Lovastatin therapy in nephrotic hyperlipidemia: Effects on lipoprotein metabolism

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Lovastatin therapy in nephrotic hyperlipidemia: Effects on lipoprotein metabolism. The nephrotic syndrome is characterized by proteinuria, hypoalbuminemia, and hypercholesterolemia. Hypertriglyceridemia often is present as well. In this study, the kinetics of plasma lipoproteins were investigated in four patients with nephrotic hyperlipidemia, and repeat studies were carried out in three of these patients during therapy with lovastatin. Before lovastatin therapy, the patients had an extremely delayed catabolism of very low density lipoproteins (VLDL) without evidence of overproduction of lipoproteins in this fraction. Three of four patients had elevated levels of low density lipoprotein (LDL) that were due mainly to increased production rates for LDL. In the three patients treated with lovastatin, the drug therapy lowered plasma concentrations of total cholesterol, triglycerides, VLDL-cholesterol, and LDL-cholesterol, and raised high density lipoprotein (HDL)-cholesterol. Lovastatin therapy decreased VLDL-triglycerides primarily by enhancing their catabolism, and lowered LDL-cholesterol levels mainly by reducing input rates for LDL. Overall, lovastatin appears to be an effective drug for the treatment of hyperlipidemia in the nephrotic syndrome.

The nephrotic syndrome is a renal disorder of diverse etiology typified by proteinuria, hypoalbuminemia, and sometimes edema. Hypercholesterolemia usually is present in nephrotic patients and is considered by some to be an essential component [1, 2]. As the disorder progresses, hypertriglyceridemia, or combined hyperlipidemia, can develop [3]. Many cases of nephrotic syndrome in adults are secondary to diabetes mellitus, while primary forms of nephrotic syndrome most often are due to membranous nephropathy, focal sclerosis, and minimal change disease [4]. Prolonged hyperlipidemia associated with the nephrotic syndrome apparently can produce accelerated atherosclerosis and premature coronary heart disease (CHD) [5, 6]. Hyperlipidemia of the nephrotic syndrome is typically resistant to therapy. Resolution of the hypoalbuminemia often but not invariably restores plasma lipids to normal [2, 7, 8], but as long as significant proteinuria remains, hyperlipidemia usually persists.

Since nephrotic hyperlipidemia seemingly predisposes to CHD, some means to reduce plasma lipid levels in nephrotics seems desirable. The recent introduction of drugs that curtail cholesterol synthesis by inhibiting 3-hydroxy-3-methylglutaryl

coenzyme A (HMG Co A) reductase offers a new promise for treatment of severe hypercholesterolemia [9]. Lovastatin is one agent in this category [10–13], and this drug could reduce plasma cholesterol, and possibly triglycerides, in patients with nephrotic hyperlipidemia. In the current study, we have examined three questions: (a) what are the defects in lipoprotein kinetics responsible for nephrotic hyperlipidemia? (b) does lovastatin significantly reduce plasma concentrations of cholesterol and triglycerides in patients with the nephrotic syndrome? and (c) if so, by what mechanisms do these changes occur?

Methods

Patients

Four patients with the nephrotic syndrome and hyperlipidemia were admitted to the metabolic ward of the Veterans Administration Medical Center, Dallas, Texas. The characteristics of these patients are presented in Table 1. They had proteinuria ranging from 6.5 to 14.5 g/day and clinically significant hypoalbuminemia; however, they did not have marked elevations of plasma creatinine, nor severe nephrotic syndrome. Three patients had the apolipoprotein (apo) E3/E3 phenotype and one had apo E3/E4. None had an increase in very low density lipoprotein (VLDL)-cholesterol/plasma total triglyceride ratio. Three of the patients (Nos. 1, 3, and 4) had previously undergone renal biopsy that revealed membranous glomerulonephritis; in the fourth patient (No. 2), a tissue diagnosis was not available. None of the patients had clinically-manifest atherosclerotic disease at time of study, but one patient (No. 1) died suddenly, possibly of myocardial infarction, several months after the study. None of the patients were on steroid or diuretic therapy, and they were not edematous. All patients were euthyroid. Each gave informed consent for the research protocol that was approved by the appropriate institutional review board.

Experimental design

Three patients (Nos. 1 to 3) underwent studies on the metabolic ward during two periods. Patient 4 underwent only the first period. Each period lasted a minimum of eight weeks. The first period was for control, during which time patients did not receive any hypolipidemic drugs. During the second period, patients received lovastatin, 20 mg twice daily. Patients were started on a metabolic diet on the fifth week of each period; they had a one-unit plasmapheresis during the sixth week, and on the

Table 1. Clinical data

Patient	Age yrs	Body mass index kg/m²	Apo E phenotype	Plasma creatinine mg/dl	Urinary protein g/day	Serum albumin g/dl	VLDL-cholesterol triglycerides ratio
1	64	24.5	E3/3	2.5	6.5	2.7	0.25
2	69	23.7	E3/3	1.7	10.2	2.6	0.20
3	47	28.9	E3/3	1.0	14.5	2.5	0.28
4	69	24.5	E4/3	1.0	12.0	2.0	0.22

VLDL-cholesterol for this table was measured on VLDL isolated at d > 1.006 g/ml.

first day of the seventh week they received intravenous injections of autologous ^{125}I-VLDL and ^{131}I-LDL. The lipoprotein turnover studies were conducted for 14 days.

