Intraperitoneal Insulin Therapy Corrects Abnormalities in Cholesteryl Ester Transfer and Lipoprotein Lipase Activities in Insulin-Dependent Diabetes Mellitus

John D. Bagdade, Frederick L. Dunn, Robert H. Eckel, Mary C. Ritter

Abstract Patients with insulin-dependent diabetes mellitus (IDDM) have proatherogenic disturbances in cholesteryl ester transfer (CET) despite intensive subcutaneous insulin therapy (ISC). Since CET is activated by insulin-sensitive lipoprotein lipase (LPL), which normally increases postprandially, we queried whether iatrogenic hyperinsulinemia from ISC stimulated CET and LPL by studying well-controlled IDDM patients after ISC and then 6 months after lowering systemic insulin levels by intraperitoneal (IP) insulin delivery. Although glycemic control (HbA1c IDDM, 6.9±1.7%; control, 4.5% to 8%) was excellent during ISC, CET was accelerated (P<.001) and both systemic insulin levels and LPL specific activity were increased (P<.05). Following IP, basal systemic insulin levels declined by more than one half (ISC, 8.2±6.5 versus IP, 2.77±2.4 μU/mL; mean±SD; P<.025), and both LPL and CET activities returned to normal. Plasma triglyceride, cholesterol, high-density lipoprotein-2 (HDL2) cholesterol, HDL3 cholesterol, cholesteryl ester transfer protein mass, and glycemic control (HbA1c, 6.3±0.8%) were unchanged and remained normal. These findings indicate that ISC is associated with high levels of basal CET and LPL. These alterations both appear to be closely linked to iatrogenic hyperinsulinemia resulting from ISC. The fact that they are both reversed when systemic insulin levels are reduced by IP suggests that insulin, acting through LPL, influences the nature of the interaction of the lipoproteins engaged in CET. Since accelerated CET is believed to result in the enrichment of certain subpopulations of apolipoprotein B-containing lipoproteins with cholesteryl ester, an alteration presumed to enhance their atherogenicity, its correction by IP therapy suggests that this more physiological mode of insulin delivery may reduce cardiovascular risk in IDDM. (Arterioscler Thromb. 1994;14:1933-1939.)

Key Words • cholesteryl ester transfer • lipoprotein lipase • hyperinsulinism • intraperitoneal insulin delivery • insulin-dependent diabetes mellitus

A ssiduous diabetic management can reduce the prevalence of the renal and retinal microvascular and neuropathic complications of insulin-dependent diabetes mellitus (IDDM)1,2 but not the premature morbidity and mortality attributable to cardiovascular disease. The failure of rigorous glycemic control achieved with multiple daily injections of insulin to slow the development of diabetic macrovascular disease has led to the suspicion that the hyperinsulinemia that inevitably results from insulin therapy might actually promote atherosclerosis.3 Since plasma triglyceride, cholesterol, and high-density lipoprotein cholesterol (HDL-C) are usually normal in treated IDDM patients,4 lipoproteins have been believed to not pose a significant cardiovascular risk in IDDM. A variety of modifications in the composition of the major plasma lipoproteins, such as the glycation of apoproteins, which is inapparent in the routinely measured lipids, are present in IDDM patients5 and could, however, alter their normal metabolism and enhance their atherogenicity in the absence of hyperlipidemia.6,7 When the apolipoprotein (apo) B moiety of low-density lipoprotein (LDL) is chemically modified by glycation, for example, its uptake by arterial wall macrophages is enhanced, and the formation of foam cells is promoted.8 Changes in the free (unesterified) cholesterol content of HDL subpopulations in IDDM9,10 and non-IDDM (NIDDM)11 patients may alter their capacity to promote cholesterol efflux from cells12 and adversely affect their participation in reverse cholesterol transport, while a relative increase in very-low-density lipoprotein (VLDL) free cholesterol has been shown in vitro to enhance its interaction with cholesteryl ester (CE) transfer protein (CETP).13 The VLDL + LDL fraction from well-controlled normolipidemic IDDM patients is relatively enriched in free cholesterol,14 and its capacity to promote CE transfer (CET) in the presence of CETP was markedly increased.15 Because increased CETP activity may promote atherogenesis,16 this abnormality could represent another mechanism that accelerates the development of macrovascular tissue in IDDM.

