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Total pancreatectomy with islet autotransplantation in diabetic and pre-diabetic patients with intractable chronic pancreatitis

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Abstract

Total pancreatectomy with islet autotransplantation (TPIAT) is an effective treatment option for non-diabetic patients with intractable chronic pancreatitis. The outcome and potential benefits for pre-diabetic and diabetic patients are less well established. Thirty-four patients underwent TPIAT were retrospectively divided into 3 groups according to pre-operative glycemic control: diabetes mellitus (DM) (n=5, 15%), pre-DM (n=11, 32%) and non-DM (n=18, 54%). Pre-operative fasting c-peptide was detectable and similar in all 3 groups. Islet yield in the DM group was comparable to pre-DM and non-DM groups (median islet equivalents [IEQ] was 191,800, 111,800, and 232,000IEQ, respectively). Patients received islet mass of over the target level of 2000IEQ/kg in pre-DM and DM at lower but clinically meaningful rates compared to the non-DM group: 45% (5/11) and 60% (3/5) for a combined 50% (8/16) rate, respectively, compared to 83% (15/18) for the non-DM group. At 1 year, fasting c-peptide and HbA1c did not differ between DM and pre-DM groups but c-peptide was significantly higher in non-DM. Islet transplantation failed (negative c-peptide) only in 1 patient. Pre-operatively, all patients experienced pancreatic pain with daily opioid dependence in 60% to 70%. Pancreatic-type pain gradually subsided completely in all groups with no differences in other painful somatic symptoms. Diabetic patients with measurable

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Author's specific contributions

PJB has contributed to research design, original draft of the manuscript, review and editing, JBM and PW contributed with original draft of the manuscript, review and editing, all authors participated equally in data analysis and data curation as well as format analysis and project administration. In addition, JF, JBM, and PW contributed in supervision of the project.

Conflicts of interest

The authors declare no conflicts of interest.

Ethics approval

The study was approved by the Institutional Review Boards at the University of Chicago.

pre-operative c-peptide can achieve similar benefit from TPIAT, with comparable outcomes to pre-diabetic and non-diabetic patients including pain relief and the metabolic benefit of transplanted islets. Not surprisingly, endocrine outcomes for diabetic and pre-diabetics patients are substantially worse than in those with normal pre-operative glucose control.

Keywords

Autotransplantation; Islets; Outcomes; Pancreatectomy; Pre-diabetes

Introduction

Total pancreatectomy (TP) with islet autotransplantation (IAT) is offered to patients with intractable abdominal pain due to chronic or acute recurrent pancreatitis after failure of alternative interventions. TP can provide long-term relief from pancreatic pain and improves the quality of daily life, while IAT allows for preservation of beta cell mass, improving glucose control in patients with postpancreatectomy diabetes.[1] Since a larger islet mass may be isolated from and transplanted into TP with IAT (TPIAT) candidates with normal glucose control and islet function before surgery, these individuals are more likely to maintain better postsurgical endocrine function than those with pre-procedural islet dysfunction.[2] However, the clinical decision to proceed with TPIAT is based mainly on the need for pain control and should not, in general, be driven by assumptions about outcomes for ultimate glycemic control. At the time of pre-operative evaluation, a specific challenge arises for patients with poor pre-operative glucose control: is IAT worthwhile, considering the higher chance of poor postoperative islet function due to a lower retrievable and transplantable islet mass?

In this study, we analyzed treatment outcomes of pre-diabetic and diabetic patients submitted to TPIAT in comparison to those with optimal glucose control before the procedure.

Materials and methods

Study design and cohort

Between 2013 and 2019, 34 consecutive patients with detectable fasting c-peptide (>0.03pmol/mL) underwent TPIAT for intractable abdominal pain due to chronic or acute recurrent pancreatitis at the University of Chicago. Patients were retrospectively divided into 3 groups based on glycemic control before TPIAT. Those with fasting glucose equal or greater than 126mg/dL (7.0mmol/L) or HbA1c≥6.5% were considered diabetic (diabetes mellitus [DM] group), those with fasting plasma glucose between 100 and 125mg/dL (5.6–6.9mmol/L) or HbA1c between 5.7% and 6.4% were classified as pre-diabetic (pre-DM group), and those who did not meet the above criteria were assigned to the non-DM group. The cutoff for fasting glucose and HbA1c were adopted from the American Diabetes Association (ADA) criteria for patients with diabetes and pre-diabetes.[3] All patients in DM group had normal or high fasting serum c-peptide level; none had type 1 DM. Glycemic control was assessed immediately before TPIAT, and after the procedure at postoperative

