VLDL and IDL apolipoprotein B-100 kinetics in familial hypercholesterolemia due to impaired LDL receptor function or to defective apolipoprotein B-100

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Abstract Mutations in the apolipoprotein (apo) B, E (LDL) receptor gene and in the apolipoprotein B-100 gene are the cause of familial hypercholesterolemia (FH) and of familial defective apo B-100 (FDB), respectively. Whether these abnormalities lead to altered production or uptake of very low density lipoprotein (VLDL) or intermediate density lipoprotein (IDL) has not been established previously. Therefore VLDL and IDL apo B-100 kinetics were measured in seven subjects with FH, in six subjects with FDB, and in five normocholesterolemic controls using primed-constant infusions of [1-^{13}C]leucine. Absolute production rates (APR) of VLDL apoB were higher in FH than in controls (27.1 ± 1.9 vs. 17.9 ± 2.1 mg/kg/day $P < 0.03$). VLDL APR in FDB were between those of FH and controls (24.3 ± 4.8 mg/kg/day), and demonstrated a relatively large inter-individual variability. The increase in VLDL APR in FH resulted in higher fasting serum triglyceride concentrations than in controls ($P < 0.05$), whereas in FDB triglycerides were between those observed in FH and in controls. A significant correlation was observed between VLDL apoB APR and serum triglycerides in FH and in FDB; the correlation coefficient for all subjects was $r = 0.84$ ($P < 0.0001$), indicating that the major determinant of serum triglyceride concentrations was VLDL apoB APR. IDL apoB APR was lower in FH and in FDB compared to controls ($P < 0.03$ $P < 0.02$, respectively): and its fractional catabolic rate (FCR) was slightly lower in FH and in FDB, resulting in similar plasma IDL apoB concentrations in all three groups of subjects. IDL apoB APR in FH were negatively correlated with LDL cholesterol concentrations ($r = -0.89$; $P < 0.001$); LDL cholesterol concentrations correlated positively with the part of VLDL that did not appear in IDL ($r = 0.82$ $P < 0.02$), bypassing therefore the delipidation cascade. In conclusion the data demonstrate increased VLDL apoB production rates in FH. VLDL and IDL kinetics differ when LDL concentrations are elevated either due to a LDL receptor defect or due to defective apolipoprotein B-100.—**Zulewski H., R. Ninnis, A. R. Miserez, M. W. Baumstark, and U. Keller.** VLDL and IDL apolipoprotein B-100 kinetics in familial hypercholesterolemia due to impaired LDL receptor function or to defective apolipoprotein B-100. *J. Lipid Res.* 1998. **39:** 380–387.

Supplementary key words apolipoprotein B-100 • VLDL • IDL • LDL • FH • FDB • kinetic study • [1-^{13}C]leucine

Apolipoprotein B-100 represents a major protein component of very low density lipoproteins (VLDL) secreted by the liver (1, 2). The amount of apoB leaving the liver in VLDL is dependent on the intracellular availability of triglyceride and cholesterol (3). After entering the circulation, VLDL are delipidated by lipoprotein lipase, leading to intermediate density lipoproteins (IDL), the main precursor of the atherogenic low density lipoproteins (LDL).

Previous studies on production rates of VLDL and IDL apoB-100 in patients with familial hypercholesterolemia (FH) yielded contradictory results. Increased, unchanged, or decreased VLDL and increased or unchanged IDL apoB secretion rates were reported using different methods for their measurement and calculation (4–6). Kinetic studies have not yet been performed comparing subjects with FH and with familial defective apoB-100 (FDB). FDB is an autosomal dominantly inherited disorder caused by a point mutation in the apoB-100 gene (7). Its prevalence in Switzerland is higher than in other countries (1:200) (8). This results in diminished binding activity of the defective apoB to the LDL (apoB, E) receptor, and finally in increased serum LDL-cholesterol concentrations.

