Low Rate of Production of Apolipoproteins B100 and AI in 2 Patients With Anderson Disease (Chylomicron Retention Disease)

Khadija Ouguerram, Yasmine Zaïr, Fatima Kasbi-Chadli, Hassane Nazih, Dominique Bligny, Jacques Schmitz, Thomas Aparicio, Maud Chétiveaux, Thierry Magot, Laurence P. Aggerbeck, Marie Elisabeth Samson-Bouma, Michel Krempf

Objective—Anderson disease is a rare inherited lipid malabsorption syndrome associated with hypocholesterolemia and linked to SAR1B mutations. The aim of this article was to analyze the mechanisms responsible for the low plasma apolipoprotein Apo-B100 and Apo-AI in 2 patients with Anderson disease.

Methods and Results—A primed constant infusion of 13C-leucine was administered for 14 hours to determine the kinetics of lipoproteins. In the 2 patients, total cholesterol (77 and 85 mg/dL versus 155±32 mg/dL), triglycerides (36 and 59 versus 82±24 mg/dL), Apo-B100 (48 and 43 versus 71±5 mg/dL), and Apo-AI (47 and 62 versus 130±7 mg/dL) were lower compared with 6 healthy individuals. Very-low-density lipoprotein-B100 production rate of the patients was lower (4.08 and 5.52 mg/kg/day versus 12.96±2.88 mg/kg/day) as the fractional catabolic rate (5.04 and 4.32 day−1 versus 12.24±3.84 day−1) with no difference in intermediate-density lipoprotein-B100 and LDL-B100 kinetic data. The production rate of high-density lipoprotein Apo-AI was lower in the patients (7.92 and 8.64 versus 11.96±1.92 mg/kg/day) and the fractional catabolic rate was higher (0.38 and 0.29 versus 0.22±0.01 day−1).

Conclusion—The low plasma Apo-B100 and Apo-AI concentrations in the patients with Anderson disease were mainly related to low rates of production.

Key Words: Anderson disease ■ apolipoprotein B100 ■ apolipoprotein AI ■ kinetic analysis ■ modeling

Apolipoprotein B (Apo-B) plays a key role in the assembly and secretion of triglyceride-rich lipoproteins in the intestine and the liver and is related to the risk of cardiovascular disease.1 Apo-B100 and Apo-B48 are the 2 forms of Apo-B found in humans. In the blood, Apo-B100 is secreted from the liver as a component of very-low-density lipoprotein (VLDL) and Apo-B48 is synthesized within the enterocytes and secreted in chylomicrons. Anderson disease (AD) (OMIM 246700) is a rare autosomal recessive intestinal disorder affecting the export of dietary lipids as chylomicrons.2-4 It is 1 of the 3 inherited lipid diseases characterized by hypocholesterolemia, eg, abetalipoproteinaemia (ABL), familial hypobetalipoproteinemia, and AD also called chylomicron retention disease.5 The main clinical feature of AD is a lipid malabsorption syndrome with persistent steatorrhea and failure to thrive6 while plasma Apo-B48 containing lipoproteins and postprandial chylomicrons are not detected whereas lipoproteins containing Apo-B100 are present although in low amounts. The main components of plasma high-density lipoprotein (HDL), Apo-AI and HDL-cholesterol, are also low.7,8

In several patients, the molecular basis for this chylomicron secretory defect has been found to be a mutation in the SAR1B gene encoding for the SAR1B protein.9 To date, 16 SARIB gene mutations (frameshift, missense, or deletion mutations) have been described in patients with chylomicron retention disease—Anderson disease.8,10 The SARIB gene is expressed in many tissues including the small intestine, the liver, muscle, and the brain. The SARIB protein is a member of the Sar1-ADP-ribosylation factor family of small GTPases.9 It is involved in the vesicular coat protein complex II–dependent transport of proteins and is required for the fusion of the intestinal specific prechylomicron transport vesicle to the Golgi apparatus.11 In patients with AD, mutations of SARIB result in an absence of secretion of chylomicrons, which subsequently accumulate within the enterocytes.

