DIABETES TECHNOLOGY & THERAPEUTICS
Volume 28, Number 4, 2026
Mary Ann Liebert, A Part of Sage

DOI: 10.1177/15209156251380857

DTT

ORIGINAL ARTICLE

Continuous Glucose Monitoring and Long-Term Assessment of Islet Function in Autologous Islet Transplantation after Total Pancreatectomy for Neoplasm: Preliminary Insights from a Prospective Study

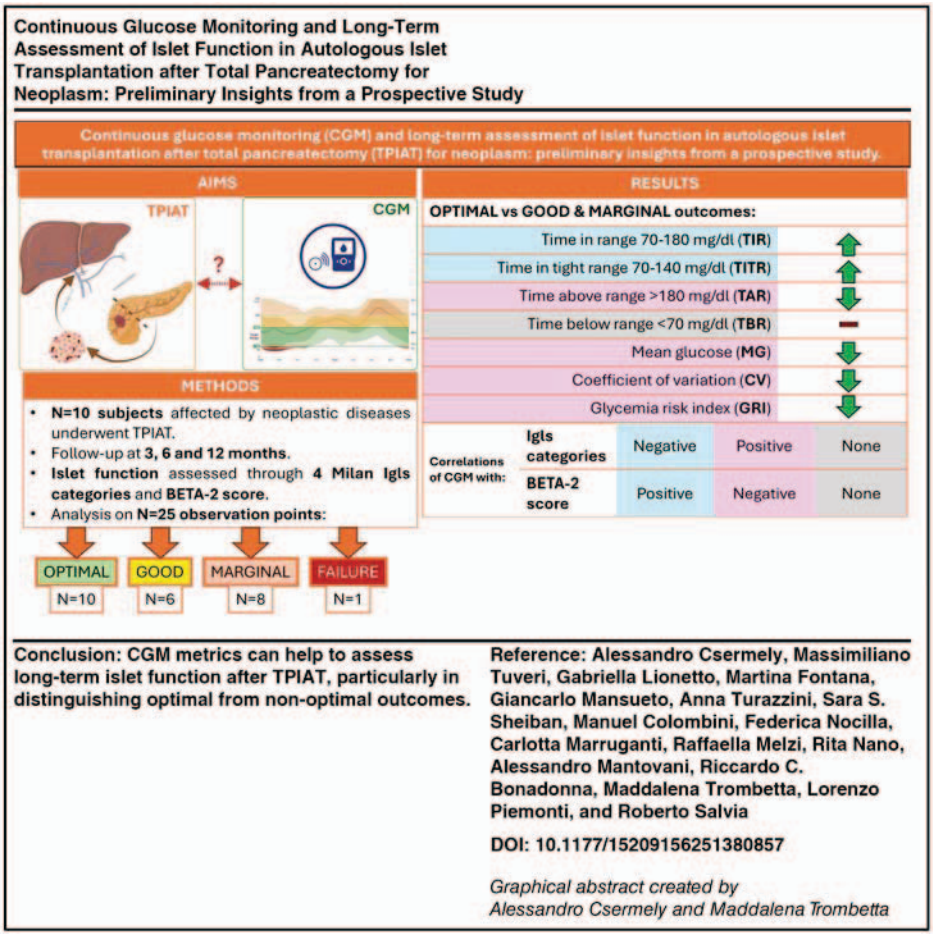
Alessandro Csermely, MD,[1] Massimiliano Tuveri, MD,[2,3] Gabriella Lionetto, MD,[2] Martina Fontana, MD,[2] Giancarlo Mansueto, MD,[4] Anna Turazzini, MD,[1] Sara S. Sheiban, MD,[1] Manuel Colombini, MD,[1] Federica Nocilla, MD,[1] Carlotta Marruganti, MD,[1] Raffaella Melzi, MSc,[5] Rita Nano, MSc,[5] Alessandro Mantovani, MD, PhD,[1] Riccardo C. Bonadonna, MD,[1,6] Maddalena Trombetta, MD, PhD,[1] Lorenzo Piemonti, MD,[5,7] and Roberto Salvia, MD, PhD[2]

Abstract

Background and Aims: Total pancreatectomy with islet autotransplantation (TPIAT) is a surgical option to mitigate the risk of anastomotic complications and preserve endogenous insulin secretion in patients undergoing pancreaticoduodenectomy. However, the utility of continuous glucose monitoring (CGM) in assessing islet graft performance remains poorly characterized. Thereby, the aim of this study was to investigate the relationship between CGM-derived glycemic metrics and islet function following TPIAT.
Materials and Methods: Ten patients with pancreatic neoplasms (male/female 5/5, median age 60 [IQR 55–68] years) underwent TPIAT between September 2023 and March 2025 at the Verona University Hospital, receiving a median islet dose of 1912 IEQ/kg [IQR 1724–3074]. CGM data were collected at 3 (n = 10), 6 (n = 8), and 12 (n = 7) months post-transplantation. Islet metabolic function was assessed using Igls criteria and BETA-2 score. CGM metrics were compared across Igls-defined graft function categories and correlated with BETA-2 scores.
Results: Of 25 total assessments, islet function was classified as optimal (n = 10), good (n = 6), marginal (n = 8), or failure (n = 1). Median BETA-2 score decreased significantly across these groups (19.4, 13.6, 5.3, 1.4, respectively; $P < 0.001$). Optimal function was associated with superior glycemic control (time in range, TIR: 97.0%; time in tight range, TITR: 86.5%; time above range, TAR: 1.5%) and lower glycemic variability (coefficient of variation, CV: 20.5%; glycemia risk index, GRI: 44.0), compared with good and marginal groups (all $P < 0.01$). These same CGM metrics were significantly correlated with both Igls classification and BETA-2 score (all $P < 0.015$).
Conclusions: CGM parameters reflect islet graft performance following TPIAT and are strongly correlated with established markers of β-cell function. Metrics such as TIR, TITR, TAR, CV, and GRI may serve as practical and sensitive tools for post-transplant metabolic surveillance in endocrine clinical practice.

Keywords: continuous glucose monitoring, time in range, glycemia risk index, islet autotransplantation, pancreatic neoplasia.

[1]Division of Endocrinology, Diabetes and Metabolic Diseases, Department of Medicine, University Hospital of Verona, Verona, Italy.
[2]General and Pancreatic Surgery Department, Pancreas Institute, University Hospital of Verona, Verona, Italy.
[3]Department of General and Oncological Surgery, G. Brotzu Hospital, Cagliari, Italy.
[4]Institute of Radiology, Department of Diagnostics and Public Health, Policlinico GB Rossi, University of Verona, Verona, Italy.
[5]Diabetes Research Institute, IRCCS Ospedale San Raffaele, Milan, Italy.
[6]Department of Medicine and Surgery, University of Parma, Parma, Italy.
[7]Università Vita-Salute San Raffaele, Milan, Italy.



