The Review of DIABETIC STUDIES

ORIGINAL DATA

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Benefits of Islet Transplantation as an Alternative to Pancreas Transplantation: Retrospective Study of More Than 10 Ten Years of Experience in a Single Center

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■ Abstract

BACKGROUND: Pancreas transplantation (PTx) represents the method of choice in type 1 diabetic patients with conservatively intractable hypoglycemia unawareness syndrome. In 2005, the Institute for Clinical and Experimental Medicine (IKEM) launched a program to investigate the safety potential of islet transplantation (ITx) in comparison to PTx. **AIM**: This study aims to compare the results of PTx and ITx regarding severe hypoglycemia elimination, metabolic control, and complication rate. **METHODS**: We analyzed the results of 30 patients undergoing ITx and 49 patients treated with PTx. All patients were C-peptide-negative and suffered from hypoglycemia unawareness syndrome. Patients in the ITx group received a mean number of 12,349 (6,387-15,331) IEQ/kg/person administered percutaneously into the portal vein under local anesthesia and radiological control. The islet number was reached by 1-3 applications, as needed. In both groups, we evaluated glycated hemoglobin, insulin dose, fasting and stimulated C-peptide, frequency of severe hypoglycemia, and complications. We used the Mann Whitney test, Wilcoxon signed-rank test, and paired *t*-test for analysis. We also individually assessed the ITx outcomes for each patient according to recently suggested criteria established at the EPITA meeting in Igls. **RESULTS**: Most of the recipients showed a significant improvement in metabolic control one and two years after ITx, with a significant decrease in HbA1c, significant elevation of fasting and stimulated C-peptide, and a markedly significant reduction in insulin dose and the frequency of severe hypoglycemia. Seventeen percent of ITx recipients were temporarily insulin-independent. The results in the PTx group were comparable to those in the ITx group, with 73% graft survival and insulin independence in year 1, 68% 2 years and 55% 5 years after transplantation. There was a higher rate of complications related to the procedure in the PTx group. Severe hypoglycemia was eliminated in the majority of both ITx and PTx recipients. **CONCLUSION**: This report proves the successful initiation of pancreatic islet transplantation in a center with a well-established PTx program. ITx has been shown to be the method of choice for hypoglycemia unawareness syndrome, and may be considered for application in clinical practice if conservative options are exhausted.

Keywords: type 1 diabetes · hypoglycemia unawareness syndrome · islet transplantation · pancreas transplantation

1. Introduction

Islet (ITx) and pancreas (PTx) transplantation are the methods of choice in type 1 diabetes patients suffering from conservatively intractable hypoglycemia unawareness syndrome caused by impaired hypoglycemia counter-regulatory mechanisms [1]. Both procedures have been demonstrated to achieve elimination of severe hypoglycemia and recovery of the counter-regulatory response [2]. Further acknowledged benefits of ITx and PTx include the prevention of the progression

Abbreviations:

BMI	body mass index
CGM	continuous subcutaneous glucose monitoring
EPITA	European Pancreas and Islet Transplant Association
GFR	glomerular filtration rate
HbA1c	glycated hemoglobin
IEQ	islet equivalents
IKEM	Institute for Clinical and Experimental Medicine
ITx	islet transplantation
IU	insulin units
MAGE	mean amplitude of glycemic excursions
PTx	pancreas transplantation

of diabetes complications (although this is not definitely proven in all studies) [3-6] and protection of the renal graft against the harmful effect of hyperglycemia [7]. However, ongoing improvements in islet isolation and transplantation techniques, resulting in lower complication rates and increased numbers of insulin-independent subjects [8, 9], may emphasize the advantage of ITx over PTx because of the greater risk of surgical complications associated with PTx [10].

The aim of this retrospective study is to evaluate the results of the first ten years of clinical islet transplantation in a single center with a well-established pancreas transplantation program, and to compare the results between patients undergoing ITx and PTx regarding the frequency of severe hypoglycemia, insulin requirements, metabolic control indicators, and complications.

2. Methods and patients

2.1 Islet transplantation

The islet transplantation program in our center was initiated in November 2005. Since then, a total number of 62 patients have received islet transplants, of whom:

- 27 patients received ITx alone
- 10 patients underwent simultaneous islet and kidney transplantation
- 5 patients underwent simultaneous islet and liver transplantation
- 8 patients received islets after kidney transplantation
- 12 patients received islet auto-transplantation after total pancreatectomy

In this study, we evaluated the results of 30 patients (15 men and 15 women) who received ITx alone (n = 24), islet after kidney transplantation (n = 4), and simultaneous islet and kidney transplantation (n = 2). Patients who received autotransplantation (12), those who underwent islet and liver transplantation (5), and those not diagnosed with severe hypoglycemia unawareness syndrome were not included in the study. The transplantations were performed between January 2006 and March 2017 in patients who suffered from hypoglycemia unawareness and severe hypoglycemia, and who were statistically comparable to those patients after pancreas transplantation alone. The patients included in this study had the following characteristics at baseline (median interquartile range, see **Table 1**):

- Aged 48.5 (37-57) years
- Undetectable C-peptide
- Diabetes duration 24 (16.5-31) years
- BMI 23.8 (21-25.7) kg/m^2

The number of ITx treatments was as follows:

- 11 patients received 3 ITx
- 9 patients received 2 ITx
- 10 patients received 1 ITx

The mean number of transplanted islets amounted to 12,349 (6,387-15,331) islet equivalents (IEQ)/kg/patient.

