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Lipoprotein profile after combined kidney-pancreas transplantation in insulin-dependent diabetes mellitus

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This paper is dedicated to the memory of our esteemed colleague and friend, Mariella Parlavecchia, who died on April 2, 1994

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Abstract In order to evaluate the effect of a combined kidney-pancreas (KP) transplantation in insulin-dependent diabetes mellitus (IDDM) patients on the lipid and lipoprotein profile, 15 KP patients were compared with 11 kidney (K)-transplanted IDDM patients, 19 IDDM patients on hemodialysis (HD), and 15 nondiabetic control subjects. Cholesterol, triglycerides, apo AI, and apo B were measured in total plasma and in VLDL, LDL, and HDL of all participants. VLDL-cholesterol, VLDL-triglycerides, and VLDL-apo B were significantly lower in KP patients, but not in K patients, than in HD patients. In addition, patients in the K, but not in the KP, group showed high levels of apo B in LDL and an increased triglyceride/apo B ratio in VLDL, compared with patients in the HD group. The percentage of apo AI associated with HDL was significantly higher in both transplanted groups than in the HD group. However, compared with a nondiabetic control population, an increase in VLDL particles and in triglyceride content in LDL and HDL still persisted following combined KP transplantation. Insulin resistance (probably due to steroid therapy) associated with high peripheral and potentially low hepatic insulin levels (due to the systemic drainage of the transplanted pancreas) could be the main causes of the remaining lipoprotein abnormalities.

Key words Lipoprotein profile, pancreas transplantation · Kidney-pancreas transplantation, lipoprotein profile · Pancreas-kidney transplantation, lipoprotein profile

Introduction

Insulin-dependent diabetes mellitus (IDDM) candidates for combined kidney-pancreas (KP) transplantation are uremic patients on dialysis with micro- and macroangiopathy in an advanced stage [10]. In fact, combined KP transplantation is performed in order to treat metabolic abnormalities and renal failure due to diabetes [27] and, hopefully, to prevent and/or to stop the progression of degenerative complications.

Cardiovascular disease is an important cause of death in a transplanted population and is frequently associated with lipid and lipoprotein abnormalities [28]; the occurrence of coronary heart disease in transplanted patients is several times higher than in a normal population. In the last few years, many studies have demonstrated that disturbances of lipid and lipoprotein metabolism are a common problem following organ transplantation [2, 5, 8] and may be one of the leading causes of accelerated atherosclerosis in transplant recipients

Table 1 Clinical characteristics of HD patients, K and KP transplanted patients, and control (CTRL) subjects. Values shown indicate mean ± SD (*n. a.* not applicable)

	HD ($n = 19$)	K ($n = 11$)	KP ($n = 15$)	CTRL ($n = 15$)
Age (years)	37.2 ± 6.7	40.1 ± 8.3	42.3 ± 8.5	40.2 ± 5.0
Sex (M/F)	7/12	5/6	8/7	8/7
BMI (kg/m^2)	24.6 ± 4.3	23.3 ± 1.6	23.2 ± 3.0	22.7 ± 2.4
Duration of diabetes (years)	24.0 ± 6.0	25.7 ± 6.7	26.7 ± 5.9	n. a.
Duration of dialysis (months)	8.4 ± 7.7	18.8 ± 11.7**	17.7 ± 13.3*	n. a.
Diuretics (%)	16	27	20	n. a.
Beta blockers (%)	10	45**	27*	n. a.
Rejections (%)	n. a.	55	73	n. a.
Steroid pulses/ rejection episodes	n. a.	3.1 ± 1.5	4.3 ± 2.3	n. a.

* $P < 0.05$ KP vs HD;
** $P < 0.01$ K vs HD

[22]. The cause of post-transplant dyslipidemia is uncertain. Some authors suggest that immunosuppressive treatment could play an important role in the pathogenesis of lipid and lipoprotein abnormalities; in fact, patients treated with steroids more frequently develop hypertriglyceridemia [26], while hypercholesterolemia is the most common form of hyperlipidemia observed in patients treated with cyclosporin [11, 21]. In addition, dietary intake after transplantation may exacerbate the tendency toward lipid and lipoprotein disorders [22].

