# Differing Effects of Pancreas-Kidney Transplantation With Systemic Versus Portal Venous Drainage on Cholesteryl Ester Transfer in IDDM Subjects

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**OBJECTIVE** — Cholesteryl ester transfer (CET) is accelerated in patients with IDDM treated with conventional (subcutaneous) insulin therapy (CIT) and a number of other disorders associated with premature cardiovascular disease. We have shown that in IDDM this disturbance is closely linked to iatrogenic hyperinsulinemia (HI), because it was reversed when insulin was administered by the intraportal (IP) route. In this study, we sought to determine whether HI after successful pancreas-kidney transplantation (PKT) has the same adverse effect on CET.

**RESEARCH DESIGN AND METHODS** — CET was measured by both mass and isotopic assays and compared in two groups of euglycemic non-insulin-requiring IDDM PKT patients with either systemically draining allografts and persistent HI or grafts with portal vein anastomoses that were normoinsulinemic (PK-P). A third group of eight nondiabetic kidney transplant (KT) patients receiving the same immunosuppressive drugs served as control subjects.

**RESULTS** — CET in pancreas-kidney transplantation subjects with systemic venous drainage (PK-S) was increased ($P < 0.001$) to the same level we have reported previously in IDDM patients receiving CIT and was significantly higher ($P < 0.001$) than in those subjects with PK-P. CET in the PK-P group did not differ from that of the KT control patients.

**CONCLUSIONS** — CET is affected by variations in systemic insulin levels in pancreas transplant patients with allografts that have differing venous drainage. Because high systemic insulin levels are linked to the activation of CET, euglycemic HI IDDM pancreas allograft recipients may continue to be at high risk for macrovascular complications.

The transfer of cholesteryl ester (CET) from HDL to the apoB-containing lipoproteins is a step in reverse cholesterol transport, which is mediated by a specific transfer protein (CETP). Normally, CET is maximal during the postprandial state when systemic insulin levels are increased and closely linked temporally to the activity of the insulin-sensitive delipidating enzyme lipoprotein lipase (LpL) (1). Because CET enriches VLDL and LDL with cholesteryl ester (CE) so they resemble lipoproteins from atherosclerosis-prone cholesterol-fed animals (2), it is generally believed that increased CET in the basal state promotes atherogenesis (3). Indeed, those disorders in which CET has been shown to be elevated in fasting plasma such as IDDM (4,5), NIDDM (6,7), dyslipidemia (8), hypercholesterolemia (9), and hypertriglyceridemia (10) are all associated with the accelerated development of cardiovascular disease.

Recently, we have reported that increased CET in conventionally treated IDDM subjects is related to systemic hyperinsulinemia and an unphysiological elevation in the basal activity of LpL (11), and these disturbances were both fully corrected when systemic insulin levels were lowered by treatment with intraperitoneal insulin delivery. These findings suggested that iatrogenic hyperinsulinemia (HI) resulting from subcutaneous insulin therapy (CIT) may simulate the postprandial state by activating LpL and CET. If this were true, one would predict that CET would be increased in other conditions in which HI is sustained.

Diem et al. (12) and Gaber and colleagues (13) have demonstrated that IDDM patients who had undergone successful pancreas transplantation with systemically draining allografts had both basal and stimulated HI, and those whose allografts had portal venous drainage had normal insulin levels. Additionally, this latter group has reported that transplant patients with portal drainage have fewer postoperative complications and a lower incidence of hypertension (14). These findings imply that elevated CET may persist in successfully transplanted IDDM patients if their pancreas grafts drain systemically. To determine whether this was the case and whether differences in systemic insulin levels related to the allograft site predicted the magnitude of CET, we performed the following studies.