The aim of the present study was to assess the impact of defective LDL receptors and of defective apoB-100 on VLDL and IDL kinetics in humans. This question was of particular interest as a recent study from our laboratory (9) demonstrated that serum triglyceride con-

Abbreviations: apo, apolipoprotein; VLDL, very low density lipoprotein; IDL, intermediate density lipoprotein; FH, familial hypercholesterolemia; APR, absolute production rate; FDB, familial defective apolipoprotein B; FCR, fractional catabolic rate; BMI, body mass index; TTR, tracer-to-tracee ratio.

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centrations were higher in subjects with FH than in controls, whereas they were not increased but more variable in subjects with FDB.

SUBJECTS AND PROCEDURES

Subjects

Thirteen hypercholesterolemic subjects (7 FH, 6 FDB) and five normocholesterolemic controls of both sexes were studied after giving their informed consent. Age and body mass index (BMI) were not significantly different between the groups. Incidentally, sex distribution differed among the groups with more females in the FH and control groups, and more men in the FDB group (**Table 1**). Patients were selected from a cohort followed regularly in our lipid clinic using the following criteria. In familial hypercholesterolemia, LDL receptor alleles were analyzed for eight restriction fragment length polymorphisms of LDL receptor alleles (10). Inheritance of the alleles in their pedigrees was then followed, haplotypes for each subject were constructed, and cosegregation analysis was performed. In two subjects without relatives, FH was diagnosed by clinical criteria (11). FDB was diagnosed by the presence of a point mutation at nucleotide 10,708 by asymmetric allele-specific PCR, as described previously (9). Lipid-lowering drugs were discontinued for at least 8 weeks prior to the study. All subjects consumed an American Heart Association Step 1 diet (12). Control subjects were selected as having total cholesterol concentrations <6.0 mmol/l and fasting triglycerides <2.0 mmol/l measured at two separate occasions within 2 weeks. ApoE genotypes (13) were E_3/E_3 in six of the seven subjects with FH, in four of six with FDB, and in five of five control subjects. One FH subject had apoE_3/E_4, one FDB apo E_2/E_3, and another FDR subject apoE_4/E_4. All subjects were healthy during the study period, consumed no drugs, maintained their body weight and their low level of physical activity; their serum liver enzymes, creatinine, creatinephosphokinase, and red and white blood cell counts were within normal limits during the study. The experimental protocol was approved by the Ethics Committee of the University Hospital of Basel, and all subjects gave their written informed consent to participate.

TABLE 1. Patient characteristics

	FH (n = 7)	FDB (n = 6)	Controls (n = 5)
Age (yrs)	50 ± 5	47 ± 7	32 ± 6
BMI (kg/m^2)	25 ± 0.9	25 ± 2	22 ± 1
Sex (female/male)	6/1	2/4	1/4

Study protocol

VLDL and IDL apoB kinetics were measured according to Cohn et al. (14) by primed-constant infusions of [1-^{13}C]leucine (99% enriched; Mass Trace Inc., Somerville, MA). Each study was started at 7:00 am after an overnight fast. The priming dose was 10 μmol/kg body weight, and the constant intravenous infusion rate was 10 μmol/kg per h for 14 h, delivered by a portable infusion pump (Secura Ft model, Braun, Melsungen, Germany). In 3 of the 18 infusion studies, the tracer dosage was increased to 20 μmol/kg (bolus) and to 20 μmol/kg per h. During the kinetic study a primed continuous postprandial state was maintained, in analogy to a previous study (14) by ingestion of a standardized liquid formula diet containing 4% (w/v) proteins, 14% carbohydrates, and 3% lipids, consisting of 1.8% essential fatty acids, and no cholesterol (Fresubin™, Fresenius, Switzerland) in hourly portions of 1/14 of total daily energy requirements during 14 h. Daily resting energy requirements were calculated using the Harris and Benedict formula (15). Blood samples (20 ml) were drawn prior to the hourly meals at 0, 1, 2, 3, 4, 5, 6, 7, 9, 11, 14 h.

