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G L Vega, S M Grundy

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Research Article

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In Vivo Evidence for Reduced Binding of Low Density Lipoproteins to Receptors as a Cause of Primary Moderate Hypercholesterolemia

Gloria Lena Vega* and Scott M. Grundy‡

*†Center for Human Nutrition, and Departments of ‡Clinical Nutrition, *Biochemistry, and †Internal Medicine, University of Texas Health Science Center; and ‡Veterans Administration Medical Center, Dallas, Texas 75235

Abstract

The causes of primary moderate hypercholesterolemia are not understood, but some patients have reduced fractional clearance rates (FCRs) for low density lipoproteins (LDL). This could be due to either decreased activity of LDL receptors or to a defect in structure (or composition) of LDL that reduces its affinity for receptors. To distinguish between these causes, simultaneous turnover rates of autologous and normal homologous LDL were determined in 15 patients with primary moderate hypercholesterolemia. In 10, turnover rates of both types of LDL were indistinguishable, which indicated that autologous LDL was cleared as efficiently as normal homologous LDL. In five others, FCRs for autologous LDL were significantly lower than for homologous LDL. Two of the latter five were treated with mevinolin, and although FCRs for both types of LDL rose during treatment, differences in FCRs between the two types of LDL persisted. In these five patients, autologous LDL appeared to be a poor ligand for LDL receptors.

Introduction

Familial hypercholesterolemia (FH)¹ is characterized by an abnormality in the gene encoding for low density lipoprotein (LDL) receptors. In heterozygous FH, one gene functions normally, and one is nonfunctional. Despite the importance of FH, most patients with hypercholesterolemia do not have classical heterozygous FH. The metabolic defects responsible for other forms of hypercholesterolemia are unknown, but our data (1) indicate that fractional clearance of LDL frequently is reduced. A possible cause for a low clearance of LDL is that LDL is a poor ligand for receptors. This study was performed to detect whether such a mechanism exists. Turnover rates of autologous and normal homologous LDL were compared simultaneously in 15 hyper-

cholesterolemic patients without classical FH. Most patients had identical turnover rates for both types of LDL, but in several, autologous LDL was cleared more slowly than homologous LDL, which suggests that their autologous LDL had a reduced affinity for LDL receptors.

Methods

Patients. 20 patients were studied on a metabolic ward. 15 (13 men and 2 women) (Nos. 1–15) had primary moderate hypercholesterolemia, and were selected for plasma total cholesterol between 250 and 300 mg/dl at time of screening. Triglyceride levels were normal (2). All but four (Nos. 11–14) had coronary heart disease (CHD), but none had myocardial infarction or coronary surgery for 6 mo previously. Mean age was 59 ± 6 (SD) yr. Mean body mass index (BMI) was 24 ± 3 kg/m². None had received hypolipidemic drugs for 4 mo before study. None had unstable angina, heart failure, gastrointestinal or endocrine disease, or secondary hypercholesterolemia. None had marked hypercholesterolemia, CHD before age 45, tendon xanthomata, or clinical evidence of FH in first-degree relatives. Although FH adults occasionally have total cholesterol in the range of 250–300 mg/dl (3), this is not common (1).

Five other patients (four men and one woman) had heterozygous FH, as evidenced by very high concentrations of LDL cholesterol, early onset of CHD, tendon xanthomata, and at least one first-degree relative with equally high LDL cholesterol. Patients 13 and 14 were brothers. The five patients' ages averaged 48 ± 6 yr. Mean BMI for the men was 25 ± 6 kg/m²; the woman was markedly obese (BMI = 47 kg/m²). None had taken hypolipidemic drugs for 2 mo before study.

All patients gave informed consent for the study, which was approved by institutional review boards.

