Effects of Pancreas Transplantation on Distribution and Composition of Plasma Lipoproteins

B. Föger, A. Königsrainer, G. Palos, A. Ritsch, G. Tröbinger, H.-J. Menzel, M. Lechleitner, A. Doblinger, P. König, G. Utermann, R. Margreiter, and J.R. Patsch

In type I (insulin-dependent) diabetic patients, peripheral hyperinsulinemia due to subcutaneous insulin treatment is associated with increased high-density lipoprotein (HDL) cholesterol, and also with an altered surface composition of HDL. Pancreas grafts also release insulin into the systemic rather than into the portal venous system, giving rise to pronounced peripheral hyperinsulinemia. We hypothesized that if peripheral hyperinsulinemia is responsible for high HDL cholesterol and/or altered surface composition of HDL in diabetic subjects, similar changes in the lipid profile should be present in pancreas-kidney transplant recipients (PKT-R). Using zonal ultracentrifugation, we isolated HDL_2, HDL_3, very-low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), and low-density lipoprotein (LDL) from fasting plasma of 14 type I diabetic PKT-R, eight nondiabetic kidney transplant recipients (KT-R), and 14 healthy control subjects and determined the level and composition of the above lipoproteins. HDL_2 cholesterol was increased in PKT-R as compared with KT-R and healthy controls (both $P < .05$), whereas HDL_3 cholesterol was unchanged. However, an altered lipoprotein surface composition was evident in PKT-R: HDL_2, HDL_3, and LDL were enriched in unesterified cholesterol ([UC] PKT-R *v* KT-R, $P = .13$, $P < .005$, and $P < .05$, respectively; PKT-R *v* controls, all $P < .005$); HDL_2 was enriched in phospholipids; and LDL was depleted of phospholipid. KT-R, in contrast, showed no changes in lipoprotein surface composition but a substantial triglyceride enrichment of HDL_2 as compared with PKT-R and healthy controls (both $P < .05$). LDL size as determined by gradient gel electrophoresis was increased in PKT-R compared with controls ($P < .005$). The plasma concentration of cholesteryl ester (CE) transfer protein (CETP), involved also in phospholipid transfer, was increased in both transplant groups compared with healthy controls (both $P < .05$). Insulin concentrations in fasting plasma were directly related to CETP levels and to the weight-percentage of UC in HDL_3, and inversely to the weight-percentage of phospholipids in LDL (all $P < .05$). We explain the increase in HDL_2 cholesterol and LDL size in PKT-R by their high lipoprotein lipase (LPL) activity conferring an excellent capacity to clear chylomicron triglycerides. Effective handling of postprandial triglycerides, high HDL_2 cholesterol, and predominance of LDL pattern A, respectively, are established indicators of a low risk of atherosclerosis. However, it is presently unclear what effects the compositional changes on the surface of HDL and LDL may have on cardiovascular risk in clinically stable PKT-R.
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WHEN TYPE I (insulin-dependent) diabetic patients show adequate glycemic control with insulin injections, their plasma lipid levels are considered desirable with respect to atherosclerosis prevention: low-density lipoprotein (LDL) cholesterol is normal, triglycerides are normal or low, and high-density lipoprotein (HDL) cholesterol is high.[1,2] Nevertheless, these patients have a higher risk of atherosclerosis than normal subjects. This apparent paradox has been explained by an increase in nonlipid risk factors or by the presence of lipid risk factors not readily detected by routine lipid measurements,[3] namely altered lipoprotein surface composition.[4-8] The altered lipoprotein surface composition in diabetic patients could be due to elevated glucose levels and/or to the nonphysiological insulin administration. Subcutaneous injection directs insulin into the systemic rather than the portal venous system, and by avoiding insulin extraction during the first liver passage, it causes peripheral hyperinsulinemia.[9]

