Plasma lipoproteins in familial combined hyperlipidemia and monogenic familial hypertriglyceridemia[1]

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Abstract Plasma lipoprotein concentration, composition, and size were evaluated in two common familial forms of hypertriglyceridemia and compared with those in normal subjects. The very low density lipoproteins (VLDL) were triglyceride-enriched in familial hypertriglyceridemia (triglyceride/apoprotein B ratio: 25.7 ± 8.9) as compared to normal (9.6 ± 12.2, $P < 0.001$) or familial combined hyperlipidemia (9.7 ± 3.3, $P < 0.001$). The diameter of VLDL was larger in familial hypertriglyceridemia (3.27 ± 0.28 pm) than in familial combined hyperlipidemia (2.87 ± 0.16 pm, $P < 0.02$). Although in familial hypertriglyceridemia VLDL tended to be larger, and in familial combined hyperlipidemia VLDL tended to be smaller than normal (3.08 ± 0.48 pm), neither of these differences were significant. While VLDL was normally distributed in the control population, the size was skewed to larger particles in familial hypertriglyceridemia with fewer small particles ($P < 0.05$) and skewed to smaller particles in familial combined hyperlipidemia with fewer large particles ($P < 0.05$). VLDL was reciprocally related to low density lipoproteins (LDL) in familial combined hyperlipidemia ($r = -0.80$ to -0.87) suggesting that the concentrations of these individual lipoprotein groups were somehow interrelated. There was no significant relationship between these two lipoprotein classes in familial hypertriglyceridemia or in normals. In familial combined hyperlipidemia, the apoprotein A-I/A-II ratio was below normal ($P < 0.01$) suggestive of low HDL_2 levels. This change in apoprotein composition was independent of VLDL or LDL concentration. In familial hypertriglyceridemia, high density lipoprotein (HDL) cholesterol was reduced (33% below mean normal) and HDL triglyceride was increased (by 46%), while the concentration of apoA-I and apoA-II was normal. VLDL triglyceride was inversely related to HDL cholesterol in familial hypertriglyceridemia ($r = -0.74$, $P < 0.005$), but not in familial combined hyperlipidemia. The large, triglyceride-enriched VLDL observed in familial hypertriglyceridemia is compatible with the reported increase in VLDL triglyceride synthesis seen in this disorder. The increase in VLDL apoprotein B synthesis previously reported in familial combined hyperlipidemia was associated with VLDL of normal composition. The changes in HDL cholesterol in these two disorders might reflect exchange of triglyceride between VLDL and HDL or could be related to transfer of surface components during the catabolism of VLDL. The reciprocal relationship between various components of VLDL and LDL seen in familial combined hyperlipidemia, but not in familial hypertriglyceridemia or in normal subjects, might provide some insight into the pathological abnormalities in these disorders. The differences between these two common familial forms of hypertriglyceridemia provide further support that they are distinct entities.—**Brunzell, J. D., J. J. Albers, A. Chait, S. M. Grundy, E. Groszek, and G. B. McDonald.** Plasma lipoproteins in familial combined hyperlipidemia and monogenic familial hypertriglyceridemia. *J. Lipid Res.* 1983. **24:** 147–155.

Supplementary key words very low density lipoprotein • high density lipoprotein • apoprotein B

Familial combined hyperlipidemia (FCHL) has been recently described as a disorder in which multiple lipoprotein phenotypes (IIA, IIB, and IV) occur in the same family (1–3). Further, the lipoprotein phenotype in a single individual with this disorder can change from time to time. FCHL appears to be distinct from the two apparently monogenic disorders familial hypercholesterolemia and familial hypertriglyceridemia (FHTG) (1–3) because *a*) these two disorders do not occur frequently enough to account for the families with multiple lipoprotein phenotypes, and *b*) a combination of these two disorders is incompatible with analysis of informative matings (1).

VLDL apoprotein B synthetic rates appear to be elevated above the range of normal in hypertriglyceridemic subjects (phenotype IIB and IV) with FCHL (4, 5). Patients with FHTG, however, have normal (5) or mildly elevated (4) VLDL apoprotein B synthetic rates

Abbreviations: VLDL, very low density lipoproteins; LDL, low density lipoproteins; HDL, high density lipoproteins; FCHL, familial combined hyperlipidemia; FHTG, familial hypertriglyceridemia.

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that are lower than those seen in FCHL (4, 5). In contrast, plasma triglyceride synthetic rates are higher in individuals with FHTG than in those with FCHL (4). Thus, the increase in VLDL levels in FCHL appears to be due mainly to overproduction of VLDL apoprotein B with a relative removal defect for VLDL triglyceride, while that seen in FHTG seems to be mainly due to overproduction of VLDL triglyceride.