Although lipid levels have been measured in most of the studies of KP patients, there is still little and conflicting data concerning lipoprotein profile [3, 4, 13–16, 25, 32]. Therefore, we have designed a protocol to investigate and, ultimately, identify a specific lipid and lipoprotein profile associated with KP transplantation in IDDM patients.

Patients and methods

Patients

The study was carried out with two groups of transplanted patients [15 KP recipients and 11 kidney (K) recipients], 19 IDDM patients on hemodialysis (HD), and 15 healthy nondiabetic control subjects. Clinical characteristics of the study population are reported in Table 1. Retinopathy, neuropathy, and macroangiopathy affected all three groups of patients similarly. End-stage renal failure was secondary to diabetes mellitus in all patients. Kidney transplantation was performed according to conventional techniques [17]. Pancreatic duodenocystostomy was carried out according to Leach's technique [17]. Pancreas transplantation was performed using the segmental neoprene-injected technique [6]. All transplanted patients were treated with the same immunosuppressive protocol that consisted of: (a) antilymphocyte globulins during the first 10 days; (b) cyclosporin A (CyA: 7.5 mg/kg), monitored with blood levels; (c) steroids (methylprednisolone: 500 mg before surgery, then 1 mg/kg/day, tapered in the postsurgical period and, ultimately, 10 mg/day chronically; pulses of 500 mg only in case of kidney rejection); and (d) azathioprine (50–150 mg/day). The number of steroid pulses, the requirement of diuretic drugs, and the episodes of kidney rejection were similar in both transplanted groups. However, the use of beta blocker drugs was significantly higher in both transplanted groups than in the HD group ($P < 0.01$ vs K; $P < 0.05$ vs KP). HD patients were adequately treated 4 h a day, 3 days a week; however, the duration of dialysis treatment was significantly higher in both K ($P < 0.01$) and KP ($P < 0.01$) patients than in HD patients. KP patients were not receiving any exogenous insulin, whereas K and HD patients were on conventional subcutaneous insulin therapy. All patients were instructed to follow a weight-maintaining diet throughout the study. Healthy control subjects were 15 nondiabetic volunteers carefully matched with the KP group for age, sex, and BMI. None of the participants was taking lipid-lowering drugs.

The study protocol was approved by the Ethics Committee of the San Raffaele Institute, and informed consent was obtained from each subject participating in the study.

Study design

Blood samples were obtained at 8:00 a.m. after an overnight fast with the subjects in recumbent position. Total cholesterol, triglycerides, and apo AI and B were measured in plasma and in major lipoprotein fractions (VLDL, LDL, and HDL). Glycometabolic control and renal function were evaluated by determining HbA_{1c}, free insulin, and creatinine concentrations. Blood samples were obtained 18 ± 3 (SEM) months after transplantation, and thus quite some time after the treatment with steroid pulses following episodes of kidney rejection.

Methods and assays

Human VLDL (d < 1.006 g/ml) was isolated from plasma by ultracentrifugation [9] using a Beckman ultracentrifuge with a TLA 100.3 rotor at 100,000 rpm for 2.5 h. HDL fraction was separated from plasma by precipitation of apo B-containing lipoproteins with polyethilene glycole [33]. LDL fraction was calculated as the difference between bottom (infranatant after flotation of VLDL) and HDL fraction. Plasma apo AI and apo B were determined following an immunonephelometric procedure [20] using a Behring Nephelometric Analyzer (Behring, Germany); antisera for apo AI and apo B were commercially available (Behring, Germany). Total cholesterol and triglycerides were measured by enzymatic methods using a Ciba Corning 550 Express Analyzer (Ciba, Italy) [30]. HbA_{1c} was evaluated via a chromatographic method (normal values 4.0 %–6.0 %), and creatinine via an automated analysis ac-

Table 2 Plasma concentrations of glucose, HbA_{1c}, creatinine, cyclosporin, and insulin in HD patients, K and KP transplanted patients, and control (CTRL) subjects. Values shown indicate mean ± SD (*n. a.* not applicable)

