CETP Gene Variation Has Pronounced Independent Effects on HDL Levels and HDL Particle Size in Type 1 Diabetes

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Abstract

Cholesteryl Ester Transfer Protein (CETP) is a plasma glycoprotein that mediates the transfer of cholesterol esters, phospholipids, and triglycerides between plasma lipoproteins. A CETP gene polymorphism (*Taq*IB rs708272) located in intron1 has been reported to affect plasma CETP activity and HDL cholesterol (HDL-C) levels; however, limited data are available in Type 1 Diabetes (T1DM). To determine the impact of CETP gene variation in T1DM, we genotyped 837 patients enrolled in DCCT/EDIC and measured fasting plasma lipids and lipoprotein subclasses by NMR. The distribution of *TaqIB* genotypes was 36.8% (n=308) B1B1 (B1 has TaqIB restriction site), 45.6% (n=382) B1B2, and 17.6% (n=147) B2B2. This distribution conforms to Hardy-Weinberg equilibrium. We found that HDL-C was highest in B2B2 (60±15 mg/dl), intermediate in B2B1 (57±15), and lowest in B1B1 (54±13) (p<0.0001), due to increased concentrations of large HDL particles (p=0.025) and mean HDL particle size (p<0.0001) associated with B2 allele dosing. The effects of the B2 allele on HDL parameters persisted after adjusting for age, gender, BMI, waist to hip ratio, HbA1c, and DCCT group. CETP TaqIB polymorphism explained independently 3.6% of overall variation in HDL-C in males and 1.4% in females. There were minimal or no relationships between CETP genotype and VLDL or LDL subclasses, and no association with diabetes complications. Conclusion: CETP gene variation exerts a pronounced independent effect on HDL levels and HDL particle size in T1DM in the DCCT/EDIC cohort.

Background

Vascular disease is the leading cause of complications and death in patients with diabetes. Risk markers and underlying mechanisms have not been fully elucidated, and may differ from those in non-diabetes individuals. The overall objectives are to define these unique processes and to elucidate underlying biochemical, metabolic, and genetic determinants of vascular disease complications in diabetes. We are collaborating with Diabetes Control and Complications Trial/Epidemiology of Diabetes Intervention and Complications. The specific aim of the study is to determine the impact of CETP gene variation on lipid and lipoprotein phenotypes and vascular complications in Type 1 Diabetes. A CETP gene polymorphism (*Taq*IB rs708272) located in intron1 has been reported to affect plasma CETP activity and HDL cholesterol (HDL-C) levels; however, limited data are available in Type 1 Diabetes.

