Cholesteryl Ester Transfer Protein Gene Polymorphism Is a Determinant of HDL Cholesterol and of the Lipoprotein Response to a Lipid-Lowering Diet in Type 1 Diabetes

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The *Taq*IB cholesteryl ester transfer protein (CETP) gene polymorphism (*B1B2*) is a determinant of HDL cholesterol in nondiabetic populations. Remarkably, this gene effect appears to be modified by environmental factors. We evaluated the effect of this polymorphism on HDL cholesterol levels and on the lipoprotein response to a linoleic acid–enriched, low-cholesterol diet in patients with type 1 diabetes. In 44 consecutive type 1 diabetic patients (35 men), CETP polymorphism, apolipoprotein (apo) E genotype, serum lipoproteins, serum CETP activity (measured with an exogenous substrate assay, $n = 30$), clinical variables, and a diet history were documented. The 1-year response to diet was assessed in 14 type 1 diabetic patients, including 6 *B1B1* and 6 *B1B2* individuals. HDL cholesterol was higher in 10 *B2B2* than in 14 *B1B1* homozygotes (1.63 ± 0.38 vs. 1.24 ± 0.23 mmol/l, $P < 0.01$). HDL cholesterol, adjusted for triglycerides and smoking, was 0.19 mmol/l higher for each *B2* allele present. CETP activity levels were not significantly different between CETP genotypes. Multiple regression analysis showed that VLDL + LDL cholesterol was associated with dietary polyunsaturated:saturated fatty acids ratio ($P < 0.02$) and total fat intake ($P < 0.05$) in the *B1B1* homozygotes only and tended to be related to the presence of the apo E_4 allele ($P < 0.10$). In response to diet, VLDL + LDL cholesterol fell ($P < 0.05$) and HDL cholesterol remained unchanged in 6 *B1B1* homozygotes. In contrast, VLDL + LDL cholesterol was unaltered and HDL cholesterol decreased ($P < 0.05$) in 6 *B1B2* heterozygotes ($P < 0.05$ for difference in change in VLDL + LDL/HDL cholesterol ratio). This difference in response was unrelated to the apo E genotype. Thus, the *Taq*IB CETP gene polymorphism is a strong determinant of HDL cholesterol in type 1 diabetes. This gene effect is unlikely to be explained by a major influence on the serum level of CETP activity, as an indirect measure of CETP mass. Our preliminary data suggest that this polymorphism may be a marker of the lipoprotein response to dietary intervention. *Diabetes* 46:2082–2087, 1997

Epidemiological studies have demonstrated a strong inverse relationship between serum HDL cholesterol and risk of coronary heart disease (1). Genetic, metabolic, and environmental factors influence HDL cholesterol level (2,3).

In addition to other factors, the cholesteryl ester transfer protein (CETP), which catalyzes the transfer of cholesteryl ester from HDL to VLDL and LDL, plays a key role in HDL metabolism (2–4). HDL cholesterol is elevated in subjects with structural CETP gene mutations that cause partial or complete CETP deficiency (3,5). Conversely, HDL cholesterol is lowered in transgenic mice that express human CETP (3,6). Recently, the *B1B2* polymorphism of intron 1 of the CETP gene (presence or absence of a *Taq*IB restriction site) was shown to be a determinant of HDL cholesterol in most (7–9), but not all (10), surveys. Remarkably, this gene effect appears to be relatively strong in women and relatively weak in smokers and obese subjects (7,11,12). Furthermore, this CETP gene polymorphism may act synergistically with alcohol in changing HDL cholesterol (13), although its effect seems to be abolished in alcohol abusers (14). Taken together, these findings suggest that the influence of the CETP gene polymorphism on HDL cholesterol is modified by environmental factors.

In the present study, we documented the effect of the CETP gene polymorphism on HDL cholesterol levels in type 1 diabetic patients. In addition, we evaluated whether this polymorphism is a determinant of the lipoprotein response to a linoleic acid–enriched, low-cholesterol diet in type 1 diabetes.

