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Determinants of leukocyte adenosine triphosphate–binding cassette transporter G1 gene expression in type 2 diabetes mellitus

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Abstract

Cellular cholesterol efflux is regulated by cholesterol transporters including adenosine triphosphate–binding cassette transporter A1 (ABCA1), ABCG1, and scavenger receptor class B type I (SR-BI). We have investigated whether the expression of these transporters is affected by type 2 diabetes mellitus and the association with glycemic indexes and oxidized low-density lipoprotein (oxLDL). Messenger RNA of ABCA1, ABCG1, and SR-BI in peripheral monocytes was measured in 30 diabetic patients and 30 matched controls. Plasma oxLDL and advanced glycation end products (AGEs) were assayed by enzyme-linked immunosorbent assay. Cellular cholesterol efflux from monocytes to serum was determined in a subgroup chosen randomly. The expression of ABCG1 was decreased in diabetic patients ($P < .05$), whereas the levels of ABCA1 and SR-BI were comparable between the 2 groups. Fasting glucose, hemoglobin A_{1c}, AGEs, and oxLDL were all significantly increased in diabetic patients. There was an inverse correlation between serum AGEs and ABCG1 ($r = -0.44$, $P < .05$) that remained significant after adjusting for potential confounding factors. No associations between fasting glucose, hemoglobin A_{1c}, plasma lipids, or oxLDL and the expression of ABCG1, ABCA1, or SR-BI were found. Cholesterol efflux from monocytes to standard serum or autologous serum was significantly impaired in diabetic patients, and the reduction in efflux to autologous serum correlated with the expression of ABCG1 ($r = 0.60$, $P < .05$). The expression of ABCG1 in monocytes is reduced in type 2 diabetes mellitus and is partly related to serum AGEs concentration. The reduction in ABCG1 is associated with impairment in cholesterol efflux and may contribute to accelerated foam cell formation in diabetic patients.

1. Introduction

Reverse cholesterol transport (RCT) is a pathway that transports cholesterol from extrahepatic cells and tissues to the liver for excretion and is the primary mechanism by which high-density lipoprotein (HDL) and its major protein, apolipoprotein (apo) A-I, protect against atherosclerosis [1]. Cholesterol efflux from macrophages is particularly important in this respect because it represents the first critical step of RCT [2]. Macrophage adenosine triphosphate–binding cassette transporter A1 (ABCA1), ABCG1, and scavenger receptor class B type I (SR-BI) have been shown to be involved in determining macrophage cholesterol efflux in vitro and in animal models [3]. Adenosine triphosphate–binding cassette transporter A1 mediates cholesterol efflux from macrophages to lipid-free apo A-I, whereas ABCG1 was recently identified as being a mediator of macrophage cholesterol efflux to mature HDL in vitro. Scavenger receptor class B type I is expressed in hepatocytes and macrophages and mediates cholesterol efflux to mature HDL in vitro. Using an assay of macrophage RCT in mice, Wang et al [4] recently showed that macrophage ABCA1 and ABCG1 but not SR-B1 promoted macrophage RCT in vivo.

There are data suggesting that diabetes may affect these important regulators of cholesterol efflux and adversely influence this process. The effect of glucose remains controversial, and some but not all in vitro studies have shown that glucose can activate ABCA1, ABCG1, and SR-BI expression in HepG2 cells [5-7]. In contrast, ABCG1 was down-regulated when macrophages were cultured in elevated glucose for 7 days; and the time course of ABCG1 down-regulation by glucose suggests the possibility that other factors mediated by glucose, such as the generation of reactive oxygen species and/or advanced glycation end products (AGEs), may be the cause of ABCG1 down-

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regulation [8]. There are in vitro data showing that AGEs or their precursors can down-regulate ABCG1 and ABCA1 but up-regulate SR-BI expression [9-11]. In addition to hyperglycemia, the increased formation of oxidized low-density lipoprotein (oxLDL) in diabetic state may also influence these regulators of cholesterol efflux. Several in vitro studies have suggested that oxLDL can up-regulate ABCA1 and ABCG1 expression [12,13] and alter SR-BI expression [14-16]. Whether the expression of ABCA1, ABCG1, and SR-BI in vivo may be regulated by these factors is unclear.

