

# Effect of Intensive Diabetes Treatment on Low-Density Lipoprotein Apolipoprotein B Kinetics in Type I Diabetes

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**The metabolism of low-density lipoprotein (LDL) was studied in six insulin-dependent (type I) diabetic patients during a 7-wk period of conventional and intensive therapy with insulin. Plasma glucose and HbA<sub>1c</sub> were normalized, demonstrating the effectiveness of our intensive treatment program. Plasma lipoprotein profiles and LDL apolipoprotein B kinetic parameters were estimated during conventional and then during intensive therapy for each patient. Intensive therapy resulted in a significant reduction of plasma and LDL cholesterol and an increase in high-density lipoprotein (HDL) cholesterol. The lower LDL levels resulted from a decreased production of lipoprotein rather than an increased fractional catabolic rate. These results are consistent with our previous observations of very-low-density lipoprotein (VLDL) metabolism during intensive therapy. VLDL production is significantly reduced; thus, a decreased production of LDL supports the contention that intensive therapy with insulin in normolipemic type I diabetic patients reduces the production of lipoproteins containing apolipoprotein B rather than increasing the clearance, and therapy also increases HDL cholesterol. Both of these effects may be beneficial in reducing the risk for coronary heart disease in type I diabetes. *Diabetes* 37:393-97, 1988**

**P**atients with diabetes mellitus are at an increased risk for premature atherosclerosis (1,2). The reason for this is unclear, but when these patients' diabetes is poorly controlled, hyperglycemia and

hyperlipidemia ensue (3). Both metabolic abnormalities seemingly are interrelated in that degrees of hyperglycemia are accompanied by proportional hypertriglyceridemia. Plasma lipid levels usually return to normal with improved diabetic control (4,5); failure of plasma lipids to normalize with treatment for diabetes suggests primary rather than secondary hyperlipidemia (6). Secondary hypertriglyceridemia occurs often in poorly controlled diabetes, yet epidemiological studies fail to demonstrate that elevated levels of plasma triglyceride (TG) alone are a risk factor for premature atherosclerosis (7). Serum TG levels have been found to be more strongly related to incidence of arterial disease than serum cholesterol, particularly in obese non-insulin-dependent (type II) diabetic patients (8). However, the study did not rule out that the relationship may simply be a marker of low levels of high-density lipoprotein cholesterol (HDL-cho), which is known to be a risk factor for arterial disease (8,9). Despite this contention, hypertriglyceridemia may be a significant risk factor in the pathogenesis of atherosclerosis related to diabetes.

Pietri et al. (10) have shown that significant decreases in plasma lipid and lipoprotein cholesterol levels can be achieved by 3 wk of intensive insulin therapy in insulin-dependent (type I) diabetic patients. Levels of HDL-cho rise after 2 mo of such treatment (11), and these changes persist for at least 3 yr of follow-up if the intensive diabetes treatment program is continued (12). In these studies, near normoglycemia was attained with continuous subcutaneous insulin infusion and systematic self-monitoring of blood glucose (13-15). These observations agree with those of other workers (16-18).

Pietri et al. (19) have shown that intensive therapy results in marked decrease in production of very-low-density lipoprotein TG (VLDL-TG) without a change in the rate of clearance of the lipoprotein. In this study, we evaluate the effect of this therapy on low-density lipoprotein apolipoprotein B (LDL-apoB). Our study shows that euglycemia achieved by intensive treatment of diabetes also results in decreased production of LDL-apoB without a change in clearance.

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**MATERIALS AND METHODS**

**Subjects.** Six subjects with type I diabetes mellitus were studied. Their ages were 18–42 yr (mean ± SE 32 ± 4); none of the patients was obese. Diabetes duration was 11–21 yr (mean ± SE 16 ± 1). Clinical characteristics for each subject are summarized in Table 1. None had history suggesting clinical coronary artery disease, and all had a normal resting electrocardiogram. All subjects were free of hepatic, renal, and coronary heart disease and took no medication other than insulin. All patients had normal plasma lipid levels while on conventional insulin at the time of the study. Each patient gave informed consent to participate in the study.

