Lovastatin enhances hepatic uptake of low density lipoprotein in humans

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Abstract A noninvasive method for visualizing the uptake of low density lipoprotein (LDL) was used to investigate the effect of hypolipidemic drugs on LDL uptake by the human liver in vivo. Fourteen hypercholesterolemic patients (six with familial hypercholesterolemia and eight with common hypercholesterolemia) were studied. Autologous LDL particles were isolated and divided into two aliquots; one was labeled with ^{99m}TC and the other with ^{131}I, and both preparations were reinjected simultaneously. The labeled LDL was visualized 24 h later by scanning the thorax and abdomen with a gamma camera, and the liver/heart ratio was calculated as an estimate of the hepatic uptake of LDL. The results of ^{99m}TC-labeled LDL scintigraphy were compared with conventional determinations of the fractional catabolic rate (FCR) for ^{131}I-labeled LDL. The latter correlated best with the liver/heart ratio ($r = 0.80$, $P < 0.001$). Lovastatin treatment increased the liver/heart ratio (15%, $P < 0.01$) in the patients with polygenic hypercholesterolemia and the FCR for LDL in both groups (22%, $P < 0.05$, for those with familial hypercholesterolemia and 37%, $P < 0.01$ for those with polygenic hypercholesterolemia). Scanning of the liver using the ^{99m}TC-labeled LDL method provides a noninvasive method for visualizing the hepatic uptake of LDL in vivo in humans. This study also provides direct proof that lovastatin, a drug that enhances LDL receptor activity in the liver, also increases the hepatic uptake of LDL in humans.—**Kervinen, K., M. J. Savolainen, J. I. Heikkilä, and Y. A. Kesäniemi.** Lovastatin enhances hepatic uptake of low density lipoprotein in humans. *J. Lipid Res.* 1993. **34:** 1975–1982.

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The activity of LDL receptors on the plasma membranes of the liver cells is a major determinant of the plasma cholesterol level (1); about two-thirds of the plasma LDL is removed via the specific LDL receptor pathway (2, 3). The number of LDL receptors is regulated by the availability of cholesterol within the hepatocyte (4), a finding that has led to the discovery and development of a new type of hypolipidemic drug, 3-hydroxy-3-methylglutaryl-CoA reductase inhibitors, which reduce the availability of cholesterol within the cell by inhibiting the rate-limiting enzyme of cholesterol synthesis (4).

The in vivo quantification of changes occurring in LDL receptor activity in various diseases or in response to drug therapy is difficult in humans. Most previous tests have used LDL labeled in the apolipoprotein moiety (apoB), estimating the magnitude of the LDL receptor activity by measuring the fractional catabolic rate (FCR) for LDL particles (2, 3, 5). Recently, liver biopsy specimens have been used in studies investigating the effects of hypocholesterolemic drugs on the LDL receptor expression in humans (6, 7).

In the present study we applied a previously described method that allows noninvasive estimation of hepatic LDL uptake in humans. The method is based on the labeling of LDL particles with radioactive technetium (^{99m}Tc) by the method of Lees et al. (8) and scanning of the liver and thorax with a gamma camera. The activity of the hepatic LDL receptors is shown as an accumulation of radioactivity in the liver, whereas the radioactivity in the heart represents that in the circulatory pool. The liver/heart ratio can be computed from the digital images of the organs. The changes in the fractional catabolic rate for LDL and hepatic LDL uptake produced by two hypolipidemic drugs, lovastatin and colestipol, in patients with familial or polygenic hypercholesterolemia were used to help validate the method.

PATIENTS AND METHODS

Patients

Fourteen patients, ages 27–59 years, referred to the Lipid Clinic of Oulu University Central Hospital were studied. Six were heterozygous for familial hypercholesterolemia and eight had polygenic hypercholesterolemia.

Abbreviations: LDL, low density lipoprotein; FCR, fractional catabolic rate; FH, familial hypercholesterolemia; HDL, high density lipoprotein.

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During the screening visit they underwent physical and laboratory examinations and were instructed to consume a low cholesterol, fat-controlled diet (American Heart Association Phase 1 diet). Their initial clinical characteristics and values for total cholesterol, triglycerides, and lipoprotein-cholesterol are in **Table 1.**

None of the patients had any signs or symptoms of cardiac insufficiency or hepatic or renal dysfunction, but four of them had coronary heart disease (two had undergone a coronary by-pass operation, one had suffered a myocardial infarction, and one had angina pectoris). None were on hypolipidemic drugs when entering the trial, but four were receiving anti-hypertensive or anti-anginal medication.

