Lipoprotein Metabolism in Subjects With Hepatic Lipase Deficiency

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A heritable deficiency of hepatic lipase (HL) provides insights into the physiologic function of HL in vivo. The metabolism of apolipoprotein B (apoB)-100 in very–low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), and low-density lipoprotein (LDL) and of apoA-I and apoA-II in high-density lipoprotein (HDL) particles lipoprotein (Lp)(AI) and Lp(AI:AII) was assessed in 2 heterozygous males for compound mutations L334F/T383M or L334F/R186H, with 18% and 22% of HL activity, respectively, compared with 6 control males. Subjects were provided with a standard Western diet for a minimum of 3 weeks. At the end of the diet period, apo kinetics was assessed using a primed-constant infusion of [5,5,5-$^2H_3$] leucine. Mean plasma triglyceride (TG) and HDL cholesterol levels were 55% and 12% higher and LDL cholesterol levels 19% lower in the HL patients than control subjects. A higher proportion of apoB-100 was in the VLDL than IDL and LDL fractions of HL patients than control subjects due to a lower VLDL apoB-100 fractional catabolic rate (FCR) (4.63 *v* 9.38 pools/d, respectively) and higher hepatic production rate (PR) (33.24 *v* 10.87 mg/kg/d). Delayed FCR of IDL (2.78 and 6.31 pools/d) and LDL (0.128 and 0.205 pools/d) and lower PR of IDL (3.67 and 6.68 mg/kd/d) and LDL 4.57 and 13.07 mg/kg/d) was observed in HL patients relative to control subjects, respectively. ApoA-I FCR (0.09 and 0.13 pools/d) and PR (4.01 and 6.50 mg/kg/d) were slower in Lp(AI:AII) particles of HL patients relative to control subjects, respectively, accounting for the somewhat higher HDL cholesterol levels. HL deficiency may result in a lipoprotein pattern associated with low heart disease risk.

HEPATIC LIPASE (HL) is a lipolytic enzyme synthesized by hepatocytes.[1-3]. The majority of HL resides at the microvilli of the parenchymal cells of the liver. The enzyme exhibits both triglyceride (TG) and phospholipid hydrolase activity. HL participates in the conversion of intermediate-density lipoprotein (IDL) to low-density lipoprotein (LDL)[1-3] and the delivery of high-density lipoprotein (HDL) cholesteryl ester to the liver.[4] HDL consists of 2 distinct subpopulations of particles; particles that have apolipoprotein (apo) A-I without apoA-II, lipoprotein (Lp) (AI) and particles with apoA-I and apoA-II, Lp(AI:AII).[5] HDL particles containing both apoproteins, Lp(AI:AII), have been reported to be preferential substrates for HL in comparison to Lp(AI).[6]

Human HL is a 476-amino acid glycoprotein. The human HL gene has been located to chromosome 15q21 and spans over 60 kb containing 9 exons and 8 introns.[7] Four mutations of HL gene that associate with HL deficiency, T383M, S267F, L334F, and R186H, have been characterized.[8,9] In vitro expression of the mutants demonstrated that the S267F mutation results in a nonactive enzyme. The T383M mutation, which has been reported in 2 Canadian families with heritable HL deficiency, results in the production of lipase molecules with partial enzyme activity.[10,11] The L334F mutation results in the production of a HL protein that is secreted, but has only 30% of the activity of wild-type HL and R186H mutation leads to a protein that is not secreted.[9,12]

The most consistent finding in HL-deficient patients is the elevation of HDL2-cholesterol.[13,14] The appearance of large buoyant LDL particles in HL-deficient patients has also been documented.[12] The concentration of these large buoyant LDL particles is negatively correlated with HL activity and positively with the concentration of HDL2-cholesterol.[15]