In animal models of diabetes, ABCA1 gene expression was severely decreased in the liver and peritoneal macrophages in streptozotocin-induced diabetic mice; and this was due to down-regulation of ABCA1 by unsaturated fatty acids and acetoacetate [6]. In type 2 diabetes mellitus *db/db* mice, ABCG1 expression in peritoneal macrophages was decreased; and macrophage cholesterol efflux to HDL was impaired [8]. Hepatic SR-BI expression has been reported to be increased [17] or decreased [18] in diabetic rats. There are only limited data on these cholesterol transporters in human studies of diabetes. It has been reported that fasting glucose is negatively associated with ABCA1 level in leukocytes in healthy male subjects [19] and that blood monocyte ABCA1 expression is reduced in patients with type 2 diabetes mellitus [20]. The aims of this study were, therefore, to investigate the expression of ABCG1, ABCA1, and SR-BI in peripheral monocytes in type 2 diabetes mellitus patients and its associations with glycemic control, circulating oxLDL, and AGEs, and to determine whether the alteration of these cellular cholesterol transporters might affect cellular cholesterol efflux from monocytes ex vivo.

2. Methods

Thirty type 2 diabetes mellitus patients with normal renal and liver function and proteinuria <1 g/d were recruited. Patients on insulin therapy were eligible if they had been previously managed with diet and an oral agent at some point and had no known history of diabetic ketoacidosis. Patients on lipid-lowering drugs or thiazolidinediones or those who had a history of cardiovascular complications were excluded. The mean duration of diabetes of the recruited subjects was 13 ± 1.7 years; 67% of the patients were on oral hypoglycemic agents, and the rest were on insulin therapy. Forty percent of the patients had retinopathy, and 43% had microalbuminuria or albuminuria. Thirty age-matched healthy control subjects were recruited from the community. The study was approved by the Ethics Committee of the University of Hong Kong, and informed consent was obtained from all subjects.

Blood samples were taken after an overnight fast. Plasma total cholesterol and triglyceride were determined enzymatically on a Hitachi 912 analyzer (Roche Diagnostics, Basel, Switzerland). The HDL cholesterol was measured using a homogenous method with polyethylene glycol–modified enzymes and α-cyclodextrin. The LDL cholesterol was calculated by the Friedewald equation or measured directly if plasma triglyceride was >4.5 mmol/L. Apolipoprotein A-I and apo B were measured by rate nephelometry using the Beckman Array System (Beckman Instruments, Fullerton, CA). Plasma oxLDL was determined by an enzyme-linked immunosorbent assay (ELISA) kit (Mercodia AB, Uppsala, Sweden) that was a solid-phase 2-site enzyme immunoassay based on the direct sandwich technique in which 2 monoclonal antibodies were directed against separate antigenic determinants on the oxidized apo B molecule. Fasting glucose was determined by the glucose oxidase method, and hemoglobin A_{1c} (HbA_{1c}) was measured in whole blood using ion-exchange high-performance liquid chromatography by the Bio-Rad Variant Analyzer System (Bio-Rad Laboratories, Hercules, CA).

Serum AGEs was measured by a competitive ELISA developed in-house using a well-characterized polyclonal rabbit antisera raised against AGE-RNase as previously described [21]. The polyclonal anti-AGEs antibody recognizes N^{ε}-(carboxymethyl)lysine as well as other AGE epitopes including nonfluorescent cross-link arginine-lysine imidazole and can therefore detect most of the circulating AGEs. In brief, 96-well plates were coated with 50 μL per well of AGE-RNase (3.75 μg/mL). Fifty microliters of serum (1:4 dilution) was added, followed by 50 μL of 1:500 diluted anti-AGE antibody. Alkaline phosphate–conjugated anti-rabbit immunoglobulin G (1:2000) in dilution buffer was then added to each well and incubated for 1 hour at 37°C. After washing, color was developed by addition of 100 μL P-nitrophenyl phospate (pNPP) substrate (Sigma, St Louis, MO). Optical density (OD) at 405 nm was determined by an ELISA reader. Results were calculated as 1 − [(experimental OD − background OD)/(total OD − background OD)], and a 50% competition was defined as 1 U of AGEs.