Introduction

Total pancreatectomy with islet autotransplantation (TPIAT) has been proposed as a safe and effective alternative to partial pancreatectomy followed by high-risk pancreatic anastomosis for the treatment of pancreatic neoplasms. This approach aims to mitigate the risk of postoperative complications, such as clinically relevant pancreatic fistulas, while preserving endogenous insulin secretion and minimizing the incidence of unstable pancreatogenic diabetes.[1]

In the context of islet allotransplantation for type 1 diabetes (T1D), the Igls criteria were developed as a standardized framework to classify beta cell graft outcomes.[2] However, adaptation was necessary for their application to islet autotransplantation (IAT), as recipients typically do not have pre-existing diabetes at the time of surgery. To address this, several centers have proposed modified versions of the Igls criteria tailored to the autologous setting, including adaptations from Chicago,[3] Minnesota,[4] Leicester,[5] and Milan:[6] almost all these Igls-derived islet evaluation methods rely on hematological exams (such as C-peptide and HbA1c values) and on clinical parameters (like the incidence of severe hypoglycemia episodes and the exogenous daily insulin intake), providing a categorical evaluation of each factor based on four different classes (optimal, good, marginal and failure) as defined by thresholds set by each center, and then assigning a composite overall evaluation of the graft function according to the lowest class function achieved for any of the categorizing parameters;[3,4,6] in this framework, the Milan criteria have been proposed among the most recent classification systems for TPIAT, providing more granular C-peptide ranges for identifying intermediate categories and having been validated in a large cohort of TPIAT recipients.[6] In addition to Igls-derived criteria, continuous surrogate indices based on single fasting blood samples have been developed to assess islet graft function following TPIAT. Among these, the BETA-2 score has demonstrated superior performance, showing a strong correlation with Igls-derived functional categories and providing a reliable estimate of residual beta cell activity.[3,7]

Traditional islet graft evaluation methods rely primarily on biochemical parameters—such as fasting C-peptide, glucose, and HbA1c—as well as clinical indicators including daily exogenous insulin requirements and the occurrence of severe hypoglycemia. However, the growing accessibility of continuous glucose monitoring (CGM) technologies has introduced a more dynamic and granular approach to assessing glycemic control in islet transplant recipients. CGM-derived metrics provide superior insight into blood glucose fluctuations and glycemic variability compared with static blood-based measures. Notably, in the context of islet allotransplantation for T1D, several studies have demonstrated strong concordance between CGM profiles and Igls-based functional classification,[2] underscoring the potential of CGM as a complementary tool in evaluating graft performance. In the context of autologous islet transplantation, preliminary studies have identified significant associations between selected CGM metrics, particularly time in range, and modified auto-Igls classification systems.[4] However, comprehensive data on the distribution and performance of both established and emerging CGM-derived metrics across recently proposed classification frameworks remain limited. Therefore, the main aim of this pilot study, based on initial data from the first TPIAT procedures completed at the University Hospital of Verona, was to preliminarily explore the potential associations between selected CGM metrics and the recently proposed Milan modified Igls criteria for IAT.[6] Such exploratory analysis sought to provide insights to inform future, more comprehensive investigations into this relationship.

Materials and Methods

This prospective study enrolled patients undergoing TPIAT at the University Hospital of Verona. Clinical and biochemical data, including islet function parameters and CGM metrics, were systematically collected during follow-up. The primary objective was to evaluate the distribution of key CGM-derived metrics across the functional outcome categories defined by the most recent Milan-modified Igls criteria for autologous islet transplantation.[6] The secondary objective was to assess potential associations between CGM metrics and the BETA-2 score, a validated surrogate marker of beta cell function.

The study protocol was approved by the Institutional Ethics Committee of the University Hospital of Verona and conducted in accordance with the ethical standards outlined in the Declaration of Helsinki. Written informed consent was obtained from all participants prior to enrollment.

Subject Eligibility

All patients who underwent TPIAT for pancreatic or ampullary neoplasms at the University Hospital of Verona between September 2023 and March 2025 were consecutively and prospectively enrolled as surgical procedures and IAT were completed and as their further glucometabolic monitoring and follow-up could start. The eligibility criteria for TPIAT followed the Milan protocol:[8] adult patients with localized, resectable neoplastic disease for which conventional partial pancreatectomy was associated with a high risk of postoperative complications related to pancreatic anastomosis. Patients were excluded if they had a preoperative diagnosis of diabetes mellitus, defined by confirmed fasting plasma glucose ≥126 mg/dL and/or HbA1c ≥6.5%.[9] Additional exclusion criteria included a diagnosis of multiple endocrine neoplasia, intraductal papillary mucinous neoplasm with multifocal lesions unless excluded by endoscopic ultrasound, and involvement of the pancreatic transection margin.[8]

Surgical Procedure and Islet Isolation

Once deemed eligible, patients underwent total pancreatectomy. Splenic preservation was considered on a case-by-case basis, according to individual anatomical and clinical factors. A 1 cm margin of pancreatic tissue adjacent to the transection site was submitted for intraoperative frozen section analysis to confirm the absence of residual tumor. The disease-free portion of the resected pancreas was immediately preserved in cold University of Wisconsin solution and transported to the islet isolation facility at San Raffaele Hospital, Milan. There, enzymatic digestion, islet isolation, and purification were carried out according to previously established protocols.[8,10,11] On postoperative day 1, the purified autologous islets were transported back to Verona and infused into the patient's liver via percutaneous transhepatic cannulation of the portal vein, performed by the same surgical team.

Postoperative Management and Follow-up

Following TPIAT, patients underwent in-hospital monitoring for postoperative complications and adverse events. During this period, glycemic control was maintained with low dose multiple daily insulin injections, and hematological parameters—including fasting blood glucose and C-peptide levels—were regularly assessed. Upon clinical stabilization, patients were discharged and scheduled for structured follow-up visits at 1, 3, 6, and 12 months postprocedure. These visits included assessment of glycemic control, insulin requirements, and routine biochemical parameters. All patients were equipped with second-generation intermittently scanned CGM (isCGM) systems (Abbott™ FreeStyle Libre 2). Strict glycemic targets were pursued using low-dose basal-bolus insulin therapy to support islet engraftment during the critical early post-transplant period.[12] This regimen was maintained for the first 2 months and then progressively tapered during the initial 2 weeks of the third month, provided adequate glycemic control was achieved without hypoglycemia. At 3, 6, and 12 months post-TPIAT, follow-up evaluations included clinical assessment, fasting laboratory testing, and—when feasible—a standardized mixed meal tolerance test (MMTT). Islet graft function was classified using the Milan-modified Igls criteria and quantified by the BETA-2 score.

