External Validation of the Newly Developed BETA-2 Scoring System for Pancreatic Islet Graft Function Assessment

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ABSTRACT

Background. BETA-2 score using a single fasting blood sample was developed to estimate beta-cell function after islet transplantation (ITx) and was validated internally by a high ITx volume center (Edmonton). The goal was to validate BETA-2 externally, in our center.

Methods. Areas under receiver operating characteristic curves (AUROCs) were obtained to see if beta score or BETA-2 would better detect insulin independence and glucose intolerance.

Results. We analyzed values from 48 mixed meal tolerance tests (MMTTs) in 4 ITx recipients with a long-term follow-up to 140 months (LT group) and from 54 MMTTs in 13 short-term group patients (ST group). AUROC for no need for insulin support was 0.776 (95% confidence interval [CI] 0.539–1, $P = .02$) and 0.922 (95% CI 0.848–0.996, $P < .001$) for beta score and 0.79 (95% CI 0.596–0.983, $P = .003$) and 0.941 (95% CI 0.86–1, $P < .001$) for BETA-2, in LT and ST groups, respectively, and did not differ significantly. In LT group BETA-2 score $\geq$ 13.03 predicted no need for insulin supplementation with sensitivity of 98%, specificity of 50%, positive predictive value (PPV) of 93%, and negative predictive value (NPV) of 75%. In ST group the optimal cutoff was $\geq$13.63 with sensitivity of 92% and specificity, PPV, and NPV 82% to 95%. For the detection of glucose intolerance BETA-2 cutoffs were <19.43 in LT group and <17.23 in ST group with sensitivity > 76% and specificity, PPV, and NPV > 80% in both groups.

Conclusion. BETA-2 score was successfully validated externally and is a practical tool allowing for frequent and reliable assessments of islet graft function based on a single fasting blood sample.

THE assessment of beta cell mass and function in patients with diabetes and after islet transplantation (ITx) is complex. The most precise tools involve islet stimulation with meal, glucose, arginine, or glucagon and are time-consuming and difficult to perform, creating a logistical challenge for both patients and physicians. As a result, a need exists for simple metabolic tests based on a single fasting blood sample or patient's history for the assessment of islet graft function. A number of such surrogate indices have been developed: The Secretory Unit of Islet Transplant Objects [1–8], transplant estimated function [9,10],

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homeostasis model assessment 2-B% [11], C-peptide-to-glucose ratio, C-peptide-to-glucose creatinine ratio [12], and recently introduced BETA-2 score [13]. However, there is still limited experience with these surrogate tools in clinical practice to help guide the clinical management of patients.

The BETA-2 score was developed and validated in a high volume islet transplant center (Edmonton) on a cohort comprised of 114 mixed meal tolerance tests (MMTTs) [13]. BETA-2 ranges between 0 and 42 points and the higher the score, the higher the chance for insulin independence. It is of particular interest given its higher degree of discrimination for glucose intolerance (cutoff < 20) and insulin independence (cutoff ≥ 15) than the previously developed beta score, which involves the value of C-peptide after standardized mix meal stimulation [13]. It is crucial that limitations and applicability of assessment tools are recognized prior to the use in clinical practice; therefore, the objective of this study was to independently evaluate the performance and clinical utility of BETA-2 score, externally at our medium-volume ITx program.

MATERIALS AND METHODS

Study Design

The performance of BETA-2 score was evaluated by comparing the relationship against reference indices of MMTT 90-minute glucose and beta score [14], which were commonly used in clinic and research for the assessment of islet graft function. Data were collected prospectively and analyzed retrospectively. The analysis included available data of patients with brittle type 1 diabetes mellitus (T1DM), who participated in clinical studies involving pancreatic islet allotransplantation at the University of Chicago from March 2005 to March 2015. Patients were dived into 2 groups according to the length of follow-up: short-term (ST) group and long-term (LT) group. Participants provided written informed consent, and the study was approved by the University of Chicago Institutional Review Board and conducted in accordance with the principles endorsed by the Declaration of Helsinki.

Islet Isolation and Transplantation

The pancreas was obtained during a multiorgan procurement and preserved in cold storage with standard preservation solutions: SPS1 (Organ Recovery System, Chicago, Ill, USA) or HTK (Köhler Chemie GmbH, Bensheim, Germany). Islets were isolated using the Ricordi method with a standard semiautomated procedure, and islets were infused via catheter placed intraportally and percutaneously by interventional radiologist as we described elsewhere [15]. Patient received immunosuppression with or without anti-inflammatory agents based on different study protocols.

