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Type 2 Diabetes Mellitus Phenotype and Graft Survival after Islet Transplantation¹

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Abstract

Background—Body fat accumulation decreases insulin sensitivity. It has been associated with earlier onset of type 1 diabetes mellitus (DM) and islet graft failure. The aim of this study was to evaluate whether insulin resistance, characterized by risk factors for type 2 diabetes mellitus (DM), can predict islet graft survival in type 1 DM islet transplant (ITx) recipients.

Methods—Demographic, anthropometrical and laboratory data, as well as family history of type 2 DM (first degree relatives), were collected from 44 ITx recipients. Risk factors for type 2 DM, such as positive family history of type 2 DM (n=11) and overweight (BMI >25 kg/m²; n=14), were analyzed separately and in combination, which was designated as “type 2 DM phenotype” (n=5). Differences in outcomes (time-to-graft dysfunction and failure) were compared using Kaplan-Meier curves. Cox-regression analysis was performed to control for possible confounding factors.

Results—Neither positive family history of type 2 DM nor overweight at baseline could predict islet function outcomes after ITx. However, when both risk factors were grouped, the “type 2 DM phenotype” was associated with earlier islet graft failure (mean estimate graft survival 25.7±9.1 vs.

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54.1±5.2 months, $P=0.022$). These results were sustained after adjustments for confounding variables (OR5.20, 95% CI1.12-24.0).

Conclusions—Predisposition for type 2 DM can coexist with the type 1 DM phenotype and is associated with earlier decline in islet graft function. Prospective clinical trials should address whether it is associated with decreased insulin sensitivity and if insulin sensitizers play a role in prolonging islet graft survival.

Keywords

Type 1 diabetes; islet transplantation; family history of type 2 diabetes; overweight; hypotoxicity

Transplantation of allogeneic islets of Langerhans is an option for treating patients with unstable type 1 diabetes mellitus (DM) (1). Infused islets lead to blood glucose stabilization, resulting in better metabolic control, lower incidence of hypoglycemia and improvement in long-term quality of life (2,3,4,5,6). However, not all patients are able to achieve insulin independence after transplant and a gradual decrease in islet function has been observed over time (5).

Several factors have been associated with graft dysfunction and failure after islet transplantation (ITx) (6). Among them, recipient's body mass index (BMI) appears to play an important role (7). Body fat accumulation decreases insulin sensitivity, resulting in increased insulin demands (8) which has been associated with metabolic disarrangement in other models of beta-cell loss. In type 2 DM subjects, overweight/obesity is a well-known risk factor for hyperglycemia onset in genetic predisposed individuals (9). Similarly, type 1 DM, which is caused by an association of human leukocyte antigen (HLA) susceptibility genes and ambient triggers can initiate earlier if excessive weight is gained during childhood (10). Recently, clinical features of type 2 DM were recognized in adults with type 1 DM and the mixed phenotype, known as “double diabetes”, was associated with increased risk for chronic complications (11).

So far, the effects of a mixed DM phenotype on islet graft function in ITx recipients have not been studied. The aim of this study was to determine if risk factors for type 2 DM, particularly genetic predisposition and increased BMI, could affect islet graft function in type 1 DM ITx recipients.

Methods

Subjects

A retrospective cohort study was conducted in 44 subjects [37 ITx alone and 7 islet after kidney (IAK)] with type 1 DM, post allogeneic ITx between 2000 and 2007 (follow-up: 40.9 ± 23.5 months) that have been followed in a single center. Inclusion and exclusion criteria were described formerly (3). Subjects with BMI $>26\text{ kg/m}^2$ in the first screening visit were excluded as per protocol. However, some patients gained weight while in the waiting list and were transplanted with BMI slightly higher than 26 kg/m^2 ($n=4$).

Transplant related procedures

The pancreatic islet isolation, infusion and immediate post-transplant management were performed as previously described (3). The maintenance immunosuppressive regimen was composed of tacrolimus (Prograf®, Astellas-Pharma US, Inc., Deerfield, IL, USA), target trough level 4–6 ng/mL and sirolimus (Rapamune®, Wyeth Pharmaceuticals, Inc., Madison, NJ, USA), target trough level 10–15 ng/mL for 3 months, 8–12 ng/mL thereafter. Three IAK recipients were on maintenance doses of corticosteroids (5 mg of prednisone).