The clinical diagnosis of familial hypercholesterolemia was based on the presence of severe hypercholesterolemia (serum cholesterol above 8 mmol/l and LDL cholesterol above the 90th percentile (9)) in association with tendon xanthomas in the patient or a first-degree relative or coronary heart disease at an early age in the first-degree relative. In addition, the FH-Helsinki mutation, a large deletion in the LDL receptor gene (10), responsible for a major portion of familial hypercholesterolemia in northern Finland (11) was analyzed by amplification of the DNA sequences flanking the deletion in the LDL receptor gene by polymerase chain reaction (12).

Five out of six patients in the FH group had the FH-Helsinki mutation (Table 1). A deletion in exon 6 of the LDL receptor gene, designated as the FH-North Karelia mutation (13), was found in one patient. None of the patients in this study had the familial defective apolipoprotein B-100 mutation, apoB-3500 (14), in their apoB gene. The patients with familial hypercholesterolemia were younger than those with polygenic hypercholesterolemia but still had more atherosclerotic complications. There were no significant differences in body mass index or sex distribution between the groups. Both total plasma cholesterol and LDL cholesterol were significantly higher in the patients with familial hypercholesterolemia than in those with polygenic hypercholesterolemia.

Each patient gave informed consent for the research protocol, which was approved by the Ethical Committee of the University of Oulu.

Drug treatment

The trial consisted of a minimum of 6 weeks' treatment with colestipol followed by a minimum of a 12-week period of treatment with lovastatin. All the four patients examined during the colestipol treatment used 10 g colestipol t.i.d. After the colestipol period, the patients were switched without any washout period to a 20-mg q.p.m. therapy with lovastatin. After 4 weeks, the dose of lovasta-

TABLE 1. Baseline characteristics of the patients

Patient Number	Sex	Age	Body Mass Index	Total Chol	LDL Chol	HDL Chol	TG	ApoE Phenotype	Tendon Xanthoma	LDL Receptor Gene Mutation	Coronary Heart Disease
		yr	*kg/m²*		*mmol/l*						
Familial hypercholesterolemia											
1	M	37	21.4	13.30	11.00	1.38	1.47	3/3	+	H	B
2	M	30	22.2	10.80	8.34	0.91	2.49	3/3	+	H	
3	F	27	23.6	9.92	8.38	0.77	1.77	4/3	+	NK	
4	F	38	31.5	8.45	6.55	0.88	1.01	2/3	+	H	
5	F	47	28.6	8.33	6.36	1.24	1.53	3/3	–	H	MI
6	F	46	26.2	10.80	8.72	1.14	1.67	3/3	+	H	B
Mean		38	25.6	10.27	8.23	1.05	1.66				
± SD		8	3.9	1.84	1.69	0.24	0.49				
Polygenic hypercholesterolemia											
7	M	52	27.2	7.59	4.35	2.67	1.26	3/3	–	n.d.	
8	F	59	20.8	8.80	6.41	1.36	1.40	4/4	–	–	AP
9	F	40	21.2	7.83	5.31	1.48	1.36	4/3	–	–	
10	F	43	25.3	8.36	5.22	1.52	1.04	3/3	–	–	
11	F	58	27.7	7.84	5.43	1.25	1.52	3/3	–	–	
12	M	47	25.3	7.69	4.72	1.31	2.44	3/3	–	–	
13	F	52	23.9	8.29	5.93	1.88	0.94	3/3	–	–	
14	F	57	24.6	9.04	6.62	0.76	1.66	4/3	–	–	
Mean		51[a]	24.5	8.18[a]	5.50[a]	1.53	1.45				
± SD		7	2.5	0.53	0.79	0.56	0.46				

Abbreviations: Chol, cholesterol; TG, triglyceride; H, FH-Helsinki mutation of LDL receptor gene; NK, FH-North Karelia mutation of LDL receptor gene; B, coronary by-pass operation; MI, myocardial infarction; AP, angina pectoris; n.d., not determined.

[a] $P < 0.01$ for the difference between the patients with familial and polygenic hypercholesterolemia.

tin was doubled to 40 mg q.p.m., and after 4 more weeks, it was further increased to 80 mg q.p.m. This dose was continued until the protocol was completed.