Experimental design. Donors of homologous LDL were first- or second-year medical students meeting the following criteria: (a) plasma LDL cholesterol between the 40th and 60th percentile for their age (2); (b) no history or exposure to hepatitis; (c) no exposure to autoimmune deficiency disease or practice of homosexuality; (d) no history of receiving blood transfusions or any other human blood products; (e) no current or recent illnesses; (f) normal hemogram, negative comprehensive hepatitis profile, and normal liver function tests; and (g) nonreactivity to anti-human T lymphotropic virus-III (4). Each laboratory test was performed twice. The first testing was done upon selection for study, and the second at blood donation for isolation of LDL. All tests were reviewed independently by Dr. Burton Combes (Liver Diseases Division, Department of Internal Medicine) and each donor was approved by him. Donor LDL was designated homologous LDL.

Hypercholesterolemic patients were admitted to the metabolic ward for turnover studies, where they were started on a solid-food diet consisting of 40% of calories as fat (18% saturates, 17% monounsaturates, and 5% polyunsaturates), 45% as carbohydrates, and 15% as protein. Dietary cholesterol was ~150 mg/1,000 calories. 2 wk later, the turnover rate of LDL was measured. Each patient received two different preparations of radiolabeled LDL, the patient's own LDL (autologous LDL) and homologous LDL. The turnover rates of the two forms of LDL were com-

Address reprint requests to Dr. Vega, Center for Human Nutrition, University of Texas Health Science Center, 5323 Harry Hines Boulevard, Dallas, TX 75235.

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1. *Abbreviations used in this paper:* apo, apolipoprotein; BMI, body mass index; CHD, coronary heart disease; FCR, fractional clearance rate; FH, familial hypercholesterolemia; IDL, intermediate density lipoprotein; LDL, low density lipoprotein.

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Table I. Concentration of Plasma Lipids, Lipoproteins, and Composition of LDL for All Patients

Group	Plasma lipids				LDL composition					
	TC	TG	LDL-C*	HDL-C	TC	TG	PL	Prot	CHO	LDL P/C
	mg/dl±SD	mg/dl±SD	mg/dl±SD	mg/dl±SD	%	%	%	%	%	ratio±SD
Donors (n = 11)	163±13	85±24	102±7	48±8	36±3	7±1	28±2	22±1	7±1	0.59±0.08
Moderate HCH										
Group A (Nos. 1–10)	285±15	138±37	200±9	37±9	39±2	6±2	26±2	23±1	5±0.8	0.60±0.03
Group B (Nos. 11–15)*	278±19	147±53	194±16	36±6	44±1‡	5±1	23±3	22±3	6±0.3	0.54±0.05
Familial HCH										
(Nos. 13–17)	368±38	129±21	296±41	31±12	41±1‡	4±1	27±2	23±1	4±0.3	0.55±0.04

CHO, carbohydrate; HCH, hypercholesterolemia; LDL C and HDL C, LDL and HDL cholesterol, respectively; P/C, protein-cholesterol ratio; PL, phospholipids; Prot, protein; TC, total cholesterol. * LDL cholesterol for donors represents LDL + IDL ($d = 1.006\text{--}1.063$ g/ml) as in the Lipid Research Clinic procedure (2); the LDL cholesterol for hypercholesterolemic patients represents $d = 1.019\text{--}1.063$ g/ml lipoproteins and excludes IDL ($d = 1.006\text{--}1.019$ g/ml). LDL composition for all subjects was obtained from $d = 1.019\text{--}1.063$ g/ml lipoproteins. All group B patients had the apoE3/E3 genotype (10). ‡ Significantly higher than donors LDL at $P < 0.05$.

pared. Another study was performed on six patients (Nos. 1–3, 5, 11, and 12). After the first turnover study, they began mevinolin 20 mg twice daily. 1 mo later, they were readmitted on mevinolin to repeat the same turnover study.