day ~75, 1 year, and annually thereafter. Islet function was assessed by fasting plasma glucose, c-peptide, HbA1c and insulin requirements. BETA-2 score was calculated according to a previously published formula.[4] Insulin independence was recognized in patients based on HbA1c<6.5% without the support of exogenous insulin or oral hypoglycemic agents. Pain magnitude was assessed based on opioid use as reported by each patient, from electronic medical records and Illinois Prescription Monitoring Program database.[5] The location of the pain was assessed based on patient history, physical examination, and medical records.

Statistical analysis

Descriptive statistics were expressed as median with range between the minimum and the maximum values. To assess the statistical significance between analyzed groups we used the Wilcoxon signed-rank test and Mann–Whitney *U* test for numerical variables and Fisher's exact test for categorical variables. A *P* value of less than .05 was considered statistically significant. Statistical analyses were performed using GraphPad Prism 8.0 (GraphPad Software, San Diego, CA).

Results

Demographics

Patient characteristics are presented in Table 1. The median patient age at the time of TPIAT was 36 years (range 15–51) in the DM group, 36 (16–52) in the pre-DM group, and 41 (9–60) in the non-DM diabetic group (not significant, NS). Median BMI of the DM group was significantly higher than that of the non-DM group (33 [24–39] vs 24 [18–39] [*P*=.03]), but did not differ significantly from that of the pre-DM group (26 [18–38] [*P*=.06]).

Metabolic control

Before TPIAT.—Islet function measured before the procedure using the BETA-2 score was significantly lower in the DM than the pre-DM and non-DM groups (median 9.68 [0.83–30.9] vs 24.09 [17.5–37.63; *P*=.03] and 27.01 [18.12–56.46; *P*=.01]), respectively. There was no statistically significant difference in BETA-2 score between the pre-DM and non-DM groups. Fasting c-peptide did not differ significantly between the 3 groups (median 0.76 [0.36–2.21], 0.61 [0.43–2.58], and 0.51 [0.17–1.01]pmol/mL for the DM, pre-DM, and non-DM groups, respectively [*P*=.09]). In our cohort, diabetic patients required a median of 30 (0–90)U of insulin daily.

After TPIAT.—Islet mass expressed in islet equivalents (IEQ) isolated and transplanted in the DM group did not differ significantly from that in the pre-DM and non-DM groups: median 191,800 (2500–257,500) IEQ vs 232,000 (67,000–379,000; *P* =.32) and 111,800 (30,000–322,000; *P* =.6), respectively (Fig. 1A). However, islet mass transplanted in the pre-DM group was significantly lower than that in the non-DM group (*P* =.03). Islet mass transplanted in IEQ per patient body weight in kilograms (IEQ/kg) was comparable between the DM and in pre-DM groups: median 2013 IEQ/kg (34–2700) vs 1297 (407–4190; *P* =.9). Median islet mass in the non-DM group was 3400 IEQ/kg (680–5190), significantly higher than that in both other groups (*P* <.05) (Fig. 1B). Patients in the DM and non-DM groups

received a clinically relevant target of islet mass greater than 2000 IEQ/kg during transplantation: 60% (3/5) and 83% (15/18; 83.3%) (NS), respectively. Of note, significantly fewer patients received such islet mass in the pre-DM group (45%; 5/11) than in the non-DM group (P =.04) (Fig. 2).

The rate of insulin independence at 1-year follow-up was significantly lower in the DM and pre-DM groups (0% and 13% [1/8], respectively) than in the non-DM group (53% [9/17]; P<.05) (Fig. 3). Similarly, fasting c-peptide did not differ between the DM and pre-DM groups (median 0.08 [0–0.16] and 0.18pmol/mL [0.03–0.52] [P=.18]), but was significantly higher in the non-DM (0.36pmol/mL [0.1–0.65]) than the DM group (P=.04). Nearly 80% of patients from the non-DM group had optimal glucose control with (HbA1c<6.5%), whereas only 37% and 25% of patients from pre-DM and DM group had such outcome, respectively (NS) (Fig. 4).