At the time of the study, the follow-up times of the patients were as follows:

- 16 patients had the last ITx more than 5 years ago
- 8 patients had the last ITx 24 months ago
- 6 patients had shorter follow-up periods

Two patients after ITx with a marginal islet graft function stopped immunosuppression because of adverse effects and were lost to follow up after ITx for two years.

Islets were isolated according to the modified Edmonton protocol. Collagenase NB1 Premium® (Serva) or CIzyme Collagenase HA® (Vitacyte) was used [11, 12]. After purification, the tissue was collected and cultured for a maximum of 24 hours at 37°C. Islet infusion was administered under radiological control via transhepatic access (portal vein) or via laparoscopy. The immunosuppression protocol consisted of:

- Induction with anti-T lymphocyte globulin (total dose 9 mg/kg, one dose pre-transplant and one dose at day one post-transplant)

- Methylprednisolone
- One dose of etanercept (followed by maintenance treatment based on sirolimus and low-dose tacrolimus using the intention-to-treat approach)

Heparin and insulin were administered intravenously in the first 24 hours in accordance with previously published protocols [13]. Pancreas donors had a medium age of 49 (44-57) years and BMI 26 (24-29) kg/m^2. The most common cause of death was intracranial hemorrhage in 78%, and cold ischemia time was 4.5 (2.6-7.4) hours.

In our ITx recipients, we prospectively analyzed indicators of metabolic compensation (glycated hemoglobin, insulin requirements, frequency of severe hypoglycemia, and C-peptide) and kidney function 1, 3, 6, 12, and 24 months after the last ITx (with the maximal islet-mass) and complications. The frequency of severe hypoglycemia (accompanied by impaired consciousness or the need for another person's assistance) according to the Clarke/Gold score used for hypoglycemia unawareness evaluation [14, 15] was followed up before, 12, and 24 months after ITx.

Since 2013, we have enriched our follow-up investigation with mixed-meal stimulation test and continuous subcutaneous glycemia monitoring (CGM). Stimulated C-peptide was measured after 120 minutes of a mixed-meal test containing 60 g saccharides, 12.5 g proteins, and 12.6 g lipids. Patients with normal renal function were included for statistical evaluation only. Data are shown as median (interquartile range). Statistical analyses were performed using the Wilcoxon-signed rank test and Mann-Whitney test (**Table 2**).

When evaluating CGM (using a Dexcom® sensor) we assessed the excursions of glycemia (MAGE) [16] and the percentage of time spent in hypoglycemia (<3.5 mmol/l), normoglycemia (3.5-7.2 mmol/l), and hyperglycemia (>7.2 mmol/l). MAGE was calculated as mean ± SD, and Wilcoxon signed-rank test was applied for statistical analyses. We report these results as well, but they do not apply to the entire group included in this study.

Our primary objective in the follow-up investigations was to find out how many patients achieved a "composite endpoint" 6 and 12 months after ITx consisting of:

Table 1. Baseline characteristics of islet and pancreas recipients and donors

Characteristic	Islet transplant recipients (n = 30)	Pancreas transplant recipients (n = 49)
Sex	15 M / 15 F	22 M / 27 F
Age (years)	48.5 (37-57)	39 (33-50)
Duration of diabetes (years)	27.5 (19.25.34)	24 (16.5-31)
BMI (kg/m²)	23.18 (20.9-25.3)	23,8 (21-25.7)
Insulin dose before Tx (IU/kg)	0.51 (0.44-0.59)	0,53 (0.41-0.66)
Frequency of severe hypoglycemia/patient/year	6 (4-8)	3 (2-6)
HbA1c before Tx (mmol/mol)	73.5 (65-87)	74 (69.5-81)
C-peptide before Tx	Undetectable	Undetectable
GFR (CKD-EPI) ml/s/1.73 m2	1.45 (1.09-1.66)	1.31 (1.06-1.63)
Pancreas donor age	49 (44-57)*	36 (29-38.5)*
Pancreas donor BMI	26 (24-29)**	23 (20-27)**
Total dose of islet equivalents (IEQ/kg)	12,349 (6,387-15,331)	-

Legend: *p < 0.05, **p = 0.00468.

- Significantly detectable C-peptide (level >0.2 nmol/l)
- More than 30% daily insulin dose reduction
- Absence of severe hypoglycemia (requiring another person's assistance or hospitalization)
- Improved metabolic control with HbA1c of 53 mmol/mol or less

For the purpose of this article, we decided to view our results in the light of the recently agreed criteria for islet graft function (2017 Igls IPITA workshop, not yet published, see section 3.3).

2.2 Pancreas transplantation

Between April 1996 and April 2017, 49 patients underwent PTx treatment in our center, all of whom were C-peptide-negative and suffering from severe hypoglycemia. 36 patients received PTx alone (PTA), while in 13 patients PTx was performed after kidney transplantation (PAK) from a living or deceased donor. The study population consisted of 22 men and 27 women aged 39 (33-50) years with diabetes duration of 24 (16.5-31) years (**Table 1**). Our surgical technique has been evolving throughout this time. In the first 19 patients (transplanted 1996-2004), the pancreatic graft was drained into the urinary bladder and placed extraperitoneally in the right iliac fossa. In 2004, enteric exocrine drainage with an extraperitoneal graft placement was introduced and performed in 14 patients of the followed group. Since 2011, this technique was improved further and, while main-