The fact that during the postprandial state CET in normal subjects is maximal and synchronous with that of the insulin-sensitive enzyme lipoprotein lipase (LPL)17,18 and that in vitro exposure of VLDL to LPL enhances its capacity to participate in CET19 implies that the actions of these two proteins are related and possibly influenced by postprandial increases in...
insulin levels. These observations in nondiabetics suggest that the sustained nonphysiological elevation of insulin levels associated with subcutaneous insulin therapy might simulate the effects of postprandial hyperinsulinaemia and in the basal state activate LPL and CET in IDDM. If this were true, then the basal activities of LPL and CET should both be increased in IDDM patients receiving conventional insulin treatment and normalized when systemic insulin levels are reduced. To test this hypothesis, we studied CET and LPL serially in the same IDDM patients following a period of conventional management with intensive ISC and again 6 months after their insulin levels had been lowered with intraperitoneal (IP) insulin therapy.

Methods

Human Subjects

The 11 subjects (6 men and 5 women) with clinically stable IDDM (age, 38.5±7.9 years; range, 25 to 48 years; duration, 13.6±2.5 years [mean±SEM]; range, 2 to 21 years) were recruited to Duke University Medical Center for potential participation in a study of long-term insulin treatment with a permanently implanted insulin pump. All had a history of ketoadiposis and required insulin treatment for its prevention but were otherwise healthy. The triglyceride and cholesterol levels of all participants were within the 75th percentile for their age according to Lipid Research Clinic standards.\(^\text{20}\) None had evidence of renal insufficiency or proteinuria (150 mg/24 h), were taking drugs known to affect lipid metabolism, or were vegetarians, cigarette smokers, or athletes. The study protocol was approved by the Duke University Medical Center Human Investigation Committee and explained to all subjects. Informed consent was obtained, and the study was performed according to the principles of the Declaration of Helsinki.

Study Design

After their entry into the study, the participants' diabetic control was intensified with conventional ISC treatment for 3 months to achieve and maintain glycemic levels as near normal as possible without significant hypoglycemia. Treatment was individualized and in general took the form of injections of short-acting (regular) insulin before each meal combined with longer acting insulin to achieve fasting and preprandial blood glucose levels of 70 to 120 mg/dL and postprandial (90 to 120 mg/dL) h, were taking drugs known to affect lipid metabolism, or were vegetarians, cigarette smokers, or athletes. The study protocol was approved by the Duke University Medical Center Human Investigation Committee and explained to all subjects. Informed consent was obtained, and the study was performed according to the principles of the Declaration of Helsinki.

Assays to estimate both the mass and isotopic transfer of CE in incubated plasma systems were employed. The mass transfer of CE in intact plasma from native HDL to the apoB-containing lipoproteins was measured during incubation at 37°C in a metabolic shaker in the presence of 1.5 mmol/L dithio-bis(2-nitrobenzoic acid) to inhibit plasma lecithin:cholesterol acyltransferase (LCAT).\(^\text{26}\) Aliquots of plasma were removed prior to and after 1, 2, 4, and 6 hours of incubation and chilled on ice, and VLDL+LDL was precipitated with 0.1 vol heparin/MnCl\(_2\) (final concentration: MnCl\(_2\), 0.092 mol/L; heparin, 1.3 mg/mL).\(^\text{27}\) At each sampling interval, the mass of free and total cholesterol present in the supernatant was measured, and the amount of CE transferred into the apoB-containing lipoproteins was calculated from the difference between the two values. The mass of CE transferred at each time interval was determined by subtracting this value from zero-time CE in HDL.

In the isotopic assay, an aliquot of HDL (d=1.063 to 1.21 g/mL) from a control subject that was radiolabeled in the 1, 2, 6, and 7 positions of the sterol ring with [\(^{1}\)H]cholesteryl oleate/CE (7.5 μg cholesterol and 10,000 cpm CE radioactivity) and incubated with plasma from each subject for 1 hour as described by Quig and Zilverstreelt.\(^\text{28}\) The transfer of CE radioactivity was calculated at 15-minute intervals from the amount of radioactivity in VLDL+LDL after precipitation with heparin/MnCl\(_2\) and was expressed as a percent of the added HDL:CE counts. CETP was measured by radioimmunoassay.\(^\text{17}\)

Analyses

Venous blood samples were collected after an overnight fast in Na-EDTA-containing tubes, and plasma was separated promptly at 4°C by low-speed centrifugation.