To isolate peripheral blood monocytes, 20 mL fasting blood was collected from each subject using 4 mL 3.8% sodium citrate as anticoagulant. Blood monocytes were isolated using Ficoll-Paque solution (Amersham Biosciences, Piscataway, NJ) according to manufacturer's instruction. Briefly, blood sample was layered carefully on Ficoll-Paque solution and centrifuged at 400*g* for 30 minutes at 18°C to 20°C. Mononuclear cells at the interface were collected, washed with sterile phosphate-buffered saline for 3 times, and then resuspended with RPMI 1640 culture medium (Gibco, Invitrogen, Carlsbad, CA). The mononuclear cells in the medium were added to culture plates and incubated in cell culture incubator for 2 to 3 hours. Unattached lymphocytes were removed gently. Attached monocytes were collected and stored −70°C for RNA extraction and protein measurement.

Total RNA was extracted using Total RNA Extraction Miniprep System (GR1001, Viogene, Sunnyvale, CA) according to the protocol provided by the manufacturer and quantified spectrophotometrically. Complementary DNA (cDNA) was synthesized using TaqMan reagents (Applied Biosystems, Foster City, CA) according to the manufacturer's

Table 1
Clinical characteristics and metabolic parameters of controls and diabetic subjects

	Healthy controls (n = 30)	Type 2 diabetes mellitus (n = 30)
Male/female (%)	37/63	53/47
Age (y)	47.5 ± 1.5	50.3 ± 1.2
BMI (kg/m^2)	23.9 ± 0.6	26.1 ± 0.7*
Smokers (%)	10	17
Fasting glucose (mmol/L)	4.83 ± 0.08	8.06 ± 0.24‡
HbA_{1c} (%)	5.56 ± 0.07	7.70 ± 0.41‡
Serum AGEs	2.54 ± 0.20	3.10 ± 0.10*
Total cholesterol (mmol/L)	4.96 ± 0.13	4.83 ± 0.14
LDL cholesterol (mmol/L)	2.88 ± 0.12	2.89 ± 0.09
HDL cholesterol (mmol/L)	1.53 ± 0.07	1.29 ± 0.06*
Triglyceride (mmol/L)	0.90 (0.93)	1.15 (0.63)
Apolipoprotein A-I (g/L)	1.54 ± 0.06	1.33 ± 0.07†
Apolipoprotein B (g/L)	0.82 ± 0.04	0.86 ± 0.04
Plasma oxLDL (mU/L)	9.2 ± 1.3	13.2 ± 0.9*

Data were expressed as mean ± SEM or median (interquartile range).
*$P < .05$, †$P < .01$, and ‡$P < .001$ vs healthy controls.

instructions. Commercial primer/probe sets for target genes ABCA1 (Hs00194045_m1), ABCG1 (Hs00245154_m1), and SR-BI (Hs00194092_m1) and endogenous reference gene glyceraldehyde-3-phosphate dehydrogenase (GAPDH) were used. Polymerase chain reaction was performed in 96-well plates using 50 ng cDNA mixed with primers, probes, and Taqman Universal PCR Master Mix in a total volume of 20 μL in an ABI PRISM 7700 sequence detector (Applied Biosystems). All cDNA samples were assayed in duplicate. Each target gene and GAPDH were assayed on the same samples in separate tubes. This allowed standardization of the amount of target gene to the internal reference gene to control for different amounts of cDNA used. The standardized target gene was then compared with reference sample and expressed as the folds of a reference sample.