Table 2. Metabolic indicators in islet transplant recipients

Time after ITx	HbA1c (mmol/mol)	p	Insulin dose (IU/kg/day)*	p	Fasting C-peptide (nmol/l)	p	GFR (ml/s/1.73 m^2)	p	Severe hypoglycemia /patient /year	p
1 mo	52 (49–58)	<0.0001	0.3 (0.2-0.42)	<0.0001	0.24 (0.13-0.34)	<0.0001	1.46 (1.0-1.65)	0.2423		
3 mo	45 (42-49)	<0.0001	0.29 (0.22-0.37)	<0.0001	0.22 (0.08-0.37)	<0.0001	1.38 (1.12-1.56)	0.0809		
6 mo	49 (42-57)	<0.0001	0.26 (0.14-1.36)	<0.0001	0.24 (0.05-0.46)	<0.0001	1.24 (1.06-1.47)	0.0523		
12 mo	54 (44-53)	<0.0001	0.23 (0.13-0.41)	<0.0001	0.22 (0.05-0.42)	<0.0001	1.27 (1.04-1.61)	0.1007	1 (0.8-2)	0.00256
24 mo	54 (52-71)	<0.0001	0.29 (0.18-0.61)	0.0149	0.21 (0.05-0.26)	<0.0001	1.16 (1.01-1.54)	0.0303	4 (3-5)	0.02938
5 yr	58 (51-76)	0.0026	0.33 (0.25-0.61)	0.0263	0.15 (0.03-0.29)	0.001	1.39 (0.9-1.46)	0.0709	1 (0.25-4)	

Legend: *17% of patients after ITx were transiently insulin-independent.

taining enteric exocrine drainage, the pancreatic graft is placed intraperitoneally and anastomosed with the portal vein and common iliac artery. This procedure was used in 16 patients.

As for immunosuppression regimen, induction was achieved by anti-T-lymphocyte globulin (4 mg/kg pre-transplant dose) and methylprednisolone in PTA recipients, while basiliximab was used in PAK recipients. Ongoing intention-to-treat immunosuppression consisted of tacrolimus with mycophenolate mophetil and tapered doses of corticosteroids within the first 6 weeks. The immunosuppressive regimen used before 2004 and the surgical procedures are described in detail by Girman and colleagues [17]. Pancreas donor medium age was 36 (29-38.5) years and BMI 23 (20-27) kg/m^2. The most frequent cause of death was intracranial hemorrhage in 65% of donors, and cold ischemia time was 5.2 (4-6.5) hours.

In PTA recipients, we retrospectively evaluated HbA1c, fasting C-peptide, insulin requirements, frequency of severe hypoglycemia, and kidney function 12 and 24 months post-transplant and 5 years post-transplant along with patient and graft survival. We also assessed 120-minute stimulated C-peptide by oral glucose tolerance test (OGTT) using 75 g glucose 12 and 24 months after PTx. Furthermore, we analyzed complications of the transplant procedure. The data are presented as median (interquartile range). Wilcoxon-signed rank test and Mann-Whitney test were used for statistical analyses.

3. Results

3.1 Metabolic outcomes of islet transplantation

Patients on the waiting list for islet transplantation were all C-peptide-negative. Despite intensive clinical management they had very poor diabetes control, with HbA1c of 73.5 mmol/mol (65-87 mmol/mol) (median (interquartile range)) (**Figure 1A**), daily insulin dose of 0.51 IU/kg (0.44-0.59 IU/kg) (**Figure 1C**), and with a frequency of severe hypoglycemia (requiring help of other person or leading to a loss of consciousness) of 6 (4-8)/patient/year (**Table 1**).

In the first month after ITx, HbA1c decreased significantly to 52 (49-58) mmol/mol ($p < 0.0001$), fasting C-peptide levels were 0.24 nmol/l (0.13-0.34 nmol/l) ($p < 0.0001$), and insulin dose decreased to 0.3 IU/kg (0.2-0.42 IU/kg) ($p < 0.0001$). Graft function further improved at 3 months post-transplant (**Figure 1A-C**), with:

- HbA1c 45 mmol/mol (42-49 mmol/mol) ($p < 0.0001$)
- Fasting C-peptide 0.22 nmol/l (0.08-0.37 nmol/l) ($p < 0.0001$)
- Stimulated C-peptide 0.84 nmol/l (0.315-1.3 nmol/l)
- Insulin dose 0.29 IU/kg (0.22-0.37 IU/kg) ($p < 0.0001$)

The values characterizing graft function remained stable until 12 months after transplantation:

- HbA1c 54 mmol/mol (44-53 mmol/mol) ($p < 0.0001$)
- Fasting C-peptide 0.22 nmol/l (0.05-0.42 nmol/l) ($p < 0.0001$)
- Stimulated C-peptide 0.88 nmol/l (0.5-1.4 nmol/l)
- Insulin dose 0.23 IU/kg (0.13-0.41 IU/kg) ($p < 0.0001$)

The frequency of severe hypoglycemia varied around 1 (1-2)/patient/year ($p = 0.00256$). The values also remained stable even at 2 years post-