	HD ($n = 19$)	K ($n = 11$)	KP ($n = 15$)	CTRL ($n = 15$)
Glucose (mmol/l)	13.3 ± 4.8	10.8 ± 4.4	5.0 ± 0.8[*1,*2]	4.7 ± 0.6
HbA_{1c} (%)	8.3 ± 1.4	8.0 ± 0.9	5.6 ± 1.0[*1,*2]	5.0 ± 0.8
Creatinine (μmol/l)	760 ± 194	124 ± 44[*3]	106 ± 26[*2]	80 ± 44
Cyclosporin (ng/ml)	n. a.	462 ± 258	299 ± 146	n. a.
Insulin (pmol/l)	227 ± 138	172 ± 79	108 ± 47[*2,*4]	66 ± 40

[*1] $P < 0.01$ KP vs K; [*2] $P < 0.01$ KP vs HD; [*3] $P < 0.01$ K vs HD; [*4] $P < 0.05$ KP vs control

cording to the Jaffé method. Free immunoreactive insulin was assayed according to the method of Nakagawa et al. [23]. Blood cyclosporin concentration was evaluated by radioimmunoassay techniques on whole blood using monoclonal antibodies.

Statistical analysis

Chi-square analysis was used to compare clinical variables. Nonparametric analysis using the Mann-Whitney U-test was carried out to compare the different groups (differences of P less than 0.05 were considered significant). Since the control subjects were carefully matched (for number, age, sex, and BMI) only with the KP group, the control group was only compared to the double transplanted group.

Results

The HbA_{1c} concentration was lower in the KP group than in either the HD ($P < 0.01$) or K group ($P < 0.01$; Table 2). Normal renal function was achieved in both transplanted groups, as indicated by creatinine values ($P < 0.01$ vs HD; Table 2). Plasma free insulin concentrations were markedly lower in the KP group than in either the HD ($P < 0.01$) or K group ($P = 0.06$); however, KP patients still showed significantly higher plasma insulin levels than controls ($P < 0.05$; Table 2).

Total plasma triglyceride levels in KP patients were still significantly higher than those in control subjects ($P < 0.01$; Table 3). VLDL-cholesterol, VLDL-triglycerides, and VLDL-apo B significantly decreased in the KP group as compared to the HD group; however, these VLDL components still remained significantly higher than those in the control group (Table 3). The triglyceride-to-apo B ratio in VLDL of the K group was markedly higher than in both the HD ($P < 0.05$) and KP groups ($P = 0.08$). No significant changes were observed between the HD group and the two transplanted groups with regard to LDL- and HDL-triglycerides; consequently, KP patients still showed significantly higher levels of both LDL-triglycerides ($P < 0.05$) and HDL-triglycerides ($P < 0.01$) than control subjects. To-

Table 3 Lipid and apolipoprotein (apo) concentrations in plasma and lipoprotein fractions of HD patients, K and KP transplanted patients, and control (CTRL) subjects. Values shown indicate mean ± SD