Diets

Two weeks before and throughout the lipoprotein turnover study in each period, the patients ate a solid food diet containing 40% of calories as fat (17% saturates, 18% monounsaturates, and 5% polyunsaturates), 45% as carbohydrates, and 15% as protein; intakes of cholesterol were approximately 300 mg/day [14]. The patients were maintained at constant weight throughout the study.

Plasma lipids and lipoproteins

Plasma total cholesterol and triglycerides were measured enzymatically [15, 16]. Chylomicrons were removed by ultracentrifugation before lipoprotein analyses were performed [17]. VLDL-cholesterol was measured on the fraction of lipoproteins isolated at d < 1.019 g/ml by preparative ultracentrifugation [17, 18], and [LDL + HDL]-cholesterol was determined in the infranatant. HDL-cholesterol was measured after precipitation of LDL from the infranatant with heparin-manganese, and LDL-cholesterol was calculated by the difference. Isoforms of apo E were determined on VLDL by isoelectric focusing; focusing was carried out on two samples of VLDL-protein, one incubated with β-mercaptoethylamine and another with 2-β-mercaptoethanol [19].

Kinetics of apo B-containing lipoproteins

The kinetic parameters for apo B were estimated in VLDL (d < 1.019 g/ml) and in LDL (d 1.019 to 1.063 g/ml). The details of these measurements and justification for including all lipoproteins of d < 1.019 g/ml in the VLDL fraction were presented recently [20]. The procedures employed in the turnover study will be described briefly. Each patient began the metabolic diet ten days before plasmapheresis and remained on the diet throughout the turnover study. Five days before starting the turnover study, 200 ml of plasma were obtained by plasmapheresis, and patients were started on supersaturated potassium iodide (0.5 g/day) to inhibit thyroidal uptake of radioactive iodine. VLDL and LDL were isolated from plasma by preparative ultracentrifugation; VLDL was labeled with ^{125}I and LDL was labeled with ^{131}I, both with the iodine-monochloride technique, as described previously [20]. Both isotopically-labeled lipoproteins were injected intravenously at the same time. For the first two days of the turnover study, the day's total caloric intake was divided into six meals of identical calories consumed

every four hours. The composition of these meals was identical to that consumed over the whole study.

Blood samples were collected 18 times in the first 48 hours and then daily for the remaining 14 days. The details of the procedure for isolation of lipoprotein fractions and determination of radioactivity and mass of apo B in each fraction have been described before [20]. Briefly, VLDL and LDL were isolated by preparative ultracentrifugation, and radioactivity in apo B in VLDL and LDL was determined in each of the 18 samples collected during the first 48 hours. The technique for determination of radioactivity in apo B of each fraction has been outlined previously [20]; the procedure employed isopropanol for the precipitation of apo B to separate it from soluble apoproteins. A single pool was made of all samples obtained over the first 48 hours for determination of plasma VLDL-apo B concentration for the purpose of estimating the plasma pool size of VLDL-apo B.

Radioactivity in LDL was monitored in 30 samples obtained during the entire period of study. Aliquots of fasting plasma samples in the last 12 days of the study were combined into four 3-day pools for determinations of plasma lipids, lipoprotein-cholesterol, and LDL-apo B concentrations. A single pool of all samples was made for estimation of concentration and pool size of LDL-apo B. Radioactive decay curves for VLDL-apo B and LDL-apo B were constructed, and kinetic parameters were determined by multicompartmental analysis.

Simulation analysis was employed to estimate kinetic parameters of apo B in VLDL and LDL. A multicompartmental model, modified from Beltz et al [21] and reported recently [20] was employed in the analysis of the data. Figure 1 is a schematic representation of this model, which is our hypothesis of apo B metabolism in plasma. Although this model obviously is an oversimplication of apo B metabolism as a whole, it nonetheless appears to represent the major components of apo B metabolism. Typical isotopic decay curves for VLDL-apo B and LDL-apo B for a normal subject are presented in Figure 2. The multicompartmental model shown in Figure 1 is designed to account for the various components of these curves. It consists of three subsystems: one describes the kinetics of LDL-apo B, another VLDL-apo B, and a third, nascent lipoproteins.