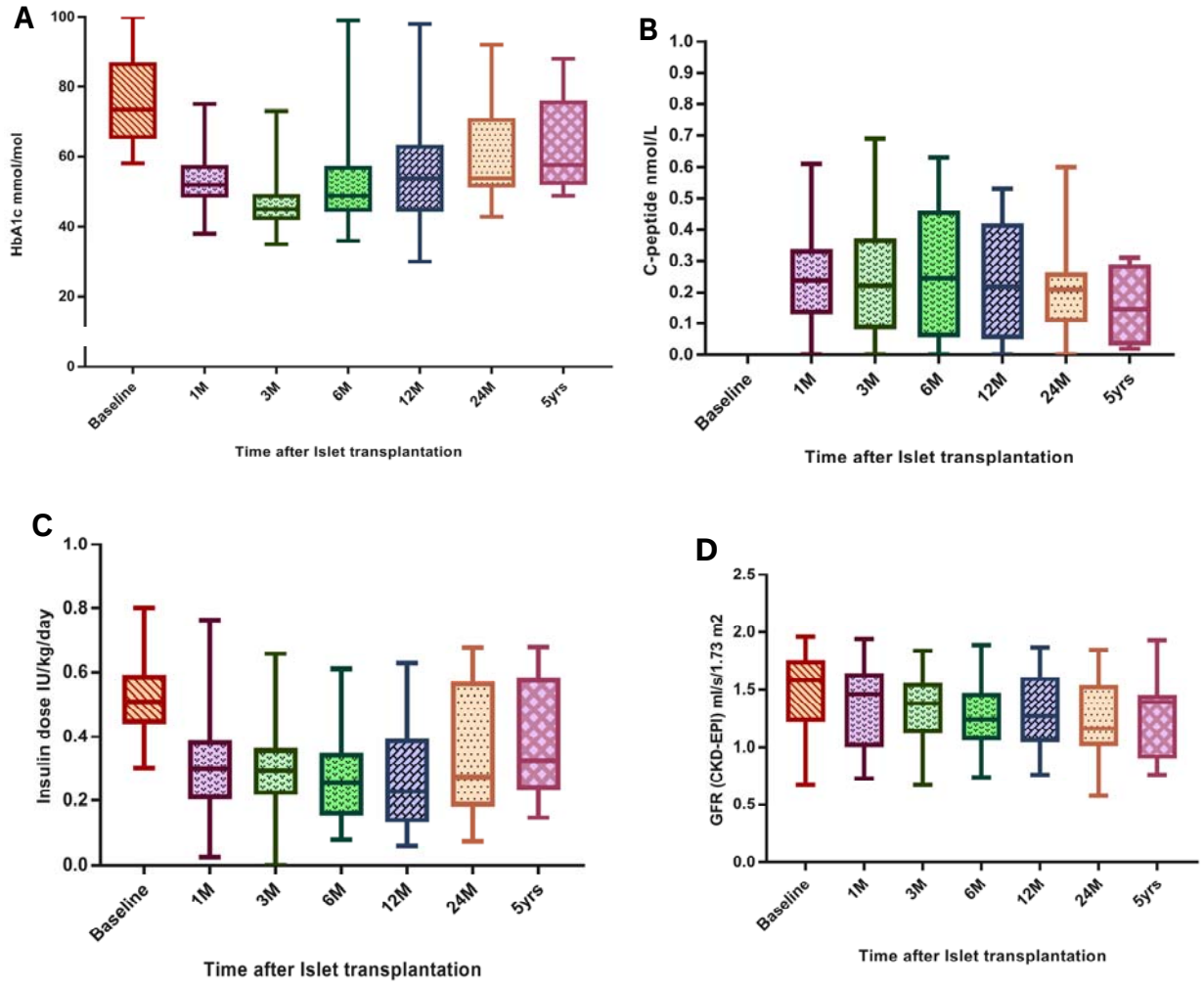

Figure 1. Glycemic control parameters and kidney function after islet transpolantation. A: HbA1c in mmol/mol, comparing baseline, 1, 3, 6, 12, 24 months, and 5 years after ITx. **B**: Fasting C-peptide levels in nmol/L at baseline, 1, 3, 6, 12, 24 months, and 5 years after ITx. **C**: Daily insulin dose in IU/kg at baseline, 1, 3, 6, 12, 24 months, and 5 years after ITx. **D**: Kidney function after ITx (eGFR in ml/s/1.73m² at baseline, 1, 3, 6, 12, 24 months, and 5 years after ITx).

transplant with a small rise in insulin dose to 0.29 IU/kg (0.18-0.61 IU/kg) (p = 0.0149). The frequency of severe hypoglycemia at 2 years post-transplant remained significantly lower than under pre-transplant conditions, i.e. 4 (3-5) (p = 0.02938), see **Table 2** and **Figures 1A-C**. Six patients had undetectable C-peptide levels, five of them because of early graft failure by the end of the third month, and one by the end of the first year post-transplant.

3.2 Complications of islet transplantation

Bleeding was the most frequent serious complication associated with the ITx procedure, especially in the initial years of the transplant program. This complication occurred in 10 patients (33%). In terms of implantations, the complication rate was 18% (11 of a total of 62 implantations). In 8 (27%) of these patients, urgent operation was necessary. Four patients (13%) developed an intrahepatic hematoma without the need for surgical procedure and with favorable outcome. One patient developed partial portal vein thrombosis with the need for long-term anticoagulation therapy. One patient had an orthostatic syncope shortly after the transplantation procedure with the need for vasopressive medication. Biliary tract irritation was reported in two patients.