Fourteen subjects were converted from tacrolimus or sirolimus to Mycophenolate Mofetil (CellCept®, Roche, Nutley, NJ, USA) or Mycophenolic Acid (Myfortic®, Novartis, East Hanover, NJ, USA), targeting maximum tolerable dosage (maximum of 2000 mg and 1440 mg, respectively), as per protocol (n=6) or due to immunosuppressive related side-effects (n=8).

Another variations within protocols was the use of different induction agents: five-dose course of daclizumab (Zenapax®, Roche, Nutley, NJ, USA; 1 mg/kg biweekly; n=38); or alemtuzumab (Campath®, Genzyme, Cambridge, MA, USA; 20 mg IV on -1 and 0 POD; n=6), and use of anti-inflammatory agents infliximab (Remicade®, Centocor, Malvera, PA, USA; 5-10 mg/kg 2 h prior to islet infusion, single dose) or etanercept (Enbrel®, Amgen and Wyeth Pharmaceuticals, Thousand Oaks, CA, USA 50 mg IV 1 h prior to islet infusion and 25 mg twice a week for 2 weeks). All subjects received antiviral prophylaxis for cytomegalovirus and *P. carinii* pneumonia.

All protocol procedures were approved by the University of Miami health research ethics board (IRB) and appropriate informed consent was obtained from each subject.

Clinical data assessment

Clinical variables [age, gender, ethnicity, diabetes duration, family history of type 2 DM in first degree relatives, body weight and height (without shoes or coats, obtained with an anthropometric scale), systolic and diastolic blood pressure (BP)], insulin dosage per kilogram of body weight (U/kg), the presence of islet auto anti-bodies, number of infusions and islet equivalents (IEQ) infused, exenatide use and immunosuppressive medication data were recorded. BMI was calculated with the formula: weight/height^2 (kg/m^2) and overweight was defined as $\text{BMI} \geq 25 \text{ kg/m}^2$ at the time of first transplant. To evaluate the effect of tacrolimus-sirolimus combination on islet function, a perceptual exposed time was calculated [%exposed time = (time on combination in months*100/total follow-up in months)*100]. Diabetic retinopathy (DR) was classified as absent, nonproliferative, or proliferative based on ophthalmologic report. Autonomic and peripheral neuropathies were diagnosed by clinical symptoms and/or compatible physical examination and cardiovascular disease by history and stress test.

Laboratory analysis

Glycemic profiles were evaluated by fasting plasma glucose (hexokinase method) and HbA1c [high performance liquid chromatography (HPLC), Variant II Hemoglobin Testing System, BioRad, Richmond, CA, inter- and intra-assay variation: 1.7% and <2.0%]. C-peptide was measured by double antibody radioimmunoassay (detection limits: 0.3–5.0 ng/mL, inter- and intra-assay variation coefficient <10%, cross-reactivity with insulin and pro-insulin: 20%) at fasting and during a mixed meal test (Boost high protein; 240 kcal, protein: 15 g, carbohydrates: 33 g, fat: 6g; Novartis/Sandoz – Nestle Nutrition). Anti-GAD56, anti-IA2 and anti-insulin auto anti-bodies were measured by standard radioimmunoassay. Fasting lipids (total cholesterol, HDL-cholesterol and triglycerides) were measured by the enzymatic method and LDL-cholesterol was determined by the Friedewald equation. Serum creatinine was measured by Jaffé method (Roche Diagnostics, Roche Cobas-Mira, inter- and intra-assay variation: 1.4% and 2.1%) and albuminuria by immunoturbidimetry (Beckman-Synchron/CX9, Ramsey, Minnesota, USA). Diabetic nephropathy (DN) classification was performed as follows: normoalbuminuria (UAER <30 mg/24 h), microalbuminuria (30–299 mg/24 h) or macroalbuminuria ($\geq 300 \text{ mg/24 h}$) based on 2-out-of-3 pre-transplant measurements.