Analytical methods

Serum cholesterol was determined enzymatically (kit from Boehringer, Mannheim, Germany). HDL cholesterol (HDL-C) was determined similarly after precipitation of apoB-containing particles using reagents from Boehringer, Mannheim, Germany. Serum triglycerides were determined enzymatically (kit from Boehringer, Mannheim, Germany). Plasma VLDL was isolated by sequential ultracentrifugation at a 1.006 g/ml, IDL at d 1.019 g/ml using a Type Ti 70.1 rotor (Beekman, Nyon, Switzerland) for both fractions. Sodium azide was added to a final concentration of 0.1 mg/ml as antimicrobial agent, and EDTA to a final concentration of 0.5 mm. Samples were kept at 4°C during preparation of the fractions, and stored at −70°C. Total plasma apoB, VLDL and LDL apoB concentrations were assayed by nephelometry using a Behring apparatus and a rabbit anti-human antibody (Behring AG, Marburg, Germany). VLDL and IDL apo/B concentrations were determined in duplicates of each sample. As there were no significant changes of VLDL and IDL apoB concentrations during the infusion period, the mean of all measurements was used for calculation of kinetics. The coefficient of variation of VLDL apoB concentrations was 17%, that of IDL apoB 13%. LDL apoB concentrations were calculated as the difference between total apoB and the sum of VLDL and IDL apoB.

For measurement of [^{13}C]leucine content, apoB-100 was isolated from the VLDL and IDL fractions by preparative SDS electrophoresis, and thyroglobuline from Bio-Rad, Glattbrugg, Switzerland. VLDL and IDL apoB-100 bands were excised from the polyacrylamide gels and hydrolyzed at 110°C for 16 h in 6 m HCl. The hydrolysates containing amino acids were added directly to cation exchange columns (Bio-Rad, Glattbrugg, Switzerland) to separate free leucine by eluting with 5 m NH_4OH. The samples were dried in a Speed Vac evaporator (Savant Instruments, Farmingdale, NY), and 100 μl acetonitrile and 100 μl of MBDSTFA (Fluka, Buchs, Switzerland) were added. Samples were analyzed using a gas chromatograph mass spectrometer (5890/5870, Hewlett-Packard, Palo Alto, CA). Selective ion monitoring at 301 and 302 m/e was used to determine sample tracer to tracee ratio (TTR) in leucine (16). Plasma α-ketoisocaproate (α-KIC) was derivatized by *o*-phenylenediamine (Sigma, St. Louis, MO) and MBDSTFA, and selective ion monitoring at 259 and 260 m/e was used to determine α-KIC TTR. All stable isotope analyses were run in duplicates.

Calculations

For estimation of fractional catabolic rates (FCR), the Leverberg-Marquardt method (Quantum Soft, Zurich, Switzerland) was used for non-linear curve fitting and slope estimation of the change of leucine TTR with time. Data were calculated by the function: $A_{apoB}(t) = A_{\alpha\text{-KIC}}(1 - e^{-\beta(t-0.5)})$, where $A_{apoB}(t)$ was the TTR of [1-^{13}C]leucine in apoB at time t, $A_{\alpha\text{-KIC}}$ the TTR of plasma [1-^{13}C]-α-KIC, reflecting intracellular [^{13}C]leucine enrichment (17), β the rate constant, and −0.5 (h) the intrahepatic delay time. The latter was determined from the time course of [l-^{13}C]leucine TTR reported previously (18), and from the data of the present study (Fig. 1).

FCR was then calculated as:

$$\text{FCR(pools/day)} = \frac{\text{rate of increase of leucine apoB TTR/h}}{[1 - {}^{13}\text{C}]\text{–}\alpha\text{–KIC TTR}} \times 24\ \text{h}$$

The mean of three consecutive measurements of [1-^{13}C]-α-KIC TTR obtained between 9 and 14 h at plateau was used.

Absolute production rates (APR) of VLDL and IDL apoB were calculated as:

$$\text{APR (mg/kg/day)} = \frac{\text{FCR (pools/day)} \times \text{apoB pool size (mg)}}{\text{body weight (kg)}}$$

where the apoB pool size was the apoB concentration (mg/dl) in the respective lipoprotein fraction × plasma volume (0.045 L/kg). The fraction of VLDL apoB that did not appear in IDL, and therefore bypassed the delipidation cascade, was calculated as:

$$\text{VLDL apoB bypass fraction (\%)} = \frac{(\text{VLDL APR} - \text{IDL APR}) \times 100}{\text{VLDL APR}}$$

Statistical analyses

Results are means ± SEM. Mann-Whitney-U-tests were performed using Statview (Abacus Concepts Inc.) on Macintosh computers. For correlation analyses the Spearman rank correlation method was applied.