RESEARCH DESIGN AND METHODS

Subjects and study design. Forty-four consecutive type 1 diabetic patients were recruited from the outpatient clinic. All participants had ketosis-prone diabetes, and their age at onset was <35 years. Insulin dependence was confirmed in all of them by a postglucagon C-peptide level <0.2 nmol/l. Exclusion criteria were ketoacidosis within 3 months before the study, pregnancy, diabetic nephropathy (overnight urinary albumin excretion [UAE] persistently >200 µg/min), liver disease, untreated thyroid disorders, and a history of familial hyperlipidemia. Lipid-lowering drugs were withheld for 6 weeks before the study. Antihypertensive medication was continued. In addition, we reevaluated 14 of 16 patients who had pre-

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Received for publication 7 May 1997 and accepted in revised form 21 August 1997.

apo, apolipoprotein; CETP, cholesteryl ester transfer protein; PCR, polymerase chain reaction; UAE, urinary albumin excretion.

TABLE 1
Clinical characteristics, diet composition, and lipoprotein parameters in 44 IDDM patients according to CETP genotype

	B2B2	*B1B2*	*B1B1*
n	10	20	14
Age (years)	43 ± 13	39 ± 11	51 ± 7
Diabetes duration (years)	23 ± 8	23 ± 11	26 ± 12
Men/women	6/4	17/3	12/2
BMI (kg/m^2)	24.0 ± 2.9	24.3 ± 2.8	25.6 ± 2.3
Smokers	2	12	7
Cardiovascular disease	3	2	2
Microalbuminuria	6	11	9
UAE excretion rate (μg/min)	25 (10–173)	25 (11–113)	27 (13–200)
Hypertension	3	1	3
GHb (%)	8.0 ± 1.8	7.5 ± 1.1	7.2 ± 1.1
Total fat (E%)	39.5 ± 8.3	39.9 ± 5.5	41.2 ± 5.9
Linoleic acid (E%)	5.4 ± 3.2	7.2 ± 3.3	7.4 ± 3.5
Polyunsaturated:saturated fatty acids ratio	0.44 ± 0.25	0.59 ± 0.29	0.60 ± 0.20
Cholesterol (mg/day)	270 ± 127	296 ± 115	248 ± 71
Alcohol drinkers	3	8	5

Data are means ± SD, median (range), or numbers of patients. The *B1B2* CETP gene polymorphism was detected by the presence (*B1*) or absence (*B2*) of a *Taq*IB restriction site. Microalbuminuria is defined as overnight UAE persistently between 20 and 200 μg/min. Hypertension is defined as blood pressure >160/95 mmHg or antihypertensive treatment. E%, energy %.

viously participated in a diet study and were randomized to increase their dietary polyunsaturated:saturated fatty acids ratio to 1.0 by replacement of saturated fat with linoleic acid (15). Venous blood was obtained after a 10-h fast. To get equally spaced time intervals, the lipoprotein parameters at baseline and at 4, 8, and 12 months after dietary intervention were used for the present analysis. Nutrient intake was documented by a dietitian using the recall technique (16). Diet composition was estimated with a computer-assisted nutrient database (17). In the dietary intervention trial, butter and saturated margarines were replaced by polyunsaturated margarines, and saturated fat from meat and dairy products was restricted (15). Cholesterol was reduced, but total fat intake was unchanged. The diets were isocaloric. At each visit, further dietary advice was provided, and a full dietary history was again obtained after 1 year. The studies were approved by the local medical ethics committee, and all participants gave informed consent.

Laboratory methods. Lipids were measured in whole serum and in the HDL cholesterol supernatant fraction after precipitation of apolipoprotein (apo) B–containing lipoproteins with sodium phosphotungstate and $MgCl_2$ (15). Cholesterol and triglycerides were measured enzymatically. VLDL + LDL cholesterol was calculated as the difference between total and HDL cholesterol. Apos AI and B were assayed by immunoturbidimetry with kits purchased from Boehringer Mannheim (Almere, The Netherlands, cat. no. 726478 and 726494, respectively). Serum for measurement of CETP activity was stored at –20°C and assayed within 6 weeks. CETP activity was measured with excess exogenous substrates in an isotope system that detects the bidirectional transfer of [1-^{14}C]oleate-cholesteryl ester between labeled LDL and unlabeled HDL, as described previously (18). The serum level of CETP activity obtained by this method (expressed in nanomoles cholesteryl ester transfer per milliliter per hour) correlates well with CETP mass (19).