The aim of the present study was to ascertain the mechanisms responsible for the low plasma concentrations of...
Apo-B100 and Apo-AI containing lipoproteins in 2 patients with AD with different mutations in the SAR1B gene. This is the first report of in vivo kinetics of Apo-B100 and Apo-AI in patients with this disease. We found that the low plasma concentrations of Apo-B100 and Apo-AI mainly involved defects in their rates of production.

Patients
The patient JOU/Ca was born in 1967 from nonconsanguineous, French, Caucasian parents.11 From the age of 1 year, she has manifested persistent steatorrhea and low plasma concentrations of cholesterol and fat-soluble vitamins (vitamin E<1 µmol/L). Chylomicrons were not found in the plasma after ingestion of a fat load. Endoscopy showed white stippling, such as hoar frosting, covering the mucosal surface of the small intestine. Histochemistry and electron microscopy of intestinal biopsies showed an accumulation of free lipids and lipoprotein-like structures in the enterocytes. A frameshift mutation in the SAR1B gene (c.109G>A), with an amino acid change (p.Gly37Arg) that presumably decreased the affinity of SAR1B for GDP/GTP, was stopped in 2006. Subsequently, vitamin E levels have markedly decreased. The patient has a mutation in the SAR1B gene. This is

Experimental Protocol
Kinetic Studies
The protocol used in these studies was approved by the ethical committee of the Nantes University Hospital. Informed, written consent was obtained from all participants (INSERM, RBM 0256, CCPRPB Bichat-C. Bernard 2003/05). The kinetic studies were conducted in the Nantes University Hospital Clinical Investigation Center for the patient JOU/Ca and in the University Hospital of Dijon, France, for the patient MK.

For at least 1 month before the study, the patients did not receive any medication affecting carbohydrate or lipid metabolism. They underwent the kinetic study in the fasting state. The results obtained from the study of these patients were compared with the kinetic data previously obtained in our laboratory for 6 normolipidemic, healthy individuals matched for body mass index with the patients and using a similar protocol.17–19 In brief, after an overnight fast, the subjects received an intravenous priming dose of 10 µmol/kg [13-C]-leucine (Cambridge Isotope Laboratories, Andover, MA) followed by a constant infusion (10 µmol/kg per hour) for 14 hours. Venous blood samples were drawn into EDTA-containing tubes (Venoject, Paris, France) at baseline and at 15, 30, 45 minutes, 1, 1.5, 2, 2.5 hours, and then hourly up to 14 hours after the start of the infusion. Sodium azide, an inhibitor of bacterial growth and Pefabloc SC (Interchim, Montluçon, France), a protease inhibitor, were added to the blood samples to final concentrations of 1.5 and 0.5 mmol/L, respectively.

Analytical Procedures
Measurement of Lipid Concentrations
Measurements were made from plasma samples obtained at baseline. Plasma total cholesterol, triacylglycerol, and nonesterified fatty acids concentrations were measured using commercially available enzymatic kits (BioMerieux, Marcy l’Etoile, France, for cholesterol and triacylglycerol, and Wako Chemicals, Richmond, VA for nonesterified fatty acids). Plasma concentrations of Apo-B100 and Apo-AI were measured with a nephelometric method (Boehringer, Paris).

Isolation of Apo-B100 and Apo-AI and Measurement of Isotopic Enrichment
Lipoproteins were isolated and the leucine enrichment in Apo-B100 and Apo-AI were performed as described previously.17–19 In brief, lipoproteins were separated by ultracentrifugation and Apo-B100 and Apo-AI were isolated by polyacrylamide gel electrophoresis. Amino acids obtained by hydrolysis were esterified, derivatized, and analyzed by electron-impact gas chromatography-mass spectrometry (5891A gas chromatograph connected with a 5971 A quadrupole mass spectrometer). The isotopic ratio was determined by selected ion monitoring at m/z ratios of 282 and 285. The calculation of Apo-B100 kinetic parameters was based on the tracer-to-tracee mass ratio.