**Experimental design.** The metabolism of LDL-apoB was evaluated first during conventional therapy, then during intensive therapy with insulin. Each period of study lasted at least 7 wk. During conventional therapy, the patients received no more than two daily subcutaneous insulin injections; during intensive therapy, euglycemia was achieved with portable insulin infusion pumps. The latter procedure has been detailed previously (13,14). During each period of study, the levels of total cholesterol, TG, and lipoprotein lipids were measured six times throughout the turnover study. Also, a turnover study of autologous <sup>125</sup>I-labeled LDL-apoB was carried out for 20 days after admission to the General Clinical Research Center at Parkland Memorial Hospital (Dallas, TX) after 3 wk of either conventional or intensive treatment. There were no significant differences in the body weight of the patients during either of the two turnover studies.

**Diet.** On admission to the General Clinical Research Center the patients received a diet designed to maintain their weight; it consisted of 40% calories as fat (polyunsaturated-to-saturated ratio <0.3), 45% as carbohydrates, and 15% as protein. Daily cholesterol intake did not exceed 300 mg. This diet composition resembled the patients' home diet.

**Glucose profiles and glycosylated hemoglobin (HbA<sub>1c</sub>).** Blood samples for 24-h glucose profiles were obtained at hourly intervals from 0700 to 2300 h and at 2-h intervals from 2300 to 0700 h as described previously (20). Plasma glucose concentrations were measured in a glucose analyzer (Beckman, Houston, TX). Each glucose profile consisted of 20 measurements over a 24-h interval.

HbA<sub>1c</sub> was determined by ion-exchange high-performance liquid chromatography with an automated Daiichi Auto A<sub>1c</sub> (Helena, Beaumont, TX) (21). Cells were washed three times with 0.9% NaCl and dialyzed overnight against 0.9% NaCl to remove the labile fraction (22).

**Plasma and lipoprotein lipids.** Plasma total cholesterol and TG were measured by enzymatic procedures as detailed

previously (11). VLDL-cholesterol and VLDL-TG were measured after isolation of the lipoprotein from plasma by preparative ultracentrifugation as detailed in the manual for lipoprotein procedures of the Lipid Research Clinics Program (23). The HDL-cholesterol was determined in the plasma infranate after precipitation of intermediate-density lipoprotein (IDL) and LDL with heparin manganese (24). IDL-cholesterol and LDL-cholesterol were estimated as described previously (25). IDL-cholesterol was estimated as follows. Two aliquots of 4 ml plasma were adjusted to a density of 1.0063 and 1.019 g/ml, respectively. VLDL (density <1.0063 g/ml) and VLDL + IDL (density <1.019 g/ml) were separated by preparative ultracentrifugation. Total cholesterol was measured in each lipoprotein fraction, and IDL-cholesterol was estimated as the difference between VLDL + IDL and VLDL. The IDL-cholesterol measured in this way correlated well with the IDL-cholesterol estimated as described by Vega et al. (25). Because the percent recovery of cholesterol was determined accurately for the 1.0063-g/ml spins, the IDL-cholesterol shown in Table 3 are those calculated as described by Vega et al. (25). Mass ratios of IDL to LDL (*R<sub>m</sub>*) were estimated as

$$R_m = (0.283 \times 10^{-10})\text{VLDL-TG} + 0.1144$$

where VLDL-TG was measured six times during each turnover study.

**Turnover study of LDL-apoB.** LDL-apoB turnover studies were performed as detailed by Vega et al. (25). A unit of plasma was obtained from each patient during each period of study after plasmapheresis. LDL (density 1.019–1.063 g/ml) was isolated by preparative ultracentrifugation; the LDL was purified and concentrated by recentrifugation. Thereafter, the lipoprotein was dialyzed extensively against 0.15 M NaCl, 0.01% EDTA, pH 7.0. A portion of the LDL was radioiodinated as described previously (20). Each patient was injected with 20–40 μCi of autologous LDL. Blood samples were collected serially after injection, and the disappearance of radioactivity from plasma was monitored for 20 days. Pool sizes of apoB were estimated as follows. Plasma volumes were measured by isotope dilution of <sup>125</sup>I-LDL with the 10-min plasma sample. LDL-apoB concentrations were estimated six times during each turnover study. The LDL (density 1.019–1.063 g/ml) was isolated by preparative ultracentrifugation; total protein was determined by a modification of the Lowry procedure (26), and apoB was estimated after precipitation with isopropyl alcohol (27). The ratio of apoB to cholesterol was multiplied by the LDL-cholesterol determined in plasma to determine the absolute concentration of LDL-apoB.

