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Defining Outcomes for β-Cell Replacement Therapy in the Treatment of Diabetes: a Consensus Report on the Igls Criteria from the IPITA/EPITA Opinion Leaders Workshop

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Abbreviations:

AP	Artificial pancreas (closed loop automated insulin delivery)
CFRD	Cystic Fibrosis Related Diabetes
CGM	Continuous glucose monitoring
CV	Coefficient of variation (= SD/mean)
EPITA	European Pancreas & Islet Transplant Association
HbA_{1c}	Glycated hemoglobin
IPITA	International Pancreas & Islet Transplant Association
JDRF	Juvenile Diabetes Research Foundation
MMTT	Mixed-meal tolerance test
OGTT	Oral glucose tolerance test
PRO	Patient-reported outcome
SD	Standard deviation
SMBG	Self-monitoring blood glucose
T1D	Type 1 Diabetes
T2D	Type 2 Diabetes

Abstract: β-cell replacement therapy, available currently as pancreas or islet transplantation, has developed without a clear definition of graft functional and clinical outcomes. The International Pancreas & Islet Transplant Association (IPITA) and European Pancreas & Islet Transplantation

Association (EPITA) held a workshop to develop consensus for an IPITA/EPITA Statement on the definition of function and failure of current and future forms of β-cell replacement therapy. There was consensus that β-cell replacement therapy could be considered as a treatment for β-cell failure, regardless of etiology and without requiring undetectable C-peptide, accompanied by glycemic instability with either problematic hypoglycemia or hyperglycemia. Glycemic control should be assessed at a minimum by glycated hemoglobin (HbA_{1c}) and the occurrence of severe hypoglycemia. Optimal β-cell graft function is defined by near-normal glycemic control (HbA_{1c} ≤6.5% [48 mmol/mol]) without severe hypoglycemia or requirement for insulin or other antihyperglycemic therapy, and with an increase over pre-transplant measurement of C-peptide. Good β-cell graft function requires HbA_{1c} <7.0% (53 mmol/mol) without severe hypoglycemia and with a significant (>50%) reduction in insulin requirements and restoration of clinically significant C-peptide production. Marginal β-cell graft function is defined by failure to achieve HbA_{1c} <7.0% (53 mmol/mol), the occurrence of any severe hypoglycemia, or less than 50% reduction in insulin requirements when there is restoration of clinically significant C-peptide production documented by improvement in hypoglycemia awareness/severity, or glycemic variability/lability. A failed β-cell graft is defined by the absence of any evidence for clinically significant C-peptide production. Optimal and good function are considered successful clinical outcomes.

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Pancreas and islet transplantation are established approaches for providing β-cell replacement therapy in the treatment of diabetes, and stem-cell derived and xenogeneic sources of islet cell tissue for transplantation have entered early-phase clinical trials. Understanding the therapeutic effectiveness of existing and future forms of β-cell replacement therapy is currently limited by the lack of a clear definition of graft functional and clinical outcomes. Moreover, glycemic control metrics have been poorly aligned with the field of artificial pancreas (AP) development. This limitation was identified as a significant barrier to progress in the field of pancreas and islet transplantation at the IPITA-TTS Opinion Leaders Meeting on the Future of β-Cell Replacement.[1,2] As AP systems become available that promise to provide improved glycemic control, similar metrics for assessing glycemic control are needed to compare effectiveness across β-cell replacement and AP approaches. The current lack of clear definitions for clinical

success or failure of available β-cell replacement therapies and glycemic metrics has impacted acceptance from the endocrinology community that has turned attention away from cellular treatment with potential to cure diabetes in hopes that a technologic solution may provide acceptable glycemic control for most patients. Only with comparable methods of assessment for the various approaches to achieving glycemic control available now and in the future can we identify those patients most likely to derive benefit from each type of therapy.