## RESEARCH DESIGN AND METHODS

### Subjects

Three groups of transplant patients were studied: one IDDM group (nine men; four

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CET, cholesteryl ester transfer; CETP, cholesteryl ester transfer protein; CIT, conventional insulin therapy; HI, hyperinsulinemia; IP, intraportal; K, nondiabetic kidney control group; KT, kidney transplant; LCAT, lecithin:cholesterol acyltransferase; LpL, lipoprotein lipase; PK-P, pancreas-kidney transplantation with portal venous drainage; PK-S, pancreas-kidney transplantation with systemic venous drainage; PKT, pancreas-kidney transplantation.

women) from the University of Chicago who underwent combined pancreas-kidney transplantation (PKT) with systemic venous drainage (PK-S) (pelvic placement of the pancreas allograft with anastomosis of the pancreatic vein to the iliac vein); a second IDDM group (four men; eight women) from the University of Tennessee who underwent transplantation with portal venous drainage (PK-P) (abdominal placement of the pancreas allograft with anastomosis of the pancreatic vein to the portal vein); and a third group of nondiabetic subjects (four men; four women) from the University of Chicago who underwent kidney transplantation (KT) only.

All subjects in each group were euglycemic, had normally functioning renal allografts, and none were taking insulin or oral hypoglycemic agents. The majority received immunosuppression treatment with three drugs: prednisone, azathioprine, and cyclosporine. No participant had a history of hyperlipidemia, took medications other than immunosuppressive agents that affected lipid metabolism, drank more than 3 oz of alcohol daily, or had liver disease. Informed consent was obtained, and the experimental protocol was approved by human investigation at each institution.

**Table 1—*Clinical features of groups of transplant patients***

| | PK-S | PK-P | Kidney |
|---|---|---|---|
| Age (years) | 37.2 ± 8.0 | 34.4 ± 10 | 36.6 ± 13.8 |
| Weight (kg) | 75.3 ± 14.4 | 68.1 ± 9.7 | 79.2 ± 23.8 |
| Fasting glucose (mg/dl) | 90 ± 12 | 84 ± 10 | 98 ± 20 |
| Creatinine (mg/dl) | 1.8 ± 0.3 | 1.5 ± 0.4 | 1.6 ± 0.4 |
| Duration post-transplant (months) | 19 ± 15 | 13 ± 9 | 13 ± 11 |
| Immunosuppression (mg/day) | | | |
| Prednisone | 11.4 ± 1.9 | 16.9 ± 9.5 | 12.8 ± 7.0 |
| Azathioprine | 58.3 ± 51.5 | 74.1 ± 32.6 | 122.5 ± 39 |
| Cyclosporine | 316.7 ± 109 | 280 ± 186 | 356.3 ± 156 |
| Triglyceride (mg/dl) | 128.9 ± 54 | 128.7 ± 49 | 133.5 ± 56.5 |
| Cholesterol (mg/dl) | 173.4 ± 43 | 185 ± 39 | 205.8 ± 39 |
| HDL-C (mg/dl) | 35.1 ± 12 | 41.0 ± 10 | 39.5 ± 18 |
| CETP (ug/dl) | 1.97 ± 0.56* | 1.43 ± 0.53 | 2.29 ± 1.2 |

Data are means ± SD.*$P < 0.05$ (PK-S vs. PK-P).

## 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. Cholesterol (Boehringer Mannheim) and triglycerides (Sigma) were measured enzymatically in whole plasma with kits. HDL carbohydrate was determined by a precipitation method using heparin/$MnCl_2$ (15). For the CET assay, free cholesterol was quantified with a kit in which cholesterol ester hydrolase was omitted. CE was calculated from the difference between total and free cholesterol.

## CET

Assays to estimate both the mass and isotopic transfer of CE in incubated plasma systems were used. 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-dinitrobenzoic acid to inhibit plasma lecithin:cholesterol acyltransferase (LCAT) (9). Aliquots of plasma were removed before and after 1, 2, 4, and 6 h of incubation, were 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) (15). 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 the zero-time CE in HDL.