The *B1B2* CETP gene polymorphism and the apo E genotype were analyzed as described previously (13,20). Venous blood (300 μl) was used for DNA extraction. Erythrocytes were removed by ammonium chloride treatment. Phenol/chloroform extraction was performed to extract genomic DNA from leukocytes. Polymerase chain reaction (PCR) mixtures contained 500 ng of template DNA, 50 pmol of the primers, deoxy nucleotide triphosphates (200 μmol/l), 2.5 U Taq polymerase (Pharmacia, Uppsala, Sweden), and 5 μl of Taq Pol buffer in a total volume of 50 μl. PCR was carried out using a Perkin Elmer Gene Amp PCR System 2400 (Foster City, CA). Primers, encompassing a 535–base pair DNA fragment containing a polymorphic site in intron 1 of the CETP gene, were according to Fumeron et al. (13). Primers for apo E gene amplification spanned a 244–base pair DNA fragment, including amino acid positions 112 and 158 (20). For CETP gene

TABLE 2
Serum (apo)lipoproteins, CETP activity, and apo E genotype in 44 type 1 diabetic patients according to CETP genotype

	B2B2	*B1B2*	*B1B1*
n	10	20	14
Serum cholesterol (mmol/l)	6.23 ± 1.87	6.42 ± 1.21	5.80 ± 1.18
VLDL + LDL cholesterol (mmol/l)	4.60 ± 0.85	5.02 ± 1.18	4.56 ± 1.28
HDL cholesterol (mmol/l)	1.63 ± 0.38*	1.39 ± 0.28	1.24 ± 0.23
Serum triglycerides (mmol/l)	1.15 ± 0.78	1.55 ± 1.24	1.17 ± 0.82
Serum apo AI (g/l)	1.89 ± 0.21†	1.74 ± 0.28	1.68 ± 0.24
Serum apo B (g/l)	0.87 ± 0.21	0.95 ± 0.24	0.86 ± 0.26
Serum CETP activity (nmol · ml^{-1} · h^{-1})	136 ± 46 (*n* = 6)	136 ± 37 (*n* = 16)	148 ± 49 (*n* = 8)
Apo E genotype‡			
E_2/E_3	—	1	1
E_2/E_4	—	1	—
E_3/E_3	7	8	12
E_3/E_4	3	8	1
E_4/E_4	—	2	—

Data are means ± SD. The *B1B2* CETP gene polymorphism was detected by the presence (*B1*) or absence (*B2*) of a *Taq*IB restriction site. *P < 0.01 and †P < 0.05 from *B1B1*; ‡P < 0.02 for difference in frequency of apo E_4 allele carriers between *B1B2* and *B1B1* subjects.

polymorphism, 30 cycles were performed using the following cycle times and temperatures: 30 s at 94°C, 30 s at 60°C, and 60 s at 72°C. To detect the *B1B2* polymorphism (the *B1* allele contains the restriction site, and upon restriction, 361– and 174–base pair products are obtained), 15-µl aliquots of PCR products were digested with 8 U of *Taq*IB (Pharmacia) for 2 h at 65°C. For apo E genotyping, 30 cycles of denaturation, annealing, and extension for 60 s at 95°C, 60 s at 60°C, and 120 s at 72°C, respectively, were used. *Hha* I (5 U) (Pharmacia) was then added, and the PCR products were digested for at least 3 h at 37°C. The apo E_2 (112 cys, 158 cys), E_3 (112 cys, 158 arg), and E_4 (112 arg, 158 arg) alleles are detected as 91– and 81–; as 91–, 48–, and 33–; and as 72–, 48–, and 33–base pair bands, respectively. Restriction fragments were separated by agarose (CETP gene polymorphism) or by polyacrylamide (apo E genotype) gel electrophoresis with ethidium bromide staining, followed by visualization on an ultraviolet transilluminator. GHb was measured by colorimetry (15).

Statistical analysis. Data are given in means ± SD or in medians (ranges). Statistical analysis included Kruskal-Wallis analysis of variance, Mann-Whitney *U* test, and χ^2 analysis to compare variables between groups. Duncan's method was used to correct for multiple comparisons. The (apo)lipoprotein responses to dietary intervention were evaluated by comparing the mean changes at 4, 8, and 12 months to baseline by paired Wilcoxon's test. Between-group differences in changes were compared by Mann-Whitney *U* test. Multiple regression analysis was used to assess the independent contribution of variables. A two-sided *P* value < 0.05 was considered significant.