Criteria for Discontinuing or Resuming Exogenous Insulin

Subjects were considered insulin independent if they were able to titrate off insulin therapy for at least 2 weeks and all of the following criteria were fulfilled: HbA1c no higher than 6.5%, fasting capillary glucose level no higher than 140 mg/dL (7.8 mmol/L) more than 3 times in the past week (based on measuring capillary glucose levels a minimum of 7 times in a 7-day period), 2-hour postprandial capillary glucose no higher than 180 mg/dL (10.0 mmol/L) more than 3 times in the past week (based on measuring capillary glucose levels a minimum of 21 times in a 7-day period), fasting serum glucose level no higher than 126 mg/dL (7.0 mmol/L), and fasting or stimulated C-peptide levels of at least 0.5 ng/mL (0.17 nmol/L). For the period of insulin independence, recipients had fewer than 2 episodes of fasting blood glucose higher than 180 mg/dL (10 mmol/L) per week. Subjects were requested to self-monitor blood glucose at least 4 times per day.

The criteria for resuming insulin were as follows: HbA1c over 6.5%, fasting capillary glucose level over 140 mg/dL (7.8 mmol/L) more than 3 times in the past week, 2-hour postprandial capillary glucose over 180 mg/dL (10.0 mmol/L) more than 3 times in the past week, fasting serum glucose level over 126 mg/dL (7.0 mmol/L), and fasting or stimulated C-peptide levels below 0.5 ng/mL (0.17 nmol/L).

Mixed Meal Tolerance Test

MMTT was performed after 8 to 12 hours of fasting. Blood samples were collected for the measurement of insulin, glucose, and C-peptide concentrations at baseline and at 0, 30, 60, 90, and 120 minutes after ingesting 360 mL (6 mL/kg if body weight < 60 kg) of BOOST High-protein (Nestlé Health Science, Epalinges, Switzerland; 360 calories, 9 g fat, 49.5 g carbohydrate, 22.5 g protein).

Beta Score

The beta score was calculated from the daily insulin requirement, HbA1c, fasting plasma glucose concentration, and stimulated C-peptide levels according to the method described by Ryan et al [14]. Two points were given for: (1) normal fasting glucose ($\leq$5.5 mmol/L or $\leq$99 mg/dL), HbA1c ($\leq$6.1%), stimulated C-peptide ($\geq$0.3 nmol/L or $\geq$0.9 ng/mL), and absence of insulin or oral hypoglycemic agent use. No point was awarded if fasting glucose was in the diabetic range ($\geq$7 mmol/L or $\geq$126 mg/dL), HbA1c was higher than 6.9%, C-peptide secretion was undetectable on stimulation ($<$0.1 nmol/L or $<$0.3 ng/mL), or daily insulin use was more than 0.24 U/kg. One point was given for intermediate values. The beta-score ranges from 0 (no graft function) to 8 points (excellent graft function).

BETA-2 Score

BETA-2 score was calculated based on fasting blood glucose (mmol/L), C-peptide (nmol/L), hemoglobin A1c (%), and insulin dose (units per kilogram per day) as described by Forbes et al [13]:

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

Statistical Analysis

Descriptive statistics are expressed as mean ± standard deviation or median with interquartile range (IQR) as appropriate. Data was tested for normality. A 2-tailed Student t-test or Mann-Whitney *U* test was used for comparison of means between groups with continuous variables, as appropriate. A χ^2 or Fisher exact test was used to compare categorical variables. Receiver operating characteristic curves were made for BETA-2 values. The area under the receiver operating characteristic (AUROC) curves were compared with the beta score and 90-minute MMTT glucose concentration to determine which of the indices detected the outcome (ie, no need for insulin support and glucose intolerance) with greater discrimination. An AUROC $\leq$ 0.5 was considered no discrimination, an AUROC between 0.7 and 0.8 was considered acceptable, an AUROC between 0.8 and 0.9 was considered excellent, and an AUROC $>$ 0.9 was considered outstanding. Youden index was calculated as (specificity + sensitivity −1) and was used to select the optimal cutoffs for each index. Optimal cutoff value for each surrogate index was estimated. A *P* value of less than .05 was considered statistically significant. The statistical analyses were performed using the Statistica 12.0 (StatSoft, Poland).