In the isotopic assay, an aliquot of HDL ($d$ – 1.063 – 1.21 g/ml) from a control subject that was radiolabeled in the 1, 2, 6, and 7 positions of the sterol ring with [$^3$H] cholesteryl oleate (0.5 µg cholesterol and ~20,000 cpm CE radioactivity added) and incubated with plasma from each subject for 1 h as described by Quig and Zilversmit (16). The transfer of CE radioactivity was calculated at 15-min intervals from the amount of radioactivity in VLDL+LDL after precipitation of an aliquot of plasma with heparin $MnCl_2$ (15) and was expressed as a percentage of the added HDL-CE counts. CETP was measured by radioimmunoassay (17).

The means for each variable were compared by Student's $t$ test. The $P$ values reported correspond to two-tailed $P$ values obtained by unpaired $t$ tests. $P < 0.05$ was considered statistically significant.

**RESULTS** — The clinical features of each group are displayed in Table 1. The two pancreas transplant groups in general were well matched for each variable except for sex: PK-S was predominantly men and PK-P women. The nondiabetic kidney control group (K) contained an equal number of men and women, but they tended to be somewhat heavier, have higher cholesterol and fasting glucose levels, and receive more azathioprine and cyclosporine. Plasma lipids in the three groups also were similar, although cholesterol levels tended to be somewhat lower in PK-S than in renal transplant subjects.

## CET

Because the sex distribution within the PK-S and PK-P groups differed, the CET responses of men and womens were first compared within each group. Since no between-sex differences were detected in either the PK-S or the PK-P groups (data not shown), their responses were pooled, and between-group comparisons were then performed. The PK-S group with pelvic allografts transferred significantly more CE mass from HDL to VLDL + LDL at 1, 2, and 4 h ($P < 0.001$) than the two other groups (Fig. 1); the PK-S CET profile of accelerated transfer closely resembled the one we have previously reported in IDDM (4). In contrast, the CET response of the PK-P group with portal anastomoses was significantly lower than that of the PK-S pelvic group and resembled that of the renal subjects and healthy nondiabetic subjects (4).

A similar distribution of responses was observed with the isotopic assay (Fig. 2). Here, the PK-S pelvic group showed the most rapid movement of labeled CE from HDL to VLDL + LDL. The rate of loss from the HDL CE label in the PK-P portal group again was significantly lower than

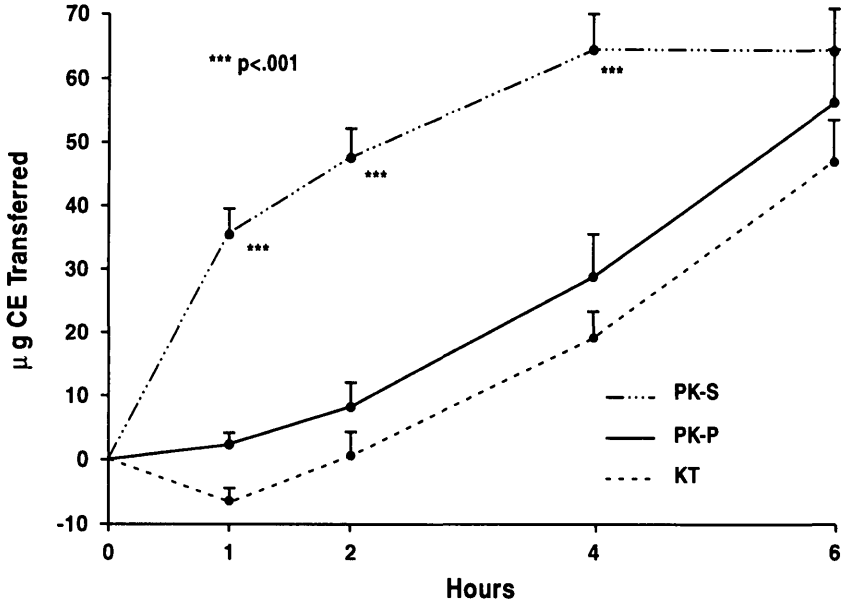


**Figure 1**—*Line graph showing mass of CE in plasma transferred from HDL to the apoB-containing lipoproteins in pancreas transplant patients with pelvic (PK-S;* n = *13) and portal (PK-P;* n = *12) drainage and eight patients who have undergone KT only during incubation of 37°C for 6 h.*

that of the PK-S patients ($P < 0.05$) and approximated that of the nondiabetic renal allograft recipients.