Islet transplantation failed as defined by undetectable fasting c-peptide on day 75 and afterward only in 1 patient overall (2.9%). This patient, from the DM group (1/5, 20%), had before TPIAT a fasting c-peptide of 0.36pmol/mL, HbA1c of 7.9%, and required 0.42U/kg of insulin daily. His HbA1c, fasting c-peptide, blood glucose, insulin dose, and BETA-2 score did not differ significantly from those of the remaining 4 (80%) diabetic patients from the DM group (P>.05). However, whereas his BMI was 24, that of the remaining 4 patients was over 33. Of note, he had previously received a distal pancreatectomy and only a minimal islet mass was retrieved and transplanted (2500IEQ in 3mL of final product tissue).

In our cohort, the lowest islet mass transplanted, which was found to have a metabolic effect as indicated by positive fasting c-peptide at 1-year postprocedure was 30,000IEQ.

Pain control

Before surgery, all patients (100%) from all 3 groups suffered from typical pancreatic pain localized to the upper–mid–abdominal region and radiating to the back, which necessitated pain control with opioid therapy. The majority of the patients (60%–70%) required opioids on a daily basis in all 3 groups and a minority only periodically (NS) (Fig. 5A). After TPIAT, pancreatic pain gradually subsided completely, within 1 year for all patients in the DM group, within 2 years for those in the non-DM group, and by 3 years for those in the pre-DM group.

The percentage of patients requiring prolonged opioid therapy, periodically or daily, during follow-up due to incisional or hernia-related pain (or other medical problems) did not differ statistically between the groups (Fig. 5B).

Discussion

TPIAT is a major surgical undertaking with a significant risk of morbidity including postsurgical diabetes.[6] Treatment outcomes are directly related to the timing of the operation. On the one hand, patients with prolonged pancreatic disease and opioid dependence who have already progressed to severe endocrine insufficiency (trace or negative c-peptide) have the least favorable outcomes with respect to both relief of pain and

postoperative glycemic control. On the other hand, patients with preserved islet function and less intractable pain have better metabolic outcomes but may be otherwise adversely affected by postoperative sequelae such as exocrine insufficiency or postsurgical complications. For these patients, the morbidity related to the procedure might outweigh the metabolic benefits of TPIAT. Understanding how the timing of TPIAT affects outcomes is critical for therapeutic decision-making, patient counseling, and the establishment of realistic expectations.

In our study, we assessed how the timing of the operation with regard to pre-procedural glucose control affected the resolution of pancreatic pain and the metabolic endocrine outcomes. Our patients included those with and without diabetes as well as those with pre-diabetes based on fasting blood glucose and HbA1c criteria according to the ADA.

Patients with pre-diabetes had significantly fewer isolated and transplanted islets, which may have contributed to worse metabolic outcomes at 1-year follow-up with an insulin-independence rate of only 13% compared to 57% among patients with optimal glucose control before surgery. The intensity of pancreatic pain before and after surgery and the rate of pain resolution were similar between the pre-DM and non-DM groups during follow-up. This indicates that proceeding with TPIAT before HbA1c rises over 5.7 and fasting glucose over 100mg/mL may provide a much better metabolic outcome. Of note, pre-operative BMI does not seem to have influenced this outcome since it did not differ significantly between these groups.

Our study also evaluated the outcomes of diabetic patients, but only those with a serum fasting c-peptide in normal or high range, who had retrievable islets and could potentially benefit from islet transplantation. Interestingly, metabolic outcomes in diabetic and pre-diabetic patients were very similar. Median isolated and transplanted islet mass was 70% higher in the DM group than in the pre-DM group, although this difference was not statistically significant. This intriguing outcome might reflect small sample bias. However, it is also possible that the need for insulin supplementation in our DM group was driven mostly by high insulin resistance with preserved islet mass as reflected by normal or high level of serum c-peptide and high patient BMI, whereas the pre-DM group contained more lean patients with loss of substantial islet mass driving glucose intolerance before the surgery.