RESULTS

Demographics

Patients were divided into 2 groups according to the length of the follow-up.

Cohort 1, the LT group, included 4 subjects with T1DM, 1 man and 3 women, aged 42, 36, 51, 48 years, with a follow-up of 140, 131, 119, 81 months, respectively. All received second and third islet infusions after they resumed insulin support following previous transplants. Each subject was scheduled to have MMTT every 6 months. Overall, 48 MMTTs were performed: 42 tests when patients were insulin independent, and 6 tests in patients requiring insulin support.

Cohort 2, the ST group, consisted of 13 T1DM subjects, 4 men and 9 women, at the median age of 45 years (IQR 36–51) at the time of first islet transplant with median follow-up of 33 months (IQR 30–38). Patients received a second or third islet infusion when they remained or became insulin dependent after previous transplant. Each subject underwent an MMTT after ITx on day 75, at 12 months, and then annually. Overall, 54 MMTTs were performed: 38 when patients were insulin independent, and 16 when insulin support was required.

The compositions of internal and external validation cohorts differed as presented in Table 1. Our external validation cohort was significantly smaller and included no ITx after kidney cases with a much longer follow-up period, whereas the total number of MMTTs included in the analysis for both LT and ST groups together, the mean age, and duration of diabetes were similar to the internal validation cohort from the study by Forbes et al [13].

Correlation of BETA-2 Score With MMTT 90-Minute Glucose and Beta Score

In both groups, BETA-2 was well correlated with both beta score and MMTT 90-minute scores with the correlation coefficients of 0.57 and −0.53 in the LT group and 0.7 and −0.73 in the ST group, respectively ($P < .001$).

BETA-2 Score Discriminative Ability to Identify No Need for Insulin Support (Insulin Independence)

LT Group. All patients from the LT group on all follow-up evaluations had measurable fasting C-peptide concentrations with median of 1.25 nmol/L (IQR 1.08–1.5 nmol/L), and all but one participant had detectable concentration for stimulated C-peptide of 4.55 nmol/L (IQR 3.14–5.73 nmol/L). Fasting plasma glucose was 99.9 mg/dL (5.55 mmol/L) (IQR 4.9–6.1 mmol/L; 88.2–109.8 mg/dL), HbA1c was 5.9% (IQR 5.8%–6.2%), stimulated glucose was 133.2 mg/dL (7.4 mmol/L) (IQR 5.8–10.8 mmol/L; 104.4–194.4 mg/dL), and the insulin dose range was 0–0.32 U/kg per day.

The BETA-2 score demonstrated a range of values 7.8 to 29.2 with median of 19 (IQR 17–23) with significantly lower scores in insulin-dependent vs insulin-independent participants: 15 (IQR 8–19) vs 19.8 (IQR 18–23, $P < .001$). AUROC for insulin independence for beta score was 0.776 (95% confidence interval [CI] 0.539–1, $P = .02$) and for BETA-2 was 0.79 (95% CI 0.596–0.983, $P = .003$) and did not differ significantly ($P = .87$) (Fig 1A). BETA-2 score ≥13.03 predicted "no need for insulin supplementation" with sensitivity

Table 1. Baseline Characteristics of the Internal and External Validation Cohorts

		External Validation Cohort (Chicago)		
	Internal Validation Cohort (Edmonton)	Long-Term Group	Short-Term Group	*P*
Number of patients	114	4	13	<.05
ITx after kidney	109	4	13	
ITx alone	5	0	0	
Number of MMTTs included in analysis	112	48	54	NS
Age (y)	49 ± 0.9	44 ± 3	43 ± 10	NS
Male (%)	Not stated	1 (25)	4 (31)	N/A
Duration of diabetes (y)	31.5 ± 1.0	30 ± 14	31 ± 10	NS
Length of follow-up (mo)	8 ± 0.5 after last ITx	118 ± 26 after first ITx	35 ± 8 after first ITx	<.05

External validation cohort included lower number of patients but similar number of MMTTs compared with internal validation cohort. The length of follow-up was longer for external validation cohort ($P < .05$).

Abbreviations: ITx, islet allotransplantation; MMTT, mixed meal tolerance test; N/A, not available; NS, not significant.