RESULTS

Baseline lipid and apo- and lipoprotein concentrations (Table 2)

Subjects with FH and FDB had higher total and LDL cholesterol and apoB concentrations than controls ($P < 0.005$ and $P < 0.02$, respectively). VLDL apoB and serum triglyceride concentrations were increased in FH compared to controls ($P < 0.05$); HDL-C concentrations were lower in FH and in FDB than in controls (both $P < 0.005$).

Kinetic studies

Figure 1 shows the time course of [1-^{13}C]leucine TTR in VLDL and IDL apoB in FH subjects during the 14-h tracer infusion. VLDL and IDL TTR increased after a delay of approx. 0.5 to 1 h, reaching a near-plateau for VLDL after approx. 10 h. [1-^{13}C]leucine TTR in IDL increased during the entire study and did not reach an entirely steady state during the final sampling period. VLDL apoB APR (**Fig. 2**, Table 2) were higher in FH than in controls ($P < 0.03$). Mean VLDL apoB APR in subjects with FDB were between those of FH and controls. VLDL apoB FCR was not significantly different among the three groups of subjects. The VLDL apoB pool was increased in FH compared to controls ($P < 0.01$); in FDB subjects, the mean VLDL apoB 13 pool was between FH and controls. IDL apoB APR was lower in FH and in FDB than in controls ($P < 0.03$, $P < 0.02$, respectively). FCR and apoB pool size of IDL was similar in the three groups of subjects. The fraction of VLDL apoB not appearing in IDL and therefore not entering the delipidation cascade was 24 ± 18% in controls and higher in FH (72 ± 5%; $P < 0.04$), and in FBD (75 ± 7%; $P < 0.01$). Individual VLDL and IDL kinetic data are shown in **Table 3**. The results demonstrate a relatively large inter-individual variability of the data. The fact that two control subjects demonstrated a

TABLE 2. Serum lipoprotein and apolipoprotein B concentrations and VLDL and IDL apoB kinetics

	FH (n = 7)	FDB (n = 6)	Controls (n = 5)
Serum lipid and lipoprotein concentrations			
Triglycerides (mmol/l)	2.0 ± 0.4[a]	1.6 ± 0.4	1.0 ± 0.3
Total cholesterol (mmol/l)	9.2 ± 0.5[c]	7.7 ± 0.6[b]	5.3 ± 0.2
LDL-C (mmol/l)	7.3 ± 0.5[c]	6.0 ± 0.5[c]	2.8 ± 0.2
HDL-C (mmol/l)	1.3 ± 0.1[c]	1.2 ± 0.2[c]	2.0 ± 0.1
Apoprotein B concentrations			
Total apoB (mg/dl)	245 ± 20[c]	202 ± 19[b]	107 ± 11
VLDL apoB (mg/dl)	10.0 ± 1.5[a]	7.8 ± 1.8	5.8 ± 0.5
IDL apoB (mg/dl)	5.0 ± 0.7	4.5 ± 1.2	5.4 ± 0.5
LDL apoB (mg/dl)	230 ± 16[c]	190 ± 20[c]	96 ± 6
VLDL and IDL kinetics			
VLDL apoB pool (mg)	309 ± 43[b]	249 ± 45	162 ± 21
VLDL apoB FCR (pools/day)	6.6 ± 0.8	7.0 ± 0.8	6.9 ± 0.8
VLDL apoB APR (mg/kg/day)	27 ± 2[a]	24 ± 5	18 ± 2.1
IDL apoB pool (mg)	156 ± 21	133 ± 25	146 ± 8
IDL apoB FCR (pools/day)	3.4 ± 0.5	2.7 ± 0.4	5.6 ± 1.5
IDL apoB APR (mg/kg/day)	7.4 ± 1.1[a]	5.5 ± 1.5[b]	1.25 ± 1.9
Percentage of VLDL APR not appearing in IDL	72 ± 5[a]	75 ± 7[b]	24 ± 18

Results are means ± SEM.
[a]$P < 0.05$; [b]$P < 0.02$; [c]$P < 0.005$ versus controls.

negative VLDL fraction bypassing IDL suggests de novo IDL production.

