

Islet Transplantation at the Dresden Diabetes Center: Five Years' Experience

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Key words

- diabetes mellitus
- hypoglycemia
- unawareness
- insulin deficiency

Abstract

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For the majority of patients with type 1 diabetes intensive insulin therapy is effective and safe for maintaining glycemia and minimizing diabetes-associated complications. However, a rare number of patients show highly labile metabolic control and experience repeated and unpredictable hypoglycemic episodes. Such condition is often caused by defective counter-regulatory mechanisms and autonomous neuropathy. Patients are at high risk for severe acute and chronic complications, and quality of life is considerably impaired. For this small subset of patients, restoration of endogenous insulin secretion can substantially improve metabolic control and quality of life. In our experience, this is irrespective of insulin independency. Here, we report on our 5 years' experience with implementing islet transplantation as a poten-

tial treatment option for type 1 diabetes. All patients were treated by long-term insulin pump therapy prior to enrolment. The main indication was severely unstable diabetes and repeated hypoglycemia. From 2008 to 2013, 10 patients have been transplanted with single islet infusion; mean follow-up time was 35 months. All patients show persistent graft function, stable glycemic control with a reduction in HbA1c in the absence of hypoglycemia. All patients are kept on minimal exogenous insulin. In conclusion, islet transplantation can be an excellent therapy for selected patients. Key prerequisite for success is a strict indication. The primary goal for islet transplantation should be stable glycemia and prevention of hypoglycemia rather than insulin independence. In fact, maintaining minimal exogenous insulin may protect the islet graft from metabolic stress and even prolong islet graft function.

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Introduction

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The major therapeutic goals in the treatment of diabetes mellitus type 1 (T1DM) are near-normal glycemic control without hypoglycemia, the avoidance of diabetes-associated complications, and an acceptable quality of life [1]. Despite substantial improvements in pharmacological diabetes therapy and technically advanced aids for blood glucose monitoring and insulin application, a subset of patients fail to meet the target parameters by far [2, 3]. The reasons are manifold and include impaired counterregulatory mechanisms and severe autonomous neuropathy, psychological barriers such as coping with the disease, repeated experience of hypoglycemia, deficient patient education, and most importantly the inherent limitations of exogenous insulin therapy.

In our specialized type 1 diabetes outpatient clinic, we have therefore pursued individualized treatment regimens that comprehend the current clinically available options including intensive insulin therapy (ICT), insulin pump therapy (CSII), sensor assisted blood glucose monitoring (CGMS), intraperitoneal insulin infusion (CIPII), and beta-cell replacement therapy by pancreas or islet transplantation.

Here, we report on our 5 years' experience with implementing single islet transplantation as a treatment option in patients with T1DM and high metabolic lability with frequent severe hypoglycemia. All patients were recruited from the own outpatient clinic assuring for exhausted conventional treatment regimen and compliance.

Although islet transplantation is a very promising approach in this subset of patients, it is not widely available due to a number of limitations.

Patient #	Age (years)	Gender (M/F)	BMI (kg/m ²)	Diabetes duration (years)	Insulin requirement pre-Tx (units/day)	HbA1c pre-Tx mmol/mol (%)	Diabetes management pre-Tx
1	55	F	24	51	25	69 (8.5)	CSII
2	27	M	22	26	68	77 (9.2)	CSII
3	55	M	24	38	30	73 (8.8)	CSII
4	48	F	28	38	30	66 (8.2)	CSII
5	50	F	29	40	50	81 (9.6)	CSII
6	49	F	28	36	43	60 (7.6)	CSII
7	42	F	24	12	32	61 (7.7)	CSII
8	36	F	24	17	44	66 (8.2)	CSII
9	53	F	27	17	38	62 (7.8)	CSII
10	47	M	26	11	33	63 (7.9)	CSII

BMI: Body mass index; T1DM: Diabetes mellitus type 1; CSII: Continuous subcutaneous insulin infusion

Table 1 Baseline demographic data for islet recipients.

