modifies HDL, LDL and very low density lipoprotein (VLDL) levels. It transfers cholesterol esters (CE) from CE rich particles (HDL and LDL) to triglyceride rich particles (VLDL) in exchange of triglyceride from the latter. Several genetic polymorphisms have been reported which may be associated with alteration in CETP activity. TaqI B polymorphism has been most widely studied, which results from a silent mutation in nucleotide 277, in intron 1 of the gene. The polymorphism has been associated with decreased CETP mass and an increase in HDL-cholesterol. The TaqI polymorphism B1 allele of CETP has been shown to be an independent risk factor for development of cerebral vascular disease, in patients with T2DM.

Keywords: CETP; Lipoprotein; Diabetes mellitus; Polymorphism

Abbreviations

T2DM: Type 2 Diabetes Mellitus; HDL: High Density Lipoprotein; LDL: Low Density Lipoprotein; CETP: Cholestryl Ester Transfer Protein; CE: Cholesterol Esters; VLDL: Very Low Density Lipoprotein; TG: Triglycerides

Introduction

Plasma *CETP* facilitates the transfer and exchange of cholesteryl ester (CE) and triglyceride (TG) between the plasma lipoproteins, and plays an important role in HDL-CE and apo A-I catabolism. In some primary and secondary hyperlipidemias (e.g., familial hypercholesterolemia, dysbetalipoproteinemia, hypertriglyceridemia, and nephrotic syndrome) and during postprandial lipemia, accelerated CETP-mediated CE transfer results in increased CE net mass transfer from HDL to VLDL or chylomicron, possibly contributing to reduced HDL-CE levels and CE enrichment of potentially atherogenic chylomicron and VLDL remnants [1]. Apolipoprotein E (Apo E) plays a central role in clearance of lipoprotein remnants by serving as a ligand for LDL and apo E receptors. HDL has a unique ability to facilitate cholesterol efflux from cells, including those within atherosclerotic lesions, and subsequently to transport excess cholesterol to the liver [2]. There are several well-known environmental factors influencing HDL-C levels. Alcohol consumption, exercise, and female sex increase HDL-C levels. On the other hand, smoking, obesity, male sex, and diets high in polyunsaturated fat decrease HDLC levels. These environmental factors often influence HDL levels through the activities of lipases or lipid transfer proteins [3,4].

In a normolipidemic population, the plasma CETP concentration differ mostly over a 3-fold range and is influenced by environmental factors. Plasma CETP has been shown to be elevated in smokers and to be decreased by heavy alcohol drinking and physical training [5-8]. CETP is known to transfer CE from HDL to very low density lipoprotein (VLDL) in exchange for triglyceride (TG). While the CE in the VLDL/LDL pool is delivered to the liver and eliminated from the body as a component of bile, the TG in low density lipoprotein (LDL) and HDL is hydrolyzed by hepatic lipase (HL) resulting in smaller, denser particles [9]. HL is involved in the metabolism of IDL (intermediate density lipoprotein) and large LDL to sdLDL particles and in the conversion of HDL2 to HDL3, in addition to its key role in reverse cholesterol transport [10].

Association between *Taq1B* polymorphism and HDL-C concentration was found to depend upon the environmental factors that modulate HDL-C. It was blunted by obesity and smoking [11,12] while it was found conserved and even improved in alcohol drinkers. Additionally, the association of *Taq1B* polymorphism with HDL-C was recently considered as independent of that with CETP concentrations. However, in none of these studies was the net mass CET measured, and only HDL-C concentration was examined as a direct consequence of the CETP-mediated reaction [13].

Polymorphism Effect of *CETP* Gene

Genetic polymorphisms of the enzymes and proteins involved in lipid metabolism like cholesteryl ester transfer protein CETP have been shown to affect plasma lipid concentrations [14]. Genetic polymorphisms have been shown which may be associated with alteration in CETP activity. *TaqI* B polymorphism has been mostly studied, which results from a silent mutation in nucleotide 277, in intron 1 of the gene. The polymorphism has been associated with

decreased CETP mass and an increase in HDL-cholesterol [15-17]. A recently described relatively uncommon mutation in the *CETP* gene promoter causes decreased transcriptional activity and marked hyper alpha-lipoproteinemia, reflecting impaired reverse cholesterol transport [18]. Genetic deficiency of CETP results in reduced CE contents in VLDL, intermediate density lipoprotein, and LDL, producing a potentially antiatherogenic lipoprotein profiles [19,20]. This mutant allele frequency is high in Japanese subjects with HDL-C levels 60 mg/dl.