RESULTS

Of the 44 type 1 diabetic patients, 23% had *B2B2*, 46% had *B1B2*, and 32% had *B1B1* CETP genotype (Table 1), resulting in a *B2* allele frequency of 46%. The genotype distribution was in Hardy-Weinberg equilibrium ($\chi^2_{df2} = 0.15$, NS). Furthermore, the genotype distribution was not different from that reported in 1,182 healthy subjects ($\chi^2_{df2} = 0.84$, NS) in whom the *B2* allele frequency was 42% (9,11,13). When the diabetic patients were divided according to CETP genotype, no significant differences in clinical parameters, gender distribution, GHb levels, or UAE were found (all $P > 0.15$) (Table 1). Cardiovascular drugs were used in three *B2B2*, two *B1B2*, and three *B1B1* subjects. Oral contraceptives were used in one *B2B2* and in one *B1B1* woman. Levothyroxine was used in one patient from each group. Lipid-lowering drugs were initially used in two *B2B2*, four *B1B2*, and two *B1B1* subjects. No between-group differences in dietary fat composition or in alcohol use were noted (Table 1).

In the whole group, HDL cholesterol and serum apo AI levels were higher in *B2B2* compared with *B1B1* homozygotes (Table 2, Fig. 1*A*). HDL cholesterol and serum apo AI levels were also higher in *B2B2* compared with *B1B1* homozygote men (1.66 ± 0.33 vs. 1.19 ± 0.20 mmol/l and 1.95 ± 0.21 vs. 1.62 ± 0.21 g/l, respectively, $P < 0.01$ for both). No differences in other lipoprotein parameters were observed among CETP genotype groups. Serum CETP activity levels were, on average, 9% higher in the *B1B1* compared with the *B2B2* subjects, but this difference was not significant. More apo E_4 allele carriers were present among the *B1B2* heterozygotes than among the *B1B1* homozygotes ($\chi^2_{df1} = 6.53$, $P < 0.02$), but there was no difference in apo E genotype distribution between the *B2B2* and *B1B1* homozygotes. Multiple regression analysis (multiple $r = 0.58$) demonstrated that the HDL cholesterol level was independently associated with the CETP genotype ($P = 0.009$), serum triglycerides (logarithmically transformed, $P = 0.035$), and the number of cigarettes smoked daily ($P = 0.044$), without significant effects of other clinical parameters, including age and gender, dietary factors and alcohol intake, as well as the presence of the apo E_4 allele (all $P > 0.15$). After adjustment for serum triglycerides and the number of cigarettes smoked daily, HDL cholesterol was 0.19 mmol/l higher for each *B2* allele present. Serum apo AI and CETP activity were not independently associated with CETP gene polymorphism ($P > 0.20$).