LDL turnover studies. 5 d before the turnover study, 250 ml of plasma was obtained by plasmapheresis. Simultaneously, 500 ml of blood was taken from the donors. Patients received 0.5–0.9 g/d of potassium iodide orally in divided doses to suppress thyroidal uptake of radioiodine. Autologous and homologous LDL were isolated by identical procedures. The plasma was ultracentrifuged at 1.019 g/ml to remove very LDL and intermediate density lipoprotein (IDL). LDL was isolated at a density of 1.019–1.063 g/ml, and was labeled with either ^{125}I or ^{131}I , as described previously (1). Autologous LDL usually was labeled with ^{125}I and homologous LDL with ^{131}I . Plasma die-away curves were followed for 14 d. Each curve was analyzed by the Matthews two-pool model (5), and FCRs were estimated using the conversational version of the stimulation analysis and modeling program of Berman and Weiss (6), in a VAX 11/780 computer (Digital Equipment Corp., Nashua, N.H.). Plasma lipids, lipoprotein-cholesterol, and composition of LDL were determined, as described previously (7).

Results

Table I gives concentrations of lipids, lipoproteins, and composition of LDL for donors and patients. Lipid levels and LDL cholesterol concentrations for donors averaged near the 50th percentile for their age group, according to the Lipid Research Clinic survey (2). Patients with moderate hypercholesterolemia were divided into groups A and B, depending on their LDL kinetics (see below). The cholesterol in LDL ($d = 1.019\text{--}1.063$ g/ml) of these patients equaled or exceeded the 90th percentile for their age and sex (2). LDL cholesterol levels for FH patients averaged 296 ± 41 mg/dl. Compositional analysis revealed no distinct abnormalities for LDL in any group, although cholesterol contents of LDL in patients of group B and in FH patients were mildly increased, as reflected by mildly reduced LDL-protein/cholesterol ratios.

Table II gives concentrations of LDL cholesterol for donors and recipients and FCRs for autologous and homologous LDL. From the 30 data points for each curve collected over a 14-d period, the resulting activity-time curves were modeled separately for the two types of LDL. A reduced model, fitting a single curve through the within-subject pooled data, was also estimated. A

Table II. Concentrations of LDL-Cholesterol in Donors and Patients and FCRs of Autologous and Homologous LDL

Patients	LDL cholesterol		FCR for LDL		F test*
	Patient	Donor (No.)	Autologous	Homologous	
	mg/dl	mg/dl	pools/d	pools/d	
Moderate hypercholesterolemia					
Group A					
1C	195	98 (1)	0.162	0.179	NS
1M	139	98 (1)	0.215	0.253	NS
2C	197	112 (2)	0.178	0.187	NS
2M	118	112 (2)	0.245	0.281	NS
3C	215	111 (3)	0.257	0.236	NS
3M	134	93 (4)	0.281	0.296	NS
4C	188	115 (5)	0.289	0.242	NS
4M	98	115 (5)	0.272	0.267	NS
5C	200	96 (6)	0.219	0.226	NS
6C	205	115 (5)	0.186	0.235	NS
7C	196	104 (7)	0.266	0.238	NS
8C	182	110 (8)	0.270	0.250	NS
9C	205	103 (9)	0.374	0.315	NS
10C	215	103 (9)	0.328	0.327	NS
Group B					
11C	205	97 (10)	0.233	0.295	<0.005
11M	112	111 (3)	0.379	0.593	<0.005
12C	175	93 (4)	0.225	0.295	<0.025
12M	114	103 (9)	0.395	0.607	<0.005
13C	190	103 (9)	0.182	0.282	<0.005
14C	184	111 (3)	0.262	0.393	<0.025
15C	215	96 (11)	0.210	0.410	<0.001
Familial hypercholesterolemia					
16C	310	116 (10)	0.250	0.255	NS
17C	244	111 (3)	0.212	0.200	NS
18C	359	112 (2)	0.220	0.183	NS
19C	318	93 (4)	0.171	0.140	NS
20C	269	93 (4)	0.261	0.212	<0.05

C, control period; M, mevinolin treatment period; NS, not significant at $P < 0.05$. P values are shown for those that were significant.