Separation of Plasma Lipoproteins by FPLC
VLDL, intermediate-density lipoprotein (IDL), LDL, and HDL were isolated as described previously using fast protein liquid chromatography (FPLC) DIRECTOR software (Amersham Pharmacia Biotech Inc).20 Concentrations in FPLC samples of Apo-B100 and Apo-AI were measured with a nephelometric method (Boehringer, Paris). The percentage recovery of Apo-B100 and Apo-AI after FPLC separation was 70–80%.

Kinetic Analysis
The kinetic analysis of tracer-to-tracee ratios was performed using computer software for simulation, analysis, and modeling (SAAM II, Resource Facility for Kinetic Analysis; SAAM Institute, Seattle, WA). In brief, as previously described,16 our approach started with the simplest model based on minimal assumptions, then the complexity of the model was progressively increased by including more known or credible physiological parameters until the optimal fit was obtained. For each model, fitted curves were compared to experimental data. The best model was retained when close agreement between the experimental data and the derived model was obtained. This step was validated by F test and the Akaike information criterion.22 The model used for Apo-B100 was previously developed in normolipidemic subjects18 and is presented in Figure 1. In this model, plasma leucine was used as a forcing function to drive the appearance of leucine tracer into the Apo-B100 of the different lipoprotein fractions. Apo-B100 entered into plasma through VLDL secretion (PR1) and direct production of IDL (PRd2) and LDL (PRd3). Apo-B100 direct removal occurred from VLDL

Apo-B100 and Apo-AI containing lipoproteins in 2 patients with AD with different mutations in the SAR1B gene. This is the first report of in vivo kinetics of Apo-B100 and Apo-AI in patients with this disease. We found that the low plasma concentrations of Apo-B100 and Apo-AI mainly involved defects in their rates of production.
Apo-B100, and Apo-AI Metabolism in Anderson Disease

Fractional catabolic rate (FCR in day$^{-1}$ or pool/day) was calculated as the sum of total output rate constant for each lipoprotein: k01+k21 for VLDL, k02+k32 for IDL, and k03 for LDL. For IDL and LDL, production rate (PR) corresponded to the sum of direct production from liver (respectively, PRd2 and PRd3) and production through conversion of lower density lipoprotein (VLDL and IDL, respectively).

For Apo-AI metabolism, we applied a single compartment model to HDL-AI (Figure 1) as previously developed for normolipidemic subjects. The plateau of the VLDL-B100 tracer-to-tracee ratio was used as precursor pool enrichment, assuming that Apo-B100 and most of Apo-AI are synthesized by the liver. This model leads to the determination of the FCR (k04 in day$^{-1}$).

The Apo-B100 or Apo-AI PR in mg/kg per day was the product of the FCR and the pool size of Apo-B100 or Apo-AI in the lipoprotein fractions. Pools of Apo-B100 in VLDL, IDL, LDL, and of Apo-AI in HDL were calculated by multiplying the Apo-B100 or Apo-AI concentration by 0.045 (L/kg) assuming a plasma volume of 4.5% of body weight. As only 2 patients were studied, no statistical analysis was made for comparison.

Results

The 2 patients were not underweight (body mass index, respectively, 19 and 21 kg/m$^2$, compared with 23±1 kg/m$^2$, for control subjects). They were considered to be in good health and did not exhibit any neurological or visual manifestations other than decreased or absent deep tendon reflexes and mild muscle pain.

When compared with healthy subjects, JOU/Ca and MK had lower plasma concentrations of total cholesterol (50% and 55%, respectively), triglycerides (44% and 72%), Apo-B100 (67% and 60%), Apo-AI (36% and 48% of normal), LDL-C (52% and 85%), and HDL-C (51% and 59%), as shown in Table 1 (and Table I in the online-only Data Supplement). FPLC elution positions of the VLDL, IDL, LDL, and HDL fractions were similar for the patients and healthy subjects, as shown in triglyceride and cholesterol profiles (Figure 2A and 2B).

During the kinetic study, the Apo-B100 concentrations in VLDL, IDL, and LDL and the plasma Apo-AI concentrations remained constant (coefficient of variation <5% over the 14 hours of the exploration), suggesting that each subject remained in a metabolic steady state.