Figures

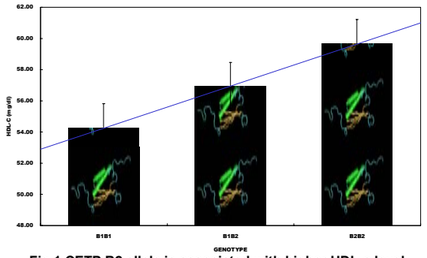

Fig.1 CETP B2 allele is associated with higher HDL-c level

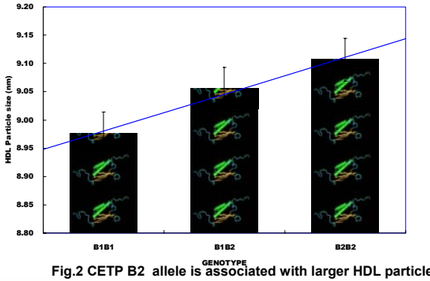

Fig.2 CETP B2 allele is associated with larger HDL particle size

Table

Parameter	B1B1 Mean	B1B1 SD	B1B2 Mean	B1B2 SD	B2B2 Mean	B2B2 SD	*p*	*p**	*p***
n	307		382		147				
HDL cholesterol (mg/dl)	54.2569	13.3968	56.9116	14.6738	59.6569	15.2944	0.0010	0.0001	0.0000
HDL particle size (nm)	8.9761	0.4396	9.0551	0.4793	9.1064	0.4720	0.0140	0.0014	0.0002
Large HDL concentration (mg/dl)	33.2254	14.8394	35.8028	16.2106	37.3164	15.4068	0.0220	0.0030	0.0007
Small HDL concentration (mg/dl)	17.7933	6.5346	17.1482	7.2416	17.7357	6.5253	0.4436	0.5262	0.4660
VLDL size (nm)	50.6894	17.3011	49.3310	17.3522	51.7536	19.0427	0.3382	0.2622	0.2441
Small VLDL concentration (mg/dl)	19.8310	16.0099	19.3413	16.3888	16.5436	14.1952	0.1176	0.1649	0.0388
LDL size (nm)	20.8975	0.6485	20.9247	0.6183	20.9586	0.5723	0.6287	0.7444	0.3780
intermediate LDL concentration (L2) (mg/dl)	41.5116	35.1770	35.6211	35.0116	34.2164	33.9352	0.0493	0.0672	0.0394
ApoB (mg/dl)	90.2371	26.9082	88.9241	26.4964	84.2056	21.2866	0.0694	0.1082	0.0163
BMI	27.0139	4.4965	26.9760	3.8642	25.9154	4.1295	0.0187		0.0137
Internal carotid wall thickness (dfy1-y6)	0.0924	0.2744	0.0632	0.2441	0.0995	0.2909	0.2597	0.4060	0.3215
Common carotid wall thickness (dfy1-y6)	0.0385	0.1198	0.0263	0.0883	0.0281	0.0912	0.3034	0.3524	0.3484
Albuminuria (AER) (mg/24hr)	73.2519	310.4009	117.4507	781.8254	71.2880	275.3791	0.5361	0.5344	0.5433
Retinopathy score (Last ETDRS)	4.5449	3.5453	4.4122	3.1475	4.3082	3.2812	0.7575	0.7183	0.6942

*Adj for age, gender, DCCT group, BMI, WHR
**Adj for age, gender, DCCT group, HbA1c
*** dfy1-y6 means the difference between year one and year six

Table1. Selected Mean Values and Standard Deviations by CETP Genotype with P-values from 41 variables analyzed

Methods

-Lipids/lipoproteins: conventional lipid panel, apoprotein levels, and full NMR lipoprotein subclass profile.

-Genotyping: All genotyping was done at Genetic Core Facility of Center for Nutrition Research Unit, Department of Nutrition Sciences at University of Alabama at Birmingham. RFLP method was employed as previously described using the ABI 310 Genetic Analyzer (Applied Biosystems, Foster City, CA.). The results of 837 patients with a list of 41 variables were analyzed by SAS 9.0.

Conclusions

1. CETP gene variation exerts a pronounced independent effect on HDL-c levels and HDL particle size in T1DM in the DCCT/EDIC cohort.

2. At present, there is no significant association between CETP TaqIB polymorphism and vascular complications.

Discussion

The CETP Taq1B polymorphism exerts a significant effect on HDL-cholesterol levels in Type 1 Diabetes. There is a gene dosing effect such that B2B2 carriers have the highest HDL-C levels, and B1B2 heterozygotes intermediate levels, compared with the lower HDL-c concentrations in B1B1 homozygotes. The increase in HDL-c levels, as a consequence of the CETP B2 allele, is the result of increased concentrations of large cardio-protective HDL particles consistent with the observed increments in mean HDL particle size. While the most prominent effects involved HDL, the B2 allele was also associated with decrements in small VLDL and intermediate LDL particle concentrations, and a decrease in circulating concentrations of apoB. Individuals with B2B2 genotype exhibited a reduction in BMI; however, the effects of CETP gene polymorphism on lipoproteins was independent of BMI, age, gender, DCCT treatment group, and current HbA1c. Despite the independent effects on HDL, there was no association between the CETP polymorphism and measures of carotid wall thickness, retinopathy, and nephropathy. It remains possible that the CETP gene could contribute significantly to vascular disease risk in Type 1 Diabetes over time through its effects on HDL cholesterol.