Sixty percent of patients in the DM group received a clinically relevant islet mass of over 2000IEQ/kg in contrast to 40% of those in the pre-DM group. This is a very important finding since the isolated and transplanted islet mass remains the strongest predictor of postprocedural endocrine outcome.[7,8] The low rate of insulin independence in both groups is consistent with previous findings, indicating that a higher islet mass is required for the achievement of insulin independence.[7,8]

Nevertheless, fasting c-peptide levels were detected and did not differ between groups at 1-year follow-up, reflecting some preservation of metabolically significant islet graft function. This has a clinically meaningful metabolic impact when compared to patients without any beta cell function, such as those with type 1 diabetes. It has been well described that the

presence of fasting c-peptide reflects some islet function, which improves blood glucose control and eases adjustments of insulin dose without creating labile blood glucose fluctuation. This residual islet function protects patients from the development of hypoglycemic unawareness and the risk of severe hypoglycemia, which are severely debilitating and may have life-threatening consequences.[9,10]

Not all of our diabetic patients clearly benefited from TPIAT. In 1 case, the isolated and transplanted islet mass was too low to produce enough c-peptide to be detected in the circulation. Fasting glucose, c-peptide, HbA1c, insulin dose, and even the BETA-2 score were insufficient to differentiate this patient from others and the prediction of this outcome before the procedure. Of note, the BMI of this patient was 24, whereas that of all remaining patients from this group was over 33. This may indicate that insulin resistance with preserved islet mass rather than islet exhaustion and beta cell mass decline was driving the need for insulin support in those diabetic patients that benefited from the TPIAT procedure. Likely, stimulation tests before the procedure would allow for the differentiation of these 2 population of diabetic patients with opposite metabolic outcomes.

The demand for daily or periodic opioids before surgery was similar among all 3 groups, indicating that endocrine deterioration was not parallel to the progression of the disease in the pancreas which caused the same level of severe debilitating pain and triggered surgery in our series.

Our study provided valuable data for therapeutic decision-making regarding the timing of the operation as well as patient counseling. When the decision to proceed with TPIAT is solely based upon the presence of severe intractable pancreatic pain, the probability of improved endocrine outcomes is much higher if the patient is not yet pre-diabetic or diabetic (HbA1<5.8%, fasting glucose<100mg/mL). In addition, if the patient is already diabetic, a high BMI may suggest that the patient has retained sufficient islet function but developed insulin resistance. In such cases, TPIAT will allow for the achievement of the same endocrine outcomes and pain relief as in pre-diabetic patients who are not on yet dependent on insulin therapy. However, isolated positive fasting c-peptide does not guarantee a positive endocrine outcome, and stimulation test might be considered for further differentiation between the state of insulin resistance and islet exhaustion. In addition, based on our data, some patients may choose to undertake the procedure at an earlier stage of the disease, especially those with identified genetic mutations driving active inflammation and its inevitable progression in the pancreas, rather than postponing the pancreatectomy until they become pre-diabetic and lose their chance for insulin independence after TPIAT.

In conclusion, diabetic patients that still have a positive c-peptide can benefit from TPIAT, with outcomes comparable to those of pre-diabetic patients including full pain relief and the long-term metabolic benefit of transplanted islets. Endocrine outcomes of TPIAT in diabetic and pre-diabetic patients are substantially worse than in those with optimal glucose control before the procedure.

Limitations of our study include the retrospective character of the analysis and the limited number of patients from our single-center cohort. In addition, the lack of pre-transplant

evaluation with the oral glucose tolerance test might have underestimated the number of patients with “true” pre-diabetes as defined by the ADA criteria. Nevertheless, this study provides important practical information regarding the outcomes of TPIAT in pre-diabetic patients who we identified based on HbA1c and fasting blood glucose.