The time courses of plasma tracer enrichments in VLDL, IDL, and LDL and the plasma Apo-AI concentrations remained constant (coefficient of variation <5% over the 14 hours of the exploration), suggesting that each subject remained in a metabolic steady state.

The kinetic data are presented in Table II in the online-only Data Supplement. The kinetic data are presented in Table II in the online-only Data Supplement. The pool size of the patients’ Apo-B100 and Apo-AI was ≈30% to 50% lower compared with controls. The FCR in the 2 patients was lower for VLDL-B100 (41% and 35% of control value), related to lower conversion rate (k21) (34% and 39% of control value). FCR were not different for IDL (80% and 140% of the control value for Jou/Ca and MK, respectively) whereas the conversion rate of IDL-B100 to LDL-B100 (k32) was higher in both patients (1.4- and 2.1-fold for Jou/Ca and MK, respectively). The total Apo-B100 production rate was lower in the patients (52% and 41%) related to lower VLDL-B100 PR1 (31% for JOU/Ca and 43 % for MK of controls’ value). A lower total production rate of IDL (PR2, 25% and 45% of normal) and LDL (PR3, 74% and 58% of normal) was also observed. The production rate of HDL-AI was lower

Table 1. Biological Data of Patients with Anderson Disease (Jou/Ca and mk) and 6 Healthy Subjects

<table>
<thead>
<tr>
<th></th>
<th>Jou/CA</th>
<th>MK</th>
<th>Mean controls</th>
<th>SEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>F</td>
<td>M</td>
<td>M</td>
<td>2</td>
</tr>
<tr>
<td>Age</td>
<td>35</td>
<td>39</td>
<td>24</td>
<td>2</td>
</tr>
<tr>
<td>BMI</td>
<td>19</td>
<td>21</td>
<td>23</td>
<td>1</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>77</td>
<td>85</td>
<td>155.0</td>
<td>32.4</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>36</td>
<td>59</td>
<td>82.3</td>
<td>23.9</td>
</tr>
<tr>
<td>LDL-C</td>
<td>36</td>
<td>59</td>
<td>69.1</td>
<td>16.5</td>
</tr>
<tr>
<td>HDL-C</td>
<td>26.3</td>
<td>30.5</td>
<td>51.7</td>
<td>7.2</td>
</tr>
<tr>
<td>VLDL</td>
<td>2.4</td>
<td>3.7</td>
<td>3.2</td>
<td>0.5</td>
</tr>
<tr>
<td>IDL</td>
<td>1.0</td>
<td>1.0</td>
<td>3.4</td>
<td>1.1</td>
</tr>
<tr>
<td>LDL</td>
<td>30.6</td>
<td>25.6</td>
<td>53.0</td>
<td>2.5</td>
</tr>
<tr>
<td>Plasma</td>
<td>48</td>
<td>43</td>
<td>71</td>
<td>5</td>
</tr>
<tr>
<td>Pool</td>
<td>21.6</td>
<td>19.3</td>
<td>32.1</td>
<td>1.6</td>
</tr>
<tr>
<td>HDL</td>
<td>37.6</td>
<td>48.98</td>
<td>104.7</td>
<td>5.2</td>
</tr>
<tr>
<td>Plasma</td>
<td>47</td>
<td>62</td>
<td>130.5</td>
<td>6.7</td>
</tr>
<tr>
<td>Pool</td>
<td>21.1</td>
<td>27.9</td>
<td>58.7</td>
<td>2.6</td>
</tr>
</tbody>
</table>

LDL indicates low-density lipoprotein; BMI, body mass index; HDL, high-density lipoprotein; VLDL, very-low-density lipoprotein.

Age (years), BMI (kg/m$^2$), plasma concentrations of total cholesterol, triglycerides, LDL-C, HDL-C, Apo-B100 and Apo-AI (mg/dL), and pool size (mg/kg).
(66 and 72%) and the HDL-AI FCR was higher in the patients (respectively, 1.7- and 1.3-fold for JOU/Ca and MK) when compared with healthy individuals (Table II in the online-only Data Supplement).

