Available online at www.sciencedirect.com
ScienceDirect
Metabolism Clinical and Experimental 58 (2009) 74 – 79
Metabolism
Clinical and Experimental
www.metabolismjournal.com

Relationships between common polymorphisms of adenosine triphosphate–binding cassette transporter A1 and high-density lipoprotein cholesterol and coronary heart disease in a population with type 2 diabetes mellitus

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Received 22 April 2008; accepted 28 August 2008

Abstract

Patients with type 2 diabetes mellitus (T2D) have a high coronary risk partly because of low levels of high-density lipoprotein-cholesterol (HDL-C). The adenosine triphosphate–binding cassette transporter A1 (ABCA1) plays a key role in HDL metabolism. We studied the association of common single nucleotide polymorphisms (SNPs) in the *ABCA1* gene with HDL-C levels and coronary risk in a cohort of subjects with T2D. We studied 5 SNPs: +69C>T, +378G>C, R219K, I883M, and R1587K. The C allele of +378G>C was significantly associated with lower HDL-C concentrations (P = .04); and the M allele of I883M, with higher HDL-C concentrations (P = .03). No significant association was found between these SNPs and the incidence of new coronary events. Nevertheless, cross-sectional data on entry showed that the frequency of K219 was lower in patients with previous coronary heart disease (angina pectoris and/or myocardial infarction) (odds ratio, OR [95% confidence interval, CI] = 0.80 [0.65-0.98], P = .03, after adjustment for multiple risk factors other than HDL-C). The frequency of K1587 was higher in patients with angina pectoris (OR [95% CI] = 1.27 [1.01-1.58], P = .04, after multiple adjustment). The TT genotype of the C69T SNP was less frequent in subjects with prior myocardial infarction (OR [95% CI] = 0.28 [0.13-0.61], P = .001, after multiple adjustment). These associations persisted after further adjustment for HDL-C levels. In conclusion, common genetic variations of *ABCA1* had a moderate influence on HDL-C levels and/or coronary heart disease in patients with T2D. These 2 effects were independent.

1. Introduction

Patients with type 2 diabetes mellitus (T2D) have a high risk of coronary heart disease (CHD), partly attributable to low concentrations of high-density lipoprotein cholesterol (HDL-C), a common finding in patients with insulin resistance [1,2]. The adenosine triphosphate–binding cassette transporter A1 (*ABCA1*) gene encodes a key protein regulating the efflux of lipids from peripheral cells to the extracellular space [3]. Defects in the *ABCA1* gene cause rare forms of genetic HDL deficiencies, such as Tangier disease and familial hypoalphalipoproteinemia [4]. Many common genetic variations in *ABCA1* have been reported to be associated with variations in serum lipid levels, HDL-C levels in particular, and may also be associated with coronary artery disease risk [5]. Moreover, the ABCA1 transporter is thought to play a role at the β-cell level; and *ABCA1* genetic variability has been tested with respect to T2D risk [6-8]. *ABCA1* gene variability probably affects the lipid profile

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doi:10.1016/j.metabol.2008.08.009

and cardiovascular risk of T2D patients; however, to our knowledge, no study has addressed this issue. We assessed the impact of 5 common *ABCA1* single nucleotide polymorphisms (SNPs) on HDL-C levels and CHD in a large cohort of patients with T2D: the French participants in the Noninsulin-Dependent Diabetes, Hypertension, Microalbuminuria or Proteinuria, Cardiovascular Events, and Ramipril (DIABHYCAR) study [9]. We chose to study 2 noncoding SNPs located in 5′ untranslated regions—+69C>T and +378G>C—and 3 nonsynonymous SNPs—R219K, I883M, and R1587K—based on their potential regulatory role or their influence on lipid levels or CHD, as described in other population studies [5].