In the last decade, combined pancreas-kidney transplantation has been established as a treatment modality in type I diabetic patients with chronic renal failure. The procedure eliminates the need for exogenous insulin treatment and affords near-normoglycemia in both the fasting and postprandial state.[10] However, pancreas grafts, implanted heterotopically in the pelvic cavity, secrete insulin into the iliac vein, causing peripheral hyperinsulinemia.[10] Elevated plasma insulin levels upregulate lipoprotein lipase (LPL) activity in adipose tissue. A high activity of LPL, the rate-limiting enzyme for catabolism of triglyceride-rich lipoproteins (TGRLP), keeps postprandial accumulation of triglycerides low.[11] When postprandial lipemia is low, only a limited amount of the cholesteryl esters (CEs) transported with HDL are lost to TGRLP by neutral core lipid transfer during each postprandial phase. These mechanisms explain why the concentration of HDL cholesterol is increased in pancreas-kidney transplant recipients (PKT-R).[12]

We hypothesized that if peripheral hyperinsulinemia is responsible for altered lipoprotein surface composition in diabetic subjects, the same changes should be present in PKT-R. We therefore set out to carefully characterize the level and composition of plasma lipoproteins and to measure the plasma concentration of cholesteryl ester transfer protein (CETP),[13] a glycoprotein catalyzing the facilitated transport of lipoprotein core and surface components, in PKT-R and compare the results with those obtained in nondiabetic kidney transplant recipients (KT-R) to control for immunosuppression, and with results obtained in healthy controls.

From the Departments of Medicine, Surgery, and Medical Biology and Human Genetics, University of Innsbruck, Innsbruck, Austria.

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Address reprint requests to B. Föger, MD, Department of Medicine, University of Innsbruck, Anichstr. 35, A-6020 Innsbruck, Austria.

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SUBJECTS AND METHODS

Subjects

At the Department of Surgery of the University of Innsbruck, simultaneous pancreas-kidney transplantation in type I diabetic patients with end-stage kidney disease has been performed since 1979.[14] In this study, 14 type I diabetic PKT-R, eight nondiabetic KT-R with end-stage kidney disease due to chronic glomerulonephritis, and 14 healthy control subjects were matched for age, body mass index (BMI), and sex. Age and BMI (mean ± SD) were 40.3 ± 7.3 years and 23.7 ± 3.9 kg/m^2 in PKT-R, 46.1 ± 8.8 years and 24.3 ± 3.0 kg/m^2 in KT-R, and 45.4 ± 10.4 years and 23.5 ± 2.9 kg/m^2 in controls, respectively (all $P > .15$). Each study group had 50% women and 50% men. The two transplant groups were also matched for time elapsed since transplantation, for antihypertensive therapy, and for modality and dosage of immunosuppressive therapy. Time elapsed since transplantation was 43 ± 31 months in PKT-R and 54 ± 53 months in KT-R ($P = .57$). The daily dosage of prednisone, azathioprine, and cyclosporine A was 7 ± 3, 71 ± 38, and 255 ± 95 mg in PKT-R, and 9 ± 1, 68 ± 37, and 209 ± 100 mg in KT-R, respectively (all $P > .09$). The dosage of cyclosporine A was adjusted to maintain plasma levels of 150 to 200 ng/mL plasma. All pancreas grafts were implanted in the pelvis with endocrine drainage into the iliac vein. Graft function was intact in all PKT-R. Informed consent was obtained from all subjects.

Eight PKT-R and four KT-R required antihypertensive medication, which included metoprolol in three PKT-R and one KT-R. No other medications affecting lipoprotein metabolism were used in either transplant group. No control subject required drug treatment. The apolipoprotein E phenotype distribution was six E3/3, three E4/3, four E3/2, and one E2/2 in PKT-R; three E3/3, three E4/3, and two E3/2 in KT-R; and nine E3/3, one E4/3, three E3/2, and one E2/2 in controls. All subjects were physically fit. One PKT-R, two KT-R, and three control subjects smoked, and none consumed alcohol regularly. No subject had hepatic disease, thyroid disease, or macroalbuminuria.