Polymorphisms in the *CETP* gene have been associated with CETP activity, HDL and LDL particle size and risk of CAD [21]. The I405 V missense polymorphism (rs5882) in the *CETP* gene has been associated with increase in HDL-C and lipoprotein subclasses [22]. The -629C/A promoter polymorphism (rs1800775), on the contrary affects 50% of CETP activity and has showed HDL-C raising effect [6]. The I405 V polymorphism has been reported to be associated with LDL size [23]. In a study by Bruce et al. [24] in a subpopulation with high plasma TG, the HDL-C levels were significantly higher in theVVgroup and sowas the CHD prevalence. The V allele has been associated with decreased CETP activity as a result of which the transfer of CE from HDL-C to LDL and VLDL in exchange for TG would be affected. This would lead to an increase in HDL-C concentration and simultaneously increase the proportion of TG in VLDL and LDL. The latter being a good substrate for HL and would result in formation of sdLDL [17,25]. The increased sdLDL concentration in our II carriers as compared to VV carriers. Two other *CETP* gene mutations have been characterized. One of these is a missense mutation, changing the codon of amino acid 442 from aspartate to glycine (D442G).

The locus has also been reported to modulate the risk for diabetic complications in patients with T2DM and effect seems to be different between men and women [26]. Another polymorphism D442G (Asp442-->Gly) in exon 15 of CETP is located close to the active site of the enzyme and leads to reduced plasma CETP mass and specific activity [27] The mutation is more prevalent in Japanese subjects with high HDL-levels (>100 mg/dL) [28-30].

Effects of CETP polymorphisms on lipids and lipoproteins profile and CETP activity have been reported. Ordovas et al showed that Taq1B polymorphism of *CETP* gene is associated with changes in lipoprotein size, CETP activity and HDL-C levels. -971 G/A polymorphism has been shown to be significantly invovled in plasma HDL-C levels and CETP concentrations [27].

Conclusion

No association of *CETP TaqI* B polymorphism with the disease was found but B1B2 genotype was risk factor for hypertension along with diabetes. However, B1B1 was found to be protective.

Plasma CETP mass and activity are elevated in CVD patients and with high CVD risk, resulting in decreased HDL and increased triglycerides (TG). CETP quantity and activity also reflect atherosclerosis status. Some pilot studies have revealed a positive correlation between the carotid intima media thickness (IMT) and CETP concentration. Three single nucleotide polymorphisms in the *CETP* gene are associated with decreased CETP activity and elevated HDL-C levels in carriers and inversely related with coronary risk, making CETP inhibitors reasonable HDL-C based therapeutic agents. CETP inhibitors comprise of a drug class which, includes: torcetrapib, dalcetrapib (JTT-705), anacetrapib, evacetrapib. They could inhibit CETP activity and thus increase the formation of high density lipoprotein levels in various degrees. There are some early clinical trials showing the inspiring results of CETP inhibitors in the treatment of patients with dyslipidemia.

References

1. Tall AR (1993) Plasma cholesteryl ester transfer protein. J Lipid Res 34: 1255-1274.
2. Tall AR, Small DM (1978) Plasma high-density lipoproteins. N Engl J Med 299: 1232-1236.
3. Tall AR (1990) Plasma high density lipoproteins. Metabolism and relationship to atherogenesis. J Clin Invest 86: 379-384.
4. Patsch JR, Prasad S, Gotto AM Jr, Patsch W (1987) High density lipoprotein2. Relationship of the plasma levels of this lipoprotein species to its composition, to the magnitude of postprandial lipemia, and to the activities of lipoprotein lipase and hepatic lipase. J Clin Invest 80: 341-347.
5. Agellon LB, Quinet EM, Gillette TG, Drayna DT, Brown ML, et al. (1990) Organization of the human cholesterylester transfer protein gene. Biochemistry 29: 1372-1376.
6. Takahashi K, Jiang XC, Sakai N, Yamashita S, Hirano K, et al., (1993) A missense mutation in the cholesteryl ester transfer protein gene with possible dominant effects on plasma high density lipoproteins. J Clin Invest 92: 2060–2064.
7. Arashiro R, Katsuren K, Maung KK, Fukuyama S, Ohta T (2001) Effect of a common mutation (D442G) of the cholesteryl ester transfer protein gene on lipids and lipoproteins in children. Pediatr Res 50: 455–459.
8. Marcel YL, McPherson R, Hogue M, Czarnecka H, Zawadzki Z, (1990) Distribution and concentration of cholesteryl ester transfer protein in plasma of normolipidemic subjects. J Clin Invest 85: 10–17.
9. Dullaart RP, Hoogenberg K, Dikkeschei BD, van Tol A (1994) Higher plasma lipid transfer protein activities and unfavorable lipoprotein changes in cigarettesmoking men. Arterioscler Thromb 14: 1581-1585.
10. Hannuksela M, Marcel YL, Kesäniemi YA, Savolainen MJ (1992) Reduction in the concentration and activity of plasma cholesteryl ester transfer protein by alcohol. J Lipid Res 33: 737–744.
11. Seip RL, Moulin P, Cocke T, Tall A, Kohrt WM, et al. (1993) Exercise training decreases plasma cholesteryl ester transfer protein. Arterioscler Thromb 13: 1359-1367.
12. Collet X, Tall AR, Serajuddin H, Guendouzi K, Royer L, et al. (1999) Remodeling of HDL by CETP in vivo and by CETP and hepatic lipase in vitro results in enhanced uptake of HDL CE by cells expressing scavenger receptor B-I. J Lipid Res 40: 1185-1193.
13. Santamarina-Fojo S, Haudenschild C, Amar M (1998) The role of hepatic lipase in lipoprotein metabolism and atherosclerosis. Curr Opin Lipidol 9: 211-219.
14. Koizumi J, Inazu A, Yagi K, Koizumi I, Uno Y, et al. (1991) Serum lipoprotein lipid concentration and composition in homozygous and heterozygous patients with cholesteryl ester transfer protein deficiency. Atherosclerosis 90: 189-196.
15. Inazu A, Koizumi J, Haraki T, Yagi K, Wakasugi T, et al. (1993) Rapid detection and prevalence of cholesteryl ester transfer protein deficiency caused by intron 14 splicing defect in hyperalphalipoproteinemia. Hum Genet 91: 13-16.
16. Zuliani G, Hobbs HH (1990) EcoNI polymorphism in the human cholesteryl ester transfer protein (CETP) gene. Nucleic Acids Res 18: 2834.
17. Freeman DJ, Griffin BA, Holmes AP, Lindsay GM, Gaffney D, et al. (1994) Regulation of plasma HDL cholesterol and subfraction distribution by genetic and environmental factors. Associations between the TaqI B RFLP in the CETP gene and smoking and obesity. Arterioscler Thromb 14: 336-344.
18. Nagano M, Yamashita S, Hirano Ki, Kujiraoka T, Ito M, et al. (2001) Point mutation (–69 g→a) in the promoter region of cholesteryl ester transfer