Protocol

The fractional catabolic rate (FCR) for LDL apoB and the tissue distribution of the LDL particles were investigated after the simultaneous injection of two autologous LDL preparations, each labeled with either ^{131}I for the determination of the apoB FCR or ^{99m}Tc for estimation of tissue distribution. All except one of the patients were examined before any hypocholesterolemic medication was commenced and again 4–11 months later, during treatment with lovastatin (80 mg q.p.m.). Four patients were also examined during the colestipol treatment, but one of these, a patient with familial hypercholesterolemia, was examined only during the drug treatment periods.

Isolation of the LDL fraction

After 3 weeks of maximal colestipol or lovastatin treatment, fasting blood was obtained and the LDL fraction was isolated by sequential ultracentrifugation (15). The plasma was adjusted to a density of 1.019 g/ml with a NaCl-NaBr solution and centrifuged in a Beckman 60 Ti rotor (Beckman Instruments Inc., Spinco Div., Palo Alto, CA) at 160,000 *g* and 15°C for 18 h. Lipoproteins floating to the surface were removed by tube-slicing. The infranatant was adjusted to a density of 1.063 g/ml and centrifuged as above. The LDL fraction (1.019–1.063 g/ml) was washed by ultracentrifugation in a TFT 45.6 rotor (Kontron AG, Zurich, Switzerland) at 105,000 *g* and 15°C for 18 h after overlaying with an equal volume of a NaCl-NaBr solution of density 1.070 g/ml. The LDL fraction was dialyzed extensively overnight against 0.15 M NaCl-1 mM EDTA adjusted to pH 7.4 with NaOH.

Labeling of LDL with radioactive isotopes

The LDL fraction was divided into two parts. One was labeled with ^{131}I (16, 17) as adapted for LDL (18) and the other with ^{99m}Tc using a direct protein labeling method (8). The LDL preparations of one patient (no. 4) were labeled under nitrogen. However, this procedure gave lower incorporation of the technetium label than the original one; therefore, the liver/heart ratio for this patient is given in Table 2, but omitted from Figs. 1 and 2. In fact, recent data verify that the previously described method (8) which was used in all the other patients produces a stable radionuclide-LDL complex (19). The labeled LDL preparations were filtered through a Millipore 22-μm filter before injection. Aliquots of the LDL preparations were set aside for bacterial culture and pyrogen testing.

Protocol for the isotope examinations

Technetium labeling was performed immediately before the preparation was injected intravenously together with the iodine-labeled preparation (within 30 min). Approximately 300 MBq (8.2 mCi) of ^{99m}Tc and 440 kBq (12 μCi) of ^{131}I were injected.

The clearance of ^{131}I-labeled LDL from the plasma (fractional catabolic rate, FCR) was used as a reference measurement for LDL catabolism and LDL receptor activity. For this purpose, fasting blood samples were taken 15 and 30 min, and 1, 2, 3, 4, 24, and 48 h after the injection of the labeled LDL preparations and sampling was continued three times a week for 14 days. The body weights and plasma cholesterol levels remained constant during the sampling period. The fractional catabolic rate for LDL was calculated from the plasma decay curves using the Matthews method (20) as described in our previous LDL turnover investigations (2, 5, 18). In brief, double-exponential equations were fitted to each plasma decay curve using an interactive curve-peeling programme (W. F. Beltz and T. E. Carew, unpublished method) on a VAX-VMS computer.

The distribution of the injected ^{99m}Tc-labeled LDL was visualized by scanning the thorax and the upper abdomen 5 min, and 4 and 24 h after the injection with a large field view of the computerized gamma camera (Elscint Apex 409 ECT).

Analysis of the gamma scanning digital image

Scanning of the thorax produced figures for the label distribution in the heart as well as in the lungs. The first scan at 5 min was performed in order to assess the radioactivity in the plasma pool, i.e., that representing the LDL particles in the sinusoids and other blood vessels of the liver before any receptor-mediated uptake of LDL had occurred. The mean liver/heart ratio at 5 min was 0.67 ± 0.04 (mean ± SD). The liver/heart ratio at 24 h was used as an estimate for the amount of radioactivity taken up by the liver versus the radioactivity in the LDL particles circulating in the plasma pool. The 5-min scintigraphy was not performed in all of the patients, and thus the liver/heart ratio at 24 h without base-line correction was used in all the patients. Consequently, the percentage changes in the liver/heart ratios are smaller than they would have been if the 5-min value had been subtracted.