Because of the differences between the kinetics of apoprotein B and triglyceride in these two disorders, this study was designed *a*) to ascertain whether the kinetic differences in FHTG and FCHL were reflected in alterations in the composition and size of VLDL, and *b*) to compare lipoprotein relationships in these two disorders.

METHODS

Subjects for this study were obtained from a group of individuals originally referred to the University of Washington for evaluation of hypertriglyceridemia. Those with lipoprotein lipase deficiency, broad-beta disease, and hypertriglyceridemia secondary to other disease states were excluded, as were subjects on drugs known to affect lipoprotein metabolism (6). The distribution of lipid levels was determined in the families of the propositi in order to obtain a genetic diagnosis. Propositi with either FHTG or FCHL then were selected for evaluation of their lipoproteins.

To eliminate a bias that might affect the data in this study, the propositi were not utilized to determine the existence, or type of familial form of hyperlipidemia in each family studied. Plasma triglyceride and cholesterol levels were measured after an overnight fast in the relatives of these hypertriglyceridemic subjects. Based on previously published criteria (1, 7), the families were divided into three groups: FHTG, FCHL, and "no diagnosis possible", i.e., families in which there were too few affected relatives to permit a precise diagnosis to be made. Because FHTG and FCHL occasionally are difficult to distinguish (8), propositi were selected for study of their lipoprotein composition only if they came from *a*) FHTG families in which all affected relatives were lipoprotein phenotype IV or *b*) from families with FCHL in which at least one affected relative was lipoprotein phenotype IIA, one IIB, and one IV. Thus, the familial form of hypertriglyceridemia in the propositus was determined by the lipid levels in his relatives and was independent of his own particular lipid abnormality. Thirteen male propositi with FCHL and 14 male propositi with FHTG from the above families were compared with age-matched normal males evaluated as part of a local population study in Seattle (9, 10) (**Table 1**). One additional subject with FCHL (number 11) was the brother of another (number 10) and was persistently hypercholesterolemic. Although all of the propositi were hypertriglyceridemic at the instigation of the family studies, by the time of the present study (5 to 6 years later), the lipid phenotype had changed in some of the propositi with FCHL (Tables 2 and 3). All 14 subjects with FHTG remained lipoprotein phenotype IV.

Lipoprotein studies were performed on subjects who were consuming an ad libitum diet, without any special restriction of any component, such as cholesterol or saturated fat. All samples were drawn in the morning after an overnight fast of 12–14 hr.

The samples for lipoprotein analysis were drawn into EDTA, plasma was refrigerated at 4°C, and ultracentrifugation was performed within 1 week (11). Lipoprotein lipids were measured in 14 subjects with FHTG, all of whom had a type IV lipoprotein phenotype (**Table 2**). Apoprotein levels were measured in eight of these subjects. On a separate occasion VLDL was examined by electron microscopy in nine of the subjects with FHTG (**Table 3**). Lipoprotein lipids were measured in 12 subjects with FCHL (Table 2). Apoprotein levels were measured in seven of these subjects. On a separate occasion VLDL was examined by electron microscopy in five hypertriglyceridemic subjects with FCHL (Table 3).

Cholesterol was determined by the Liebermann-Burchard reagent method and triglyceride was determined by a fluorometric 2,4-pentanedione procedure using the Lipid Research Clinics continuous flow Auto-Analyzer II procedure (11). The coefficient of variation for cholesterol analysis was less than 2% and accuracy was within 3% of the target values; for triglyceride analysis, the coefficient of variation was less than 3% and accuracy was within 4% of the target values. To measure HDL cholesterol, 0.10 ml of 1 M $MnCl_2$ and 0.08 ml of sodium heparin (5000 USP units/ml or approximately 35 mg/ml, Riker Laboratories, Northridge, CA 91324) were added to 2 ml of plasma and cholesterol was measured in the supernatant (12). To check for completeness of precipitation of LDL and VLDL, apoprotein B was quantitated in the heparin-Mn^{2+} supernatants and found to be less than 2 mg/dl by a sensitive radial immunodiffusion method (9). The cholesterol and triglyceride levels were measured in whole plasma and on the d 1.006 g/ml infranatant fraction and the levels of VLDL, LDL, and HDL lipids were determined (11).

