High-Fat and Fructose Intake Induces Insulin Resistance, Dyslipidemia, and Liver Steatosis and Alters In Vivo Macrophage-to-Feces Reverse Cholesterol Transport in Hamsters\textsuperscript{1–3}

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Abstract

Reverse cholesterol transport (RCT) promotes the egress of cholesterol from peripheral tissues to the liver for biliary and fecal excretion. Although not demonstrated in vivo, RCT is thought to be impaired in patients with metabolic syndrome, in which liver steatosis prevalence is relatively high. Golden Syrian hamsters were fed a nonpurified (CON) diet and normal drinking water or a high-fat (HF) diet containing 27\% fat, 0.5\% cholesterol, and 0.25\% deoxycholate as well as 10\% fructose in drinking water for 4 wk. Compared to CON, the HF diet induced insulin resistance and dyslipidemia, with significantly higher plasma non-HDL–cholesterol concentrations and cholesteryl ester transfer protein activity. The HF diet induced severe liver steatosis, with significantly higher cholesterol and TG levels compared to CON. In vivo RCT was assessed by i.p. injecting \textsuperscript{3}H-cholesterol labeled macrophages. Compared to CON, HF hamsters had significantly greater \textsuperscript{3}H-tracer recoveries in plasma, but not HDL. After 72 h, \textsuperscript{3}H-tracer recovery in HF hamsters was 318\% higher in liver and 75\% lower in bile (\textit{P} < 0.01), indicating that the HF diet impaired hepatic cholesterol fluxes. However, macrophage-derived cholesterol fecal excretion was 45\% higher in HF hamsters than in CON hamsters. This effect was not related to intestinal cholesterol absorption, which was 89\% higher in HF hamsters (\textit{P} < 0.05), suggesting a possible upregulation of transintestinal cholesterol excretion. Our data indicate a significant increase in macrophage-derived cholesterol fecal excretion in a hamster model of metabolic syndrome, which may not compensate for the diet-induced dyslipidemia and liver steatosis. J. Nutr. 142: 704–709, 2012.

Introduction

The prevalence of metabolic syndrome, type 2 diabetes, and cardiovascular diseases is dramatically increasing worldwide and more specifically in developing countries (1). The impact of these metabolic diseases is expected to be even worse with a world urbanization level projected to be \textasciitilde 60\% in 2025 (2). Increased consumption of energy-dense foods containing high amounts of animal fats, SFA (3), and fructose (4) is thought to be the major contributor to the metabolic disorders (obesity, insulin resistance, nonalcoholic steatohepatitis, dyslipidemia, high blood pressure, and atherosclerosis) seen in type 2 diabetes, which increase cardiovascular risk and result in premature mortality (5).

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\textsuperscript{3} Supplemental Table 1 and Figure 1 are available from the “Online Supporting Material” link in the online posting of the article and from the same link in the online table of contents at http://jn.nutrition.org.
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The RCT\textsuperscript{4} pathway would be one of the impaired biological processes contributing to increase cardiovascular risk in metabolic syndrome (6). The role of RCT is to return the excess cholesterol accumulated in peripheral tissues to the liver for excretion into the bile and ultimately into the feces (6). The key player mediating RCT is HDL, which mediates the efflux of cholesterol from peripheral tissues (e.g., macrophages in the vessel walls) to the plasma for transport back to the liver (7). Hence, an inverse relationship exists between HDL-C levels and cardiovascular diseases (8). In type 2 diabetes, dyslipidemia is characterized by increased TG and low HDL-C levels. These changes are amplified by increased CETP activity, which mediates the transfers of cholesteryl esters from HDL to apoB-containing particles (VLDL and LDL) in exchange of TG (9).

\textsuperscript{4} Abbreviations used: CON, nonpurified diet; FPLC, fast protein liquid chromatography; HDL-C, HDL-cholesterol; HF, high-fat diet; RCT, reverse cholesterol transport; TICE, trans-intestinal cholesterol excretion.

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contribute to atherosclerosis and thus cardiovascular risk in patients with type 2 diabetes.