Transplant #	Donor age (years)	Donor BMI (kg/m ²)	CIT (h:min)	Number of IEQ transplanted	Total IEQ/kg T1DM	In vitro islet SI
1	48	36	08:40	350 835	5.482	2.5
2	41	31	08:00	932 000	14.563	4.5
3	36	35	5:55	642 650	10.041	2.3
4	48	30	10:29	642 150	10.034	3.8
5	41	33	8:27	976 500	15.258	4.3
6	28	49	09:00	719 850	11.248	4.5
7	56	25	06:30	400 050	6.251	3.2
8	45	31	04:03	400 770	6.263	2.8
9	57	25	07:00	376 800	5.888	3.2
10	37	26	08:31	540 000	6.429	3.8

BMI: Body mass index; CIT: Cold ischemia time; IEQ: Islet equivalents; T1DM: Diabetes mellitus type 1; SI: Stimulation index

Table 2 Donor and isolation/transplant characteristics.

Irrespective of the persistent shortage of donor organs, the successful application of this technique requires a specialized infrastructure and highly skilled and trained personnel. Due to the small number of cases worldwide, the amount of data regarding islet transplantation is still very limited and registry data as well as single-center studies are an important contribution to foster the data base and evaluate the most suitable indications and clinical effectiveness of this therapeutic approach [4,5]. At present, the university medical center at Carl Gustav Carus in Dresden runs the only active islet transplantation program in Germany. Here, we present our 5 year experience with respect to glycemic control and graft function after single islet transplantation in metabolically critical T1DM patients and evaluate the potential of islet transplantation to achieve the major treatment goals in this subset of patients.

Subjects and Methods

Subjects

Since 2008, 10 patients with a mean age of 46 ± 9 years and long standing T1DM (mean diabetes duration of 29 ± 14 years) received a single islet transplantation at the Dresden transplantation center. Demographic data are summarized in **Table 1**. All patients had a complete loss of islet function prior to transplantation as determined by negative stimulated C-peptide and a history of highly problematic diabetes control, including hypoglycemia unawareness, and severe metabolic lability characterized by distinct blood glucose excursions.

Islet isolation and transplantation

Human pancreata were obtained through organ allocation by eurotransplant with consent obtained for tissue processing.

Islets were isolated using a modification of the automated Ricordi method [6]. Briefly, Collagenase NB1, neutral protease (Serva Electrophoresis, Heidelberg, Germany), and Pulmozyme (Roche, Grenzach, Germany,) were infused into the main pancreatic duct. Islets were separated from exocrine tissue by centrifugation on a continuous Biocoll gradient (Biochrom AG, Berlin, Germany) in a COBE 2991 cell processor (Lakewood, CO, USA). Islets were cultured in CMRL 1066 (Mediatech, Herndon, VA, USA) containing 2.5% human serum albumin at 37 °C in a 5% CO₂ incubator prior to transplantation. Donor and isolation characteristics are summarized in **Table 2**. Islet transplantation was performed intraportally via minilaparotomy over a 30-min period under continuous monitoring of portal vein pressure. All patients received only a single islet transplant.

Immunosuppression

For induction therapy, an interleukin 2 receptor antagonist (Daclizumab/Basilixumab) was used and a combination of calcineurin inhibitor (Tacrolimus) and inosine monophosphate dehydrogenase inhibitor (mycophenolic acid) was applied for maintenance of immunosuppression. In addition, an inhibitor of TNF- α (Etanercept) was given as anti-inflammatory therapy.

Post transplantation follow-up

Upon transplantation, patients were treated by i.v.-insulin for 24h and CSII, adapted to metabolic requirements, was continued thereafter. Glycemic control was documented by self-monitoring blood glucose and regular determination of HbA1c. Graft function was tested by frequent sampling of i.v.-glucose tolerance test (dextrose 0.5 g/kg body weight applied by bolus injection) at 3 and 6 months after transplantation and yearly thereafter. Metabolic stability was assessed on the basis of blood

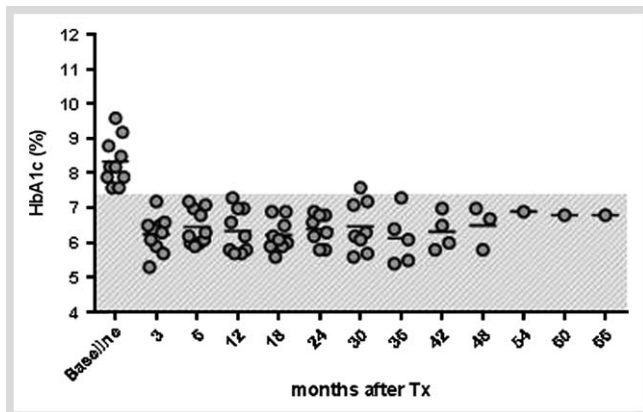


Fig. 1 Changes in glycaemic control following islet transplantation. HbA1c levels of individual patients, pre- and after single islet transplantation.