protein gene in japanese hyperalphalipoproteinemic subjects. Arterioscler Thromb Vasc Biol 21: 985-990.

19. Boekholdt SM, Kuivenhoven JA, Hovingh GK, Jukema JW, Kastelein JJ, et al. (2004) CETP gene variation: relation to lipid parameters and cardiovascular risk. Curr Opin Lipidol 15: 393-398.
20. Borggreve SE, Hillege HL, Wolffenbuttel BH, de Jong PE, Bakker SJ, et al. (2005) The effect of cholesteryl ester transfer protein -629C-A promoter polymorphism on high density lipoprotein cholesterol is dependent on serum triglycerides. J Clin Endocrinol Metab 90: 4198-4202.
21. Fidani L, Goulas A, Crook R, Petersen RC, Tangalos E, et al. (2004) An association study of the cholesteryl ester transfer protein TaqI B polymorphism with late onset Alzheimer's disease. Neuroscience Letters 357: 152-154.
22. Bernard S, Moulin P, Lagrost L, Picard S, Elchebly M, et al. (1998) Association between plasma HDLcholesterol concentration and Taq1B CETP gene polymorphism in non-insulin-dependent diabetes mellitus. J Lipid Res 39: 59-65.
23. Brown ML, Inazu A, Hesler CB, Agellon LB, Mann C, et al. (1989) Molecular basis of lipid transfer protein deficiency in a family with increased high-density lipoproteins. Nature 342: 448-451.
24. Inazu A, Jiang XC, Haraki T, Yagi K, Kamon N, et al. (1994) Genetic cholesteryl ester transfer protein eficiency caused by two prevalent mutations as a major determinant of increased levels of high density lipoprotein cholesterol. J Clin Invest 94: 1872-1882.
25. Fumeron F, Betoulle D, Luc G, Behague I, Ricard S (1995) Alcohol intake modulates the effect of a polymorphism of the cholesteryl ester transfer protein gene on high density lipoprotein and the risk of myocardial infarction. J Clin Invest 96: 1664-1671.
26. Ordovas JM, Cupples LA, Corella D, Otvos JD, Osgood D, et al. (2000) Association of cholesteryl ester transfer protein – Taq IB polymorphism with variations in lipoprotein subclasses and coronary heart disease risk: the Framinghon study. Arterioscler Thromb Vasc Biol 20: 1323-1329.
27. Le Goff W, Guerin M, Nicaud V, Dachet C, Luc G, et al. (2002) A novel cholesteryl ester transfer protein promoter polymorphism (-971G/A) associated with plasma high-density lipoprotein cholesterol levels. Interaction with the TaqIB and –629C/A polymorphisms. Atherosclerosis 161: 269-279.
28. Durlach A, Clavel C, Girard-Globa A, Durlach V (1999) Sex dependent association of a genetic polymorphism of cholesteryl ester transfer protein with high-density lipoprotein cholesterol and macrovascular pathology in type II diabetic patients. J Clin Endocrinol Metab 84: 3656-3659.
29. Kastelein JJ (2007) Refocusing on use of cholesteryl ester transfer protein inhibitors. Am J Cardiol 100: n47-n52.
30. Schaefer EJ, Asztalos BF (2007) Increasing high-density lipoprotein cholesterol, inhibition of cholesteryl ester transfer protein, and heart disease risk reduction. Am J Cardiol 100: n25-n31.