Metabolic Effects of Restoring Partial β-Cell Function After Islet Allotransplantation in Type 1 Diabetic Patients

Livio Luzi, Gianluca Perseghin, Mathias D. Brendel, Ileana Terruzzi, Alberto Battezzati, Michael Eckhard, Daniel Brandhorst, Heide Brandhorst, Schirin Friemann, Carlo Socci, Valerio Di Carlo, Lucia Piceni Sereni, Stefano Benedini, Antonio Secchi, Guido Pozza, and Reinhard G. Bretzel

Successful intraportal islet transplantation normalizes glucose metabolism in diabetic humans. To date, full function is not routinely achieved after islet transplantation in humans, with most grafts being characterized by only partial function. Moreover, the duration of full function is variable and cannot be sufficiently predicted with available methods. In contrast, most grafts retain partial function for a long time. We hypothesized that partial function can restore normal protein and lipid metabolism in diabetic individuals. We studied 45 diabetic patients after islet transplantation. Labeled glucose and leucine were infused to assess whole-body glucose and protein turnover in *1*) 6 type 1 diabetic patients with full function after intraportal islet transplantation (FF group; C-peptide > 0.6 nmol/l; daily insulin dosage 0.03 ± 0.02 U · kg^{-1} body wt · day^{-1}; fasting plasma glucose < 7.7 mmol/l; $HbA_{1c} \leq$ 6.5%), *2*) 17 patients with partial function (PF group; C-peptide > 0.16 nmol/l; insulin dosage < 0.4 U · kg^{-1} body wt · day^{-1}), *3*) 9 patients with no function (NF group; C-peptide < 0.16 nmol/l; insulin dosage > 0.4 U · kg^{-1} body wt · day^{-1}), and *4*) 6 patients with chronic uveitis as control subjects (CU group). Hepatic albumin synthesis was assessed in an additional five PF and five healthy volunteers by means of a primed-continuous infusion of [3,3,3-$^2H_3$]leucine. The insulin requirement was 97% lower than pretransplant levels for the FF group and 57% lower than pretransplant levels for the PF group. In the basal state, the PF group had a plasma glucose concentration slightly higher than that of the FF (P = 0.249) and CU groups (P = 0.08), but was improved with respect to the NF group (P < 0.01). Plasma leucine (101.1 ± 5.9 μmol/l) and branched-chain amino acids (337.6 ± 16.6 μmol/l) were similar in the PF, FF, and CU groups, and significantly lower than in the NF group (P < 0.01). During insulin infusion, the metabolic clearance rate of glucose was defective in the NF group versus in the other groups (P < 0.01). Both the basal and insulin-stimulated proteolytic and proteosynthetic rates were comparable in the PF, FF, and CU groups, but significantly higher in the NF group (P = 0.05). In addition, the PF group had a normal hepatic albumin synthesis. Plasma free fatty acid concentrations in the PF and FF groups were similar to those of the CU group, but the NF group showed a reduced insulin-dependent suppression during the clamp. We concluded that the restoration of ~60% of endogenous insulin secretion is capable of normalizing the alterations of protein and lipid metabolism in type 1 diabetic kidney recipients, notwithstanding chronic immunosuppressive therapy. The results of the present study indicate that "success" of islet transplantation may be best defined by a number of metabolic criteria, not just glucose concentration/metabolism alone. *Diabetes* 50:277–282, 2001