2. Patients and methods

2.1. Patients

The design and results of the DIABHYCAR study have been reported elsewhere [9]. The DIABHYCAR study was a multicentric, randomized, double-blind, parallel-group trial comparing cardiovascular and renal outcomes between subjects taking a low-dose ramipril (1.25 mg/d) in addition to their usual treatment and those taking placebo in addition to their usual treatment. The participants were men or women with T2D and high urinary albumin excretion (≥ 20 mg/L, at 2 consecutive tests), aged at least 50 years, and with serum creatinine concentration not exceeding 150 μmol/L. The investigators examined the participants every 6 months for at least 3 years. The mean duration of follow-up was 4 years. The low dose of ramipril tested proved ineffective [9]. We studied only the French participants in this study (3129 of the 4912 participants). The study design was approved by the Angers University Ethics Committee. All participants provided written informed consent.

For the cross-sectional analysis of CHD, 482 subjects with a personal history of myocardial infarction (MI) and/or angina pectoris were considered (Table 1). In this prospective analysis, MI, whether fatal or nonfatal, and sudden death occurring during the follow-up were considered as incident coronary events. Sudden death was defined as death occurring instantaneously or within 1 hour of the onset of new cardiac symptoms (cardiac insufficiency, arrhythmia, and other cardiovascular symptoms), or nonwitnessed deaths in which the body of the deceased was found and no clear cause of death could be identified. During follow-up, 95 subjects had MI, 137 died (sudden death), and 223 were classified as incident CHD cases (MI and/or sudden death). The characteristics of the patients are presented as a function of personal coronary history and coronary event incidence (Table 1).

2.2. Genotyping

The +69C>T (rs1800977), +378G>C (rs1800978), and R219K (+1051G>A, rs2230806) SNPs were genotyped using a polymerase chain reaction–molecular beacon technique [10]. The I883M (rs4149313) and the R1587K (rs2230808) SNPs were genotyped using Taqman LNA probes (Applied

Table 1
Baseline characteristics of subjects in the DIABHYCAR study as a function of the prevalence and incidence of CHD events

	Prevalent CHD (at entry)		Incident CHD (during follow-up)	
	Without	With	Without	With
	n = 2647	n = 482	n = 2906	n = 223
% Male	71.8	79.7***	72.8	75.8
Age (y)	65.2 ± 8.3	68.0 ± 8.0***	65.4 ± 8.2	68.6 ± 9.1***
BMI (kg/m^2)	29.4 ± 4.7	29.1 ± 4.4	29.4 ± 4.6	28.9 ± 4.6
% Smokers	15.1	10.4**	14.5	12.6
HbA_{1c} (%)	7.87 ± 1.79	7.86 ± 1.64	7.85 ± 1.76	8.06 ± 1.83
Diabetes duration (y)	10.0 ± 7.6	11.8 ± 8.1***	10.2 ± 7.7	11.5 ± 8.1**
SBP (mm Hg)	145.0 ± 14.1	144.9 ± 14.0	144.8 ± 14.1	147.7 ± 13.2**
DBP (mm Hg)	82.2 ± 8.4	81.7 ± 8.7	82.1 ± 8.5	82.7 ± 8.0
% Hypertension	54.4	66.0***	55.5	65.0*
Total cholesterol (mmol/L)	5.79 ± 1.08	5.83 ± 1.06	5.78 ± 1.06	5.98 ± 1.06**
LDL-C (mmol/L)	3.52 ± 0.89	3.57 ± 0.86	3.51 ± 0.88	3.67 ± 0.94*
HDL-C (mmol/L)	1.32 ± 0.36	1.28 ± 0.34*	1.32 ± 0.36	1.25 ± 0.29**
TG (mmol/L)	1.89 (1.85-1.93)	2.00 (1.91-2.10)*	1.90 (1.86-1.93)	2.03 (1.90-2.17)*
Serum creatinine (μmol/L)	86.5 (85.7-87.2)	90.1 (88.2-92.0)***	86.7 (86.0-87.4)	91.9 (89.4-94.5)***
Urinary albumin (mg/L)	94.8 (90.9-99.0)	118.7 (106.5-132.4)***	95.8 (91.9-99.8)	135.6 (113.7–161.7)***
Serum CRP (mg/L)	3.12 (2.99-3.25)	3.33 (3.02-3.67)	3.11 (2.99-3.24)	3.76 (3.27-4.34)**
% Previous MI	–	–	5.0	11.7***
% Ramipril	–	–	49.6	49.5
% Lipid-lowering treatment	33.8	39.2*	34.6	34.5