Correlation analyses

VLDL apoB APR and serum triglyceride concentrations were significantly correlated in the subjects with FH and with FDB ($r = 0.86$, $r = 0.95$, respectively). The correlation of VLDL apoB APR and serum triglycerides in all three groups of subjects together was $r = 0.84$, $P < 0.0001$ (**Fig. 3**). IDL kinetics were dependent on LDL cholesterol plasma concentrations in FH subjects: IDL production rates were decreased in subjects with increased serum LDL-C concentrations ($r = -0.89$, $P < 0.01$), and the fraction of VLDL disappearing without conversion into IDL was correlated with LDL-C concentrations ($r = 0.82$, $P < 0.02$; **Fig. 4**). The fraction of VLDL disappearing without conversion to IDL correlated negatively in FDB subjects ($r = -0.94$, $P < 0.005$; Fig. 4, bottom panel); this was of interest as thereby normocholesterolemic FDB subjects demonstrated a considerably higher fraction of VLDL disappearing without conversion into IDL compared to subjects of the control group with similar cholesterol concentrations.

DISCUSSION

The results demonstrate that subjects with FH have higher VLDL apoB production rates than normocholesterolemic controls, whereas VLDL apoB APR in FDB subjects are between those of FH and controls. In comparison, the fractional catabolic rates of VLDL were similar in the three groups of subjects, indicating that neither the defective LDL receptor function nor the defective apoB-100 results in impaired VLDL removal.

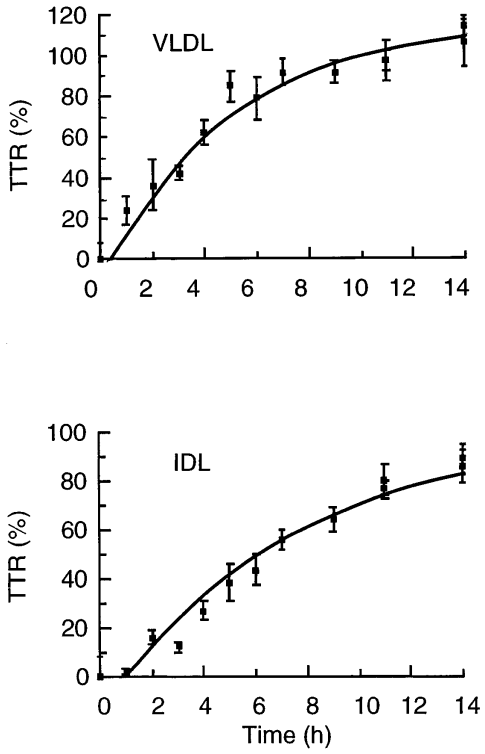

Fig. 1. Time course of tracer to tracee ratio (TTR) of [1-^{13}C]leucine in VLDL (top) and IDL (bottom) apoB in 7 FH subjects, expressed as percent of plasma α-KIC–TTR (means ± SEM).