**Estimation of kinetic parameters of LDL-apoB.** The percent of injected dose remaining in plasma was a biexponential function of time. The two-pool mammillary model of Matthews (28) was used to estimate fractional catabolic rate and other kinetic parameters. The analysis was done with the Conversational Version of the Simulation, Analysis and Modeling Program (CONSAM27) developed by Berman and Weiss (29). Transport rates were calculated as the product of fractional catabolic rate and pool sizes. These rates were normalized to kilogram of body weight.

**Statistical analysis.** Student's paired *t* test was used for comparison between the two periods of study.

TABLE 1  
Clinical characteristics of diabetic patients

Subject no.	Age (yr)	Sex	Body weight		Duration of diabetes (yr)
			lb	% ideal	
1	41	M	163	121	11
2	43	M	184	113	19
3	29	M	172	117	21
4	29	F	119	93	16
5	18	F	111	97	14
6	23	F	131	105	14
Mean ± SE	33 ± 4		147 ± 12	108 ± 5	16 ± 1

TABLE 2  
Concentrations of plasma glucose and HbA<sub>1c</sub>

Subject	Plasma glucose* (mg/dl)		HbA <sub>1c</sub> † (mg/dl)	
	Conventional therapy	Intensive therapy	Conventional therapy	Intensive therapy
1	186	131	8.1	6.8
2	176	117	7.0	5.5
3	168	104	6.3	5.3
4	230	130	10.1	8.3
5	168	125	10.8	7.4
6	269	132	8.4	6.2
Mean ± SE	198 ± 17	123 ± 4	8.5 ± 0.7	6.6 ± 0.5

\*Average of 24-h glucose levels obtained during each period of treatment before turnover study.

†Values obtained during each period of treatment before turnover study.

**RESULTS**

**Levels of plasma glucose and HbA<sub>1c</sub>.** Mean 24-h glucose level was 198 ± 17 mg/dl while on conventional therapy; with intensive therapy the levels were reduced significantly (*P* < .05) to 123 ± 4 mg/dl. Similar reductions occurred with HbA<sub>1c</sub>: mean levels were 8.5 ± 0.7 and 6.6 ± 0.5%, respectively (Table 2). The significant improvement in both of these glycemic indices demonstrates the effectiveness of our intensive treatment program. Both of these values are in the range of values for a group of nondiabetic individuals of the same age, sex, and body weight (30).

**Lipoprotein profiles.** The concentrations of plasma and lipoprotein lipids were normal during conventional therapy (Table 3). After 3 wk of intensive treatment there was a sig-

TABLE 3  
Concentrations of lipids in plasma and lipoproteins and kinetic parameters of LDL apolipoprotein B

	Conventional therapy	Intensive therapy
Plasma lipids (mg/dl)		
Total cholesterol	162 ± 126	153 ± 11*
Triglyceride	107 ± 28	97 ± 15
Lipoprotein lipids (mg/dl)		
VLDL cholesterol	14 ± 3	14 ± 2
VLDL triglyceride	52 ± 6	43 ± 9
IDL cholesterol	7 ± 1	6 ± 1
LDL cholesterol	100 ± 9	88 ± 9*
HDL cholesterol	41 ± 2	47 ± 5*
LDL apolipoprotein B kinetic parameters		
Apolipoprotein B (mg/dl)	75 ± 9	61 ± 9*
Pool size (mg)	2292 ± 275	1840 ± 211
Fractional catabolic rate (pools/day)	0.38 ± 0.04	0.34 ± 0.03
Transport rate (mg · kg <sup>-1</sup> · day <sup>-1</sup> )	13.4 ± 2.8	9.8 ± 1.9*
Apolipoprotein B-cholesterol ratio	0.75 ± 0.06	0.70 ± 0.06

Lipid concentration values are average of 6 individual determinations made during turnover study. LDL, low-density lipoprotein; VLDL, very-low-density lipoprotein; IDL, intermediate-density lipoprotein; HDL, high-density lipoprotein.