In order to address the lack of standardized outcome definitions for β-cell replacement therapy, the International Pancreas & Islet Transplant Association (IPITA) joined with the European Pancreas & Islet Transplant Association (EPITA) for a two-day workshop on "Defining Outcomes for β-Cell Replacement Therapy in the Treatment of Diabetes" in January 2017 in Igls, Austria. The workshop objectives were to: develop consensus for an IPITA/EPITA Statement on the definition of function and failure of current and future forms of β-cell replacement therapies; review the metabolic and immunologic outcome measures used to select patients and assess the efficacy of β-cell replacement therapies and guide therapeutic decisions; ensure consistency of definitions for glycemic control metrics with the field of artificial pancreas device development; and build a network of collaborators to foster scientific synergy in the clinical investigation of various β-cell replacement and artificial insulin delivery approaches to diabetes.

In order to review relevant information required to formulate a consensus definition for functional and clinical outcomes for β-cell replacement therapy, individual sessions were designed with specified objectives (Table 1). Historically, success in pancreas transplantation has been defined by independence from exogenous insulin, without consideration of the resultant degree of glycemic control, while in islet transplantation success has been defined by near-normal glycemic control determined by glycated hemoglobin (HbA_{1c}) in the absence of severe hypoglycemia. Recently, JDRF International (formerly known as the Juvenile Diabetes Research Foundation) led an initiative to identify and define clinically meaningful outcomes for patients with type 1 diabetes (T1D) beyond HbA_{1c}, prioritizing standardization of outcomes such as hypoglycemia, hyperglycemia, time in range (based on continuous glucose monitoring [CGM]), and diabetic ketoacidosis. This T1D Outcomes Program also evaluated patient reported outcomes (PROs) but existing evidence were not able to support the selection of any specific PRO for the assessment of T1D-related care or research.[3] The T1D research community is also

emphasizing the need to assess benefit beyond reduction in HbA_{1c}, arguing that even an increase in HbA_{1c} may be acceptable with an AP system if previously frequent hypoglycemia was improved.[4] With the International Hypoglycemia Study Group providing further consensus on definitions of hypoglycemia for clinical trials,[5] the evaluation of hypoglycemia in addition to some average metric of glycemic control such as HbA_{1c} will be necessary for the selection of patients for and assessment of all forms of β-cell replacement and AP therapies, as has already been established for islet transplantation.[6] Moreover, consistent outcomes definitions are needed for quality assurance in the performance assessment of programs offering various forms of β-cell replacement and AP therapies.

Indications for and Approaches to β-cell Replacement Therapy

The principal indications for β-cell replacement therapy have been to treat insulin-dependent patients (T1D and insulin-requiring type 2 diabetes [T2D]) with end-stage renal disease or experiencing problematic hypoglycemia.[7] Success following a pancreas or islet transplant has been judged in part by the elimination of insulin requirements; however, discontinuation of insulin should not be at the expense of sub-optimal glycemic control. A reasonable expectation for insulin-independence is the maintenance of non-diabetic levels of glycemic control (HbA1c ≤6.5% [48 mmol/mol]) off exogenous insulin or other antihyperglycemic therapy.[8] Importantly, use of insulin or other antihyperglycemic therapy following pancreas or islet transplantation is not synonymous with graft loss or failure, as patients may require low doses of exogenous insulin or other glucose lowering agents to maintain glycemic control in the non-diabetic range, which is only possible to achieve when a portion of the insulin requirement is provided endogenously from a functioning graft.

Such "partial" function of a β-cell replacement therapy has been viewed as successful when particular challenges in glycemic control, such as the occurrence of severe hypoglycemia, are eliminated following restoration of endogenous insulin secretion. Indeed, patients with problematic hypoglycemia, defined by two or more episodes per year of severe hypoglycemia or as one episode in the context of impaired awareness of hypoglycemia, extreme glycemic lability, or major fear and maladaptive behavior, should be considered for either pancreas or islet transplantation.[7] Other patients to consider are those with problematic hyperglycemia, defined by the presence of recurrent episodes of diabetic ketoacidosis or severe, rapidly progressing

secondary complications of diabetes. All patients should have completed a structured education program on basal-bolus insulin delivery with flexible dosing of modern insulin analogs using pump or multi-dose injection delivery based on frequent self-monitoring of blood glucose (SMBG) with or without continuous glucose monitoring (CGM).

