Reduced Expression of ATP-Binding Cassette Transporter G1 Increases Cholesterol Accumulation in Macrophages of Patients With Type 2 Diabetes Mellitus

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Background—Patients with type 2 diabetes mellitus are at increased risk for the development of atherosclerosis. A pivotal event in the development of atherosclerosis is macrophage foam cell formation. The ATP-binding cassette (ABC) transporters ABCA1 and ABCG1 regulate macrophage cholesterol efflux and hence play a vital role in macrophage foam cell formation. We have previously found that chronic elevated glucose reduces ABCG1 expression. In the present study, we examined whether patients with type 2 diabetes mellitus had decreased ABCG1 and/or ABCA1, impaired cholesterol efflux, and increased macrophage foam cell formation.

Methods and Results—Blood was collected from patients with and without type 2 diabetes mellitus. Peripheral blood monocytes were differentiated into macrophages, and cholesterol efflux assays, immunoblots, histological analysis, and intracellular cholesteryl ester measurements were performed. Macrophages from patients with type 2 diabetes mellitus had a 30% reduction in cholesterol efflux with a corresponding 60% increase in cholesterol accumulation relative to control subjects. ABCG1 was present in macrophages from control subjects but was undetectable in macrophages from patients with type 2 diabetes mellitus. In contrast, ABCA1 expression in macrophages was similar in both control subjects and patients with type 2 diabetes mellitus. Macrophage expression of ABCG1 in both patients and control subjects was induced by treatment with the liver X receptor agonist TO-901317. Upregulation of liver X receptor dramatically reduced foam cell formation in macrophages from patients with type 2 diabetes mellitus.

Conclusions—ABCG1 expression and cholesterol efflux are reduced in patients with type 2 diabetes mellitus. This impaired ABCG1-mediated cholesterol efflux significantly correlates with increased intracellular cholesterol accumulation. Strategies to upregulate ABCG1 expression and function in type 2 diabetes mellitus could have therapeutic potential for limiting the accelerated vascular disease observed in patients with type 2 diabetes mellitus. (Circulation. 2008;117:2785-2792.)

Key Words: cholesterol ■ diabetes mellitus ■ atherosclerosis ■ lipoproteins ■ macrophages

Atherosclerosis is accelerated several-fold in patients with type 2 diabetes mellitus.1–4 A critical event in the development of atherosclerosis occurs when monocytes transmigrate into the subendothelial space and differentiate into macrophages.5 On differentiation, macrophages upregulate expression of scavenger receptors (SR-A, LOX-1, and CD36), which have the ability to take up modified lipoproteins.6,7 Likewise, members of the ATP-binding cassette (ABC) transporter family, including ABCA1 and ABCG1, also are upregulated during macrophage differentiation and have been shown to regulate cellular lipid metabolism.8–10 Of particular importance in atherosclerosis is the balance between the influx and efflux of modified low-density lipoproteins (LDLs) because when the net influx of cholesterol supercedes that of efflux, the macrophages become lipid-laden foam cells.11

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Much is known about the role of ABCA1 because mutations in the ABCA1 gene cause Tangier disease, a condition characterized by severely reduced high-density lipoprotein (HDL) levels.12 ABCG1 is ubiquitously expressed and is highly expressed in lipid-loaded macrophages.13 Both proteins are known regulators of macrophage cholesterol homeostasis and are key players in reverse cholesterol transport.9,10,13,14

Although much is known about the roles that ABCA1 and ABCG1 play in macrophage foam cell formation and the development of atherosclerosis, little is known about how cholesterol metabolism is altered in the setting of type 2 diabetes mellitus. Previous work in our laboratory has shown that macrophage ABCG1 expression and function are de-
increased in mouse models of type 2 diabetes mellitus. We found that the elevated glucose environment was partially responsible for this reduction in ABCG1 in diabetic macrophages. Here, we examine the effects of type 2 diabetes mellitus on the function of human monocyte-derived macrophages in reverse cholesterol transport. We show for the first time that ABCG1 expression is decreased in macrophages isolated from patients with type 2 diabetes mellitus, leading to decreased cholesterol efflux to HDL and resulting in increased macrophage cholesteryl ester content.

