ORIGINAL ARTICLE

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

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SUMMARY

We investigated six indices based on a single fasting blood sample for evaluation of the beta-cell function after total pancreatectomy with islet autotransplantation (TP-IAT). The Secretory Unit of Islet Transplant Objects (SUITO), transplant estimated function (TEF), homeostasis model assessment (HOMA-2B%), C-peptide/glucose ratio (CP/G), C-peptide/glucose creatinine ratio (CP/GCr) and BETA-2 score were compared against a 90-min serum glucose level, weighted mean C-peptide in mixed meal tolerance test (MMTT), beta score and the Igls score adjusted for islet function in the setting of IAT. We analyzed values from 32 MMTTs in 15 patients after TP-IAT with a follow-up of up to 3 years. Four (27%) individuals had discontinued insulin completely prior to day 75, while 6 out of 12 patients (50%) did not require insulin support at 1-year follow-up with HbA1c 6.0% (5.5–6.8). BETA-2 was the most consistent among indices strongly correlating with all reference measures of beta-cell function (r = 0.62–0.68). In addition, it identified insulin independence (cut-off = 16.2) and optimal/good versus marginal islet function in the Igls score well, with AUROC of 0.85 and 0.96, respectively. Based on a single fasting blood sample, BETA-2 score has the most reliable discriminant value for the assessment of graft function in patients undergoing TP-IAT.

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Introduction

Islet autotransplantation (IAT) in patients undergoing total pancreatectomy (TP) for long-lasting pain relief offers a unique opportunity to avoid or minimize the impact of potentially brittle postoperative diabetes [1,2]. Beta-cell mass of transplanted islets remains the most important predictor of postsurgical islet graft function [2–6]. The number of 2000–2500 islet equivalents (IE) per kilogram of patient body weight (IE/kg) usually ensures meaningful clinically stable glucose control, often with insulin independence [2,4,6]. Even in those

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cases, islet graft function may decline over time. Therefore, a validated, accurate and logistically feasible tool for islet graft function measurement is indispensable for adequate adjustments in insulin support. Mixed meal tolerance test (MMTT) has been used as a standard tool for islet graft assessment, but has the disadvantage of being logistically challenging. Another standard scoring tool, beta score, also utilizes serum C-peptide after stimulation with MMTT.

A number of mathematical formulas utilizing readily available laboratory tests and patient derived information have been developed for the assessment of islet function [7–19]. Those include: Secretory Unit of Islet Transplant Objects (SUITO), transplant estimated function (TEF), homeostasis model assessment (HOMA-2B%), C-peptide/glucose ratio (CP/G), C-peptide/glucose creatinine ratio (CP/GCr), and BETA-2 score. However, those indices were developed primarily for islet graft assessment after allotransplantation in patients with T1DM. We previously demonstrated the indices reliability in patients with islet allografts, especially BETA-2 score and SUITO [20,21]. It is uncertain whether these surrogate indices can also accurately assess function of islet autografts. Therefore, our objective was to test the application of those equations in the context of TP-IAT by comparing them against standard tests: 90-min glucose during the MMTT, clinical outcome measured by the beta score, beta-cell function assessed by the means of weighted mean C-peptide measured based on AUC from a 2-h [22] and 4-h MMTT, as well as the Igls Classification [23]. In addition to the standard 2-h MMTT, we also evaluated indices against a 4-h MMTT to account for possible delayed glucose absorption and decreased motility after gastrointestinal surgery (TP).

Additionally, we sought to determine, if pre TP-IAT islet function estimation with the use of surrogate indices is predictive of TP-IAT outcome measured by islet yield, insulin independence at 1-year postsurgery and the TP-IAT optimal/good outcome defined by the Igls classification.

Patients and methods

Data were prospectively collected in 15 consecutive patients undergoing TP-IAT at the University of Chicago between 2014 and 2017. Patients were evaluated at different time points including baseline prior to TP-IAT, day 75, 1 year and annually afterwards. The study was approved by the University of Chicago Institutional Review Board. All participants provided written informed consent.

We used criteria for discontinuing or resuming exogenous insulin established earlier for allo-islet transplant recipients [24].