RCT therefore represents an attractive target to reduce cardiovascular risk and prevent premature death. Toward this goal, several animal models (e.g., rabbit, mouse and hamster) have been used over the last 30 y to investigate this biological process and develop novel therapies to prevent cardiovascular diseases (7,10,11). To our knowledge, however, the effects of metabolic syndrome on the rate of RCT remain to be assessed in vivo. Meanwhile, an animal model that reflects the human situation (e.g., fat and fructose overconsumption) would be helpful to evaluate novel therapies targeting metabolic syndrome. We recently demonstrated the relevance of the hamster model for studying RCT (11–13), because this CETP-expressing species has a similar lipoprotein metabolism to humans (11). In the present study, Golden Syrian hamsters were fed a high fat/fructose-enriched (HF) diet to induce the main features of human metabolic syndrome. We then investigated the potent effects of such a diet on macrophage-to-feces RCT in vivo.

Methods

Hamsters and diet. All animal protocols were approved by the local ethical committee (Comité régional d’éthique de Midi-Pyrénées). Male Golden Syrian hamsters (91–100 g, 6 wk old, Elevage Janvier) were housed in plastic cages (4–6 hamsters/cage) containing wood shavings and maintained in a room with a 12-h-light cycle with free access to food and tap water. Hamsters were adapted to these conditions and fed a commercial nonpurified diet containing 214 g/kg protein, 51 g/kg fat, and 0.1 g/kg cholesterol (diet no. A03, Safe Diets) for 1 wk. This nonpurified diet was defined as the control diet.

A total of 44 hamsters were used to perform the 3 in vivo experiments described below (plasma and tissue collection, macrophage-to-feces RCT, and intestinal cholesterol absorption). Hamsters were separated into 2 groups of 22 hamsters each and they consumed ad libitum over 4 wk either the control diet (CON) with normal drinking water or a HF diet with 10% fructose in the drinking water. Body weight was monitored weekly. Food and water intake were measured over 24 h on the last week of diet using individually caged hamsters (n = 8/group). The HF diet was prepared by mixing 762.5 g of the CON diet with coconut oil (115 g), corn oil (115 g), cholesterol (5 g), and deoxycholate (2.5 g) to obtain 1 kg of HF diet (pelleted from Safe Diets). Essential nutrients were not adjusted in the HF diet and were thus not equal in the 2 diets. The HF diet was previously described to reliably induce insulin resistance, dyslipidemia, and liver steatosis (14).

Plasma and tissue collection. After 4 wk of treatment, 16 hamsters (n = 8/group) were feed deprived overnight, blood glucose was monitored using a glucometer (Roche Diagnostics), and a blood sample (1 mL) was collected by retro-orbital bleeding under isoflurane anesthesia at 3, 5, and 6 h to measure plasma total cholesterol (cholesterol RTU, Biomerieux), TG (triglyceride PAP 150, Wako Chemicals) levels and fatty acid [NEFA-HR (2), Wako Chemicals] levels. Blood glucose was also monitored using a glucometer (Roche Diagnostics). Plasma total cholesterol and TG levels were respectively 409 ± 55 mg/dL and 35 ± 7 mg/dL. Plasma insulin was assayed using a commercial ELISA kit (Insulin ELISA kit, Abcys). Commercial kits were used to measure plasma total cholesterol (cholesterol RTU, Biomerieux), TG (Triglyceride PAP 150, Biomerieux), alanine aminotransferase (Enzyline ALAT/GPT, Biomerieux), and aspartate aminotransferase (Enzyline ASAT/GOT, Biomerieux). HDL-C was determined using the phosphotungstate/MgCl2 precipitation method. Non-HDL-C levels were then determined by subtracting HDL-C values from total plasma cholesterol.

Plasma CETP activity was measured by fluorescence using a commercial kit (RB-CETP kit, Roarbiomedical). FPLC lipoprotein profiles analysis (total cholesterol) using pooled plasma was performed as previously described (12). Commercial kits were used to measure hepatic cholesterol (cholesterol RTU, Biomerieux), TG (triglyceride PAP 150, Biomerieux), and fatty acid [NEFA-HR (2), Wako Chemicals] levels from liver homogenate incubated with deoxycholate, as described (16).

Oil red O/hematoxylin staining procedure. After fixation of a 5-μm frozen liver section in a 10% formalin solution for 1 h, section were washed and stained with Oil red O for 5 min. Sections were then washed and stained with Harris’ hematoxylin for 1 min.