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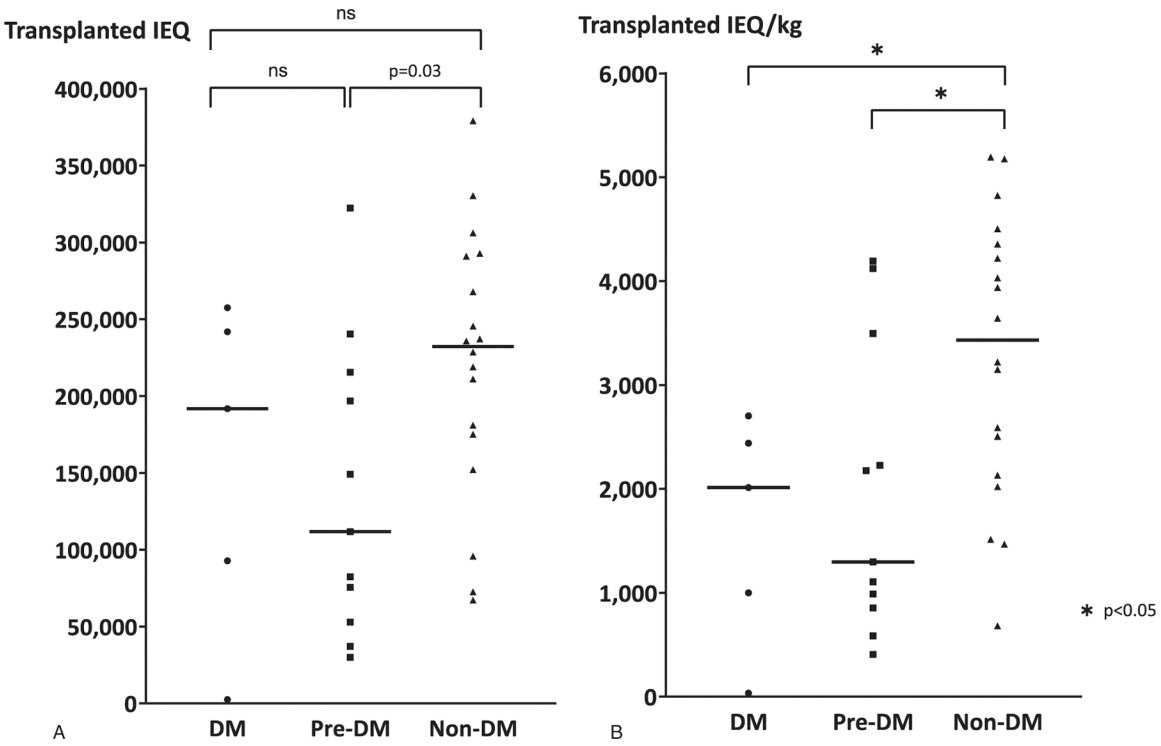

Figure 1.

Islet mass retrieved and transplanted from diabetic, pre-diabetic, and non-diabetic patients. (A) Islet mass expressed in islet IEQ isolated and transplanted in the DM group did not differ significantly from that in the pre-DM and non-DM groups (NS). However, islet mass in the pre-DM group was significantly lower than that in the non-DM group (P=.03)*. (B) Islet mass transplanted per patient body weight in kilograms (IEQ/kg) did not differ significantly between the DM and pre-DM groups. However, it was significantly higher in the non-DM group than both other groups (P<.05). DM = diabetes mellitus, IEQ = islet equivalents, NS = not significant.

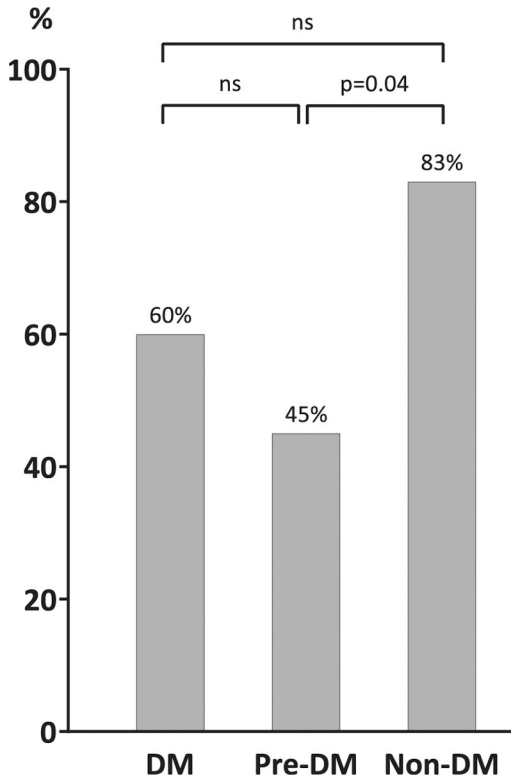

Figure 2.

Rate of patients receiving a transplanted islet mass of over 2000IEQ/kg. A similar proportion of patients received a clinically relevant islet mass of over 2000IEQ/kg during the transplantation in the DM and non-DM groups: 60% (3/5) and 83% (15/18) (83.3%) (NS), respectively. Of note, significantly fewer patients received such an islet mass in the pre-DM group (45% [5/11]) as compared to the non-DM group (*P*=.04). DM = diabetes mellitus, IEQ = islet equivalents, NS = not significant.

