ORIGINAL ARTICLE

Performance of modified Igls criteria to evaluate islet autograft function after total pancreatectomy with islet autotransplantation – a retrospective study

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SUMMARY

The Igls criteria assess islet function after islet allotransplant, based on C-peptide, insulin use, hemoglobin A1c, and severe hypoglycemia. However, these criteria as currently defined cannot be applied to total pancreatectomy islet autotransplant (TPIAT) patients. We tested modified criteria for assessing islet function in a large cohort of TPIAT patients ($n = 379$). Metabolic outcomes were assessed. We assigned Auto-Igls class to each patient as able and evaluated the utility, validity, and perioperative risk factors of Auto-Igls at 1-year post-IAT. We tested the association of Auto-Igls with independent measures of islet graft function, specifically continuous glucose monitoring (CGM) data or acute C-peptide response to glucose (ACRglu) from intravenous glucose tolerance tests. An Auto-Igls class was assigned to 264 patients (69%). Among patients who could not be classified, most were missing exact insulin dose. Seventy-three percent of TPIAT recipients were classified as optimal or good at 1 year. The only significant predictor of Auto-Igls class was islet mass transplanted ($P < 0.0001$). Auto-Igls class was associated with percent time in range (70–140 mg/dl) on CGM ($P = 0.02$) and ACRglu ($P < 0.0001$). Modified Igls classification for IAT permits simple, comprehensive assessment of metabolic outcomes after TPIAT and is associated with other islet functional measures.

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Introduction

Beta cell replacement with pancreas or islet *allo*transplantation is used to treat patients with insulin-dependent (usually type 1) diabetes complicated by glycemic instability, severe hypoglycemia, or microvascular complications including renal failure [1]. Islet *auto*transplantation (IAT) is performed as an adjunct to total pancreatectomy (TP), which has been used increasingly over the past two decades to treat refractory, painful chronic pancreatitis, and more rarely for benign neoplasms or cancer [2–6]. After pancreatectomy, islets are isolated from the pancreas and infused back to the patient, usually via the portal vein, where they engraft in the liver sinusoids. Because

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the vast majority of patients undergoing TPIAT are not diabetic at the time of surgery, the autotransplant procedure is performed to ameliorate postsurgical diabetes while obviating the need for immunosuppression [7]. It is similar to islet allotransplantation in that islets are subject to loss during the isolation and purification procedures [8–10], further loss during the infusion and engraftment phases [11–13], and graft attrition over time [14].

In 2016, the International Pancreas and Islet Transplant Association (IPITA)—The Transplantation Society (TTS) opinion leaders' meeting identified lack of a clear uniform definition of graft functional and clinical outcomes as a significant barrier to progress in pancreas and islet allotransplantation, and in comparing cell-based therapies to the developing field of artificial pancreas research [15]. In response, in 2017 IPITA and the European Pancreas and Islet Transplant Association (EPITA) sponsored a 2-day workshop on "Defining Outcomes for β-Cell Replacement Therapy in the Treatment of Diabetes" in Igls, Austria, at which experts in the field developed the "Igls criteria" for classifying clinical outcomes of beta cell replacement therapy [16]. The Igls classification system uses four categories of islet graft function to describe the success of pancreas or islet transplant: optimal, good, marginal, and failed. The categories are determined using hemoglobin A1c (HbA1c) level, severe hypoglycemia episodes (SHE) [17], reduction in insulin needs from baseline, and increase in C-peptide levels from baseline (C-peptide is most often not measurable before allotransplant) (Table 1a).

Necessarily, the Igls criteria were designed to classify success of an islet graft by comparing each patients' clinical outcomes with their own baseline prior to transplant. However, this classification system cannot be applied as is to autotransplant patients because of baseline differences in this population: Beta cell function before TPIAT is much better than in allotransplant patients, with the majority not on insulin, having normal HbA1c, and with measurable C-peptide levels. Some loss of beta cell function from baseline is, in fact, expected in autotransplant patients, as islet mass is lost during isolation and infusion. To date, adaptation of the Igls criteria to autotransplant patients has only been attempted in one group of 15 TPIAT patients [18].

In order to develop a comparable metric of islet *auto*-graft functional clinical outcomes that can be easily obtained and applied, our objective was to define and validate modified Igls criteria in a large cohort of TPIAT patients.