Apoprotein B levels were determined by radioimmunoassay of the supernatant and infranatant after ultracentrifugation (9). The coefficient of variation was

TABLE 1. Characteristics of FCHL and FHTG propositi

Subject	Age	Sex	Height	Weight	RBW	Range of Total Triglyceride		Range of Total Cholesterol	
						Low	High	Low	High
						mg/dl		*mg/dl*	
FCHL									
1	65	M	165	70.5	117	318	474	274	358
2	57	M	160	72.3	126	174	207	242	310
3	56	M	173	72.7	110	121	251	244	259
4	51	M	175	65.9	97	117	500	209	348
5	27	M	175	77.3	114	310	340	183	198
6	35	M	168	78.6	127	307	438	217	228
7	48	M	171	74.6	116	141	501	188	288
8	48	M	183	116.5	158	174	402	240	309
9	46	M	168	77.5	125	117	262	197	300
10	60	M	174	80.5	121	203	513	190	256
11	55	M	178	78.2	113	82	170	291	332
12	34	M	188	84.1	108	96	370	250	339
13	61	M	176	78.9	116	171	438	176	328
14	47	M	180	95.8	133	516	540	272	292
FHTG									
15	48	M	183	83.9	114				
16	42	M	178	88.6	127				
17	55	M	166	96.6	159				
18	48	M	170	88.6	139				
19	68	M	180	79.5	111				
20	34	M	178	93.2	134				
21	65	M	175	89.5	132				
22	49	M	177	77.3	112				
23	38	M	183	78.3	106				
24	53	M	183	95.5	130				
25	40	M	182	80.6	110				
26	62	M	175	72.7	107				
27	48	M	169	85.0	135				
28	57	M	165	90.3	149				

6%. Apoprotein A-I and A-II levels were measured by radial immunodiffusion on whole plasma (10, 12); the coefficient of variation for A-I was 5% and for A-II 6%.

Electron microscopy of VLDL was performed on a Zeiss EM-10, using negative staining with 1% phosphotungstic acid (Electron Microscopy Sciences) adjusted to pH 7.2 with 1.0 N NaOH. The method employed recently has been described in detail (13). Grids (500 mesh) were carefully cleaned by sequential washes in chloroform, acetone, 44% formic acid, 0.01 N NaOH, and glass-distilled water. Thin films of formvar (Ted Pella Co.) were prepared by dipping a microscope slide into a 0.5% solution of polymer dissolved in reagent grade 1,2-dichloroethane and allowing the excess to drain off the slide in an atmosphere saturated with solvent. The formvar film was floated in water and lowered onto grids that were dried for 2 hr at 30°C and then very lightly carbon coated. Grids were used within 7 days and were deionized within 24 hr of use. Deionization was carried out for 10 min at 20 milliamperes between 100 and 150 mm Hg in a Denton vacuum evaporator. Particle size distributions were obtained from electron micrographs using a 48-channel Zeiss TGZ-3 particle analyzer. Micrographs were taken of areas where particles were clearly shown. Only one micrograph was taken per grid square for a total of seven to ten micrographs. The diameter of 500 to 1500 particles from each subject was then determined. Data obtained for hyperlipidemic patients were compared with those from ten healthy nonobese adults, ages 22–32 years, with normal plasma triglyceride and cholesterol levels.

Statistical methods included analysis of covariance, regression analysis, the Student's *t* test, and the unpaired Wilcoxon two-sample test (14).

RESULTS

VLDL of abnormal composition was observed in FHTG, while no abnormality was seen in VLDL composition in FCHL (**Table 4**). VLDL in FHTG was triglyceride-enriched (increased VLDL TG/apoprotein B ratio) as compared with normal subjects ($P < 0.001$) and FCHL ($P < 0.001$). Accordingly, a lower VLDL cho-

