Effect of Fenofibrate on Plasma Lipoprotein Composition and Kinetics in Patients With Complete Hepatic Lipase Deficiency

Isabelle L. Ruel, Benoît Lamarche, Jean-François Mauger, Karen O. Badellino, Jeffrey S. Cohn, Michel Marcil, Patrick Couture

Objective—The goal of this study was to characterize the effect of microcoated fenofibrate (160 mg/day for 6 months) on plasma lipoprotein composition and kinetics in 2 patients with complete hepatic lipase (HL) deficiency.

Methods and Results—Fenofibrate treatment normalized the plasma lipoprotein profile of patients with complete HL deficiency, as evidenced by significant reductions in the plasma concentration of cholesterol (−49%) and triglycerides (−82%) and a significant increase in low-density lipoprotein (LDL) size (251.5±1.8 versus 263.5±0.7 Å). The in vivo kinetics of very low–density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), and LDL apolipoprotein (apo)B-100 and plasma apoA-I and apoA-II were studied using a primed-constant infusion of L-[5,5,5-D3]-leucine for 12 hours in the fasted state. Fenofibrate treatment in complete HL-deficient patients substantially decreased plasma concentrations of VLDL, IDL, and LDL apoB-100 attributable to important increases in VLDL (+325%), IDL (+129%), and LDL (+218%) apoB-100 fractional catabolic rates (FCR). LDL apoB-100 FCR nevertheless remained 60% lower after treatment compared with values obtained in controls (n=5). The kinetics of plasma apoA-I and apoA-II as well as the capacity of high-density lipoprotein particles to efflux cellular cholesterol from normal human skin fibroblasts was not altered by fenofibrate.

Conclusion—Fenofibrate therapy exerts a pronounced antiatherogenic effect on triglyceride-rich lipoproteins even in the complete absence of HL. (Arterioscler Thromb Vasc Biol. 2005;25:2600-2607.)

Key Words: lipids ■ primary prevention ■ genetics of cardiovascular disease ■ lipid and lipoprotein metabolism

Since the early 1960s, fibric acid derivatives have been widely used to treat atherogenic dyslipidemias. Their principal action is to reduce plasma triglyceride (TG) and cholesterol, and increase plasma high-density lipoprotein (HDL) levels, leading to a significant reduction in risk for coronary heart disease (CHD). In humans, fibrates exert their effects on plasma lipids by modifying the expression of genes involved in lipoprotein metabolism in the liver. The lipid-modifying effects of fibrates have recently been elucidated at the molecular level and involve the activation of peroxisome proliferator-activated receptor-α (PPARα), a transcription factor belonging to the nuclear receptor family. After ligand activation, PPARα binds to specific response elements, termed peroxisome proliferator-response elements (PPREs), and regulates the expression of genes involved in lipoprotein metabolism. Functional PPREs have been identified in the regulatory regions of the human lipoprotein lipase (LPL) and apolipoprotein (apo)C-III, apoA-I, and apoA-II genes.

Complete hepatic lipase (HL) deficiency is a very rare genetic disorder that has been identified in only 7 families to date. This disorder, which appears to be inherited as an autosomal recessive trait, is generally associated with a dyslipidemic profile characterized by an elevation in the plasma concentration of cholesterol and TG, and an increased prevalence in CHD. We previously described 2 brothers with complete HL deficiency (compound heterozygotes for the A174T and T383M mutations) from the Québec-based HL deficiency (QHLD) kindred. Kinetic studies revealed that hypertriglyceridemia and hypercholesterolemia in these individuals resulted from an accumulation of remnant lipoproteins attributable to a reduction in apoB-containing lipoprotein catabolism. They also had marked TG-enriched HDL and low-density lipoprotein (LDL) particles and reduced HDL catabolism compared with TG-matched controls.

To date, the extent to which fibrates can beneficially alter...
lipoprotein composition and metabolism in the absence of lipolytically active HL in humans is unknown.

The aim of the present study was therefore to characterize the effects of microcoated fenofibrate, the long-acting form of fenofibrate, on lipoprotein composition and metabolism in 2 males with complete HL deficiency from the QHLD kindred. The in vivo kinetics of very low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), and LDL apoB-100 and plasma apoA-I and apoA-II were investigated before and after treatment. The effect of fenofibrate on the capacity of total plasma and of HDL particles to efflux cellular cholesterol and the distribution of apoA-I among various HDL subfractions was also examined.