Outcomes

Graft function was determined by the combination of C-peptide measurements, fasting and postprandial capillary glucose levels and HbA1c values, and categorized in the following manner:

Insulin independence—positive C-peptide, fasting plasma glucose <140 mg/dl and postprandial plasma glucose <180 mg/dl, with an HbA1c <6.5%, for at least 2 weeks.

Graft dysfunction—positive C-peptide, fasting plasma glucose >140 mg/dl and/or postprandial plasma glucose >180 mg/dl more than 3 times in one-week period and/or HbA1c >6.5% in 2 consecutive measurements.

Graft failure—fasting C-peptide ≤ 0.10 ng/ml in 2 consecutive measurements (in absence of hypoglycemia) or mixed meal stimulated C-peptide ≤ 0.3 ng/ml.

Statistical analysis

Statistical analysis and graphics were done using Excel[®] for Windows[®] and SPSS[®] 15.0 software. Continuous variables are expressed as means $\pm$ SD except for triglycerides [median (interquartile range)] and categorical data as number of cases (%). Kaplan-Meier curves [Log Rank (Mantel-Cox) test] were used to evaluate the association between risk factors for type 2 DM: family history of type 2 DM, overweight or their combination, designed as “type 2 DM phenotype”; and outcomes: graft dysfunction and failure. Student t-test and chi-square test were used to compare clinical and laboratory variables between subjects with and without “type 2 DM phenotype”. Adjustments for possible confounders (variables associated with “type 2 DM phenotype” in the univariate analysis and/or those with possible biological relevance) were performed with Cox-regression analysis. P values of <0.05 (2-tailed) were considered significant.

Results

Recipient mean age at first transplant was 43.0 ± 8.6 years and the mean diabetes duration was 29.3 ± 11.7 years. Eighteen (41%) recipients were male and all were white. Chronic diabetes complications at baseline included DR in 71% of the subjects (n=31; 18 proliferative), DN in 32% (n=14, 30 normo-, 7 microalbuminuria and 7 with a kidney graft), peripheral neuropathy in 30% (n=13), autonomic neuropathy in 25% (n=11) and cardiovascular disease in 4.5% (n=2). Twenty-five percent (n=11) of the cohort reported a positive family history of type 2 DM in first degree relatives and 32% were overweight (n=14; mean BMI 26.2 ± 1.3 kg/m²) at the time of first transplant.

Family history of type 2 DM could not predict time to graft dysfunction (family history absent: 12.3 ± 2.5 vs. present: 10.1 ± 3.0 months, P=0.57) or time to graft failure (family history absent: 51.2 ± 5.7 vs. present: 45.0 ± 7.7 months, P=0.82) (Figure 1A). In the same way, being overweight at baseline was not associated with any of the outcomes (graft dysfunction – overweight absent: 10.2 ± 2.0 vs. present: 15.7 ± 4.8 months, P=0.32; graft failure - overweight absent: 47.7 ± 5.7 vs. present: 56.4 ± 8.2 months, P=0.55) (Figure 1B showing graft failure).

However, when recipients with both risk factors (n=5) were compared to the others (n=39), those with “type 2 DM phenotype” showed a trend to earlier graft dysfunction (“type 2 DM phenotype” absent: 12.6 ± 2.1 vs. present: 4.2 ± 3.3 months, P = 0.089) and significant shorter time to graft failure (absent: 54.1 ± 5.2 vs. present: 26.7 ± 9.1 months, P = 0.022; Figure 2).

In order to further investigate if other factors co-expressed with the “type 2 DM phenotype” could be confounding the results, we compared clinical and laboratory characteristics between those with and without the “type 2 DM phenotype” (Table 1). Patients had similar clinical and laboratory characteristics in most of the studied variables, except for gender (males - “type 2 DM phenotype” absent: 33% vs. present: 100%, $P = 0.004$) and tacrolimus-sirolimus % exposure time (“type 2 DM phenotype” absent: 81.9% vs. present: 94.4%, $P = 0.03$). Interestingly, the group with “type 2 DM phenotype” had trends to lower HDL-cholesterol (“type 2 DM phenotype” absent: 1.82 ± 0.37 vs. present: 1.50 ± 0.33 mmol/l, $P = 0.08$) and higher triglycerides levels [“type 2 DM phenotype” absent: 0.69 (1.26) vs. present: 0.96 (0.57) mmol/l, $P = 0.053$] when compared to the others, although without achieving conventional statistical significance and with values still within the normal range.

