Lipoprotein metabolism in APOB L343V familial hypobetalipoproteinemia

Abbreviated title: Lipoprotein metabolism in APOB L343V FHBL

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Abstract

Context: Familial hypobetalipoproteinemia (FHBL) is a co-dominant disorder of lipoprotein metabolism characterized by decreased plasma concentrations of low density lipoprotein (LDL)-cholesterol and apolipoprotein (apo) B.

Objective: To examine the effect of heterozygous APOB L343V FHBL on postprandial triglyceride-rich lipoprotein (TRL) and fasting lipoprotein metabolism.

Methods: Plasma incremental area under the curve (iAUC) apoB-48 and apoB-48 kinetics were determined after ingestion of a standardized oral fat load using compartmental modeling. Very low density lipoprotein (VLDL)-, intermediate density lipoprotein (IDL)-, and LDL-apoB kinetics were determined in the fasting state using stable isotope methods and compartmental modeling.

Results: The postprandial iAUC (0-10 h) in FHBL subjects (n=3) was lower for large TRL-triglyceride (-77%; *P*<0.0001), small TRL-cholesterol (-83%; *P*<0.001), small TRL-triglyceride (-88%; *P*<0.001), and plasma triglyceride (-70%; *P*<0.01) and apoB (-63%, *P*<0.0001) compared with controls. Compartmental analysis showed that apoB-48 production was lower (-91%; *P*<0.05) compared with controls. VLDL-apoB concentrations in FHBL subjects (n=2) were lower by more than 75% compared with healthy, normolipidemic control subjects (*P*<0.01). VLDL-apoB fractional catabolic rate (FCR) was more than 5-fold higher in the FHBL subjects (*P*=0.07). ApoB production rates and IDL- and LDL-apoB FCRs were not different between FHBL subjects and controls.

Conclusions: We conclude that when compared to controls, APOB L343V FHBL heterozygotes show lower TRL production with normal postprandial TRL particle clearance. In contrast, VLDL-apoB production was normal, while the FCR was higher in heterozygotes compared with lean control subjects. These mechanisms account for the marked hypolipidemic state observed in these FHBL subjects.
Introduction

Familial hypobetalipoproteinemia (FHBL) is a codominant disorder of lipoprotein metabolism characterized by low plasma levels of LDL-cholesterol and apolipoprotein (apo) B, and caused by mutations in the APOB gene (1-4). FHBL heterozygotes have apoB concentrations about 1/4 to 1/3 of normal and are likely to have fatty liver, while homozygotes have very low or absent plasma apoB and have a variable clinical phenotype, ranging from asymptomatic through to severe gastrointestinal and neurologic dysfunction.

ApoB is essential for the formation of the triglyceride-rich lipoproteins (TRL), namely chylomicrons and VLDL. The APOB mutations causing FHBL are usually nonsense, splicing and frameshift mutations that cause the production of a truncated apoB. While case studies with apoB-48.4 and apoB-76 have shown ‘normal’ postprandial responses (5,6), heterozygous FHBL subjects with apoB truncations shorter than apoB-48, and therefore only a single fully-functional apoB-48 allele, have decreased TRL production, but normal postprandial TRL particle clearance (7).

More recently, several missense mutations in the N-terminal βα1 domain of apoB causing FHBL have been described (8-10). The mutation R463W was shown to cause impaired secretion of VLDL by impaired endoplasmic reticulum exit and enhanced binding of the mutant protein to the microsomal triglyceride transfer protein (MTP) (8). Intestinal fat accumulation has been observed in FHBL R463W heterozygotes accompanied by an impaired postprandial lipid response (11). In vitro studies showed that L343V resulted in altered apoB folding and reduced secretion efficiency (9). However, the effect of L343V on lipoprotein metabolism in vivo is unknown.

In this manuscript, we examined the effect of heterozygous APOB L343V FHBL on postprandial and fasting lipoprotein metabolism.

Materials and Methods

Participants

Postprandial studies were performed on three heterozygous APOB L343V FHBL subjects and ten healthy, normolipidemic controls from a previous study (12). Stable isotope studies were performed
on two heterozygous APOB L343V FHBL subjects and four healthy, normolipidemic controls from a previous study (13). All subjects provided written consent and the study was approved by the Royal Perth Hospital Human Ethics Committee (EC 2006/078).