The liver/heart ratio showed a somewhat better correlation with the FCR for LDL than did the liver/lung ratio. In addition, scanning at 24 h after the injection correlated better with the FCR for LDL than scanning at 4 h. Therefore, the liver/heart ratio at 24 h was used in the subsequent analyses.

Analysis of lipids and apolipoproteins

The concentrations of total cholesterol and triglycerides were determined by enzymatic methods using a Gilford analyzer (Gilford Instruments Laboratories, Inc., Oberlin, Ohio). HDL cholesterol was determined after precipitation of apoB-containing lipoproteins by addition of

heparin-manganese to the plasma sample (21); the protein content of the LDL fraction was determined by the method of Lowry et al. (22).

The occurrence of the familial defective apolipoprotein B-100 mutation, apoB-3500 (14), was analyzed by amplifying a segment of genomic DNA spanning the site of mutation in the apoB gene by polymerase chain reaction, followed by hybridization with radioactive oligonucleotide probes (23). The apoE phenotype was determined using isoelectric focusing and immunoblotting techniques (24).

Statistical analysis

All values are expressed as means ± the standard deviation (SD). The statistical significances of the differences between the groups were calculated using the paired or nonpaired Student's *t* test, as appropriate. Nonparametric method (Wilcoxon signed rank sum test) was used to analyze the statistical significance of the changes in the liver/heart ratio and liver/lung ratio. Correlations were tested by calculating Pearson's coefficient of correlation.

RESULTS

The hypolipidemic drugs, colestipol and lovastatin, altered the catabolism of the LDL particles of the patients with familial hypercholesterolemia (**Table 2**). The 31% reduction in LDL cholesterol concentration during lovastatin treatment was associated with a 29% decrease in the LDL protein concentration ($P < 0.02$), whereas there was no change in the protein/cholesterol mass ratio. The FCR for apoB increased by 22% ($P < 0.02$) and the corresponding increase in the liver/heart ratio was 8% (N.S., not significant).

The changes in LDL protein concentration were greater in the patients with polygenic hypercholesterolemia (**Table 3**) than in the patients with familial hypercholesterolemia. The decrease in LDL protein brought about by lovastatin treatment was 41% ($P < 0.001$). The FCR for LDL apoB increased by 31% during colestipol treatment and by 37% ($P < 0.01$) during lovastatin therapy. The FCR for LDL-apoB showed a negative correlation with the LDL cholesterol level in both patient groups (**Fig. 1;** in the total series $r = -0.86$; $P < 0.001$).

The individual responses of the liver/heart ratio to the drugs in the patients with familial and polygenic hypercholesterolemia are shown in **Fig. 2.** In the former group the liver/heart ratio of the technetium label tended to be slightly higher (8%, N.S.) during treatment with lovastatin than during the baseline period, although it did not change significantly. Patients with polygenic hypercholesterolemia had an increase in the liver/heart ratio of 15% with lovastatin ($P < 0.01$). Colestipol tended to increase the liver/heart ratio in all three subjects studied.

A good correlation was observed between the liver/heart ratio and the FCR values for LDL-apoB in the total series (**Fig. 3;** $r = 0.80$; $P < 0.001$). The drug-induced

TABLE 2. Effects of colestipol and lovastatin on the composition and clearance of LDL particles in patients with familial hypercholesterolemia

Patient	Drug	LDL-Chol	LDL-Prot	Prot/Chol	ApoB-FCR	L/H Ratio	L/L Ratio
		mmol/l	*mg/dl*	*mg/mg*	*pools/day*		
1	C	7.48	152	0.536	0.224	1.25	1.92
	L	7.16	142	0.574	0.234	1.24	2.06
2	–	8.34	156	0.506	0.200	1.31	1.98
	C	5.39	121	0.659	0.216	1.47	2.60
	L	6.04	126	0.556	0.209	1.31	2.01
3	–	8.38	180	0.603	0.231	1.65	2.80
	L	4.92	107	0.506	0.300	1.85	3.07
4	–	6.55	118	0.531	0.275	1.16	1.59
	L	4.03	109	0.520	0.338	1.34	2.36
5	–	6.36	166	0.656	0.249	1.39	2.93
	L	4.30	84	0.521	0.285	1.60	2.26
6	–	8.72	172	0.519	0.191	1.48	2.82
	L	5.20	103	0.539	0.267	1.45	2.36
Mean (5)	–	7.67	158	0.563	0.229	1.40	2.42
± SD		1.12	24	0.064	0.035	0.18	0.27
Mean (5)	L	4.90[b]	106[a]	0.528	0.280[a]	1.52	2.41
± SD		0.79	15	0.019	0.047	0.22	0.18