**Methods**

**Subjects**

The 2 complete HL-deficient males from the QHLD kindred have been described in detail elsewhere.6 Briefly, the 2 patients (1-5 and 1-6) were compound heterozygous for the A174T and T383M mutations in the HL gene, which were associated with extremely low to undetectable HL activity and normal LPL activity. They were apoE3 homozygotes. At their baseline evaluation, the 2 complete HL-deficient patients were characterized by hypertriglyceridemia (mean±SD: 7.17±3.74 mmol/L) and were therefore submitted to treatment with microcoated fenofibrate for 6 months (Lipidil Supra, 160 mg/day. One compound heterozygous male (1-5) was being treated for hypothyroidism with 100 g/day of levothyroxine before treatment. The other patient with complete HL deficiency (1-6) was being treated for hypothyroidism with 100 g/day of levothyroxine before and during fenofibrate therapy. We also investigated 5 unrelated normotriglyceridemic male subjects recruited at the Lipid Research Center in Québec that were matched for gender, age, weight, and body mass index (BMI) and were not using hypolipidemic medications. All participants gave their written informed consent to participate in this study, which received the approval from local ethics committees.

**Lipid and Lipoprotein Analyses**

Fasted blood samples were drawn into tubes containing 0.15% EDTA, and plasma was isolated by centrifugation (3000 rpm at 4°C, 15 minutes). The lipid content of plasma and lipoprotein subfractions isolated by sequential ultracentrifugation and precipitation methods was determined by enzymatic methods with an AutoAnalyzer RA-1000 (Technicon Instruments Corporation).10 Plasma apoB-100, apoA-I, and apoA-II levels were measured by nephelometry (Dade Behring). VLDL, IDL, and LDL apoB-100 levels, plasma apoC-III, cholesteryl ester transfer protein (CETP), HL, and endothelial lipase (EL) concentrations were determined by ELISA.6,9,11-13 Remnant-like particles (RLP) were isolated as reported.8 Post-heparin (60IU/kg body weight) LPL and HL activities were measured as previously described.6 Nondenaturing polyacrylamide gradient gel electrophoresis (PAGGE) was used to determine LDL and HDL particle size.6,9

**Apolipoprotein Kinetic Studies**

The kinetics of VLDL, IDL, and LDL apoB-100 and plasma apoA-I and apoA-II were performed in the fasted state using a primed constant infusion of [1H]cholesteryl (0.2µCi/mL; New England Nuclear-Dupont) for 48 hours and were then loaded with nonlipoprotein cholesterol (20 µg/mL) for 24 hours. Efflux studies were carried out in the presence of 50 µg/mL HDL apoA-I (d=1.063 to 1.21g/mL) or with 20% total fasting plasma. Efflux at 8 hours was determined in triplicate as the percent total cholesterol in the medium (1H in medium divided by 1H in medium plus 1H in cells after 0.1N NaOH hydrolysis).9

**Cholesterol Efflux Studies**

Skin fibroblasts from normal subjects were labeled with [3H]cholesteryl (0.2µCi/mL; New England Nuclear-Dupont) for 48 hours and were then loaded with nonlipoprotein cholesterol (20 µg/mL) for 24 hours. Efflux studies were carried out in the presence of 50 µg/mL HDL apoA-I (d=1.063 to 1.21g/mL) or with 20% total fasting plasma. Efflux at 8 hours was determined in triplicate as the percent total cholesterol in the medium (1H in medium divided by 1H in medium plus 1H in cells after 0.1N NaOH hydrolysis).9

**Two-Dimensional Nondenaturing Gradient Gel Electrophoresis**

Lipoproteins in fasted plasma were separated by two-dimensional nondenaturing gradient gel electrophoresis as described previously.9 Quantification of apoA-I–containing HDL subpopulations was carried out by densitometric scanning (AlphaInnotech Co) by multiplying the total plasma apoA-I concentrations (mg/dl) by the relative area of each integrated HDL subpopulations.