Heritable deficiency of HL provides insights into the physiologic function of HL in vivo. The aim of this study was to explore the effects of reduced HL activity in the metabolism of apoB-100 in very–low-density lipoprotein (VLDL), IDL, and LDL and of apoA-I and apoA-II in 2 HDL subfractions, Lp(AI) and Lp(AI:AII). Using a primed-constant infusion of [5,5,5-$^2H_3$] leucine, we studied the in vivo metabolism of apolipoproteins in 2 heterozygous males for compound mutations, L334F/T383M or L334F/R186H, with 18% and 22% of HL activity, respectively, and described these data relative to control male subjects with normal HL activity.[9,12]

MATERIALS AND METHODS

Two HL-deficient patients, 1 carrying the compound mutation L334F/T383M of the HL gene (patient 1) and the other carrying the compound mutation L334F/R186H (patient 2), and 3 healthy, age-matched, male subjects were included in the study. Patient 1 was a 45-year-old male with a high HDL2/HDL3 mass ratio and large buoyant LDL particles compared with normal healthy males.[12] His HL activity measured in postheparin plasma was 18% of the age and gender-adjusted normal values, and the immunoreactive HL mass was decreased by 50% of the respective age- and gender-adjusted normal values.[12] Patient 2 was a 36-year-old male with very high HDL2/HDL3 cholesterol ratio (1.3) and high cholesterol content of HDL2. His postheparin HL activity was 22% of the age- and gender-adjusted normal values, and the HL mass was 30% of normal.[9] Both patients 1 and 2 were apparently healthy. All study subjects underwent a complete physical examination, and blood samples were collected for laboratory analysis in the morning after a 12-hour fast. None of the subjects included in the study had signs or symptoms of coronary heart disease,

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thyroid, or other endocrine diseases. Renal or hepatic disorders were excluded on the basis of laboratory tests and medical history. None of the control subjects were receiving medication known to influence plasma lipid levels.

At least 3 weeks before the kinetic studies, the subjects were provided with an isocaloric natural-food diet consisting of 36% fat (15% saturated, 15% monounsaturated, and 6% polyunsaturated), 15% protein, 49% carbohydrate, and a cholesterol content of about 150 mg/1,000 kcal. The study protocol was approved by the Ethics Committee of Helsinki University Central Hospital and the Human Investigation Review Committee of New England Medical Center and Tufts University.

Study Protocol

Each study began in the morning (6 AM) following a 12-hour fast. An intravenous line was inserted into one forearm for the infusion solution, and another line was placed into the opposite arm for blood sampling. At zero hour (11 AM), a priming dose of 10 μmol/kg per body weight of [5,5,5-$^2H_3$] leucine was given intravenously and was followed by a constant infusion of [5,5,5-$^2H_3$] leucine at a rate of 10 μmol/kg/h for the next 15 hours. Blood samples were collected into tubes containing EDTA at zero minute, 5 minutes, 10 minutes, 15 minutes, 25 minutes, 35 minutes, 45 minutes, 1 hour, 1.5 hours, 2 hours, and at every hour thereafter through the 15-hour study period for plasma enrichment measurements. Deuterium enrichment of apoB in VLDL, IDL, and LDL was performed from samples taken at zero hour, 1 hour, 2 hours, 4 hours, 6 hours, 8 hours, 10 hours, 12 hours, and 15 hours, and apoA-I and apoA-II within HDL subspecies was performed from samples taken at zero hour, 6 hours, 10 hours, 12 hours, and 15 hours. The metabolic studies were performed in all study subjects in the fed state as previously described.[16] The subjects received 20 identical small meals comparable to the prestudy diet given every hour starting 5 hours (−5 hours) before the stable isotope infusion. Each small meal contained 1/20 of their daily caloric intake. The 2 patients with HL deficiency were studied in the Clinical Research Unit at the Helsinki Central Hospital, Helsinki, Finland, and the control subjects in the Metabolic Research Unit of the Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University, Boston, MA. The [5,5,5$^2H_3$] leucine infusion solution were prepared in Boston and shipped to Helsinki together with special food items to assure the identical content of the small meals during the metabolic studies. The isolation of lipoprotein classes from fresh plasma of the 2 patients was performed in Helsinki and lipoprotein fractions were shipped with plasma samples on dry ice to Boston. Isolation of lipoprotein classes from fresh plasma of control subjects was performed in Boston, where all the laboratory work and data analysis were performed.