**Liver fat content**

Single voxel proton magnetic resonance spectroscopy of liver was performed on a 1.5T Siemens Sonata system. Sequence and qualification procedures for liver fat content were undertaken as previously described (14).

**Oral fat tolerance test**

Postprandial studies were performed as previously described (7). In brief, after a 12 h fast, subjects ingested a fatty ‘milk shake’ within 5 min yielding 1305 kcal; 87% from fat, 7% from carbohydrates, and 6% from protein. During the study, the subjects ate no calories, but were allowed to drink water as required.

Venous blood samples were drawn and collected into tubes containing EDTA-Na$_2$ before the test meal, then every 2 h for the 10 h study. Plasma was isolated by centrifugation (10 min, 3000 rpm). Ultracentrifugation (20,000 rpm, 30 min, 80 Ti rotor, Beckman) was performed on 5 mL plasma samples in Quick-Seal tubes (Beckman) overlaid with $d=1.006$ kg/L solution. The top 1 mL containing CM was removed using a Beckman Tube Slicer and designated the ‘large TRL’ fraction. The infranatant was again overlaid with $d=1.006$ kg/L solution and further ultracentrifugation (40,000 rpm, 18 h) was carried out to obtain chylomicron remnants, VLDL and VLDL-remnants (designated the ‘small TRL’ fraction).

**Biochemical analyses**

Cholesterol and triglyceride concentrations in plasma and fractions were measured enzymatically (Abbott, USA). Total apoB concentrations were determined by immunoturbidimetry (Abbott, USA), whereas apoB-48 concentrations were determined by ELISA (Shibayagi, Japan). ApoB-48 concentrations for control subjects were measured as described (12), and total plasma apoB-48 was
estimated by adding the large TRL and small TRL fractions. Concentrations for all analytes in large and small TRL fractions were corrected back to plasma concentrations.

The incremental area under the curve (iAUC) was calculated for plasma cholesterol, triglyceride, and apoB-48, and for large- and small-TRL cholesterol, and triglyceride using Microsoft Excel.

**Stable isotope studies**

Advice was given to continue on isocaloric diets and maintain physical activity constant during the study. All subjects were admitted to the metabolic ward in the morning after a 12 h overnight fast. They were studied semi-recumbent and allowed water only for the initial 16 h of the study. Venous blood was collected for biochemical measurements. Body weight and height were measured and arterial blood pressure recorded using a Dinamap 1846 SX/P monitor (Critikon, Tampa, FL).

A single bolus of D₃-leucine (1 mg/kg) was administered intravenously within a 2 min period into an antecubital vein via a Teflon cannula. Blood samples were taken at baseline and at 15, 30 and 45 min, and 1, 2, 4, 5, 6, 8, 10 and 16 h after isotope injection. Additional blood samples were collected in the morning on the four following days (24, 48, 72 and 96 h) after a 12 h fast.

**Isolation and measurement of isotopic enrichment of apoB**

VLDL-, IDL- and LDL-apoB was isolated from 2 mL of plasma by ultracentrifugation, and the procedures for isopropanol precipitation, delipidation, hydrolysis and derivatization of leucine using the oxazolinone method were as previously described (15). Plasma-free leucine was isolated by cation-exchange chromatography using AG 50W-X8 resin (Biorad, Richmond, CA) following removal of plasma protein with 60% perchloric acid. Isotopic enrichment was determined using gas chromatography-mass spectrometry with selected ion monitoring of samples at a mass-to-charge ratio of 212 and 209 and negative ion chemical ionization. Tracer-to-tracee ratios were derived from isotopic ratios of each sample.