TABLE 2. Lipid and apoprotein concentrations[a] in FCHL and FHTG

Subject	Total Plasma TG	Chol	A-I	A-II	Phenotype	VLDL TG	Chol	ApoB	LDL TG	Chol	ApoB	HDL TG	Chol
FCHL													
1	318	274			IV	251	114		46	126		21	34
2	207	269	123	42	IIB	125	55	10.7	61	169	200	21	45
3	168	244	123	36	NL	107	60	21.7	50	138	123	11	46
4	258	248	126	35	IV	210	58		28	145		20	53
5	310	183	124	36	IV	256	67	18.7	41	85	118	13	31
6	307	217			IV	211	61		67	122		29	34
7	171	263	101	30	IIA	111	35	11.5	40	197	150	20	31
8	161	309	100	37	IIA	112	42	13.8	48	228	187		39
9	177	264	113	33	IIA	119	46	12.9	47	186	157	11	32
10	435	231	136	39	IV	358	84	24.6	55	114	92.7	22	33
11	74	320			IIA	22	7		43	253	128	9	60
12	96	258			IIA	44	16		43	208		9	44
$\bar{x}$	224	248	118	36		160	54	16.3	47	164	144	17	40
SD	±104	±46	±13	±4		±98	±29	±5.4	±10	±51	±36	±7	±10
vs. FHTG	$P<$		NS	NS		0.001	0.02	0.05	NS	0.05	NS	NS	0.01
vs. NL	$P<$		NS	NS		0.001	0.001	0.05	0.001	0.001	0.001	0.02	NS
FHTG													
15	860	282	124	42	IV	797	100	37.9	52	150	134	11	32
16	283	236			IV	223	43		51	162		9	31
17	565	279	118	31	IV	494	106	19.3	54	146	101	17	27
18	1136	267	98	29	IV	1003	166		100	81	94.0	33	20
19	844	214	105	30	IV	763	133	25.6	57	64	115	24	17
20	440	239			IV	401	26		34	180		5	33
21	596	200	102	26	IV	541	102	22.4	35	75	89.0	20	23
22	207	202	130	33	IV	165	53		30	110		12	39
23	322	234	125	34	IV	253	61	17.8	53	141	100	16	32
24	376	249			IV	293	74		52	131		31	44
25	330	222			IV	257	46		45	132		28	44
26	510	234	132	33	IV	456	100	20.0	38	107	117	16	27
27	1072	320			IV	948	164	30.0	103	145	108	21	20
28	890	313	159	32	IV	810	151	18.9	52	133	105	28	29
$\bar{x}$	602	249	121	32		529	95	24.0	54	126	107	19	30
SD	±305	±38	±18	±4		±286	±46	±6.9	±22	±34	±14	±9	±8
vs. NL	$P<$		NS	NS		0.001	0.001	0.001	0.001	NS	0.01	0.001	0.001
Normal (n)			172	172		145	145	145	145	145	145	213	213
$\bar{x}$			121	33		53	14	10	17	120	88	13	45
SD			±20	±5		±26	±7	±7	±8	±25	±18	±5	±11

[a] mg/dl.

lesterol/triglyceride ratio was observed in FHTG than in normal subjects ($P < 0.001$) and FCHL ($P < 0.01$). The ratio of VLDL cholesterol/apoprotein B was also higher in FHTG than the other two groups of subjects (Table 4). Since there was no correlation between VLDL triglyceride and VLDL apoprotein B levels in any group, the relative triglyceride enrichment of VLDL in FHTG does not appear to account for the higher VLDL triglyceride concentrations in these patients.

The diameter of VLDL was greater in FHTG (3.27 ± 0.28 pm) than in FCHL (2.87 ± 0.16 pm, $P < 0.02$) (Table 3). Although the VLDL in FHTG tended to be larger than normal and the VLDL in FCHL tended to be smaller than normal, neither of these differences was significant. However, there were fewer VLDL below a diameter of 2.5 pm in FHTG than normal ($P < 0.05$) and fewer VLDL above a diameter of 3.5 pm in FCHL than normal ($P < 0.05$) (**Fig. 1**). Thus, the VLDL was skewed to particles of increased size in FHTG and decreased size in FCHL.

LDL cholesterol concentrations were normal in

TABLE 3. Size distribution of VLDL in FCHL and FHTG

Subject	TG	Chol	Phenotype	VLDL Diameter				
				Mean Diameter	SD	<2.5 pm	2.5–3.5 pm	>3.5 pm
	mg/dl			*pm*		%	%	%
FCHL								
4	162	231	NL	2.87	0.44	12	8.2	6
7	226	265	IIB	2.94	0.64	20	67	12
8	268	301	IIB	2.60	0.93	51	35	14
13	292	241	IV	2.97	0.82	39	56	5
14	516	272	IV	2.99	0.95	24	53	24
$\bar{x}$				2.87		29 ± 16	57 ± 17	12 ± 8
SD				±0.16				
FHTG								
17	984	308	IV	3.32	0.82	9	65	27
18	620	316	IV	3.05	0.89	25	52	23
20	378	292	IV	3.41	0.82	4	64	41
65	660	233	IV	3.42	0.84	8	58	34
23	289	234	IV	3.19	0.63	4	75	19
24	376	249	IV	3.25	0.58	0	80	19
25	330	222	IV	2.98	0.67	18	67	13
27				3.87	1.28	9	38	64
28	444	264	IV	2.99	1.03	36	37	26
$\bar{x}$				3.27		13 ± 12	60 ± 15	30 ± 15
SD				±0.28				
Normal $\bar{x}$ ± SD (n = 10)				3.08 ±0.48		25 ± 12	45 ± 16	30 ± 13
FHTG vs. FCHL				0.02		NS	NS	NS
FHTG vs. NL				NS		0.05	NS	NS
FCHL vs. NL				NS		NS	NS	0.05