Isolation of Plasma Lipoprotein

Plasma lipoprotein fractions were isolated by sequential ultracentrifugation in a Beckman L8-70 ultracentrifuge (Beckman Instruments, Palo Alto, CA) using a Beckman 50TI rotor as previously described.[17] VLDL, IDL, LDL, and HDL were isolated at densities 1.006, 1.019, 1.063, and 1.21 g/mL, respectively. ApoB-100 was isolated from VLDL, IDL, and LDL by preparative sodium dodecyl sulfate (SDS)-polyacrylamide gradient (4% to 22.5%) gel electrophoresis by using a Tris-glycine buffer system as previously described.[18]

Separation of Lp(AI) and Lp(AI:AII)

Lp(AI) and Lp(AI:AII) particles were separated from plasma using immunoaffinity chromatography columns as previously described.[5] In brief, monoclonal antibodies against human apoA-I and apoA-II were conjugated, separately, to CNBr-Sepharose 4B and crosslinked using glutaldehyde according to the method described by Kowal and Parsons.[19] A total of 1 mL plasma was applied first to the anti-A-I column. The bound lipoproteins were eluted with 3 mol/L NaSCN, pH 8.0, and dialyzed overnight against 0.01 mol/L Tris, 0.01 mol/L NaCl, pH 8.0, at 4°C. Next, the apoA-I containing lipoproteins isolated with the first column were applied onto an anti-apoA-II column. The unretained fraction containing Lp(AI) and other lipoproteins with apoA-I were collected and dialyzed overnight against 0.01 mol/L Tris, 0.01 mol/L NaCl, pH 8.0, at 4°C. The retained fraction containing Lp(AI:AII) was eluted with 3 mol/L NaSCN and dialyzed overnight against 0.01 mol/L ammonium bicarbonate solution at 4°C. The fraction containing Lp(AI) and apoB-100 containing lipoproteins was applied to an anti-apo-B column. The unretained fraction containing Lp(AI) was dialyzed overnight against 0.01 mol/L ammonium bicarbonate solution at 4°C. The Lp(AI) and Lp(AI:AII) fractions were lyophilized and apoA-I and apoA-II were isolated from Lp(AI) and Lp(AI:AII) using SDS-polyacrylamide gradient gel (7% to 20%) electrophoresis and Tris-glycine buffer system.[20,21] Apolipoproteins were identified by comparing migration distances with those of known molecular weight standards.

Determination of Deuterium Enrichment

ApoB-100, apoA-I, and apoA-II protein bands were excised from the polyacrylamide gels and hydrolyzed in 12 N HCl at 110°C for 24 hours and dried under nitrogen. The hydrolyzates were converted to n-propyl ester, N-heptafluorobutyramide derivatives and then dried under nitrogen as previously described.[16] After adding 400 μL ethyl acetate, the clear supernatant was placed in autosampler vials (Kimble/Kontes, Vineland, NJ). All samples were analyzed with a 5973N gas chromatograph-mass spectrometer (Agilent Technologies, Palo Alto, CA) using negative chemical ionization and methane as the reagent gas.