We have recently shown that successful intraportal islet transplantation can normalize hepatic glucose production and insulin action in type 1 diabetic patients with a kidney transplant (1). This procedure, now performed in several centers worldwide (2–6), is relatively safe, noninvasive (percutaneous puncture of the liver), and repeatable. The major factors limiting the large-scale application of islet graft in diabetic patients receiving chronic immunosuppression for a kidney graft are *1*) the low percentage of patients reaching insulin independence and a complete normalization of glucose homeostasis (1) and *2*) the limited survival of fully successful grafts. Most diabetic patients receiving an islet graft achieve only partial function and a reduction of the pretransplant insulin requirement (2–6); they are characterized by fasting C-peptide concentrations in the near-normal range, but frankly abnormal fasting glucose and GHb values (1–6). In the last decade, we (7–10) and others (11,12) found that protein and lipid metabolism had greater sensitivity to acutely infused insulin than did glucose metabolism, both in diabetes and uremia. Conventional insulin administration (one or two insulin injections per day according to the Diabetes Control and Complications Trial criteria) was also shown to normalize protein and lipid metabolism but left glucose homeostasis mildly altered (7). Insulin treatment does not replace normal plasma concentrations of other peptides commonly cosecreted with insulin, such as C-peptide and proinsulin. Very recent data in diabetic rodents (13) have suggested a biological activity for the

From the Departments of Medicine and Surgery (L.L., G.Pe., I.T., A.B., C.S., V.D.C., L.P.S., S.B., A.S., G.Po.), Istituto Scientifico H. San Raffaele and the University of Milan, Milan, Italy; and the Center of Internal Medicine (M.D.B., M.E., D.B., H.B., S.F., R.G.B.), Justus-Liebig Universität, Giessen, Germany.

Address correspondence and reprint requests to Dr. Livio Luzi, Head, Amino Acid and Stable Isotope Laboratory, Istituto Scientifico H. San Raffaele, via Olgettina 60, 20132 Milan, Italy. E-mail: luzi.livio@hsr.it.

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CU, chronic uveitis; EGP, endogenous glucose production; FF, full function group; FFA, free fatty acid; FSR, fractional synthetic rate; GC, gas chromatography; KIC, ketoisocaproate; MS, mass spectrometry; NF, no function group; PF, partial function group.

TABLE 1
Clinical and biochemical parameters of study groups

	Islet-transplanted patients		Control patients	
	FF	PF	NF	CU
n	6	17	9	6
Sex (F/M)	1/5	9/8	1/8	2/4
Age (years)	50 ± 2	40 ± 1	40 ± 2	46 ± 3
BMI (kg/m^2)	22.95 ± 1.92	22.46 ± 0.68	22.92 ± 0.68	24.17 ± 0.61†
Pretransplant insulin (U · kg^{-1} · day^{-1})	0.80 ± 0.13	0.68 ± 0.06	0.94 ± 0.21	0
Prednisone (mg/day)	5.4 ± 1.9‡	7.8 ± 1.4‡	12.5 ± 2.6	10.4 ± 2.8
Cyclosporin A (mg · kg^{-1} · day^{-1})	7.03 ± 2.44§	5.68 ± 0.44§	4.26 ± 0.25§	1.69 ± 0.30
Days after transplant	284 ± 80	602 ± 142	517 ± 192	—
Creatinine (mg/dl)	1.72 ± 0.32	1.47 ± 0.25	1.30 ± 0.14	0.95 ± 0.30
n Islets (EQ)	436,433 ± 132,807	483,007 ± 61,052	613,003 ± 124,937	—

Data are means ± SE. †P = 0.05 vs. FF, PF, and NF; ‡P = 0.05 vs. NF and CU; §P = 0.002 vs. CU.

C-peptide, namely the restoration of the Na^+–K^+ ATPase pump activity. This effect of C-peptide may play an important role in the delay and prevention of microvascular complications of diabetes (14,15). At present, islet and pancreas transplantation are the only available treatments for type 1 diabetes that replace the whole β-cell function. To test whether a partial function induced by intraportally implanted islets can normalize protein turnover and intermediary metabolism, we selected three groups of diabetic kidney recipients after an associated intraportal islet graft (full function, partial function, and no function; representative of diabetic patients after islet transplantation) and studied them with glucose and leucine tracers to quantify glucose and protein turnover in the basal and insulin-stimulated state. Our results demonstrated that the achievement of partial function permits the normalization of protein and lipid homeostasis in immunosuppressed type 1 diabetic patients, with the persistence of a mild alteration of glucose homeostasis, similar to that observed in type 1 diabetic patients on conventional insulin therapy. It is noteworthy that this result was obtained notwithstanding the fact that the islet recipients were on immunosuppressive drugs.