**Biochemical analyses of lipoprotein subfractions and plasma**
Lipoprotein fractions were isolated using a density gradient flotation procedure as described (16). This method divided the VLDL lipoproteins into subclasses of Sf>100, Sf>60 and Sf>20. Following the 24 h ultracentrifugation, distinctive fractions representing IDL, LDL and HDL were obtained. Plasma total cholesterol, triglycerides and HDL-cholesterol concentrations were determined by enzymatic methods (Abbott, USA) as were fraction total cholesterol and triglyceride concentrations, and LDL-cholesterol calculated by the Friedewald formula (17). Plasma total apoB concentrations were determined by immunoturbidimetry (Abbott, USA). ApoB in VLDL, IDL and LDL fractions was quantified by the Lowry method (18).

**Kinetic analyses**

The postprandial apoB-48 data were analyzed using the multicompartiment modeling program SAAM II (The Epsilon Group, Charlottesville, VA). The model structure (Figure 1A) and assumptions made in developing the model have previously been described (19). A single plasma compartment was required to describe plasma apoB-48 kinetics. Fitting the model to the respective data provided estimates of the adjustable parameters from which the FCR and delay time for synthesis and secretion apoB-48 were determined.

SAAM II was also used to model the VLDL, IDL and LDL apoB tracer data (Figure 1B). The details and assumptions of the model were described previously (13). In brief, part of the model consists of a four-compartment subsystem that describes plasma leucine kinetics. This subsystem is connected to an intrahepatic delay compartment that accounts for the time required for the assembly, synthesis and secretion of apoB into plasma. The model provides for the direct secretion of apoB into a quickly turning over VLDL compartment. From this compartment apoB can be converted to IDL, LDL, a slowly turning over VLDL compartment or be removed directly from plasma. ApoB in compartment 4 can be converted to IDL or cleared from plasma. Plasma IDL kinetics are described by a single compartment. ApoB in this compartment can be converted to LDL or cleared directly from plasma. The kinetics of LDL apoB are described by a single plasma compartment, compartment 6. The fractional catabolic rates (FCR) of VLDL, IDL and LDL-apoB were derived from the model parameters giving the best fit. The corresponding production rates (PR) were calculated as the product.
of FCR and pool size, which equals the plasma concentration multiplied by plasma volume; plasma volume was estimated as 4.5% of body weight.

Statistical analysis
Statistical significance of differences in biochemical and kinetic parameters between APOB L343V FHBL heterozygotes and control subjects were compared by unpaired Student’s t test using Microsoft Excel. A P value <0.05 was considered significant.

Results
Compared with controls, APOB L343V FHBL subjects had significantly lower fasting plasma total cholesterol (3.0 ± 0.3 vs. 4.8 ± 0.5 mmol/L), LDL-cholesterol (1.0 ± 0.2 vs. 3.0 ± 0.5 mmol/L), and apoB (0.35 ± 0.08 vs. 0.95 ± 0.14 g/L) concentrations (all P<0.001), and significantly lower plasma triglyceride (0.6 ± 0.2 vs. 1.5 ± 0.5 mmol/L) concentrations (P<0.05). Liver fat contents in the three L343V FHBL heterozygotes were 13%, 30% and 41% (Normal <5%).

In the postprandial study, plasma cholesterol did not change over the 10 h in either group; large TRL cholesterol peaked at 4 h and again at 8 h in APOB L343V FHBL subjects compared to the single 6 h peak in controls (Figure 2). The postprandial plasma and TRL-triglyceride peaked earlier at 2 h in FHBL subjects than controls (4 h). Plasma apoB-48 concentrations in the L343V subjects remained low and showed little response over the 10 h, while in controls apoB-48 mirrored triglycerides, peaking at 4 h (Figure 3).

The iAUC in APOB L343V FHBL subjects was significantly lower for large TRL-triglyceride (-77%; P<0.0001), small TRL-cholesterol (-83%; P<0.001), small TRL- triglyceride (-88%; P<0.001), and plasma triglyceride (-70%; P<0.01) compared with controls (Table 1). ApoB-48 production (represented by ‘Input’) was significantly lower in APOB L343V FHBL subjects (-91%; P<0.05), accompanied by a shorter delay time compared with controls (1.11 vs. 3.01 h, P<0.05). The
fractional rate constant for apoB-48 was 36% lower in the APOB L343V FHBL subjects, but this was not statistically significant.