Standard measures for beta-cell function based on stimulation studies

Mixed meal tolerance test

A MMTT was performed after 8–12 h of fasting. Blood samples were collected for the measurement of glucose, C-peptide and insulin concentrations at baseline and then at 0, 15, 30, 60, 90, and 120 min for the 2-h MMTT and additionally at 180 and 240 min for the 4-h MMTT after ingesting 6 ml/kg body weight of BOOST® High-protein (Nestlé Health Science, Epalinges, Switzerland; 360 calories, 9 g fat, 49.5 g carbohydrate, 22.5 g protein) with a maximum of 360 ml. The area under curve (AUC) of the C-peptide values at 0, 15, 30, 60, 90, and 120 min for the 2-h MMTT and additionally at 80 and 240 min for the 4-h MMTT were both calculated using the trapezoidal method. The weighted mean C-peptide in the 2-h MMTT and the 4-h MMTT were computed as AUC divided by the time period of the test, that is, 120 min or 240 min, respectively [22].

Beta score

The beta score was calculated from the patient's daily insulin requirements (DIR), HbA1c, fasting plasma glucose concentration, and stimulated/fasting C-peptide levels according to the method described by Ryan *et al.* [25]. DIR was calculated as the mean of doses in a patient's log during a 3-day period the week before each MMTT visit.

Calculation of surrogate indices of beta-cell function based on fasting blood sample

SUITO (Secretory Unit of Islets in Transplantation) was calculated from the fasting blood glucose (mmol/l) and C-peptide (nmol/l) according to the Takita's description [7–10].

$$\text{SUITO} = \frac{250 \times \text{fasting C-peptide [nmol/l]}}{\text{fasting plasma glucose [mmol/l]} - 3.43}$$

Transplant estimated function was calculated from the DIR and HbA1c according to the formula published by Caumo *et al.* [15].

$$\mathrm{TEF} = \left[\mathrm{DIRpreTx} + \frac{\mathrm{HbA1cpreTx}}{5.43}\right] - \left[\mathrm{DIR} + \frac{\mathrm{HbA1c}}{5.43}\right]$$

Homeostasis model assessment was calculated based on paired fasting plasma glucose and C-peptide [16,17] using web-based HOMA calculator [26].

C-peptide/glucose ratio was estimated from the fasting blood glucose (mg/dl) and C-peptide (ng/ml) levels as proposed by Faradji *et al.* [18]

$$\mathrm{CP/G} = \frac{\text{fasting C-peptide concentration [ng/ml]}}{\text{fasting plasma glucose concentration [mg/dl]}}$$

C-peptide/glucose creatinine ratio was calculated from the fasting blood glucose (mg/dl), C-peptide (ng/ml) and creatinine concentrations as described by Faradji *et al.* [18]

$$\mathrm{CP/GCr} = \frac{\text{fasting C-peptide concentration [ng/ml]}}{\text{fasting plasma glucose concentration [mg/dl]} \times \text{creatinine concentration [mg/dl]}}$$

BETA-2 score was calculated from the fasting blood glucose (mg/dl), C-peptide (ng/ml), HbA1c (%), and insulin dose (U/kg/day) as described by Forbes *et al.* [19]

$$\text{BETA-2 score} = \left(\frac{\sqrt{\text{fasting C-peptide [nmol/l]} \times (1 - \text{insulin dose [units/kg]})}}{\text{fasting plasma glucose [mmol/l]} \times \mathrm{HbA1c}\,[\%]}\right) \times 1000$$

Igls classification of beta-cell graft function was introduced during the 1st IPITA/EPITA Opinion Leaders Workshop in Igls, Austria in 2017 [23]. Since that classification was developed specifically for assessment of the islet allograft function in patients with type 1 diabetes, we adjusted it in order to assess islet graft function in the setting of IAT in patients after total pancreatectomy (Table 1A,B). We applied the same criteria and cut-offs as the authors of the original classification. The optimal or good islet function based on adjusted Igls classification was defined as success of the procedure.

Statistical analysis

Data were tested for normality, and Pearson or Spearman rank correlation coefficients were determined, as appropriate. To account for repeated measurements with the same individual, the mixed effects approach described in Hamlett *et al.* [27] was performed. A Mann–Whitney *U* test was used for comparison between groups with continuous variables. ROC curves were constructed for participant's SUITO, TEF, HOMA2-B%, CP/G, CP/GCr, and BETA-2. The area under the ROC curves (AUROC) was compared to the AUROC's for beta score and 90-min glucose MMTT to determine which of the surrogate indices detected the outcome with sufficient discrimination. Youden's index was calculated (specificity + sensitivity − 1) and used to select the optimal cut-offs for each index. For these analyses, the bootstrap [28] was used to account for repeated measurements by resampling patients. The

Table 1. (A) The Igls classification of beta-cell graft function after islet allotransplantation [23]. (B) We adjusted Igls classification of beta-cell graft function for islet autotransplantation.