Mixed meal tolerance test

The MMTT was performed using a 386-kcal test meal, consisting of approximately 48.0 g carbohydrates, 13.2 fats, and 16.0 g proteins. Specifically, the meal consisted of composite portions of Parmesan cheese (34 g: 136 kcal, 0.0 g carbohydrates, 10.2 g fats, 10.8 g proteins), breadsticks (30 g: 126 kcal, 21.0 g carbohydrates, 2.8 g fats, 3.6 g proteins), and peach juice (250 g: 124 kcal, 27.0 g carbohydrates, 0.2 g fats, 1.6 g proteins). The meal was consumed within 10 min, and blood samples for blood glucose, C-peptide and insulin were collected at baseline (−15 and 0 min), followed by 10, 20, 30, 45, 60, 90, 120, 140, and 180 min after ingestion. The highest C-peptide measurement during the test, referred to as "stimulated C-peptide," was recorded. Since the MMTT required quite a long time and collaboration from the patients in order to complete it adequately, such procedure was suggested but not mandatory for the follow-up.

Islet function classification methods

Milan Igls-derived criteria[6] were used for the evaluation of islet function, including four categories of success (optimal, good, marginal, and failure) based on four parameters: HbA1c, incidence of severe hypoglycemia episodes, exogenous insulin daily dose and fasting or stimulated plasma C-peptide (that is, C-peptide peak during a stimulation test like an oral glucose tolerance test, a mixed meal tolerance test or an arginine test).

Islet outcomes were also assessed by calculating the BETA-2 score,[7] as follows:

$$BETA-2\,score = \left(\frac{\sqrt{fasting\ C-peptide_{nmol/l}} * (1 - insulin\,dose_{IU/kg/day})}{fasting\,blood\,glucose_{mmol/l} * HbA1c_{\%}}\right) * 1000$$

CGM data

At 3, 6, and 12 months after TPIAT, isCGM-derived data regarding the last 14 days prior to visits were collected and the following metrics were calculated:

- time in range 70–180 mg/dL (TIR)
- time in tight range 70–140 mg/dL (TITR)
- time above range >180 mg/dL (TAR) and its components 181–250 mg/dL and >250 mg/dL
- time below range <70 mg/dL (TBR) and its components 54–69 mg/dL and <54 mg/dL
- coefficient of variation (CV)
- mean glucose (MG)
- glycemia risk index (GRI) and its hyper- and hypoglycemia components, calculated according to previously proposed formulas[13]

CGM readings were considered adequate for analysis with sensor use >70% over the chosen 14-day-long periods, according to the most recent recommendations.[14]

Statistical Analysis

Continuous variables are reported as medians with interquartile ranges (IQR), while categorical variables are expressed as absolute counts and relative frequencies (%). To account for repeated measures across multiple follow-up time points (3, 6, and 12 months post-TPIAT), a panel data structure was constructed with patient identifiers and corresponding time points.

Comparisons of continuous variables across Igls-derived functional categories were conducted using the Kruskal–Wallis test, followed by Dunn's post hoc tests for pairwise comparisons. Nonparametric Spearman's rank correlation analyses were employed to evaluate associations between key isCGM-derived metrics and both categorical (Milan modified Igls criteria) and continuous (BETA-2 score) indices of islet graft function, as well as the total infused islet equivalents (IEQ/kg).

A two-sided P value <0.05 was considered statistically significant. Given the exploratory nature of the study, no adjustments were made for multiple comparisons.

All statistical analyses were performed using STATA software, version 18.0 (StataCorp, College Station, TX, USA).

Results

Subjects

Between September 2023 and March 2025, a total of 10 patients underwent TPIAT at the University Hospital of Verona (male/female: 5/5). Median [IQR] values at baseline were: age 60 [55–68] years, BMI 24.8 [22.2–27.6] kg/m^2, fasting plasma glucose 95 [83–102] mg/dL, fasting C-peptide 2.1 [1.3–2.9] ng/mL, and HbA1c 5.3% [4.9–5.7]. The median islet yield was 1912 [1724–3074] IEQ/kg. Of the 10 patients, 7 had malignant neoplasms (pancreatic, ampullary, or duodenal adenocarcinoma), 2 had pancreatic neuroendocrine tumors, and 1 had a high-grade ampullary adenoma; the median [IQR] time from diagnosis to surgical treatment was 5 [3–9] months, ranging from 0 to 12 months. Two patients had a history of pancreatitis (acute, $n = 1$; chronic calcific, $n = 1$). Regarding complications related to percutaneous portal vein infusion, two subjects experienced bleeding that was managed with angiographic hemostasis, and one of these cases was associated with portal vein thrombosis. A summary of baseline characteristics is provided in Table 1. Detailed individual patient data, along with all further surgery-related adverse events, are presented in Supplementary Table S1.

Islet function outcomes

Follow-up visits were conducted at 3, 6, and 12 months after TPIAT, yielding a total of 25 evaluable observation points with paired CGM data and islet function assessments. The number of patients contributing to the data at each time

Table 1. Baseline Characteristics of Subjects Undergoing TPIAT

Variables	*Values*
N	10
Sex (M/F, %M)	5/5 (50%)
Age (years)	60 (55–68)
Body weight (kg)	72 (52–87)
BMI (kg/m^2)	24.8 (22.2–27.6)
Fasting plasma glucose (mg/dL)	95 (83–102)
Fasting C-peptide (ng/mL)	2.1 (1.3–2.9)
HbA1c	
(%)	5.3 (4.9–5.7)
(mmol/molHb)	35 (30–39)
Original pancreatic disease (*n*, %):	
• Ampullary adenocarcinoma	3 (30)
• Biliopancreatic adenocarcinoma	1 (10)
• Duodenal adenocarcinoma	1 (10)
• High-grade ampullary adenoma	1 (10)
• Intraductal papillary mucinous neoplasm with associated pancreatic adenocarcinoma	1 (10)
• Pancreatic adenocarcinoma	1 (10)
• Pancreatic neuro-endocrine tumor	2 (20)
Infused islets (IEQ/kg)	1912 (1724–3074)

Baseline characteristics of the 10 patients undergoing TPIAT.

Categorical variables presented as absolute frequencies (percentage); continuous variables presented as median (IQR).

BMI, body mass index; HbA1c, hemoglobin A1c.

point was 10 at 3 months, 8 at 6 months, and 7 at 12 months, according to the available follow-up duration reached by each subject at the time of data collection and analysis. At each time point, islet function was categorized according to the Milan-modified Igls criteria (Table 2), and BETA-2 scores were calculated.