The stable isotope studies showed that VLDL-apoB concentrations in FHBL subjects were lower by more than 75% compared to controls (P<0.01). VLDL-apoB FCR was more than 5-fold higher in the FHBL subjects (P=0.07) (Table 2). ApoB production rates and IDL- and LDL-apoB FCRs were not different between FHBL subjects and controls.

Discussion

While individuals with heterozygous APOB L343V FHBL carry one normal apoB allele, the mutated allele, although able to produce apoB-48 and apoB-100 of the correct length, produces apoB containing a leucine-to-valine missense mutation in the βα1 domain. This domain of apoB contains elements critical for the assembly of TRL including MTP binding. We have studied the effect of heterozygous APOB L343V FHBL on fasting and postprandial TRL metabolism in vivo.

In the postprandial studies, the iAUC over the 10 h in L343V FHBL subjects was lower for both large- and small-TRL-triglyceride, which is consistent with their lower fasting plasma triglyceride concentrations, and also observed in FHBL R463W heterozygotes (11). Interestingly, lipid accumulation in the enteric mucosa can be observed in R463W heterozygotes after a 12 h fast (11). Consistent with this observation, our studies show that the lower postprandial response in L343V FHBL appears to be due to a lower production of TRL; compartmental modeling analysis showed that apoB-48 production was 91% lower in L343V FHBL compared with controls, whereas the clearance of apoB-48 was not different. This is consistent with our previous findings in heterozygous FHBL subjects who have truncation-causing mutations of apoB shorter than apoB-48 (7). In addition and in support of a defect in hepatic fat export, the L343V subjects had fatty liver, with a mean hepatic fat content of 28%. This is much higher than the liver fat contents observed in a general population; the Dallas Heart Study population showed a median liver fat of 4.69%, with a median of 1.9% in those low-risk subjects who were healthy, lean, nondiabetics with no clinical or biochemical evidence of liver disease (20). New lipid-lowering therapies reducing VLDL synthesis,
e.g. mipomersen (21), an apoB antisense oligonucleotide, have been troubled by the development of hepatic steatosis as a side effect. Our observation of a liver fat content of 13% in the one lean L343V FHBL subject suggests that therapies targeting this domain of apoB would also suffer these same complications. Long term follow-up of the L343V subjects is ongoing. One of the subjects in our present study, L343V-1, subsequently developed non-alcoholic steatohepatitis-related cirrhosis (22).

The stable isotope studies showed that VLDL-apoB concentrations in L343V FHBL subjects were less than 25% of control concentrations, while the VLDL-apoB FCR was more than 5-fold higher in the FHBL subjects \((P=0.07)\). In contrast, apoB production rates were not different between FHBL subjects and controls. This finding is unexpected given the postprandial data showing a defect in TRL production in FHBL L343V heterozygotes and the \textit{in vitro} experiments showing that the apoB L343V mutation disrupts apoB folding and reduces apoB secretion efficiency (9). Previous apoB kinetic studies in FHBL individuals with apoB truncations show lower apoB-100 production rates with normal FCRs (23-25). However, FHBL heterozygotes for apoB-89 had normal apoB-100 production with enhanced clearance (26). In addition, two previous apoB kinetic studies including eight individuals with FHBL without an identifiable apoB truncation, showed that seven individuals had normal apoB production with higher apoB catabolism (27,28), with the eighth having lower production and catabolism (27).

Our study was limited by small sample size, and the L343V FHBL subjects were significantly older and heavier than the normolipidemic controls. However, older subjects and those with a higher body mass index typically have a greater postprandial triglyceride response compared with younger and lower-weight subjects (29,30). As this is opposite to the differences we observed, these differences are unlikely to impact our findings in these FHBL subjects.

We conclude that when compared with controls, \textit{APOB} L343V FHBL heterozygotes show lower TRL production with normal postprandial TRL particle clearance. In contrast, VLDL-apoB production was normal, while the FCR was higher in heterozygotes compared with lean control subjects. These mechanisms account for the marked hypolipidemic state observed in these FHBL subjects.
Acknowledgments

This work was supported by National Health and Medical Research Council Project Grant 1010133 (to A.J.H., J.R.B. and F.M.v.B.) and a Practitioner Fellowship from the Royal Perth Hospital Medical Research Foundation (to J.R.B.). P.H.R.B. is a NHMRC Senior Research Fellow.