**Discussion**

This study provides new information that further elucidates the decreased plasma Apo-B100 and Apo-AI concentrations in patients with AD. Using a stable isotope kinetic analysis, we show that 2 patients with AD, with different SAR1B gene mutations, had a substantial lower production rate of both Apo-B100 and Apo-AI.

Apo-B48 and Apo-B100 play important structural roles in the formation of lipoproteins in the intestine and the liver, respectively. In patients with AD, mutations in the SAR1B gene lead to an absence of plasma postprandial Apo-B48 due to a defect in the secretion of chylomicrons from the intestine. We also found in our 2 patients a lower rate of production of Apo-B100 from the liver. Three hypotheses can be advanced to explain this result: (1) the lack of chylomicon remnant delivery to the liver could decrease the production of Apo-B100 containing lipoproteins. This hypothesis appears unlikely because after orthotopic liver transplantation of patients with ABL characterized by a total deficiency of both intestinal and hepatic Apo-B (OMIM 200100), the plasma Apo-B100 concentration was normalized despite the persistent absence of chylomicrons. Similarly, in a transgenic mouse model, knocked out for the mouse Apo-B gene but expressing a human Apo-B transgene in the liver but not in the intestine, the absence of chylomicon synthesis in the intestine did not appear to have any effect on the plasma liver-derived human Apo-B-containing lipoproteins.

(2) the decreased production of Apo-B100 could be related directly to a secretory defect of hepatic VLDL linked to the SAR1B mutations. Indeed, SAR1B is expressed in the liver and has been reported to be essential for the traffic of VLDL-containing vesicles from the endoplasmic reticulum and subsequent secretory mechanisms.

In this case, accumulation of fat in the liver would be expected but it was reported in only a few patients with AD. (3) the decreased production of Apo-B100 may be related to a low availability of lipids within liver. Lipid homeostasis of liver cells is SREBP dependent and it has been reported that the coat protein complex II–coated vesicles carrying Scap-SREBP bind the Sar1, Sec23/24, and Sec13/31 complexes. Whether mutations within the sequence of the binding site of Sar1 for Sec23 prevent this binding and the subsequent activation of the Scap-SREBP complex (leading to decreased cholesterol availability for lipoprotein synthesis) is unknown.

The catabolism of Apo-B100-LDL in the patients is similar compared to healthy subjects. However, the conversions of VLDL to IDL (k21, reflecting lipoprotein lipase activity) and of IDL to LDL (k32, reflecting hepatic lipase activity) were respectively lower and higher in the patients when compared with healthy individuals. These data are in agreement with a lower, in vitro, lipoprotein lipase activity found in patients with AD but is conflicting with a lower in vitro hepatic lipase activity previously reported. The reason for this discrepancy is not clear but it is likely that activity of lipases in vivo is not adequately reflected by in vitro measurements.

With respect to the low plasma Apo-AI level in patients with AD, we have found that our 2 patients exhibited low