	HD ($n = 19$)	K ($n = 11$)	KP ($n = 15$)	CTRL ($n = 15$)
Plasma				
Cholesterol (mmol/l)	5.56 ± 1.37	5.84 ± 1.11	5.20 ± 1.16	5.04 ± 0.90
Triglyceride (mmol/l)	2.29 ± 1.05	1.96 ± 0.75	1.62 ± 0.75[*6]	0.89 ± 0.25
Apo AI (mg/dl)	142 ± 36	143 ± 25	129 ± 40	145 ± 25
Apo B (mg/dl)	120 ± 35	126 ± 28	103 ± 29	102 ± 14
VLDL				
Cholesterol (mmol/l)	0.93 ± 0.52	0.62 ± 0.44	0.49 ± 0.36[*2,*5]	0.23 ± 0.10
Triglyceride (mmol/l)	1.41 ± 0.88	1.13 ± 0.64	0.80 ± 0.50[*1,*6]	0.40 ± 0.16
Apo B (mg/dl)	31 ± 21	17 ± 11	16 ± 11[*2,*5]	9 ± 3
Triglyceride/Apo B (mol/mg)	4.9 ± 1.9	7.8 ± 3.9[*4]	5.9 ± 3.2	4.6 ± 1.4
LDL				
Cholesterol (mmol/l)	3.41 ± 0.98	3.85 ± 0.90	3.34 ± 0.90	3.31 ± 0.67
Triglyceride (mmol/l)	0.54 ± 0.24	0.50 ± 0.25	0.52 ± 0.30[*5]	0.34 ± 0.09
Apo B (mg/dl)	89 ± 27	109 ± 25[*4]	88 ± 25[*3]	92 ± 23
Cholesterol/Apo B (mol/mg)	3.9 ± 0.5	3.6 ± 0.4	3.9 ± 0.6	3.7 ± 0.5
HDL				
Cholesterol (mmol/l)	1.21 ± 0.46	1.40 ± 0.39	1.37 ± 0.57	1.47 ± 0.31
Triglyceride (mmol/l)	0.34 ± 0.26	0.32 ± 0.22	0.30 ± 0.12[*6]	0.14 ± 0.06
Apo AI (mg/dl)	97 ± 25	122 ± 31[*4]	106 ± 39	126 ± 28
Cholesterol/Apo AI (mol/mg)	1.3 ± 0.4	1.2 ± 0.3	1.3 ± 0.3	1.2 ± 0.3

[*1] $P < 0.05$; [*2] $P < 0.01$ KP vs HD; [*3] $P < 0.05$ KP vs K; [*4] $P < 0.05$ K vs HD; [*5] $P < 0.05$; [*6] $P < 0.01$ KP vs control

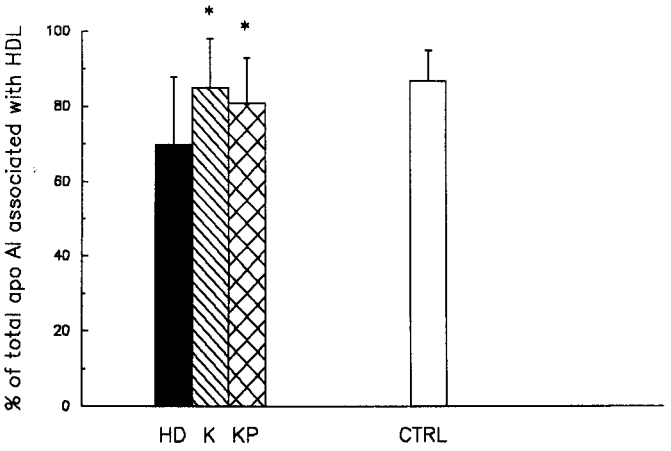

Fig. 1 Mean ± SD percentage of total apo AI associated with HDL in HD patients, K and KP transplanted patients, and control (CTRL) subjects. * $P < 0.05$ vs HD

tal plasma apo B levels in HD and K patients were slightly higher than in KP patients ($P = 0.06$; Table 3). The high total apo B levels in K patients were mainly due to the significant elevation of apo B in the LDL fraction, in comparison with HD ($P < 0.05$) and KP patients ($P < 0.05$). Apo AI levels in the HDL of K patients were significantly higher than in HD patients ($P < 0.05$; Table 3).

It is interesting to note from Fig. 1 that only an average (± SD) of 70 % (± 18 %) of total apo AI was associated with HDL in the HD group, as compared with 85 % (± 13 %) for K ($P < 0.05$) and 81 % (± 12 %) for KP transplants ($P < 0.05$). The percentage of apo AI associated with HDL was 87 % (± 8 %) for nondiabetic control subjects.