Gene expression analysis. Tissue for mRNA analysis was homogenized and RNA was isolated using Trizol reagent (Invitrogen) according to the manufacturer’s instructions. Real-time qPCR analysis was performed using an Applied Biosystems 7300 sequence detector, as previously described (17). Primers sequences are detailed in Supplemental Table 1. Relative quantities of mRNA were calculated from C_T values by the comparative C_T method. A serial dilution of a standard was run on each plate for each mRNA and used to calculate the relative levels of mRNA. Data were normalized to cyclophilin mRNA and expressed as fold of the CON group.
Western-blot analysis. Protein expression of hepatic LDLR and SR-BI was evaluated from liver homogenates by using Western-blot analysis as previously described (18), using antibodies reacting with hamster LDLR (Biovision) and SR-BI (Novus Biological). Pan-cadherin (AbCam) antibody was used for loading control. For densitometry analysis of bands obtained via Western-blot analysis, we applied ImageJ software based analysis (19). The AUC of the specific signal was corrected for the AUC of the loading control.

Statistical analysis. Values are presented as mean ± SEM. Comparisons between groups were conducted using the Student’s t test (2-tailed). A 2-tailed P-value of P < 0.05 was considered significant.

Results
HF diet induces insulin resistance, dyslipidemia, and liver steatosis in Golden Syrian hamsters. After 4 wk of treatment, the groups did not differ in body weight, food intake, or water intake (Table 1). Blood glucose and plasma insulin concentrations and HOMA-IR were 62, 237, and 547% greater, respectively, in HF hamsters than in CON hamsters (P < 0.001). Plasma TG and total cholesterol concentrations were 363 and 146% higher, respectively, in HF hamsters (P < 0.001). Compared to CON hamsters, plasma HDL-C was 93% higher in HF hamsters (P < 0.001). However, total cholesterol in the non-HDL-C fraction (VLDL+LDL) was 258% greater in HF hamsters than in CON hamsters (P < 0.001), and this resulted in a 21% lower HDL-C:total cholesterol ratio in HF hamsters (P < 0.001). Plasma CETP activity was 55% higher in HF than in CON hamsters (P < 0.001). FPLC analysis of pooled plasma samples confirmed the dyslipidemic state of HF hamsters, with higher total cholesterol concentrations in fractions corresponding to VLDL, LDL, and HDL in HF hamsters than in CON hamsters (Fig. 1A).

Compared to CON hamsters, liver mass was 37% higher in HF hamsters (P < 0.001) (Table 1), with concomitant liver steatosis, as shown by the oil-red-O analysis (Supplemental Fig. 1). Compared to CON hamsters, hepatic total cholesterol, TG, and fatty acid concentrations were 283, 115, and 239% higher in HF hamsters, respectively (P < 0.001) (Table 1). Although apolipoprotein B expression was less in HF hamsters (65% lower), expression of hepatic ABCG5 and ABCG8 was 63 and 56% lower in HF hamsters (P < 0.001) (Table 1). Also, hepatic ACAT2 expression was 61% lower (P < 0.001). The expression of genes involved in biliary cholesterol excretion, namely ABCG5 and ABCG8, was 63 and 56% lower in HF hamsters (P < 0.001). In the intestine (Table 2), expression of both ABCG5 and ABCG8 did not differ between both groups. However, expression of NPC1L1, which mediates the intestinal absorption of cholesterol, was 56% lower in HF hamsters (P < 0.001).

Whereas SR-BI expression did not differ between the groups, LDLR expression was less in HF hamsters (65 ± 11 arbitrary units) than in the CON group (100 ± 11 arbitrary units) (P = 0.013) (Fig. 1B).