Materials and methods

Patient population

We reviewed metabolic outcomes for all patients undergoing TPIAT at the University of Minnesota from 2010 to 2018 inclusive who consented to participate in our prospective cohort study assessing outcomes of TPIAT (n = 379). In the time interval reviewed, a total of 399 islet autotransplant procedures were performed at the University of Minnesota, with 12 cases were excluded from analyses due to partial pancreatectomy and eight for lack of informed consent. The study protocol was reviewed and approved by the University of Minnesota Institutional Review Board. Informed consent was obtained from all adult participants and for pediatric patients, parental consent with assent as age-appropriate was obtained.

Assessment of outcomes

We assessed metabolic outcomes at one-year post-TPIAT (range 6–24 months, when 1-year data were not available) based on these four criteria defined as follows:

HbA1c

Laboratory assessments are performed at the University of Minnesota or the patient's local laboratory. HbA1c level is routinely recommended at 3 months, 6 months, 1 year, and yearly after surgery for all patients, more often if needed to manage insulin-dependent diabetes.

C-peptide levels

Patients undergoing TPIAT at our institution are recommended to undergo mixed-meal tolerance tests (MMTT) at 3 months, 6 months, 1 year, and yearly after surgery to assess islet graft function. For this test, the patient drinks 6 ml/kg (maximum 360 ml) of Boost High Protein (HP) and glucose and C-peptide levels are obtained fasting and then at 1 and 2 h after the Boost HP. For the modified Igls classification, as defined subsequently, stimulated C-peptide values were used preferentially to assess beta cell function, with fasting C-peptide used if a stimulated value was not available (i.e., the patient declined or was unable to complete mixed-meal testing).

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Table 1. (a) Original Igls classification scheme. (b) Proposed criteria for Auto-Igls classifications used for study. (c) Revised proposed Auto-Igls for use in clinical monitoring and clinical research of autotransplant recipients.

(a) Igls	Hemoglobin A1c	SHE (per year)	Insulin dose	C-peptide
Optimal	≤6.5%	None	None	>Baseline
Good	<7%	None	<50% Baseline	>Baseline
Marginal	Baseline	<Baseline	≥50% Baseline	>Baseline
Failed	Baseline	Baseline	Baseline	Baseline
(b) Auto-Igls	Hemoglobin A1c	SHE	Insulin dose	C-peptide
Optimal	≤6.5%	None	None	>0.5 ng/ml
Good	<7%	None	<0.5 units/kg/day	>0.5 ng/ml
Marginal	≥7%	≥1	≥0.5 units/kg/day	>0.5 ng/ml
Failed	–	–	–	≤0.5 ng/ml*
(c) Modified Auto-Igls	Hemoglobin A1c	SHE	Insulin dose†	C-peptide Stimulated (Fasting)‡
Optimal	≤6.5%	None	None	>0.5 ng/ml (≥0.2 ng/ml)
Good	<7%	None	<0.5 units/kg/day	>0.5 ng/ml (≥0.2 ng/ml)
Marginal	≥7%	≥1	≥0.5 units/kg/day	>0.5 ng/ml (≥0.2 ng/ml)
Failed	–	–	–	≤0.5 ng/ml (<0.2 ng/ml)

*Stimulated C-peptide value is preferred for classifying a patient as failed. Fasting C-peptide used in the absence of a stimulated value.

†Might include nondiabetic anti-hyperglycemic agents, in accordance with the original Igls criteria [13].

‡Meal-stimulated C-peptide preferred, when available. In absence of stimulated C-peptide, use fasting C-peptide with threshold as indicated in parenthesis.

Insulin dose

Insulin is the first-line anti-hyperglycemic medication for all patients at our institution who require ongoing pharmacologic therapy for diabetes mellitus, recognizing that the primary physiologic cause for hyperglycemia post-TPIAT is insulin deficiency. Insulin is continued or restarted after surgery if a patient cannot meet the following targets off treatment: A1c $\leq$ 6.5%, fasting glucose $\leq$ 125 mg/dl, and postprandial glucose $<$ 180 mg/dl. Insulin use was abstracted from multiple historical sources including medical records review, patient logs, and historical data from several clinical trials in which some patients were participants. Patient weight from these sources was used to calculate insulin dose as units/kg/day.

Severe hypoglycemic episodes (SHE)

For the purpose of this study, we defined severe hypoglycemia episodes as any occurrence in the past year of hypoglycemia resulting in loss of consciousness or seizure. This definition was selected based on observations that these episodes are reported by patients more accurately and documented in medical records more reliably than broader definitions of SHE (altered mental or physical state requiring assistance to treat). We used data abstracted from electronic medical records, patient report from study surveys, and patient reported events documented in prior clinical trials to assess SHE as absent or present in as many patients as feasible.