**Table 2.** Kinetic Data for Apolipoprotein-B100 and Apolipoprotein-AI in Patients (JOU/Ca, MK) and Healthy Individuals

<table>
<thead>
<tr>
<th></th>
<th>VLDL</th>
<th>IDL</th>
<th>LDL</th>
<th>HDL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jou/Ca</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TPR</td>
<td>8.88</td>
<td>4.08</td>
<td>5.04</td>
<td>3.60</td>
</tr>
<tr>
<td>PR1</td>
<td>3.36</td>
<td>0.48</td>
<td>9.84</td>
<td>9.80</td>
</tr>
<tr>
<td>FCR</td>
<td>7.68</td>
<td>4.32</td>
<td>0.74</td>
<td>7.92</td>
</tr>
<tr>
<td>CR</td>
<td>11.96</td>
<td>0.22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MK</td>
<td>6.96</td>
<td>5.52</td>
<td>4.32</td>
<td>4.08</td>
</tr>
<tr>
<td>TPR</td>
<td>6.01</td>
<td>0.72</td>
<td>17.52</td>
<td>15.12</td>
</tr>
<tr>
<td>PR2</td>
<td>10.32</td>
<td>2.40</td>
<td>0.67</td>
<td>11.96</td>
</tr>
<tr>
<td>FCR</td>
<td>8.64</td>
<td>0.29</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>11.96</td>
<td>0.22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Healthy subjects</td>
<td>17.04</td>
<td>12.96</td>
<td>12.24</td>
<td>10.56</td>
</tr>
<tr>
<td>TPR</td>
<td>13.44</td>
<td>1.92</td>
<td>12.24</td>
<td>7.20</td>
</tr>
<tr>
<td>PR3</td>
<td>3.84</td>
<td>4.16</td>
<td>4.56</td>
<td></td>
</tr>
<tr>
<td>FCR</td>
<td>1.92</td>
<td>0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>11.96</td>
<td>0.22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>5.76</td>
<td>2.88</td>
<td>3.84</td>
<td>2.40</td>
</tr>
<tr>
<td>TPR</td>
<td>6.01</td>
<td>0.72</td>
<td>17.52</td>
<td>15.12</td>
</tr>
<tr>
<td>PRd2</td>
<td>10.32</td>
<td>2.40</td>
<td>0.67</td>
<td>11.96</td>
</tr>
<tr>
<td>FCR</td>
<td>8.64</td>
<td>0.29</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>11.96</td>
<td>0.22</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| VLDL, very-low-density lipoprotein; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; HDL, high-density lipoprotein; FCR, fractional catabolic rate; TPR, total production rate in mg/kg/day of Apo-B100; PR, production rate; PRd, direct production rate; CR, conversion rate in day–1 (see Figure 1 for details).
rates of production and high rates of catabolism of plasma Apo-AI. It should be noticed that we did not observe any decrease of HDL-C or Apo-AI in the other members of the family (data not shown), suggesting no other familial genetic and specific defect other than SAR1B mutations. It has to be pointed out that low HDL-C was a clear phenotype in both parents (obligate heterozygote) in a previous study but it is clearly not the case for the present 2 families. This would indicate slight differences between kindred that might be related to differing effects of various mutations.

The low rate of production of Apo-AI is consistent with the 1.5- to 2-fold lower intestinal secretion of Apo-AI we observed after metabolic labeling of biopsies of 2 other patients with AD (unpublished data from the laboratory). Similarly, stronger intensity of the immunostaining of Apo-AI in the enterocytes of biopsies from patients with AD when compared with healthy subjects has been reported previously. However, previous isotope studies suggest that the major contributor to Apo-AI production is the liver (90%) and an intestinal defect alone cannot explain the data. The liver must be involved and 2 hypotheses can be advanced to explain the decrease in HDL-Apo-AI production observed in the patients: (1) an Apo-AI secretory defect could be a consequence of the absence of intestinal Apo-B48-containing lipoproteins. In a transgenic mouse model producing human Apo-B in the liver but not in the intestine, a significant decrease of HDL and Apo-AI was observed. Low levels of HDL-C and Apo-AI are also seen in cases of ABL related to a low rate of production of Apo-AI. Furthermore, liver transplantation of ABL patients corrected the hepatic defect in secretion of Apo-B100 whereas the level of plasma Apo-AI remained low. This supports the concept that the absence of intestinal Apo-B-containing lipoproteins may affect hepatic Apo-AI production. (2) The second hypothesis is related to the formation of HDL through lipolysis of triglyceride-rich particles, which could be affected in the patients with AD because of the absence of chylomicrons and the low levels of VLDL. Then, markedly low levels of TG-rich lipoproteins, which are the substrates for lipolysis-generated HDL, could lead to the low rate of production for HDL.

The higher catabolic rate of Apo-AI could be related to the composition of the HDL. HDL particles are reported to be enriched in Apo-E in AD, leading to a better affinity for the LDL receptor on fibroblast when compared with HDL from healthy subjects and a higher in vivo catabolism. Another hypothesis is related to higher hepatic lipase activity as suggested by our kinetic data. The action of hepatic lipase on TG-enriched HDL could result in the shedding of lipid-poor Apo-AI from HDL and, thus, high Apo-AI catabolism. To support this hypothesis, it has been shown that overexpression of hepatic lipase using either a recombinant adenovirus or genetic manipulation significantly decreases plasma HDL-C concentration.