RESEARCH DESIGN AND METHODS

Subjects. Table 1 shows the clinical and biochemical data of the study groups. All diabetic patients enrolled in this study were kidney graft recipients on chronic immunosuppressive treatment receiving the islet along with or after the kidney. After islet transplantation, diabetic subjects were usually treated with subcutaneous injections of regular insulin (three injections per day) eventually combined with intermediate insulin (one to two injections per day), when necessary. Table 2 summarizes the classification criteria for full, partial, and no function (FF, PF, and NF). Postabsorptive C-peptide concentrations and daily insulin dosage were considered major criteria. Glucose and HbA_{1c} were classified as minor criteria because in PF and NF patients they were determined by the intensity of insulin treatment (HbA_{1c}) in the 4 weeks preceding the study.

Experimental protocol. In the 2 weeks before the study, all subjects consumed an isocaloric diet containing at least 250 g carbohydrate and 70–90 g protein per day. All studies were performed while patients were hospitalized. Patients were admitted to the Department of Internal Medicine I of the Istituto Scientifico H San Raffaele (Milan, Italy) or to the Third Department of Medicine of the Justus-Liebig Universität (Giessen, Germany) for the execution of the insulin clamp 1–2 days before the study. Patients on subcutaneous insulin treatment received the last doses of intermediate and short-acting insulin 18 and 12 h, respectively, before the experimental procedure. The next morning, after a 10-h overnight fast, two indwelling catheters were placed in an antecubital vein for the infusions and retrogradely in the wrist vein of the opposite arm for blood sampling, as previously described (1). Arterialization was obtained via a heated box at the sampling site. Subjects received [3-^{3}H]glucose and [1-^{14}C]leucine (in Milan, Italy) and [6,6-$^2H_2$]glucose and [1-^{13}C]leucine (in Giessen, Germany) as boluses followed by continuous infusions to assess whole-body rates of glucose and protein metabolism for 300 min (1,16–18). After a 150-min tracer equilibration period, a 40 mU · m^{-2} · min^{-1} insulin infusion was given while maintaining euglycemia via a 20% dextrose solution (1). Indirect calorimetry was performed in the basal postabsorptive condition and during the last 45 min of the clamp, as previously described (16–20). Blood samples were taken every 10 min in the last hour of the equilibration period and throughout the insulin/glucose infusion for the measurement of tracer enrichments and specific activities as well as substrate and hormone concentrations. Breath samples were collected every 10 min in the last hour of each the basal state and the insulin/glucose infusion for the measurement of $^{14}CO_2$ radioactivity (17,21) and $^{13}CO_2$ enrichment (22). We also studied five additional type 1 diabetic patients with partial function and five healthy volunteers to assess plasma albumin synthetic rates in the postabsorptive condition. These subjects received a primed-continuous infusion of [3,3,3-$^2H_3$]leucine (bolus 7 µmol/kg; continuous infusion 7 µmol · kg^{-1} · h^{-1} for 5 h). Blood sam-

TABLE 2
Classification of intraportal islet allografts on the basis of functional criteria

	n	C-peptide (nmol/l)	Insulin dose (U · kg^{-1} body wt · day^{-1})	FPG (mmol/l)	HbA_{1c} (%)
FF	6	0.986 ± 0.149	0	6.05 ± 0.39	6.4 ± 0.2
PF	17	0.540 ± 0.072*	0.29 ± 0.06*	8.05 ± 0.61	6.6 ± 0.3
NF	9	0.113 ± 0.043*	0.82 ± 0.08*	14.93 ± 2.50†	7.0 ± 0.4‡
CU	6	0.970 ± 0.189	—	4.88 ± 0.11	5.9 ± 0.4

Data are means ± SE. Major criteria—C-peptide (nmol/l): FF > 0.6; PF > 0.16; NF < 0.16; insulin dose (U · kg^{-1} body wt · day^{-1}): FF = 0; PF < 0.4; NF > 0.4. Minor criteria—fasting glucose (mmol/l): FF < 7.77; HbA_{1c} (%): FF < 6.5. *P = 0.01 vs. FF and CU; †P = 0.01 vs. all groups; ‡P = 0.05 vs. CU.