Overall, among the whole sample of 25 observation points from 3 to 12 months of follow-up, islet function was classified as optimal in 10 observation points (40%), good in 6 (24%), marginal in 8 (32%), and failed in 1 observation point (4%) (Table 3). Significant differences across categories were observed in HbA1c ($P < 0.001$) and exogenous insulin requirements ($P = 0.003$), whereas fasting C-peptide levels and the incidence of severe hypoglycemia episodes did not differ significantly. Patients in the "optimal" group had the lowest HbA1c values (5.6% [5.4–5.9]), were insulin-independent, and maintained fasting C-peptide within normal range (1.06 [1.00–1.33] ng/mL). Those classified as "good" and "marginal" had higher HbA1c levels (6.3% [6.1–6.7] and 7.5% [7.4–8.1], respectively) and required low-to-moderate multiple daily insulin injection (MDII) therapy (0.11 [0.00–0.11] IU/kg/day and 0.20 [0.12–0.50] IU/kg/day, respectively) using once-daily glargine 300 IU/mL (0.08 [0.00–0.11] IU/kg/day and 0.14 [0.09–0.31] IU/kg/day, respectively) and lispro 100 IU/mL at meal times (0.00 [0.00–0.02] IU/kg/day and 0.08 [0.01–0.19] IU/kg/day, respectively) as long-acting and rapid-acting insulin analogues, respectively, while maintaining measurable fasting C-peptide (1.24 [1.15–1.42] and 1.00 [0.77–1.64] ng/mL, respectively). The single "failure" case showed minimal residual C-peptide secretion (0.23 ng/mL), required the highest insulin dose (0.75 IU/kg/day total insulin: 0.46 IU/kg/day long-acting and 0.29 IU/kg/day rapid acting insulin), yet maintained relatively acceptable glycemic control (HbA1c6.4%). No severe hypoglycemia was reported in any group. Across follow-up intervals (Fig. 1), the proportion of patients with optimal islet function remained stable: 40% at 3 months (4/10), 38% at 6 months (3/8), and 43% at 12 months (3/7). At 12 months, one subject (14%) was classified as failure. Seven participants accepted to undergo MMTTs at 3 ($n = 3$), 6 ($n = 6$), and 12 months ($n = 6$). Peak stimulated C-peptide was used for islet classification in addition to fasting values. However, no reclassification occurred when using stimulated instead of fasting C-peptide based on the proposed cut-offs. The BETA-2 score decreased consistently across Igls functional categories: median [IQR] values were 19.4 [17.7–19.8] for optimal, 13.6 [11.8–15.7] for good, 5.3 [3.5–10.4] for marginal, and 1.4 for failure ($P < 0.001$).

CGM metrics and their association with islet function

CGM profiles demonstrated significantly different distributions across Igls-derived categories for several key metrics (Table 3). These included TIR ($P = 0.013$), TITR ($P = 0.002$), TAR ($P = 0.008$), mean glucose ($P = 0.002$), CV ($P = 0.048$), and the GRI (total and hyperglycemia component: $P = 0.026$ and $P = 0.006$, respectively). In contrast, no significant differences were observed for TBR or the hypoglycemia component of GRI, both of which remained consistently low across all Igls groups (<1% and <1, respectively). As illustrated in Figure 2, post-hoc Dunn's multiple comparison analyses revealed that subjects in the "optimal" islet function category exhibited significantly better glycemic control than those in the "good" and "marginal" groups. Specifically, they had higher TIR (97.0% vs. 75.5%, $P = 0.005$; vs. 68.0%, $P = 0.002$) and TITR (86.5% vs. 41.0%, $P = 0.004$; vs. 38.0%, $P < 0.001$), and lower TAR (1.5% vs. 24.5%, $P = 0.004$; vs. 31.0%, $P = 0.001$), mean glucose (112 vs. 156 mg/dL, $P = 0.002$; vs. 162 mg/dL, $P < 0.001$), CV (20.5% vs. 30.1%, $P = 0.008$; vs. 29.6%, $P = 0.016$), GRI (4.0 vs. 22.0, $P = 0.007$; vs. 32.0, $P = 0.004$), and GRI hyperglycemia component (0.5 vs. 8.0, $P = 0.006$; vs. 15.0, $P < 0.001$). No significant differences were found between "good" and "marginal" categories for any CGM metric. Due to the single data point in the "failure" group ($n = 1$), statistical comparisons with this category were not feasible. Full results of post-hoc comparisons are reported in Supplementary Table S2. Further sub-analyses regarding the longitudinal trends of CGM metrics within optimal and not-optimal subgroups who reached the whole 12-month time period of follow-up did not unveil any significant within-group differences through the observed time points, except for a slightly increasing trend in CV and GRI, albeit not statistically significant (Supplementary Table S3).

Correlation analyses using Spearman's method (Table 4) confirmed that several CGM-derived metrics were significantly associated with both the Milan Igls-derived classification and the BETA-2 score. Strong correlations were observed for TIR (rho = –0.588 and 0.815), TITR (–0.696 and 0.856), TAR (0.617 and –0.828), mean glucose (0.665 and –0.798), CV (0.487 and –0.699), total GRI (0.535 and –0.743), and GRI hyperglycemia component (0.612 and –0.827), with all P values <0.05 for Igls classification

TABLE 2. MILAN IGLS-DERIVED CRITERIA FOR THE ASSESSMENT OF ISLET FUNCTION AFTER AUTOLOGOUS TRANSPLANTATION[6]

				Plasma C-peptide (ng/mL)	
Category of success	*HbA1c (%)*	*SHE* (n)	*Insulin dose (IU/kg/day)*	*Stimulated*	*Fasting*
Optimal	≤6.5	0	0.0	>0.50	>0.50
Good	>6.5 and <7.0	—	>0.0 and <0.5	—	—
Marginal	≥7.0	≥1	≥0.5	—	>0.30 and ≤0.50
Failure	—	—	—	≤0.50	≤0.30

Islet function can be classified as optimal, good, marginal, or failure according to the worst mark achieved in each of the four parameters: HbA1c, incidence of severe hypoglycemia events, daily insulin dose needed or C-peptide (fasting or stimulated, i.e., peak of C-peptide during a stimulation test, like OGTT, MMTT, or arginine test).

HbA1c, hemoglobin A1c; SHE, severe hypoglycemia episode.

Table 3. Igls-Related Parameters, BETA-2 Scores, and isCGM-Derived Metrics Across Multiple Observation Points During Follow-Up of Subjects After Total Pancreatectomy with Islet Autotransplantation