Methods

Blood was drawn after an overnight fast from an antecubital vein into vials containing EDTA to produce a final concentration of 1 mg/mL. Two 10-mL aliquots of postabsorptive plasma were subjected to rate zonal ultracentrifugation in a Ti 14 rotor at 42,000 rpm and 15°C (1) for 140 minutes using a linear NaBr gradient in the density range of 1.0 to 1.3 g/mL to separate very-low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), and LDL, and (2) for 22 hours using a discontinuous NaBr gradient in the density range of 1.0 to 1.4 g/mL to separate HDL_2 and HDL_3, respectively.[15] By determining protein, triglycerides, CE, unesterified cholesterol ([UC] Boehringer, Mannheim, Germany), and phospholipids in zonal rotor fractions representing VLDL, IDL, LDL, HDL_2, and HDL_3, the compositions of the respective lipoproteins were obtained. Stokes diameters of the LDL subfraction were determined by electrophoresis under nondenaturing conditions on PAA 2/16 polyacrylamide gradient gels (Pharmacia Biotechnology, Uppsala, Sweden).[16] CETP mass was quantified with an immunoradiometric assay using a polyclonal antibody.[17] Apolipoprotein E phenotypes were determined by isoelectric focusing of delipidated plasma, Western blotting, and immunostaining.[18]

Glucose level was measured by the hexokinase method (Glucose HK, Uni-Kit III; Roche, Basel, Switzerland) and fructosamine by a colorimetric test using nitroblue tetrazolium (normal range, 205 to 285 μmol/L, Fructosamine Test; Roche). For both procedures, a Cobas Mira Autoanalyzer (Roche) was used. Insulin and plasma C-peptide levels were measured by the radioimmunoassay (RIA) procedures, Insulin RIA (normal range, 5 to 20 mU/L; and RIA-coat C-Peptide (normal range, 0.17 to 0.99 nmol/L; Byk-Sangtec Diagnostica, Dietzenbach, Germany), respectively.

Statistical Analysis

The mean ± SD values of the tested parameters were calculated. Variables of the study groups were compared by Student's *t* test for independent samples. Two-tailed tests and a significance level of *P* less than .05 were chosen. Relationships between variables were evaluated by Pearson product-moment correlation coefficients for all subjects combined.

RESULTS

In all three study groups, plasma glucose levels and fructosamine, ie, glycated protein used as a measure of glycemic control over the past 3 weeks, were normal (Table 1). Insulin levels in fasting plasma were increased approximately fourfold in PKT-R compared with healthy controls and about twofold compared with KT-R (Table 1). C-peptide levels were also clearly increased in PKT-R compared with healthy controls, albeit to a lesser extent than insulin levels (Table 1). Creatinine levels were increased in both transplant groups compared with healthy controls.

Plasma levels of total cholesterol associated with VLDL, IDL, and HDL_3 were similar in all study groups (Table 2). LDL cholesterol was increased in KT-R. HDL_2 cholesterol, in contrast, was increased in PKT-R compared with the other study groups (Table 2). The composition of VLDL and IDL in PKT-R was not significantly different from that in KT-R and controls, respectively (Table 3). The other lipoprotein classes of PKT-R showed small but consistent differences with respect to surface components; LDL, HDL_2, and HDL_3 of PKT-R were enriched in UC (PKT-R *v* KT-R, $P < .05$, $P = .13$, and $P < .005$; PKT-R *v* controls, all $P < .005$; Table 3). In PKT-R, HDL_2 was enriched in phospholipids; LDL, in contrast, was depleted of phospholipids (PKT-R *v* KT-R, $P = .053$ and $P < .05$; PKT-R *v* controls, both $P < .05$). A decrease in LDL protein and HDL_3 protein of borderline significance ($P = .049$ and $P = .040$) was noted in PKT-R compared with healthy controls. The only compositional change distinguishing

Table 1. Parameters of Carbohydrate Metabolism and Renal Function (mean ± SD) in PKT-R, KT-R, and Healthy Control Subjects

Index	PKT-R (n = 14)	K-TR (n = 8)	Controls (n = 14)
Glucose (mg/dL)	89.7 ± 14.05	93.8 ± 11.21	100.0 ± 13.34
Fructosamine (μmol/L)	239.9 ± 24.87	223.7 ± 31.58	224.2 ± 36.00
Insulin (mU/L)	25.09 ± 13.82*†	12.38 ± 10.27	7.28 ± 3.16
C-peptide (nmol/L)	1.33 ± 0.76‡	1.33 ± 1.04	0.69 ± 0.45
Creatinine (mg/dL)	1.37 ± 0.55§	1.34 ± 0.45‖	0.92 ± 0.15

NOTE. *P* values were obtained by the 2-tailed Student's *t* test for independent samples.

*PKT-R *v* KT-R, $P < .05$.

†PKT-R *v* controls, $P < .001$.