Contributorship: A.J.H. and J.R.B. wrote the manuscript. A.J.H., P.H.R.B., F.M.v.B. and J.R.B. contributed to study concept and design. All authors contributed to the acquisition, analysis, and interpretation of data, editing the manuscript.

References

**Figure Legends**

**Figure 1.** Compartmental model used for the analysis of (A) postprandial plasma apoB-48 metabolism and (B) fasting VLDL-, IDL- and LDL- apoB metabolism. A, Compartment 1 represents the dosing compartment; compartment 2, a delay compartment consisting of compartments in series, included in the model to account for the time required for synthesis and secretion of apoB-48 into plasma; compartment 3, the plasma apoB-48 compartment, from which apoB-48 samples are collected. The arrows connecting compartments describe paths by which material moves from one compartment to another. B, Compartment 1 represents the plasma leucine pool, compartment 2 is a delay compartment, which accounts for the time required for the synthesis and secretion of VLDL apoB into plasma. Plasma VLDL apoB is represented by two compartments, 3 and 4, which represent fast and slow turning over pools of VLDL particles, respectively. Compartment 5 represents plasma IDL apoB, and compartment 6 represents plasma LDL particles. The arrows between compartments represent the transport of apoB from one state to another, while the loss arrows represent catabolism from plasma.

**Figure 2.** Postprandial cholesterol and triglyceride responses in FHBL subjects and controls. Left panel, plasma, large TRL and small TRL cholesterol response to a fatty meal in FHBL subjects and controls; right panel, plasma, large TRL and small TRL triglyceride response. Squares indicate FHBL subjects, whereas triangles represent controls (mean ± SD).

**Figure 3.** Plasma apoB-48 response to a fatty meal in FHBL subjects and controls. Squares indicate FHBL subjects, whereas triangles represent controls (mean ± SD).
Table 1. Summary of fasting lipids and incremental AUC after an oral fat load for lipids and apoB-48, and apoB-48 kinetics, in APOB L343V FHBL subjects (L343V 1-3) and controls.

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>L343V-1 (F)</th>
<th>L343V-2 (F)</th>
<th>L343V-3 (M)</th>
<th>FHBL n=3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>30 ± 2</td>
<td>54</td>
<td>32</td>
<td>64</td>
<td>51 ± 17 b</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>22 ± 3</td>
<td>43</td>
<td>24</td>
<td>31</td>
<td>33 ± 9 b</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>4.8 ± 0.5</td>
<td>2.9</td>
<td>3.3</td>
<td>2.8</td>
<td>3.0 ± 0.3 c</td>
</tr>
<tr>
<td>Triglyceride (mmol/L)</td>
<td>1.5 ± 0.5</td>
<td>0.7</td>
<td>0.4</td>
<td>0.7</td>
<td>0.6 ± 0.2 a</td>
</tr>
<tr>
<td>LDL-cholesterol (mmol/L)</td>
<td>3.0 ± 0.5</td>
<td>1.1</td>
<td>0.8</td>
<td>1.1</td>
<td>1.0 ± 0.2 c</td>
</tr>
<tr>
<td>HDL-cholesterol (mmol/L)</td>
<td>1.2 ± 0.2</td>
<td>1.5</td>
<td>2.3</td>
<td>1.4</td>
<td>1.7 ± 0.5 a</td>
</tr>
<tr>
<td>ApoB (g/L)</td>
<td>0.95 ± 0.14</td>
<td>0.43</td>
<td>0.26</td>
<td>0.35</td>
<td>0.35 ± 0.08 c</td>
</tr>
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*iAUC*