### Methods

**Reagents**

Rosette Sep Human Monocyte Enrichment Cocktail was ordered from StemCell Technologies, Inc (Tukwila, Wash). Ficoll-Paque PREMIUM was purchased from GE Healthcare (Waukesha, Wis). DMEM and antibiotic-antimycotic solution came from Gibco (Invitrogen, Carlsbad, Calif). Human macrophage colony-stimulation factor (M-CSF) came from PeproTech, Inc (Rocky Hill, NJ). Fetal bovine serum was purchased from Hyclone (Logan, Utah). Human HDL was ordered through IntraceL (Frederick, Md); [1,2-3H(N)]-cholesterol came from Perkin Elmer (Boston, Mass). NuPAGE 4% to 12% denaturing gels came from Invitrogen. Anti-ABCA1 antibody was a kind gift of John Parks (Wake Forest University, Winston-Salem, NC). In addition, horseradish peroxidase–linked secondary antibodies were ordered from Amersham Biosciences UK Ltd (Little Chalfont, Buckinghamshire, UK). TO-901317 was purchased from Cayman Chemicals (Ann Arbor, Mich). Whole human HDL was purchased from Intracel; apolipoprotein A-I (apoA-I) was isolated as described previously.

**Human Monocyte Isolation and Macrophage Differentiation**

Willing human subjects volunteered their blood in agreement with the University of Virginia’s Institutional Review Board for Health Science Research Protocol No. 12454. Both male and nonpregnant female subjects 18 years of age participated. All participants were patients of the University of Virginia Cardiovascular Prevention Clinic and were undergoing aggressive risk factor modification. Up to 100 mL additional blood was drawn into heparinized blood collection tubes. Human monocytes were isolated with Rosette Sep Human Monocyte Enrichment Cocktail, following the manufacturer’s protocol. Monocytes were then plated in tissue culture using DMEM containing 1.5 g/L glucose, 10 ng/mL human M-CSF, 10% autologous serum, and 1% antibiotic/antimycotic mixture. Autologous serum was used in an effort to maintain the in vivo milieu as much as possible. Although diluted, the use of autologous serum maintains the relative composition of blood components that the cells are exposed to in vivo, except for glucose, which was supplemented. Monocytes were allowed to differentiate for 3 days before being used in experiments. Glucose values were monitored in media throughout the 3-day culture and did not vary >5% for each sample (data not shown). In some experiments, macrophages were incubated for 24 hours in the presence of 3 μmol/L of the well-characterized liver X receptor (LXR) agonist TO-901317 before analysis. The monocyte recovery from 100 mL blood was not sufficient to conduct every experiment on each blood sample. Thus, although the Table shows the laboratory profile of the entire study population, results shown in the Figures represent random subsets of the total study population.

### Table. Laboratory Profile of the Study Population: Average Fasting Plasma Total Cholesterol, Triglyceride, HDL, LDL, Glucose, Hemoglobin A1c, Insulin, and HOMA Calculations

<table>
<thead>
<tr>
<th>Population</th>
<th>T Chol, mg/dL</th>
<th>Trig, mg/dL</th>
<th>HDL, mg/dL</th>
<th>LDL, mg/dL</th>
<th>Glucose, mg/dL</th>
<th>HbA1c, %</th>
<th>Insulin, μU/mL</th>
<th>HOMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls (n=31)</td>
<td>175±6</td>
<td>137±8</td>
<td>49±2</td>
<td>99±5</td>
<td>83±2</td>
<td>5.8±0.1</td>
<td>31±2</td>
<td>191±27</td>
</tr>
<tr>
<td>Type 2 diabetes (n=24)</td>
<td>172±10</td>
<td>194±13*</td>
<td>39±2*</td>
<td>97±9</td>
<td>127±9*</td>
<td>7.9±1*</td>
<td>56±9</td>
<td>499±107*</td>
</tr>
<tr>
<td>Ideals</td>
<td>&lt;200</td>
<td>55-150</td>
<td>&gt;40 (men), &gt;50 (women)</td>
<td>&lt;130</td>
<td>74-100</td>
<td>&lt;6%</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

HOMA indicates homeostasis model assessment; T Chol, total cholesterol; Trig, triglycerides; HbA1c, hemoglobin A1c; and NA, not applicable. Values are mean±SEM.

*Significantly different from control patients, P<0.01 for each parameter.