Functional status	HbA1c (%)	Severe hypo events (SH)	Insulin requirement (U/kg/day)	C-peptide	Treatment success
(A)					
Optimal	≤6.5	None	None	>50% Baseline	Yes
Good	<7.0	None	<50% Baseline	>50% Baseline	Yes
Marginal	Baseline	<Baseline	>50% Baseline	>50% Baseline	No
Failure	Baseline	Baseline	Baseline	Baseline	No
(B)					
Optimal	≤6.5	None	None	Detected†	Yes
Good	<7.0	None	Yes*	Detected†	Yes
Marginal	≥7.0	Yes	Yes*	Detected†	No
Failure	≥7.0	Yes	Yes	Undetected	No

*Includes also noninsulin antihyperglycemic agents.

†C-peptide detected- means >0.5 ng/ml (>0.17 nmol/l) fasting or stimulated.

Andersen and Gill [29] Cox model was fit to accommodate multiple events. Throughout, a *P*-value of less than 0.05 was considered statistically significant. The statistical analyses were performed using the STATISTICA 12.0 and STATA 14.0 software packages.

Results

Mean patient age was 39 ± 12.8 years (range 17–60). There were 8 (53%) women and 7 (47%) men. The median observation period was 28 months (range 3–36 months). Nine out of 15 (60%) patients had recognized genetic mutations or variations in CFTR or PRSS1. Patients had chronic pancreatitis or recurrent acute pancreatitis diagnosed an average of 7.0 years prior to TP-IAT (range 1–39 years). The detailed baseline characteristics of the study group are presented in Table 2. Patients received an average islet mass of 208 600 IEQ (72 600–379 000 IEQ) and 2918 IEQ/kg (664–5200 IEQ/kg). They were supported with insulin for several weeks after TP-IAT for islet engraftment, while two patients already required insulin supplementation prior to the surgery. Four patients (27%) stopped insulin support completely and maintained proper glucose control at day 75 follow-up with a median HbA1c of 5.8% (range 5.2–6.3). At 1-year follow-up, 7 out of 15 (47%) patients were already off insulin with a median HbA1c of 5.9% (5.5–6.8). The percentage of patients off insulin remained around 50% during 2- and 3-year follow-ups with a median HbA1c of 5.8% (5.5–6.2) and 6% (5.4–6.6), respectively.

During follow-up visits, 32 MMTTs were performed (15 on day 75, 12 at 1 year follow-up visit, 3 at 2 year follow-up visit and 2 MMTTs at 3-year follow-up visit): 15 tests on patients off insulin, and 17 tests on patients with insulin support. In six cases, it was impossible to calculate HOMA-2B% as either glucose or C-peptide values exceeded range limits accepted by the HOMA-2 calculator (required range for glucose from 54.1 to 450.5 mg/dl and for C-peptide from 0.2 to 3.5 nmol/l). Islet function assessed with the Igls classification was optimal in 14 time points, good in 13 time points, marginal in five time points (in four different patients) and none with failures.

Relationship between reference and surrogate indices

Four indices (SUITO, CP/G, TEF, and BETA-2) were modestly/well correlated with both beta score and MMTT 90-min (*r* in the range 0.5–0.75; Table 3, Figs S1–S3). Of note, TEF and BETA-2 showed the strongest correlation with the reference tools, whereas CP/GCr and HOMA-2B% showed no statistical significance. All surrogate indices apart HOMA-2B% showed modest/strong correlation with the mean-weighted C-peptide from both 120- and 240-min MMTT. The association was strongest, as expected, in the case of CP/G and CP/GCr.

Table 2. Demographic and baseline patient characteristics.