CETP mass was slightly higher ($P < 0.05$) in the PK-S than in the PK-P group (Table 1). The highest CETP concentration was present in the KT group; it did not, however, differ significantly from the PK-S and PK-P groups.

**CONCLUSIONS** — The actions of lipid transfer proteins influence significantly the metabolism and composition of lipoproteins in plasma (18). Studies in humans and experimental animals suggest that the activity of one of these, CETP, a 74-kDa protein with neutral lipid and phospholipid transfer activities (19), is a major determinant of the core lipid composition of lipoproteins and their potential atherogenicity. CET may contribute to atherogenesis in a broad range of metabolic disorders including diabetes by promoting the formation of CE-enriched VLDL and LDL particles that resemble β-VLDL, the cholesterol-rich apoB-containing lipoproteins that appear in the plasma of experimental animals fed large amounts of cholesterol (2). Moreover, if the recognition of CETP-modified particles by hepatic B,E receptors is impaired, they might be more susceptible to further modifications such as oxidation and instead be taken up by arterial wall macrophages.

Species such as the rat and dog that have little CET are resistant to dietary-induced atherosclerosis, whereas the rabbit, which is known to have very high levels of CET activity, is highly susceptible. When mice, an atherosclerosis-resistant species, are made transgenic for simian CETP, they become susceptible (20). In clinical disorders in humans in which atherosclerosis is accelerated, the activity of CETP is increased (21). In the present study, we report for the first time that CET also is elevated in the basal state in PKT recipients with systemically draining grafts, who like other transplant patients experience premature morbidity and mortality from cardiovascular disease (22). Despite the expanding list of incriminating associations between the presence of CETP, levels of its activity, and species differences in susceptibility to atherosclerosis, it is still not uniformly believed that CET is deleterious. Because of its central role in reverse cholesterol transport, some still believe that its purpose may be predominantly beneficial.

Because the lipolytic actions of LpL are required to maximize the physiological activation of CETP (21,23,24), its activity normally peaks postprandially when insulin levels peak. It is well recognized that insulin is a major regulator of LpL (25); hence, this delipidation step central to the metabolism of triglyceride-rich lipoproteins may be impaired in insulinopenic diabetic patients when glycemic control is poor. Conversely, in intensively treated IDDM patients who are well insulinized and in excellent control, LpL activity in plasma measured both in the basal state (11) and after heparin (26) may be elevated.