In vivo macrophage-to-feces RCT is altered in hamsters fed a HF diet. To investigate whether the HF diet affected the

### Table 1

<table>
<thead>
<tr>
<th>Variable</th>
<th>CON</th>
<th>HF</th>
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<tbody>
<tr>
<td>Body weight, g</td>
<td>120 ± 2.0</td>
<td>121.7 ± 2.3</td>
</tr>
<tr>
<td>Food intake, g/d</td>
<td>65 ± 0.7</td>
<td>61.9 ± 0.3</td>
</tr>
<tr>
<td>Water intake, mL/d</td>
<td>7.9 ± 0.9</td>
<td>7.3 ± 0.8</td>
</tr>
<tr>
<td>Blood glucose, mmol/L</td>
<td>40 ± 0.3</td>
<td>64.6 ± 0.2*</td>
</tr>
<tr>
<td>Plasma insulin, pmol/L</td>
<td>34.2 ± 2.4</td>
<td>115 ± 15.0*</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>0.8 ± 0.1</td>
<td>5.4 ± 0.6*</td>
</tr>
<tr>
<td>Plasma TG, mmol/L</td>
<td>0.9 ± 0.1</td>
<td>4.4 ± 0.6*</td>
</tr>
<tr>
<td>Plasma total cholesterol, mmol/L</td>
<td>3.2 ± 0.1</td>
<td>7.9 ± 0.3*</td>
</tr>
<tr>
<td>Plasma HDL-C, mmol/L</td>
<td>2.2 ± 0.1</td>
<td>4.2 ± 0.2*</td>
</tr>
<tr>
<td>Plasma non HDL-C, mmol/L</td>
<td>1.0 ± 0.1</td>
<td>3.7 ± 0.4*</td>
</tr>
<tr>
<td>Plasma HDL-C:total cholesterol ratio</td>
<td>0.68 ± 0.01</td>
<td>0.54 ± 0.04*</td>
</tr>
<tr>
<td>Plasma CETP activity, mmol · L⁻¹ · h⁻¹</td>
<td>52 ± 2</td>
<td>80 ± 2*</td>
</tr>
<tr>
<td>Plasma alanine aminotransferase, μmol/L</td>
<td>78.5 ± 2.5</td>
<td>116 ± 4.0*</td>
</tr>
<tr>
<td>Plasma aspartate aminotransferase, μmol/L</td>
<td>62.0 ± 2.4</td>
<td>59.0 ± 4.6</td>
</tr>
<tr>
<td>Liver weight, g</td>
<td>3.7 ± 0.1</td>
<td>5.8 ± 0.3*</td>
</tr>
<tr>
<td>Liver total cholesterol, μmol/mg tissue</td>
<td>22.7 ± 1.1</td>
<td>87.0 ± 1.3*</td>
</tr>
<tr>
<td>Liver TG, μmol/mg tissue</td>
<td>145 ± 1.2</td>
<td>31.1 ± 1.3*</td>
</tr>
<tr>
<td>Liver fatty acids, mmol/mg tissue</td>
<td>235 ± 1.7</td>
<td>79.5 ± 2.5*</td>
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</table>

1 Values are mean ± SEM, n = 8. *Different from CON, P < 0.001. CON, nonpurified diet; HDL-C, HDL-cholesterol; HF, high fat.
2 HOMA-IR index was calculated from individual blood glucose (mmol/L) and plasma insulin (mU/L) values as follows: HOMA-IR = [blood glucose (mmol/L) × plasma insulin (mU/L)]/22.5. Conversion factor used for calculation: 1 mU/L insulin = 6 pmol/L.
rate of RCT in vivo, CON and HF hamsters were injected with $^3$H-cholesterol labeled/cholesterol loaded macrophages after 4 wk of treatment (Fig. 2). Compared to CON hamsters, $^3$H-tracer appearance was ~50% higher in HF hamsters at 24, 48, and 72 h (all $P < 0.01$) after $^3$H-cholesterol labeled macrophage injection (Fig. 2A). However, $^3$H-tracer appearance in HDL did not differ between the groups at any time (Fig. 2B), suggesting that most of the $^3$H-tracer was carried by non-HDL lipoproteins (VLDL+LDL) in HF hamsters. After 72 h, the $^3$H-tracer recovery in liver was 318% greater in HF hamsters than in CON hamsters ($P < 0.01$) (data not shown). This difference was related to greater hepatic $^3$H-cholesterol and $^3$H-bile acid recoveries, which were 293 and 254% higher, respectively ($P < 0.01$), in HF hamsters (Fig. 2C). Inversely, the $^3$H-tracer recovered into the bile (Fig. 2D) was 75% lower in HF compared to CON hamsters ($P < 0.01$). However, $^3$H-tracer recovery in fecal cholesterol (Fig. 2E) was 45% higher in HF hamsters ($P < 0.01$), whereas $^3$H-tracer recovered in fecal bile acids did not differ between the groups. HF hamsters had a 55% higher fecal cholesterol excretion ($P < 0.01$) compared to CON hamsters (Fig. 2F). Inversely, the mass of total bile acids excreted in feces was 47% lower in HF hamsters ($P < 0.01$).