The ABCG1 protein in monocytes was measured by immunoblot. Monocytes were lysed in homogenization solution (20 mmol/L Tris-HCl [pH 7.6], 150 mmol/L NaCl, 1% NP-40, 1 mmol/L phenylmethylsulfonyl fluoride, 1 μg/mL leupeptin, 1 mmol/L aprotinin), and lysates were passed through 26-gauge needles. Twenty micrograms of protein from each subject was mixed with sample running buffer (0.25 mol/L Tris-HCl [pH 6.8], 4% sodium dodecyl sulfate, 10% glycerol, 0.02% bromophenol blue). After heating at 98°C for 5 minutes, whole cell lysates were subjected to 7.5% sodium dodecyl sulfate–polyacrylamide gel electrophoresis and electrotransferred onto polyvinylidene difluoride membranes. After blocking nonspecific binding with milk overnight, membranes were rinsed with Tris-buffered saline/0.1% Tween 20, incubated with anti-rabbit ABCG1 polyclonal antibody (Santa Cruz Biotechnology, Santa Cruz, CA) at 1:1500 dilution for 3 hours, and then washed 3 times. Protein-antibody complexes were detected using the enhanced chemiluminescence kit.

Cellular cholesterol efflux from fresh monocytes was evaluated in 8 type 2 diabetes mellitus patients and 6 healthy controls selected randomly. Blood monocytes were isolated from 40 mL blood and incubated with acetylated LDL (80 μg/mL) for 48 hours in serum-free medium. Cellular cholesterol was labeled with tracer [3H]cholesterol (1 μCi, 0.01 μg per well, 10^6 mononuclear cells) during the incubation with acetylated LDL. Five percent diluted pooled standard serum or autologous serum was then used to induce cholesterol efflux from the labeled cells for 4 hours. Cholesterol efflux, expressed as a percentage, was calculated as count in the medium divided by the total count of medium and cells in each well. Each sample was determined in triplicate.

Numerical data were expressed as mean and standard error mean. Data that were not normally distributed were logarithmically transformed before analyses were made. Comparisons between diabetic patients and controls were done using independent-sample t test, and χ^2 test was used to compare differences in proportions between groups. Pearson's correlations were used to test the relationship between variables, and univariate general linear model was used to assess the relationships between ABCG1 expression and various variables simultaneously.

3. Results

The general characteristics and metabolic parameters of the subjects are shown in Table 1. Age and sex were matched between the 2 groups, but diabetic patients had higher body mass index (BMI). There was no significant difference in the proportion of smokers between diabetic patients and controls. As expected, fasting glucose and HbA_{1c} were significantly higher in type 2 diabetes mellitus patients; and serum AGEs was also increased ($P < .05$). The diabetic patients had significantly lower levels of plasma HDL cholesterol and apo A-I. Although LDL cholesterol was similar in the 2 groups, diabetic subjects had significantly higher concentration of oxLDL.

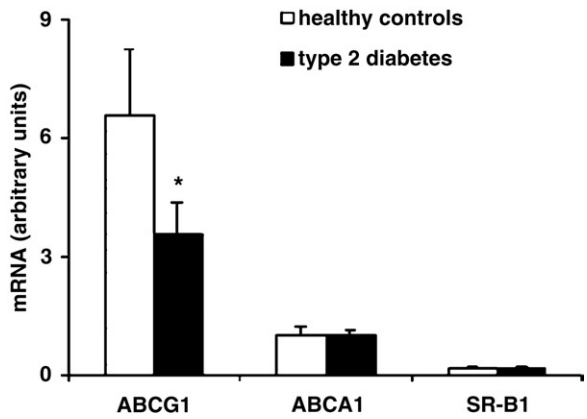

Fig. 1. Messenger RNA expression of ABCA1, ABCG1, and SR-BI in blood monocytes from healthy controls and type 2 diabetes mellitus patients. Data were expressed as mean ± SEM. *$P < .05$ compared with healthy controls.