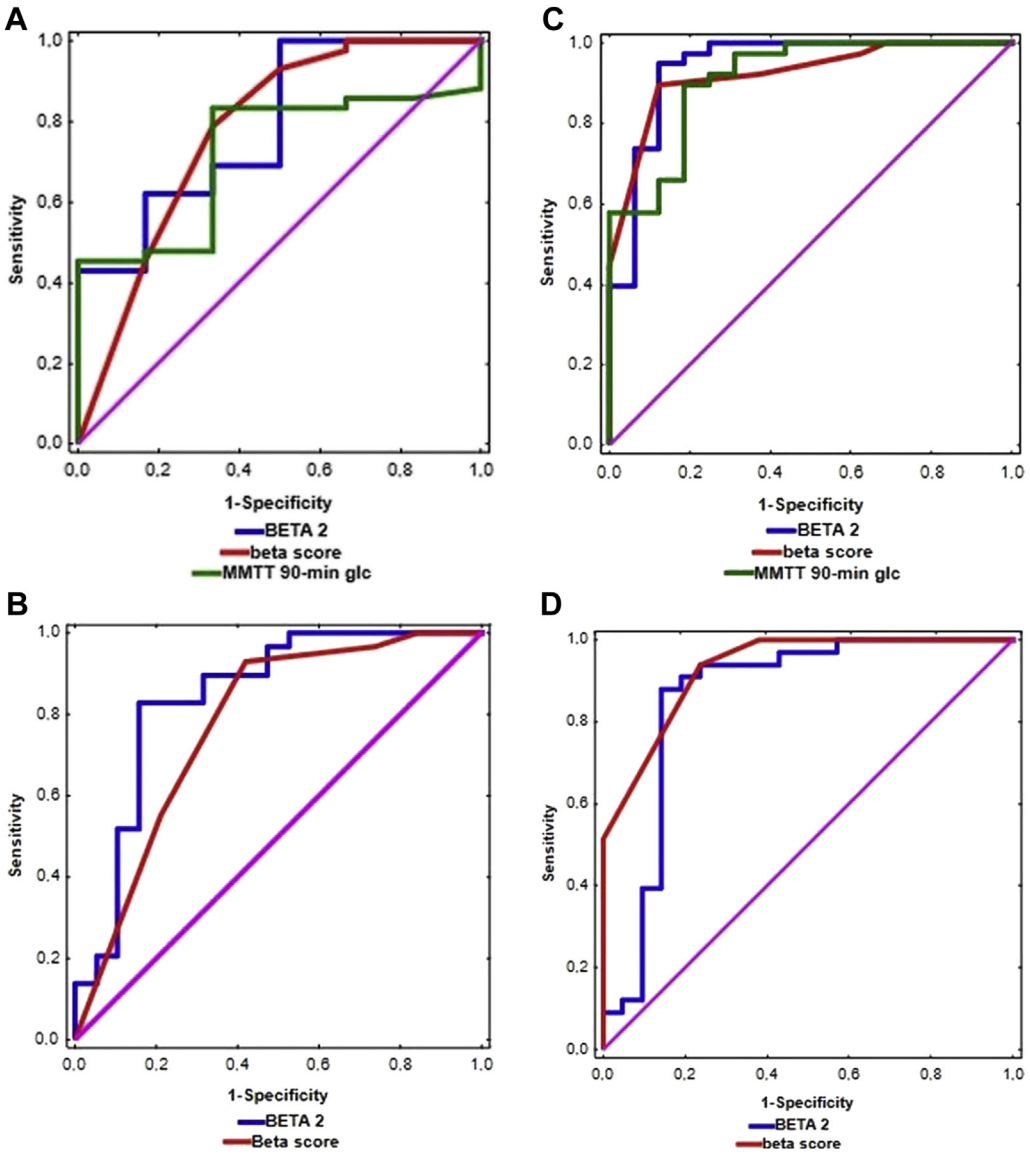

Fig 1. Receiver operating characteristic curves of **(A)** BETA-2, beta score, and 90-minute mixed meal tolerance test (MMTT) glucose for the detection of need for insulin support in long-term (LT) group; **(B)** BETA-2 and beta score for the detection of glucose intolerance (90-minute MMTT glucose ≥144 mg/dL) in LT group; **(C)** BETA-2, beta score and 90-minute MMTT glucose for the detection of need for insulin support in short-term (ST) group; **(D)** BETA-2 and beta score for the detection of glucose intolerance (90-minute MMTT glucose ≥144 mg/dL) in ST group.

of 98% (95% CI 87%–100%), specificity of 50% (95% CI 12%–88%), positive predictive value (PPV) of 93%, and negative predictive value (NPV) of 75%.