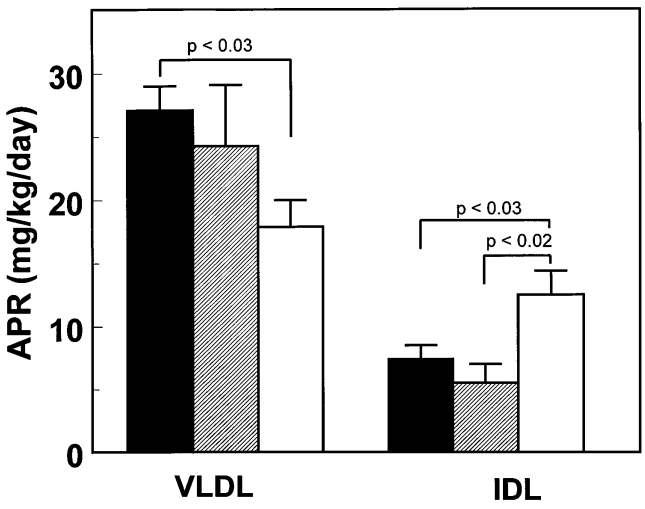

Fig. 2. VLDL and IDL apoB absolute production rates (APR) in FH (■, n = 7), FDB (*SS, n = 6), and control (□, n = 5) subjects. Data are means ± SEM.

Compared to previously published data, the absolute production rates of VLDL apoB in control subjects of the present study were in a similar range (present study: 17.9 mg/kg/day; previous reports: 17.6 (9.9–36.7) mg/kg/day [mean, range] (5, 7, 14, 19–26). The control subjects of the present study were on the average 18 yrs younger than the subjects with FH; Millar et al. (27) reported that VLDL apoB APR increased slightly with age, however not to an extent explaining the present results in FH subjects. Increased VLDL apoB APR in FH were also reported by Cummings et al. (4), using similar tracer methods and data analysis, except that their subjects were studied in the fasting state. This may explain the lower absolute VLDL apoB APR observed in their study as the present subjects received a liquid formula diet in order to mimic a postprandial state, resulting in increased VLDL apoB secretion (14).

The positive correlation between VLDL apoB APR and fasting serum triglycerides observed in the present study indicates that increased production of triglyceride-containing lipoproteins explains the modest increase in serum triglycerides in FH (11). Increased uptake of cholesterol via receptor-independent pathways may stimulate VLDL apoB production in FH as intrahepatic cholesterol availability has been reported to be rate limiting for VLDL secretion (28–30). In contrast to the present data, Fisher et al. (5) described slightly but not significantly lower VLDL apoB APR in FH compared to controls. These discrepancies were presumably due to patient selection as the seven FH subjects (5) happened to have fasting serum triglycerides similar to their control subjects. In addition, the tracer method did not include a direct measurement of VLDL apoB plasma concentrations.

The mean IDL apoB APR in control subjects of the present study (12.5 ± 1.9 mg/kg/day) was similar to that reported previously (11.1 [6.2–14.8 mg/kg/day] [median, range]) (6, 21, 22, 25, 26). IDL apoB APR in the present study were lower in FH and in FDB subjects than in controls. These data are in agreement with a previous study (21) but at variance with other reports demonstrating similar (6) or increased (5) IDL apoB production rates in FH. Possible reasons for these dis-

TABLE 3. Individual data of VLDL and IDL apoB kinetics

Subject	Diagn.	Sex	VLDL ApoB Conc.	VLDL ApoB Pool	VLDL ApoB FCR	VLDL ApoB APR	IDL ApoB Conc.	IDL ApoB Pool	IDL ApoB FCR	IDL ApoB APR	VLDL bypassing IDL[a]
			mg/dl	*mg*	*pools/d*	*mg/kg/d*	*mg/dl*	*mg*	*pools/d*	*mg/kg/d*	*%*
A. D.	FH	f	16.9	510	4.1	31.1	7.8	236	1.9	6.6	78.8
A. K.	FH	f	8.5	279	6.5	24.7	3.6	120	2.4	3.9	84.4
F. J.	FH	f	12.1	339	5.8	31.5	5.1	143	2.9	6.7	78.9
T. M.	FH	f	7.9	234	5.8	20.4	4.4	130	5.8	11.4	44.3
V. Y.	FH	f	9.4	284	6.0	25.4	5.4	162	3.8	9.3	63.4
W. E.	FH	f	10.8	369	7.0	33.8	6.6	224	3.4	9.9	70.6
W. A.	FH	m	4.5	151	11.0	22.5	2.4	78	3.8	4.1	81.9
B. E.	FDB	f	5.7	157	8.9	22.9	7.2	197	3.4	10.8	52.5
B. F.	FDB	m	7.2	222	8.9	28.6	4.0	123	3.6	6.4	77.6
N. R.	FDB	m	3.7	115	5.5	9.1	2.1	67	1.4	1.4	85.2
W. G.	FDB	f	15.9	386	5.3	37.8	8.7	211	1.9	7.4	80.4
W. M.	FDB	m	5.6	239	4.8	12.2	3.0	125	3.8	5.1	57.9
W. Y.	FDB	m	8.9	375	8.9	35.4	1.8	77	2.2	1.8	94.8
C. N.	Control	f	7.3	190	7.9	25.9	6.2	162	3.6	10.0	61.3
D. N.	Control	f	4.6	112	8.9	18.4	5.5	134	3.1	7.7	58.0
H. B.	Control	f	6.0	149	5.3	14.3	5.3	131	6.0	14.3	−0.4
K. C.	Control	f	5.0	135	7.4	16.7	6.3	170	4.1	11.6	30.9
R. C.	Control	m	6.3	227	5.0	14.3	3.7	133	11.3	18.8	−31.4