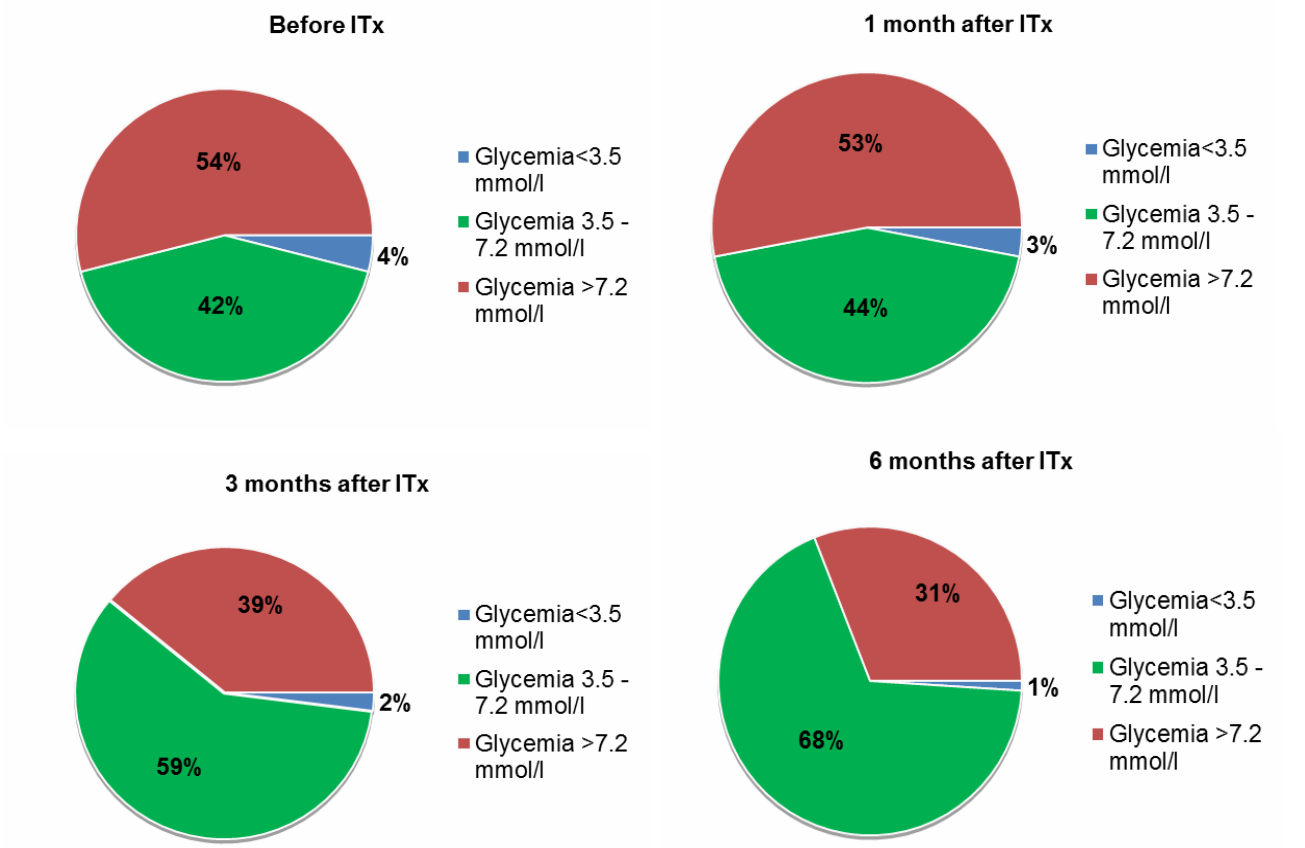

Figure 2. Evaluation of continuous glucose monitoring (CGM). The figure shows the change in time periods patients spent in hypoglycemia (< 3.5 mmol/l, blue), normoglacemia (3.5-7.2 mmol/l, green), and hyperglycemia (>7.2 mmol/l, red) after islet transplantation (ITx).

Regarding infectious complications, one patient was implanted with a graft infected by hemolytic E. Coli, resulting in severe sepsis, but the patient recovered with no sequelae. One patient had cholecystitis, 3 patients were treated for urinary tract infections, and 1 patient acquired pneumonia during hospitalization after the transplantation. Thrombocytopenia was present in 4 patients, and leucopenia with neutropenia was observed in 10 cases, which was due to immunosuppressive medication.

We evaluated the continuous glucose monitoring (CGM) reports and found that before ITx the patients had hypoglycemia in 4% (2.8-5.3%) of the measured time, normoglycemia in 42% (31-52%) of the time, and hyperglycemia in 54% (46-67%) of the time (**Figure 2**). These values improved gradually over 6 months after ITx to yield:

- Hypoglycemia 1% (0.9-1.9%) (p = 0.04746)
- Normoglycemia 68% (48-71%) (p = 0.03673)
- Hyperglycemia 31% (27-41%) (p = 0.00798)

We also calculated the mean amplitude of glycemic excursion (MAGE) values. The values decreased gradually from 7.4 ± 3.9 mmol/l before ITx to 5.0 ± 0.8 mmol/l 6 months after ITx (p = 0.01786) (**Figure 3**).

3.3 Islet graft function according to 2017 Igls classification (Tables 3 and 4)

As for the overall assessment of islet function, our primary composite endpoint (C-peptide >0.2 nmol/l, >30% daily insulin dose reduction, absence of severe hypoglycemia, HbA1c ≤53 mmol/mol) was achieved in 17 patients (60%) 6 months after ITx and in 14 patients (50%) 12 months after ITx. Two years after ITx, 10 patients (42%) still met the criteria. In relation to the "Igls classification", no pa-

tient fulfilled the definition of long-term optimal graft function with total insulin independence. This was achieved for a short period in five patients (17%) only. However, the criteria for good islet graft function and successful therapy were met by 17 patients (57%) after 6 months, 13 patients (46%) after 12 months, and 9 patients 24 months post-transplant. In five patients (17%), the graft failed shortly after transplantation, and in two more by the end of the second year post-transplant. In total, 29% of grafts failed by the end of year 2. Marginal, yet stable, graft function was maintained in 8 patients in year 2.