\**P* < .05 vs. conventional therapy.

nificant decrease (*P* < .05) in the levels of plasma cholesterol (162 ± 12 to 153 ± 11 mg/dl) and LDL-cholesterol (100 ± 9 to 88 ± 9 mg/dl). HDL-cholesterol increased significantly (42 ± 2 to 47 ± 5 mg/dl, *P* < .05). No significant changes occurred in plasma TG, VLDL lipids, and IDL-cholesterol (Table 3).

**LDL-apoB metabolism.** The concentration of LDL-apoB averaged 75 ± 9 mg/dl during conventional therapy (Table 3). These levels are similar to those of nondiabetic subjects matched for age and sex (26). Significant reductions (*P* < .05) of LDL-apoB levels (mean ± SE 61 ± 9 mg/dl), pool sizes (2292 ± 275 to 1840 ± 211 mg), and transport rates (13.4 ± 2.8 to 9.8 ± 1.9 mg · kg<sup>-1</sup> · day<sup>-1</sup>) were induced by intensive therapy. However, no significant changes occurred in the fractional catabolic rates (0.38 ± 0.104 to 0.34 ± 0.03 pools/day) or in the LDL ratio of apoB to cholesterol (0.75 ± 0.06 to 0.70 ± 0.06).

The effect of intensive therapy on LDL-apoB transport rates and fractional catabolic rate in the individual diabetic patients is shown in Figs. 1 and 2. With intensive treatment of diabetes the transport rate of LDL-apoB fell in each of the six patients, and the decrease was proportional to the fall in cholesterol level. The fractional catabolic rate fell in four patients, but this effect was not uniform.

**DISCUSSION**

This study confirms the previous observation that normoglycemia can be attained by intensive insulin therapy in type I diabetic patients (10). Also, this therapy markedly lowers the levels of plasma cholesterol and LDL-cholesterol. In this study we show that the hypocholesterolemic effect resulted from a reduced production of LDL when the patients were normolipidemic. An additional benefit of intensive therapy is the gradual increase of HDL-cholesterol levels, and, as demonstrated previously, greater increases in this lipoprotein can be attained with prolonged intensive therapy (11,12). Thus, the long-term significance of the hypocholesterolemic effect on the risk for coronary heart disease needs further investigation.

A previous study showed that treatment of normolipidemic type I diabetic subjects with intensive insulin therapy mark-

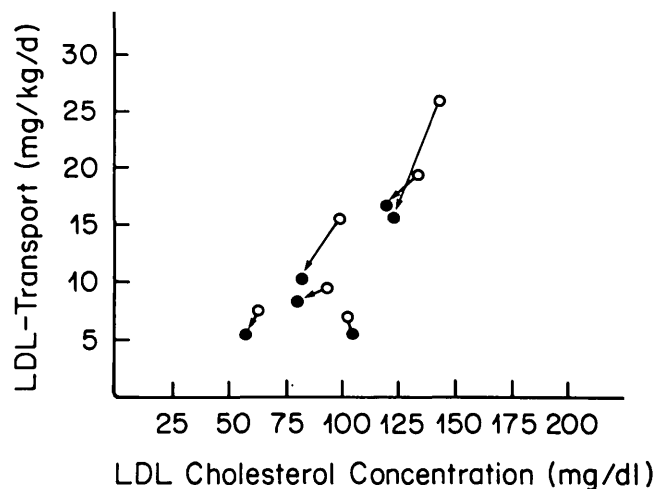
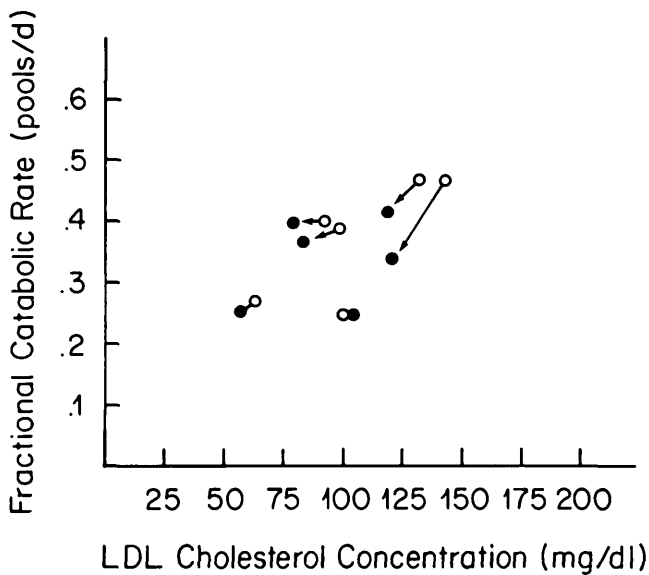