ST Group. Patients on evaluations had measurable fasting C-peptide concentrations with median of 0.4 nmol/L (IQR 0.3–0.5 nmol/L) and stimulated C-peptide of 1.46 nmol/L (IQR 1.03–1.83 nmol/L). Fasting plasma glucose was 103.5 mg/dL (5.75 mmol/L) (IQR 5.39–6.44 mmol/L; 97.02–115.92 mg/dL), HbA1c was 5.75% (IQR 5.6–6.1%), stimulated glucose was 136.44 mg/dL (7.58 mmol/L) (IQR 6.17–9.67 mmol/L; 111.06–174.06 mg/dL), and the insulin dose range was 0–0.53 U/kg per day. The BETA-2 score demonstrated a range of values from 0.0 to 25.9 with median of 19 (IQR 12–23) with significantly lower scores in insulin-dependent vs insulin-independent participants: 9 (IQR 4–12) vs 21 (IQR 18–24, $P < .001$).

AUROCs were 0.922 (95% CI 0.848–0.996, $P < .001$) for beta score and 0.941 (95% CI 0.86–1, $P < .001$) for BETA-2, and as in the LT group did not differ significantly ($P = .67$) (Table 2; Fig 1B). In the ST group, the optimal cutoff for the identification of no need for insulin support introduction was ≥13.63 with sensitivity of 92% (95% CI

Table 2. The AUROCs of Beta Score and BETA-2 and 90-Minute MMTT Glucose (When Appropriate) for the Detection of No Need for Introduction of Insulin Support as Well as for Glucose Intolerance, Defined as 90-Minute MMTT Glucose ≥ 8 mmol/L (144 mg/dL)

	LT Group				ST Group			
	AUROC	95% CI	*P*	Cutoff	AUROC	95% CI	*P*	Cutoff
Detection of no need for insulin support introduction (insulin independence)								
BETA-2	0.79	0.6–0.98	.003	13.03	0.941	0.86–1	<.001	13.63
90-min MMTT glucose	0.72	0.54–0.9	.016	197	0.911	0.84–1	<.001	158
Beta score	0.77	0.54–1	.02	7.0	0.922	0.85–1	<.001	7.0
Detection of glucose intolerance 90-min MMTT glucose ≥8 mmol/L (144 mg/dL)								
BETA-2	0.842	0.72–0.97	<.001	19.43	0.86	0.74–0.98	<.001	17.23
Beta score	0.775	0.63–0.92	<.001	7.0	0.931	0.87–1	<.001	7.0

Abbreviations: AUROC, area under receiver operating curve; CI, confidence interval; LT, long-term group; MMTT, mixed meal tolerance test; ST, short-term group.

79%-98%), specificity of 87.5% (95% CI 12%-88%), PPV of 95%, and NPV of 82% (Table 3).

BETA-2 Score Discriminative Ability to Identify Glucose Intolerance Defined by 90-Minute MMTT Glucose ≥ 8 mmol/L (144 mg/dL)

LT Group. BETA-2 showed significantly lower scores in participants with a 90-minute MMTT glucose level ≥ 8 mmol/L vs < 8 mmol/L, that is, 16.6 (IQR 14–19) vs 20.8 (IQR 19.5–23, $P = .02$). A 90-minute MMTT glucose level ≥ 8 mmol/L was equally well discriminated with the BETA-2 score and the beta score. AUROC for the identification of glucose intolerance at 90-minute MMTT glucose ≥ 8 mmol/L (144 mg/dL) for beta score was 0.775 (95% CI 0.63–0.92, $P < .001$) and for BETA-2 was 0.842 (95% CI 0.72–0.97, $P < .001$) and did not differ significantly ($P = .37$) (Fig 1C). A BETA-2 score < 19.43 predicted glucose intolerance with sensitivity of 76% and specificity of 89% (Table 3).