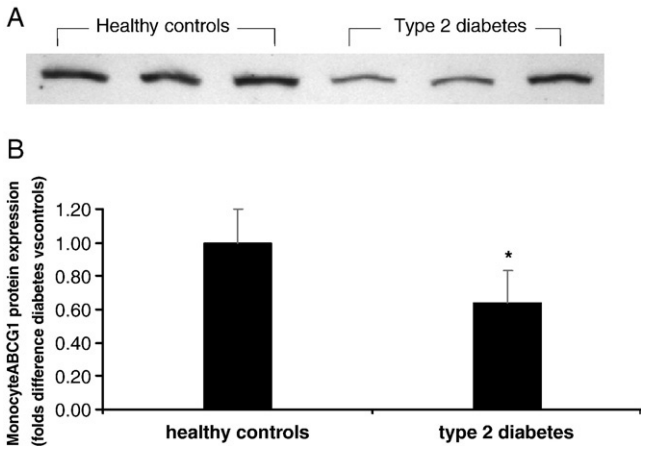

Fig. 2. A, Western blot demonstrating ABCG1 protein expression in monocytes from healthy controls and type 2 diabetes mellitus patients (lanes 1-3 represent healthy controls; lanes 4-6 represent diabetic patients). B, The ABCG1 protein expression in monocytes measured by Western blot. Data were expressed as mean ± SEM. *$P < .05$ compared with healthy controls.

Peripheral blood monocytes mainly expressed ABCG1 and ABCA1, and the expression of SR-BI was low (Fig. 1). There was a significant reduction in the messenger RNA (mRNA) level of ABCG1 in diabetic patients when compared with the controls, whereas the levels of ABCA1 and SR-BI were comparable between the 2 groups. Protein levels of ABCG1 in monocytes were also reduced in patients with diabetes (Fig. 2A, B). The decrease in ABCG1 in diabetic patients remained significant after adjusting for age, sex, BMI, and smoking status. We did not find any significant difference of ABCG1, ABCA1, and SR-BI expression in those diabetic patients with nephropathy or retinopathy compared with those without complications, or between those on oral hypoglycemic agents compared with those on insulin therapy.

On univariate analyses of all subjects, there was an inverse correlation between serum AGEs and ABCG1 (Table 2). However, no significant associations between fasting glucose, HbA_{1c}, plasma lipids, or oxLDL and the expression of ABCG1, ABCA1, and SR-BI were found. Because ABCG1 expression was reduced in type 2 diabetes mellitus patients, further multiple regression analysis was performed

Table 2
Correlations between serum AGEs, fasting glucose, HbA_{1c}, and plasma oxLDL and the mRNA expression of ABCG1, ABCA1, and SR-BI in monocytes in all subjects

	log (ABCG1)	log (ABCA1)	log (SR-BI)
Fasting glucose	−0.07	0.07	0.10
HbA_{1c}	−0.24	0.06	−0.21
Plasma oxLDL	−0.19	0.21	0.02
Serum AGEs	−0.44 *	−0.03	−0.29

Pearson correlation coefficients are shown. ABCG1, ABCA1, and SR-BI mRNA were logarithmically transformed before analysis.
* $P < .05$.

Table 3
Multiple linear regression analysis with ABCG1 mRNA expression in monocytes as the dependent variable in all subjects

	Regression coefficient	SE of regression coefficient	Standardized coefficients	P
Intercept	3.91	1.32		.004
Serum AGEs	−0.44	0.16	−0.34	.009
Plasma oxLDL	0.02	0.04	0.07	.591
The presence of diabetes	−0.49	0.32	−0.22	.132
Age	−0.01	0.02	−0.09	.493
Sex	0.34	0.31	0.15	.274
BMI	−0.04	0.04	−0.14	.299
Smoking	0.48	0.43	0.14	.265
Insulin therapy	0.58	0.44	0.18	.196

R^2 of the model = 27.0% ($P = .020$).

to investigate what were the main determinants of ABCG1 expression in monocytes; and the results are shown in Table 3. Serum AGEs remained a significant independent determinant of ABCG1 expression after adjusting for potential