Data are presented as mean ± SD, geometric mean (95 % CI), or percentages, as appropriate. Prevalent CHD = MI or angina pectoris; "with" vs "without": *$P \leq .05$, **$P \leq .01$, and ***$P \leq .001$ (by analysis of variance or χ^2); incident CHD = MI or sudden death; "with" vs "without": *$P \leq .05$, **$P \leq .01$, and ***$P \leq .001$ (by analysis of variance or χ^2). SBP indicates systolic blood pressure; DBP, diastolic blood pressure; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides; CRP, C-reactive protein.

Table 2
Sequences of primers and probes used for genotyping *ABCA1* SNPs

SNP	Primers (5′-3′)	Allele-specific probes (5′-3′)
+69C>T (rs1800977) [a]	U: GAGGAGGGAGAGCACAGG	Fam-GCGACAACTAGTCCCGGCAAAAGTCGC-dabcyl
	L: CTCACTCTCGCTCGCAATTA	Tamra-GCGACAACTAGTCTCGGCAAAAGTCGC-dabcyl
+378G>C (rs1800978) [a]	U: CCTGCTGTGAGCTCTGG	Fam-GCGACACGCTGGGGGTGCTGGCGTCGC-dabcyl
	L: AGGTTCTTCCACAGCAGCA	Tamra-GCGACACGCTGGGCGTGCTGGCGTCGC-dabcyl
R219K (rs2230806)[a]	U: GATTCAACTTGGTGACCAAG	Fam-GCGACCCTACCAAAGGAGAAACGTCGC-dabcyl
	L: GAACGAAGTACTCGCTCTGC	Tamra-GCGACCCTACCAAGGGAGAAACGTCGC-dabcyl
I883M (rs4149313)[b]	U: CTACTGGTTTGGCGAGGAAA	Fam-CTTTCTGATATTCTCTTC-Bhq
	L: AGCAGGAGGTCAACAGCACT	Hex-CTTTCTGACATTCTCTTC-Bhq
R1587K (rs2230808)[b]	U: CCCTGCCAACTTTACCATGA	Fam-CATTATTTTTGGTGTCC-Bhq
	L: CGATTTCTCAACAGCTTGGG	Hex-CATTATTTCTGGTGTCC-Bhq

[a] Molecular beacon.
[b] Taqman.

Biosystems, Foster City, CA, USA). All sequences of primers and probes are shown in Table 2. For each SNP, only a few subjects could not be genotyped.

2.3. Statistical analysis

The association between *ABCA1* SNP genotypes and HDL-C levels was assessed by multiple linear regression, with genotypes coded (0, 1, 2) according to the number of minor alleles, with age, sex, body mass index (BMI), hemoglobin A_{1c} (HbA_{1c}), smoking, and the use of lipid-lowering drugs included as covariates. All variables with a skewed distribution were Ln transformed before use (BMI, serum triglyceride and creatinine levels, urinary albumin concentration, C-reactive protein levels).

The association between SNPs and cardiovascular events was assessed by χ^2 tests. When a trend was found by χ^2 test ($P < .10$), adjusted odds ratios (ORs) with 95% confidence intervals (95% CIs) for coronary events were calculated by logistic regression. All calculations, except those for haplotype data, were performed with SYSTAT 11 for Windows (Systat Software Inc, San Jose, CA, USA). Haplotype analyses and linkage disequilibrium calculations were performed with THESIAS software (INSERM U525, Paris, France) [11,12].