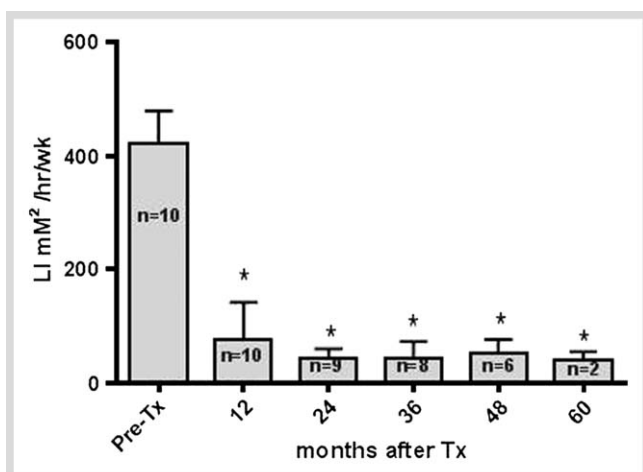


Fig. 2 The LI-scores for pre- and post-transplants. Post-transplant scores for years 1–5 were significantly improved compared to pre-transplant values (* $p < 0.05$). Data are expressed as mean \pm SD.

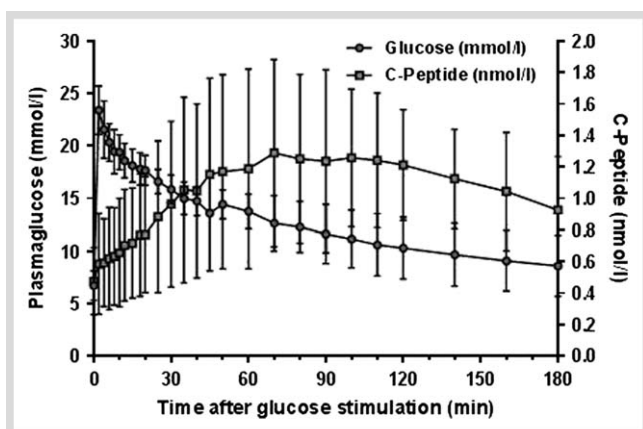


Fig. 3 Intravenous glucose tolerance test in islet transplant recipients at 12 months post-transplant ($n = 10$). Blood glucose levels in all patients returned to pre-stimulation levels within 180 min after stimulation accompanied by slightly delayed C-peptide release. Data are expressed as mean \pm SD.

glucose self-measurements by calculation of the lability index (LI-score) according to Ryan et al. at regular intervals [7].

Data analysis

Data processing was performed using GraphPad Prism 4 (GraphPad Software, La Jolla, CA, USA). Student's *t*-test was used to establish comparisons between groups. Results are shown as mean \pm SD. Significance was established at a *p*-value of < 0.05 .

Results

Glycaemic control

Prior to islet transplantation, the mean HbA1c under CSII was 68 ± 7 mmol/mol ($8.4 \pm 0.7\%$). After transplantation, all patients showed a fast and persistent reduction of HbA1c within a therapeutically optimal range of below 55 mmol/mol (7.2%), indicating a sustained, robust and adequate glycaemic control (○ Fig. 1). This normalization of HbA1c was achieved without any hypoglycaemic episodes following transplantation that might influence HbA1c.

The metabolic stability was assessed by calculation of the lability index (LI-Score), which is the most accepted measure for blood glucose fluctuations (○ Fig. 2). Based on this method, blood glucose instability was highly pronounced prior to transplantation with a mean LI-Score of 422 ± 58 . Following transplantation, the LI-Score was reduced significantly in all patients and was maintained throughout the follow-up period. Severe hypoglycemia was prevented in all patients after transplantation.

Graft function

In order to analyze graft function, intravenous glucose tolerance tests were performed with determination of blood glucose, insulin and C-peptide. During the follow-up period of up to 5 years, all patients showed a return of blood glucose values to pre-stimulation levels within 3 h (○ Fig. 3). However, the kinetic profile of insulin and C-peptide secretion following supraphysiological glucose challenge was delayed compared to healthy controls (data not shown).