A unifying concept is the consideration of β-cell replacement therapy as treatment for β-cell failure, regardless of etiology, when β-cell failure is associated with glycemic instability and either problematic hypoglycemia or hyperglycemia despite availability of and adherence to optimized medical care. This allows consideration of candidates beyond T1D to include some with advanced insulinopenic T2D, or any cause of insulin-deficient diabetes such as cystic fibrosis-related diabetes and other pancreatogenic forms of diabetes (e.g. chronic pancreatitis or following pancreatectomy). While it is expected that C-peptide levels in such individuals would be low, the importance of assessing C-peptide levels (as well as insulin requirements) is to identify elevated levels consistent with insulin resistance that might impart stress on a β-cell graft and compromise the potential for benefit from replacement therapy. Undetectable levels of C-peptide, while making it easier to attribute post-transplant C-peptide to graft function, should not be required. Thus, levels of C-peptide should be measured prior to transplantation in order to determine post-transplant graft function.

Outcome Measures of Glucose Homeostasis

Average glycemic control, particularly over the long-term, remains best assessed by measurement of HbA_{1c}. However, for shorter term assessment of average glycemia, mean glucose can be assessed from frequent SMBG (most valid with 5 times daily monitoring)[9] or CGM. Average blood or CGM glucose can be used to estimate the HbA_{1c} under situations such as marked anemia or use of dapsone[10] when the HbA_{1c} is not accurate. While there is inter-individual variability in the mean glucose-HbA_{1c} relationship, the relationship within an individual is very reproducible and most influenced by the prior month of glycemia.[11] Consistency of average glucose measures depends, however, on the duration of observation and becomes most reliable with 14 or more days. The frequency and duration of SMBG and CGM are also important for measures of glycemic variability, which are readily assessed from the SD

of glucose measurements or glucose CV (=SD/mean). The glucose SD has been validated against clinical assessment of glycemic lability using only 48 hours of CGM data.[12] Glycemic lability incorporates the temporal aspect to glycemic variability and may also be assessed by the glycemic lability index (LI) using at least 4 times daily SMBG over a 4 week period.[13,14] LI has been validated against clinical assessment of glycemic lability,[13] and is highly reproducible over time.[14] Glucose time in range, available only from CGM and being promoted for shorter-term assessment of AP systems,[4] requires further study to understand and validate its use.

The most important measure of hypoglycemia is the occurrence of severe hypoglycemia, defined as an event associated with loss of consciousness or requiring third party assistance for recovery.[15] A recent history of experiencing severe hypoglycemia, impaired awareness of hypoglycemia, and marked glycemic lability are established risk factors for experiencing future severe hypoglycemia. Thus, problematic hypoglycemia has been defined as two or more episodes per year of severe hypoglycemia or as one episode associated with impaired awareness of hypoglycemia, extreme glycemic lability, or major fear and maladaptive behavior.[7] Impaired awareness of hypoglycemia is assessed by validated questionnaires concerning the glucose threshold at which symptom recognition occurs, with the Clarke survey assessing thresholds at both 50 and 60 mg/dl (2.8 and 3.3 mmol/l)[16] and the Gold survey assessing thresholds at an intermediate 54 mg/dl (3.0 mmol/l).[17] Both questionnaires provide a score up to 7 with a score of ≥4 indicating impaired awareness of hypoglycemia that is highly correlated, supporting either survey as an appropriate assessment tool even if not directly comparable. While more laborious to collect and requiring 4 weeks of prospective diary keeping together with SMBG records, the HYPO score also captures hypoglycemia severity by tabulating the frequency and associated symptoms of, and assistance required for treating a glucose level of <54 mg/dl (<3.0 mmol/l). The HYPO score can be used to identify those with problematic hypoglycemia,[13] and is reproducible.[14] More practically, the frequency of episodes or percent time with glucose <54 mg/dl (<3 mmol/l) can be assessed using either SMBG or CGM. The International Hypoglycemia Study Group defined a glucose level <54 mg/dl (<3 mmol/l) as sufficiently low to indicate serious, clinically important hypoglycemia that should be reported in clinical trials.[5]