Analyses of Kinetic Data

The kinetics of apoB-100 in VLDL, IDL, and LDL were calculated using a previously described multicompartmental model[22] and apoA-I and apoA-II as previously described.[20,21] A 0.5 hour lag period representing the mean of the study subjects data on the appearance of total apoA-I was factored into the calculations. Simultaneous measurement of the apoA-I productions rates (PRs) in Lp(AI) and Lp(AI:AII) represents the 2 compartments in models previously used for calculations of apoA-I kinetic parameters.[23,24]

Analytical Methods

Cholesterol and TG concentrations in plasma and lipoproteins were analyzed with standardized enzymatic methods.[21] HDL cholesterol concentration was measured in plasma using the dextran sulfate/$MgCl_2$ precipitation method.[25] LDL cholesterol was calculated as the 1.006 g/mL infranatant cholesterol minus the HDL cholesterol. Plasma apoB-100 and apoA-I concentration was assayed with a noncompetitive, enzyme-linked immunosorbent assay (ELISA) using immunopurified polyconal antibodies.[16,26] The concentration of Lp(AI) particles was measured using immunoelectrophoresis with commercially available kits consisting of hydrated agarose gels and monospecific antisera to apoA-I and apoA-II (Sebia, Issyles-Moulineaux, France). The concentrations of apoA-I in Lp(AI) and of apoA-II in Lp(AI:AII) were determined using standards provided by the manufacturer. The concentration of apoA-I in Lp(AI:AII) particles was calculated by subtracting the Lp(AI) concentration from the total apoA-I plasma concentration as analyzed by ELISA. Between and within runs coefficients of variation for lipid assays was $<5\%$ and for other assays $<10\%$.

RESULTS

Plasma Lipids, Lipoproteins, and Apolipoproteins

The mean body mass index (BMI) and total cholesterol concentration of the HL patients and control subjects were

Table 1. Characteristics of the HL Patients and Control Subjects

	Age (yr)	BMI (kg/m^2)	TC (mmol/L)	HDL-C (mmol/L)	LDL-C (mmol/L)	TG (mmol/L)
HL patients						
1	45	24.5	5.28	1.60	2.79	1.87
2	36	23.8	5.09	1.33	3.14	2.19
Mean	41	24.2	5.19	1.47	2.97	2.03
Control subjects						
1	41	23.8	5.09	1.40	3.22	1.02
2	41	25.0	6.09	1.32	4.03	1.66
3	45	26.4	5.55	1.21	3.77	1.25
Mean (SD)	42 (2)	25.1 (1.1)	5.58 (0.41)	1.31 (0.08)	3.67 (0.34)	1.31 (0.26)

Abbreviations: BMI, body mass index; TC, total cholesterol; HDL-C, HDL cholesterol; LDL-C, LDL cholesterol; TG, triglyceride.

similar (Table 1). As anticipated, mean TG concentration was 55% higher in the patients with HL deficiency, 2.03 mmol/L, than control subjects, 1.31 ± 0.26 mmol/L. The mean HDL cholesterol concentrations of the HL patients, 1.47 mmol/L, was 12% higher compared with control subjects, 1.31 ± 0.08 mmol/L. In contrast, the mean LDL cholesterol concentration of the HL patients, 2.97 mmol/L, was 19% lower than the mean of the control subjects, 3.67 ± 0.34 mmol/L.

The mean total plasma apoB concentration of the HL patients, 92 mg/dL, was 20% lower than the mean apoB concentration of the control subjects, 121 ± 17 mg/dL (Table 2). Additionally, the apoB distribution among the Lp fractions differed between the 2 groups of subjects. The HL patients had higher VLDL apo B levels and lower LDL apoB levels compared with control subjects. This was reflected in a mean LDL/VLDL apoB ratio in the HL patients of 4.54, which was less than one half that of the control subjects.[22,25]

Effects of HL Deficiency on apoB-100 Metabolism in VLDL, IDL, and LDL

The kinetic data for apoB-100 are summarized in Table 3. The mean pool size of VLDL apoB-100 was 214% larger in HL patients than control subjects. This elevated pool size was determined, in part, by a fractional catabolic rate (FCR) of the apoB-100 that was one half of the mean value observed in the control subjects (4.63 and 9.02 ± 4.31 pools/d, respectively). Concomitantly, the mean PR of VLDL apoB-100 of the HL patients was about 3-fold that of the control subjects (33.24 and 10.87 ± 2.91 mg/kg/d, respectively). These data suggest a slower turnover rate of VLDL apoB-100 in the HL patients attributable to a lower catabolic rate, somewhat offset by a higher PR.