Plasma glucose was measured with a glucose oxidase method. HbA\(_1c\) (reference range, 3.9% to 6.4%) was assayed with a liquid chromatographic method.\(^\text{22}\) Free insulin was separated from antibody-bound insulin by precipitation with polyethylene glycol,\(^\text{23}\) and the unbound free insulin was then measured with a charcoal-dextran assay.\(^\text{24}\) Cholesterol (Boehringer Mannheim) and triglycerides (Sigma) were measured enzymatically in whole plasma and in the lipoprotein fractions with kits. For the CET assay, free cholesterol was quantified with a kit in which cholesterol esterase hydrolysed CE. CE was calculated from the difference between total and free cholesterol. The fatty acid composition of lysolecithin in plasma was assayed from an aliquot of a total lipid extract of plasma from which lysolecithin was separated from other lipids by thin-layer chromatography. The lysolecithin spot was eluted from the plate, and fatty acid methyl esters were prepared with boron trifluoride in methanol (Supelco).\(^\text{25}\) Analysis was performed on a gas-liquid chromatograph equipped with a capillary column and flame ionization detector. The fatty acid methyl esters were identified with the use of standards run under the same conditions, and the percentage composition was then determined.\(^\text{25}\)

CET

Assays to estimate both the mass and isotopic transfer of CE in incubated plasma systems were employed. The mass transfer of CE in intact plasma from native HDL to the apoB-containing lipoproteins was measured during incubation at 37°C in a metabolic shaker in the presence of 1.5 mmol/L dithio-bis(2-nitrobenzoic acid) to inhibit plasma lecithin:cholesterol acyltransferase (LCAT).\(^\text{26}\) Aliquots of plasma were removed prior to and after 1, 2, 4, and 6 hours of incubation and chilled on ice, and VLDL+LDL was precipitated with 0.1 vol heparin/MnCl\(_2\) (final concentration: MnCl\(_2\), 0.092 mol/L; heparin, 1.3 mg/mL).\(^\text{27}\) At each sampling interval, the mass of free and total cholesterol present in the supernatant was measured, and the amount of CE transferred into the apoB-containing lipoproteins was calculated from the difference between the two values. The mass of CE transferred at each time interval was determined by subtracting this value from zero-time CE in HDL.

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Assay of Lipolytic Enzymes

Fasting lipolytic activities derived separately from hepatic triglyceride lipase (HTGL) and LPL were measured in 10 of the 11 patients after ISC and 6 months after IP as described by Glaser et al.\(^\text{29}\) employing a method in which each activity was eluted from plasma with a heparin-Sepharose column. LPL mass was measured by an enzyme-linked radioimmunoassay.\(^\text{30}\) The reference group values for the LPL-related
TABLE 1. Effects of Intensive Subcutaneous (ISC) and Intraperitoneal (IP) Insulin Delivery on Parameters of Glycemic Control

<table>
<thead>
<tr>
<th></th>
<th>ISC</th>
<th>IP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight, kg</td>
<td>70.6±10.5</td>
<td>68.1±13.1</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>7.0±1.7</td>
<td>6.18±0.70</td>
</tr>
<tr>
<td>24-h Glucose, mg/dL*</td>
<td>163±63</td>
<td>147±68</td>
</tr>
<tr>
<td>Insulin dose, U/24 h</td>
<td>42.6±17.1</td>
<td>47.4±21.0</td>
</tr>
<tr>
<td>24-h Insulin, µU/mL†</td>
<td>12.68±10.7</td>
<td>7.37±1.3</td>
</tr>
<tr>
<td>Fasting insulin, µU/mL†</td>
<td>8.22±6.5</td>
<td>2.77±2.4†</td>
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</tbody>
</table>

Values are mean±SD.  
* To convert values for glucose to millimoles per liter, multiply by 0.05551.  
† To convert values for insulin to picoconcentrations per liter, multiply by 6.00.  
P<.025.

measurements were obtained from 18 healthy young adults (8 women and 10 men).

Statistical Methods

A paired t test and sign tests were used for comparison of the ISC and IP responses. Pearson correlations were obtained to determine linear relations between the variables examined.

Results

HbA1c, 24-hour integrated glucose measurements, and the mean daily insulin dose for the group did not change significantly during the two insulin treatment regimens, although there was a trend toward higher insulin requirements during IP (Table 1). While the change in body weight after IP treatment was not statistically significant, a good deal of variation was present, with four patients gaining (range, 0.5 to 4.4 kg) and six losing (range, -1.6 to -5.7 kg) weight. Despite these directional differences in weight and in the trend toward larger amounts of insulin received, both fasting and integrated 24-hour systemic free insulin concentrations fell after 6 months of IP therapy (fasting ISC, 8.22±6.5 versus IP, 2.77±2.4 µU/mL, P<.025; 24-hour ISC, 12.68±10.7 versus IP, 7.37±1.3, P<.1; mean±SD). Fasting and 24-hour systemic insulin were weakly correlated after ISC (r=.68, P<.09), and this relation was much stronger after IP (r=.92, P<.004). Plasma lipid levels (triglycerides, total cholesterol, LDL-C, HDL₂-C, HDL₃-C) were all within the range of normal following ISC management and were not significantly changed after IP (Table 2).