	Median (*n*)	Range
Age at TP-IAT, year	44	17–60
Sex M/F	7/8	
BMI at TP-IAT, kg/m^2	24.8	18.5–37.9
Duration diagnosed pancreatitis, year	7	1–39
Etiology (*n*)		
Genetic		
Cationic trypsinogen (PRSS1)	3	
Cystic fibrosis transmembrane conductance regulator gene (CFTR)	6	
Calcium-sensing receptor (CASR)	0	
Chymotrypsin C gene (CTRC)	0	
Pancreatic secretory trypsin inhibitor gene (SPINK1)	0	
Autoimmune	1	
Pancreas divisum	3	
Unknown etiology	2	
Islet mass transplanted		
Total islet equivalent (IEQ)	208 600	72 600–379 000
IEQ/kg body weight	2918	664–5200

CASR, Calcium-sensing receptor; CFTR, cystic fibrosis transmembrane conductance regulator; CTRC, Chymotrypsin C gene; ERCP, endoscopic retrograde cholangiopancreatography; IEQ, islet equivalents; IQR, interquartile range; PRSS1, protease serine 1; SPINK1, Pancreatic secretory trypsin inhibitor gene; TP-IAT, total pancreatectomy with islet autotransplant.

Table 3. The relationships between each of the surrogate indices (SUITO, TEF, HOMA2-B%, CP/G, CP/GCr, BETA-2 score) and the reference indices of beta-cell function derived from MMTT and beta score (n = 15, 32 MMTT).

	With beta score		With MMTT 90-min glucose		With 2-h MMTT-weighted mean C-peptide		With 4-h MMTT-weighted mean C-peptide	
Correlation	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*
SUITO	0.56	<0.001	−0.60	<0.001	0.64	<0.001	0.63	<0.001
TEF	0.75	<0.001	−0.53	<0.001	0.51	0.003	0.44	0.01
HOMA2-B%	0.26	0.18	−0.61	<0.001	0.28	0.17	0.35	0.08
CP/G	0.45	0.011	−0.46	<0.001	0.72	<0.001	0.75	<0.001
CP/GCr	0.29	0.25	−0.36	0.037	0.7	<0.001	0.77	<0.001
BETA 2	0.68	<0.001	−0.62	<0.001	0.65	<0.001	0.66	<0.001

BETA 2, BETA-2 score; CP/G, C-peptide/glucose ratio; CP/GCr, C-peptide/glucose creatinine ratio; HOMA2-B%, homeostasis model assessment; MMTT, mixed meal tolerance test; SUITO, The Secretory Unit of Islet Transplant Objects; TEF, transplant estimated function.

Surrogate indices and detection of need for insulin support

The analysis of AUROC curve for all surrogate indices showed homogeneous results, with good discriminative ability of insulin independence versus insulin dependence. This was prominent for all surrogate indices besides HOMA-2B%, which displayed a borderline performance. Overall, BETA-2 and TEF showed the best performance (95% confidence interval 0.7–1.0, $P < 0.001$). These findings differed slightly from the results of the correlation analyses. BETA-2 $\geq$ 16.2 detected insulin independence (Table 4, Fig. 1a).

Table 4. The areas under receiver operating curves of the surrogate indices for the detection of need for insulin support (n = 15, 32 MMTT).

	AUROC	95% CI	*P*-value	Cut-off
SUITO	0.78	0.64–0.92	<0.001	39.3
TEF	0.91	0.82–1	<0.001	−0.21
HOMA2-B%	0.67	0.46–0.88	<0.001	64.6
CP/G	0.79	0.67–0.92	<0.001	0.83
CP/GCr	0.76	0.62–0.9	<0.001	1.4
BETA 2	0.85	0.7–1	<0.001	16.2
MMTT 90-min glc	0.72	0.49–0.96	<0.001	152

AUROC, area under receiver operating curve; BETA 2, BETA-2 score; CI, confidence interval; CP/G, C-peptide/glucose ratio; CP/GCr, C-peptide/glucose creatinine ratio; HOMA2-B%, homeostasis model assessment; MMTT, mixed meal tolerance test; SUITO, The Secretory Unit of Islet Transplant Objects; TEF, transplant estimated function.

Surrogate indices and detection of optimal/good versus marginal islet function as defined by the Igls classification of beta-cell graft function

All surrogate indices, apart from HOMA2-B%, showed excellent performance in identifying optimal/good versus marginal islet function as defined by the modified Igls classification of beta-cell graft function with AUROCs >0.9 and $P < 0.001$ (Table 5). The AUROCs for BETA-2, SUITO, and CP/G did not differ significantly when compared to AUROC for 90-min glucose MMTT. BETA-2 $\geq$ 8.24 differentiated between good and marginal islet function according to our modification of Igls score for IAT (Table 5, Fig. 1b).