**Results**

Patient characteristics, plasma lipids, and lipoprotein concentrations are shown in Table 1. It should be noted that 10% and 6% reductions in BMI and waist circumference were observed in HL-deficient patient 1-6, which was not seen in the other patient with complete HL deficiency. Thus, taken as a group, mean BMI and waist circumference in the 2 complete HL-deficient patients before and after fenofibrate were essentially similar to those of control subjects. Fenofibrate resulted in a 49% reduction (on average) in total plasma cholesterol concentration and a 41% reduction in plasma phospholipid concentration. Fasting plasma TG levels were 4-fold higher in complete HL-deficient patients than in control subjects but were decreased by 82% on average by fenofibrate, reaching values similar to those in control subjects. The major changes induced by fenofibrate therapy were observed in the VLDL fraction, with a 16-fold decrease in VLDL cholesterol and VLDL-TG levels. RLP-cholesterol was reduced 85% by treatment. Plasma LDL-TG and HDL-TG levels were reduced by 59% and 53%, respectively, but nevertheless remained significantly higher than values in control subjects (186% and 90%, respectively). Additionally, a marked treatment-induced increase in LDL particle size (from 251.5±74.3 to 263.5±0.7 Å) was observed. The 2 male patients at baseline were characterized by HDL cholesterol levels that appeared as being relatively low for complete HL deficiency, as previously discussed,9 and were not increased by fenofibrate treatment. Finally, fenofibrate did not significantly affect plasma CETP mass, postheparin HL mass, or activity in complete HL-deficient patients but led to a 25% decrease in plasma EL concentrations, a 62% increase in LPL activity, and a concomitant 63% decrease in plasma apoC-III levels.

Plasma leucine enrichment remained constant for all subjects throughout the 12-hour infusion experiments (data not shown). Averaged VLDL, IDL, and LDL apoB-100 leucine tracer/tracer ratios in patients before and after fenofibrate therapy and in control subjects are shown in Figure 1. Fenofibrate treatment restored the VLDL, IDL, and LDL apoB-100 tracer/tracer enrichment curves toward those obtained in control subjects. Fenofibrate reduced VLDL apoB-100 concentrations by 80% in patients with complete HL deficiency, which was predominantly attributable to a 325% increase in the fractional catabolic rates (FCR) of VLDL apoB-100 (Table 2). Treatment with fenofibrate was associated with a reduction in VLDL apoB-100 production rate (PR) only in patient 1-6 (39.9 versus 20.3 mg/kg per day, before and after treatment, respectively). The 2 complete HL-deficient patients were characterized by an accumulation of IDL particles at baseline compared with controls (pool size: 899±305 versus 74±33 mg). Fenofibrate treatment
reduced IDL apoB-100 concentrations by 89% through a 74% decrease in the PR of IDL apoB-100 combined with a 129% increase in the FCR of IDL apoB-100, which remained 60% lower than in control subjects. A significant 3-fold increase in LDL apoB-100 FCR and a 2-fold increase in the LDL apoB-100 PR were also induced by fenofibrate. Both LDL apoB-100 FCR and PR values were normalized by fenofibrate treatment.

Table 3 shows plasma apoA-I and apoA-II kinetics in the 2 groups. ApoA-I and apoA-II concentrations and pool sizes were higher in the 2 complete HL-deficient patients at baseline compared with control subjects and were not further modified by fibrate therapy. Treatment with fenofibrate had only marginal effects on apoA-I and apoA-II kinetics in patients with HL deficiency.

To determine whether fenofibrate-mediated modifications in the lipoprotein-lipid profile might influence cellular cholesterol efflux, we measured the capacity of total plasma and HDL particles (d=1.006 to 1.063 g/mL) except for LDL particle size, which was computed while excluding IDL particles.
HDL (α₃) were evident in complete HL-deficient patients at baseline compared with the control subject, whereas levels of pre−β₁-migrating HDL–apoA-I appeared to be slightly above normal. Quantification of apoA-I–containing HDL subpopulations also showed that treatment with fenofibrate was associated with an increase in α₁- and pre−α-migrating particles in subject 1-6, whereas it was principally associated with a decrease in pre−α₁-migrating HDL subpopulations in patient 1-5. Both subjects with HL deficiency were characterized by an apparent normalization of pre−β₁-migrating HDL–apoA-I particles after fibrate therapy.