Based on the close physiological and functional relationship among insulin,

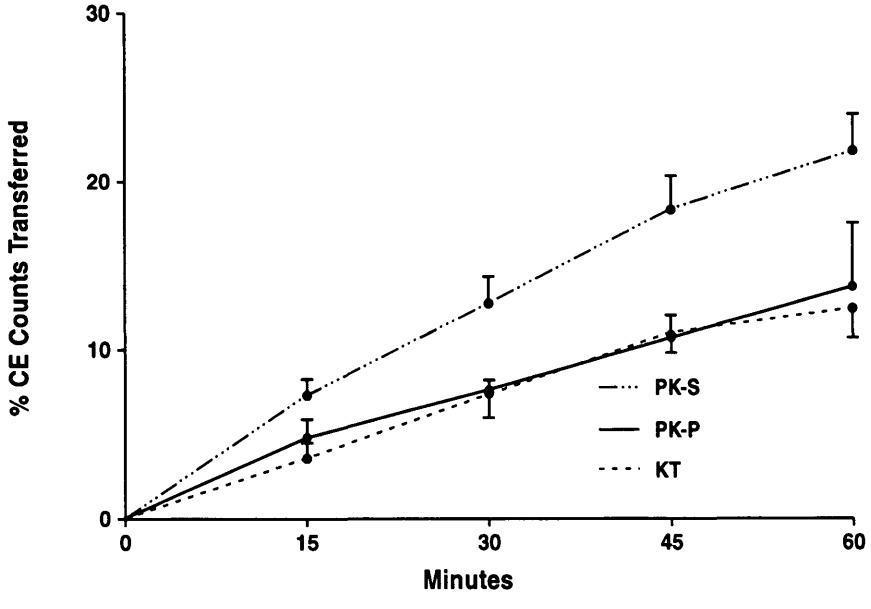


**Figure 2**—*Line graph showing transfer of labeled [³H] cholesteryl oleate from HDL to the apoB-containing lipoproteins in pancreas transplant patients with pelvic (PK-S;* n = *13) and portal (PK-P;* n = *12) drainage and eight patients who have undergone KT only, during incubation at 37°C for 1 h.*

LpL, and CETP, it is not surprising that systemic insulin levels affect CETP activity. We have recently shown that HI in conventionally treated IDDM subjects stimulates LpL and activates CET inappropriately in the basal (unfed) state (11). Moreover, these changes were fully reversed when systemic insulin levels were reduced by delivering insulin from implanted pumps into the portal circulation. These same associations may continue to be important in IDDM patients who have undergone successful pancreas transplantation, because their systemic insulin levels may differ considerably depending on the anatomic location of the allograft.

When grafts are placed in the pelvis and drain systemically into the iliac vein, for example, insulin levels are persistently elevated (12). On the other hand, with intra-abdominal grafts that drain into the portal circulation, both basal and stimulated insulin levels are normal (12). Consistent with our previous findings in IDDM (11), we show in the present study that even in the absence of clinical diabetes, systemic insulin levels in pancreas allograft recipients influence CET responses. Although insulin and LpL were not assessed here, others have shown that insulin levels (12,27) and LpL activity (28) are both increased in PKT patients. Therefore, the profile of alterations we find in CET in PK-S and PK-P patients here is likely to be attributable to the effects of differing systemic insulin levels on LpL activity. It is also possible, however, that qualitative changes in the plasma lipoproteins that result from HI rather than lipase-related changes alone affected the increase we found in CET. For example, alterations in the free cholesterol (29) and phospholipid content may have increased the affinity of lipoproteins in the PKT patients with systemically draining grafts for CETP. Additionally, insulin levels may also influence the activity of the CETP-inhibitory protein (30). Further studies are required to assess these possibilities.

It is of interest that we find no correlation between either the net mass or isotopic transfer of CE and the mass of CETP. Indeed, the renal transplant control group with the lowest CET responses had the highest CETP concentrations. One explanation for this observation is that CET is a substrate-driven reaction (10) and that the concentration of CETP in the plasma of normolipidemic subjects is not rate limiting. Another possibility relates to the fact that CE is also transferred within the apoB-containing lipoproteins from LDL to VLDL, and this is not estimated with the assay used in the present study. The CETP substrates that have been shown to exert a strong positive influence on the rate of CET are the concentrations of the CE acceptor lipoproteins VLDL (10) and LDL (21). To control for this effect, the transplant recipients in each group in this study were normolipidemic and well matched.

Concern has been expressed that HI resulting from the supraphysiological amount of insulin that must be injected into peripheral tissues to control hepatic glucose production in insulin-requiring diabetic patients may contribute to the development of macrovascular complications (31). Insulin's many potential atherogenic actions include not only its mitogenic effects shown on cultured cells (32), but its capacity to promote cellular cholesterol accumulation by upregulating the activity of the apo B,E LDL receptor (33) and downregulating that of the putative HDL receptor (34). Taken together with previous studies, our results suggest that another potentially atherogenic consequence of iatrogenic HI in PKT recipients, resulting from their heterotopically placed, systemically draining allografts, may be the stimulation of CET and production of atherogenic CE-enriched apoB-containing lipoproteins. It, therefore, seems ironic that patients who are technically nondiabetic and no longer require insulin treatment continue to demonstrate the same potentially adverse effect of HI on cholesterol transport that was present when they received subcutaneous insulin injections.

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