Predicting TP-IAT metabolic outcomes based on the estimation of pre TP-IAT islet function with surrogate indices

The correlations between the surrogate indices and islet yield were assessed in 12 patients who completed at least a 1-year follow-up and had all their baseline data. At 1 year follow-up, 6 out of 12 patients were off insulin. Pre TP-IAT, the TEF value was 0.0 in all the patients, hence it was not included in analyses. Pre TP-IAT beta score value was 7 in 6 out of 12 patients and a score of 8 in the remaining six patients. This diversification was insufficient to produce any statistically significant results, therefore was excluded from the analyses.

Predicting islet yield based on the estimation of pre TP-IAT islet function with surrogate indices

We found no statistically significant associations between any baseline variables and isolated islet mass. None of the baseline measurements (fasting plasma glucose, C-peptide concentration, HbA1c, 90-min MMTT

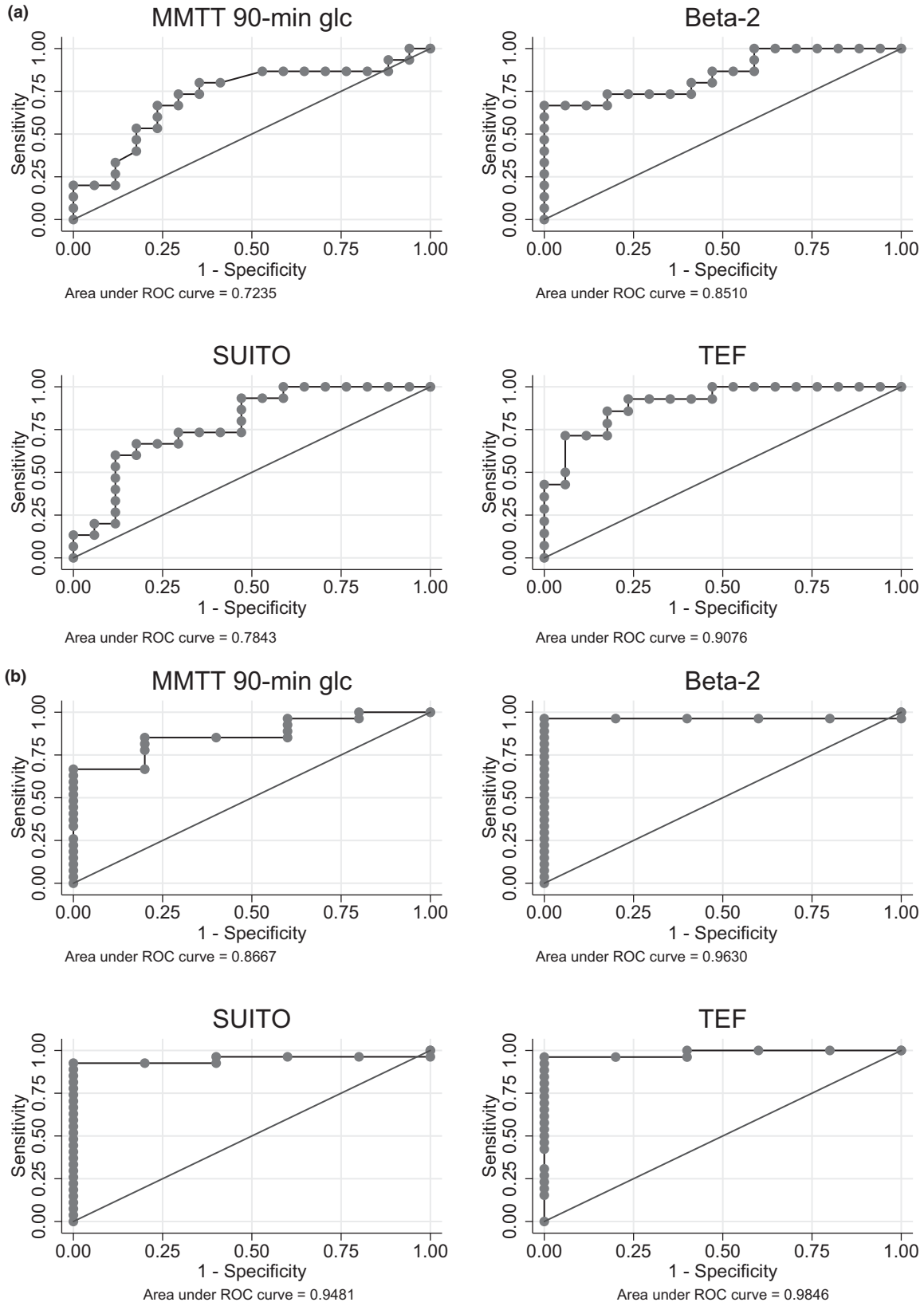

Figure 1 Receiver operating characteristic curves of 90-min mixed meal tolerance test glucose, BETA 2, Secretory Unit of Islet Transplant Object and transplant estimated function (a) for the detection of need for insulin support, (b) for the detection of optimal/good versus marginal islet function according to modified Igls score.