TABLE 3
Plasma leucine, branched-chain amino acids, and nonesterified fatty acids in the postabsorptive state and after hyperinsulinemia

		Postabsorptive			Hyperinsulinemia		
	n	Leucine (μmol/l)	BCAA (μmol/l)	NEFA (μmol/l)	Leucine (μmol/l)	BCAA (μmol/l)	NEFA (μmol/l)
FF	6	93.4 ± 7.6	273.2 ± 20.2†	615 ± 92	49.4 ± 5.9	167.5 ± 12.9	29 ± 9
PF	17	101.1 ± 5.9	337.6 ± 16.6	739 ± 79	50.6 ± 3.1	211.7 ± 22.6	64 ± 17
NF	9	144.7 ± 17.9*	504.3 ± 62.9*	766 ± 90	69.4 ± 10.6	307.8 ± 39.9	199 ± 89‡
CON	6	121.0 ± 5.1	442.5 ± 22.9	756 ± 139	59.4 ± 3.5	250.3 ± 16.8	107 ± 25

Data are means ± SE. *P = 0.01 vs. FF and CU; †P = 0.01 vs. all groups; ‡P = 0.05 vs. FF, PF, and CU. BCAA, branched-chain amino acids; CON, control subjects; NEFA, nonesterified fatty acids.

ples were taken before the infusion of the isotope and every 30 min thereafter. All bedside studies were directly supervised by Dr. Livio Luzi (both in Italy and Germany), and all tracer measurements were carried out in Dr. Luzi' s laboratory. The protocol was approved by the Institutional Ethical Committees of San Raphael Scientific Institute, Milan, Italy and the Justus-Liebig University, Giessen, Germany; informed consent was given by all study subjects.

Analytical determinations and calculations. Plasma glucose was measured at bedside with a Beckman glucose analyzer (1); free insulin, C-peptide, glucagon, free fatty acid (FFA), tritiated glucose–specific activity, ^{14}C-leucine–specific activity, ^{14}C-ketoisocaproate (KIC)–specific activity, and deuterated glucose enrichment were measured as previously described (16–19,21). α-Ketoacid enrichments were measured by means of electron impact gas chromatography–mass spectrometry (GC-MS) using a derivatization with boroacetylation (1). $^{14}CO_2$-specific activity in breath was measured by β-scintillation as previously described (17,21). The $^{13}CO_2/^{12}CO_2$ isotope ratio in expired air was measured by isotope ratio MS (22). Endogenous glucose production and peripheral glucose disposal were measured as previously described (1,16,19). Endogenous leucine flux (proteolytic rate), nonoxidative leucine disposal (protein synthetic rate), and leucine oxidation were calculated using both the leucine- and the α-ketoisocaproic acid–specific activity/enrichment, as previously described (17,21,22). Isolation of plasma albumin was performed according to the method of Korner and Debro (23). Plasma was deproteinized with 10% trichloroacetic acid and centrifuged. The supernatant was discarded and the pellet was resuspended in pure ethanol. The samples were centrifuged and the supernatant containing albumin was retained. The purity of each of the albumin preparations was tested in an aliquot of the supernatant by SDS-PAGE after evaporation under nitrogen stream and resuspension in distilled water. Hydrolysis of albumin was performed in a second aliquot of the supernatant that was evaporated under nitrogen and heated in 6N HCl for 24 h. The hydrolysate was filtered and then derivatized to the *N*-heptafluorobutyryl-*N*-propyl amino acid esther derivative as previously described (18). The enrichment of [3,3,3-$^2H_3$]leucine incorporated in albumin was measured in quadruplicate by GC-MS, as previously described (18). The incorporation rate of [3,3,3-$^2H_3$]leucine into albumin was expressed as mole percent excess/day, calculated by least-squares regression analysis, and was linear between the first and fifth hour of the study. The daily fractional synthetic rate (FSR) of albumin (expressed as the percentage of the protein pool renewed each day) was calculated by dividing the mean tracer incorporation rate into albumin by the precursor enrichment. The plasma enrichment of [3,3,3-$^2H_3$]KIC was assumed to represent the intracellular precursor pool enrichment for albumin synthesis. The absolute rate of albumin synthesis ($mg \cdot kg^{-1} \cdot h^{-1}$) was calculated as the product of FSR and the albumin concentration, assuming a distribution volume of 40 ml/kg.