The LDL subsystem consists of two pools of LDL [22], one representing the intravascular pool (L_p) and the other, the extravascular pool (L_x). This simple two-pool model is used to explain the biexponential decay curve of radiolabeled LDL-apo B in plasma (Fig. 2). The model assumes that all LDL is removed irreversibly from plasma, and that all LDL in the extravascular space must return to plasma for degradation. The model further assumes that LDL in the intravascular space is
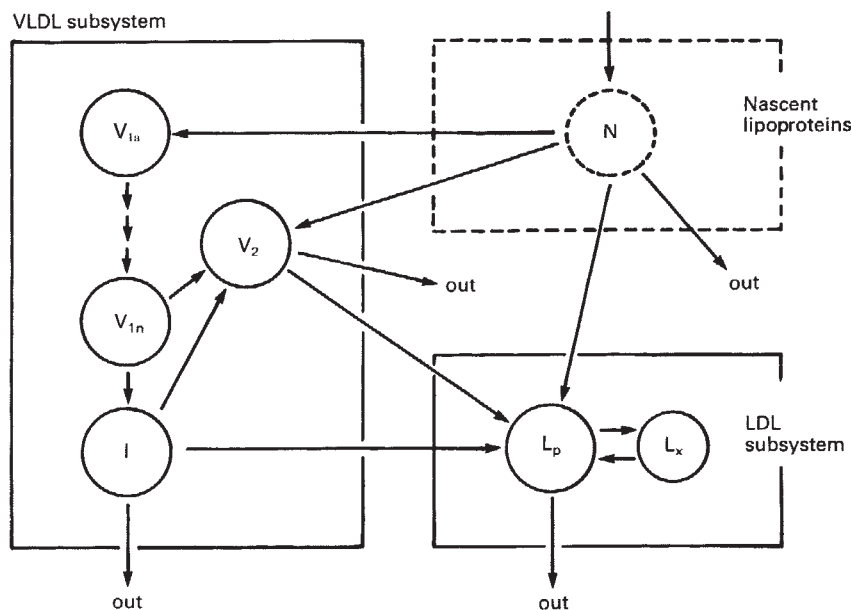
VLDL subsystem

Fig. 1. *Multicompartmental model for kinetics of apolipoprotein B.* Compartment N represents short-lived nascent lipoproteins and is a hypothetical pool that cannot be identified by current techniques. The VLDL subsystem contains two components. The chain pathway for delipidation of VLDL is represented by the $V_{1a} \rightarrow\rightarrow\rightarrow V_{1n} \rightarrow I$. The slow pathway for VLDL is compartment V_2; it may arise either as a side product of the chain pathway or from compartment N. The LDL system is represented by a two-pool model containing an intravascular compartment (Lp) and an extravascular pool (Lx). This figure shows the interconnections between the compartments.

kinetically homogenous. Although there is evidence that LDL is not always completely homogenous in its kinetic behavior, we have previously shown that the two-pool model provides a close approximation of LDL-apo B kinetics under most circumstances [23]. Plasma LDL can originate from the VLDL subsystem, or it can enter the LDL compartment independent of plasma VLDL. Although some investigators contend that LDL can be secreted directly by the liver [24], we have assumed that it is derived mainly from a compartment of nascent lipoproteins (N) that has a very fast turnover rate; evidence to support this concept has been presented before [21, 25, 26]. In our analysis, the kinetic parameters for ^{125}I-LDL-apo B and ^{131}I-LDL-apo B were assumed to be equal.

The typical shape of the decay curve for radiolabeled VLDL-apo B in plasma also is shown in Figure 2. The graph describes the fraction of injected dose of VLDL-apo B remaining in plasma at various time intervals during a two day period following injection of radiolabeled VLDL. This curve has three components: (a) a "shoulder" at the beginning of the curve when decay is relatively slow, (b) a longer phase of rapid decay, and (c) a "tail" of slow decay. The shoulder and the phase of rapid decay are represented in the model by the chain pathway $(V_{1a}\rightarrow\rightarrow\rightarrow I)$. This chain pathway is similar in principle to the delipidation cascade reported for VLDL-triglycerides [27]. Lipoproteins are assumed to enter into the first compartment of the chain from nascent lipoproteins (compartment N). The number of compartments in the chain can vary depending on the length of the shoulder of the curve. In our model, intermediate density lipoproteins (IDL) represent the last pool in the chain pathway; results obtained in our previous collaborative studies [21, 25, 26] justify this concept. In other words, IDL is assumed to be the terminal product of VLDL delipidation, whereas delipidation of IDL results in formation of LDL. VLDL-apo B in the chain pathway can have three fates: (a) direct removal from the circulation as IDL-apo B, (b) conversion to LDL, and (c) conversion to slowly catabolized VLDL (V_2).
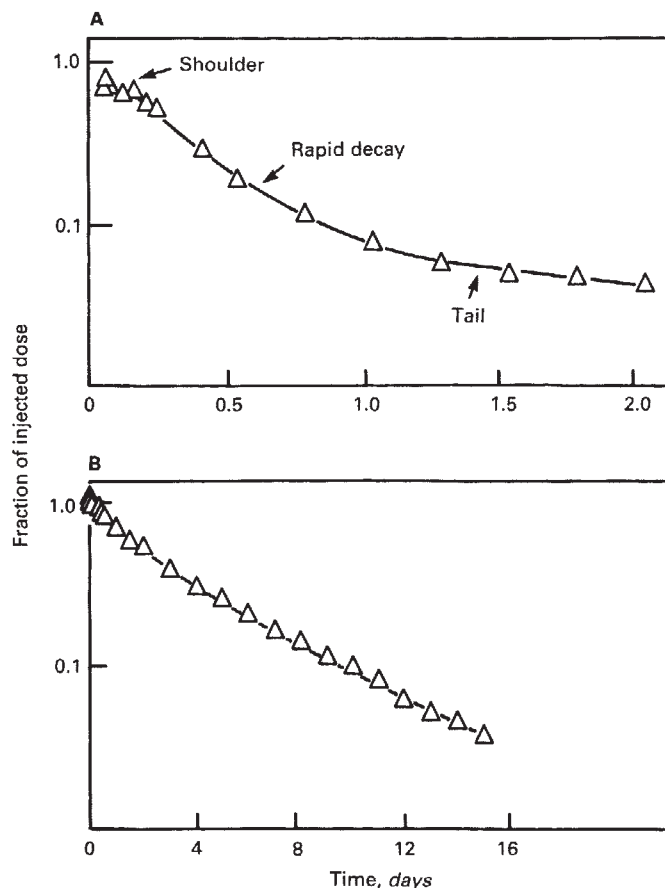