3. Results

The genotype distributions in the DIABHYCAR study were in Hardy-Weinberg equilibrium. These frequencies were consistent with those reported in white populations, including ours [13].

The M allele of the I883M SNP was associated with higher HDL-C levels (Table 3) ($P < .05$). The minor allele of the +378G>C SNP was associated with lower HDL-C levels ($P < .05$).

No significant association was found between any of the SNPs and the incidence of new coronary events (Table 4). A cross-sectional analysis of data for the patients on entry into the DIABHYCAR study showed that the prevalence of previous CHD depended on R219K genotype (Tables 4 and 5). The K219 allele was less frequent among subjects with a history of CHD than in subjects with no prior CHD events. This lower proportion of K219 carriers was similar in patients with MI and in patients with angina, and corresponded to a 20% lower risk (Table 5). K1587 was more frequent in patients with a history of CHD (Tables 4 and 5), but only as a trend. Nevertheless, the K1587 allele was significantly more frequent among subjects with angina than in subjects with no history of angina (Table 5). Analyses of the MI and angina subgroups showed that the proportion of subjects with MI homozygous for TT69 (recessive model) was about a third that of subjects without MI (Table 5). All these results were not affected by adjustment for HDL-C levels (data not shown).

Pairwise linkage disequilibrium coefficients (D′) were statistically significant but weak. No haplotype association was observed with HDL-C levels, history of CHD, or incidence of CHD (data not shown).

4. Discussion

We show here that common *ABCA1* SNPs are associated with HDL-C levels and with the prevalence of CHD in a T2D population. Nevertheless, no effect on the incidence of new CHD events was detected over a mean 4-year follow-up period.

The influence of +378G>C on HDL-C is consistent with the results we previously obtained for a sample from the French general population in the Data From an Epidemio-

Table 3
High-density lipoprotein cholesterol levels (mean ± SD; in millimoles per liter) as a function of *ABCA1* SNPs

	+69C>T	+378G>C	R219K	I883M	R1587K
0	1.30 ± 0.35	1.32 ± 0.36	1.31 ± 0.36	1.31 ± 0.35	1.33 ± 0.35
1	1.33 ± 0.37	1.30 ± 0.35	1.32 ± 0.35	1.34 ± 0.36	1.31 ± 0.36
2	1.31 ± 0.33	1.26 ± 0.24	1.33 ± 0.36	1.35 ± 0.33	1.29 ± 034
P	.18	.04	.69	.03	.06

Trend test (multiple linear regression) with genotypes coded 0, 1, or 2 according to the number of minor alleles, adjusted for sex, age, BMI, smoking, HbA_{1c}, and lipid-lowering treatment.

Table 4
Genotype distribution (percentage) of *ABCA1* SNPs as a function of CHD, with *P* values for χ^2 tests

		CHD history		MI history		Angina history		Incident CHD	
		Without	With	Without	With	Without	With	Without	With
		n = 2647	n = 482	n = 2957	n = 172	n = 2750	n = 379	n = 2906	n = 223
	CC	41.7	40.5	41.2	47.1	41.9	38.3	41.5	40.8
+69C>T	CT	45.4	48.9	45.7	48.8	45.5	48.7	45.8	47.5
	TT	13.0	10.6	13.1	4.1	12.5	13.0	12.7	11.7
	P	.23		.002		.40		.85	
	GG	75.3	74.6	75.3	73.5	75.2	74.8	75.2	74.9
+378G>C	GC	22.9	23.5	22.8	25.3	23.0	22.8	22.9	23.3
	CC	1.9	1.9	1.9	1.2	1.8	2.4	1.9	1.8
	P	.95		.63		.72		.99	
	RR	50.1	56.1	50.6	56.6	50.4	55.9	51.3	47.3
R219K	RK	41.9	36.3	41.6	33.9	41.6	37.2	40.7	45.9
	KK	8.0	7.6	7.8	9.5	8.1	7.0	8.0	6.8
	P	.05		.15		.13		.29	
	II	70.7	73.0	70.9	72.8	70.8	73.1	70.8	74.2
I883M	IM	26.9	25.2	26.7	25.4	27.0	24.5	26.9	23.1
	MM	2.4	1.9	2.3	1.8	2.3	2.4	2.3	2.7
	P	.56		.82		.61		.44	
	RR	54.8	51.2	54.3	53.5	54.8	50.4	54.0	57.5
R1587K	RK	37.8	42.9	38.4	41.9	38.0	43.2	38.9	34.8
	KK	7.3	5.9	7.3	4.7	7.2	6.4	7.1	7.7
	P	.09		.36		.16		.49	