Abbreviations: C, colestipol; L, lovastatin; L/H ratio, liver/heart ratio of the ^{99m}Tc-LDL distribution; L/L ratio, liver/lung ratio of the ^{99m}Tc-LDL distribution.

[a] and [b] denote statistical significance at the levels of $P < 0.05$ and $P < 0.001$, respectively, for the difference between the baseline and the lovastatin values. Patient 1 was omitted from the calculation of the mean values because the baseline values were not available.

TABLE 3. Effects of colestipol and lovastatin on the composition and clearance of LDL particles in patients with polygenic hypercholesterolemia

Patient	Drug	LDL-Chol	LDL-Prot	Prot/Chol	ApoB-FCR	L/H Ratio	L/L Ratio
		mmol/l	*mg/dl*	*mg/mg*	*pools/day*		
7	–	4.35				1.45	3.06
	L	3.67			0.292	1.44	2.69
8	–	6.41	137	0.535	0.234	1.62	2.48
	L	3.23	59	0.537	0.338	1.81	2.90
9	–	5.31	93	0.521	0.268	1.73	2.99
	C	2.75	41	0.528	0.327	1.83	2.98
	L	2.48	42	0.442	0.414	1.94	3.57
10	–	5.22	107	0.583	0.218	1.49	2.57
	C	4.02	75	0.506	0.309	1.89	3.28
	L	2.98	75	0.669	0.342	1.78	2.62
11	–	5.43	111	0.520	0.261	1.40	2.64
	L	3.79	91	0.697	0.330	1.68	2.76
12	–	4.72	93	0.515	0.300	1.51	2.24
	L	3.30	73	0.541	0.324	1.68	2.55
13	–	5.93	126	0.548	0.235	1.40	2.27
	L	3.28	70	0.584	0.302	1.66	2.82
14	–	6.62	147	0.565	0.240	1.45	3.25
	L	3.46	58	0.491	0.401	1.97	3.60
Mean (8)	–	5.50	116	0.541	0.251	1.51	2.69
± SD		0.79	21	0.025	0.028	0.11	0.13
Mean (8)	L	3.27[a]	67[b]	0.566	0.343[b]	1.74[c]	2.94[c]
± SD		0.41	16	0.092	0.043	0.17	0.15

Abbreviations: C, colestipol; L, lovastatin.
[a] $P < 0.001$; [b] $P < 0.01$; [c] $P < 0.05$: denote statistical significance for the difference between the baseline and lovastatin values.

change in the liver/heart ratio showed a good correlation with the corresponding change in the FCR for LDL-apoB (**Fig. 4;** in the total series $r = -0.69$; $P < 0.004$). Furthermore, the liver/heart ratio showed a negative correlation with the LDL cholesterol concentration ($r = -0.66$; $P < 0.001$).

For comparison, the liver/lung ratios are also given in Tables 2 and 3. A good correlation was observed between the liver/heart ratio and the liver/lung ratio in the total

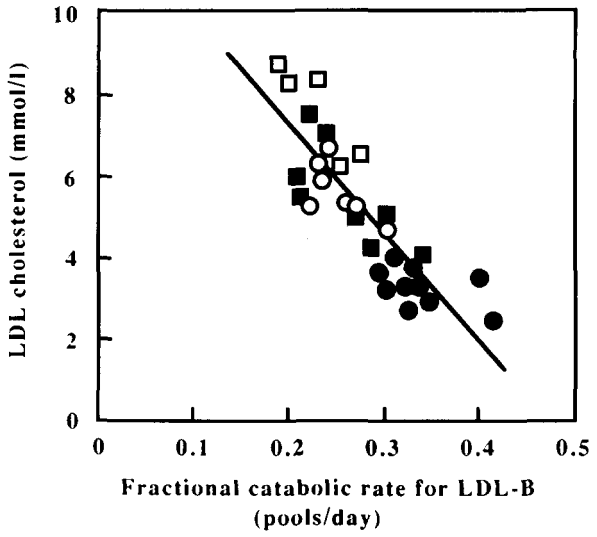

Fig. 1. Correlation between the fractional catabolic rate for LDL and LDL-cholesterol concentration. Squares, patients with familial hypercholesterolemia; circles, patients with polygenic hypercholesterolemia. Open symbols are observations during the diet period and closed symbols are results obtained during the drug treatments. $r = -0.86$; $P < 0.001$.