Defining the Igls criteria for IAT

We adapted the Igls definition for application to islet autotransplantation. Because TPIAT patients rarely have diabetes mellitus before surgery and are not expected to have improvements in diabetes measures after, we could not use their "baseline" status to assess outcomes as in the original Igls classification system. Using the original Igls criteria by Rickels *et al.* [16], and similar to the islet autotransplant criteria proposed previously by Golebiewska *et al.* [19], we defined adapted Igls criteria for islet autotransplant, hereafter called Auto-Igls.

For each TPIAT case in our population, we reviewed the individual Auto-Igls criteria and assessed the outcomes as follows (Table 1b):

• HbA1c: Optimal if ≤ 6.5%; good if < 7%; and marginal if ≥ 7%.
• SHE (as previously defined): Optimal or good if none; and marginal if 1 or more episodes.
• Insulin use: Optimal if none; good if < 0.5 unit/kg/day, and marginal if ≥ 0.5 units/kg/day.
• C-peptide: Optimal, good, or marginal if stimulated (preferred) or fasting C-peptide positive (>0.5 ng/ml) and failed if negative (≤0.5 ng/ml). Note that C-peptide ≤ 0.5 ng/ml is the only criterion that can classify the patient as failed.

The thresholds for insulin and C-peptide were adopted from the footnotes in the originally published Igls criteria for allotransplantation [16].

An overall Auto-Igls class was then assigned to each participant such that all individual criteria fell at or above the assigned class, consistent with the original Igls classification scheme. For example, an insulin-independent patient (optimal), C-peptide positive (optimal), without SHE (optimal), but with A1c of 6.9% (good) would be classified as good. In our cohort, the Auto-Igls could be inferred for a few patients who had one criterion (most commonly insulin dose) missing from the record. For example, a patient without SHE who was C-peptide positive might have an A1c ≥ 7% and be on insulin at an unknown daily dose. At best, they are classified as marginal based on A1c, and they cannot be classified as failed because they are C-peptide positive, therefore they are classified as marginal even though the exact insulin dose is unknown.

Utility of Auto-Igls in a TPIAT program

We then evaluated the utility and validity of the Auto-Igls classification scheme in a clinical TPIAT program by addressing the following questions:

1. For what proportion of patients can Auto-Igls class be reliably assigned? Because most autotransplant patients are not enrolled in comprehensive clinical trials, availability of their laboratory data, insulin dosing, and severe hypoglycemia history can be less consistent compared with islet allotransplant recipients. All four criteria are most often required to classify someone. For those who could not be classified, we evaluated which criteria were lacking.
2. What are the risks of misclassifying a patient based on Auto-Igls? Are there instances in which a single criteria, such an episode of severe hypoglycemia in an insulin-independent TPIAT recipient [20], which would result in overall classification as marginal despite an otherwise functional islet graft.
3. What are the practical limitations of Auto-Igls in accurately conveying islet graft function? Specifically, we further evaluated whether using fasting (versus stimulated) C-peptide might over-classify graft failure. While our center routinely assesses stimulated C-peptide from MMTT, there are certain practical limitations in obtaining a stimulated C-peptide level in patients who are followed at local clinics where MMTT cannot be performed.

Assessing factors associated with Auto-Igls

We next assessed whether pre- and perioperative measures were predictive of islet graft function by Auto-Igls class. To this end, we hypothesized that the following clinical measures were associated with diabetes outcomes and performed regression modeling as described in the statistical methods section: disease etiology, disease duration, age, preoperative BMI, whether patients underwent ERCP before TPIAT (yes/no), prior pancreatic operations (yes/no), whether islets were transplanted to an alternate site (yes/no), and islet mass transplanted (IEQ/kg).

Validating the Auto-Igls score based on islet function

Next, we evaluated whether Auto-Igls class was associated with other measures of islet graft function where available. For this purpose, we specifically excluded items that were used to *define* Igls (C-peptide from MMTT, HbA1c, and insulin dose). Therefore, we considered the association of Auto-Igls class with independent measures obtained from continuous glucose monitoring (CGM) reports and with the acute C-peptide response to glucose (ACRglu) from an intravenous glucose tolerance test (IVGTT), in the subsets of patients for which these measures were available at 1 year. Continuous glucose monitoring was performed with either iPro2 (study protocol) or Dexcom G5 or G6 (clinical care). Intravenous glucose tolerance testing, a measure of first-phase insulin response, was performed in a subset of patients who were participants in clinical research studies. For this test, a bolus of 0.3 g/kg of dextrose 50% is given at time zero and glucose and C-peptide are drawn at fasting baseline (three samples) and at 1, 2, 3, 4, 5, 7, and 10 min following the dextrose bolus. The ACRglu is the area under the curve of the 1- to-10-min measurements minus baseline (ng/ml-min).