logical Study on the Insulin-Resistance Syndrome (DESIR) study [13] in which the rare allele was significantly associated with lower HDL-C levels, but mostly in overweight individuals. The lack of association between +69C>T and R219K and HDL (Systat Software Inc, San Jose, CA, USA). levels is also consistent with the data obtained in the DESIR study, as effects were observed in people of normal weight but not in overweight people. The effects of I883M and R1587K on HDL-C levels are consistent with the results of various studies [14-19].

The observed associations with CHD are consistent with the key role of ABCA1 in cholesterol efflux. The T69 allele associated with a lower risk of MI in our study has been shown to increase the transcriptional activity when compared with the C allele in transfection experiments [19] (the +69C>T polymorphism was designated as −14C>T in this previous study). By contrast, in the Regression Growth Evaluation Statin Study (REGRESS) study [20], the T allele was associated with a higher risk of cardiovascular disease. Nevertheless, the frequency of the T allele in the REGRESS study was very different (0.14) from that reported here (0.35) and from that generally found in other populations of different origins (range, 0.32-0.38). This may indicate an artifact or survival bias, as all subjects included in the REGRESS study had a history of coronary artery disease. This is the first time, to our knowledge, that an association between the K1587 allele and CHD has been reported. However, this association was weak and requires confirmation in further studies. Associations between R219K and lipid levels or atherosclerosis progression and atherosclerosis have been widely reported [16,21-25]. The K219 allele is atheroprotective [14,21-23], and this effect may depend on the genetic and/or environmental background [5]. Type 2 diabetes mellitus may interact with this and other polymorphisms.

The SNPs statistically associated with previous CHD were not associated with HDL concentrations and vice versa. The atherogenic or antiatherogenic influence of genetic variation may result from local effects on ABCA1 expression not reflected by the total circulating HDL-C concentration. The cholesterol efflux from cells in the arterial wall that have the potential to transform into foam cells, primarily macrophages,

Table 5
Logistic regression analysis for CHD history (odds ratio with 95% CI)

		CHD	MI	Angina
+69C>T	Codominant	0.98 (0.84-1.14) *P* = .79	0.71 (0.56-0.91) *P* = .006	1.11 (0.94-1.30) *P* = .21
	Recessive (TT vs C+)	0.83 (0.60-1.14) *P* = .26	0.28 (0.13-0.61) *P* = .001	1.10 (0.79-1.53) *P* = .57
R219K	Codominant	0.86 (0.74-1.02) *P* = .08	0.92 (0.71-1.18) *P* = .50	0.86 (0.72-1.03) *P* = .10
	Dominant (K+ vs RR)	0.80 (0.65-0.98) *P* = .03	0.81 (0.59-1.11) *P* = .19	0.82 (0.65-1.02) *P* = .08
R1587K	Dominant (K+ vs RR)	1.22 (1.00-1.49) *P* = .06	1.04 (0.76-1.43) *P* = .79	1.27 (1.01-1.58) *P* = .04