glucose or 120- and 240-min MMTT-weighted mean C-peptide) or any of the surrogate tools estimated pre TP-IAT were significant predictors of the islet yield expressed either as IEQ or IEQ/kg (r in the range of 0.02–0.53, P = 0.08–0.77).

Comparison of pre TP-IAT islet function between insulin-dependent and insulin-free patients at 1 year after TP-IAT and the prediction of the need for insulin support at 1 year post TP-IAT based on pre TP-IAT islet function estimated with surrogate indices

The values from all the single fasting blood sample-based indices estimated pre TP-IAT, did not differ significantly between patients who were on versus off insulin 1 year after the procedure. The only variable which was significantly higher in patients with a metabolic state of acceptable blood glucose control without the need for insulin supplementation, was IEQ/kg (3743 vs. 1734 IEQ/kg, P = 0.02). Similarly, all surrogate measures estimated pre TP-IAT did not affect the long-term prognosis and were unreliable as predictors of insulin independence 1 year after TP-IAT. The only variable with very good predictive ability was islet yield. The AUROC for IEQ/kg was 0.917 (95% confidence interval 0.74–1) with $P < 0.001$ and the cut-off value of 2492 IEQ/kg. The AUROC for IEQ was 0.778 (95% confidence interval 0.49–1) with borderline P = 0.06 and cut-off value of 175 192 IEQ.

Pre TP-IAT islet function estimated with surrogate indices and the prediction of optimal/good islet function based on the Igls classification of beta-cell graft function at 1 year post TP-IAT

The results for all the surrogate indices estimated at baseline mirrored those reported for the prediction of the need for insulin support that was anticipated at 1-year postsurgery. We identified no reliable tool to predict optimal/good islet function based on the modified Igls classification of beta-cell graft function at 1-year post TP-IAT. We did not find any statistically significant association, even for IEQ or IEQ/kg.

Practical value of BETA-2 score in patients after TP-IAT

After establishing a BETA-2 cut-off of 16.2 for the need of insulin support introduction, we looked back at glucose control, BETA-2 values and need for insulin post TP-IAT in the same 15 patients. Whenever the BETA-2 score was above 16.2, patients did not require exogenous insulin supplementation to maintain satisfactory glucose control. BETA-2 value below 16.2 identified patients who required insulin support. There were several patients with a BETA-2 score below 16 but over 13, who chose not to take insulin while they followed a low glucose diet and intensive physical exercise regimen, which allowed them to maintain acceptable glucose control (HbA1c < 6.5). One patient, who decided to remain off insulin despite a HbA1c of 6.8, had a BETA-2 of 10 reflecting suboptimal glucose control (Fig. 2).

Table 5. The areas under receiver operating curves of the surrogate indices for the detection of TP-IAT optimal/good islet function as defined by the modified Igls classification of beta-cell graft function (n = 15, 32 MMTT).

	AUROC	95% CI	*P*-value	Cut-off
SUITO	0.95	0.85–1	<0.001	16.3
TEF	0.98	0.93–1	<0.001	−0.35
HOMA2-B%	*	*	*	*
CP/G	0.95	0.85–1	<0.001	0.51
CP/GCr	0.9	0.75–1	<0.001	0.87
BETA 2	0.96	0.89–1	<0.001	8.24
MMTT 90-min glc	0.87	0.68–1	<0.001	152

AUROC, area under receiver operating curve; BETA 2, BETA-2 score; CI, confidence interval; CP/G, C-peptide/glucose ratio; CP/GCr, C-peptide/glucose creatinine ratio; HOMA2-B%, homeostasis model assessment; MMTT, mixed meal tolerance test; SUITO, The Secretory Unit of Islet Transplant Objects; TEF, transplant estimated function.

*Cannot be calculated.