CET

During ISC, CET estimated by both mass and isotopic assays was significantly increased (P<.001) in IDDM compared with control subjects (Figs 1 and 2). After 6 months of IP insulin delivery, however, the mass of CE transferred to VLDL+LDL decreased markedly (P<.001) to normal levels in all subjects; the rate of transfer of radiolabeled CE also declined uniformly in a similar manner (ISC, k=0.253±0.09%/versus IP, 0.110±0.04%/counts transferred/min; P<.001; Fig 3). To demonstrate that these differing effects of ISC and IP on CET were attributable to changes in insulin concentration and not due to a time effect, CET was studied in 4 patients treated first with IP for 7 months and then after 3 months of ISC (Fig 3). As observed with the 6 other patients treated first with ISC and then IP, these subjects showed normal CET after IP and an accelerated profile after ISC.

During ISC, the mass of CETP in plasma was somewhat higher in IDDM than in control subjects (IDDM subjects, 2.19±1.08 versus control subjects, 1.46±0.42 µg/mL; P<.1); CETP mass was unchanged by IP treatment (2.14±0.95 µg/mL; P<.01). CETP mass was increased by IP treatment (2.14±0.95 µg/mL; P<.01). The magnitude of the decrease in basal IRI (fasting insulin) that occurred after IP therapy, however, correlated with the declines observed in the mass of CE transferred at 1 hour (r=.75, P<.05) and in isotopic transfer (r=.68, P<.09).

TABLE 2. Effects of Intensive Subcutaneous (ISC) and Intraperitoneal (IP) Insulin Delivery on Plasma Lipid and Lipoprotein Concentrations

<table>
<thead>
<tr>
<th></th>
<th>ISC</th>
<th>IP</th>
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</thead>
<tbody>
<tr>
<td>Cholesterol</td>
<td>156±28</td>
<td>154±15</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>79±30</td>
<td>87±48</td>
</tr>
<tr>
<td>LDL-C</td>
<td>89±24</td>
<td>85±22</td>
</tr>
<tr>
<td>HDL₂-C</td>
<td>4.7±2.1</td>
<td>6.1±4.5</td>
</tr>
<tr>
<td>HDL₃-C</td>
<td>51.8±13.9</td>
<td>54.7±14.2</td>
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LDL-C indicates low-density lipoprotein cholesterol; HDL₂-C, high-density lipoprotein cholesterol; and HDL₃-C, HDL₃ cholesterol. Values are mean±SD and are expressed in milligrams per deciliter. To convert values for cholesterol to millimoles per liter, multiply by 0.02586. To convert values for triglycerides to millimoles per liter, multiply by 0.11219.
**Discussion**

Treating IDDM patients with multiple daily subcutaneous injections of insulin results in excellent glycemic control and reduced levels of plasma cholesterol and triglycerides. That virtually the same HbA1c and integrated 24-hour blood glucose levels observed after ISC were maintained with the same total dose of insulin given by IP delivery despite a substantial reduction in circulating insulin levels is consistent with the occurrence of normal hepatic extraction of insulin.

Conventional subcutaneous insulin delivery is a non-physiological means of attaining glycemic control because the normal gradient between portal and peripheral insulin concentrations is lost when insulin is injected into peripheral tissues. Therefore, one consequence of attaining sufficiently high intrahepatic insulin levels to control hepatic glucose production when insulin is administered at conventional injection sites is that peripheral tissues are exposed to concentrations of insulin that are increased to supraphysiological levels. Even though the total insulin dose administered was very similar during ISC and IP treatment, basal and 24-hour integrated systemic insulin levels were substantially lower during IP therapy, indicating that hepatic extraction of insulin occurred.

Since the demonstration by Stout et al. that insulin is a mitogen for cultured cells, concern has grown that iatrogenic hyperinsulinemia in insulin-treated diabetic patients may contribute to the development of macrovascular disease. Insulin's capacity to promote cellular cholesterol accumulation by upregulating the activity of apoB,E LDL receptor and downregulating that of the putative HDL receptor could be amplified in the presence of sustained in vivo elevation of systemic insulin levels in IDDM patients. The fact that hyperinsulinemia is ameliorated by IP insulin delivery in which boluses of insulin are given into the portal circulation during the periprandial period suggests that this therapy may reduce these and other potentially deleterious cardiovascular effects of peripheral hyperinsulinemia.