FHTG. LDL concentration was variable in FCHL, but as a group, it was elevated above normal ($P < 0.001$) (Table 2) and above the concentrations seen in FHTG ($P < 0.05$). LDL triglyceride concentration was elevated above normal in both disorders ($P < 0.001$). LDL apoprotein B concentration was higher than normal (88 ± 18 mg/dl) (13) in FCHL (144 ± 36 mg/dl; $P < 0.001$) and in FHTG (107 ± 14; $P < 0.001$). LDL apoprotein B levels were lower in FHTG than in FCHL ($P < 0.01$), however, LDL cholesterol/apoprotein B ratios were

TABLE 4. Comparison of lipoprotein lipid and protein ratios

	Normal	Familial Hypertriglyceridemia	vs. NL	Familial Combined Hyperlipidemia	vs. NL	FHTG vs. FCHL[a]
			P<		*P<*	*P<*
VLDL TG/B[b]	9.6 ± 12.2 (145)	25.7 ± 8.9 (8)	0.001	9.7 ± 3.3 (7)	NS	0.001
VLDL Chol/B	2.50 ± 3.10 (145)	4.97 ± 1.59 (8)	0.05	2.51 ± 0.73 (7)	NS	0.01
VLDL Chol/TG	0.291 ± 0.124 (145)	0.182 ± 0.047 (14)	0.001	0.257 ± 0.067 (12)	NS	0.01
HDL Chol/A-I[c]	27 ± 5 (172)	18 ± 7 (10)	0.001	24 ± 5 (9)	NS	0.05
HDL Chol/A-II[c]	60 ± 13 (172)	39 ± 8 (10)	0.001	49 ± 10 (9)	0.005	0.05
A-I/A-II[c]	2.23 ± 0.25 (172)	2.24 ± 0.43 (10)	NS	2.01 ± 0.20 (9)	0.01	NS
HDL/LDL Chol	0.38 ± 0.18 (145)	0.24 ± 0.07 (14)	0.01	0.25 ± 0.08 (12)	0.02	NS
HDL Chol/HDL Triglyceride	4.38 ± 1.77 (213)	2.07 ± 1.59 (14)	0.001	2.70 ± 1.57 (12)	0.001	NS

[a] *P* value for level of significance between familial hypertriglyceridemia (FHTG) and familial combined hyperlipidemia (FCHL).
[b] TG: triglyceride; Chol: cholesterol; B: apoprotein B; A-I, A-II: apoproteins A; in mg/dl; $\bar{x}$ ± SD. Number in parentheses is number of subjects. *P* value for level of significance between groups.
[c] HDL cholesterol and apoprotein molar ratios.

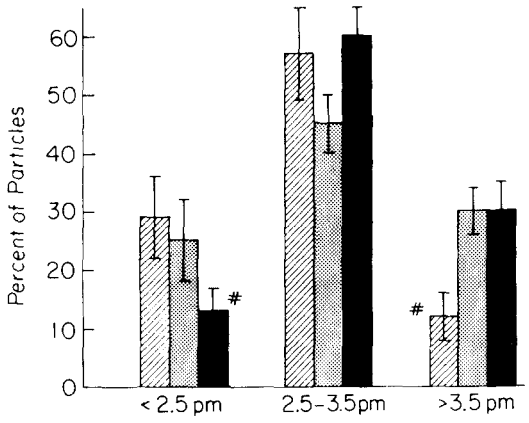

Fig. 1. Distribution of very low density lipoproteins by diameter in normal individuals (dotted bars), in subjects with familial combined hyperlipidemia (hatched bars), and in subjects with familial hypertriglyceridemia (solid bars). The percent of particles in normal individuals of less than 2.5 pm and greater than 3.5 pm is approximately equal by selection. There are significantly fewer than normal large particles in FCHL (#:$P < 0.05$) and significantly fewer than normal small particles in FHTG ($P < 0.05$).

identical in the two disorders. In FCHL those with hypertriglyceridemia had lower LDL cholesterol/apoprotein B ratios (0.93 ± 0.27) than those who had normal triglyceride concentrations (1.36 ± 0.35; $P < 0.05$).

VLDL and LDL concentrations were inversely related in the group with FCHL (VLDL triglyceride vs. LDL cholesterol: $r = -0.84$, n = 12, $P < 0.002$; **Fig. 2;** VLDL-B vs. LDL-B: $r = -0.87$, n = 7, $P < 0.01$; **Fig. 3**). In a single individual with FCHL in whom lipoprotein lipids were measured 11 times over a period of 6 years while on no antihyperlipidemic drugs, there also was an inverse relationship between VLDL triglyceride and LDL cholesterol levels ($r = -0.90$, $P < 0.001$) (**Fig. 4**). There was no correlation between VLDL and LDL in normal subjects or in FHTG.