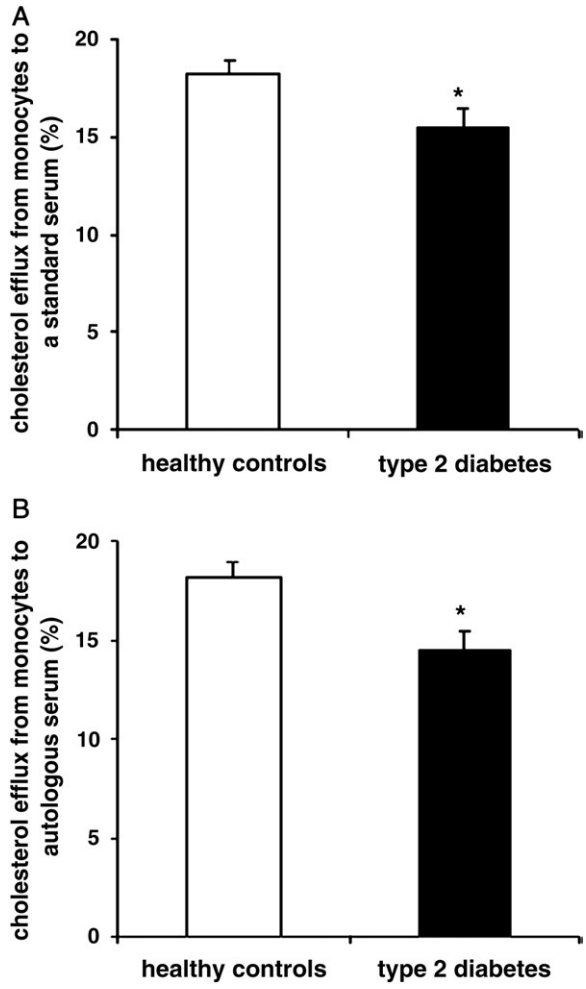

Fig. 3. A and B, Cellular cholesterol efflux from monocytes to a standard serum and to autologous serum, respectively. Data were expressed as mean ± SEM. *$P < .05$ compared with healthy controls.

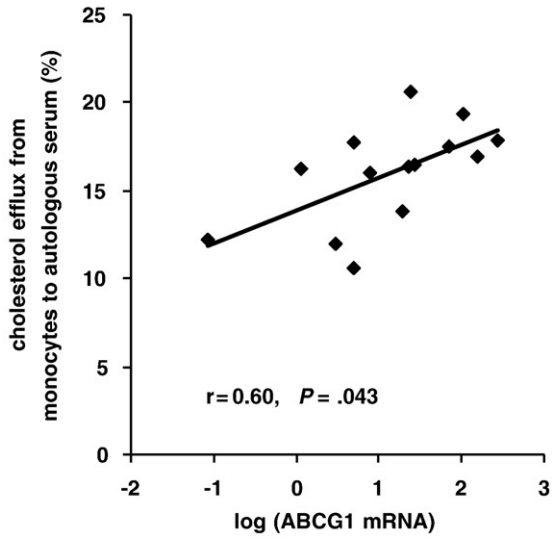

Fig. 4. The association between monocyte ABCG1 mRNA expression and cholesterol efflux from monocytes to autologous serum in all the subjects. The ABCG1 expression was logarithmically transformed before analysis.

confounding factors, suggesting that the reduction of ABCG1 expression in type 2 diabetes mellitus patients might be partly due to elevated AGEs level.

To determine whether the reduction of ABCG1 expression in diabetic subjects might have a functional effect, cellular cholesterol efflux from monocytes was measured in 8 diabetic subjects and 6 controls. Cellular cholesterol efflux from blood monocytes was measured by incubating [3H] cholesterol-labeled cells with a pooled standard serum for 4 hours. Cholesterol efflux from monocytes to the standard serum was decreased in diabetic patients compared with healthy controls (Fig. 3A). Experiments were also repeated using autologous serum, and cholesterol efflux from monocytes to autologous serum was also significantly decreased in diabetic patients (Fig. 3B). The reduction in cellular cholesterol efflux to autologous serum was more marked compared with that to the standard serum in diabetic patients. Cellular cholesterol efflux from monocytes to autologous serum was significantly correlated with the expression of ABCG1 (Fig. 4), but not with that of ABCA1 and SR-BI.