FIG. 1. Effect of intensive diabetes control on low-density lipoprotein (LDL) apolipoprotein B transport rates for individual diabetic subjects. ○, Conventional treatment; ●, intensive treatment.



**FIG. 2.** Effect of intensive diabetes control on fractional catabolic rate for low-density lipoprotein (LDL) apolipoprotein B in individual diabetic subjects. ○, Conventional treatment; ●, intensive treatment.

edly reduces the production of plasma VLDL-TG (19). These kinetic studies suggest that the biosynthesis and secretion of VLDL-TG is lowered by insulin. This interpretation also is consistent with the *in vitro* observations of Durrington et al. (31), who showed that hepatic secretion of VLDL-TG is reduced by insulin. VLDL also is a precursor of LDL (32), thus a decreased production of this lipoprotein also would be expected to affect the production of LDL. In this study we demonstrate that intensive insulin therapy of type I diabetic patients reduces the production of LDL when the patients are normolipidemic. It is likely that in normolipidemic type I diabetic individuals, insulin reduces the production of lipoproteins containing apoB. In fact, all of the changes observed in the lipoprotein profiles induced by intensive insulin therapy could be explained by a reduction in the production of these lipoproteins (10–12).

Mazzone et al. (33) recently showed that 4 h of insulin infusion in type I diabetic patients resulted in increased degradation of LDL by monocytes. They suggested that the number of LDL receptors is increased by insulin. In another study, Chait et al. (34) showed that LDL degradation by skin fibroblasts is stimulated by insulin. Both of these studies suggest that insulin can influence clearance of LDL by peripheral cells *in vitro*, and a similar effect is assumed for the liver. It is generally expected that an increase in the number of LDL receptors results in an increased fractional catabolic rate for LDL *in vivo* (35). However, a decrease in the transport rate of LDL also may reflect increased clearance of precursors of LDL, i.e., VLDL remnants, because these lipoproteins are ligands of higher affinity for the receptor than LDL (36). Thus, our kinetic data do not exclude the possibility that insulin increases the number of LDL receptors in the liver because the transport rate of LDL decreased during insulin therapy. Further work is necessary to determine the effect of insulin on the metabolism of VLDL remnants and IDL.

The levels of plasma TG and cholesterol were lowered by intensive therapy. The levels of LDL-cholesterol decreased, whereas levels of HDL-cholesterol increased. This effect may re-

duce risk for coronary heart disease, but the levels of VLDL-cholesterol were not reduced by therapy. Fielding et al. (37) recently showed the presence of an abnormal lipoprotein fraction in plasma from type I and type II diabetic patients. They suggested that the abnormal lipoprotein reflects an abnormal cholesterol transport in these patients.

In conclusion, we have shown that intensive insulin therapy of normolipidemic type I diabetic patients results in decreased production of LDL without any apparent change in clearance of the lipoproteins. The data in this and previous studies strongly suggest that the lipid-lowering effect of intensive therapy results from reduction in the production of lipoproteins containing apoB (10–12,19). This effect of insulin may be beneficial in reducing the risk of atherosclerosis in these patients.

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