Finally, we investigated whether higher cholesterol fecal excretion after the HF diet was related to lower intestinal cholesterol absorption. After 4 wk of the diet treatment, CON and HF hamsters were given $^3$H-cholesterol labeled olive oil by oral gavage to measure $^3$H-tracer appearance in plasma and HDL. Compared to CON hamsters, HF hamsters had 43, 105, and 114% higher $^3$H-tracer plasma appearance at 3, 5, and 6 h, respectively (Fig. 3A), indicating an increased cholesterol absorption in HF hamsters. The calculated AUC was 89% higher in HF hamsters ($P < 0.05$). Appearance of the $^3$H-tracer in HDL was 32 and 25% higher in HF than in CON hamsters at 5 and 6 h, respectively ($P < 0.05$) (Fig. 3B). However, the calculated AUC did not differ between the groups.

**Discussion**

Macrophage-to-feces RCT has been extensively investigated over the last 30 y. Despite the current epidemic of obesity and type 2 diabetes, little is known about the potent alterations of this antiatherogenic process in the face of metabolic syndrome. The aim of the present study was therefore to develop a nutritional model to evaluate the effects of metabolic syndrome on macrophage-to-feces RCT in vivo. Although the goal was to mimic the

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**TABLE 2** Hepatic and intestinal mRNA expression in hamsters fed a CON or HF for 4 wk.

<table>
<thead>
<tr>
<th></th>
<th>CON</th>
<th>HF</th>
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<tr>
<td>Liver mRNA expression, fold of CON</td>
<td></td>
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</tr>
<tr>
<td>LDLR</td>
<td>1.00 ± 0.08</td>
<td>0.52 ± 0.01*</td>
</tr>
<tr>
<td>ACAT2</td>
<td>1.00 ± 0.09</td>
<td>0.39 ± 0.03*</td>
</tr>
<tr>
<td>ABCG5</td>
<td>1.00 ± 0.06</td>
<td>0.37 ± 0.04*</td>
</tr>
<tr>
<td>ABCG8</td>
<td>1.00 ± 0.05</td>
<td>0.44 ± 0.07*</td>
</tr>
<tr>
<td>Jejunum mRNA expression, fold of CON</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABCG5</td>
<td>1.00 ± 0.13</td>
<td>1.22 ± 0.07</td>
</tr>
<tr>
<td>ABCG8</td>
<td>1.00 ± 0.06</td>
<td>1.01 ± 0.15</td>
</tr>
<tr>
<td>NPC1L1</td>
<td>1.00 ± 0.08</td>
<td>0.44 ± 0.04*</td>
</tr>
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</table>

1 Values are mean ± SEM, n = 8. *Different from CON, $P < 0.001$. CON, nonpurified diet; HF, high fat.
human situation in which intakes of vitamins and other micronutrients may be reduced due to overconsumption of energy-dense foods (20), the lack of adjustment for essential nutrients for the HF diet in this study is a limitation, as it may affect the outcome studied. For instance, Zn and Cu deficiencies alter lipoprotein metabolism (21,22). Despite this limitation, the main features of metabolic syndrome were induced in hamsters fed the HF diet: hyperglycemia, hyperinsulinemia, insulin resistance (as measured by HOMA-IR), and dyslipidemia. Interestingly, this hamster model also develops a severe liver steatosis, which precedes the development of nonalcoholic fatty liver disease, a common feature in patients with metabolic syndrome (23), which likely contributes to increased cardiovascular risk (24).