Fig. 2. *Typical decay curves for* (A) *VLDL-apo B and* (B) *LDL-apo B.* The VLDL-apo B contains three components. The "shoulder" at the beginning of the curve and the phase of rapid decay account for the chain pathway $(V_{1a}\rightarrow\rightarrow\rightarrow V_{1n} \rightarrow 1)$ and the tail of the curve indicates the need for a slow pathway (Fig. 1). The decay of LDL-apo B is biexponential, and can be explained by a two-pool model of the LDL subsystem.

Table 2. Plasma lipids and lipoproteins

| Patient | Total cholesterol | Total triglyceride | Lipoprotein-cholesterol | | |
| | | | VLDL | LDL | HDL |
		mg/dl $\pm$ sD[a]			
No. 1					
Control	381 $\pm$ 10	314 $\pm$ 12	102 $\pm$ 11	249 $\pm$ 14	30 $\pm$ 2
Lovastatin	261 $\pm$ 21[b]	183 $\pm$ 9[b]	60 $\pm$ 6[b]	167 $\pm$ 8[b]	34 $\pm$ 3[b]
No. 2					
Control	286 $\pm$ 9	297 $\pm$ 33	80 $\pm$ 7	168 $\pm$ 2	37 $\pm$ 4
Lovastatin	194 $\pm$ 4[b]	221 $\pm$ 12[b]	58 $\pm$ 4[b]	89 $\pm$ 8[b]	48 $\pm$ 2[b]
No. 3					
Control	546 $\pm$ 27	652 $\pm$ 228	243 $\pm$ 12	292 $\pm$ 25	12 $\pm$ 2
Lovastatin	378 $\pm$ 28[b]	349 $\pm$ 33[b]	115 $\pm$ 15[b]	239 $\pm$ 25[b]	23 $\pm$ 2[b]
No. 4					
Control	282 $\pm$ 32	516 $\pm$ 101	148 $\pm$ 9	125 $\pm$ 10	19 $\pm$ 2

[a] Mean $\pm$ sD for four 3-day pools of fasting plasma for days 2 to 14 of the turnover study.
[b] Significantly different from control by Student's *t*-test ($P < 0.05$).

Table 3. Kinetics of VLDL-apo B

| Patient | VLDL-apo B | | | | |
	Concentration *mg/dl $\pm$ sD*	Pool size *mg*	Transit time *days*	Transport rate *mg/kg-day*	Direct removal *%*
No. 1					
Control	33	1052	1.09	9.7	83
Lovastatin	23	725	0.55	18.5	58
No. 2					
Control	26	1304	1.87	8.8	40
Lovastatin	14	706	1.14	7.8	38
No. 3					
Control	60	2215	1.30	18.4	56
Lovastatin	21	814	0.47	16.9	53
No. 4					
Control	26	804	1.18	6.0	41
Normal men ($N = 5$) (mean $\pm$ sem) [Ref. 21]	14.5 $\pm$ 1.0	522 $\pm$ 36	0.43 $\pm$ 0.06	12.5 $\pm$ 2.2	29 $\pm$ 1.6

The plasma VLDL subsystem contains another compartment (V_2), which is a slowly catabolized pool. Its presence is revealed by the tail on the VLDL-apo B decay curve (Fig. 2). Compartment V_2 can arise either "directly" from nascent lipoproteins (compartment N) or as a side product of the chain pathway ($V_{1a} \rightarrow \rightarrow \rightarrow I$). Any slowly catabolized IDL is assumed to reside in the V_2 compartment. Apo B in compartment V_2 can be removed directly from the intravascular pool or be converted to LDL.

The final subsystem of the model consists of hypothetical nascent lipoproteins (compartment N). All apo B-containing lipoproteins are assumed to enter plasma as nascent particles [28]. This compartment cannot be identified in plasma because of its very high turnover rate. Its presence in the system has been deduced from several lines of evidence considered previously [21]. This compartment will henceforth be referred to as the very fast pathway. Apo B in compartment N theoretically can have three fates: (a) rapid direct removal from the circulation, (b) rapid direct conversion to LDL, and (c) passage into the chain pathway and/or slow pathway for VLDL catabolism.

In the discussion to follow, the term "transit time" is defined as the average time in which apo B entering a compartment remains in the compartment [29]. The transit time for apo B is equivalent to the reciprocal of the fractional catabolic rate (FCR), which is defined as the fraction of total apo B in a compartment that is removed in a given period of time. The transport rate (or production rate) is defined as the rate at which a species enters (and irreversibly leaves) a compartment. The term "direct removal" for VLDL-apo B refers to the fraction of the transport rate for VLDL-apo B that leaves the circulation before conversion to LDL [21]. The "direct input" for LDL-apo B is the fraction of apo B transported in LDL that is not derived directly from the chain or slow pathways for VLDL-apo B; as indicated above, the "direct" input of LDL is assumed to be derived from compartment N.