HDL cholesterol was reduced 33% below normal in

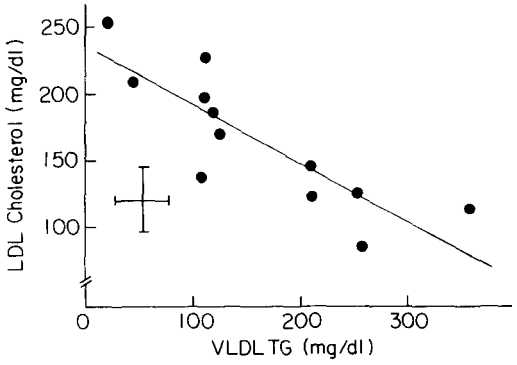

Fig. 2. Relationship between VLDL triglyceride and LDL cholesterol in group of subjects with familial combined hyperlipidemia ($r = -0.84$, $P < 0.001$). Mean values for normal individuals are represented by the cross.

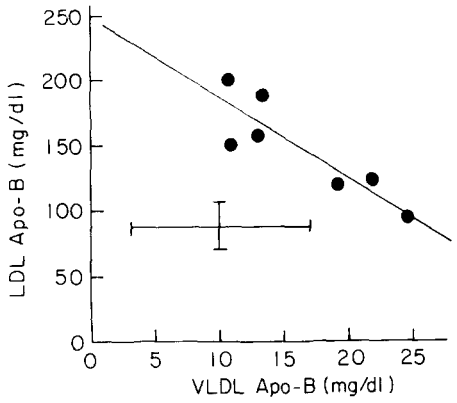

Fig. 3. Relationship between VLDL apoprotein B and LDL apoprotein B in group of subjects with familial combined hyperlipidemia ($r = -.87$, $P < 0.01$). Mean values for normal individuals are represented by the cross.

familial hypertriglyceridemia (30 ± 8 mg/dl, $P < 0.001$) and was correlated inversely with VLDL triglyceride ($r = -0.74$, $P < 0.005$) (**Fig. 5**). In FCHL, HDL cholesterol was slightly lower than normal, but this reduction did not achieve statistical significance at the 5% level, and HDL cholesterol was not correlated with VLDL triglyceride. The HDL/LDL cholesterol ratio did not differ between the two disorders (Table 4), but was significantly lower than normal in both FHTG ($P < 0.01$) and FCHL ($P < 0.02$).

The HDL cholesterol/apoprotein A molar ratios were lower than normal in both disorders (Table 4). These changes were largely accounted for by a decrease in HDL cholesterol, since apoA-I and A-II concentrations did not differ from normal in either of the genetic disorders. The A-I/A-II molar ratio in FCHL was less than that for normal controls ($P < 0.01$) (Table 4), whereas this ratio did not differ from normal in FHTG. HDL triglyceride was higher in FHTG (19 ± 9 mg/dl; $P < 0.001$) and in FCHL (17 ± 7; $P < 0.02$) than normal (13 ± 5; n = 213) (21). HDL triglyceride correlated weakly with VLDL triglyceride in the entire group of hyperlipidemic subjects ($r = 0.41$, n = 25, $P < 0.05$).

DISCUSSION

When subjects originally selected for hypertriglyceridemia are classified as having FHTG or FCHL by an independent analysis of the distribution of plasma lipid abnormalities among their relatives, differences in lipoprotein composition and lipoprotein-lipoprotein relationships are observed. These findings provide some insight into the potential pathophysiological defect in each disorder.

Subjects with FHTG have VLDL particles which are significantly larger in size than those found in subjects

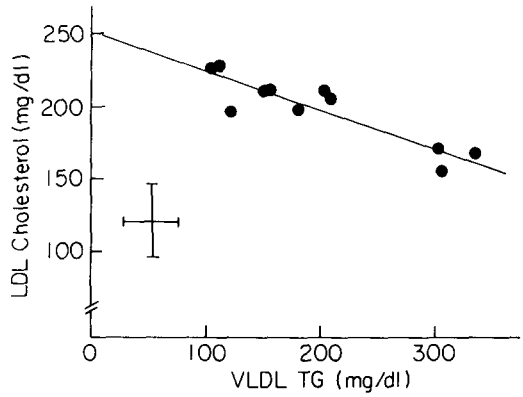

Fig. 4. Relationship between VLDL triglyceride and LDL cholesterol in a single subject with familial combined hyperlipidemia studied eleven times over a period of 6 years ($r = -0.90$, $P < 0.001$).

with FCHL. The trend for larger VLDL in FHTG appeared to be related to a shift to particles of larger diameter. The VLDL was triglyceride-enriched with a triglyceride/apoprotein B ratio twice that seen in normal subjects or in subjects with FCHL. The cholesterol/apoprotein B ratio in VLDL was also elevated in FHTG.