		Igls categories				
Variables	*All*	*Optimal*	*Good*	*Marginal*	*Failure*	P *value*
Number of observations						
Total	25	10	6	8	1	
At 3 months	10	4	3	3	0	
At 6 months	8	3	1	4	0	
At 12 months	7	3	2	1	1	
HbA1c						<0.001*
%	6.2	5.6	6.3	7.5	6.4	
	5.7–7.4	5.4–5.9	6.1–6.7	7.4–8.1		
mmol/molHb	44	38	46	59	46	
	39–57	36–41	43–50	57–65		
SHE	0	0	0	0	0	1.000
N						
Daily insulin dose						
IU/kg/day						
Total insulin	0.00	0.00	0.11	0.20	0.75	0.003*
	0.00–0.13	0.00–0.00	0.00–0.11	0.12–0.50		
Long-acting insulin	0.00	0.00	0.08	0.14	0.46	0.003*
	0.00–0.13	0.00–0.00	0.00–0.11	0.09–0.31		
Rapid-acting insulin	0.00	0.00	0.00	0.08	0.29	0.017*
	0.00–0.04	0.00–0.00	0.00–0.02	0.01–0.19		
Fasting C-peptide	1.09	1.06	1.24	1.00	0.23	0.339
ng/mL	0.85–1.33	1.00–1.33	1.15–1.42	0.77–1.64		
Stimulated C-peptide[ϕ]	4.12	5.12	5.03	2.77	—	0.373
ng/mL	3.45–5.88	3.95–5.80	3.66–6.19	2.08–4.31		
Fasting plasma glucose	120	105	120	148	138	<0.001*
mg/dL	108–140	97–111	113–130	139–177		
BETA-2 score	14.6	19.4	13.6	5.3	1.4	<0.001*
	7.6–18.9	17.7–19.8	11.8–15.7	3.5–10.4		
TIR 70–180 mg/dL	90.0	97.0	75.5	68.0	87.0	0.013*
%	68.0–96.0	94.0–99.0	66.0–90.0	60.5–85.5		
TITR 70–140 mg/dL	59.0	86.5	41.0	38.0	59.0	0.002*
%	38.0–86.0	83.0–90.0	37.0–62.0	30.5–48.0		
TAR >180 mg/dL	10.0	1.5	24.5	31.0	12.0	0.008*
%	2.0–32.0	0.0–4.0	10.0–34.0	14.5–37.0		
181–250 mg/dL	9.0	1.5	17.0	22.0	12.0	0.008*
	2.0–21.0	0.0–4.0	9.0–27.0	13.5–28.5		
>250 mg/dL	0.0	0.0	2.0	4.5	0.0	0.024*
	0.0–4.0	0.0–0.0	1.0–10.0	0.5–7.5		

(*continued*)

TABLE 3. (CONTINUED)

Variables	All	Optimal	Good	Marginal	Failure	P value
		Igls categories				
TBR <70 mg/dL	0.0	0.0	0.0	0.5	1.0	0.574
%	0.0–1.0	0.0–1.0	0.0–0.0	0.0–1.0		
54–69 mg/dL	0.0	0.0	0.0	0.5	1.0	0.554
	0.0–1.0	0.0–1.0	0.0–0.0	0.0–1.0		
<54 mg/dL	0.0	0.0	0.0	0.0	0.0	0.982
	0.0–0.0	0.0–0.0	0.0–0.0	0.0–0.0		
MG	140	112	156	162	133	0.002*
mg/dL	118–162	107–118	140–170	146–168		
CV	24.7	20.5	30.1	29.6	29.4	0.048*
%	20.3–30.3	18.6–22.6	25.3–32.7	21.8–33.1		
GRI hyper component	6.0	0.5	8.0	15.0	8.0	0.006*
	1.0–12.0	0.0–1.5	6.5–10.5	6.8–31.8		
GRI hypo component	0.0	0.8	0.0	0.4	0.8	0.414
	0.0–0.8	0.0–0.8	0.0–0.0	0.0–0.8		
GRI	12.0	4.0	22.0	32.0	12.0	0.026*
	4.8–32.0	1.6–5.6	8.8–36.8	12.0–40.4		

Cohort size = 25 observations from 10 subjects through a follow-up of 3 to 12 months after TPIAT.
Data are presented as median and interquartile range.
Comparisons for each variable across Igls categories were performed through Kruskal–Wallis tests, with a significance set for $P < 0.05$.
*$P < 0.05$.
$^{\Phi}$Stimulated C-peptide available for n = 15 observations from 7 subjects, distributed as follows: 7 optimal, 4 good, and 4 marginal outcomes.
CV, coefficient of variation; GRI, glycemia risk index; HbA1c, hemoglobin A1c; MG, mean glucose; SHE, severe hypoglycemia episode; TAR, time above range; TBR, time below range; TIR, time in range; TITR, time in tight range; TPIAT, total pancreatectomy with islet autotransplantation.

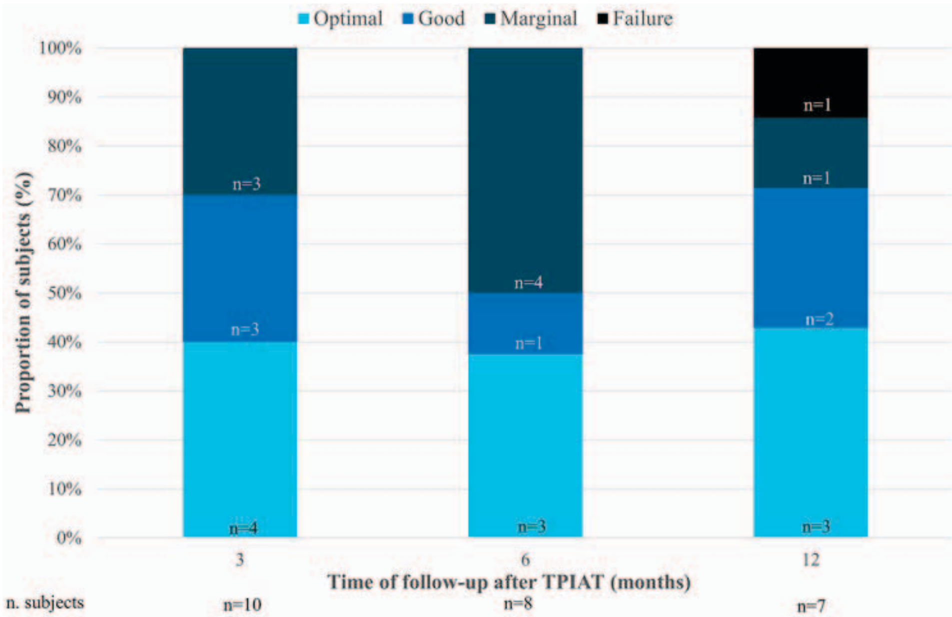


FIG. 1. Metabolic outcomes of total pancreatectomy with islet autotransplantation (TPIAT) through follow-up according to Milan modified Igls criteria. For each time point, the proportions of the four Igls outcomes across the available subjects are shown, along with the distribution of the respective subjects in each Igls category.