Statistical analysis

Linear statistical packages available in CLINFO were used. Comparison of means was carried out by paired *t*-test. Analysis of kinetic data was carried out using the Simulation Analysis and Modeling (SAAM) program of Berman and Weiss [30] in its conversational mode (CONSAM) [31], using a VAX 11/780 or VAX 11/750 computer.
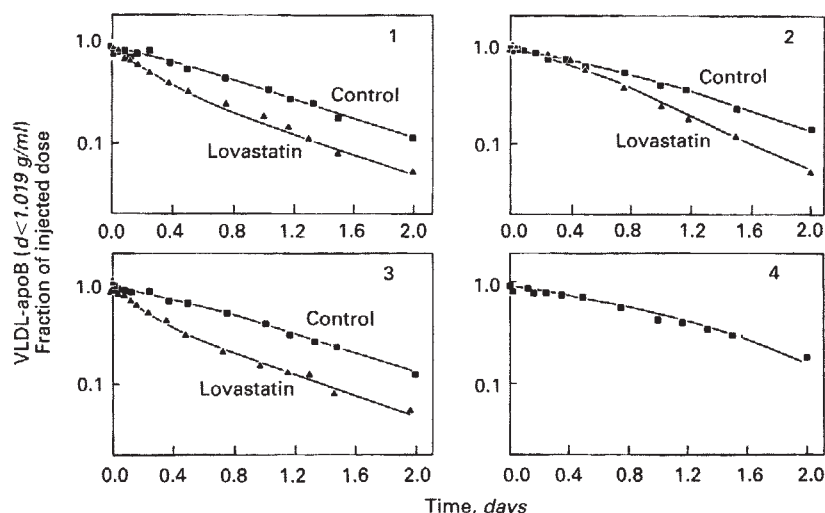
Fig. 3. *Isotope kinetic curves for VLDL-apo B for four patients with nephrotic syndrome during the control period (■, patients 1–4) and during lovastatin therapy (▲, patients 1–3).* In the control period, all of the curves demonstrated a prolonged convexity ("shoulder") without an identifiable slow component (compartment V_2). In patients 1–3, lovastatin therapy accelerated the rate of decay, and in patients 1 and 3, but not in patient 2, the prolonged convexity of the curve was eliminated.

Table 4. LDL-apo B kinetics

	LDL-apo B				
Patient	Conc mg/dl ± SD	Pool size mg	FCR pools/day	Transport rate mg/kg-day	Direct input %
No. 1					
Control	171	5455	0.28	21.2	90
Lovastatin	117	3897	0.26	14.3	54
No. 2					
Control	125	4461	0.20	11.5	54
Lovastatin	72	3420	0.24	5.2	6
No. 3					
Control	228	8591	0.29	25.6	41
Lovastatin	158	6307	0.28	18.2	43
No. 4					
Control	104	3469	0.34	16.1	78

Results

Plasma lipids and lipoproteins

In the control period, all four nephrotic patients had mild-to-moderate elevations of *both* plasma total cholesterol and tri-glycerides (Table 2). In each patient, VLDL-cholesterol levels were increased markedly. LDL-cholesterol concentrations were strikingly elevated in two patients (Nos. 1 and 3), was mildly increased in one (No. 2), and was not increased in the fourth (No. 4). HDL-cholesterol levels were uniformly reduced. Three of the patients underwent lovastatin therapy, and in them, lovastatin lowered plasma concentrations of total cholesterol, triglycerides, VLDL-cholesterol and LDL-cholesterol, and raised HDL-cholesterol. In patient 3, plasma lipid levels were severely elevated before therapy, and despite a marked reduction in lipid concentrations during treatment with lovastatin, this patient remained hyperlipidemic on drug therapy.

Metabolism of VLDL-apo B

The metabolic parameters of VLDL-apo B are presented in Table 3, and isotope kinetic curves for this fraction are given for control and lovastatin periods in Figure 3. In the control period,

the decay curves for all the four patients had a unique shape. In Figure 4, decay curves for three normal, middle-aged men, who were reported previously [25], are shown for comparison. In the nephrotic patients, rates of disappearance of radioactivity in VLDL-apo B were very slow and had a prolonged "shoulder" without a definite "tail". This unusual shape suggests that the defect in triglyceride metabolism in the nephrotic patients resided in the chain pathway ($V_{1a} \rightarrow \rightarrow \rightarrow I$), which contributes to the shoulder of the curve, and not in the slow pathway (V_2), which is responsible for the tail. Since a slow pathway (V_2) could not be identified for these patients, the turnover of the whole VLDL-apo B fraction was equated with the chain pathway (Table 3). For all four patients, concentrations of VLDL-apo B were abnormally high compared to levels in normal, middle-aged men [25]. These high levels in nephrotic patients were attributed to a prolonged transit time of apo B in the VLDL chain pathway. Transport rates in the chain pathway were not abnormally high, except in patient 3, who was obese. Percent direct removal of VLDL-apo B varied considerably among the patients.