Statistical methods

To assess perioperative measures for association with Auto-Igls class at one-year post-TPIAT, we used

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forward stepwise regression with a stopping rule based on minimum Bayesian information criterion (BIC). The results were validated using random forests. One-way ANOVA was used to test the association of Auto-Igls class with CGM measures and ACRglu. All statistical analyses used JMP (Pro version 14.0; SAS Institute Inc., Cary, NC, USA). A *P*-value of <0.05 was considered significant.

Results

Patient demographics

Table 2 contains the cohort's baseline demographics and islet transplant metrics. This included 98 children (<18 years old at time of transplant) and a wide range of islet mass transplanted (mean 4264 IEQ/kg, range 36–14 923).

Distribution of Auto-Igls scores

In the entire cohort, 264 patients (69% of 379) could be assigned an Auto-Igls class at one year (range 6–24 months) with our proposed criteria (Fig. 1). The majority (90%) were classified using 1-year data, with the remaining (10%) classified using data from 6-, 18-, or 24-month follow-up. When we divided patients into groups based on the year TPIAT was performed, we found that patients who underwent TPIAT more recently had fewer missing data for classification. Specifically, patients from 2010 to 2013 comprised 67% of the 115 unable to be classified, while patients from 2014 to 2018 made up the other 33%. We were able to classify 82% of patients from 2016 to 2018.

Table 2. Baseline demographics and islet transplant metrics.

Demographic	
Total patients, *N* (%)	379 (100%)
Female sex, *N* (%)	265 (70%)
Age, Mean (SD)	32 (16)
Under 18, *N* (%)	98 (26%)
Etiology of pancreatitis, *N* (%)	
Biliary	7 (1.9%)
Cystic Fibrosis	10 (2.6%)
Familial	140 (37%)
Idiopathic	110 (29%)
Other	14 (3.7%)
Years of pancreatitis pain, Median (IQR)	7 (3.9–12.2)
Pretransplant BMI, Mean (SD)	24 (6)
Prior pancreas surgery, *N* (%)	53 (14%)
Prior ERCP (any), *N* (%)	313 (83%)
Mean number ERCPs (SD)	3.8 (3.3)
IEQ/kg transplanted, N (%)	
Under 2500	98 (26%)
2500–4000	98 (26%)
Over 4000	183 (48%)

Characteristics of patients classified as failed

Ten patients (3.8% of the subgroup classified) were classified as failed (Table S1). By definition, all 10 had C-peptide level ≤ 0.5 ng/ml. Two of the 10 were insulin independent with normal HbA1c (5.7% and 5.6%) and appeared to be incorrectly classified as islet graft failures based solely on the C-peptide criterion. In reviewing these two cases, one was classified based on *fasting* C-peptide level alone (history of severe gastroparesis limited the patient's ability to complete a mixed-meal tolerance test). The other was a 5-year-old child with stimulated max C-peptide of 0.4 ng/ml. Considering that true graft failure is incompatible with normoglycemia off insulin therapy, these two patients were thought to be inappropriately classified and therefore excluded from subsequent analyses.

Missing criteria

To evaluate which criteria might limit the use of Auto-Igls classification, we determined which criteria were absent in the 141 patients who could not be classified based on 1-year follow-up data. Of these, exact insulin use in units/kg/day was the most common missing data point (missing in 104/141 or 74%), followed by missing C-peptide measurement (Fig. 1).

Perioperative risk factors of Auto-Igls class

In the stepwise regression analysis, total islet mass transplanted (IEQ/kg) was the only significant perioperative factor associated with Auto-Igls class at 1 year, among eight candidate risk factor (disease etiology, disease duration, age, preoperative BMI, ERCP before TPIAT, prior pancreas surgery, alternate site of transplanted islets, and IEQ/kg) (Fig. 2, Table S2). As expected, higher IEQ/kg was associated with better Auto-Igls class, such that average IEQ/kg was highest in patients classified as optimal, and declined for each subsequent class (Fig. 2, one-way ANOVA $P < 0.0001$).