Figure 1. Cholesterol efflux to HDL is reduced from macrophages of type 2 diabetic patients. Peripheral blood monocytes were isolated from control subjects (n=14) and patients with type 2 diabetes mellitus (n=11) and differentiated into macrophages with M-CSF for 3 days. Macrophages were then incubated in 2 μCi/mL of 3H cholesterol overnight, and cholesterol efflux to HDL and lipid-poor ApoA-I was measured for 4 hours. Top, Cholesterol efflux to HDL. Cholesterol efflux to HDL is reduced by 27% in macrophages from type 2 diabetic patients. Bottom, Cholesterol efflux to lipid-poor ApoA-I. No significant differences were observed in cholesterol efflux to ApoA-I. *P<0.01, diabetic vs control.
**Immunobots**

Radioimmunoprecipitation assay buffer was added to macrophages to generate whole-cell lysates. The lysates were collected, briefly sonicated, and quantified with a protein assay kit (Bio-Rad Laboratories, Hercules, Calif). Proteins were separated by SDS-PAGE, transferred to nitrocellulose, and blocked for 2 hours with Blocker-BLOTTO (Pierce Biotechnology, Inc, Rockford, Ill). Whole-cell lysate (30 μg) was used for the detection of all proteins. Blots were incubated in Tris-buffered saline plus 1% Tween 20 containing a 1:500 dilution of antibody overnight at 4°C. Blots were then incubated with a 1:5000 dilution of horseradish peroxidase–conjugated secondary antibody. Proteins were visualized with chemiluminescence and normalized to β-actin as a control for gel loading.

**Quantitative Real-Time Polymerase Chain Reaction**

Total cellular RNA was collected from macrophages with Trizol reagent, following the manufacturer’s protocol. cDNA 1 μg was then synthesized with an Iscript cDNA synthesis kit (Bio-Rad). Total cDNA was diluted 1:8 in H2O, and 4 μL was used for each real-time condition using a Bio-Rad MyIQ Single Color Real-Time Polymerase Chain Reaction Detection System and Bio-Rad iQ SYBR Green Supermix. Primers for human ABCG1 and β-actin were ordered from Ambion (Austin, Tex). Samples were normalized to β-actin using the ΔCt (cycle threshold) method.

**Isotopic Cholesterol Efflux Assays**

After 3 days of differentiation on 24-well plates, cells were washed thoroughly and radiolabeled with 2 μCi/mL [3H] cholesterol overnight in the presence of 10% bovine serum. The next day, cells were washed with PBS and equilibrated for 2 hours in the presence of serum-free medium containing 0.2% fatty-acid–free BSA. Cholesterol efflux was conducted for 4 hours at 37°C in medium containing 0.2% BSA, 0.2% BSA plus 50 μg protein/mL human HDL, or 0.2% BSA plus 15 μg protein/mL human lipoprotein ApoA-I. HDL used in these studies was identical for each group and was from the same commercial source to effectively remove any differences in HDL populations that may occur with the use of autologous HDL isolated from control subjects and patients with type 2 diabetes mellitus. The efflux medium was then removed (0.5 mL total), and a 100-μL aliquot was taken for [3H] radioactivity determination in a Beckman LS 6500 scintillation counter (Beckman Coulter, Fullerton, Calif). Adherent cells were rinsed twice with cold PBS, and 0.5 mL isopropyl alcohol was added for overnight extraction of the remaining cholesterol at room temperature. The isopropyl alcohol was removed, dried under nitrogen, and then resuspended in another 0.5 mL isopropyl alcohol. A 100-μL aliquot of the extract was taken for [3H] radioactivity determination. Results are expressed as percent efflux calculated as follows: disintegrations per minute of [3H] cholesterol in medium + ([3H] cholesterol in medium + [3H] cholesterol remaining in cells)×100. Specific efflux to HDL or ApoA-I was calculated by subtracting nonspecific efflux in the presence of 0.2% BSA only. Although the possibility of back exchange of radiolabeled cholesterol exists, it is presumably minimized during the standard 4-hour experiments commonly used.

**Plasma Analysis**

Plasma lipid levels, glucose, and hemoglobin A1c levels were determined by the University of Virginia Clinical Pathology Laboratory. Insulin was measured by the University of Virginia Metabolic Core with a radioimmunosseday kit (Linco, St Charles, Mo).

**Homeostasis Model Assessment Calculations**

Homeostasis model assessment calculations were made to illustrate the degree of insulin resistance between the study groups. The following formula was used: (fasting insulin [μU/mL]×fasting glucose [mmol/L])/22.5.