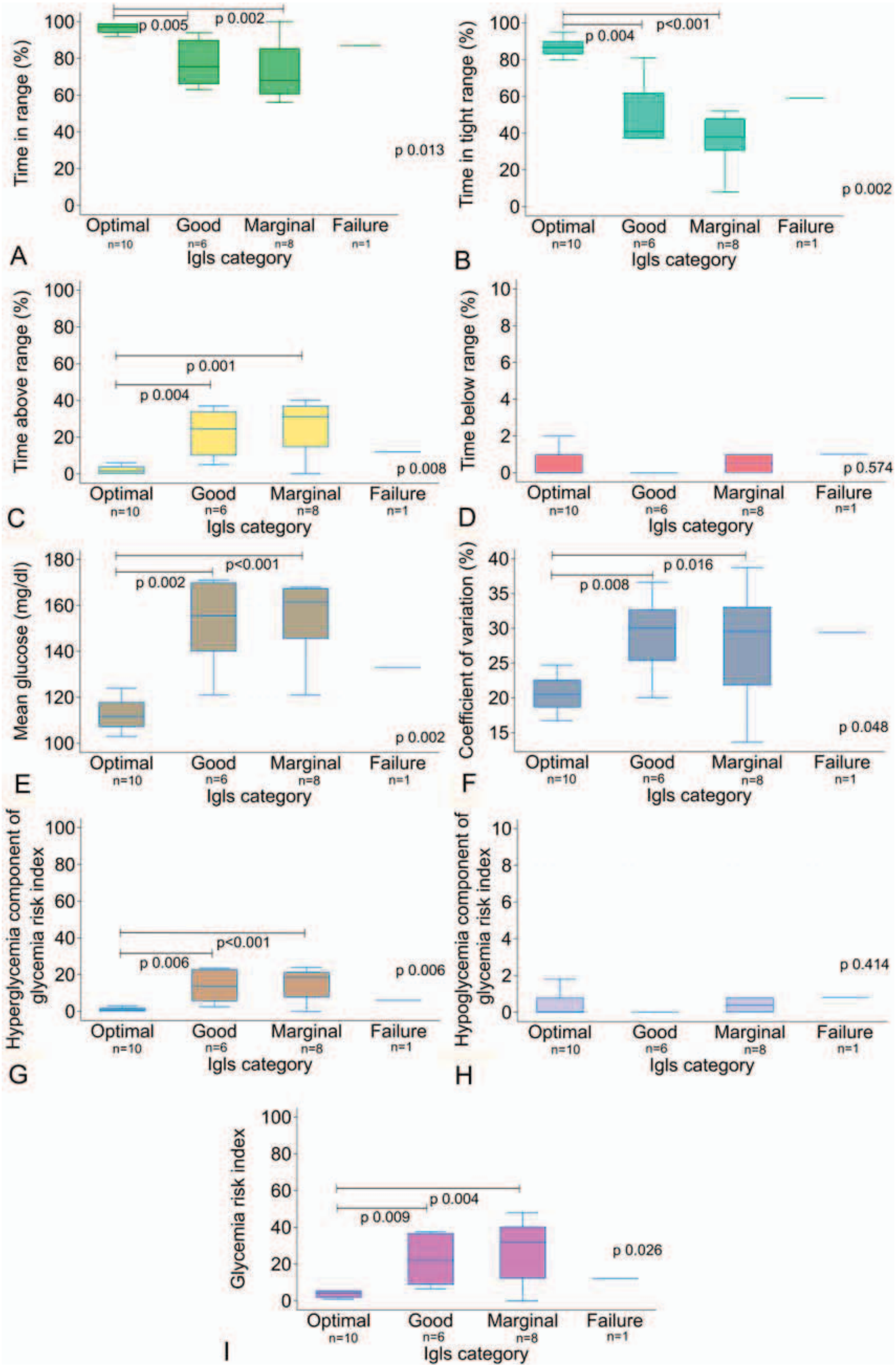
and <0.001 for BETA-2 score. These same CGM metrics were also significantly associated with the number of infused islet equivalents per kilogram (IEQ/kg), showing consistent trends (e.g., TIR: rho = 0.467, $P = 0.019$; TITR: rho = 0.535, $P = 0.007$; TAR: rho = –0.539, $P = 0.006$; full results in Supplementary Table S4). In addition, the number of IEQ/kg infused was strongly correlated with both the Igls classification (rho = –0.672, $P < 0.001$) and BETA-2 score (rho = 0.643, $P < 0.001$). Conversely, neither TBR nor the GRI hypoglycemia component were significantly associated with any islet function outcome measure (Igls classification or BETA-2 score), nor with the quantity of infused islets.

Discussion

Although the limited sample size precluded from drawing definitive conclusions about CGM's value as a tool for evaluating long-term islet function following TPIAT our study suggested a potential association between CGM-derived metrics, the Igls classification system according to the Milan criteria and the BETA-2 score. Specifically, we found that metrics related to euglycemia (TIR, TITR), hyperglycemia (TAR, GRI and its hyperglycemia component), glycemic variability (CV), and mean glucose correlated with Igls-derived classifications and BETA-2 scores, while hypoglycemia-related parameters (TBR and the hypoglycemia component of GRI) did not.

These results align with prior evidence supporting the role of preserved islet function in maintaining glucose homeostasis and minimizing therapeutic burden.[6,15] In contrast to previous studies, such as the one by McEachron et al.,[4] which investigated CGM metrics in a small sample of subjects who used glucose sensors from a larger main cohort and which found a significant association with TITR alone, our findings revealed broader associations across several CGM parameters, likely reflecting methodological differences, such as the use the same single updated type of CGM device and the inclusion of metrics from all subjects since the enrollment, regardless of the actual insulin independence, and a more comprehensive analysis, also including novel metrics, like GRI and its hyper- and hypoglycemia components, although with the limitation of a still smaller sample size. Our study also extends current knowledge by including novel CGM-derived indices such as the GRI, which may provide more granular insight into glucose fluctuations across Igls categories. Interestingly, the GRI differences were largely driven by its hyperglycemia component, while the hypoglycemia component was kept low and similar across Igls classes, reinforcing the notion that, regardless of overall classification, even partially preserved islet function can provide protection from hypoglycemia—a pattern consistent with previous findings in both T1D[16–18] and islet transplantation.[19] This is further supported by the absence of severe hypoglycemia episodes

FIG. 2. Distributions of CGM metrics across Igls categories. For each metric, the distribution of the respective values for the four Igls classes is shown, along with the number of observation points (n) classified according to each Igls class. At the right side, the P value from Kruskal–Wallis test is shown, and P values from post-hoc Dunn's multiple pairwise comparison tests are displayed when statistically significant. Presented metrics include time in range **(A)**, in tight range **(B)**, above range **(C)**, below range **(D)**, mean glucose **(E)**, coefficient of variation **(F)**, hyper- and hypoglycemia components of glycemia risk index (**G** and **H**, respectively) and glycemia risk index itself **(I)**.