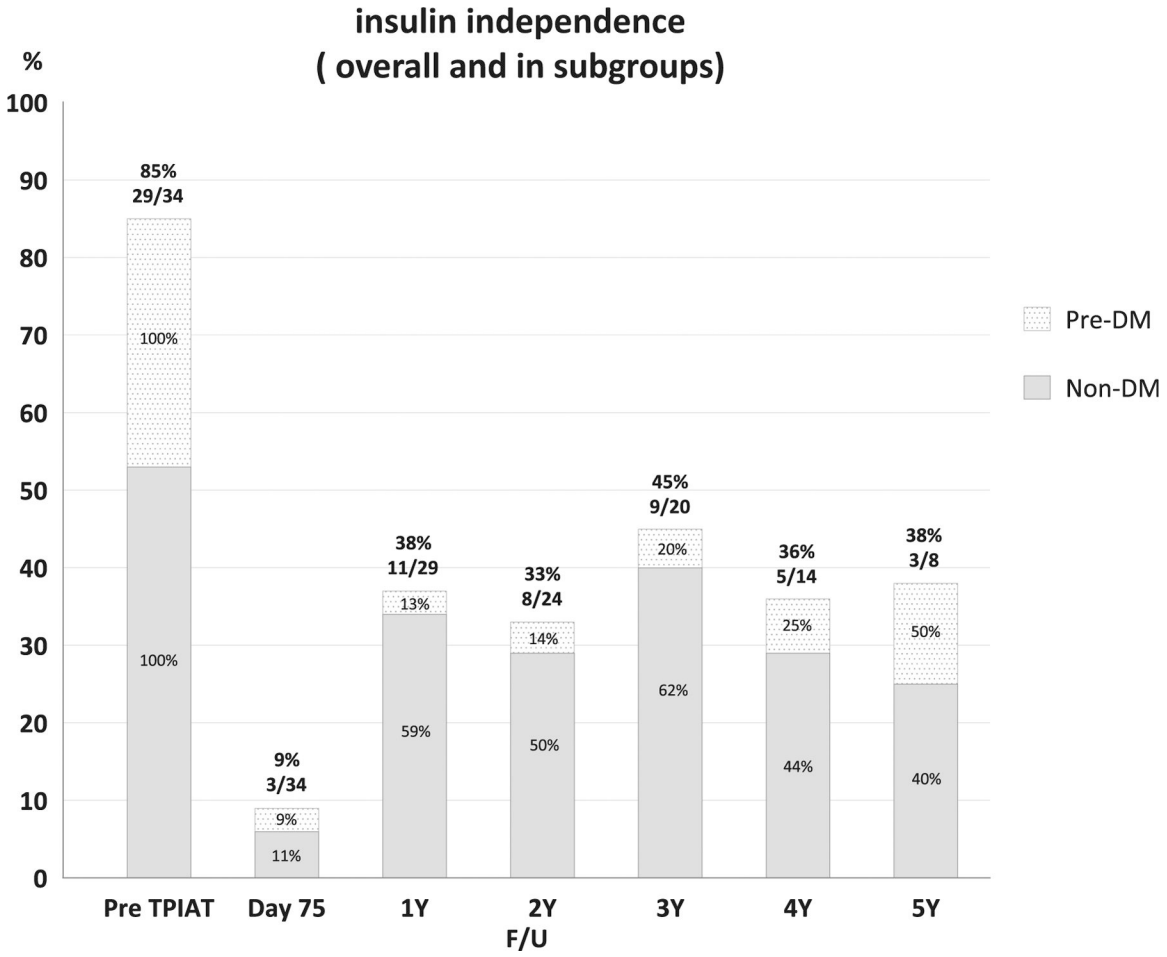

Figure 3.

Insulin independence rate during the follow-up. None of the 5 diabetic patients (DM group) became insulin independent. Only 1 out of 8 (12.5%) patients from the pre-DM group was insulin-free at 1-year and later postprocedure. The rate of insulin-independence at 1-year in the non-DM group was 53% and remained in the range of 40% to 60% afterward. DM = diabetes mellitus.