Treatment of three patients with lovastatin induced a significant fall in concentrations of VLDL-apo B (Table 3). This
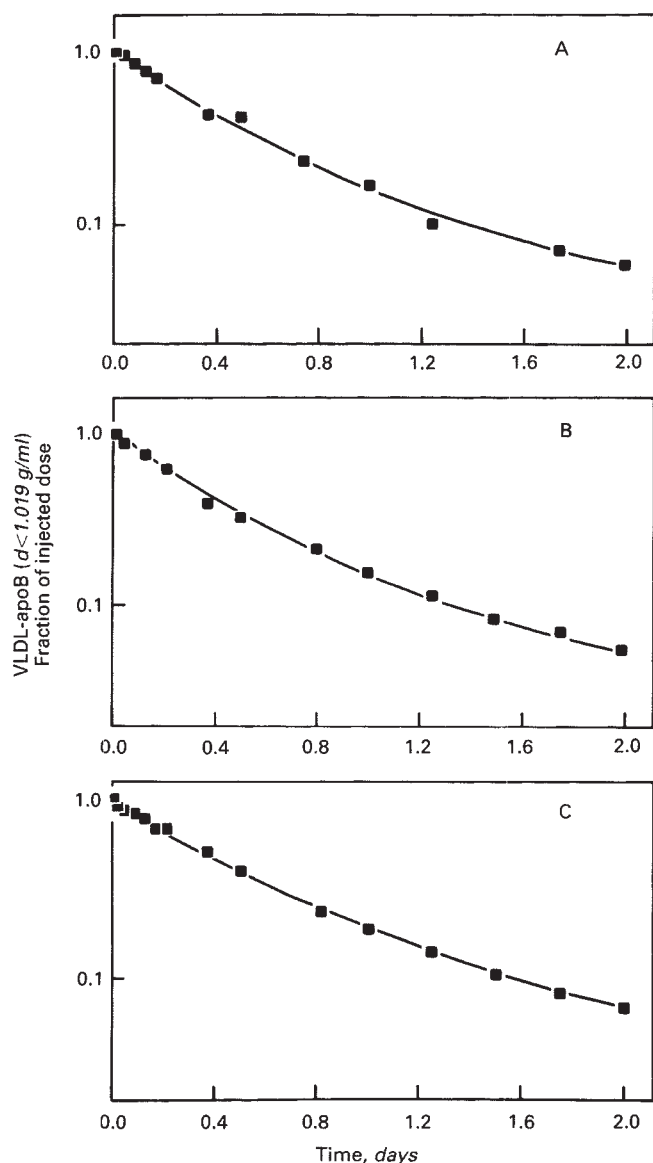
for unexplained reasons, the transport rate actually was increased in patient 1.

Metabolism of LDL-apo B

In the control period, concentrations of LDL-apo B ranged from 104 to 228 mg/dl (mean = 157 ± 27 (SE) mg/dl; Table 4). FCRs for LDL-apo B varied between 0.20 and 0.34 pools/day (mean = 0.28 ± 0.03 pools/day), and transport (input) rates for LDL-apo B varied between 11.5 and 25.6 mg/kg-day (mean = 18.6 ± 3.1 mg/kg-day). The fraction of "direct input" for LDL-apo B (N → L) ranged from 41 to 90%. Lovastatin therapy uniformly lowered plasma concentrations of LDL-apo B. The major effect of lovastatin on LDL kinetics was to decrease the transport rate for LDL-apo B; in addition, in two of the three patients, lovastatin caused a marked reduction in the "direct input" of LDL-apo B (N → L). Despite the fall in LDL-apo B concentration, FCRs for LDL-apo B were not consistently increased.

Discussion

The mechanisms for hyperlipidemia in the nephrotic syndrome have not been studied extensively in humans, but elevated plasma lipids probably are due in part to overproduction of lipoproteins by the liver [32–34]. Hypoalbuminemia and the resulting decreased plasma oncotic pressure have been reported to stimulate the synthesis of both lipids and lipoproteins in livers of experimental animals [35, 36]. A similar phenomenon has been noted in cultured hepatocytes [37, 38]. This overproduction could account for increases in plasma levels of both VLDL and LDL found in many patients with the nephrotic syndrome. When hypoalbuminemia becomes severe, however, lipolysis of plasma triglycerides also may be inhibited and thereby accentuate the hypertriglyceridemia [39]. In the current study, we examined the metabolism of VLDL-apo B and of LDL-apo B in four nephrotic patients in the attempt to define the mechanisms responsible for their diverse forms of hyperlipidemia; in addition, three of these patients were then given lovastatin to determine the actions of this drug on lipoprotein metabolism. The factors responsible for nephrotic hyperlipidemia can be considered first.

Fig. 4. *Isotope-kinetic curves for VLDL-apo B for three normal, middle-aged men reported previously* [19]. These curves were constructed from isotope kinetic curves of VLDL-apo B and IDL-apo B by computer summation. Each patient received an intravenous injection of radioiodinated VLDL. These curves typically have three components—an early "shoulder", a phase of rapid linear decay, and a slow component ("tail").