Table 2. ApoB Concentration in Plasma and VLDL, IDL, and LDL During Kinetic Studies

	Plasma (mg/dL)	VLDL (mg/dL)	IDL (mg/dL)	LDL (mg/dL)
HL patients				
1	77	15.7	2.6	57.5
2	107	16.4	3.1	88.7
Mean	92	16.1	2.9	73.1
Control subjects				
1	104	3.4	1.4	99.2
2	44	8.2	4.2	131.6
3	15	3.6	3.8	107.6
Mean (SD)	121 (17)	5.1 (2.2)	3.1 (1.2)	112.8 (13.7)

The mean pool size of IDL apoB-100 was 16% larger in the HL patients than control subjects (Table 3). The mean FCR of apoB-100 in IDL of the HL patients was less than one half that of the control subjects (2.78 and 6.31 ± 0.61 pools/d, respectively). The mean PR of apoB-100 into IDL of the HL patients was likewise reduced to about one half that of the control subjects (3.67 and 6.72 ± 3.60 mg/kg/d, respectively). These lower rates of IDL apo B-100 catabolism and production suggest delayed clearance of VLDL from plasma in the HL patients relative to the control subjects.

The mean pool size of LDL apoB-100 was 37% lower in the HL patients than control subjects (Table 3). The mean FCR and PR in HL patients were each about one half and one third that of the control subjects (0.128 and 0.265 ± 0.04 pools/d, and 4.57 and 13.07 ± 2.24 mg/kg/d), respectively. The smaller pool size of LDL cholesterol and apoB-100 in HL patients relative to control subjects is attributable to the delayed conversion of VLDL to LDL. These findings are consistent with the known role of HL in the metabolism of apoB-100 containing lipoproteins.

Effects of HL Deficiency on apoA-I and apoA-II Metabolism in Lp(AI) and Lp(AI:AII)

Mean total plasma apoA-I concentration and apoA-I in both Lp(AI) and Lp(AI:AII) particles in the HL patients was comparable to those of the control subjects (Table 4). The level of apoA-II was 14% lower in HL patients compared with control subjects (25 and 29 ± 1 mg/dL). The pool sizes of apoA-I and apoA-II reflected these data (Table 5).

The mean FCR and PR of apoA-I in Lp(AI) particles of the HL patients were similar to the mean of control subjects (Table 5). However, both the mean FCR and PR of apoA-I in Lp(AI:AII) particles in the HL patients was about one third lower than that of the control subjects. These data are consistent with the reports suggesting Lp(AI:AII) particles are the primary target for HL.[32] The FCR and PR of apoA-II in Lp(AI:AII) was similar between HL patients and control subjects.

DISCUSSION

The results of the study demonstrate that the fractional catabolism of apoB-100 in the VLDL→IDL→LDL delipida-

Table 3. Kinetic Parameters of apoB-100 in HL Patients and Control Subjects

	VLDL			IDL			LDL		
Patients	Pool Size (mg)	FCR (pools/d)	PR (mg/kg/d)	Pool Size (mg)	PCR (pools/d)	PR (mg/kg/d)	Pool Size (mg)	FCR (pools/d)	PR (mg/kg/d)
HL patients									
1	544	5.95	42.07	91	1.84	2.15	2,018	0.075	1.94
2	524	3.31	24.40	99	3.72	5.19	2,834	0.180	7.19
Mean	534	4.63	33.24	95	2.78	3.67	2,426	0.128	4.57
Control subjects									
1	125	13.45	13.9	52	6.93	4.49	3,648	0.247	10.95
2	258	4.87	8.1	134	5.72	10.88	4,154	0.217	12.85
3	129	9.81	10.6	61	6.27	4.80	3,816	0.332	15.41
Mean (SD)	170 (76)	9.38 (4.31)	10.87 (2.91)	82 (45)	6.31 (0.61)	6.72 (3.60)	3,873 (258)	0.265 (0.060)	13.07 (2.24)