Statistical analysis. Data are given as group means ± SE. Statistical differences among groups were performed using Student's *t* test and analysis of variance, with Scheffe's post hoc testing when appropriate.

RESULTS

Postabsorptive condition. FF, PF, and NF patients (Table 1) had 100, 57, and 13% reductions, respectively, in required insulin dosage compared with their pretransplant condition (Table 2). NF patients had significantly higher levels of glucose (P < 0.01) compared with the FF and PF patients and patients with chronic uveitis (CU; control subjects) (Table 2) and higher levels of branched-chain amino acids (P < 0.01) and leucine (P < 0.01) with respect to the FF and PF patients (Table 3). Plasma FFA and glycerol were comparable among groups. PF patients had a slightly higher glucose concentration (P = 0.08) (Table 2), but normal leucine and branched-chain amino acids (with a trend for lower values; P = 0.07) (Table 3) and normal FFA (Table 3) and glycerol (108 ± 27, 136 ± 23, 125 ± 45, and 86 ± 27 in the NF, PF, FF, and CU groups, respectively; P = 0.605) concentrations with respect to the CU group. FF patients had normal plasma glucose, lower plasma leucine (P = 0.07) and branched-chain amino acids (P < 0.01), and normal FFA and glycerol concentrations compared with the CU group. In the postabsorptive state, triglyceride concentration was comparable in the NF (115 ± 12), PF (133 ± 18), FF (180 ± 44), and CU groups (180 ± 26 mg/dl). Total cholesterol was higher in the NF (218 ± 7), PF (243 ± 15), and FF groups (257 ± 18) compared with the CU group (162 ± 13 mg/dl; P = 0.05) and HDL cholesterol was higher in the NF (65 ± 7; P = 0.05), PF (72 ± 6; P = 0.05), and FF groups (50 ± 9; P = 0.08) compared with the CU group (39 ± 11 mg/dl).

Insulin clamp condition. During insulin infusion, the plasma glucose concentration was maintained at the basal level in the FF and CU groups (~5 mmol/l), but allowed to decrease to ~8 mmol/l in the NF group (a value comparable with the postabsorptive level of the PF group), then subsequently clamped via a 20% dextrose infusion at those levels. Plasma leucine and branched-chain amino acids decreased to similar concentrations in the NF, PF, FF, and CU groups during the clamp (Table 3). In contrast, FFA concentration was not suppressed in a similar fashion in the NF group in comparison to the PF (P = 0.03), FF (P = 0.03), and CU groups (P = 0.05) (Table 3).