VLDL triglyceride synthetic rates are higher in FHTG than in FCHL for comparable VLDL triglyceride concentrations (4). Although VLDL apoprotein B synthetic rates are possibly slightly elevated above normal in FHTG (4, 5), they are distinctly lower than rates in subjects with FCHL who are hypertriglyceridemic. The increased triglyceride synthesis seen in FHTG is compatible with the oversecretion of the triglyceride-rich, large VLDL found in this disorder. The high normal to mildly elevated VLDL apoprotein B synthetic rates in FHTG may be in response to the need for a surface to cover the increased triglyceride prior to its secretion as VLDL. Lipoprotein lipase activity in adipose tissue is normal in FHTG (15) and thus would not appear to account for the triglyceride enrichment of VLDL. The low VLDL cholesterol/triglyceride ratio in FHTG argues against a defect in remnant removal as is seen in broad beta disease (16).

Individuals from families with FCHL have VLDL that tend to be smaller than normal apparently due to a shift to lipoproteins of smaller diameter. VLDL composition, however, as manifest by normal lipid/lipid and lipid/protein ratios is normal. Hyperlipidemic subjects with FCHL have similar VLDL triglyceride/apoprotein ratios and VLDL size regardless of lipoprotein phenotype. The accumulation of smaller VLDL particles is associated with elevated rates of VLDL apoprotein B synthesis (4, 5) in hypertriglyceridemic subjects (phenotypes IIB and IV) with FCHL. Environmental factors, such as obesity, might be important in the phenotypic expression of FCHL as phenotype IV as opposed to phenotype IIA (17), with an elevation of VLDL triglyceride production being due to the obesity (18, 19).

In FCHL various components of VLDL were inversely related to those of LDL. By contrast, in FHTG LDL cholesterol concentrations over a wide range of VLDL triglyceride were comparable to those found in normal subjects. As with FHTG, no significant correlation was observed between VLDL and LDL concentration in normal individuals, although in normals the lack of correlation might result from the inaccuracy in the measurement of the lipoprotein components of VLDL in the normal range. The inverse relation between VLDL and LDL concentration in FCHL raises the possibility that the concentrations of these lipoproteins are somehow uniquely reciprocally linked to one another. A primary generalized defect in apoprotein B synthesis might be speculated to exist: hypertriglyceridemic subjects have increased VLDL apoprotein B synthesis (4, 5) and hypercholesterolemic subjects have increased LDL B synthesis (5, 20). The interaction of this defect with environmental factors could then determine the specific phenotypic expression.

In 1970, Lees (21) noted apoprotein B enrichment in some subjects with atherosclerosis. Recently Sniderman et al. (22) have reported abnormalities in LDL composition of subjects with premature coronary artery disease. After exclusion of subjects with lipoprotein phenotype IIA, they noted apoprotein B enrichment in those who had coronary artery disease as compared to various control groups. Similar findings are present in FCHL. The hypertriglyceridemic subjects have apoprotein B-enriched LDL with low LDL cholesterol/apo B ratios as compared to the type IIA subjects with FCHL and to the normals. Since Sniderman et al. (22) did not evaluate the etiology of the changes in LDL composi-

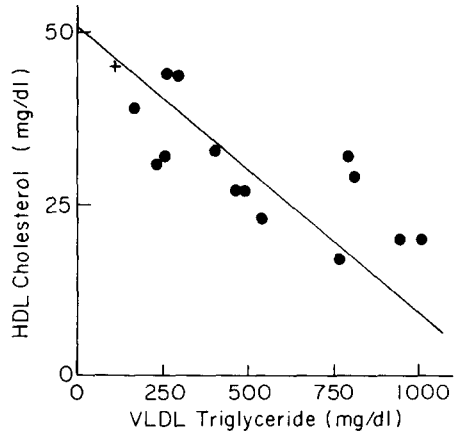

Fig. 5. Relationship between VLDL triglyceride and HDL cholesterol in group of subjects with familial hypertriglyceridemia ($r = -0.74$, $P < 0.005$). Mean values for normal individuals are represented by the cross.

tion, and the present study did not study the prevalence of FCHL, it is difficult to determine whether the two studies are looking at different aspects of the same entity.