* Fisher F test (9) compares activity-time curves for autologous and homologous LDL.

standard F test was performed to determine whether the two curves were significantly different (8). The *P* values from this set of comparisons are presented in Table II. For patients 1–10 (group A), the differences between the two curves were not significant. In patients 11–15 (group B), the two curves were significantly different at the *P* values shown. Representative curves from groups a and b are presented in Figs. 1 and 2, respectively. The two groups (A and B) were then subjected to further evaluation. A two-factor repeated measures analysis of variance was used to test for differences between groups and between FCRs for the two types of LDL. Restricting the analysis to the control period (excluding mevinolin treatment), there was a significant interaction between the two factors, i.e., both groups and both turnover curves for each patient (*P* = 0.001). There was no significant difference between the two groups for FCRs of autologous LDL or between FCRs autologous and homologous LDL for group A. The difference in FCRs between autologous and homologous LDL was significant for group B (*P* = 0.0108), and the difference between groups A and B for FCRs for homologous LDL was significant (*P* = 0.0067).

Mevinolin therapy was carried out in six patients. In patients 1–4 of group A, mevinolin therapy reduced LDL cholesterol levels and increased FCRs for autologous and homologous LDL to a similar degree, i.e., the lack of significant difference between the two curves persisted. Treatment of patients 11 and 12 of group B likewise increased FCRs for the two types of LDL, and the significant differences between the two curves persisted. Therefore, to quantify the agreement in response before and during mevinolin therapy for all six patients, the Kappa statistic (*κ*) (9) was computed. The consistency between the two studies was greater than expected by chance (*κ* = 1, *P* < 0.01), and makes it unlikely that the persistent differences between the two types of LDL noted in patients 11 and 12 were an artifact.

Plasma taken at the end of the study from patients 11–15 was tested for antibodies against their donors LDL by immu-

nodiffusion, using rabbit antihuman LDL for control. No precipitin lines were formed between the patients' plasma and donor LDL.

For four heterozygous FH men (Nos. 16–19), FCRs for autologous and homologous LDLs were not different (0.213 ± 0.028 vs. 0.195 ± 0.041 pools/d, respectively). For the markedly obese woman (No. 20), the FCR for autologous LDL was significantly higher than for homologous LDL.

In this study, one donor frequently supplied homologous LDL for multiple patients, and for all patients except Nos. 11–15, the FCRs for homologous from a single donor LDL were very similar to those of autologous LDL regardless of the FCR of the autologous LDL. For example, FCRs for LDL obtained from donor 3 were very low in patients 3 and 17, but were much higher in patients 11M and 14. Furthermore, two pairs of patients received homologous LDL from donors 4 and 11 on the same day. Patients 12 and 19 simultaneously received LDL from donor 4, and for patient 19, homologous and autologous LDL had similar FCRs, but the FCR for homologous LDL was significantly higher than autologous LDL in patient 12. Likewise, patient 15 and a subject with normocholesterolemia (LDL cholesterol = 158 mg/dl), who was not included in this paper, received LDL from donor 11 on the same day. Patient 15 had a higher FCR for homologous LDL than for autologous LDL (0.410 vs. 0.210 pools/d, respectively), whereas FCRs for homologous and autologous LDL for the other patient were similar (0.255 vs. 0.280 pools/d). These two pairs of patients demonstrate that the significantly higher FCRs for homologous LDL in patients 12 and 15 were not due to a unique property of the donor's LDL, such as partial denaturation of his LDL.