Mechanisms for elevated LDL-cholesterol

Increased plasma concentrations of LDL-cholesterol in the nephrotic syndrome could be due to overproduction of lipoproteins by the liver or to defective clearance of LDL. Isotope kinetic studies alone cannot differentiate between these two mechanisms with certainty, although they can provide strong support for one or the other. For example, we have previously shown that most patients with primary moderate hypercholesterolemia have low FCRs for LDL-apo B, suggestive of a deficiency of LDL receptors [40]. Patients with homozygous or severe heterozygous familial hypercholesterolemia (FH) likewise have marked reductions in FCRs for LDL, but they can have an increased input of LDL as well [41]; in FH patients, the enhanced input of apo B into the LDL compartment appears to be secondary to a decreased clearance of VLDL remnants, the precursors of LDL [42]. Since VLDL remnants, like LDL, are removed by LDL receptors, the marked reduction of LDL receptor activity in FH patients retards uptake of VLDL remnants resulting in a greater conversion of VLDL to LDL.

reduction was accompanied by an alteration in the shape of decay curve in two patients (Nos. 1 and 3) but not in a third (No. 2; Fig. 3). In the former two patients, the prolonged convexity of the curve was eliminated, and a more normal configuration was restored. Compared to the control period, treatment with lovastatin produced a decrease in the residence time of apo B in the VLDL chain pathway. However, the decreased residence time was not associated with a detectable increase in the percentage of direct removal of VLDL-apo B . In two patients (Nos. 2 and 3), the rate of transport in the VLDL chain pathway was not altered by lovastatin therapy, but

Table 5. Comparison of LDL kinetics in nephrotic patients to other categories of hypercholesterolemia

Group	Ref.	No. of patients	LDL-chol Conc *mg/dl*	LDL-apo B Conc *mg/dl*	FCR *pools/day*	Transport *mg/kg-day*
Nephrotic syndrome	—	4	208 ± 38	157 ± 27	0.28 ± 0.03	18.6 ± 3.1
Normal middle-aged men	56	14	144 ± 6	101 ± 5	0.30 ± 0.01	13.5 ± 0.7
Primary-moderate hypercholesterolemia	40	12	199 ± 7	129 ± 3	0.24 ± 0.01	12.9 ± 0.7
Familial hypercholesterolemia	57	22	281 ± 3	168 ± 9	0.22 ± 0.04	16.5 ± 1.3

Values are presented as means ± SEM.

However, our previous studies [40] in hypercholesterolemic patients suggest that, regardless of input rates for LDL, a decrease in FCR for LDL is almost always present in patients with reduced activity of LDL receptors.

Parameters of LDL metabolism in our four nephrotic patients can be compared to those of other groups studied previously in our laboratory: normal middle-aged men, men with primary moderate hypercholesterolemia, and patients with heterozygous familial hypercholesterolemia (Table 5). The comparison is presented to provide perspective, but the data cannot be strictly compared statistically. On the whole, the nephrotic patients had increased plasma concentrations of both LDL-cholesterol and LDL-apo B. However, compared to patients with primary (or familial) forms of hypercholesterolemia, the FCRs for LDL-apo B in the nephrotic patients were not similarly reduced; instead, elevated LDL concentrations in the nephrotic patients appeared to be due mainly to increased transport (production) rates for LDL. The absence of reduced FCRs for LDL supports the concept that overproduction of precursor lipoproteins is the major cause of the increased LDL level in nephrotic patients. As shown in Table 4, a high fraction of the increased input of LDL was via a "direct pathway", that is, by direct conversion of nascent lipoproteins to LDL; in a word, LDL was not derived exclusively from VLDL-apo B passing through the chain pathway.

Despite evidence for overproduction of precursors of LDL, we have not ruled out the possibility that a reduced activity of LDL receptors was present as well. For example, patient 2 had a very low FCR for LDL and a relatively normal input rate for LDL, suggestive of reduced receptor activity. Many years ago, Gitlin et al [43] reported that hypercholesterolemic patients with the nephrotic syndrome have defective clearance of plasma LDL, and one mechanism for a sluggish clearance of LDL could be a reduced activity of LDL receptors. For example, hepatic synthesis of LDL receptors could be curtailed by an increased production of cholesterol in the liver. Studies in laboratory animals with nephrosis suggest that hepatic cholesterol synthesis is increased [35, 36], and if so, the accumulation of cholesterol in the liver could suppress the activity of genes encoding for LDL receptors and thereby reduce the synthesis of LDL receptors [44]. Thus, the hypercholesterolemia of the nephrotic syndrome could be multifactorial, although our isotope kinetic data suggest that overproduction of precursors of LDL was the major reason for increased LDL-cholesterol concentrations in most of our patients.

Mechanism for hypertriglyceridemia

While overproduction of hepatic lipoproteins likely caused the elevated levels of LDL-cholesterol in our nephrotic patients, the data for VLDL kinetics demonstrated that defective clearance of triglyceride-rich lipoproteins was the major reason for the hypertriglyceridemia. The shape of the isotopic decay curves for VLDL-apo B strongly implied that the patients had a slow delipidation of VLDL in the chain pathway. Previously, a convexity, or "shoulder", at the beginning of the decay curve has been attributed to a stepwise transport of lipoproteins through the VLDL delipidation chain [21, 27, 45]. In the present study, this convexity persisted throughout the whole of the two days, suggesting a marked reduction in the rate of delipidation of VLDL. Indeed, considering the sluggish rate of delipidation, it is surprising that the hypertriglyceridemia was not more severe, especially if the patients had a concomitant overproduction of VLDL particles by the liver. However, transport rates for VLDL-apo B were not increased, which suggests that most of the excessive input of lipoproteins was shunted directly into LDL (N → L) without passing through the delipidation chain for VLDL. Our data therefore imply that the hypertriglyceridemia of the nephrotic syndrome is not due primarily to overproduction of VLDL, but rather to delayed lipolysis of VLDL-triglycerides.