HDL cholesterol was low in FHTG. The reduction in HDL cholesterol in FHTG was greater than that seen in FCHL and appeared to be related to the magnitude of the hypertriglyceridemia in FHTG. In FCHL the major abnormality in HDL was compositional, with a reduction in the A-I/A-II apoprotein ratio. Subjects with this disorder also had higher HDL triglyceride concentrations; however, in contrast to FHTG, there was no association between HDL cholesterol and VLDL triglyceride concentrations. The narrower range of VLDL concentration seen in FCHL than in FHTG might explain the lack of correlation between HDL cholesterol and VLDL triglyceride in FCHL. A correlation between total triglyceride and HDL triglyceride (r = 0.52) previously has been reported (23); it is similar to that found (r = 0.41) in the hyperlipidemic patients in the present study. It is conceivable that some of the decrease in HDL cholesterol seen in association with hypertriglyceridemia may be due to the transfer of triglyceride from VLDL to HDL (24), leading to a reduced capacity for cholesterol storage in the HDL core.

The reported difference in risk of developing coronary artery disease between subjects with FHTG and those with FCHL (7) is of interest in light of the present study. Perhaps the increased incidence of myocardial infarctions in FCHL is related to higher LDL in the individuals with the IIA or IIB phenotype. Even though LDL may be normal in those with phenotype IV, it is conceivable that LDL may be elevated in these patients at other times. Another possible explanation relates to the observed difference in VLDL composition. VLDL cholesterol/triglyceride ratio is higher in FCHL than in FHTG; it approaches that seen in type III hyperlipoproteinemia (16), where the risk for premature atherosclerosis is high. Finally, the decreased HDL apoprotein A-I/A-II ratio in FCHL is consistent with a relative decrease in HDL_2 compared to HDL_3 (25), a situation that has been claimed to predispose to coronary artery disease. The low concentration of HDL cholesterol in FHTG without an apparent increase in risk for coronary artery disease is also of interest. It is similar to the relationship between plasma triglyceride and HDL cholesterol seen in lipoprotein phenotype I patients in whom no increased predisposition to atherosclerosis is apparent (26).

Since the original observation that subjects with isolated hypertriglyceridemia (type IV phenotype) were found in families with two different familial disorders (1, 3), it has been suggested that FCHL is actually several different diseases (e.g., familial hypercholesterolemia coexisting with FHTG) occurring in the same family (2). However, subjects with FCHL differ from subjects with identical phenotypes who come from families with familial hypercholesterolemia or FHTG. Phenotype IIA individuals with familial hypercholesterolemia *1*) have an abnormality in LDL apoprotein B receptors in cultured skin fibroblasts (27), *2*) have a high prevalence of tendon xanthomata, and *3*) express their disease at a very young age (1). Phenotype IIA individuals with FCHL *1*) have normal LDL receptors (27) (and unpublished data in our laboratory), *2*) do not have tendon xanthomata, and *3*) often do not express their disease until the second decade of life (1). Hypertriglyceridemic subjects with FCHL also differ from those with FHTG in a number of ways apart from their apparent difference in the risk of developing atherosclerosis. They have *1*) different VLDL apoprotein synthetic rates (4, 5); *2*) different VLDL triglyceride synthetic rates (4); *3*) different relationships between triglyceride and insulin level (28); *4*) different relationships between triglyceride level and obesity (28); *5*) different prevalence of obesity (17, 28); *6*) different VLDL size; *7*) different VLDL composition; *8*) different VLDL-LDL relationships; and *9*) possible different VLDL-HDL relationships. These findings strongly suggest that individuals with familial combined hyperlipidemia differ from those with monogenic familial hypercholesterolemia and familial hypertriglyceridemia.

APPENDIX

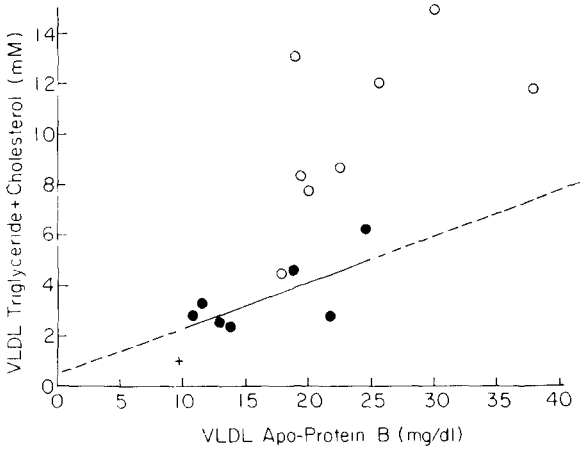

Fig. 6. Relationship between VLDL apoprotein B (mg/dl) and VLDL triglyceride plus cholesterol (mM) in familial combined hyperlipidemia (solid circles). VLDL triglyceride plus cholesterol in FCHL increases with increasing VLDL apoprotein B (r = 0.70, $P < 0.05$), however, the increase in these lipids in VLDL in familial hypertriglyceridemia is higher than can be accounted for by increases in VLDL apoprotein B (open circles).

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