‡PKT-R *v* controls, $P < .05$.

§PKT-R *v* controls, $P < .01$.

‖KT-R *v* controls, $P < .01$.

Table 2. Cholesterol Concentrations (mean ± SD, mg/dL) of Plasma Lipoprotein Density Classes Isolated by Rate Zonal Ultracentrifugation in PKT-R, KT-R, and Healthy Control Subjects

Index	PKT-R (n = 14)	KT-R (n = 8)	Controls (n = 14)
VLDL-C	6.26 ± 6.64	15.81 ± 19.67	8.79 ± 6.63
IDL-C	11.07 ± 8.84	13.96 ± 10.90	11.70 ± 6.64
LDL-C	74.45 ± 28.71*‡	123.95 ± 65.96†	73.45 ± 15.86
HDL_2-C	13.46 ± 9.27*‡	5.84 ± 3.55	7.11 ± 4.05
HDL_3-C	25.99 ± 7.84	21.42 ± 8.76	26.17 ± 5.77

NOTE. *P* values were obtained by the 2-tailed Student's *t* test for independent samples. Cholesterol concentrations in lipoprotein density classes were calculated as total cholesterol = (CE/1.682) + UC.

*PKT-R *v* KT-R, $P < .05$.

†KT-R *v* controls, $P < .05$.

‡PKT-R *v* controls, $P < .05$.

KT-R from both PKT-R and healthy controls was triglyceride enrichment of HDL_2 (both $P < .05$).

In PKT-R, both lipid surface components, ie, UC and phospholipids, combined made a larger contribution to HDL_2 mass than in KT-R or controls (39.9 ± 2.2 weight% in PKT-R, 32.6 ± 10.6 weight% in KT-R, and 36.7 ± 3.1 weight% in controls; PKT-R *v* KT-R, $P < .05$; PKT-R *v* controls, $P = .005$) and a smaller contribution to LDL mass than in controls, respectively (31.9 ± 1.5 weight% in PKT-R and 34.1 ± 2.5 weight% in controls; PKT-R *v* controls, $P = .018$). The weight% of UC and phospholipids combined in LDL of KT-R was 32.9% ± 2.5%, an intermediate value not significantly different from values in either of the other groups. With regard to HDL_2, these findings may reflect a more densely packed HDL_2 surface coat in PKT-R. With regard to LDL, it suggests the predominance of larger, more buoyant LDL particles in PKT-R. This finding, together with the lower percentage of protein, is internally consistent with the electrophoretically observed increase in LDL size mode in PKT-R compared with healthy controls (28.52 ± 0.77 *v* 27.03 ± 1.0 nm, $P = .002$). LDL size in KT-R was 28.2 ± 0.39 nm and did not differ significantly from that of either of the other groups.

Plasma CETP concentration was notably increased in both transplant groups compared with healthy controls (1.403 ± 0.51 μg/mL in PKT-R, 1.256 ± 0.28 μg/mL in KT-R, and 1.023 ± 0.18 μg/mL in controls; Fig 1).

In both patients and controls, BMI, fructosamine, and creatinine showed no significant relationships to the weight% of UC in LDL, HDL_2, and HDL_3 (data not shown). However, insulin concentrations in fasting plasma were directly related to the weight% of UC in HDL_3 and inversely related to the weight% of phospholipids in LDL (Table 4). CETP concentrations in plasma were directly related to insulin and to the enrichment of LDL and HDL_3 with UC and inversely related to the weight% of phospholipids in LDL (Table 4).

DISCUSSION

Pancreas transplantation leads to decreased plasma concentrations of cholesterol and triglycerides[19-21] and increased levels of HDL cholesterol.[14,19,20,22] In a previous

Table 3. Lipoprotein Composition (mean ± SD, weight%) in PKT-R, KT-R, and Healthy Control Subjects