How can the delayed lipolysis of VLDL-triglycerides in our patients be explained. Several possibilities can be considered. First, urinary loss might deplete VLDL of apo C-II which is required for activation of lipoprotein lipase [46]. In nephrotic animals, however, abundant apo C-II is available in plasma for activation of lipoprotein lipase [46–48], and this mechanism for hyperlipidemia seems unlikely. Second, the activity of lipoprotein lipase or hepatic triglyceride lipase could be reduced or inhibited by other mechanisms [49–51]. Finally, a delay in clearance of triglyceride-rich lipoproteins could have been due in part to a reduced activity of LDL receptors, because LDL receptors are known to remove VLDL remnants from the circulation [42]. Certainly, hypertriglyceridemia is not a characteristic of patients with a primary deficiency of LDL receptors, such as in familial hypercholesterolemia, and it is doubtful that a reduced LDL receptor activity could account fully for the elevations of triglyceride-rich lipoproteins noted in our patients. Still, a decrease in number of LDL receptors could have combined with an abnormality in the lipolytic system to reduce the rate of catabolism of these lipoproteins.

Effects of lovastatin

In the three patients treated with lovastatin, the drug caused a marked reduction in concentrations of total cholesterol and LDL-cholesterol. It further lowered levels of total triglycerides and VLDL-cholesterol. Finally, it caused a significant increase in HDL-cholesterol concentrations in all three patients. Thus, while we treated only three patients with lovastatin, the results were highly consistent for all three, and investigation of a larger number of patients likely would not have provided additional information about mechanisms for these changes. The effects of lovastatin therapy on lipoprotein kinetics can be considered briefly.

Mechanisms for LDL lowering. The major action of lovastatin on the metabolism of LDL was to decrease the transport rate of LDL-apo B. Drug therapy did not cause an increase in FCR for LDL. This finding raises the possibility that the primary mechanism for lowering of LDL levels by lovastatin was to curtail the synthesis of lipoproteins by the liver. While we cannot exclude this possibility, previously available evidence indicates that a major action of lovastatin is to increase the activity of LDL receptors [52–54]. If so, a decreased input of apo B into the LDL compartment could be explained by enhanced receptor-mediated clearance of precursors of LDL, particularly nascent lipoproteins in compartment N. Previously, we reported that lovastatin caused a reduced input of LDL in patients with primary moderate hypercholesterolemia, and it had little effect on FCRs of LDL in these patients [40]. On the other hand, we have found that lovastatin does not lower plasma concentrations or transport rates for LDL in patients with receptor-negative homozygous familial hypercholesterolemia—patients who have no functioning LDL receptors [55]. Thus, an enhanced uptake of precursors of LDL by LDL receptors likely contributed to the fall in LDL levels during lovastatin therapy, but the drug also may have inhibited the synthesis of apo B-containing lipoproteins by the liver.

Mechanisms for triglyceride lowering. Lovastatin produced a decrease in VLDL-apo B concentrations, along with triglycerides and cholesterol in the VLDL fraction, in all three patients. In contrast to LDL metabolism, lovastatin did not reduce input rates of VLDL-apo B . Instead, its major action was to enhance the removal of VLDL particles (Table 3). Since lovastatin probably does not alter the activity of lipoprotein lipase or hepatic lipase, our data are consistent with the concept that lovastatin therapy stimulates the hepatic removal of VLDL remnants by LDL receptors at several steps along the delipidation chain ($V_{1a} \rightarrow \rightarrow \rightarrow I$), and in so doing, it reduces the number of steps in the delipidation chain. The latter is shown by loss of convexity in the decay curves (Fig. 4). An enhanced direct removal of VLDL remnants could further contribute to the decrease in transport rate for LDL. The effects of lovastatin to reduce VLDL levels in nephrotic patients by promoting the clearance of VLDL-apo B illustrates that HMG CoA reductase inhibitors significantly alter the metabolism of VLDL as well as LDL.

Conclusions

Lovastatin and related HMG CoA reductase inhibitors are promising drugs for treatment of primary hypercholesterolemia. Their corresponding utility for patients with secondary forms of

hyperlipidemia, however, has not been tested. This report in a limited number of patients demonstrates that lovastatin can significantly reduce elevated levels of both cholesterol and triglycerides associated with the nephrotic syndrome. Reduction in cholesterol concentrations in both VLDL and LDL fractions most likely can be explained in large part by enhanced activity of LDL receptors, although an inhibition of hepatic synthesis of lipoproteins by the drug remains a possibility. Regardless of mechanism, this study shows that lovastatin can substantially lower plasma lipid levels in nephrotic patients and thus should reduce their risk for coronary heart disease.

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