Post transplantation diabetes management

Following islet transplantation, all patients were initially treated by i.v.-insulin for 24 h and returned to CSII thereafter. Insulin dose was adjusted according to metabolic needs and optimal blood glucose control including post-prandial glucose levels. Reduction of insulin requirement ranged from 95% to 20% compared to pre-transplantation regimen. After frequent and as needed visits during the early post transplantation period, all patients were seen once in 8 weeks during follow-up in order to allow for optimal diabetes management and subtle adjustment of immunosuppressive therapy. Throughout the observation period, no single episode of severe hypoglycemia requiring third party assistance was reported.

Discussion and Conclusions

Patients with T1DM live longer and experience less or later diabetes associated complications due to significant advances in diabetes therapy over the last decades [8,9]. Therefore, therapeutic regimens must focus more on quality of life and compat-

ibility with work and social life. However, this development also creates an increasing number of patients with very long diabetes duration and very specific challenges such as metabolic lability and hypoglycemic unawareness. Underlying factors are often defective counterregulatory mechanisms and autonomous neuropathy [10]. In these patients, a reliable synchronization of carbohydrate intake, and insulin application and action is barely feasible. The results are hyperinsulinemia or insulin deficiency often with fatal consequences. These conditions have tremendous impact on quality of life and can often be life threatening. While patients with solitary hypoglycemia unawareness may benefit from a glucose sensor assisted therapy, patients with additional high metabolic lability ultimately can only be stabilized by reconstitution of endogenous regulated insulin secretion.

Despite highly promising advances in novel approaches for beta cell generation and regeneration, pancreas and islet transplantation are still the only clinically available options for beta cell replacement therapy [11–19]. While simultaneous pancreas/kidney transplantation is the gold standard for patients with T1DM and end-stage renal disease [20], single islet transplantation has evolved into a viable treatment option for this subset of critically instable patients with T1DM and normal kidney function. Stabilization of blood glucose and prevention of hypoglycemia are established therapeutic goals and thereby the avoidance or stabilization of diabetes associated complications. Interestingly, these beneficial effects are independent of achieving insulin independence after transplantation [4, 21–23].

Here, we report on our experience with single islet transplantation as a therapeutic approach in this critical subset of patients. The main indication was metabolic lability complicated by severe hypoglycemia despite an optimal diabetes management. The primary therapeutic goal was defined as stabilization of blood glucose profile and avoidance of hypoglycemia rather than insulin independence. With respect to the need for chronic immunosuppression, a thorough risk benefit analysis has been undertaken in all cases.

We could demonstrate a consistent reduction of HbA1c in all transplanted patients and the complete elimination of severe episodes of hypoglycemia. Besides a major impact on quality of life, these achievements represent an important benefit on micro- and macrovascular complications and patient survival [24]. No major procedure or immunosuppression related complications were seen. For most patients, the most important experience after islet transplantation was the achievement of blood glucose stability and predictability of blood glucose trends. From the 10 patients described here, 50% were drastically restricted in their working ability prior to transplantation and achieved partly or complete capacity to return to their profession afterwards. This may represent a crucial perspective of islet transplantation that should be considered substantially during selection and evaluation of candidate patients.

However, achievement of long-term insulin independency is a legitimate therapeutic goal of most patients and doctors. Islet transplantation has been shown to be capable to reach insulin independence mainly after repeated islet infusions and an immunosuppressive regimen that includes T-cell depletion and anti-inflammatory agents [4, 25]. In fact, the comparison of pancreas alone and islet transplantation in respect to insulin independence has been shown to be equally effective after 5 years [5]. In respect to the safe and minimally invasive procedure of islet transplantation, adapted and more “islet-friendly” donor

selection and allocation algorithms are considered or already implemented in various countries [26–29]. In the German environment with critical lack of donor organs in general and a rather hostile regulatory environment for islet transplantation in particular, multiple transplantations for one patient are virtually not feasible. However, our positive results on reliable reconstitution of insulin secretion, stabilization of metabolic control, and significant impact on quality of life after single islet transplantation may help to promote this therapeutic approach also in our system.

In conclusion, careful identification of patients that will benefit from this therapy and a clear definition of therapeutic goals are an essential prerequisite for success. Ideally, islet transplantation should be carried out in a center that provides various alternative treatment options and state of the art technical assistance especially for “the difficult patient”. In our experience, islet transplantation is an excellent treatment option for selected patients with T1DM to reliably reconstitute endogenous insulin secretion and prevent acute and chronic complications.

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Conflict of Interest



The authors declare that they have no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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