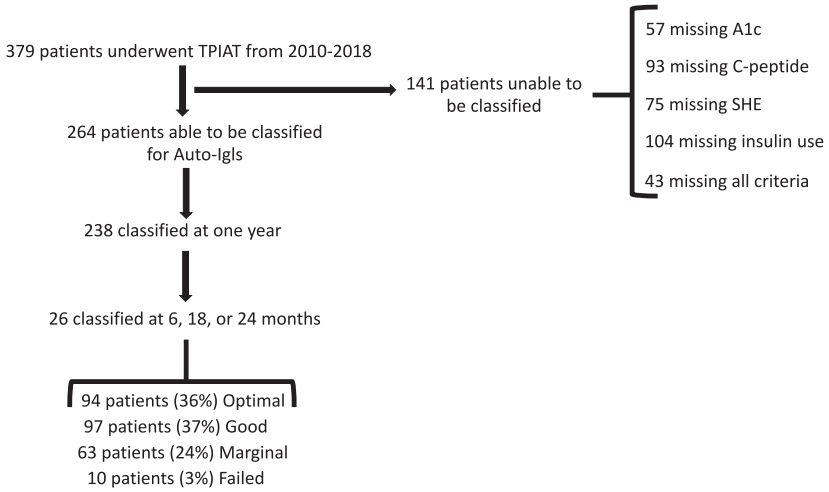

Figure 1 Study flow chart for record review and Igls criteria missing for participants who could not be classified.

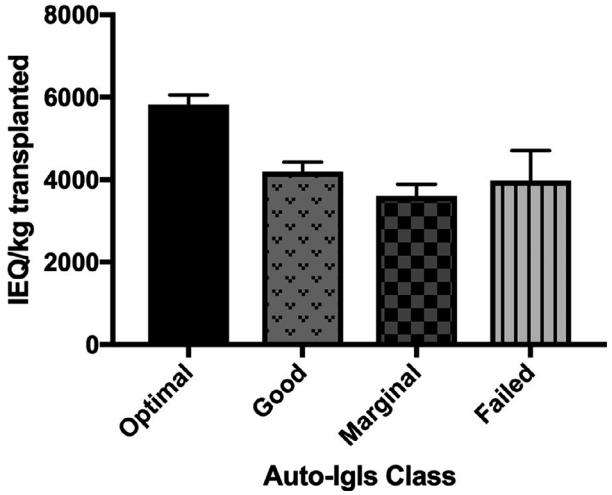

Figure 2 Transplanted islet cell mass (IEQ/kg) for each Auto-Igls class with bars representing mean ± standard error (SE). Optimal had mean 5824 IEQ/kg (SE 235.9), Good had mean 4192 IEQ/kg (SE 232.2), Marginal had mean 3601 IEQ/kg (SE 288.1), and Failed had mean 3224 IEQ/kg (SE 803.3). One-way ANOVA *P*-value < 0.0001.

Association of Auto-Igls class with islet graft functional measures

We reviewed CGM data for 21 patients (Table 3). No patients classified as failed had CGM data available. Percent time in range (TIR) for 70–140 mg/dl blood glucose levels was higher in those with a better Auto-Igls class. On average, patients classified as optimal had TIR 81% (standard error [SE] 9.1%), good had TIR 60% (SE 6.5%), and marginal had TIR 44% (SE 8.3%) (ANOVA $P = 0.02$).

The acute C-peptide response to glucose (ACRglu) from intravenous glucose tolerance tests (IVGTT) of 92 adult patients was also associated with Auto-Igls class (Table 3, Fig. 3). Higher ACRglu was significantly associated with a better class. On average, patients classified as optimal had ACRglu 15.0 ng/ml (SE 1.2 ng/ml), good had ACRglu 6.9 ng/ml (SE 1.2 ng/ml), and marginal had ACRglu 1.4 ng/ml (SE 1.6 ng/ml) (one-way ANOVA $P < 0.0001$).

Practical considerations for fasting or stimulated C-peptide

One practical consideration is the use of fasting or stimulated C-peptide level ≤ 0.5 ng/ml to designate an islet graft as failed (regardless of the other three criteria). While meal-stimulated C-peptide is preferred, using fasting C-peptide in the absence of a stimulated value may risk over-estimating islet graft failure if the same threshold is utilized for both fasting and stimulated. In 248 patients from our cohort with both fasting and stimulated C-peptide levels from MMTT (Fig. 4a), 57 (23%) had fasting C-peptide ≤ 0.5 ng/ml but stimulated C-peptide> 0.5 ng/ml and thus would be misclassified as failed (versus optimal/good/marginal) using fasting C-peptide alone (Fig. 4b).