In the extended retrospective follow-up, three patients experienced good graft function until the end of the fifth year (16%), 10 had marginal islet function (56%), and 8 grafts failed (26%). In 17 patients (57%), hypoglycemia awareness was restored and has been maintained so far despite only marginal graft function in some patients.

We observed a significant increase in C-peptide levels and a decrease in HbA1c in the first two years after ITx. The frequency of severe hypoglycemia was significantly reduced, and exogenous insulin dose decreased substantially in the first year, with some patients being insulin-free for a limited period. In patients with at least marginal graft function, increased C-peptide levels combined with lowered HbA1c and the reduction or absence of severe hypoglycemia persisted two years after ITx.

According to the CGM evaluation after transplantation, hypoglycemia and hyperglycemia events significantly decreased, while periods with optimal glucose levels increased. Lability of diabetes was also lower three and six months after ITx.

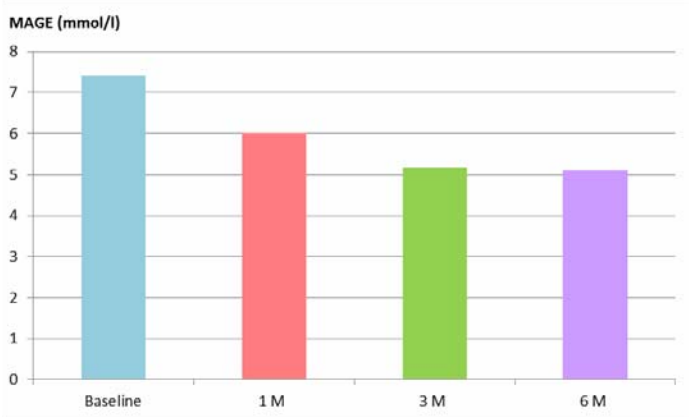

Figure 3. Analyses of glycemic variability. Mean amplitude of glycemic excursions (MAGE) in mmol/l, mean values in patients before ITx, 1, 3, and 6 months after ITx.

3.4 Metabolic outcomes, graft survival, and complications of pancreas transplantation

Candidates for PTx were C-peptide-negative, had HbA1c of 75 mmol/mol (71-84 mmol/mol) (**Table 1**), and took a daily dose of insulin 0.6 IU/kg (0.4-0.8 IU/kg). They were suffering from severe hypoglycemia with a frequency of 3 (2-6)/patient/year. One year after organ transplantation, HbA1c decreased significantly to 37 mmol/mol (34-55 mmol/mol) ($p < 0.00001$), and 36 patients (73%) with functional pancreatic graft did not need insulin injections. (**Table 5, Figures 4** and **5**). Fasting and stimulated C-peptide were 1.03 nmol/l (0.76-1.39 nmol/l) and 1.96 nmol/l (1.14-2.39 nmol/l), respectively. In eleven patients, graftectomy was performed in the first-year post-transplant. Five patients lost their graft function because of acute cellular rejection. Eight patients (18%) had 2 (1-4) severe hypoglycemia episodes/patient/year. All these patients originated from the group with graft failure or explanted graft. Two years after PTx, HbA1c was 38 mmol/mol (36-68 mmol/mol) ($p < 0.00001$), and 32 patients (68%) remained free from exogenous insulin. Fasting and stimulated C-peptide were 0.79 nmol/l (0.6-1.03 nmol/l) and 1.51 nmol/l (1.0-2.1 nmol/l), respectively (**Table 5**). Seven patients (16%) suffered from severe hypoglycemia with 4 (2-5) episodes/patient/year.

Table 3. Classification of beta-cell graft function proposed at the IPITA workshop, EPITA Conference, Igls, 2017

Functional status	HbA1c (%/ mmol/mol)	Severe hypoglycaemia events	Insulin requirements	C-peptide	Success
Optimal (1)	≤ 6.5 / ≤ 48	None	No	> Baseline	Yes
Good (2)	< 7.0 / < 53	None	< 50% Baseline	> Baseline	Yes
Marginal (3)	≥ 7.0 / ≥ 53	< Baseline	≥ 50% Baseline	> Baseline	No
Failure (4)	Baseline	Baseline	Baseline	Baseline	No

Table 4. Metabolic outcomes according to Igls criteria in transplant recipients with normal renal function (1-24) and impaired renal function (25-30) in followed time intervals since the last islet transplant

No.	1-6 mo	6-12 mo	12-24 mo	Year 3	Year 4	Year 5
1	2	2	2	3	3	3
2	2	2	2			
3	3	4	4	4	4	4
4	2	2	2	3	3	3
5	2	2	2	3	3	3
6	2	2	2	2	2	2
7	3	3	3	3	3	3
8	2	2	2	3	3	3
9	2	3	3	3	3	3
10	4	***				
11	2	3	3	3	3	3
12	4	***				
13	2	2	+			
14	2	2	3	3	3	4
15	4	4	4	4	4	4
16	3	3	3	3	3	3
17	3	3	4	4		
18	3	3	3			
19	2	2	2			
20	4	4	4	4		
21	3	3				
22	4	4	4			
23	2					
24	2					
25	3	3	3	3	3	3
26	2	2	2	2	2	2
27	2	2	2	2	2	2
28	3	3	3	3	3	3
29	2	2				
30	2	2				

Legend: For colors and numbers see Table 3. ***Patient stopped immunosuppression therapy and were temporarily lost to follow-up. + died 14 months after ITx.