**Histology**

Cells were allowed to differentiate for 3 days on chamber slides. The LXR agonist TO-901317 was added during the final 24 hours of incubation to upregulate ABCA1 and ABCG1 protein expression. On day 3, macrophages were stained with Oil Red O and hematoxylin to visualize lipid accumulation. Images were acquired with the ×20 or ×40 objective on a microscope (model BX51, Olympus, Center Valley, Pa) equipped with a digital camera (model DP70, Olympus) using the ImagePro Plus software program in the Academic Computing Health Sciences Center at the University of Virginia.

**Cholesteryl Ester Determinations**

Monocytes were allowed to differentiate for 3 days on 100-mm dishes. The LXR agonist TO-901317 was added during the final 24
hours to stimulate ABCA1 and ABCG1 expression. Cells were then washed 3 times with PBS, and 5 mL isopropl alcohol was added to extract cholesterol overnight at room temperature. 5α-Cholestane (Sigma, St Louis, Mo) was added as an internal standard before the samples were dried under nitrogen and resuspended in 200 μL hexane. Total and free cholesterol content was determined by gas-liquid chromatography and normalized to cellular protein as described previously. Esterified cholesterol was calculated as the difference between total and free cholesterol times 1.67.

Statistical Analyses

Data for all experiments were analyzed by ANOVA using the Statview 6.0 software program (SAS Institute, Inc, Cary, NC). Comparisons between groups were performed with ANOVA methods. Data are graphically represented as mean±SE, in which each mean consists of experiments performed in triplicate. Comparisons between groups and tests of interactions were made assuming a 2-factor analysis with the interaction term testing each main effect and the residual error testing the interaction. All comparisons were made with Fisher’s least-standard-difference procedure, so multiple comparisons were made at the 0.05 level only if the overall F test from the ANOVA was significant at $P<0.05$.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Study Population

The Table shows the fasting laboratory profile of the study population. The control population is within normal parameters for each category. The patients with type 2 diabetes mellitus have laboratory profiles typical of the metabolic syndrome and type 2 diabetes mellitus, with high levels of triglycerides, low HDL cholesterol, and elevated glucose, hemoglobin A1c, elevated insulin, and homeostasis model assessment. The study population included 15 male and 16 female control subjects without type 2 diabetes mellitus with an average age of 63.5 years. Because the present study was initiated as a pilot with patients with type 2 diabetes mellitus, we performed gas-liquid chromatography and found dramatic differences in lipid accumulation between the diabetic and control macrophages (A and B in Figure 3, bottom). Accumulation of neutral lipid was reduced dramatically in both macrophage groups by the addition of the LXR agonist TO-901317 (see "a" lanes for ABCA1 in Figure 3, top). ABCG1 and ABCA1 are known to be regulated by the nuclear receptor LXR. We incubated macrophages with an LXR agonist to determine whether macrophages from type 2 diabetic patients were responsive to LXR agonism. We found that both ABCA1 and ABCG1 protein levels were upregulated in the presence of the LXR agonist TO-901317 (see "4" lanes in Figure 3, top). These findings are similar to what we have recently reported for type 2 diabetic mouse models.

Increased Lipid Accumulation in Type 2 Diabetic Macrophages Is Dramatically Reduced by the LXR Agonist TO-901317

We next measured intracellular lipid accumulation in macrophages isolated from control subjects and patients with type 2 diabetes mellitus. We stained neutral lipid in macrophages using Oil Red O and found dramatic differences in lipid accumulation between the diabetic and control macrophages (A and B in Figure 3, bottom). Accumulation of neutral lipid was reduced dramatically in both macrophage groups by the LXR agonist TO-901317 (C and D in Figure 3, bottom). To quantify intracellular cholesterol accumulation accurately, we performed gas-liquid chromatography. As shown in Figure 4, choleseryl esters are increased by $\approx 60\%$ in type 2 diabetic macrophages compared with controls. In addition, intracellular cholesteryl ester concentrations are reduced by $\approx 25\%$ in type 2 diabetic macrophages by the addition of the LXR agonist TO-901317. A small yet significant reduction in cholesteryl ester content was found with the addition of TO-901317 in macrophages from control subjects (Figure 4). No significant changes in free cholesterol content were observed (Figure 4). Taken together, our findings indicate that reductions in ABCG1 expression in macrophages from patients with type 2 diabetes significantly and negatively affect cholesterol efflux, resulting in the formation of lipidd-laden macrophages. Furthermore, we demonstrate that up-regulation of ABCG1 expression through the use of an LXR agonist significantly reduces lipid accumulation in macrophages from patients with type 2 diabetes mellitus.