Abbreviations: FCR, fractional catabolic rate; PR, production rate.

tion cascade was slower in the 2 HL-deficient patients compared with control subjects. The PR of apoB-100 from the liver in VLDL particles in HL-deficient patients relative to control subjects was higher, whereas the conversion of VLDL to IDL and LDL was slower. The slower FCR of all the apoB-100 containing Lp particles in HL-deficient patients compared with that of control subjects suggests an increased period of time that apoB-100 was in circulation in the HL deficiency state. However, HL-deficient patients have not been reported to have small dense LDL as a result of a prolonged time in circulation.[9,12,27] HL deficiency, in contrast to lipoprotein lipase (LPL) deficiency, affects VLDL, IDL, and LDL catabolism, whereas LPL deficiency primarily affects VLDL metabolism. This finding reflects its action as a phospholipase, as well as a TG lipase activity.

Furthermore, the results of the present study show that HL deficiency results in a low production and slow turnover of apoA-I in Lp(AI:AII), but not in Lp(AI) particles. The lack of effect of HL deficiency on Lp(AI) metabolism supports prior observations.[28] Previous studies have indirectly shown that HL plays a key role in the conversion of HDL2 to HDL3 particles,[28] whereas LPL is involved in the conversion of HDL3 to HDL2 particles.[29] The release of apoA-I from HDL results in a decrease in HDL size and density and in the conversion of HDL2 to HDL3.[30,31] It has been suggested that the Lp(AI:AII) particles found in the HDL2 subfraction are active and crucial for the transformation of HDL2 to HDL3. It has also been suggested that the Lp(AI:AII) in HDL2 is the main target of HL action.[32] The results of the present study suggest that it is primarily the apoA-I, rather than apoA-II in Lp(AI:AII) particles, that is regulated by HL.

Table 4. Plasma Concentrations of apoA-I and A-II and apoA-I in Lp(AI) and Lp(AI:AII) in HL Patients and Control Subjects

	apoA-I (mg/dL)	apoA-II (mg/dL)	apoA-I in Lp(A-I) (mg/dL)	apoA-I in Lp(AI:AII) (mg/dL)
HL patients				
1	153	26	45	108
2	131	23	41	90
Mean	142	25	43	99
Control subjects				
1	157	28	49	108
2	166	31	52	114
3	146	28	32	114
Mean (SD)	156 (18)	29 (1)	44 (9)	112 (3)

NOTE. Lp(AI) indicates HDL particles containing apoA-I, but not apoA-II and Lp(AI:AII), HDL particles containing apoA-I and apoA-II.

The primary factors controlling plasma apoA-I levels in general are somewhat uncertain. Both the FCR[24,33,34] and PR[35,36] of HDL apoA-I have been found to be important factors. Rader et al[36] have reported that the turnover rate of apoA-I in LpAI is faster than that of apoA-I in LpAI:AII particles in young, normolipidemic adult subjects. Ikewaki et al[37] have suggested that the rate of catabolism of apoA-I is an important factor in determining Lp(AI) levels and that the rate of apoA-II production is a major determinant of the distribution of apoA-I between LpAI and LpAI:AII. In the present study, the FCR was slightly higher and PR of apoA-II was slightly lower in HL patients than in control subjects. The effect of these cumulative differences was likely related to the metabolism of apoA-I in the Lp(AI:AII) particle. We have previously shown that in male subjects, plasma A-I levels correlate with LpAI and LpAI:AII, and HDL cholesterol levels correlate with the FCR of apoAI in both Lp(AI) and Lp(AI:AII).[20] The 2 patients with HL deficiency tended to have higher plasma HDL cholesterol concentration than the control subjects. However, the PR of apoA-I into Lp(AI:AII), which carries most of the HDL apoA-I, was reduced to two thirds of control subjects, a finding which suggests a distinct role of HL in the metabolism of apoA-I in Lp(AI:AII).