ST Group. BETA-2 showed significantly lower scores in participants with a 90-minute MMTT glucose level ≥ 8 mmol/L vs <8 mmol/L, that is, 16.6 (IQR 14–19) vs 20.8 (IQR 19.5–23, $P = .02$). A 90-minute MMTT glucose level ≥8 mmol/L was equally well discriminated with the BETA-2 score and the beta score. AUROC for the identification of glucose intolerance defined as 90-minute MMTT glucose ≥8 mmol/L (144 mg/dL) for beta score was 0.931 (95% CI 0.87–1, $P < .001$) and was 0.86 (95% CI 0.74–0.98, $P < .001$) for BETA-2, and also did not differ significantly ($P = .19$) (Fig 1D). For the detection of glucose intolerance in the ST group, BETA-2 cutoff was <17.23 with sensitivity 78% and specificity 90% (Table 3).

Table 3. Sensitivity, Specificity, PPV, and NPV for the Detection of No Need for Insulin Support Introduction and Glucose Intolerance 90-Minute MMTT Glucose ≥8 mmol/L (144 mg/dL)

	LT Group		ST Group	
	%	95% CI	%	95% CI
Detection of no need for insulin support introduction (insulin independence)				
Sensitivity	97.62	87.43–99.94	92.11	78.62–98.34
Specificity	50.00	11.81–88.19	87.50	61.65–98.45
PPV	93.18	85.98–96.82	94.59	82.67–98.47
NPV	75.00	26.96–96.06	82.35	60.80–93.35
Detection of glucose intolerance 90-min MMTT glucose ≥8 mmol/L (144 mg/dL)				
Sensitivity	76.19	52.83–91.78	78.26	56.30–92.54
Specificity	88.89	70.84–97.65	90.32	74.25–97.96
PPV	84.21	64.12–94.09	85.71	66.71–94.73
NPV	82.76	68.83–91.26	84.85	71.89–92.46

Abbreviations: CI, confidence interval; MMTT, mixed meal tolerance test; PPV, positive predictive value; NPV, negative predictive value.

Illustration of Clinical Utility of the BETA-2 Score

Data from 2 patients, 1 from the LT group and 1 from the ST group, are presented in Fig 2, to compare the utility of the BETA-2 score versus the beta score.

In the first case study, a 51-year-old woman with T1DM since the age of 12 underwent 2 ITxs and had MMTT performed every 6 months (Fig 2A). Following the initial transplant, the patient was insulin independent. As time passed, the BETA-2 score dropped from 23 to 14, indicating continuous deterioration of the islet function, paralleled with an increase in fasting and stimulated glucose levels and HbA1c values, whereas the beta score remained stable at around 7. A second transplant 39 months later led to a substantial reduction in serum glucose and HbA1c concentrations, and the BETA-2 index increased to 28. Changes in BETA-2 were parallel to changes of 90-minute glucose in MMTT and HbA1c, and the beta score remained stable at around 7. BETA-2 as a continuous variable had greater resolution than the categorical beta score. As depicted in Fig 2A, the beta score of 7 reflects 4 different values of BETA-2.

In the second case study, another 51-year-old woman from the ST group with T1DM since the age of 25 experienced ITx, which failed, and 3 months later she received a subsequent procedure and successfully became insulin free. BETA-2 index increased from 0 when patient lost islet function to 24 after subsequent islet transplant and then slowly dropped to 11. Changes of BETA-2 were parallel to changes in MMTT 90-minute glucose level and beta score. Moreover, with the same beta-score result of 6, BETA-2 values differed, indicating a greater resolution of BETA-2 (Fig 2B).

DISCUSSION

Once clinical utility of a new surrogate index is established, internal and external validation is required prior to the