[a]Percentage of VLDL not appearing in IDL, calculated as described in Methods.

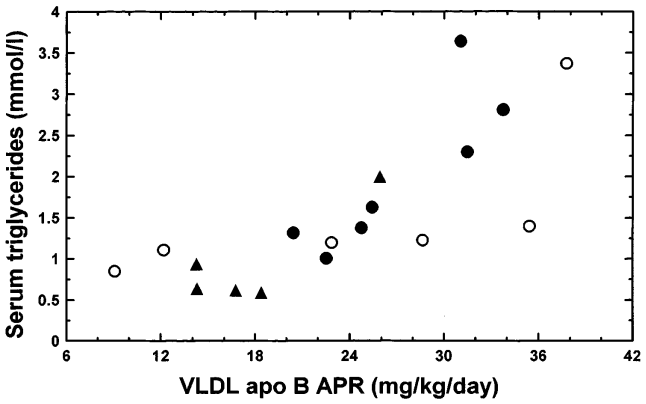

Fig. 3. Relationship between VLDL apoB APR and fasting serum triglyceride concentrations. Filled circles are subjects with FH, open circles subjects with FDB, and filled triangles control subjects, respectively. The correlation coefficient was $r = 0.84$, $P < 0.001$ (Spearman Rank test).

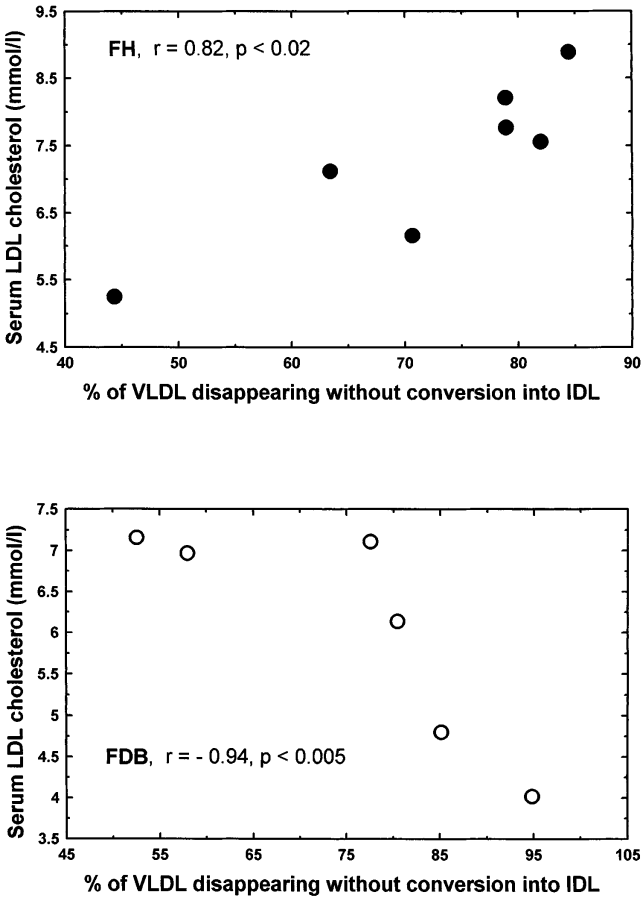

Fig. 4. Relationship between the percentage of VLDL apoB not appearing in IDL, and serum LDL-C concentrations in FH (top panel) and in FDB subjects (bottom panel). r values are Spearman Rank correlation coefficients.