Multivariate analysis was performed using Cox-regression, with time to graft failure as the dependent variable and “type 2 DM phenotype” as an independent one. The covariates included in the model were those related to the phenotype in univariate analysis (gender and tacrolimus-sirolimus % exposure time) and others that could play a role as islet function determinants: positive auto-antibodies at baseline, number of islet infusions and use of exenatide. The “type 2 DM phenotype” remained associated with earlier graft failure even after the adjustments (OR 5.2, 95% CI 1.1-24.0, $P = 0.035$) (Table 2). When HDL-cholesterol or triglycerides were added to the model, the “type 2 DM phenotype” continued to be associated with graft failure (OR 5.2, 95% CI 1.1-24.3, $P = 0.037$ and OR 6.5, 95% CI 1.3-33.3, $P = 0.032$, respectively).

Discussion

In this sample of ITx recipients, the combination of classical risk factors for type 2 DM was associated with earlier islet graft loss, although it could not be predicted independently either by family history of type 2 DM or by being overweight. Notably, the relationship between “type 2 DM phenotype” and graft failure was independent from possible confounding factors.

Increased adiposity is recognized as one of the main factors related to the increment in type 2 DM incidence over the last decades (12). Recently, it has also been associated with type 1 DM development at younger ages (10,13). In both conditions, the pathogenesis might be a decrease in insulin sensitivity caused by fat tissue accumulation. However, hyperglycemia onset can only be seen when insulin secretion capacity is not able to overcome higher insulin requirements in low insulin sensitivity states.

Similarly, shorter islet graft survival has been reported in association with higher BMI in ITx recipients (7). In the present series, overweight alone could not predict islet graft failure, but when coupled with the insulin resistant genetic background; a clear association became evident. The mechanisms of islet graft failure in ITx recipients are probably similar to those causing type 2 DM. Lower insulin sensitivity leads to an increment in insulin secretion demands in order to maintain a normal glycemia. This homeostasis is kept as long as the beta cells are able to sustain a high insulin secretion rate. In the case of ITx and beta cell marginal mass, at some point the islets cannot longer overcome the peripheral demands, resulting in diabetes recurrence.

Moreover, the high blood glucose associated with increased levels of free fatty acids, which is a characteristic of insulin resistance states, can lead to beta-cell gluco- and lypotoxicity (14), increasing the beta-cell losses even further. Recently, lypotoxicity was been associated with beta-cell mass loss after ITx in an animal model (15), and it was prevented by a lipid depleting therapy (diet or hyperexpression of leptin gene). Free fat acids can produce beta-cell apoptosis by inducing endoplasmic reticulum stress, and this phenomenon is independent from glucotoxic mechanisms (16). Another factor affecting glucose homeostasis is the ITx infusion

site, the liver, which can play a role by increasing islet exposure to the high levels of glucose and lipids present in the portal vein system. Moreover, lipidic accumulation surrounding the islets in the liver (multifocal steatosis) has been reported in ~20% of ITx recipients and has been associated with islet dysfunction (17).

Our study has some limitations. The retrospective analysis did not allow the evaluation of insulin sensitivity, either directly by euglycemic hyperinsulinemic clamp, or by surrogate markers such as waist circumference. Also, we recognize that our sample size is relatively small, which could be responsible for the lack of association between isolated positive family history of type 2 DM or overweight and islet survival. However this is a characteristic of a field in development and actually this sample accounts for ~12% of the overall ITx recipient population of US and Canada (6).

In conclusion, predisposition for type 2 DM can coexist with type 1 DM phenotype and it is associated with earlier decline in islet graft function in ITx recipients. Our findings suggest that candidates for ITx with family history of type 2 DM should have normal BMI at the time of the transplant. Prospective clinical trials should address whether or not this is associated with lower insulin sensitivity, or if therapeutic interventions, such as diet manipulation, exercise and/or insulin sensitizers/lipid depleting agents, could play a role in prolonging islet graft survival.