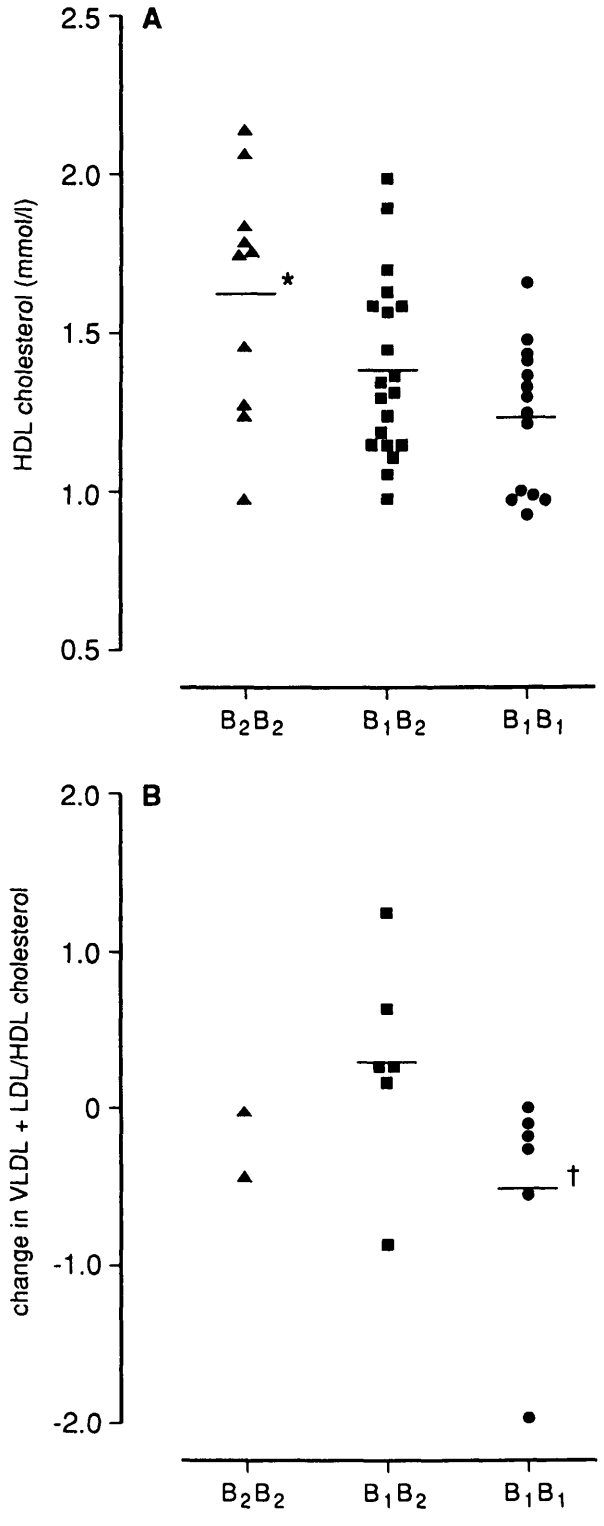

FIG. 1. Effect of CETP gene polymorphism on HDL cholesterol (*A*) and VLDL + LDL/HDL cholesterol response to linoleic acid–enriched diet during 1 year (*B*) in type 1 diabetic patients. *B1B2* CETP gene polymorphism detected by presence (*B1*) or absence (*B2*) of a *Taq*IB restriction site. *$P < 0.01$ vs. *B1B1*; †$P < 0.05$ vs. *B1B2*.

Multiple regression analysis was performed to evaluate possible interactions of CETP genotype, apo E genotype,

TABLE 3
Clinical characteristics, diet composition, and influence of CETP genotype on lipoproteins in response to a linoleic acid–enriched diet in 14 type 1 diabetic patients

	B2B2	*B1B2*	*B1B1*
n	2	6	6
Age (years)	22–60	39 ± 9	47 ± 8
Men/women	1/1	5/1	5/1
BMI (kg/m^2)			
Baseline	22.5–25.5	23.3 ± 2.9	24.9 ± 2.5
1 year	23.1–25.9	23.6 ± 2.9*	25.1 ± 2.5
GHb during study (%)			
Baseline	8.0–8.9	8.0 ± 0.9	8.3 ± 1.1
1 year	6.9–8.3	8.2 ± 1.0	8.4 ± 1.0
Total fat (E%)			
Baseline	34.9–47.8	36.4 ± 8.3	40.0 ± 5.1
1 year	32.8–46.5	37.0 ± 8.1	41.3 ± 4.7
Linoleic acid (E%)			
Baseline	2.5–5.6	7.3 ± 4.2	7.3 ± 3.9
1 year	8.4–15.5	11.0 ± 3.5*	12.8 ± 2.1*
Polyunsaturated:saturated fatty acids ratio			
Baseline	0.19–0.54	0.65 ± 0.36	0.60 ± 0.35
1 year	0.74–1.00	1.00 ± 0.21*	1.03 ± 0.19*
Cholesterol (mg/day)			
Baseline	162–541	269 ± 115	278 ± 54
1 year	157–324	191 ± 86*	181 ± 29*
Serum cholesterol (mmol/l)			
Baseline	5.14–6.31	6.02 ± 1.47	5.98 ± 1.43
1 year	5.65–5.82	5.69 ± 0.86	5.66 ± 1.38*
VLDL + LDL cholesterol (mmol/l)			
Baseline	3.35–4.85	4.63 ± 1.37	4.75 ± 1.65
1 year	3.66–4.30	4.42 ± 0.82	4.34 ± 1.55*
HDL cholesterol (mmol/l)			
Baseline	1.46–1.79	1.38 ± 0.26	1.24 ± 0.26
1 year	1.51–1.99	1.27 ± 0.26*	1.32 ± 0.27
VLDL + LDL/HDL cholesterol			
Baseline	1.87–3.32	3.41 ± 0.96	4.19 ± 2.17
1 year	1.83–2.87	3.68 ± 1.13	3.67 ± 1.78*†
Serum triglycerides (mmol/l)			
Baseline	0.45–1.55	1.73 ± 2.16	1.30 ± 1.15
1 year	0.45–1.34	1.45 ± 0.76	1.21 ± 1.03
Serum apo AI (g/l)			
Baseline	1.96–1.62	1.69 ± 0.38	1.65 ± 0.14
1 year	2.06–2.13	1.68 ± 0.28	1.75 ± 0.17
Serum apo B (g/l)			
Baseline	0.69–1.01	0.92 ± 0.32	0.93 ± 0.35
1 year	0.67–0.89	0.87 ± 0.23	0.80 ± 0.26*
Apo E genotype			
E_3/E_3	2	3	5
E_3/E_4	–	3	1