Lipoprotein	CE	UC	TG	PL	Protein
VLDL					
PKT-R	11.87 ± 5.4	4.64 ± 2.3	54.58 ± 10.4	18.26 ± 2.0	10.65 ± 3.7
KT-R	8.52 ± 1.2*	4.68 ± 0.5	58.21 ± 3.9*	19.25 ± 2.7	9.33 ± 1.6
Controls	13.95 ± 4.5	5.24 ± 0.9	51.20 ± 5.2	19.48 ± 1.9	10.12 ± 1.5
IDL					
PKT-R	23.93 ± 5.4	8.14 ± 1.7	26.86 ± 5.1	25.40 ± 4.0	15.68 ± 2.3
KT-R	26.56 ± 6.4	8.50 ± 0.9	26.08 ± 6.0	23.90 ± 1.6	14.96 ± 1.1
Controls	28.42 ± 6.3	8.85 ± 1.1	21.17 ± 9.8	24.72 ± 2.9	16.84 ± 2.6
LDL					
PKT-R	39.78 ± 4.3	10.32 ± 0.9†‡	7.54 ± 3.1	21.57 ± 2.0†§	20.79 ± 2.3‖
KT-R	41.02 ± 3.2¶	9.14 ± 1.3	7.13 ± 1.9	23.73 ± 2.2	18.97 ± 3.5¶
Controls	37.86 ± 1.7	9.0 ± 0.9	5.58 ± 1.9	25.05 ± 2.1	22.51 ± 1.8
HDL_2					
PKT-R	21.35 ± 3.8	5.71 ± 0.5‡	4.43 ± 2.1†	34.15 ± 1.9‖	34.37 ± 5.5
KT-R	20.39 ± 4.2	4.72 ± 2.2	11.90 ± 9.3¶	27.85 ± 10.9	35.13 ± 7.3
Controls	19.68 ± 2.2	4.96 ± 0.6	5.95 ± 2.6	31.69 ± 2.9	37.71 ± 1.9
HDL_3					
PKT-R	17.10 ± 1.6	3.36 ± 0.5§#	2.74 ± 1.6	28.48 ± 2.3	48.32 ± 2.9‖
KT-R	16.10 ± 2.6	2.51 ± 0.8	6.2 ± 8.4	27.98 ± 3.0	47.21 ± 5.8
Controls	15.81 ± 1.7	2.57 ± 0.4	2.78 ± 0.8	28.42 ± 1.9	50.41 ± 1.9

NOTE. *P* values were obtained by the 2-tailed Student's *t* test for independent samples.

Abbreviations: TG, triglycerides; PL, phospholipids.

*KT-R *v* controls, $P < .005$.

†PKT-R *v* KT-R, $P < .05$.

‡PKT-R *v* controls, $P < .005$.

§PKT-R *v* controls, $P < .001$.

‖PKT-R *v* controls, $P < .05$.

¶KT-R *v* controls, $P < .05$.

#PKT-R *v* KT-R, $P < .005$.

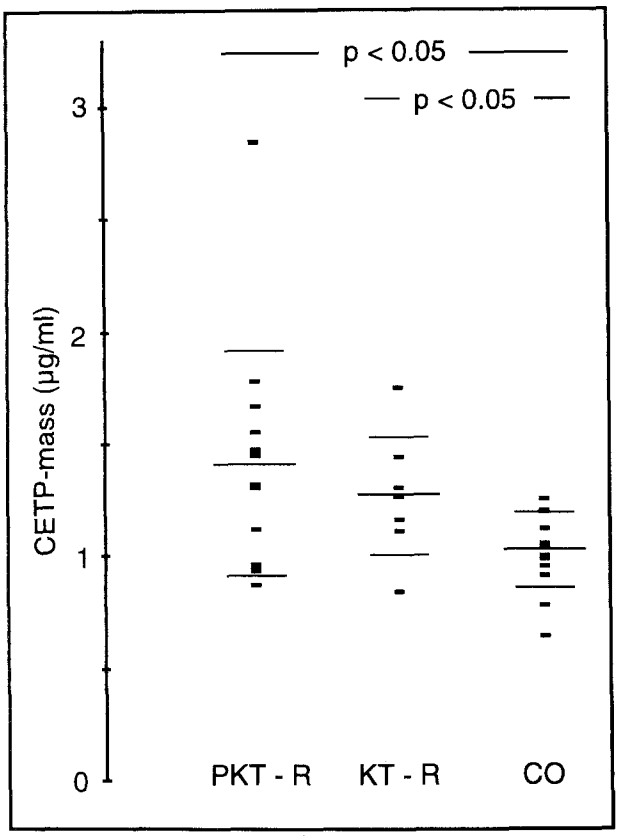

Fig 1. CETP mass in plasma in PKT-R (n = 14), KT-R (n = 7), and healthy control subjects (CO, n = 13). CETP mass is given in µg · mL^{-1} plasma. Horizontal bars indicate the mean ± 1 SD. Groups were compared by Student's *t* test for independent samples (two-tailed *P* values are shown).