crepancies could be related to the tracer method or data analysis used. Soutar, Myant, and Thompson (6) used exogenous labeling of VLDL with ^{125}I, a technique which may give rise to nonuniform labeling of VLDL or to alteration of its metabolic behavior due to the labeling process (31). Data reported by Fisher et al. (5) were derived from calculated activity and not directly measured IDL specific activity. In contrast to the lower IDL apoB APR in the present hypercholesterolemic subjects, plasma concentrations of IDL apoB were similar in all three groups of subjects. These data may be explained by the fact that a limited capacity of lipoprotein lipase to convert VLDL to IDL caused similar IDL apoB concentrations in hypercholesterolemic subjects and in controls. These results are in contrast to the increased IDL apoB concentrations reported in hypercholesterolemic Watanabe rabbits, animals with severely impaired LDL receptor function (32).

VLDL and IDL apoB metabolism in subjects with FH demonstrated several interesting features. First, IDL apoB APR were negatively correlated with LDL cholesterol concentrations. In addition, the fraction of VLDL not appearing in IDL, and therefore bypassing the delipidation cascade, was distinctly increased. In addition, this fraction correlated positively with LDL concentrations. Therefore, besides the increased VLDL production in these subjects discussed above, a larger fraction of VLDL compared to controls disappeared without conversion into IDL, presumably via non-LDL-receptor-dependent pathways. The higher the LDL concentrations were in individual FH subjects, the lower was the rate of VLDL not appearing in IDL, and therefore the lower the rate of the IDL production. These findings suggest that IDL are not the major direct precursor of LDL in FH. A direct conversion of a subfraction of VLDL to LDL was also suggested by other authors using exogenous and endogenous labeling of lipoproteins (5).

Although it is not certain that all produced IDL was isolated in this density 1.006–1.019 g/ml fraction, Beltz et al. (33) also suggested that an IDL pool sequestered in the liver in the space of Disse was transformed to LDL without previous appearance in the circulation. The metabolic pathways and mechanisms by which VLDL subfractions are directly converted to LDL are still poorly understood.

In comparison, FDB subjects demonstrated no clear increase in VLDL apoB APR. This suggests that in FH, the increase in VLDL apoB APR was due to a LDL-receptor-mediated mechanism which may have resulted from impaired catabolism of all apoB-containing particles including VLDL remnants. Nevertheless, even FDB subjects demonstrated an increased fraction of

VLDL not appearing in IDL. The subjects with the highest fraction of VLDL not appearing in IDL were those with relatively low LDL-C concentrations, suggesting that these individuals were protected from the development of hypercholesterolemia due to diminished VLDL-IDL-LDL conversion. It would be of interest to know the kinetics of the two species of apoB in lipoproteins in subjects with FDB (wild type and defective apoB); the present results are pooled data of both species; whether the defective apoB is responsible for the diminished VLDL-IDL-LDL cascade in FDB is likely but not proven by the present results.

The sex distribution in the three groups of subjects started was unbalanced, demonstrating a relatively larger number of men than women in the FDB group. The effect of gender on VLDL and IDL kinetics has not been studied; however, when looking at individual data (Table 3) there was no systematic difference between both sexes in all groups.

In conclusion, the present results suggest that increased VLDL apoB production rates in subjects with FH are the cause of an increase in fasting serum triglyceride concentrations. VLDL apoB catabolic rates and fasting triglycerides in subjects with FDB were lower but more variable compared to those in FH, suggesting that apoB, E-receptor-mediated uptake of VLDL or IDL may vary in individual FDB subjects according to other factors, e.g., dietary habits. Thus, different alterations of VLDL and IDL apoB kinetics occur when mutations affect either the function or the ligand of the apoB, E (LDL) receptor.

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