Data are means ± SD or range. The *B1B2* CETP gene polymorphism was detected by the presence (*B1*) or absence (*B2*) of a *Taq*IB restriction site. All 1-year values except for total fat, linoleic acid, polyunsaturated:saturated fatty acids ratio, and cholesterol intake are based on averaged (apo)lipoprotein levels during 1 year of dietary intervention. *P < 0.05 from baseline; †P < 0.05 from change in *B1B2*.

and dietary factors with VLDL + LDL cholesterol levels. This analysis (multiple r = 0.46) showed that VLDL + LDL cholesterol was positively associated with the interactions of *B1* homozygosity, with a low dietary polyunsaturated:saturated fatty acids ratio (P = 0.015) and with a high total fat intake (P = 0.023), and tended to be positively related to the presence of the apo E_4 allele (P = 0.092). Thus, this observation raised the possibility that *B1B1* homozygotes were particularly responsive to a cholesterol-lowering diet.

This finding prompted us to evaluate the influence of CETP genotype on lipoprotein changes induced by a linoleic acid–enriched, low-cholesterol diet (15). Of 14 type 1 diabetic patients so studied, 6 had *B1B1* and 6 had *B1B2* CETP genotype (Table 3). No differences in age, gender distribution,

GHb, or diet composition before or during the study were found between the *B1B1* and *B1B2* subjects. BMI increased slightly in the *B1B2* heterozygotes, but its change was not significantly different from the change in the *B1B1* homozygotes. Insulin dose was 59 ± 21 and 68 ± 10 U/day at baseline (NS) in the *B1B1* and *B1B2* subjects, respectively, and was 55 ± 19 and 69 ± 12 U/day at follow-up (NS). UAE was not different in the groups at baseline or at follow-up (data not shown). Three Apo E_3/E_4 carriers were present in the *B1B2* group, and one was present in the *B1B1* group. Baseline serum (apo)lipoprotein levels were not different between the groups (Table 3). In *B1B1* patients, serum cholesterol, VLDL + LDL cholesterol, and apo B decreased, whereas HDL cholesterol remained unchanged during diet intervention (Table 3). In contrast, VLDL + LDL cholesterol was essentially unaltered and HDL cholesterol decreased in *B1B2* patients (Table 3). Consequently, the VLDL + LDL/HDL cholesterol ratio fell in *B1B1* and was unchanged in *B1B2* patients ($P < 0.05$ for difference in change, Table 3, Fig. 1*B*). Serum triglycerides remained unaltered in both the *B1B1* and *B1B2* groups, indicating that the influence of the CETP genotype on the lipoprotein cholesterol response to diet was not attributable to a change in triglycerides. Serum apo AI levels did not significantly change in the *B1B1* and the *B1B2* subjects. In the 12 *B1B1* and *B1B2* patients, multiple regression analysis (multiple $r = 0.67$) showed that the difference in change in the VLDL + LDL/HDL cholesterol ratio was independently related to the CETP genotype ($P = 0.026$) and was not influenced by the interaction between the CETP genotype and the apo E genotype, or changes in BMI, GHb, or insulin dose ($P > 0.15$ for all). The lipoprotein response in two *B2B2* patients was within the range of the other groups.

DISCUSSION

This study demonstrates that the *Taq*IB polymorphism of the CETP gene is a strong and independent determinant of HDL cholesterol in type 1 diabetes. After adjustment for serum triglycerides and smoking, the difference in HDL cholesterol between *B2B2* and *B1B1* homozygotes was calculated to be 0.38 mmol/l. This is considerably larger than a maximal difference of ~0.25 mmol/l found thus far in nondiabetic populations (9,11,12). Thus, the influence of the CETP genotype on HDL cholesterol may be accentuated in type 1 diabetes. In the presently studied type 1 diabetic patients, the *B1B2* allele frequency was similar to that previously reported in healthy subjects (9,11,13), indicating that the normal to high levels of HDL cholesterol observed in type 1 diabetic subjects (21,22) are unlikely to be explained by an altered CETP gene allele distribution. The concentration and composition of HDL is regulated by a number of factors (2–4,22), and a higher level of HDL cholesterol in insulin-treated type 1 diabetic patients is related to an increased lipoprotein lipase activity in postheparin plasma (21).