Discussion

In heterozygous FH, LDL particles presumably are normal, and fractional clearance of autologous and homologous LDL should

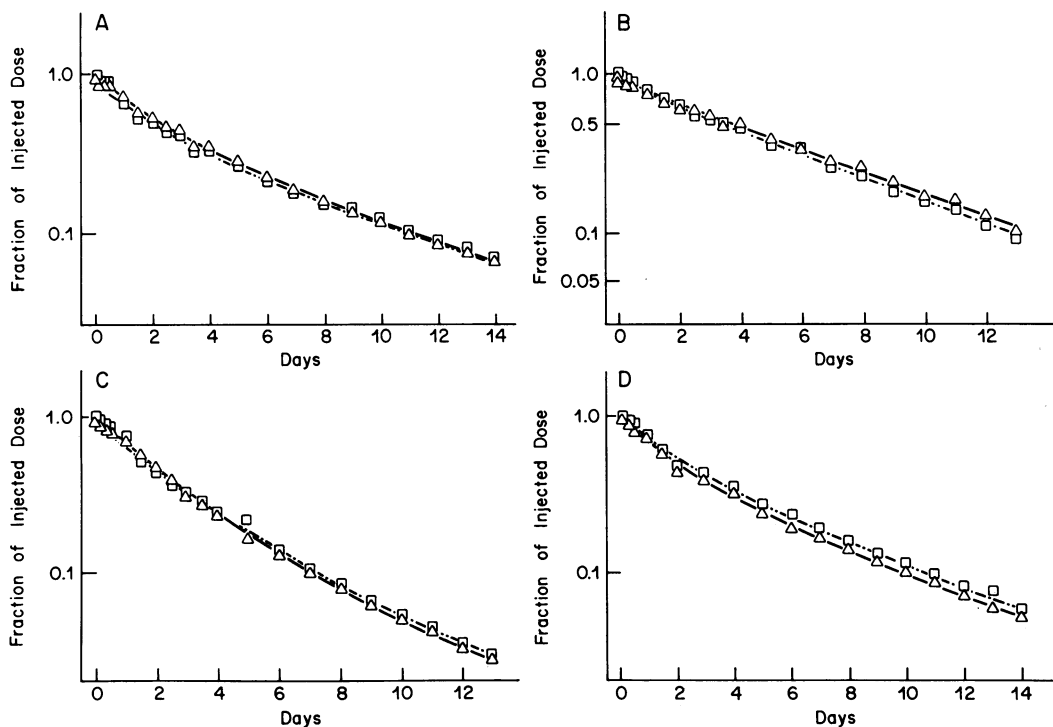


Figure 1. Plasma decay curves of radiolabeled autologous LDL (Δ) and homologous LDL (\square) for patients 5 (A), 2 (B), 10 (C), and 3 (D). See Table II for FCRs of each.