**Discussion**

The results of the present study indicate that microcoated fenofibrate is very effective in treating the dyslipidemia characterizing patients with complete HL deficiency. Results also suggest that the impact of fenofibrate on blood lipid levels is largely independent of changes in HL activity. Fenofibrate treatment led to a marked reduction in plasma and VLDL-TG, cholesterol, and phospholipid levels as well as in LDL and HDL-TG levels. VLDL, IDL, and LDL apoB-100 concentrations were markedly reduced, and kinetic studies revealed that these beneficial lipoprotein-lipid changes were mainly attributable to increased catabolism of all apoB-100–containing lipoproteins, including IDL. Fenofibrate treatment did not, however, completely eliminate the typical dyslipidemic features of HL deficiency, namely increased HDL-TG and LDL-TG levels and reduced rates of IDL apoB-100 catabolism. Despite a reduction in levels of pre−β₁-migrating HDL–apoA-I particles, no modification in the capacity of total plasma or of HDL particles to efflux cellular cholesterol from normal human skin fibroblasts was observed in the 2 complete HL-deficient patients after treatment with fenofibrate.

Fibrates exert a wide spectrum of lipid-modulating actions involving reduction in VLDL, VLDL remnants, IDL, and LDL levels, and elevation of cardioprotective HDL concentrations. Fenofibrate has been reported to bind to PPARα to modulate the expression of genes that play key roles in the metabolism of TG-rich lipoproteins, fatty acids, and HDL. Lipoprotein lipase and its inhibitor, apoC-III, are 2 genes that are regulated by fibrates. Whereas fibrates are known to suppress the expression of apoC-III, LPL is, on the other hand, a gene that is upregulated by fibrates though PPARα activation. In the present study, the reduction in the lipid content of VLDL, IDL, and LDL particles was mainly attributable to an increase in the catabolism of VLDL, IDL, and LDL apoB-100 in the 2 complete HL-deficient patients after fenofibrate treatment. A reduction in the PR of VLDL apoB-100 in patient 1-6 may also have contributed to the overall lowering of VLDL apoB-100 concentrations. In previous kinetic studies, VLDL apoB-100 PR has been reported to be strongly correlated with abdominal adipose tissue levels, before and after weight reduction in obese subjects. We hypothesize that the reduction in VLDL apoB-100 PR in patient 1-6 after fenofibrate treatment may have been modulated, at least partly, by the slight reduction in abdominal fat observed in this subject over the same period. Fenofibrate treatment did not alter plasma postheparin HL mass or activity in complete HL-deficient patients but was associated with a substantial elevation in postheparin LPL (63.8% and 62.5% increase in LPL activity for subject 1-5 and 1-6, respectively). We hypothesize that the 63% reduction in plasma apoC-III levels by fenofibrate may have contributed, together with the direct upregulation of LPL gene expression by fenofibrate, to the mean 62% elevation in intravascular LPL activity, which was most likely the primary factor contributing not only to the reduction in TG in plasma but also to the more efficient rate of conversion of VLDL to IDL and subsequently to LDL in the 2 patients with complete HL deficiency.

In addition to its beneficial action on circulating TG-rich lipoprotein levels, fenofibrate also caused a shift in the distribution of small dense LDL particles toward larger LDL in the 2 complete HL-deficient males. Large less dense LDL have been previously shown to more closely interact with the
TABLE 2. Kinetics of ApoB-100–Containing Lipoproteins in Complete HL-Deficient Patients Before and After Treatment With Fenofibrate

<table>
<thead>
<tr>
<th>VLDL</th>
<th>LDL</th>
<th>FCR, mg/kg per day</th>
<th>ACR, mg/kg per day</th>
<th>PR, mg/kg per day</th>
</tr>
</thead>
<tbody>
<tr>
<td>ApoB-100, mg/dl</td>
<td>Pool Size, mg</td>
<td>pools/day</td>
<td>mg/kg</td>
<td>pools/day</td>
</tr>
<tr>
<td>Control subjects (n = 5)</td>
<td>Mean ± SD</td>
<td>9.9 ± 3.5</td>
<td>394 ± 124</td>
<td>9.2 ± 3.5</td>
</tr>
</tbody>
</table>

Complete HL deficiency

Before treatment

1-5

20.6 1421 2.4 3446 33.4 24.0 1115 0.8 892 8.7 122.9 5709 0.08 409 4.5

1-6

33.1 1352 2.3 3176 39.9 16.7 683 1.9 1311 14.4 72.5 2967 0.14 409 4.5

Mean ± SD

31.8 ± 1.7 1386 ± 49 2.4 ± 0.1 3311 ± 191 36.7 ± 4.6 20.4 ± 5.2 899 ± 305 1.4 ± 0.8 1102 ± 296 11.6 ± 4.1 97.7 ± 35.6 4338 ± 1939 0.11 ± 0.04 436 ± 7.7 4.5 ± 0.1