There are 2 limitations to the current study: (1) because of the rarity of this disease and the limited number of patients worldwide, we were able to study only 2 patients. Then, the quality of the data is critical. It has to be emphasized that the data reported in our healthy volunteers are comparable to previous studies reported by other groups and it is worthwhile to point out that similar kinetic data were obtained with both patients from 2 different SARA2 gene mutations; (2) we cannot exclude that a part of our data could be related to a decrease of intestinal absorption and poor nutritional status. At the time of the study, the patients were in good health with no evidence of clinical or biological malnutrition as we did not observe any difference with the controls for plasma albumin, pre-albumin, iron, fatty acid profiles and concentrations, vitamin D as well as leucine turnover.

In conclusion, this is the first report of a stable isotope kinetic study of Apo-B100- and Apo-AI-containing lipoproteins in AD. It demonstrates that, in addition to the known lower secretion of Apo-B48 from the intestine in AD, the low plasma concentrations of Apo-B100- and Apo-AI-containing lipoproteins are mainly a consequence of a lower rate of their production in the liver. Although in the current study, because of the rarity of this disease and the limited number of patients worldwide, we were able to study only 2 patients, it is necessary to emphasize that similar kinetic data were obtained with both these patients who exhibit 2 different SARA2 gene mutations. Although the precise mechanism leading to the lower Apo-B100- and Apo-AI-containing lipoproteins has not been clarified, the kinetic studies in both AD/chylomicron retention disease and ABL patients as well as the results obtained with transgenic mouse models strongly suggest that chylomicron secretion and hepatic SAR1B are important for the maintenance of normal plasma LDL and HDL concentrations.

Acknowledgments

We thank Pr B Verges (Dijon) for the clinical exploration of one patient. J. Bonneau, V. Ferchaud-Roucher, and Audrey Aguesse for helpful technical assistance (INSERM U 781 and INSERM UMR 1087/ CNRS UMR 6291) and Nadine Denoual (University of Nantes).

Sources of Funding

This study was supported by a grant from “la Direction de la Recherche Clinique” of Nantes Hospital.

Disclosures

None.

References


29. Siddiqi SA. VLDL exit from the endoplasmic reticulum in a specialized vesicle, the VLDL transport vesicle, in rat primary hepatocytes. *Biochem J.* 2008;413:333–342.


Low Rate of Production of Apolipoproteins B100 and AI in 2 Patients With Anderson Disease (Chylomicron Retention Disease)
Khadija Ouguerram, Yassine Zaïr, Fatima Kasbi-Chadli, Hassane Nazih, Dominique Bligny, Jacques Schmitz, Thomas Aparicio, Maud Chétiveaux, Thierry Magot, Laurence P. Aggerbeck, Marie Elisabeth Samson-Bouma and Michel Krempf

Arterioscler Thromb Vasc Biol. published online March 22, 2012;
Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2012 American Heart Association, Inc. All rights reserved.
Print ISSN: 1079-5642. Online ISSN: 1524-4636

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://atvb.ahajournals.org/content/early/2012/03/22/ATVBAHA.112.245076