4. Discussion

Cellular cholesterol efflux, being the first step in RCT, plays an important role in reducing the accumulation of lipids in arterial wall and preventing the development of atherosclerosis. This process is regulated by cholesterol transporters, and cholesterol efflux from mouse macrophages has recently been shown to be mainly mediated by ABCA1 and ABCG1 but not by SR-BI [4]. This is the first study to examine the expression of these 3 major cholesterol transporters in human peripheral blood monocytes and evaluate the influence of type 2 diabetes mellitus. We have found that, among the 3 cellular cholesterol transporters in our human subjects, ABCG1 expression was the most abundant, followed by ABCA1, whereas the level of SR-BI expression was low. In type 2 diabetes mellitus patients, the expression of ABCG1 was significantly reduced, whereas the level of ABCA1 or SR-BI was similar to that in healthy controls. This is in keeping with data from animal studies showing that peritoneal macrophages isolated from type 2 diabetes mellitus *db/db* mice have decreased ABCG1 expression [8]. In contrast to our findings, Forcheron et al [20] have reported that the expression of ABCA1 in monocytes was decreased in hyperlipidemic type 2 diabetes mellitus patients and that the level of SR-BI was unchanged. Adenosine triphosphate–binding cassette transporter G1 was not measured in their study. These differing results in ABCA1 expression might be due to differences in the selection of patients being studied, as none of our patients had hyperlipidemia. In a recent study on a small number of type 2 diabetes mellitus patients without hyperlipidemia, monocytes-derived macrophages ABCA1 mRNA level was similar to that in controls [22].

Since we have demonstrated a reduction in ABCG1 mRNA and protein expression in monocytes from diabetic subjects, we have performed functional studies to investigate cholesterol efflux from monocytes to serum. We have chosen to use serum rather than purified acceptor particles such as HDL or apo A-I in these experiments to mimic the in vivo situation. The reduction in ABCG1 expression in patients with type 2 diabetes mellitus was associated with a reduction in cellular cholesterol efflux to serum, and the magnitude of reduction in cholesterol efflux was most marked when autologous serum was used. This would suggest that, in type 2 diabetes mellitus patients, in addition to the reduction in ABCG1 expression, changes in the acceptors for cellular cholesterol in serum like low HDL levels further contributed to the impairment in cellular cholesterol efflux.

It has been shown that the regulation of macrophage ABCA1 and ABCG1 expression is responsive to cell cholesterol status and that cholesterol-dependent transcription is mediated through activation of the nuclear receptors liver X receptor (LXR) and retinoid X receptor [3,23-25]. Data on the in vivo regulation of these cholesterol transporters in human diabetic subjects are limited, and animal studies have suggested that hyperglycaemia might play a role [6,8]. We did not find any association between glucose and oxLDL, which are known activators of LXR [7,12], and the expression of ABCG1 or ABCA1. However, the expression of ABCG1 in peripheral blood monocytes was independently related to the level of circulating AGEs. This is consistent with previous in vitro studies showing that exposure to AGE–bovine serum albumin reduced mRNA and protein levels of ABCG1 but not ABCA1 in human macrophages [9]. The effect of AGEs on ABCG1 was likely to be mediated via an LXR-independent pathway through the receptor for AGE (RAGE) because blocking RAGE with an

anti-RAGE antibody significantly limited the reduction in ABCG1 mRNA.

There are several limitations in our study. We have measured the expression of ABCG1, ABCA1, and SR-BI in peripheral blood monocytes because these cells are easily accessible. However, the expression of these molecules in peripheral blood monocytes may not directly reflect the expression level in macrophages in the arterial wall. Because the expression of ABCG1, ABCA1, and SR-BI might be altered during the differentiation of monocytes to macrophages in vitro [16,24,25], mRNA was determined in freshly isolated blood monocytes to determine the basal level of gene expression in vivo. We have demonstrated an association between serum AGEs and ABCG1 expression in monocytes, but whether this is a causal relationship needs further investigation.

In conclusion, the expression of ABCG1 in peripheral blood monocytes is reduced in patients with type 2 diabetes mellitus and is partly related to serum AGEs concentration. The reduction in ABCG1 expression is associated with impairment in cellular cholesterol efflux, and these changes may potentially contribute to accelerated foam cell formation and atherogenesis in diabetic patients.

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