After treatment

1-5

9.2 432 8.4 3650 34.9 2.8 132 2.2 294 2.8 62.7 2950 0.30 897 8.6

1-6

3.8 140 12.0 1678 20.3 1.6 60 4.3 257 3.1 64.1 2373 0.40 462 4.5

Mean ± SD

6.5 ± 3.8 286 ± 206 10.2 ± 2.5 2664 ± 1395 27.6 ± 10.3 2.2 ± 0.8 96 ± 51 3.2 ± 1.4 276 ± 27 3.0 ± 0.2 63.4 ± 1.0 2662 ± 407 0.35 ± 0.07 925 ± 39 10.1 ± 2.1

Change attributable to treatment (%)

-80% -79% +325% -19% -25% -89% -89% -129% -75% -74% -35% -39% +218% +112% +124%

Post-treated vs controls (%)

-34% -27% +11% -23% -28% +22% +30% -60% -50% -50% -26% -26% -5% -15% -16%

ACR indicates absolute clearance rate in mg/day (FCR [pools/day] * PS [mg]). Values are expressed as mean ± SD.

LDL receptor than smaller particles, thereby accelerating LDL clearance, and the 218% increase in the LDL apoB-100 FCR on fibrate therapy in patients with complete HL deficiency supports this concept. It has been reported that patients with LPL deficiency have markedly smaller LDL particles compared with healthy individuals, a change attributed in part to the TG enrichment of LDL and subsequent hydrolysis by HL. Thus, the increase in LPL activity, which contributed to the lowering of plasma TG levels, may have been responsible for the important increase in LDL particle size in patients with HL deficiency. Recent studies in mice have suggested that EL, a recently discovered lipase, may play a role in the modulation of apoB-containing lipoproteins. In the present study, EL concentrations have been found to be moderately reduced in the 2 complete HL-deficient patients after treatment with fenofibrate. It is known that EL is upregulated in endothelial cells in response to inflammatory cytokines interleukin-1β and tumor necrosis factor-α. Although no

TABLE 3. Kinetics of Plasma ApoA-I and ApoA-II in Complete HL-Deficient Patients Before and After Treatment With Fenofibrate

<table>
<thead>
<tr>
<th>Plasma ApoA-I</th>
<th>Plasma ApoA-II</th>
</tr>
</thead>
<tbody>
<tr>
<td>ApoA-I, mg/dl</td>
<td>Pool Size, mg</td>
</tr>
<tr>
<td>Control subjects (n = 5)</td>
<td>Mean ± SD</td>
</tr>
</tbody>
</table>

Complete HL deficiency

Before treatment

1-5

150 6966 0.155 1080 10.46 45 2090 0.128 267 2.59

1-6

144 5890 0.205 1207 13.31 49 2004 0.146 293 3.21

Mean ± SD

147 ± 4 6428 ± 761 0.180 ± 0.035 1144 ± 90 11.88 ± 2.01 47 ± 3 2047 ± 61 0.137 ± 0.013 280 ± 18 2.90 ± 0.44

After treatment

1-5

140 6584 0.184 1211 11.57 48 2257 0.170 384 3.67

1-6

160 5926 0.206 1221 14.84 54 2000 0.112 224 2.71

Mean ± SD

150 ± 14 6255 ± 465 0.195 ± 0.016 1216 ± 7 13.20 ± 2.31 51 ± 4 2128 ± 182 0.141 ± 0.041 304 ± 113 3.19 ± 0.68

Change attributable to treatment (%)

+2% -3% +8% +6% +11% +8% +4% +3% +9% +10%

Post-treated vs controls (%)

+5% +10% +11% +23% +21% +42% +45% -2% +39% +35%

ACR indicates absolute clearance rate in mg/day (FCR [pools/day] * PS [mg]). Values are expressed as mean ± SD.
shown that fibrate treatment increased pre-β,HDL levels at the expense of large HDL₂ in patients with hypertriglyceridemia, a change that was in part ascribed to an increase in HL activity.25 Indeed, the hydrolysis of HDL₂ by HL leads to the release of phospholipids and apoA-I that can then reassociate to form pre-β₂-HDL.26 However, in the absence of HL activity, such beneficial effect of fibrate in the 2 patients from the QHLD kindred may have been impaired.