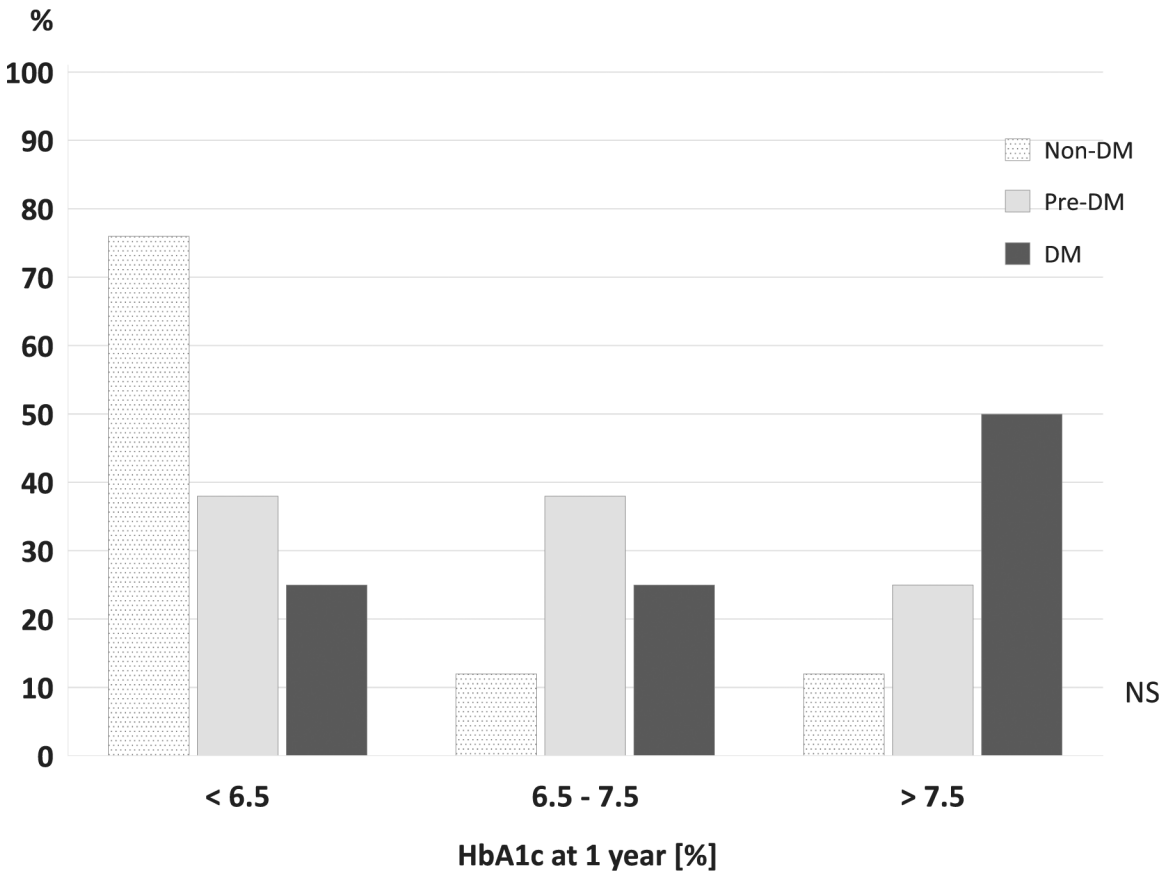

Figure 4.

Metabolic outcome: HbA1c at 1-year follow-up. Nearly 80% of patients from the non-DM group had optimal glucose control with HbA1c<6%. Interestingly, 50% of patients from the DM group and 37% from the pre-DM group had such an outcome. DM = diabetes mellitus.