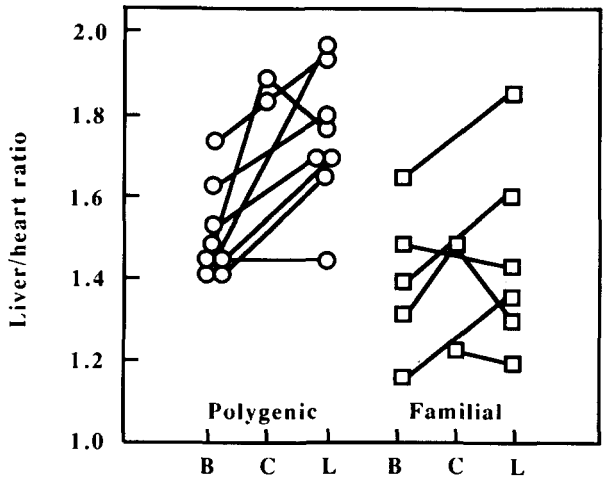

Fig. 2. Effects of colestipol and lovastatin on the hepatic uptake of LDL particles, estimated by determination of the liver/heart ratio of the radioactive label 24 h after an intravenous injection of technetium-labeled LDL. Squares, patients with familial hypercholesterolemia; circles, patients with polygenic hypercholesterolemia. B, baseline period; C, colestipol treatment period; L, lovastatin treatment period.

series ($r = 0.78$; $P < 0.001$) as well as in the patients with familial hypercholesterolemia ($r = 0.79$; $P < 0.001$) and patients with polygenic hypercholesterolemia ($r = 0.63$; $P < 0.006$).

Lovastatin tended to reduce the production rate of LDL-apoB in both the patients with familial hypercholesterolemia and patients with polygenic hypercholesterolemia, but the drug-induced change was statistically significant only in the total series (from 14.2 ± 1.0 mg/kg per day to 12.0 mg/kg per day, $P < 0.025$).

DISCUSSION

The results show that the in vivo hepatic removal of LDL, presumably representing LDL receptor activity, can be estimated in humans using imaging isotope techniques, as used previously to demonstrate the biodistribution of technetium-labeled LDL particles in vivo in experimental animals (8, 25) and in patients with myeloproliferative diseases (26). The incorporation of radioactively labeled LDL particles into atherosclerotic lesions has recently been used to visualize the degree of vascular disease in patients (27) and the uptake of LDL by tendon xanthomas in hypercholesterolemic subjects (28). In the present cases, the hepatic uptake of technetium-labeled LDL particles was determined and compared with the fractional catabolic rate, which is usually used as an estimate for the rate of LDL clearance through the LDL receptors.

The close correlation between the uptake of ^{99m}Tc-labeled LDL particles and the FCR for LDL suggests that the technetium scanning method may be a good indicator of LDL catabolism. It has been shown previously that

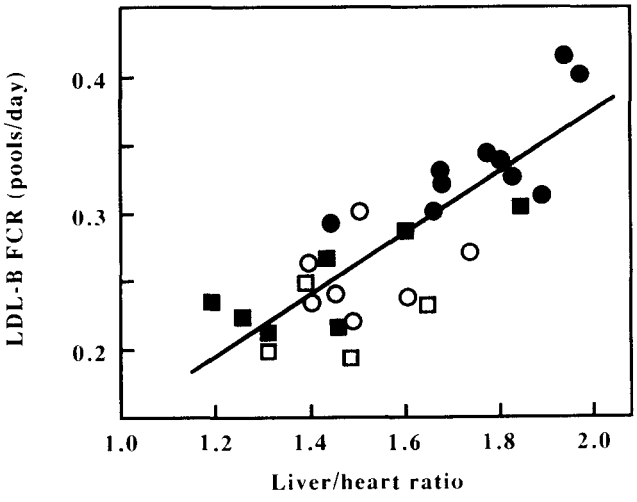

Fig. 3. Correlation between hepatic uptake of LDL particles (liver/heart ratio) and fractional catabolic rate for LDL-apoB. Symbols as in Fig. 1. $r = 0.80$; $P < 0.001$.