Discussion

The Igls classification scheme for assessing islet function after allotransplantation is a composite of clinically accessible islet functional measures. For islet allotransplant, the Igls criteria should assess whether transplantation has given the recipient an *improvement* in diabetes from pre-transplant baseline. Islet *auto*transplant patients differ from *allo*transplant patients in clinical characteristics, as

Table 3. Associations of islet functional measures with assigned Igls class based on proposed criteria (CGM = continuous glucose monitoring data; ACRglu = acute C-peptide response to glucose (ng/ml) on intravenous glucose tolerance test (IVGTT)).

Igls Class	*N* = 21	Mean BG on CGM (SE)	Lower 95% CI	Upper 95% CI	*P* = 0.7
Optimal	5	116 (13)	88.7	144.5	
Good	10	139 (9.4)	119.7	159.1	
Marginal	6	161 (12)	135.4	186.3	
Igls Class	*N* = 21	Mean %TIR 70–140 mg/dl on CGM (SE)	Lower 95% CI	Upper 95% CI	*P* = 0.02*
Optimal	5	81% (9.1%)	61.8	100.2	
Good	10	60% (6.5%)	46.7	73.9	
Marginal	6	44% (8.3%)	26.9	62.0	
Igls Class	*N* = 21	Mean %TIR 70–180 mg/dl on CGM (SE)	Lower 95% CI	Upper 95% CI	*P* = 0.2
Optimal	5	92% (8.7%)	74.3	110.6	
Good	10	80% (6.1%)	67.3	93.0	
Marginal	6	70% (7.9%)	53.8	87.0	
Igls Class	*N* = 21	Mean %CV on CGM (SE)	Lower 95% CI	Upper 95% CI	*P* = 0.5
Optimal	5	24% (4.7%)	14.3	34.1	
Good	10	29% (3.3%)	21.7	35.7	
Marginal	6	32% (4.3%)	23.0	41.0	
Igls Class	*N* = 21	Mean %Time ≤ 54 mg/dl on CGM (SE)	Lower 95% CI	Upper 95% CI	*P* = 0.6
Optimal	5	0.7% (0.7%)	−0.7	2.1	
Good	10	0.9% (0.5%)	−0.1	2.0	
Marginal	6	0.1% (0.6%)	−1.2	1.4	
Igls Class	*N* = 92	Mean ACRglu on IVGTT (SE)	Lower 95% CI	Upper 95% CI	*P* < 0.0001*
Optimal	36	15 (1.2)	12.7	17.3	
Good	37	6.9 (1.2)	4.6	9.2	
Marginal	19	1.4 (1.6)	−1.9	4.6	

No patient with available CGM data was classified as failed. *N* = number of patients with the measure in given row. BG = blood glucose in mg/dl. TIR = percent time in range. SE = standard error. CI = confidence interval. %CV = coefficient of variation, which is defined by the standard deviation divided by the mean glucose on CGM. The *P*-values are from one-way ANOVA, with * indicating statistical significance ($P < 0.05$).

they are usually insulin independent and C-peptide positive preoperatively and are expected to lose some islet function postoperatively from the isolation and engraftment processes. For these reasons, the Igls criteria cannot be directly applied to islet autotransplantation patients. We have assessed a modified set of Igls criteria, Auto-Igls, designed to be relevant for assessing islet graft function in autotransplantation patients, and validated this metric in a large cohort of TPIAT patients.

When considering islet function in islet autotransplant patients, it is important to put this in the context of the overall goal of TPIAT. The primary goal of TPIAT is to relieve pain and restore quality of life, and as such, TPIAT patients can have a "successful" surgery outcome even if islet function is marginal or failed. However, better diabetes outcomes may translate into better health-related quality of life [21–22]. In order to continue to improve the diabetes outcomes after TPIAT, establishing standardized metrics for classifying islet graft outcomes for clinical programs and for research trials is important.