study on fasting and postprandial lipoprotein transport in clinically stable PKT-R, we found attenuated postprandial triglyceridemia and increased HDL_2 cholesterol levels, determined by a precipitation procedure.[12] In the present study using rate zonal ultracentrifugation,[15] we confirm and extend this finding. In humans, CE carried within HDL particles can be passed along two metabolic routes. HDL-CE can be either directly returned to the liver or, alternatively, diverted to TGRLP in exchange for their major core lipid, ie, triglycerides. This diversion is made possible through the action of CETP.[13] The rate of net CE transfer to TGRLP depends on the concentrations of cholesterol-rich donor and triglyceride-rich acceptor particles, the surface and core composition of these particles, and the concentrations of CETP and potential inhibitor proteins. High levels of HDL-CE are usually found only in situations where the rate of neutral core lipid transfer is low, either due to low CETP activity[13] or to low concentrations of postabsorptive and/or postprandial TGRLP.[11,12] In PKT-R, peripheral hyperinsulinemia upregulates LPL activity,[12] thereby decreasing the pool of TGRLP, the major acceptor particles for HDL-CE, in the fasting state[12,19-21] and particularly in the postprandial state.[12]

Table 4. Correlation Matrix of Parameters of Carbohydrate Metabolism and CETP with Parameters of Lipoprotein Surface Composition in PKT-R, KT-R, and Healthy Control Subjects

	Insulin	CETP
CETP	.426*	1.000
UC in LDL§	.327	.457*
PL in LDL§	−.452*	−.496†
UC in HDL_2§	.237	.335
PL in HDL_2§	.020	.336
UC in HDL_3§	.428*	.563‡

NOTE. Pearson correlation coefficients were calculated for all subjects combined.

Abbreviation: PL, phospholipids.

*$P < .05$.

†$P = .005$.

‡$P = .001$.

§Weight% of UC or PL in LDL, HDL_2, and HDL_3.

However, the study presented here shows a clearly increased plasma concentration of CETP in PKT-R compared with healthy controls. Increased CETP activity has previously been reported for type I diabetic patients.[23,24] Nevertheless, no signs of increased neutral core lipid transfer in vivo are evident in PKT-R; HDL_2 levels are high rather than low, VLDL and IDL are not enriched in CE, and, conversely, LDL and HDL are not enriched in triglycerides. HDL_2, in fact, tended to be lower in triglycerides in PKT-R than in controls. In contrast, when CETP is increased in the presence of fasting and/or postprandial hypertriglyceridemia, as in our KT-R, HDL_2 becomes enriched in triglycerides and its plasma levels decrease. In in vitro studies, increasing the concentration of CETP increased the net CE mass transfer from HDL to VLDL in hypertriglyceridemic but not in normotriglyceridemic plasma samples.[25] It has thus been concluded that the triglyceride concentration determines the rate of net CE transfer in normolipidemics, whereas CETP becomes rate-limiting only in hypertriglyceridemia.[25] Our results in PKT-R and KT-R are compatible with this view, suggesting that the excellent capacity of PKT-R to clear postprandial chylomicron triglycerides[12] allows little triglyceride/CE net exchange between TGRLP and HDL_2 even in the presence of high CETP levels.

LDL particles are subject to equilibration of neutral core lipids with TGRLP in the same way as HDL particles.[13] Thus, a decrease in the rate of in vivo neutral core lipid transfer due to low concentrations of TGRLP in PKT-R would be expected to result not only in a preponderance of the larger HDL subclass, ie, HDL_2, but also in a preponderance of larger LDL subclasses. Indeed, all PKT-R—in addition to high HDL_2 levels—displayed LDL pattern A, reflecting a predominance of larger-sized LDL, and an increased LDL size when compared with healthy controls.