Pancreatic peptides. Fasting plasma free insulin levels were comparable in all study groups (65 ± 18, 73 ± 9,59 ± 12, and 78 ± 14 pmol/l in FF, PF, NF, and CU, respectively). However, the C-peptide concentration was different in the NF and PF groups, but not in the FF group when compared with the CU group, as the C-peptide concentration was considered a criterion for classification of subgroups (Table 2). Postabsorptive plasma glucagon concentration was comparable among groups (107 ± 20, 120 ± 18, 94 ± 14, and 119 ± 11 pg/ml in the NF, PF, FF, and CU groups, respectively). During hyperinsulinemia (plateau insulin concentrations of 441 ± 46, 435 ± 29, 378 ± 39, and 488 ± 25 pmol/l in the FF, PF, NF, and CU groups, respectively), the C-peptide concentrations remained low in the NF group and became physiologically suppressed in the NF (0.056 ± 0.02 nmol/l; P = 0.03 vs. basal), PF (0.30 ± 0.04 nmol/l; P < 0.01 vs. basal), and FF groups (0.57 ± 0.14 nmol/l; P = 0.01 vs. basal) compared with the CU group (0.57 ± 0.09; P < 0.01 vs. basal). Similarly,

TABLE 4
Glucose and leucine metabolism in the postabsorptive state and during the insulin clamp

	Postabsorptive				Insulin clamp			
	FF	PF	NF	CU	FF	PF	NF	CU
Glucose metabolism								
n	6	17	9	6	6	17	9	6
EGP	2.492 ± 0.250	3.006 ± 0.248	6.414 ± 1.612*	2.200 ± 0.181	0.000 ± 0.000	0.152 ± 0.084	2.028 ± 0.891	0.184 ± 0.124
Total glucose disposal	—	—	—	—	4.548 ± 1.112	4.367 ± 0.263	3.246 ± 0.770	4.678 ± 0.355
Glucose oxidation	—	—	—	—	1.131 ± 0.298	1.454 ± 0.268	1.133 ± 0.230	1.600 ± 0.153
Nonoxidative glucose disposal	—	—	—	—	3.417 ± 0.917	2.913 ± 0.201	2.113 ± 0.516	3.078 ± 0.306
MCR	2.324 ± 0.224	2.051 ± 0.113†	1.917 ± 0.169†	2.507 ± 0.229	5.073 ± 1.278	4.417 ± 0.297	2.312 ± 0.650*	5.412 ± 0.508
Leucine metabolism (primary pool)								
Endogenous leucine flux	45.3 ± 5.0	44.8 ± 4.6	60.9 ± 7.5†	43.6 ± 5.7	33.4 ± 5.7	29.5 ± 3.4	31.2 ± 9.4	25.8 ± 4.5
Leucine oxidation	—	7.4 ± 2.1	7.1 ± 1.0	6.2 ± 1.1	—	4.8 ± 2.9	3.7 ± 1.4	2.8 ± 0.7
Nonoxidative leucine disposal	—	37.4 ± 4.1	53.8 ± 7.0	37.5 ± 4.9	—	24.7 ± 4.3	27.5 ± 9.9	23.0 ± 2.7

Data are means ± SE. EGP, total glucose disposal, glucose oxidation, and nonoxidative glucose disposal are expressed as mg · kg^{-1} · min^{-1}. Glucose metabolic clearance rate (MCR) is expressed as ml · kg^{-1} · min^{-1}. Endogenous leucine flux, leucine oxidation, and nonoxidative leucine disposal are expressed as µmol · m^{-2} · min^{-1}. *P = 0.01 vs. FF, PF, and CU; †P = 0.05 vs. CU.

the plasma glucagon concentration in all groups decreased during the clamp (12 ± 6, 29 ± 9, 28 ± 14, and 18 ± 5% in the NF, PF, FF, and CU groups, respectively).