Data Supplement (unedited) at:
http://atvb.ahajournals.org/content/suppl/2012/03/22/ATVBAHA.112.245076.DC1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Arteriosclerosis, Thrombosis, and Vascular Biology can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Arteriosclerosis, Thrombosis, and Vascular Biology is online at:
http://atvb.ahajournals.org//subscriptions/
Table I: Biological data of individual healthy subjects. Age (yrs), BMI (kg/m²), plasma concentrations of total cholesterol (CH), Triglycerides (TG), LDL-C, HDL-C, ApoB100 and Apo A1 (mg/dl), Pool size (mg/kg).
<table>
<thead>
<tr>
<th>Healthy subjects</th>
<th>TPR (mg/kg/day)</th>
<th>PR1 (mg/kg/day)</th>
<th>FCR (day(^{-1}))</th>
<th>CR (day(^{-1}))</th>
<th>PR2 (mg/kg/day)</th>
<th>PRd2 (mg/kg/day)</th>
<th>FCR (d(^{-1}))</th>
<th>PR3 (mg/kg/day)</th>
<th>PRd3 (mg/kg/day)</th>
<th>FCR (day(^{-1}))</th>
<th>PR4 (mg/kg/day)</th>
<th>FCR (day(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>18.3</td>
<td>13.9</td>
<td>17.8</td>
<td>11.5</td>
<td>11.5</td>
<td>2.4</td>
<td>8.4</td>
<td>6.9</td>
<td>2.0</td>
<td>0.4</td>
<td>10.8</td>
<td>0.22</td>
</tr>
<tr>
<td>2</td>
<td>13.0</td>
<td>9.3</td>
<td>12.0</td>
<td>10.8</td>
<td>9.9</td>
<td>1.5</td>
<td>13.9</td>
<td>4.9</td>
<td>2.2</td>
<td>0.6</td>
<td>10.3</td>
<td>0.21</td>
</tr>
<tr>
<td>3</td>
<td>20.1</td>
<td>16.7</td>
<td>11.8</td>
<td>9.6</td>
<td>14.6</td>
<td>0.9</td>
<td>13.0</td>
<td>10.8</td>
<td>2.5</td>
<td>0.6</td>
<td>14.9</td>
<td>0.22</td>
</tr>
<tr>
<td>4</td>
<td>18.0</td>
<td>10.3</td>
<td>7.7</td>
<td>7.7</td>
<td>11.9</td>
<td>1.6</td>
<td>6.7</td>
<td>12.0</td>
<td>6.1</td>
<td>0.8</td>
<td>10.1</td>
<td>0.22</td>
</tr>
<tr>
<td>5</td>
<td>16.1</td>
<td>12.5</td>
<td>8.9</td>
<td>8.9</td>
<td>16.1</td>
<td>3.6</td>
<td>13.9</td>
<td>11.5</td>
<td>0.0</td>
<td>0.7</td>
<td>13.4</td>
<td>0.23</td>
</tr>
<tr>
<td>6</td>
<td>17.1</td>
<td>15.4</td>
<td>14.9</td>
<td>14.9</td>
<td>16.9</td>
<td>1.5</td>
<td>17.8</td>
<td>15.6</td>
<td>0.2</td>
<td>1.0</td>
<td>12.2</td>
<td>0.22</td>
</tr>
<tr>
<td>Mean</td>
<td>17.1</td>
<td>13.0</td>
<td>12.2</td>
<td>10.6</td>
<td>13.5</td>
<td>1.9</td>
<td>12.3</td>
<td>10.3</td>
<td>2.2</td>
<td>0.7</td>
<td>12.0</td>
<td>0.22</td>
</tr>
<tr>
<td>SD</td>
<td>2.4</td>
<td>2.9</td>
<td>3.7</td>
<td>2.5</td>
<td>2.8</td>
<td>1.0</td>
<td>4.0</td>
<td>3.8</td>
<td>2.2</td>
<td>0.2</td>
<td>1.9</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Table II: Kinetic data for apolipoprotein B100 and apolipoprotein A1 of individual healthy subjects (TPR: total production rate of ApoB100, PR1,2,3,4: production rate of B100-VLDL,IDL,LDL and A1-HDL, respectively, FCR: fractional catabolic rate, CR: conversion rate of VLDL to IDL, PRd2,d3: direct production rate of IDL and LDL).
Figure I: Time course kinetics of Apolipoprotein-B100 enrichments and fitted curves in a representative healthy subject (A), JOU/Ca (B) and MK (C) in VLDL (*), IDL (△) and LDL (*).
Figure II: Time course kinetics of Apolipoprotein AI enrichments in HDL and fitted curves in a representative healthy subject (A), JOU/Ca (B) and MK (C).