Discussion

The most important beneficial effect of combined KP transplantation on lipoprotein metabolism is represented by a significant reduction in VLDL particles circulating in plasma, compared with IDDM uremic patients. This effect is not so evident in IDDM patients undergoing kidney transplantation alone; these patients also showed larger VLDL, as indicated by the increased triglyceride/apo B ratio. The normalization of renal function is certainly one of the causes of the reduction in VLDL particles in KP patients. It is accompanied by important metabolic changes, such as a reduction in insulin resistance [18] and, consequently, in plasma insulinemia. However, a peripheral hyperinsulinemia in KP patients still persists, due to both nonportal venous drainage of the transplanted pancreas and a certain degree of persisting insulin resistance [18]. In fact, recent data have shown a reduction in insulin resistance in insulin-dependent diabetic patients undergoing combined KP transplantation, although peripheral insulin sensitivity is still slightly different from that in normal control subjects [18].

Some authors [1] have also demonstrated a significant positive correlation between VLDL triglycerides and insulin resistance, independent of insulin concentrations. The reduction in VLDL particles could also be due to a decreased synthesis of hepatic VLDL, consequent to probably decreased levels of hepatic insulin [29]. However, K patients still present increased levels of VLDL, in spite of a normal function. The persistence of diabetes mellitus in K patients, with all of the related metabolic abnormalities, could be one possible explanation: the glucose (a main substrate for VLDL production) flux to the liver is certainly decreased in KP patients, but not in K patients (this can be argued from glycosylated hemoglobin concentrations). As for the catabolic rate of VLDL, a preliminary report has shown high lipoprotein lipase activity accompanied by low hepatic lipase activity in combined transplant patients. It has been suggested that this may be due to peripheral hyperinsulinemia associated with a low level of portal insulin [12].

It is important to state that our results were not influenced by diuretic and/or beta blocker therapy (data not shown). In fact, we obtained the same statistical differences when we eliminated the few patients receiving these drugs from the analysis.

The number of LDL particles was significantly increased in K patients in comparison with both HD and KP patients, as indicated by significantly high levels of LDL apo B. This could be explained by the presence in K patients of larger VLDL that might direct these particles toward different catabolic routes, resulting in high levels of LDL. Also, elevated glycemic levels in K patients could increase the concentration of circulating glycosylated LDL, which are catabolized much more slowly [19].

The importance of normal kidney function in the catabolism of apo AI is confirmed by the percentage of apo AI not associated with HDL (free apo AI) that is clearly increased in HD patients compared to both transplanted groups [7, 24, 31]. The percent increase in apo AI associated with HDL in K patients is mainly due to the reduction in free apo AI, in comparison with the HD group.

Even though many studies [3, 4, 13–16, 25, 32] have shown the behavior of the lipid profile after KP transplantation, the data still remain difficult to interpret. This is due, first of all, to the fact that most of these investigations are published in the form of proceedings and, therefore, represent preliminary results [4, 13, 14, 25, 32]. Secondly, other studies either have a small number of patients ($n = 6$) [3] or take into consideration only total cholesterol, triglycerides, and HDL cholesterol [3,

15, 16]. However, most of the authors agree on the tendency toward a decrease in total cholesterol and triglycerides and an increase in HDL cholesterol after combined KP transplantation.

Although the lipid and lipoprotein profile in KP patients markedly improved in comparison with HD patients, it still remained significantly different from that of a nondiabetic control population, at least in some aspects. In fact, in KP patients, VLDL particles still seem to be higher than in nondiabetic control subjects, probably due to the remaining insulin resistance (and subsequent hyperinsulinemia) caused by the immunosuppressive treatment (especially prednisone) [26, 34]. The increase in triglyceride content in LDL and HDL, sometimes occurring in IDDM, is still evident in KP patients compared with a nondiabetic control population. The possibility of low levels of portal free insulin could produce low hepatic lipase activity, and this could explain the high triglyceride concentration in LDL and HDL. Alternatively, the increase in triglycerides in HDL could mean an increase in CETP (cholesterol ester transfer protein) activity.

In conclusion, combined KP transplantation near-normalizes the lipoprotein profile in IDDM uremic patients. However, compared with a nondiabetic control population, a slight increase in VLDL particles and in triglyceride content in LDL and HDL still persists following KP transplantation. Insulin resistance (probably due to steroid therapy) associated with high peripheral and low hepatic insulin levels (due to the systemic drainage of the transplanted pancreas) seem to be the main causes of the remaining lipoprotein abnormalities.

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