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<tr>
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<th>Controls</th>
<th>L343V-1 (F)</th>
<th>L343V-2 (F)</th>
<th>L343V-3 (M)</th>
<th>FHBL n=3</th>
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<tbody>
<tr>
<td>Plasma total cholesterol</td>
<td>1.27 ± 0.86</td>
<td>0.94</td>
<td>0.46</td>
<td>0.08</td>
<td>0.49 ± 0.43</td>
</tr>
<tr>
<td>Large TRL-cholesterol</td>
<td>0.43 ± 0.23</td>
<td>0.11</td>
<td>0.14</td>
<td>0.88</td>
<td>0.38 ± 0.43</td>
</tr>
<tr>
<td>Small TRL-cholesterol</td>
<td>0.86 ± 0.39</td>
<td>0.21</td>
<td>0.10</td>
<td>0.12</td>
<td>0.15 ± 0.06 a</td>
</tr>
<tr>
<td>Plasma triglyceride</td>
<td>10.24 ± 4.31</td>
<td>5.28</td>
<td>1.84</td>
<td>1.96</td>
<td>3.03 ± 1.95 b</td>
</tr>
<tr>
<td>Large TRL-triglyceride</td>
<td>6.47 ± 2.18</td>
<td>1.12</td>
<td>1.28</td>
<td>1.99</td>
<td>1.47 ± 0.47 c</td>
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<tr>
<td>Small TRL-triglyceride</td>
<td>2.68 ± 1.40</td>
<td>0.42</td>
<td>0.22</td>
<td>0.30</td>
<td>0.31 ± 0.10 c</td>
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<tr>
<td>Plasma apoB-48</td>
<td>1155 ± 411</td>
<td>0</td>
<td>-17</td>
<td>46</td>
<td>10 ± 33 c</td>
</tr>
</tbody>
</table>

*ApoB-48*

<table>
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<tr>
<th></th>
<th>Controls</th>
<th>L343V-1 (F)</th>
<th>L343V-2 (F)</th>
<th>L343V-3 (M)</th>
<th>FHBL n=3</th>
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<tr>
<td>Delay time (h)</td>
<td>3.01 ± 1.42</td>
<td>1.49</td>
<td>0.64</td>
<td>1.20</td>
<td>1.11 ± 0.44 a</td>
</tr>
<tr>
<td>Input (nmol/L)</td>
<td>747 ± 513</td>
<td>38</td>
<td>40</td>
<td>129</td>
<td>69 ± 52 a</td>
</tr>
<tr>
<td>k(0,3) (pools/h)</td>
<td>0.61 ± 0.38</td>
<td>0.25</td>
<td>0.53</td>
<td>0.37</td>
<td>0.39 ± 0.14</td>
</tr>
</tbody>
</table>

F, female; M, male. Data shown are mean ± SD. aP<0.05, bP<0.005, cP<0.001, compared with controls. DT indicates delay time; Input, input into compartment 1 of the apoB-48 model.
Table 2. Summary of VLDL-, IDL-, and LDL-apoB kinetics in controls and APOB L343V FHBL subjects (L343V-1 and L343V-2).

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>L343V-1</th>
<th>L343V-2</th>
<th>P</th>
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<tbody>
<tr>
<td></td>
<td>n=4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VLDL-apoB FCR (pools/d)</td>
<td>8.40 ± 1.68</td>
<td>22.65</td>
<td>79.24</td>
<td>0.07</td>
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<tr>
<td>VLDL-apoB production (mg/kg/d)</td>
<td>14.08 ± 5.43</td>
<td>12.69</td>
<td>18.92</td>
<td>0.72</td>
</tr>
<tr>
<td>IDL-apoB FCR (pools/d)</td>
<td>9.12 ± 5.04</td>
<td>8.88</td>
<td>13.1</td>
<td>0.65</td>
</tr>
<tr>
<td>IDL-apoB production (mg/kg/d)</td>
<td>10.68 ± 4.59</td>
<td>7.22</td>
<td>5.61</td>
<td>0.30</td>
</tr>
<tr>
<td>LDL-apoB FCR (pools/d)</td>
<td>0.62 ± 0.43</td>
<td>0.47</td>
<td>0.69</td>
<td>0.91</td>
</tr>
<tr>
<td>LDL-apoB production (mg/kg/d)</td>
<td>10.38 ± 3.80</td>
<td>7.55</td>
<td>13.68</td>
<td>0.95</td>
</tr>
</tbody>
</table>

Data shown are mean ± SD.