Discussion

The metabolic outcome of TP-IAT is highly unpredictable and management to reach optimal glucose control is challenging. To facilitate a convenient islet function assessment, a number of single fasting blood sample-based indices were introduced; however, they were developed and validated for the use in islet allotransplantation recipients. The practical aim of the current study was to verify that these equations could assist in the care of TP-IAT patients. Our results indicate that BETA-2 and TEF could safely be implemented in the assessment and management of glucose control in patients after TP-IAT. TEF outperformed other surrogate indices in the AUROC analysis unlike in our previous analysis in allogenic islet transplant recipients [21]. However, BETA-2 showed the strongest correlation with all the reference beta-cell function measures in the

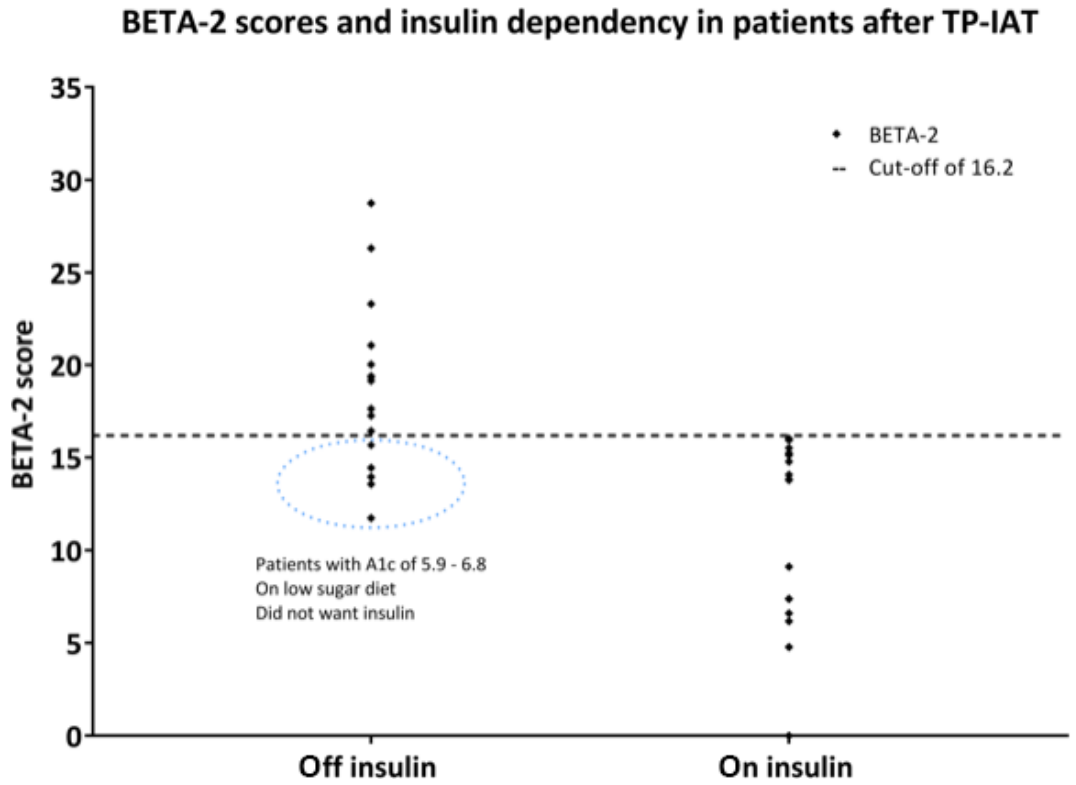

Figure 2 BETA-2 scores and insulin dependency in patients after total pancreatectomy with islet autotransplantation.

current study, and was found very efficient not only in auto- but also in allotransplantation. In the current study, both indices showed invariable and reliable performance reflecting current metabolic status with AUROC 0.85–0.99. Diagnostic tools are typically considered useful for clinical decision-making, when the AUROC is greater than 0.70 and considered strong when the AUROC exceeds 0.80 [30]. The investigated equations use variables with measurements that are not expensive or difficult to obtain, meaning they can be widely used in local laboratories without requiring the patient to travel for testing to specialized diabetic centers. Therefore, simple indices allow accurate information about islet function to be obtained much more frequently than with the MMTT. Also, simple indices do not require the burden of daily blood glucose checking and record keeping for those who are off insulin. Results from these indices allow for guidance for appropriate follow-up, implementing or adjusting diet restrictions, exercise and/or pharmacological intervention for optimal glucose control.