Hamsters fed the HF diet had several alterations in macrophage-to-feces RCT. After 3H-cholesterol labeled macrophage injection, we observed a higher 3H-tracer appearance in the plasma, but not in the HDL fraction. This might be related to the higher CETP activity (which transfers macrophage-derived cholesterol from HDL to atherogenic VLDL and LDL lipoproteins) and a lower hepatic uptake of the VLDL/LDL particles (through lower LDLR expression). These deleterious effects of a HF/high cholesterol diet increasing CETP activity and reducing LDLR-dependent uptake have been previously described in hamsters (12,25,26). Concomitant with the severe liver steatosis, the hepatic 3H-tracer recovery was dramatically higher, whereas the 3H-tracer recovery in bile was lower in HF hamsters. These data suggest an accumulation of macrophage-derived cholesterol in the liver and a severe impairment of biliary excretion. In fact, we observed a lower hepatic mRNA expression of ABCG5 and ABCG8, both known to mediate biliary cholesterol excretion (27). Taken together, these results highlight the harmful effects of liver steatosis on macrophage-to-feces RCT, suggesting that liver steatosis might contribute to increased cardiovascular risk through an impairment of liver cholesterol metabolism and biliary excretion.

Despite the strong impairment of cholesterol fluxes at the liver levels, a 45% increase in macrophage-derived cholesterol fecal excretion was observed in hamsters fed the HF diet. Because the mass of cholesterol excreted in feces was also higher, we therefore hypothesized that higher fecal cholesterol excretion was related to lower intestinal cholesterol absorption. Indeed, we observed a lower NPC1L1 expression, the protein mediating intestinal cholesterol absorption. Lower NPC1L1 expression promotes macrophage-to-feces RCT by preventing the intestinal reabsorption of cholesterol deriving from bile (17). Surprisingly, intestinal cholesterol absorption was found to be dramatically higher in HF hamsters. This suggests that the higher fecal cholesterol excretion may not be due to lower intestinal cholesterol absorption. Because the contribution of both the “classical” biliary pathway and the intestinal cholesterol absorption to promote fecal cholesterol excretion seems unlikely, we therefore propose that other mechanisms, such as increased intestinal cell shedding or upregulation of the TICE pathway could play a role. As recently investigated, TICE is a nonbiliary pathway mediating the direct excretion of cholesterol from plasma to the intestinal lumen (28). Although the molecular mechanism (29) and the contribution of TICE in the overall RCT (30) remain to determined, some studies in mice have suggested that TICE can be stimulated with pharmacologic intervention, e.g., liver X receptor agonist (31) as well as dietary manipulations. For instance, a Western-type diet, containing high fat and high cholesterol levels, was found to upregulate TICE in mice (32). In another study, Brown et al. (33) showed that mice deficient in hepatic ACAT2 had an increased fecal cholesterol excretion without a changed biliary cholesterol excretion. These authors suggested that hepatic ACAT2 depletion might result in the secretion of specific lipoprotein particles redirecting cholesterol toward TICE (33). In the present study, we also observed a reduction in hepatic ACAT2 mRNA expression in hamsters fed the HF diet. It is thus possible that both the reduction in hepatic ACAT2 and high levels of dietary fat may have contributed to stimulate TICE in HF hamsters, which would have led to the ~50% increase in fecal cholesterol excretion. Although further investigations are needed to measure the contribution of TICE in hamster RCT, the present study suggests that HF-fed hamsters could be a potential model to investigate this alternative pathway.

From a physiologic point of view, the upregulation of TICE could actually represent an alternative mechanism against the cholesterol overflow when consuming the HF diet. However, the 45% increase in macrophage-derived cholesterol fecal excretion does not appear to compensate for metabolic disorders (e.g., hypercholesterolemia and liver steatosis) induced by dietary fat and fructose overloading. In the present study, the most impaired steps of RCT were localized in the liver. Upon liver steatosis, macrophage-derived cholesterol would accumulate in the liver, with a concomitant reduction in biliary excretion, thereby contributing to nonalcoholic fatty liver disease and cardiovascular risk (23). Regarding novel treatments of diabetic dyslipidemia, it would be important to evaluate whether a given therapy targeting RCT also improves liver steatosis to promote cholesterol fluxes toward biliary excretion. For instance, raising HDL levels with CETP inhibition has emerged as a promising therapy in humans (34,35). CETP inhibition has shown a potential to promote RCT in normalipi-
ademic hamsters (36,37), but this remains to be investigated in dyslipidemic hamsters with liver steatosis. Because the hamster has a similar lipoprotein metabolism to humans, our data also suggest that this animal model could be useful for evaluating the effects of therapies targeting RCT in patients with metabolic syndrome.

Acknowledgments

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Literature Cited


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