A
Time in range (%)
p 0.005
p 0.002
p 0.013
Optimal n=10
Good n=6
Marginal n=8
Failure n=1
Igls category
B
Time in tight range (%)
p 0.004
p<0.001
p 0.002
Optimal n=10
Good n=6
Marginal n=8
Failure n=1
Igls category
C
Time above range (%)
p 0.001
p 0.004
p 0.008
Optimal n=10
Good n=6
Marginal n=8
Failure n=1
Igls category
D
Time below range (%)
p 0.574
Optimal n=10
Good n=6
Marginal n=8
Failure n=1
Igls category
E
Mean glucose (mg/dl)
p<0.001
p 0.002
p 0.002
Optimal n=10
Good n=6
Marginal n=8
Failure n=1
Igls category
F
Coefficient of variation (%)
p 0.016
p 0.008
p 0.048
Optimal n=10
Good n=6
Marginal n=8
Failure n=1
Igls category
G
Hyperglycemia component of glycemia risk index
p<0.001
p 0.006
p 0.006
Optimal n=10
Good n=6
Marginal n=8
Failure n=1
Igls category
H
Hypoglycemia component of glycemia risk index
p 0.414
Optimal n=10
Good n=6
Marginal n=8
Failure n=1
Igls category
I
Glycemia risk index
p 0.004
p 0.009
p 0.026
Optimal n=10
Good n=6
Marginal n=8
Failure n=1
Igls category

Table 4. Spearman's Correlation Analyses Between CGM Metrics and Islet Assessment Methods: Milan Modified Igls Classification and BETA-2 Score

	Milan igls classification		*BETA-2 score*	
CGM metrics	*Rho*	P *value*	*Rho*	P *value*
TIR	−0.588	0.003*	0.815	<0.001*
TITR	−0.696	<0.001*	0.856	<0.001*
TAR	0.617	0.001*	−0.828	<0.001*
TBR	0.093	0.653	−0.051	0.807
Mean glucose	0.665	<0.001*	−0.798	<0.001*
CV	0.487	0.015*	−0.699	<0.001*
Hyper comp. of GRI	0.612	0.002*	−0.827	<0.001*
Hypo comp. of GRI	0.093	0.653	−0.051	0.807
GRI	0.535	0.007*	−0.743	<0.001*

Cohort size = 25 observations from 10 subjects through a follow-up of 3 to 12 months after TPIAT.

Spearman's nonparametric correlations for the main CGM metrics versus Igls-driven islet function categorization and versus BETA-2 score as alternative assessment method. Statistical significance set for $P < 0.05$.

*$P < 0.05$.

CV, coefficient of variation; GRI, glycemia risk index; TAR, time above range; TBR, time below range; TIR, time in range; TITR, time in tight range; TPIAT, total pancreatectomy with islet autotransplantation.

in our cohort. Such preservation of safety from hypoglycemia, even among patients with marginal islet function, emphasizes the clinical relevance of autologous transplantation beyond glycemic control.

Moreover, the BETA-2 score, a composite index incorporating both glycemic and insulin secretory parameters, showed a strong correlation with Igls outcomes and with the same CGM metrics that tracked with clinical classifications. This suggests a high degree of internal consistency across different methods used to assess islet function. However, while CGM metrics discriminated well between optimal and sub-optimal outcomes, they were less effective in distinguishing between intermediate categories (i.e., good vs marginal), implying that CGM data alone may not suffice for precise functional stratification. These findings are in line with previous studies, such as that by McEachron, where TITR showed significant differences only between optimal and marginal outcomes.[4] However, it might also be noted that optimal outcomes could differ substantially from not-optimal ones, particularly when considering HbA1c and insulin independence criteria, as these represented the only category without concrete evidence of diabetes mellitus. Therefore, while the diabetes-free definition of optimal outcomes may partially account for the most notable differences in CGM metrics between optimal and suboptimal groups, it is also true that most not-optimal outcomes needed some degree of insulin therapy; thus, the therapeutic intervention and insulin dose titration by the patients themselves, coupled with a proper use of the CGM sensors, could enhance glucose control and improve CGM metrics,[20] possibly contributing to the challenge of identifying significant differences in sensor metrics across intermediate Igls functional classes. However, a larger sample size might be required to provide sufficient power to detect any actual differences across sub-optimal outcomes. Such observations support the need for integrated evaluation systems, potentially combining CGM with hematological and clinical data, as proposed in the updated Igls criteria for allotransplantation.[2]

To our knowledge, this is the first study specifically designed to assess the relationship between CGM metrics and long-term islet function using both Igls-derived classification and BETA-2 score in a TPIAT population treated for neoplastic diseases. As highlighted in a recent systematic review,[21] prior investigations into CGM use in this setting are limited in number and scope, often involving pediatric populations,[22–24] outdated sensor technologies,[4] or short-term postoperative monitoring.[25] Although a recent study by Somani et al.[26] proposed CGM-based thresholds to identify favorable HbA1c outcomes after TPIAT in chronic pancreatitis, it focused on a single parameter and lacked robust evaluation of insulin independence, thus limiting its generalizability.

While our results provide novel insights, several limitations should be acknowledged. Chief among them is the relatively small sample size, which may limit statistical power and generalizability. Furthermore, although we evaluated outcomes up to 12 months post-TPIAT, longer follow-up periods would be necessary to confirm the durability of our findings. Variability in CGM device use, lack of standardization in TPIAT procedures, and the evolving nature of the Igls classification system may also influence broader applicability.

Conclusions

Our findings support the potential role of CGM metrics in assessing long-term islet function after TPIAT, particularly in distinguishing optimal from nonoptimal outcomes. However, CGM should be considered as part of a multimodal assessment strategy rather than a standalone diagnostic tool.

Future studies with larger, multi-center cohorts and standardized methodologies are needed to validate these results and enhance our understanding of post-TPIAT glucose dynamics.

Authors' Contributions

A.C., L.P., R.C.B., M.Tr., and M.Tu. designed the study. M.Tu., M.F., R.S., G.M., and G.L. performed the surgical procedures. L.P., R.N., and R.M. supervised islet processing. A.C., M.Tu., G.L., C.M., A.T., S.S.S., M.C., and F.N. collected the clinical data. A.C., M.Tu., G.L., A.M., M.Tr., R.C.B., and L.P. contributed to data interpretation. A.C. performed the statistical analyses. A.C. wrote the first draft of the article. G.L., M.Tu., M.Tr., R.C.B., R.S., and L.P. contributed to further revisions of the article. A.C. and M.T. created the graphical abstract. All authors have contributed to the final version of the article.

Author Disclosure Statement

No competing financial interests exist.

Funding Information

The study was supported by research grants from the University of Verona (to M.Tr., A.M., A.C., G.L., M.Tu., and R.S.), from the San Raffaele Hospital (to L.P. and R.M.)

and by "FIL" funds for research from the University of Parma (to R.C.B.).