Interestingly, multiple regression analysis suggested that VLDL + LDL cholesterol levels were higher in *B1B1* type 1 diabetic patients whose dietary polyunsaturated:saturated fatty acid ratio was low and whose fat intake was high. In keeping with this observation, *B1B1* homozygotes had a more favorable lipoprotein response to a linoleic acid–enriched, low-cholesterol diet than *B1B2* heterozygotes. Therefore, our data suggest that the *Taq*IB CETP gene polymorphism may be a determinant of the lipoprotein response to a cholesterol-lowering diet. This finding needs to be confirmed in larger groups, including relatively more *B2B2* individuals. It is unknown at present whether these results can be extrapolated to nondiabetic subjects.

Substitution of saturated fat with linoleic acid decreases serum total and LDL cholesterol, and a low-cholesterol diet causes comparable lipoprotein changes (23,24). HDL also tends to fall after both dietary manipulations (23,24). The well-known variability in lipoprotein response to dietary intervention can be explained, in part, by the apo E genotype. Serum cholesterol is higher in healthy subjects and type 1 diabetic patients with the apo E_4 allele compared with apo E_3 homozygotes (25,26). In accordance, a positive trend between the presence of the apo E_4 allele and VLDL + LDL cholesterol was found in the present study. This may be due to a more efficient dietary cholesterol absorption and a slower LDL apo B removal associated with the apo E_4 allele (27,28). Consequently, the fall in LDL cholesterol in response to a low-fat, low-cholesterol, polyunsaturated fatty acids–enriched diet was found to be enhanced in apo E_4 allele carriers (28,29). The presently observed influence of the CETP genotype on diet-induced lipoprotein changes is unlikely to be caused by an overrepresentation of apo E_3/E_4 allele carriers in the *B1B2* group. First, theoretically, this would have resulted in a somewhat more pronounced fall in VLDL + LDL cholesterol, whereas the opposite was observed. Second, multiple regression analysis revealed that the influence of the CETP genotype on the lipoprotein response was indeed not confounded by variation in the apo E genotype.

The mechanisms responsible for the relationship between the CETP gene polymorphism, HDL cholesterol levels, and the lipoprotein response to diet are not well understood. Importantly, the process of cholesteryl ester transfer, whereby cholesteryl ester is transferred from HDL to VLDL and LDL, is governed not only by the serum CETP level but also by the chemical composition of the lipoproteins involved and possibly by substrate specificity (3,4,11). The *B1B1* genotype is associated with a higher serum CETP level in several (8,9,12,13), but not all, studies (11). Serum CETP activity levels were slightly but not significantly higher in *B1B1* than in *B2B2* homozygotes in the present study. Thus, the *B1B1* genotype could be associated with an accelerated transfer of cholesteryl esters out of HDL, which is, in part, unrelated to a higher serum CETP level per se (13). Because the rate of cholesteryl ester transfer out of HDL is increased in normotriglyceridemic type 1 diabetic patients (30), it is tempting to speculate that this provides a clue to the larger effect of the CETP polymorphism on HDL cholesterol in type 1 diabetic compared with nondiabetic subjects. Serum CETP activity levels are increased during cholesterol feeding (3,24), and changes in VLDL + LDL cholesterol after a polyunsaturated fatty acids–enriched diet are well-related to changes in CETP activity (31). A linoleic acid–enriched diet, with concomitant cholesterol lowering, is likely to inhibit cholesteryl ester transfer, which could contribute to a decrease in the VLDL + LDL/HDL cholesterol ratio (32). Such a dietary effect may be most pronounced in *B1B1* homozygotes, if their cholesteryl ester transfer out of HDL is indeed highest before intervention.

In conclusion, the present study shows a marked association between the *Taq*IB CETP gene polymorphism and HDL cholesterol in type 1 diabetes. Our preliminary data suggest that this polymorphism may be a new marker of the lipopro-

tein response to dietary treatment in this patient category. Prospective studies are warranted to demonstrate whether the CETP gene polymorphism is related to cardiovascular disease in type 1 diabetic patients.

ACKNOWLEDGMENTS

B.J. Beusekamp performed diet analyses. The technical assistance of Dr. J. Brouwer and of E. van Ramshorst is appreciated.

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