Using the Auto-Igls criteria would allow transplant centers to track metabolic outcomes in a cost-effective but comprehensive manner, even in the absence of more sensitive but cumbersome measures of islet function such as IVGTT. We were able to classify 69% of our patients with clinically available data alone, with more patients able to be classified in the modern era (82% of those transplanted in 2016–2018). In order to apply an Auto-Igls classification scheme, transplant centers would need to track at least yearly: (i) hemoglobin A1c level, (ii) C-peptide levels; (iii) history of severe hypoglycemia; and (iv) total daily insulin dose (and noninsulin anti-hyperglycemic agents) by patient recall. The latter can be obtained from a simple patient

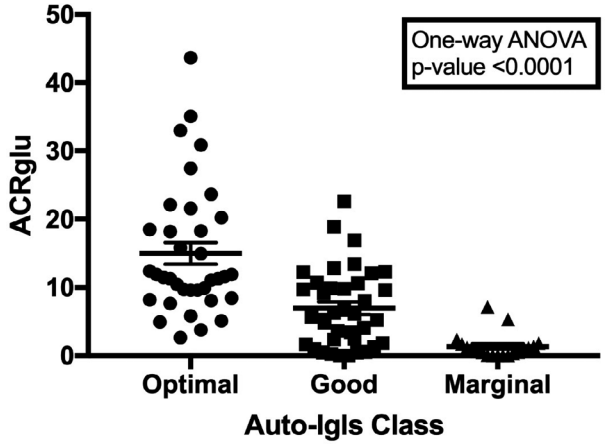

Figure 3 Acute C-peptide response to glucose (ACRglu, ng/ml-min) for each Auto-Igls class with bars representing mean ± standard error (SE). Optimal had 15 ng/ml (SE 1.2), Good had 6.9 ng/ml (SE 1.1), and Marginal had 1.3 ng/ml (SE 1.6). One-way ANOVA *P*-value < 0.0001.

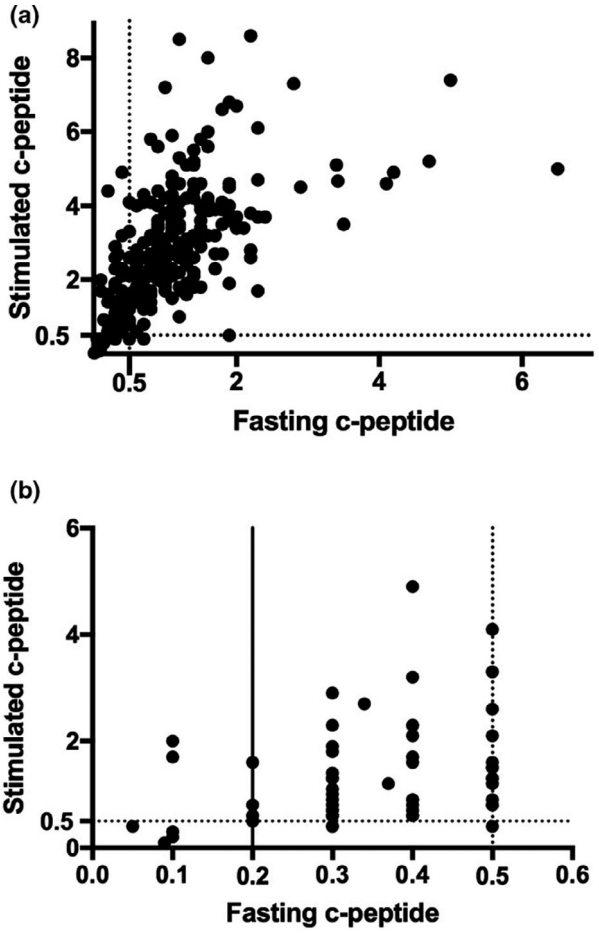

Figure 4 (a) Stimulated versus fasting C-peptide levels (ng/ml) for all patients who had both a fasting and at least one stimulated value (n = 248). (b) Stimulated versus fasting C-peptide levels only for patients with fasting C-peptide ≤ 0.5 (n = 57). Panel (b) has a solid line at fasting C-peptide = 0.2; both panels have dashed lines at fasting C-peptide = 0.5 and stimulated C-peptide = 0.5.

history. Laboratory studies would preferably include a meal-stimulated C-peptide level. This should be considered particularly if glycemic control and insulin use appear discordant with a low fasting C-peptide.

If only fasting C-peptide is available, we suggest that a lower threshold be used to define graft failure, given that the majority of the patients in our cohort who had a fasting C-peptide ≤ 0.5 ng/ml had a meal-stimulated C-peptide> 0.5 ng/ml (Fig. 4a). Consideration for the optimal fasting threshold of C-peptide warrants ongoing consideration in future studies, but in our cohort, a fasting C-peptide < 0.2 ng/ml was consistently associated with a stimulated C-peptide ≤ 0.5 ng/ml. For young children, in whom C-peptide levels are expected to be lower than older children and adults [23,24], the C-peptide threshold for graft failure should be used with caution. Our proposed modified Auto-Igls criteria based on our cohort is summarized in Table 1c.