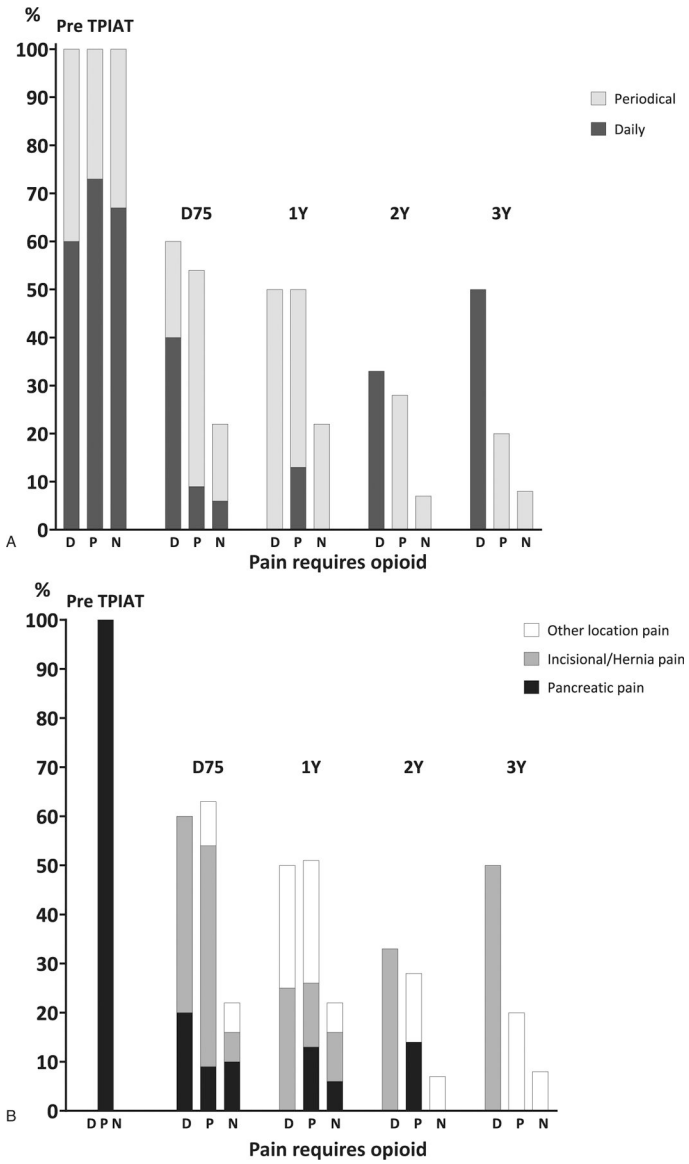

Figure 5.

Pain required opioids. (A) All patients required opioid-based therapy due to pancreatic pain before TPIAT. The majority of the patients (60%–70%) required opioids on a daily basis in all 3 groups. (B) Pancreatic pain gradually subsided completely, within 1 year in all patients in the DM group, within 2 years in all the non-DM group and by 3 years in the pre-DM group. The percentage of patients requiring prolonged opioid therapy, periodically or daily, during follow-up due to incisional or hernia-related pain (or other medical problems) did not differ statistically between the groups. DM = diabetes mellitus, TPIAT = total pancreatectomy with islet autotransplantation.

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Table 1

Baseline characteristics of the 34 patients undergoing TPIAT divided into 3 groups based on pre-TPIAT glycemic control into non-diabetic, pre-diabetic, and diabetic groups according to ADA 2019 fasting blood glucose and HbA1c criteria

	Non-DM (N = 18)	Pre-DM (N = 11)	DM (N = 5)	
		Median and range		*P*
Age at diagnosis (yr)	20 (1–51)	21 (2–40)	21 (3–45)	NS
Age at TPIAT (yr)	41 (9–60)	36 (16–52)	36 (15–51)	NS
Sex M/F	6/12	4/7	2/3	NS
BMI at TPIAT (kg/m^2)	24 (18–39)*	26 (18–38)	33 (24–39)*	
Average daily insulin/d (pre-TPIAT) (U/d)	0	0	30 (17–90)	
Average daily insulin/kg/d (pre-TPIAT) (U/kg/d)	0	0	0.31 (0.18–0.91)	
Duration of pancreatitis (mo)	107 (12–468)	168 (45–420)	144 (18–180)	NS
Etiology (n)				
Genetic mutation (SPINK1, PRSS1, CFTR)	8	6	3	
Other hereditary	3	1	0	
Pancreas divisum	4	1	1	
Autoimmune	0	1	0	
Other	3	2	1	
Pancreatic surgery (n)	2†	0	1‡	

ADA = American Diabetes Association, CFTR = cystic fibrosis transmembrane conductance regulator, DM = diabetes mellitus, NS = not significant, PRSS1 = protease serine 1, SPINK1 = serine protease inhibitor Kazal type 1, TPIAT = total pancreatectomy with islet autotransplantation.

*P<.05.

†Surgical drainage.

‡Distal resection.