Glucose and protein turnovers. Postabsorptive endogenous glucose production (EGP) was higher in the NF group when compared with the PF, FF, and CU groups (P = 0.01) (Table 4). In contrast, the PF and FF groups showed similar rates when compared with the CU group (P = 0.71). Also, the insulin-dependent suppression of EGP during the clamp was defective in the NF group (P < 0.01); the PF and FF groups showed a normal pattern of suppression in comparison with the CU group (Table 4). Insulin-stimulated glucose metabolism calculated during the last hour of the clamp study did not show any differences among groups (P = 0.306), albeit it did show a trend for lower rates in the NF group (P = 0.101). The metabolic clearance rate of glucose was lower in the NF group than in the other groups (P < 0.01). Postabsorptive endogenous leucine flux was higher in the NF group than in the other groups, using either the primary or reciprocal pool model (P = 0.05) (Table 4). Endogenous leucine flux decreased to similar values during the clamp in all groups (Table 4). Basal leucine oxidation and nonoxidative leucine disposal (index of protein synthesis) were higher in the NF (P < 0.05) than in the other groups; during insulin infusion, both parameters decreased similarly in all groups (Table 4). Using either the primary or reciprocal pool model, data were comparable and differences among groups were similar. For the FF group, data on only the endogenous leucine flux were available, due to technical difficulties in collecting expired breath samples in Giessen.

Lipid oxidation. Postabsorptive lipid oxidation was increased in the NF group (1.710 ± 0.462 mg · kg^{-1} · min^{-1}; P = 0.03) versus all other groups (0.826 ± 0.229, 1.130 ± 0.158, and 1.183 ± 0.181 mg · kg^{-1} · min^{-1} in the FF, PF, and CU groups, respectively). During the insulin clamp, lipid oxidation was suppressed similarly in the CU, FF, and PF groups (0.487 ± 0.041, 0.489 ± 0.296, and 0.607 ± 0.184 mg · kg^{-1} · min^{-1}, respectively), but was still persistently higher in the NF group (1.200 ± 0.474 mg · kg^{-1} · min^{-1}; P = 0.01).

Albumin synthetic rate. Type 1 diabetic patients with intraportal islet transplantation had a normal albumin concentration (38.3 ± 1.4 vs. 40.8 ± 2.3 g/l; P = 0.416), hepatic albumin synthetic rate (7.0 ± 0.8 vs. 8.2 ± 0.9 mg · kg^{-1} · h^{-1}; P = 0.670) and albumin fractional synthetic rate (11.16 ± 1.56 vs. 12.08 ± 0.58%; P = 0.855) when compared with that of normal healthy subjects.

DISCUSSION

Intrahepatic islet transplantation entails the injection of ~1–2 ml of packed islet tissue in the portal vein under angiographical guide. The procedure is minimally invasive, relatively safe, and repeatable (1). However, the success rate 1 year after islet transplantation is considerably lower than after whole-pancreas transplantation (24). The aim of the present study was to examine the metabolic effects of the full and partial islet functions (based on criteria given in Table 2) with special regard to intermediary metabolism and pancreatic peptides secretion. This study showed that the restoration of partial function (with an ~60% reduction of pretransplant insulin requirement) normalized postabsorptive and insulin-mediated protein and lipid metabolism. In contrast, glucose homeostasis remained mildly abnormal. A full function of the islet allograft (with an ~100% reduction of pretransplant insulin requirement) can also normalize glucose homeostasis. Our findings are particularly important in light of the high prevalence of partial function in experienced centers. Table 5 represents the percentage of FF and PF patients in the Milan (n = 23 patients) and Giessen (n = 22 patients) populations during the first 4 years after the transplantation. Based on the present data, 81% of patients in the 1st year, 43% in the 2nd year, 29% in the 3rd year, and 16% in the 4th year had either full or partial function, and therefore normal lipid and protein homeostasis.