The abnormal composition of HDL particles in the complete HL-deficient patients before treatment with fenofibrate was not associated with alterations in cellular cholesterol efflux and was not further modified after treatment with fenofibrate. PPARα activators such as fibrates have been shown to influence reverse cholesterol transport (RCT) by accelerating cholesterol efflux from peripheral cells through stimulation of ABCA₁27 and by increasing the selective uptake of cholesterol esters by the liver through an increase in murine and human cell-surface receptors SR-BI and CLA-1.24 We therefore hypothesize that overall RCT may have been enhanced in the complete HL-deficient patients after treatment with fenofibrate. The 2 patients were characterized by large α-migrating particles, as observed on 2D-PAGGE. However, the effect of fenofibrate treatment on all apoA-I-containing HDL subpopulations was slightly different for subject 1-5, who presented with a reduction in pre-α₁-migrating HDL. Because the formation of pre-α₁-migrating HDL depends firstly on the presence of lipid-free apoA-I,23 this difference between the 2 patients may have resulted from a differential effect of fenofibrate on apoA-I kinetics, subject 1-5 showing a reduction in apoA-I pool size attributable to a larger increase in apoA-I FCR compared with his brother. Moreover, the mobility of pre-α particles has been shown to be related to their phospholipid content.23 Using phospholipid transfer protein (PLTP)- and PPARα-deficient mice, Boulby et al28 showed that fenofibrate increases plasma PLTP as a result of upregulation of PLTP gene expression through PPARα, and this mechanism may account for the large HDL particles observed in complete HL deficiency after fenofibrate, despite a 53% decrease in HDL-TG levels. However, the extent to which changes in PLTP activity are responsible for the changes in lipoprotein metabolism in HL-deficient subjects remains to be established. The reduced EL concentrations after treatment with fenofibrate in HL deficiency may also have played a role in the regulation of these apoA-I-containing HDL particles.

In summary, we have shown that microcoated fenofibrate treatment in complete HL deficiency in the QHLD kindred was associated with a marked reduction in hypertriglyceridemia and improvements in the composition and metabolism of all apoB-containing lipoproteins despite the absence of HL, with marginal effects on HDL. The beneficial effects of fenofibrate on apoB-containing lipoproteins were likely mediated by an activation of PPARα and the subsequent regulation of genes involved in lipoprotein metabolism, principally LPL, and was clearly not dependant on HL. Our results thus demonstrate that HL is not necessary for the normalization of apoB-containing lipoprotein clearance with fenofibrate. We therefore propose that fenofibrate treatment is an effective agent to treat the dyslipidemia associated with functional PPRE has been found on the EL gene, fenofibrate-mediated activation of PPARα is involved in the control of the inflammatory response through an attenuation of expression of inflammatory proteins.20 Thus, these pleiotropic effects of fenofibrate may have downregulated the expression of EL, thereby potentially contributing to the shift of LDL toward larger particle size in complete HL deficiency.

It has been shown that HL is responsible for the hydrolysis of phospholipids and TG within HDL₂ particles, thus contributing to the regeneration of smaller HDL₁ particles.21 In the present study, fenofibrate therapy led to a small increase in the PR of plasma apoA-I, possibly through activation of genes regulating PPARα.22 Together with the enhanced LPL lipolytic production of surface fragments from TG-rich lipoproteins, this may have resulted in the observed small increase in plasma HDL cholesterol levels after fenofibrate in the 2 males with complete HL deficiency. However, a slight enhancement of apoA-I FCR with fenofibrate was also seen in 1 of the 2 complete HL-deficient patients. We hypothesize that this may in part be related to an increased activity of hepatic HDL receptors with fenofibrate.23 Indeed, scavenger receptor class B type 1 (SR-BI) and its human homologue, CD36-LIMPII-analagous 1 (CLA-1), are hepatic receptors whose gene expression are upregulated through a PPARα-mediated action of fibrates.24 A reduction in pre-β₁-HDL in the 2 subjects with HL deficiency was also observed after fibrate therapy. In a previous study using bezafibrate, it was
HL deficiency, presumably leading to a clinically meaningful reduction in the risk of premature atherosclerosis associated with this dyslipidemia. The extent to which beneficial pleiotropic effects of fenofibrate, such as antiinflammatory effects, influence the risk of CVD in complete HL-deficient patients remains to be established.

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