The earlier demonstration that abnormalities in lipoprotein composition persist after rigorous conventional insulin treatment in both IDDM and NIDDM patients has implied that they may result more from the high insulin levels associated with subcutaneous therapy than from the diabetic state itself. Reports showing that VLDL was enriched in CE and HDL in triglyceride in plasma obtained after an overnight fast from insulin-treated diabetic patients has suggested that the activity of their neutral lipid transfer protein (ie, CETP), which

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**Table 3. Effects of Intensive Subcutaneous (ISC) and Intraperitoneal (IP) Insulin Delivery on Basal Lipoprotein Lipase Activity**

<table>
<thead>
<tr>
<th></th>
<th>ISC</th>
<th>IP</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total, mEq · mL⁻¹ · h⁻¹</td>
<td>37.1±13.1</td>
<td>27.2±6.9</td>
<td>34.6±1.4</td>
</tr>
<tr>
<td>Hepatic lipase, mEq · mL⁻¹ · h⁻¹</td>
<td>15.6±8.9</td>
<td>18.1±7.0</td>
<td>20.9±0.8</td>
</tr>
<tr>
<td>Lipoprotein lipase, mEq · mL⁻¹ · h⁻¹</td>
<td>22.5±12.7</td>
<td>9.1±4.1*</td>
<td>13.7±1.0</td>
</tr>
<tr>
<td>Lipoprotein lipase, mass ng/mL</td>
<td>22.9±9.7</td>
<td>23.4±8.4</td>
<td>21.2±12.3</td>
</tr>
<tr>
<td>Specific activity, nEq · FFA⁻¹ · ng⁻¹ · h⁻¹</td>
<td>1.08±0.60</td>
<td>0.46±0.15*</td>
<td>0.64±0.6</td>
</tr>
</tbody>
</table>

FFA indicates free fatty acid. Values are mean±SD.

* * P < .025.
TABLE 4. Plasma Lysolecithin Molecular Species

<table>
<thead>
<tr>
<th></th>
<th>IDDM&lt;sub&gt;sc&lt;/sub&gt;</th>
<th>IDDM&lt;sub&gt;p&lt;/sub&gt;</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ratio, 18:2/16:0</td>
<td>0.63±0.11&lt;sup&gt;*&lt;/sup&gt;</td>
<td>0.35±0.81</td>
<td>0.41±0.09</td>
</tr>
</tbody>
</table>

<sup>*</sup> P<.001 IDDM<sub>sc</sub> vs control.

<sup>†</sup> P<.001 IDDM<sub>sc</sub> vs IDDM<sub>p</sub>.

normally mediates the redistribution of core lipids postprandially, may be inappropriately increased in the basal state. CET may have particular relevance to the accelerated development of macrovascular complications in diabetes because evidence is accumulating that suggests that CET may promote atherosclerosis. First, animals such as the rabbit and humans that are susceptible to dietary-induced atherosclerosis have very active CET, and those species such as the rat, dog, and pig that are resistant have very little. Moreover, clinical disorders in which atherosclerosis is accelerated such as dyslipidemia, hypertriglyceridemia, hypercholesterolemia, and both IDDM and NIDDM are all associated with increases in CET. Conversely, subjects who are deficient in CETP and lack CET and who have extended life expectancies and very high HDL have been described in Japan.

The mass transfer of CE in control subjects is nonlinear, a phenomenon that Van Tol et al. have shown is due to the early net mass movement of CE from LDL to HDL. Since IDDM LDL also is capable of transferring CE to HDL, the sharp increase we find in the net movement of CE from IDDM HDL indicates that the amount of CE transferred to VLDL far exceeds the mass of CE moving to HDL from LDL. Here, in addition, we find that the isotopic transfer of labeled CE from an exogenous HDL source to VLDL+LDL is abnormally increased when added to intact IDDM plasma and that CET estimated by both techniques is normalized when insulin is administered by the intraperitoneal route.