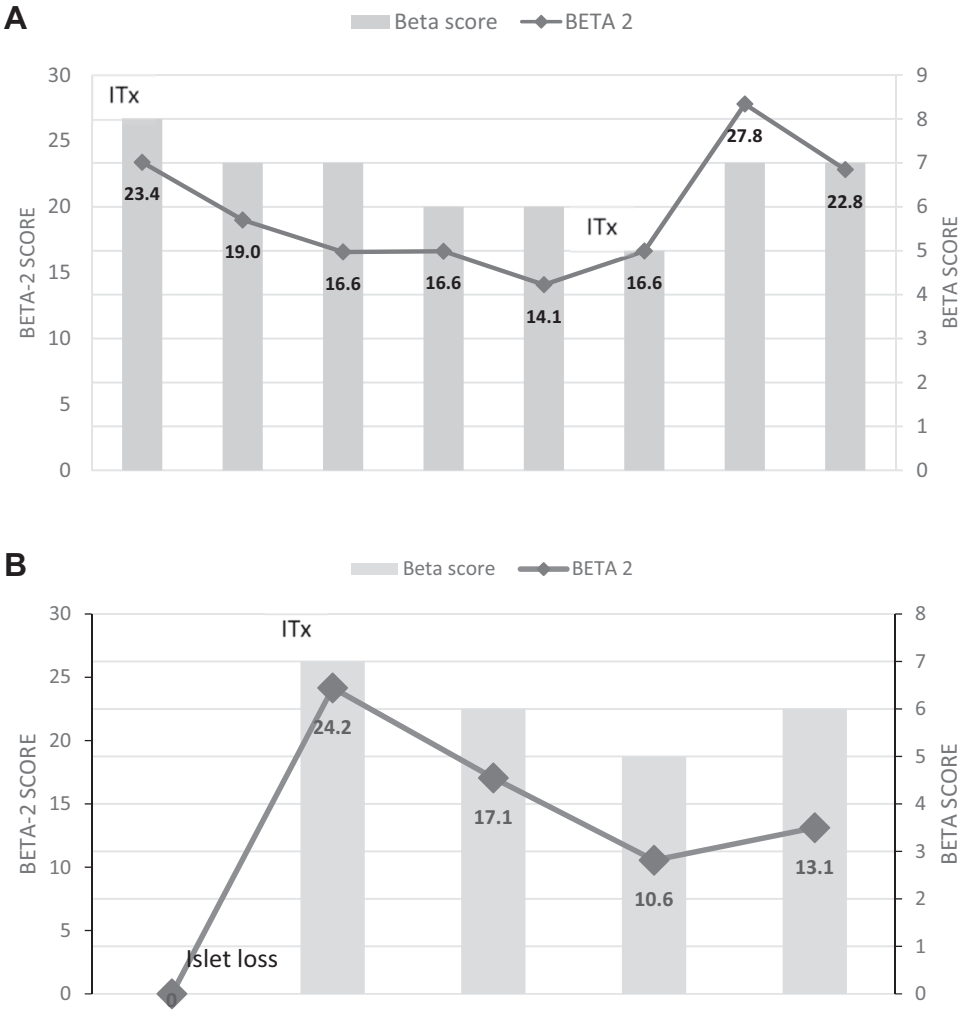

Fig 2. Examples of beta versus BETA-2 scores in patients after ITx **(A)** from long-term (LT) group and **(B)** from short-term (ST) group. Changes of BETA-2 were parallel to changes of 90-minute glucose in mixed meal tolerance test and HbA1c whereas beta score was stable around 7. BETA-2 as a continuous variable has greater resolution than categorical beta score. **(A)** Beta score of 7 reflects 4 different values of BETA-2. **(B)** Again, with the same beta-score result of 6, BETA-2 values differed indicating greater resolution of BETA-2.

implementation into clinical practice. Beta score, which involves values after islet stimulation, has been the mainstay of islet graft function assessment since its introduction in 2005 and has been validated in many islet centers, proving its clinical value. Although different surrogate indices utilizing only fasting blood samples have been proposed, they were validated only internally [1–13]. Our study is the first external validation that assesses the performance of the BETA-2 score in a population external to and independent from the original validation cohort.

In our 2 cohorts of patients, unlike in the original study by Forbes et al [13], BETA-2 did not outperform the beta score. This finding supports the importance of evaluating the islet allograft function assessment indices using local data for relevance and suitability of the routine use. Nevertheless, the BETA-2 score's discriminative ability to identify insulin independence and glucose intolerance defined as 90-minute MMTT glucose $\geq$8 mmol/L (144 mg/dL) was noninferior to the beta-score performance with comparable AUROCs. In all cases it had high sensitivity, specificity, PPVs, and NPVs. Furthermore, we found similar cutoff values effective for BETA-2 compared with ones proposed by Edmonton: 13 and 15 for insulin independence and 19 and 20 for glucose intolerance, respectively. With reproducible and comparable performance, the main advantage of BETA-2, in contrast to the beta score, is that BETA-2 can be calculated utilizing only the fasting values of C-peptide and glucose, which are easier and more frequently obtained than MMTT, allowing for closer monitoring and alternations in management for

improved outcomes. Similarly to the beta score, BETA-2 includes information on exogenous insulin use and HbA1c levels to provide an integrated overview of the patient's metabolic state. Moreover, when we analyzed individual cases, it was clear that BETA-2, as a continuous variable, had much greater resolution opposed to the categorical beta score.