In the long term follow-up, the recipients' renal function measured by glomerular filtration rate decreased significantly in the first two years post-transplant, but remained stable thereafter (**Table 5, Figure 5**).

Acute rejection caused graft failure in eight cases, chronic allograft rejection was diagnosed in one patient, and in two patients the cause of failure remained unknown. Of the total number of 53 PTx (including retransplantations), eleven graftectomies (20%) took place within the early post-transplant period. Four patients subsequently underwent re-transplantation. Explantation was performed because of venous thrombosis (n = 6), infection (n = 2), bleeding (n = 2), and acute rejection (n = 1).

Overall, surgical revision (including graftectomy) had to be performed in 23 patients (47%); major causes were infection (n = 10) or bleeding (n = 6). When comparing the evolving surgical methods, we found that within the first period (1996-2004) either graftectomy or re-operation had been performed in 9 of 19 patients (47%), and in the period 2004-2011 in 8 of 14 patients (57%). Since 2011, surgical revision has been performed in 6 of 16 patients (37%).

In summary, in the first year of PTx, 73% of patients had good graft function without the need for exogenous insulin injections, 5% had partial function, and 22% experienced graft failure or removal of the graft because of rejection or surgical complications. In the second year of PTx, 68% of the recipients were still insulin-independent and 5-year graft survival was 55%. 47% of patients required surgical revision, most commonly due to thrombosis, infection, and/or bleeding. After the introduction of new surgical techniques with intraperitoneal graft placement, there has been a decrease in the rate of complications requiring re-operation.

4. Discussion

Our reported results highlight the importance of considering islet transplantation as an alterna-

Table 5. Metabolic indicators in pancreas transplant recipients

Time after PTx	HbA1c (mmol/mol)	p	Patients free of insulin	p	Fasting C-peptide (nmol/l)	p	GFR ml/s/1.73 m2	p	Severe hypoglycemia /patient /year	p
12 mo	38 (34-65)	<0.0001	73 %	<0.00001	1.03 (0.71-0.46)	<0.0001	1.03 (0.79-1.33)	0.0041	2 (1-4) in 18%	
24 mo	38 (36-68)	<0.0001	66 %	<0.00001	0.79 (0.56-1.06)	<0.0001	1.02 (0.66-1.28)	0.0002	4 (2-5) in 16 %	
5 yr	41 (36-65)	<0.0001	55%	<0.00001	0.69 (0.4-0.82)	0.0039	0.98 (0.69-1.29)	0.0057		

tive treatment option in intractable hypoglycemia unawareness syndrome. It must be noted that this attempt was made in a center with extensive experience and excellent results in pancreas transplantation [17]. The study reflects the difficulties to be overcome at the beginning of a program before pancreatic islet transplantation becomes an effective and safe treatment of hypoglycemia unawareness syndrome to attain stabilization of glucose metabolism in properly selected patients. Achievement of long-term insulin-independence is the target. However, at present, it does not represent a prerequisite for the assessment of success. How can we interpret the data and what lesson can we learn from it?

In our islet transplant group, good metabolic control and elimination of severe hypoglycemic episodes could be achieved in most of the recipients. Insulin therapy could be stopped completely in 5 out of 30 patients, and in most of the remaining patients the insulin dose was significantly reduced. Based on these results, ITx was approved as a treatment modality for type 1 diabetic patients suffering from the hypoglycemia unawareness by the Czech medical authorities and insurance providers. Despite these achievements, we have not yet reached the level of insulin-independence some leading centers in the world achieve [8, 9, 18-22].

The definition of "a successful beta-cell therapy" still remains a challenge. Therefore, a set of criteria based on parameters of metabolic control (HbA1c and fasting C-peptide), insulin dose, and presence of hypoglycemia was suggested at the meeting of the European Pancreas and Islet Transplant Association (EPITA) in 2017 held in Igls (Austria). In previous studies, our group had used its own composite endpoints. In this study, we included the "Igls" criteria in addition (see **Tables 3** and **4**) to enable more effective comparison with other groups. When the newly introduced classification was used, our patients did not fit into the optimal function category. It is evident that overall transplant success was evaluated in a similar way.

Generally, there are several areas in need of improvement. Islet isolation and donor allocation processes should be mentioned first and foremost. Besides improving isolation techniques, we need to focus on thoughtful donor selection and the poten-