While the results of our studies do not identify the precise mechanism(s) responsible for the stimulation of CET in conventionally treated IDDM patients nor how IP insulin delivery reverses this disturbance, our data strongly suggest that these events are closely linked to the effects of changes in circulating insulin concentrations on the insulin-sensitive enzyme LPL. Nikkila et al. were the first to draw attention to the relation between insulin and LPL when they observed that well-treated IDDM patients had high LPL values and that the lipolytic activity in plasma after heparin, an indirect means of estimating LPL, correlated with fasting insulin levels. Sammett and Tall later established a link between CET and LPL when they showed that in vitro exposure of VLDL to LPL enhanced CET activity. The fact that there is a high level of CETP mRNA in tissues containing LPL implies that CETP not only may participate in the local distribution of cholesterol during the postprandial state but also that CETP and LPL may share certain regulatory influences.

Because the capacity of the endocrine pancreas to normally secrete insulin in a pulsatile manner in the postprandial state and return insulin to low basal levels is lost in IDDM, it is not surprising that the present study suggests that in conventionally treated IDDM patients with chronic hyperinsulinemia that LPL is tonically stimulated and CET is activated in vivo. It is also possible that systemic hyperinsulinemia associated with ISC may increase the activity of LPL in plasma by reducing its metabolic clearance rate.

LPL and CETP have phospholipase actions, but their positional specificities for lecithin differ. As a result, they form distinctive molecular species of lysolecithin that can then be used as indexes of their respective activities. When CETP, eg, acts on the sn-2 position of lecithin, which is occupied by an unsaturated fatty acid, the lysolecithins that are formed are saturated because the fatty acid remaining at the sn-1 position is usually saturated. In contrast, the lipases that hydrolyze fatty acids at the sn-1 position produce unsaturated lysolecithins. Therefore, when the activity of LPL is increased, as we found in the IDDM subjects after ISC treatment, the proportion of unsaturated (18:2) to saturated (16:0) lysolecithins in their plasma would be expected to increase. That we observed the predicted increase in the 18:2/16:0 ratio when their basal LPL activity was elevated and a reduction to normal when LPL declined after IP insulin delivery is indirect evidence supporting the directional changes in LPL activity we observed in vitro.

If hyperinsulinemia underlies the observed abnormalities in LPL and CETP in IDDM patients, then one would predict they would be reversed if insulin levels could be lowered toward normal. Fortunately, devices are now available that deliver insulin into the intraperitoneal space and portal circulation in a pulsatile manner and reestablish a hepatic first-pass effect. When this type of technology was applied and both fasting and 24-hour free insulin levels were lowered, we did in fact observe a decline in the absolute and specific activity of LPL. In addition, we found a trend toward increases in HTGL during IP treatment, suggesting that IP insulin delivery may have stimulated the activity of hepatic lipase as Ruotolo et al. have reported in similarly treated IDDM patients. It is also possible that IP insulin increased the metabolic clearance rate of LPL. In concert with these observations, Kasumi et al. have shown directional changes in insulin similar to those observed in the present study in streptozocin-induced diabetic rats treated with IP or subcutaneous insulin.

Our findings support the hypothesis that insulin may regulate CET through its capacity to modulate the activity of LPL and the composition of the lipoproteins that interact with CETP. It is noteworthy that CET, systemic insulin levels, and LPL activities all fell to normal with no significant change in either CETP or LPL mass, plasma lipid concentrations, or glycemic control. IP insulin treatment may have reduced LPL specific activity either by altering its affinity for its substrates, reducing the pool size of predominantly active LPL molecules, or by modifying the apolipoprotein cofactors that are known to modulate the activity of LPL. The decrease observed in CET could result from a reduction in the free cholesterol content of lipoproteins, which has been shown to be a major regulator of CET, or an increase in the activity of a CETP inhibitory protein. Further studies are required to assess these possibilities. Preliminary observations showing that the same abnormalities in CET and lipoprotein...
core lipids in IDDM patients\textsuperscript{14,15}, persist following successful treatment of diabetes,\textsuperscript{5,16} when the patients are no longer diabetic but continue to be hyperinsulinemic,\textsuperscript{5,9} are consistent with the present findings.

In summary, we have addressed the question of whether a pathophysiological link exists between iatrogenic hyperinsulinism and accelerated CETP in IDDM patients. Our findings show that this abnormality in CETP is closely related to the inappropriate activation of LPL in the nonfasting state resulting from sustained hyperinsulinemia in patients receiving conventional subcutaneous insulin treatment. The fact that these disturbances are reversed when insulin levels are lowered during IP therapy suggests that this more physiological route of insulin administration may attenuate a proatherogenic step in lipoprotein transport in plasma and thereby reduce the risk of macrovascular complications in IDDM.

Acknowledgments

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