Discussion

Type 2 diabetes mellitus significantly increases the risk for the development of atherosclerosis. Previous work in our
laboratory found that macrophage ABCG1 protein expression was reduced in mouse models of type 2 diabetes mellitus, leading to decreased cholesterol efflux to HDL and increased intracellular cholesteryl ester accumulation. Furthermore, we show for the first time that human monocyte-derived macrophages from patients with type 2 diabetes mellitus have significantly reduced cholesterol efflux to HDL, leading to an increase in macrophage intracellular cholesterol accumulation. Furthermore, we show that this reduction in cholesterol efflux to HDL is due primarily to decreased ABCG1 expression. Moreover, treatment of diabetic macrophages with the LXR agonist TO-901317 significantly upregulates ABCG1 and ABCA1 expression and reduces intracellular cholesterol accumulation in macrophages from patients with type 2 diabetes mellitus.

Three primary scavenger receptors are expressed on macrophages: SR-A, LOX-1, and CD36. These macrophage

**Figure 3.** Increased lipid accumulation in macrophages from patients with type 2 diabetes mellitus is dramatically reduced by the LXR agonist TO-901317. Peripheral blood monocytes were isolated from control subjects (n=9) and patients with type 2 diabetes mellitus (n=5) and differentiated into macrophages with M-CSF for 3 days. Macrophages were stimulated with the LXR agonist TO-901317 (3 μmol/L) for the final 24 hours of incubation to upregulate ABCG1 and ABCA1. Top, ABCG1 and ABCA1 expression. Whole-cell lysates were analyzed by SDS-PAGE and immunoblotting for ABCG1 and ABCA1. β-Actin is shown as a control for loading. Bottom, Lipid staining. Macrophages were stained with Oil Red O to visualize lipid accumulation. Fluorescent images of the Oil Red O are shown on the right. A, Macrophages from control subjects. B, Macrophages from patients with type 2 diabetes mellitus. C, Macrophages from control subjects plus 3 μmol/L LXR agonist. D, Macrophages from patients with type 2 diabetes mellitus plus 3 μmol/L LXR agonist.
receptors internalize oxidized lipids and are considered proatherogenic. Recent studies have shown that elevated glucose increased both SR-A and LOX-1 expression in macrophages. Fukuwara-Takaki et al. showed increases in both mRNA and protein expression of SR-A in human monocyte-derived macrophages incubated in high glucose and in streptozotocin-induced diabetic mice. In addition, Li et al. have shown that LOX-1 mRNA and protein levels are increased in human monocytes after incubation in high glucose. Griffin et al. also demonstrated increased expression of CD36 in human monocyte-derived macrophages in a high-glucose environment, which they determined was due to an increase in CD36 translation, not transcription. Our mRNA measurements of CD36 (data not shown) are in line with these findings.

In addition to the scavenger receptors that regulate the influx of cholesterol to macrophages, several equally important ABC transporters are involved in the efflux of cholesterol from cells: ABCA1, ABCG1, and ABCG4. Vaughan and Oram have shown that these ABC transporters act sequentially to eliminate excess cholesterol from the cell, with ABCA1 acting first by effluxing cholesterol to lipid-poor ApoA-I. ABCG1 can then efflux cholesterol to newly made HDL moieties before ABCG4 can add additional cholesterol. However, macrophages do not express ABCG4, leaving ABCA1 and ABCG1 as the known primary regulators of cholesterol efflux in macrophages. The scavenger receptor SR-B1 also can efflux cholesterol from cells, although recent elegant work by Wang et al. indicates that SR-B1 is not a major protein involved in reverse cholesterol transport in vivo. From our findings in the present study using human macrophages and our prior studies using mouse macrophages, we anticipate that ABCG1 is the primary protein in macrophages affected by the setting of diabetes that regulates cholesterol efflux to HDL. However, we cannot rule out a small contribution of SR-B1 to this process.