It is particularly important that all the cut-offs for detection of the need for insulin support are similar to those in allogenic islet transplantation recipients: BETA-2 score below 13 indicating insulin dependence, between 13 and 18 signifying glucose intolerance and score over 18 was correlated with insulin independence [20,21]. Due to a limited number of MMTT measurements in our patients, we stratified patients only as "on insulin" and "off insulin" and found a cut-off of 16.2, which is in the middle between 13 and 18 found in islet allograft patients. The score around 16 may represent islet graft status, which allows some patients to still be off insulin while others require insulin support for optimal glucose control depending on other factors including carbohydrate consumption, insulin sensitivity, and/or physical activity. It should be highlighted that both TEF and BETA-2 contain HbA1c and insulin dose, which are the most important elements reflecting current blood glucose control, so it was not a full surprise to us that they correlate the best among other indices. The goal of our study was to identify a tool to detect changing islet function without the stimulation test and to quantify the change. Of course, a single value of HbA1c above 7 or a high dose of daily insulin indicates insulin dependence. However, such an assessment, based on a single value might be not accurate when the islet graft is gradually failing and the

patient is transitioned from insulin independence to insulin dependence. In such a case, utilization of simultaneous use of a constellation of factors and calculation of BETA-2 score allows for easier detection of declining islet function or confirming stable status of glucose control.

We also tested six surrogate indices as a tool to predict the metabolic outcome of TP-IAT. Such information would help set more accurate expectations about the burden of glucose control after TP-IAT. Our study suggests that baseline islet function measures are not good predictors of either islet yield or the final metabolic outcome in TP-IAT patients. In line with previous reports by various authors, we showed that the islet mass transplanted was the most, and in our case, the only significant predictor of TP-IAT metabolic outcome. Bellin *et al.* [31] showed that a single fasting blood glucose level and the patient's weight were good predictors of islet yield in children. The same authors found in a group of 60 adult patients, that stimulated C-peptide on MMTT ≥4 ng/ml was a strong predictor of islet yield ≥2500 IEQ/kg, while there was only a modest correlation between parameters obtained from frequent sample IV glucose tolerance tests and islet isolation outcomes [32]. Another study, found a detrimental effect of fibrosis and acinar atrophy in the pancreas on islet yield [33]. Preliminary reports suggested that islet oxygen consumption rate (OCR) [34], islet size index [35], and finally miR-375 and miR-200c [36] could have some predictive values as well.

The major limitation of the study is that it was based on results from a single center with a limited number of patients and a particular strategy for patient's clinical management. We had no failed IATs and the outcome was marginal in only 5 of 32 time points. Further studies will likely be necessary to more accurately determine the utility of indices where function is lower. Second, the study was based on follow-ups on day 75 and then annually. Examinations performed once a year do not allow for evaluation of any possible fluctuation in plasma glucose or C-peptide concentrations.

Despite these limitations, we believe that our results have an important clinical value and are complementary to findings after islet allotransplantation. To our knowledge, this is the first study to attempt to apply all currently available surrogate indices based on a single fasting blood sample in autologous islet recipients. We emphasize the need for independent validation of our findings in several populations before implementation in routine use.

In conclusion, BETA-2 was the most consistent among indices correlating strongly with all reference measures of beta-cell function and additionally showed invariable good performance for the identification of insulin independence and optimal/good versus marginal islet function in the Igls score.

BETA-2 provides a simple and accurate strategy that could be used for frequent assessments of graft function to guide management in patients undergoing TP-IAT.

Authorship

JG: concept/design, data collection, data analysis/interpretation, drafting article, statistics. PB: data collection, data analysis, critical revision and approval of the article. NF, MK, LB, KG, L-jW and MT: data collection, critical revision and approval of the article. AD-Ś, CT, JMM and JF: critical revision and approval of the article. PW: concept/design, data analysis/interpretation, Critical revision and approval of the article.

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Conflicts of interest

The authors have declared no conflicts of interest.

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SUPPORTING INFORMATION

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

Figure S1. Correlation between (a) SUITO and beta score, (b) SUITO and 90-min MMTT glucose.

Figure S2. Correlation between (a) BETA-2 and beta score, (b) BETA-2 and 90-min MMTT glucose.

Figure S3. Correlation between (a) CP/G and beta score, (b) CP/G and 90-min MMTT glucose.

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