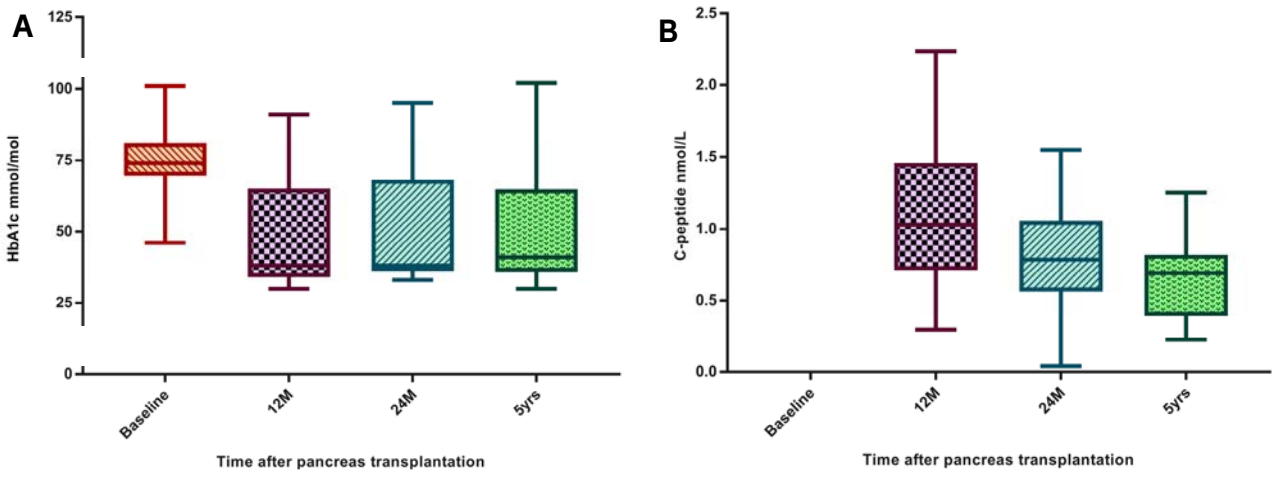

Figure 4. Glycemic control parameters before and after PTx. A: HbA1c before and after pancreas transplantation. **B**: Fasting C-peptide before and after pancreas transplantation.

tial for enlarging the donor pool. As a very active pancreas transplantation center, we are "competing" with ourselves when it comes to suitable pancreas donors. The pancreas donors for islet transplants were observed to be significantly older in our cohort (49 yr (44-57 yr) vs. 36 yr (29-38.5 yr), $p < 0.05$) and had significantly higher BMI (26 kg/m^2 (24-29 kg/m^2) vs. 23 kg/m^2 (20-27 kg/m^2), $p = 0.00468$) than those assigned for organ transplantation (**Table 1**). Our results support the findings of Niclauss *et al*. who reported better clinical outcomes of islet transplantation from younger donors (<45 years) [23].

In relation to patient and graft survival, the outcome of our pancreas transplant program is comparable to other centers. The rate of surgical complications has decreased since the implementation of new surgical technique. The assessment of clinical success in pancreas transplantation is more straightforward and mainly based on insulin independence. In patients with a functioning pancreas graft, we have been able to achieve excellent long-term metabolic control, without the need for insulin therapy and recurrence of severe hypoglycemia.

Since islet transplantation is a minimally-invasive procedure with fewer expected procedure-related risks, the initial transplantations at our center, which were complicated by bleeding, raised concerns about suitable safety measures. In 2013, we introduced fibrin glue (Avitene™ Collagen Hemostat, Davol, A Bard Company, USA) which is placed into the intrahepatic channel immediately after islet infusion. This has reduced the bleeding episodes significantly. In the case of an expected increased risk of bleeding, we also considered the option of using mini-laparotomy (a small incision) to put the islet infusion straight into the inferior mesenteric vein similarly to the procedures of simultaneous islet and kidney transplantation. Compared to percutaneous transhepatic application, this procedure poses a low risk of bleeding into the abdominal cavity and of liver hematoma development [24].

Another issue to be determined concerns the selection of suitable candidates who would profit from one or other therapeutic option. The scale of modern technologies available is incomparable to the opportunities in the previous decades when we were launching the transplant program. Therefore, we should be certain that all options of conservative management are exhausted before considering ITx. It must be clear that the patient will benefit from the therapy weighed against the burden of immunosuppression.

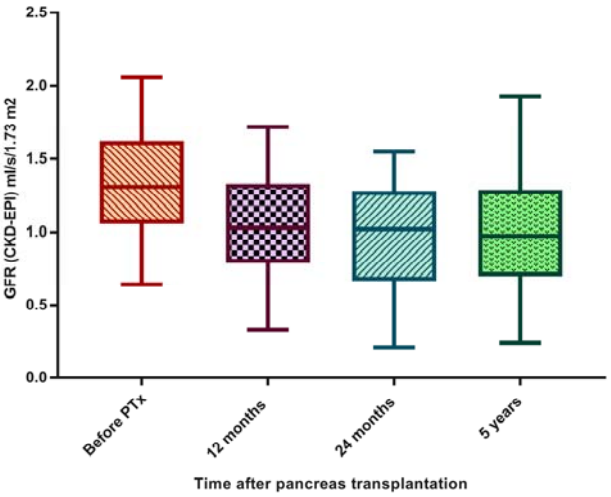

Figure 5. Kidney function before and after PTx.

Until recently, there has also been a substantial difference in the health care and economic policy in relation to these two procedures. While pancreas transplantation has been fully covered by health insurance, islet transplantation had been considered an experimental therapy, and has been only partially funded. Islet isolation procedures in particular needed to be supported by research grants. The situation has improved since 2016 when islet transplantation was approved as a therapeutic modality covered by insurance for indicated cases in the Czech Republic.

5. Conclusions

Islet and pancreas transplantation have become established treatment modalities for type 1 diabetes patients suffering from hypoglycemia unawareness and severe hypoglycemia when all means of conservative therapy fail. We have compared retrospectively the long-term outcomes obtained with our pancreas and islet transplant program. The results show that pancreas and islet transplantation are not competing therapies, but rather complementary procedures [25, 26].

The final decision for this therapy should be made considering the overall health condition and comorbidities of the patient and the desired objectives, while the patient's preferences need to be acknowledged. Our results contributed to the appreciation by national health authorities of islet transplantation as a viable alternative to organ transplantation. The availability of both PTx and ITx can significantly widen the number of diabetic

recipients profiting from transplantation of insulin-producing tissue and improve their health.

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