In conclusion, the ease of utilizing a single fasting blood sample as well as data on daily insulin use makes the BETA-2 score a practical new tool. It allows for frequent and reliable assessment of islet graft function in contrast to the logistically challenging beta score, which requires mixed meal stimulation. As a simple test that can be assessed at any time point during the post-transplant period, it could have an immediate application either to reassure adequate islet graft function or to identify early graft dysfunction, determining the need for more sophisticated metabolic and immunologic workup.

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REFERENCES

[1] Takita M, Matusmoto S. SUITO index for evaluation of clinical islet transplantation. Cell Transplant 2012;21:1341–7.

[2] Takita M, Matsumoto S, Shimoda M, Chujo D, Itoh T, Iwahashi S, et al. Association between the secretory unit of islet transplant objects index and satisfaction with insulin therapy among insulin-dependent islet recipients. Transplant Proc 2011;43:3250–5.

[3] Takita M, Matsumoto S, Qin H, Noguchi H, Shimoda M, Chujo D, et al. Secretory unit of islet transplant objects (SUITO) index can predict severity of hypoglycemic episodes in clinical islet cell transplantation. Cell Transplant 2012;21:91–8.

[4] Takita M, Matsumoto S, Noguchi H, Shimoda M, Chujo D, Itoh T, et al. Secretory unit of islet transplant objects (SUITO) index can predict outcome of intravenous glucose tolerance test. Transplant Proc 2010;42:2065–7.

[5] Matsumoto S, Noguchi H, Takita M, Shimoda M, Tamura Y, Olsen G, et al. Excellence of SUITO index for assessing clinical outcome of islet transplantation. Transplant Proc 2010;42:2062–4.

[6] Matsumoto S, Noguchi H, Hatanaka N, Shimoda M, Kobayashi N, Jackson A, et al. SUITO index for evaluation of efficacy of single donor islet transplantation. Cell Transplant 2009;18:557–62.

[7] Matsumoto S, Noguchi H, Hatanaka N, Kobayashi N, Jackson A, Naziruddin B, et al. Evaluation of engraftment after single islet transplantation from a brain-dead donor by the secretory unit of islet transplant objects (SUITO) index. Transplant Proc 2008;40:364–6.

[8] Matsumoto S, Yamada Y, Okitsu T, Iwanaga Y, Noguchi H, Nagata H, et al. Simple evaluation of engraftment by secretory unit of islet transplant objects for living donor and cadaveric donor fresh or cultured islet transplantation. Transplant Proc 2005;37:3435–7.

[9] Caumo A, Maffi P, Nano R, Bertuzzi F, Luzi L, Secchi A, et al. Transplant estimated function: a simple index to evaluate beta-cell secretion after islet transplantation. Diabetes Care 2008;31:301–5.

[10] Caumo A, Maffi P, Nano R, Luzi L, Hilbrands R, Gillard P, et al. Comparative evaluation of simple indices of graft function after islet transplantation. Transplantation 2011;92:815–21.

[11] Wallace TM, Levy JC, Matthews DR. Use and abuse of HOMA modeling. Diabetes Care 2004;27:1487–95.

[12] Faradji RN, Monroy K, Messinger S, Pileggi A, Froud T, Baidal DA, et al. Simple measures to monitor β-cell mass and assess islet graft dysfunction. Am J Transplant 2007;7:303–8.

[13] Forbes S, Oram RA, Smith A, Lam A, Olateju T, Imes S, 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;16:2704–13.

[14] Ryan EA, Paty BW, Senior PA, Lakey JR, Bigam D, Shapiro AM. Beta-score: an assessment of beta-cell function after islet transplantation. Diabetes Care 2005;28:343–7.

[15] Tekin Z, Garfinkel MR, Chon WJ, Schenck L, Golab K, Savari O, et al. Outcomes of pancreatic islet allotransplantation using the Edmonton Protocol at the University of Chicago. Transplant Direct 2016;2:e105.