In HDL cholesterol and apoA-I-deficient states, the turnover of apoA-I is increased. In HDL deficiency secondary to Tangier disease, there is hypercatabolism of HDL protein constituents, with apoA-I being catabolized much more rapidly than apoA-II.[24,38,39] Patients with low HDL cholesterol, apoA-I and Lp(AI:AII) concentrations due to an apoA-I gene mutation (apoA-ILys_{107}60) have high turnover of apoAII and nearly normal turnover of apoAI in Lp(AI:AII).[21] Simultaneously, they have fast turnover of apoAI in Lp(AI).

Neither of the HL-deficient patients had signs or symptoms of coronary heart disease. It is unclear at the current time whether this observation suggests that HL deficiency may be protective or that the clinical significance of this observation may be mitigated by the relatively young age of the patients. With respect to the potential effect of a partial HL deficiency in

Table 5. Kinetic Parameters of apoA-I and apoA-II in Lp(AI) and Lp(AI:AII) Particles and Pool Size of apoA-I and apoA-II in Lp(A-I) and Lp(AI:AII) in HL Patients and Control Subjects

	Pools Size (mg)			FCR (pool/d)			PR (mg/kg/d)		
	apoA-I in LpAI	apoA-I in LpAI:AII	apoA-II in LpAI:AII	apoA-I in LpAI	apoA-I in LpAI:AII	apoA-II in LpAI:AII	apoA-I in LpAI	apoA-I in LpAI:AII	apoA-II in LpAI:AII
HL patients									
1	1,580	3,791	913	0.12	0.09	0.10	2.43	4.37	1.17
2	1,309	2,876	735	0.19	0.09	0.11	3.50	3.64	1.14
Mean	1,445	3,334	824	0.16	0.09	0.11	2.97	4.01	1.16
Control subjects									
1	1,857	4,092	1,033	0.14	0.13	0.08	3.18	6.50	1.01
2	1,647	3,612	977	0.13	0.12	0.10	3.06	6.19	1.40
3	1,158	4,125	995	0.17	0.13	0.09	2.5	6.81	1.13
Mean (SD)	1,554 (293)	3,943 (234)	1,002 (23)	0.15 (0.02)	0.13 (0.01)	0.09 (0.01)	2.92 (0.29)	6.50 (0.25)	1.18 (0.16)

the presence of hyperlipidemia, it likewise may be protective or can result in increased cardiovascular disease burden due to increased remnant Lp levels. The role of HL deficiency in the pathogenesis of coronary heart disease is controversial. Connelly et al[10] have described a familial HL deficiency in which some of the affected subjects had significant ischemic vascular disease. However, these subjects had hyperlipidemia, and the investigators concluded that the presence of additional genes causing hyperlipidemia was associated with ischemic vascular disease. In contrast, Carlson et al[14] did not find ischemic vascular disease in their HL-deficient patients.

Only 2 patients with HL deficiency were available for this investigation. The absolute values of the kinetic parameters assessed frequently fell within the range of values observed for the control subjects. However, clear trends were observed between the mean data in the HL patients and control subjects that were consistent with the known functions of HL. For this reason, we feel the observations, albeit preliminary, are helpful in understanding the role of HL.

The results of the present study demonstrate that HL deficiency results in lower levels of LDL cholesterol and apoB-100 due to a delayed conversion of VLDL to LDL. The abnormality observed in apoAI metabolism was primarily attributed to a decreased turnover of apoAI in Lp(AI:AII) particles. It is possible that decreased HL activity would protect against coronary heart disease.

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