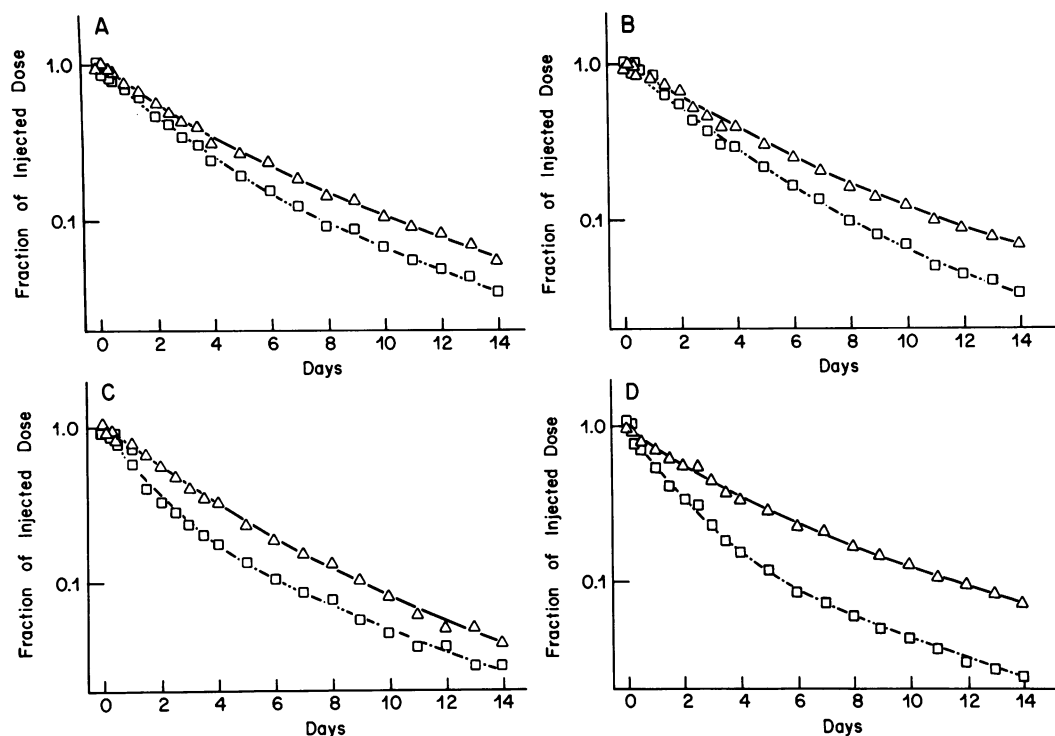


Figure 2. Plasma decay curves of radiolabeled autologous LDL (Δ) and homologous LDL (\square) for patients 11 (A), 13 (B), 14 (C), and 15 (D).

be identical. This identity was observed in our four FH men, as noted previously by others in FH patients (11). Autologous LDL was cleared more rapidly in one markedly obese woman with FH, but as shown before (12), obesity can impart changes in LDL chemical composition that may cause it to be cleared more rapidly than normal. None of the FH patients had significantly higher FCRs for homologous LDL, which indicated that their own LDL did not have reduced affinity for LDL receptors.

The metabolic defects responsible for primary moderate hypercholesterolemia are not known. A reduced affinity of LDL for receptors was suggested as a distinct possibility by a recent study from our laboratory (1); we showed that mevinolin, which markedly increases FCRs for LDL in FH heterozygotes (13), does not greatly increase FCRs in patients with primary moderate hypercholesterolemia, as if LDL in the latter carried a ligand defect. These results prompted the present study, but the current data indicate that most patients with moderate hypercholesterolemia do not have an abnormality in receptor-binding properties of LDL.

Some patients, however, may have a ligand defect. In five patients (group B), FCRs for homologous LDL generally were in the normal range for middle-aged adults (14). In contrast, FCRs for autologous LDL were significantly lower, which suggests that the patients' own LDL was a poor ligand for receptors. A difference between the two FCRs was noted twice in two patients, both before and during mevinolin therapy; this adds consistency to the finding.

How can we explain reduced FCRs of autologous LDL, but not homologous LDL, in group B patients? Was the difference artifactual? The following arguments suggest not: (a) no antibodies against homologous LDL could be detected; (b) the responses for six patients treated with mevinolin were highly consistent before and during drug therapy; (c) in 26 turnover studies, homologous LDL had higher FCRs than autologous LDL in seven instances, and vice versa in only one, which makes a ran-

dom denaturation of the two LDLs unlikely; and (d) when one donor was used multiple times, the responses were internally consistent among different patients.

If the differences in turnovers for group B were in fact due to an abnormality in the ligand properties of autologous LDL, several mechanisms might be responsible. The primary structure of apolipoprotein B-100 could have been abnormal, causing it to bind poorly to receptors. Several laboratories (15–20) are actively working on the amino acid sequence of apo B-100; the protein appears polymorphic, and thus LDLs from different individuals may vary in their binding capacity for receptors. Alternatively, autologous LDL could have abnormal contents of other proteins (e.g., apo E), lipids, or carbohydrates and thus adversely affect binding to receptors.

In summary, we have shown that most patients with primary moderate hypercholesterolemia do not have a defect in receptor-binding properties of LDL. In contrast, a minority of patients seemingly do have an abnormal LDL, causing it to be removed slowly. The current paper describes a method by which these two types of patients can be distinguished, and this method could prove useful for evaluating the biological significance of polymorphism of LDL apolipoproteins.

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