As predicted, higher Auto-Igls class was associated with higher islet mass transplanted. Our classification scheme also appears to be valid compared to independent measures of glycemic control (CGM) and of first-phase insulin secretion as a metric of beta cell function and health (ACRglu). The pattern of declining ACRglu as the Auto-Igls went from optimal to good to marginal islet graft function is consistent with observations in patients at risk for type 1 diabetes that a decline in first-phase insulin secretion is an early marker of insulin deficiency and development of diabetes [25,26]. CGM measurements showed a clear glycemic benefit of higher TIR 70–140 comparing marginal to optimal classification. While this was the only CGM metric significantly associated with the Auto-Igls, the available sample with CGM measures was small and other CGM measures showed similar trends toward association with Auto-Igls class. Larger sample sizes may be needed to detect clinically important associations with confidence.

Despite these potential applications of Auto-Igls, we did find limitations to implementing this multi-factorial classification system. Missing data are a problem, although the subgroup of more recent patients had fewer missing data; 18% from 2016 to 2018 could not be classified even with a follow-up window of 6–24 months. This was most often because exact insulin dose was unknown or not in the medical record. While it is feasible to collect this information, data collection protocols would need to be established to ensure that the average daily insulin dose is recorded.

Another potential limitation of both the Auto-Igls and the original Igls classification systems is that a single criterion can classify a patient as marginal (or failed) when the other three criteria indicate optimal or good islet function. We identified 41 participants (16% of those with data for all four criteria available), where marginal graft function was defined by only 1 criterion, whereas the other three criteria would have defined the patient as having good or optimal function. The criteria that downgraded these patients from optimal or good to marginal were primarily HbA1c ($n = 26$), and less often insulin dose ($n = 8$) or severe hypoglycemic episodes ($n = 7$). While in some cases this lower classification of marginal is justified, practitioners may bear in mind that some data elements (like hemoglobin A1c) may improve over time with appropriate treatment. It should also be noted that Auto-Igls will not be applicable to partial pancreatectomy with IAT, as function of the transplanted islets vs function of the native pancreas cannot be distinguished in that setting.

The current study's limitations include the retrospective single-center design; however, we included over 300 patients with a high rate of follow-up for analysis. Fewer patients had CGM data or IVGTT; these data were all from subjects eligible and willing to participate in clinical trials and thus introduce risk for selection bias. We also included a few patients in the Igls scoring who could be classified with incomplete criterion (usually marginal graft function based on other parameters where exact insulin dose is unknown). This introduces a risk of incorporating bias in our inclusion, but, practically, also reflects how use of auto-Igls may be implemented clinically. Patients at our institution are exclusively insulin treated and not managed with other noninsulin agents; if other centers regularly use noninsulin anti-hyperglycemic medications, these should be considered if the patient is off insulin. A patient off insulin but requiring another medication to maintain euglycemia should, at best, be classified as good not optimal. Although our center routinely performs MMTT for graft surveillance, this is not the case at all centers nor feasible for some patients who are followed at remote local clinics. A transplant center would need to obtain stimulated levels from MMTT or consider using a lower C-peptide level as a cutoff for graft failure when assessing outcomes based on fasting laboratories only.

In conclusion, based on our data, we propose that this revised classification scheme for functional clinical outcomes of islet autotransplantation ("Auto-Igls"), adapted from the original Igls criteria for allotransplantation, is feasible in most TPIAT recipients as a composite measure of islet graft function. The Auto-Igls criteria would allow simple, comprehensive assessment of metabolic outcomes after TPIAT, and are independently associated with other more sensitive measures of islet function.

Authorship

MDB, KRM, JSH, and YY: participated in research design. MDB, KRM, GJB, VAK, TLP, SC, and BJH: participated in performance of research. YY and JSH: participated in data analysis. MDB, KRM, JSH, and YY: participated in interpretation of results/analyses. MDB and GJB: provided funding for research. MDB and KRM: participated in writing of initial draft of paper. JSH, YY, GJB, VAK, TLP, SC, and BJH: participated in critical revisions of the paper. All authors approved final version of the manuscript.

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Conflicts of interest

Melena D. Bellin has received research support from Dexcom and ViaCyte, and has served on a data safety and monitoring board for Insulet. All other authors declare no conflicts of interest.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1 Characteristics of patients classified by Auto-Igls as having a failed islet graft.

Table S2 Candidate perioperative risk factors of Auto-Igls and their simple associations with Auto-Igls class at 1 year post-transplant.

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