Odds ratios (95% CI) for minor alleles of *ABCA1* SNPs adjusted for age, sex, smoking, BMI, diabetes duration, hypertension, lipid-lowering treatment, serum creatinine, plasma triglyceride, and urinary albumin concentrations. After further adjustment for HDL-C levels, ORs and *P* values remained unchanged.

is directly relevant to atherosclerosis [26]; however, it has been shown that the contribution of monocyte/macrophage ABCA1 to overall plasma HDL-C levels is minimal [27]. The selective inactivation of ABCA1 in the macrophages of hyperlipidemic mice leads to a marked increase in atherosclerosis and foam cell accumulation, demonstrating the antiatherogenic properties of ABCA1, independent of plasma lipid and HDL-C levels [28]. The absence of ABCA1 leads to significant changes in the morphology, properties, and functional activities of macrophages, resulting in increases in cholesterol deposition and the response to chemotactic factors [29]. Our results suggest that the variation in the *ABCA1* gene associated with CHD exerts its effects principally by modifying reverse cholesterol transport in macrophages, as no major change in overall HDL-C concentration was observed. This hypothesis is consistent with the effects of +69C>T. The *ABCA1* gene uses several transcriptional start sites; but only one, the class 2 transcriptional start site, is used in macrophages [30]. The +69C>T SNP is located between a TATA box and this class 2 transcriptional start site. The increase in transcription rate induced by the T69 allele may therefore be particularly efficient in macrophages.

The clinical effects of *ABCA1* SNPs were observed in the cross-sectional analysis, but not in prospective data. This is clearly a limitation of this study and indicates that the influence on CHD risk of these *ABCA1* SNPs may not be of major importance in patients with T2D. However, the subjects in our study had a mean age of 65 years; and the impact of genetic effects is probably stronger in younger individuals [21]. In a recent study, *ABCA1* SNPs influenced the age of symptom onset in patients with coronary artery disease [31]. Otherwise, the duration of follow-up might have been too short in the DIABHYCAR study.

In conclusion, common genetic variations of *ABCA1* influenced HDL-C levels and/or CHD in patients with T2D. These effects appear to be independent.

Acknowledgment

The DIABHYCAR study group included the following: Principal Investigator: Prof M Marre (Bichat Hospital, Paris, France); National Coordinators: Austria: G Schernthaner; Belgium: R Rottiers; Croatia: V Profozic; Czech Republic: J Perusicova; France: M Marre; Germany: J Mann; Greece: S Pappas; Hungary: G Pogatsa; Morocco: J Belkhadir and F Hakkou; the Netherlands: J Jonker; Slovenia: G Schernthaner; Spain: F Hawkins; Switzerland: K Scheidegger; Tunisia: M Gueddiche; Turkey: U Gorpe; United Kingdom: GC Viberti; Steering Committee: F Alhenc-Gelas, JP Boissel, F Cambien, S Etienne, A Girault-Louvel, P Gueret, M Lièvre, J Mann (Vice-Chairman), M Marre, J Ménard, P Passa (Chairman), PF Plouin, D Vasmant, L Vaur (Secretary), GC Viberti, and C Weisselberg; Central Coordinating Center: JP Boissel and M Lièvre; Executive Committee: JP Boissel, V Bost, M Cambien, Y Gallois, N Genes, J Gillet, M Hervé, M Lièvre, M Marre, L Martin, A Perret-Hantzperg, PF Plouin, and L Vaur; Biological Committee: F Alhenc-Gelas (Chairman), F Cambien, A Girault-Louvel (Vice-Chairman), M Lièvre, M Marre, and J Ménard; Central End Point Committee: E Bonnefoy, G Chatellier (Chairman), T Moreau, and L Pinède; Independent Data and Safety Committee: E Eschwege, CE Mogensen, N Victor, and S Weber.

The design, funding, and interpretation of this genetic association analysis were independent of the sponsor of the DIABHYCAR trial (Sanofi-Aventis, Paris, France).

This work was supported by a grant from the *Association Française des Diabétiques*.

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