Because the LDL cholesterol and total cholesterol values between the control subjects and patients with type 2 diabetes mellitus are nearly identical (see the Table), we conclude that the large increase in intracellular lipid content in macrophages isolated from patients with type 2 diabetes mellitus (see B in Figure 3, bottom) is probably not due to differences in plasma LDL concentrations between the 2 study groups. However, there are indeed lower HDL concentrations in the serum of type 2 diabetic patients (the Table), and it is unclear whether the autologous diabetic serum used in the experiments in Figures 3, bottom, and 4 contained lower levels of pre-β-HDL that could act as an acceptor for the ABCA1 pathway. Changes in pre-β-HDL concentrations could certainly influence ABCA1-mediated efflux. In vivo, changes in HDL concentration or HDL composition could affect both ABC transporter-mediated and SR-B1-mediated cholesterol efflux and possibly even influence passive diffusion of cholesterol from cells. Therefore, it is possible that differences in total HDL concentrations or pre-β-HDL concentrations in the patient’s serum may have affected the lipid accumulation that we observed in the macrophages (see Figures 3, bottom, and 4). Nevertheless, our measurements of cholesterol efflux (Figure 1) indicate that macrophages from patients with type 2 diabetes mellitus indeed have significant reductions in ABCG1-specific cholesterol efflux.

The role of ABCG1 in atherosclerotic development remains unresolved. Several studies with conflicting results using bone marrow transplantation in mice to study the role of macrophage ABCG1 in atherosclerosis have been published. The most plausible hypothesis based on the known functions of ABCG1 is that a deficiency of ABCG1 would cause increased atherosclerosis development. However, 2 recent studies surprisingly found a decrease in atherosclerosis formation in mice receiving ABCG1-deficient bone marrow, whereas 1 study observed a very slight increase in atherosclerosis. In addition, work by Basso et al. found that overexpression of ABCG1 in LDL receptor–deficient mice fed a Western diet had increased atherosclerotic plaque formation. Clearly, more research on the definitive role of ABCG1 in atherogenesis is warranted. However, our studies in type 2 diabetic mice and the present study in humans suggest that the increased intracellular cholesterol accumulation in macrophages and subsequent foam cell formation associated with decreased ABCG1 expression could have important physiological consequences with respect to the acceleration of atherosclerosis in patients with type 2 diabetes mellitus.

Pharmacologically, it is well known that synthetic LXR agonists or their endogenous ligands, oxysterols, can upregu-
late the expression and function of ABCA1 and ABCG1 because LXR appears to be the main transcription factor regulating these proteins.16,19,34,35 Unfortunately, the synthetic agonists available are pan-LXR agonists that cannot differentiate between the LXRα and LXRβ isoforms. Pan-LXR agonists may not be useful as therapies because LXRα is highly expressed in the liver and its activation greatly increases liver and plasma triglyceride concentrations through the activation of SREBP-1.36 Potentially, an LXRβ-specific agonist could be used as a beneficial therapy because LXRβ is not highly expressed in hepatocytes and thus its activation does not increase plasma triglyceride concentrations.37,38 Therefore, an LXRβ agonist could be used to upregulate ABCA1 and ABCG1 and to encourage reverse cholesterol transport, possibly inhibiting or even reversing atherosclerosis. Studies using LXRα and LXRβ knockout mice support these hypotheses,37,38 yet isoform-specific LXR agonists remain elusive to date.

Of additional interest is the fact that the monocye-derived macrophages from patients with type 2 diabetes mellitus retained a reduction in ABCG1 protein levels despite being differentiated in culture for 3 days. One plausible explanation is the diabetic environment (the glycemic “memory” effect) in which cells removed from the diabetic milieu retain their diabetic phenotype.39–41 An alternative explanation is a genetic effect in which ABCG1 variants (single-nucleotide polymorphisms) are associated with diabetes risk (data not shown). In this case, the ABCG1 single-nucleotide polymorphisms found in patients with diabetes mellitus may affect basal expression of ABCG1 in macrophages. Determination of the functional characteristics of the ABCG1 genetic effect in macrophages requires further study.

Because this is a pilot study based on expedited institutional review board oversight, this study has limitations. Without access to patient identification information, we were not able to correlate the observed data to age, sex, medications, and medical history. However, because all participants were patients of the University of Virginia Cardiovascular Prevention Clinic, uniform guidelines for risk factor modification were applied. Thus, variations in treatments and therapeutic goals (ie, total and LDL cholesterol; see the Table) were minimized. Despite this limitation, this pilot study is the first to implicate the reduction of ABCG1 with associated cholesteryl ester accumulation as a potential mechanism for accelerated vascular disease in patients with type 2 diabetes mellitus. Follow-up studies to confirm these findings in a carefully phenotyped population are needed. Nevertheless, therapies to upregulate ABCG1 in type 2 diabetes mellitus most likely will be important for the prevention of atherosclerosis and diabetic vascular complications.

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Disclosures

None.

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