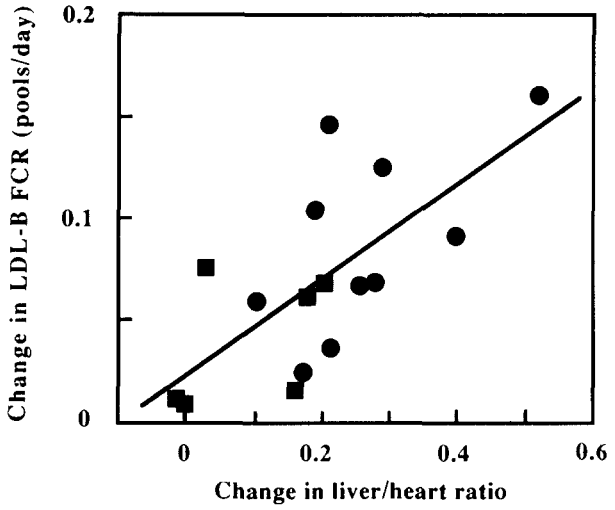

Fig. 4. Correlation between the lovastatin-induced changes in hepatic uptake of LDL particles (liver/heart ratio) and fractional catabolic rate for LDL-apoB. Squares, patients with familial hypercholesterolemia; circles, patients with polygenic hypercholesterolemia. $r = 0.69$, $P < 0.004$.

^{99m}Tc-labeled LDL particles act in a manner similar to tyramine cellobiose-labeled LDL and are accumulated quantitatively after uptake into tissues (29). Furthermore, ^{99m}Tc-labeled LDL is recognized by the LDL receptor just as well as ^{125}I-labeled LDL (25). We were not able here to introduce a third isotope to measure the uptake of LDL particles through the receptor-mediated pathway, but it is known that this usually parallels the total catabolism of LDL (2, 3). It is therefore probable that the present accumulation of technetium label into the liver reflects the activity of hepatic LDL receptors (4).

The fractional catabolic rate for LDL was seen here to increase during drug treatment in both groups, although the increase was lower in the patients with familial hypercholesterolemia. An increase in the FCR for LDL has previously been observed in patients with familial hypercholesterolemia treated with lovastatin (30), but no increase during treatment with the same drug has been observed in patients with moderate primary hypercholesterolemia (31). The different response of the patients with polygenic hypercholesterolemia in the present case may be due to the higher dose of lovastatin (80 mg/day) and higher pretreatment cholesterol levels. In this study, the patients with familial hypercholesterolemia were somewhat younger than those with polygenic hypercholesterolemia. The higher age of patients with polygenic hypercholesterolemia may have reduced the difference in the FCR for LDL between the groups, as there is an established effect of age on the FCR for LDL (32, 33).

The drug-induced increase in the hepatic uptake of LDL, with subsequent lowering of LDL cholesterol, suggests that the major part of the effect of bile acid binding resins or lovastatin on serum cholesterol concentration in

humans is also mediated through enhancement of the hepatic LDL receptor activity (34, 35), although lovastatin also reduces the synthesis rate of LDL-apoB as observed here in accordance with previous studies (36, 37). The importance of the LDL receptors in the liver as regulators of serum LDL cholesterol level is further emphasized by the fact that the drug-induced increase in hepatic LDL receptor activity is more accentuated in the patients with polygenic hypercholesterolemia than in those with familial hypercholesterolemia, as the latter have a lower capacity to synthesize LDL receptors.

The major benefit of the present method for estimating the hepatic uptake of LDL particles is its rapidity. The method does not obviate the isolation of LDL particles or labeling of the LDL with an isotope, but 14-day blood sampling can be avoided. Scanning of the thorax and upper abdomen with a computerized gamma camera could, in the future, be performed immediately after intravenous injection of the ^{99m}Tc-labeled LDL preparation in order to obtain a background image of the distribution of the label in the circulation, i.e., the amount of blood residing in the liver. A repeat scan 24 h later would then enable the increase in the liver/heart ratio to be calculated.

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