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Abbreviations

DM	diabetes mellitus
DN	diabetic nephropathy
DR	diabetic retinopathy
IAK	islet after kidney
IEQ	islet equivalents
ITx	islet transplant
IRB	health research ethics board

A Family history of type 2 diabetes **B Overweight at baseline** **Figure 1.**

Islet graft survival in subjects with and without risk factors for type 2 diabetes:

(A) family history of type 2 diabetes (present: continuous line vs. absent: dashed line),

(B) baseline overweight (body mass index ≥ 25 mg/kg²; present: continuous line vs. absent: dashed line). Comparisons were done with Kaplan-Meier curves and Log Rank (Mantel-Cox) test.

Family history of type 2 diabetes and overweight (type 2 DM phenotype)

Figure 2.

Islet graft survival in subjects with and without the combination of family history of type 2 diabetes and baseline body mass index ≥ 25 mg/kg²: “type 2 diabetes phenotype” (present: continuous line vs. absent: dashed line). Comparisons were done with Kaplan-Meier curves and Log Rank (Mantel-Cox) test.

Table 1

Clinical and laboratory characteristics according to “type 2 DM phenotype” presence.

	Type 2 diabetes family history + overweight		
	“Type 2 DM phenotype”		P
	NO (n=39)	YES (n=5)	
Age (years) *	43.2±7.9	41.4±13.8	0.79
Diabetes duration (years) *	29.2±11.3	29.6±16.3	0.94
Males - n (%)	13 (33)	5 (100)	0.004
Dyslipidemia - n (%) *	19 (49)	3 (60)	0.64
Hypertension - n (%) *	13 (33)	1 (20)	0.55
Systolic Blood Pressure (mm Hg) *	121.4±16.2	112.0±7.5	0.21
Diastolic Blood Pressure (mm Hg) *	70.1±14.7	72.8±6.6	0.69
Body mass index (kg/m ²) *	23.4±2.4	25.8±0.5	NA
Insulin dosage (UI/kg) *	0.53±0.12	0.56±0.16	0.69
Positive auto-antibody - n (%) *	23 (59)	4 (80)	0.36
Fasting glucose (mmol/l) *	8.85±3.52	7.55±4.88	0.47
HbA1c (%) *	7.3±1.2	7.3±0.4	0.98
Total-cholesterol (mmol/l) *	4.68±0.89	4.67±0.59	0.98
LDL-cholesterol (mmol/l) *	2.50±0.71	2.71±0.36	0.54
HDL-cholesterol (mmol/l) *	1.82±0.37	1.50±0.33	0.08
Triglycerides (mmol/l) *	0.69 (1.26)	0.96 (0.57)	0.053
Creatinine (mmol/l) *	88.4±20.3	88.4±14.1	0.77
Number of infusions	1.77±0.78	1.80±0.84	0.93
Induction with daclizumab	33 (85%)	5 (100%)	0.345
Number of islet/body weight (IEQ/kg)	13874±5763	14449±4194	0.85
Conversion to Mycophenolate – n (%)	13 (33%)	1 (20%)	0.547
ITx alone/Islet after kidney - n (%)	32 (82%)/7 (18%)	5 (100%)/0 (0%)	0.302
Tacrolimus and sirolimus (%exposed)	81.9	94.4	0.03
Exenatide use - n (%)	17 (45)	1 (20)	0.47

Data are expressed as mean ± SD, median (interquartile range) or number of cases (%).

* Baseline values.

ITx = islet transplantation.

Table 2

Cox-regression analysis with time to islet graft failure as the dependent variable

	OR	95%CI	P
“Type 2 DM phenotype”	5.2	1.1-24.0	0.035
Gender (male)	0.3	0.1-1.2	0.096
Tacrolimus and sirolimus (%exposed)	1.0	0.9-1.1	0.060
Auto anti-bodies at baseline (positive)	0.8	0.3-2.2	0.694
Number of transplants	0.3	0.1-0.7	0.005
Use of exenatide	0.3	0.1-0.8	0.020