Supplementary Material

Supplementary Tables

References

1. Balzano G, Zerbi A, Aleotti F, et al. Total Pancreatectomy with Islet Autotransplantation as an Alternative to High-risk Pancreatojejunostomy after Pancreaticoduodenectomy: A Prospective Randomized Trial. Ann Surg 2023;277(6): 894–903; doi: 10.1097/SLA.0000000000005713
2. Landstra CP, Andres A, Chetboun M, et al. Examination of the Igls Criteria for Defining Functional Outcomes of β-cell Replacement Therapy. IPITA Symposium Report. Journal of Clinical Endocrinology and Metabolism 2021;106; doi: 10.1210/clinem/dgab386
3. Gołębiewska JE, Bachul PJ, Fillman N, et al. Assessment of simple indices based on a single fasting blood sample as a tool to estimate beta-cell function after total pancreatectomy with islet autotransplantation – a prospective study. Transplant International 2019;32; doi: 10.1111/tri.13364
4. McEachron KR, Yang Y, Hodges JS, et al. Performance of modified Igls criteria to evaluate islet autograft function after total pancreatectomy with islet autotransplantation – a retrospective study. Transplant International 2021;34; doi: 10.1111/tri.13762
5. Pollard CA, Chung WY, Garcea G, et al. Assessment of long-term graft function following total pancreatectomy and autologous islet transplantation: The Leicester experience. Hepatobiliary Surg Nutr 2023;12(5):682–691; doi: 10.21037/hbsn-21-558
6. Piemonti L, Melzi R, Aleotti F, et al. Autologous Pancreatic Islet Cell Transplantation Following Pancreatectomy for Pancreas Diseases Other Than Chronic Pancreatitis: A 15-y Study of the Milan Protocol. Transplantation 2024;108(9): 1962–1975; doi: 10.1097/TP.0000000000005037
7. Forbes S, Oram RA, Smith A, et al. Validation of the BETA-2 Score: An Improved Tool to Estimate Beta Cell Function After Clinical Islet Transplantation Using a Single Fasting Blood Sample. Am J Transplant 2016;16(9): 2704–2713; doi: 10.1111/ajt.13807
8. Balzano G, Piemonti L. Autologous Islet Transplantation in Patients Requiring Pancreatectomy for Neoplasm. Curr Diab Rep 2014;14(8):512; doi: 10.1007/s11892-014-0512-2
9. ElSayed NA, McCoy RG, Aleppo G, et al.; American Diabetes Association Professional Practice Committee. 2. Diagnosis and Classification of Diabetes: Standards of Care in Diabetes—2025. Diabetes Care 2025;48(Supplement_1): S27–S49; doi: 10.2337/dc25-S002
10. Balzano G, Maffi P, Nano R, et al. Extending Indications for Islet Autotransplantation in Pancreatic Surgery. Ann Surg 2013;258(2):210–218; doi: 10.1097/SLA.0b013e31829c790d
11. Balzano G, Maffi P, Nano R, et al. Autologous Islet Transplantation in Patients Requiring Pancreatectomy: A Broader Spectrum of Indications Beyond Chronic Pancreatitis. Am J Transplant 2016;16(6):1812–1826; doi: 10.1111/ajt.13656
12. Szempruch KR, Walter K, Ebert N, et al. Pharmacological management of patients undergoing total pancreatectomy with auto-islet transplantation. Pancreatology 2022;22(5): 656–664; doi: 10.1016/j.pan.2022.04.009
13. Klonoff DC, Wang J, Rodbard D, et al. A Glycemia Risk Index (GRI) of Hypoglycemia and Hyperglycemia for Continuous Glucose Monitoring Validated by Clinician Ratings. J Diabetes Sci Technol 2023;17(5):1226–1242; doi: 10.1177/19322968221085273
14. Battelino T, Alexander CM, Amiel SA, et al. Continuous glucose monitoring and metrics for clinical trials: An international consensus statement. Lancet Diabetes Endocrinol 2023;11(1):42–57; doi: 10.1016/S2213-8587(22)00319-9
15. Nanno Y, Wastvedt S, Freeman ML, et al. Metabolic measures before surgery and long-term diabetes outcomes in recipients of total pancreatectomy and islet autotransplantation. Am J Transplant 2021;21(10):3411–3420; doi: 10.1111/ajt.16573
16. Sørensen JS, Johannesen J, Pociot F, et al.; Danish Society for Diabetes in Childhood and Adolescence. Residual β-Cell Function 3–6 Years After Onset of Type 1 Diabetes Reduces Risk of Severe Hypoglycemia in Children and Adolescents. Diabetes Care 2013;36(11):3454–3459; doi: 10.2337/dc13-0418
17. Marren SM, Hammersley S, McDonald TJ, et al.; TIGI consortium. Persistent C-peptide is associated with reduced hypoglycaemia but not HbA_{1c} in adults with longstanding Type 1 diabetes: Evidence for lack of intensive treatment in UK clinical practice? Diabet Med 2019;36(9):1092–1099; doi: 10.1111/dme.13960
18. Gibb FW, McKnight JA, Clarke C, et al. Preserved C-peptide secretion is associated with fewer low-glucose events and lower glucose variability on flash glucose monitoring in adults with type 1 diabetes. Diabetologia 2020;63(5): 906–914; doi: 10.1007/s00125-020-05099-3
19. Forbes S, Olateju TO, Lam A, et al. CGM Shows Islet Transplantation Prevents Hypoglycemia, Correcting Time in Range and Reducing Glycemic Variability, Despite Subnormal Beta-Cell Function. Diabetes 2018;67(Supplement_1); doi: 10.2337/db18-143-OR
20. Davidsen L, Cichosz SL, Stæhr PB, et al. Efficacy and safety of continuous glucose monitoring on glycaemic control in patients with chronic pancreatitis and insulin-treated diabetes: A randomised, open-label, crossover trial. Diabetes Obes Metab 2025;27(6):3379–3388; doi: 10.1111/dom.16356
21. Bashir A, Joseph N, Hammond JS, et al. Evaluating Continuous Glucose Monitoring After Total Pancreatectomy With or Without Islet Autotransplantation. Pancreas 2025;54(3):e268–e277; doi: 10.1097/MPA.0000000000002424
22. Elder DA, Jiminez-Vega JM, Hornung LN, et al. Continuous glucose monitoring following pancreatectomy with islet autotransplantation in children. Pediatr Transplant November 2017;21(7):10.1111/petr.12998; doi: 10.1111/petr.12998
23. Segev N, Hornung LN, Tellez SE, et al. Continuous Glucose Monitoring in the Intensive Care Unit Following Total Pancreatectomy with Islet Autotransplantation in Children: Establishing Accuracy of the Dexcom G6 Model. J Clin Med 2021;10(9):1893; doi: 10.3390/jcm10091893
24. Tellez SE, Hornung LN, Courter JD, et al. Inaccurate Glucose Sensor Values After Hydroxyurea Administration.

Diabetes Technol Ther 2021;23(6):443–451; doi: 10.1089/dia.2020.0490

25. Vonderau JS, Williams BM, DeCherney S, et al. Use of Continuous Glucose Monitoring for evaluation of hypoglycemia pre- and post-operatively for patients undergoing Total Pancreatectomy with Autologous Islet Cell Transplant. Clin Transplant 2021;35(11):e14450; doi: 10.1111/ctr.14450
26. Somani Z, Hodges JS, Chinnakotla S, et al. Defining Targets for Continuous Glucose Monitoring After Total Pancreatectomy With Islet Autotransplantation. Clin Transplant 2025; 39(6):e70202; doi: 10.1111/ctr.70202

Address correspondence to:
Alessandro Csermely, MD
Division of Endocrinology, Diabetes and Metabolic Diseases
Department of Medicine
University Hospital of Verona
Verona, Italy
Piazzale Stefani 1
37126, Verona
Italy

E-mail: alessandro.csermely@univr.it