Analysis of studies in which the amino acid and lipid concentrations were measured in type 1 diabetic patients on conventional or intensive insulin treatment (25,26) suggests that the metabolic abnormalities of islet-transplanted patients with partial function are comparable with those of

TABLE 5
Islet allografts in patients with type 1 diabetes

Posttransplant (years)	Giessen (n = 23)		Milano (n = 22)		Giessen and Milano (n = 45)	
	PF	FF	PF	FF	PF	FF
0	12 (52)	5 (22)	12 (55)	7 (32)	24 (53)	12 (27)
1	5 (22)	4 (17)	5 (23)	5 (23)	10 (22)	9 (20)
2	4 (17)	3 (13)	1 (5)	5 (23)	5 (11)	8 (18)
3	1 (4)	1 (4)	5 (23)	0	6 (13)	1 (2)

Data are n (%).

type 1 diabetic patients on insulin treatment. If one considers that in grafted patients insulin is secreted intrahepatically, undergoing the first-pass cleavage by the liver and avoiding peripheral hyperinsulinemia, islet transplantation is seen as being even more efficacious, even in conditions characterized by only partial function. Moreover, the degree of metabolic compensation of type 1 diabetic patients with an islet transplant is obtained notwithstanding the chronic immunosuppressive treatment. This observation is noteworthy in light of the fact that all the immunosuppressive drugs are administered orally, therefore having a major first-pass effect on hepatic metabolism as well as an adverse effect on islet secretory capacity. The finding that type 1 diabetic patients with only partial function had a normal albumin secretion rate underlines the efficacy of such a procedure in restoring normal hepatic glucose and protein metabolism. Furthermore, it is striking to note that the NF patients were all on intensified insulin therapy, but with immunosuppression; this regimen may have been responsible for the increased proteolytic rates in NF patients when compared with insulin-treated type 1 diabetic patients (7). Interestingly, FF patients showed a normalization of glucose homeostasis and low plasma concentration of amino acids. This clinical pattern resembles the pattern of type 1 diabetic patients on intensive treatment (25–27). However, in the latter group, metabolic control was obtained at the expense of a high prevalence of hypoglycemia (27), whereas no hypoglycemic episode was seen in islet-transplanted patients. This finding is very likely secondary to the near-physiological insulin secretion of islet allografts in FF patients.

Kahn et al. (28) proposed a disposition index for glucose metabolism, correlating insulin secretion and BMI with insulin sensitivity (28). Although such additional analysis of data would have been appropriate for our PF and FF patients, extending the correlation to protein and lipid metabolism and permitting the definition of discrete insulin regulatory thresholds for protein, glucose, and lipid metabolism, it was not possible to do so with the small number of available subjects (n = 23) in this study.

The high value of residual EGP during the insulin clamp (Table 4) confirmed our previous findings in type 1 diabetic patients with islet transplantation (1). Because an appropriate steady state of specific activities/enrichments of tracers was achieved after 100 min of insulin infusion, other factors, such as increased intrahepatic glucagon delivery, variability of the islet reinnervation pattern, and local effect of immunosuppressive drugs may explain the EGP values.

Recent reports have suggested a physiological role for the C-peptide molecule also, mainly via activation of the Na^+-K^+ ATPase pump (13,14). C-peptide was shown to affect both metabolism (29–31) and diabetic complications (14,32,33). Overall, the new set of data on C-peptide function may help to explain the good metabolic control of type 1 diabetic patients with a partially functioning graft. A positive effect of pancreas transplantation (yielding the same levels of plasma C-peptide as PF patients) is already established for diabetic neuropathy (34). In addition, a reversal of the morphological lesions of diabetic nephropathy after 10 years of successful pancreas transplantation has been shown recently (35). We hypothesize that this effect might be linked to the restoration of C-peptide and proinsulin secretion along with insulin (36). Finally, we recently found higher postabsorptive C-peptide levels in type 1 diabetic patients without renal complications than in patients with micro- and macroalbuminuria (37). Our data did not demonstrate a cause-effect relationship between C-peptide level and the described metabolic effects, as it is likely that the results would have been similar with aggressive insulin treatment.

In conclusion, restoring partial function to the secretory capacity of β-cells can lead to the normalization of protein and lipid metabolism, leaving glucose metabolism only moderately impaired The present study indicates that the "success" of islet transplantation may best be defined by a number of metabolic criteria, not just glucose concentration/metabolism alone.

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