Regarding lipoprotein composition, we found that HDL_2, HDL_3, and LDL showed small but consistent and therefore statistically highly significant enrichment in UC in PKT-R. HDL_2 were also enriched in phospholipids, while LDL were relatively depleted in this lipid class. Increased abundance of UC[4-8,22] and lecithin in HDL_2[4] and reduced abundance of lecithin in VLDL and LDL[6] have previously been observed in diabetic patients.

Our PKT-R differed from healthy controls in several

major aspects: peripheral hyperinsulinemia, immunosuppressive medication, and discretely impaired renal function. Since the changes in the level and composition of plasma lipoproteins in PKT-R outlined above were also evident compared with KT-R, we believe that immunosuppressive medication and impaired renal function can be discounted in this respect. Peripheral hyperinsulinemia and/or an abolished gradient between portal vein and peripheral vein insulin concentrations are more likely the cause for the observed lipoprotein alterations. First, diabetic patients taking subcutaneous insulin injections also exhibit peripheral hyperinsulinemia and are known to have low VLDL, high HDL_2, enrichment of lipoprotein surfaces with UC,[1,4-8,22] and increased plasma CETP.[23,24] Second, when peripheral hyperinsulinemia is avoided by delivering insulin directly to the portal circulation by intraperitoneal insulin pumps, fasting and postprandial triglycerides increase,[26] HDL_2[27] and/or HDL decrease,[26] and altered lipoprotein composition and accelerated in vitro CE transfer are normalized.[28] Third, in our subjects, insulin concentrations in fasting plasma were directly related both to CETP concentrations and to the enrichment of HDL with UC. However, our study was not designed to address the mechanism(s) responsible for the peculiar lipoprotein pattern in PKT-R and thus does not prove causality. It will be interesting to see what effect intraportal islet allografting, a procedure that is expected not to cause peripheral hyperinsulinemia, will have on these parameters.

The mechanisms by which hyperinsulinemia may cause the observed changes in surface composition of plasma lipoproteins are unclear and therefore subject to speculation. Hyperinsulinemia stimulates cholesterol synthesis in diabetic humans[29] and in animal models of diabetes.[30] Conceivably, increased cellular cholesterol synthesis may account for an enrichment of lipoproteins with UC. An increase in intracellular cholesterol derivatives may induce transcription of CETP mRNA in adipose tissue and/or in the liver.[13] CETP catalyzes not only neutral core lipid transfer in plasma but also phospholipid transfer, accounting for approximately 50% of the latter process.[13,31] Since CETP contributes to the transfer of surface components of TGRLP to HDL during lipolysis—and LPL activity is high in iatrogenic peripheral hyperinsulinemia—increased CETP plasma levels could help to explain the altered lipoprotein surface composition of PKT-R. The other plasma lipid transfer protein transferring lipoprotein surface components[32] is called phospholipid transfer protein. Although not quantified in this study, its activity has been directly related to CETP activity[33] and could also help to explain the altered lipoprotein surface composition of PKT-R.

The clinical relevance of the changed lipoprotein surface composition in PKT-R is unclear. Two clinical trials relating lipoprotein surface composition to the risk of atherosclerosis have produced discrepant results. One found a direct relationship between a high UC to phosphatidylcholine ratio and cardiovascular risk in nondiabetic patients,[34] whereas the other arrived at the conclusion that high levels of UC in HDL were indicative of a low cardiovascular risk in nondiabetic men.[35]

The peculiar lipoprotein pattern observed in PKT-R, ie, low postabsorptive and postprandial triglycerides, high HDL_2, and predominance of LDL pattern A, is reminiscent of the antiatherogenic lipoprotein phenotype induced by endurance training.[36,37] In fact, the similarity may extend even further; the major proximal cause of both lipid patterns is an increase in the activity of LPL, the major enzyme governing triglyceride catabolism.[12,37] In PKT-R, a high activity of LPL most probably results from increased insulin action in adipose tissue.

In conclusion, in type I diabetic PKT-R, high LPL activity causes efficient handling of fasting and postprandial triglycerides, producing the antiatherogenic lipoprotein profile with a preponderance of large-sized HDL (high HDL_2 levels) and LDL (pattern A). With regard to lipoprotein surface composition, HDL and LDL are enriched in UC and show an altered phospholipid content. Whether these changes in lipoprotein surface composition counterbalance the strong favorable effects of an effective triglyceride clearance capacity on cardiovascular risk remains a matter of speculation.

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