The goal, then, for glycemic control outcomes of β-cell replacement therapies should be attainment of target levels of HbA_{1c} <7.0% (53 mmol/mol), and ideally near-normal HbA_{1c} ≤6.5% (48 mmol/mol), in the absence of severe hypoglycemia (Table 2). Additional goals may

be driven by the indication for treatment: impaired awareness of hypoglycemia (Clarke or Gold score ≥4) should be resolved (score <4), serious, clinically important hypoglycemia (glucose <54 mg/dl [<3 mmol/l]) should be lessened or eliminated; marked glycemic variability or lability should be improved. Where CGM data are available, time with serious hypoglycemia (glucose <54 mg/dl [<3 mmol/l]), time with any hypoglycemia (<70 mg/dl [<3.9 mmol/l]), time on-target (70 – 140 mg/dl [3.9 – 7.8 mmol/l]), time-in-range (70 – 180 mg/dl [3.9 – 10 mmol/l] or 54 – 180 mg/dl [3 – 10 mmol/l]), and time with any hyperglycemia (>180 mg/dl [>10 mmol/l]) should be considered and maybe useful for making comparisons to AP systems.[4] While safety considerations differ between β-cell replacement and AP system approaches, their detailed assessment is critical and qualitative assessment of patient satisfaction will need to be part of future treatment comparisons. In particular, the complicated patient groups so far treated with pancreas and islet transplantation, those with end-stage renal disease or experiencing problematic hypoglycemia, have been excluded from clinical trials of AP systems, and may not derive similar benefit with AP as trial participants with relatively uncomplicated diabetes. Future assessment of AP systems in patients with end-stage renal disease and those with problematic hypoglycemia is needed. Furthermore, use of PROs including health-related quality of life, diabetes distress, and fear of hypoglycemia requires further attention.[18-20]

Outcome Measures of β-cell Graft Function and Demand

Both insulin requirements and levels of stimulated C-peptide reflect the contribution of β-cell replacement therapy to the resultant state of glycemic control, but at the same time are dependent on the degree of glycemic control and underlying insulin sensitivity. With improvement in glycemic control, and consequently insulin sensitivity,[21] following β-cell replacement therapy, a reduction in insulin requirements can be attributed to restoration of endogenous insulin secretion from the β-cell graft. However, in the absence of meeting glycemic control targets, a measured reduction in insulin requirements cannot be attributed to the effectiveness of β-cell replacement therapy. Moreover, a patient withdrawn from insulin who is not meeting glycemic control targets as defined above should not be considered insulin-independent, since insulin therapy would be indicated to achieve appropriate glycemic control.

C-peptide levels, when undetectable prior to treatment, can be used to assess function of a β-cell graft, but depend on the metabolic demand for secretion (fasted or stimulated, underlying

insulin sensitivity, and glucose level) and renal clearance. With increasing sensitivity of assays for detection of C-peptide, low levels of questionable clinical significance are often detected (e.g. <0.3 ng/ml [<0.1 nmol/l] fasting or <0.6 ng/ml [<0.2 nmol/l] post-prandial) despite clinical β-cell failure,[22] and may be even higher in the presence of uremia or sub-total β-cell loss (e.g. with cystic fibrosis-related diabetes and advanced insulinopenic T2D). Nevertheless, pre-transplant testing of C-peptide is critical to inform post-transplant monitoring, and should be performed fasting together with a concomitant glucose level with or without stimulated measures. Testing of C-peptide should be done the same way before as after transplant.

β-cell replacement therapy aims to restore non-diabetic fasting and post-prandial glucose without hypoglycemia. Oral glucose tolerance can be assessed by a standardized liquid nutrient meal containing a reasonable amount of carbohydrate (~50 grams) in place of the standard 75 gram oral glucose tolerance test (OGTT) used for diagnosis of diabetes. The 90-minute glucose during the standard mixed-meal tolerance test (MMTT) is highly correlated with the 120-minute glucose during the OGTT.[23] The post-transplant ratio of fasting C-peptide-to-glucose is predictive of the 90-minute glucose,[24] and so may allow for more frequent assessment of β-cell graft function while the MMTT may be most useful to resolve uncertainty regarding the interpretation of more routine clinical assessment.

The β-score is a composite measure of β-cell graft function that incorporates the HbA_{1c}, insulin requirement, fasting glucose, and C-peptide, and so may be calculated during routine clinical assessment, although C-peptide assessment may require a stimulation test.[25] More recently, the β2-score models the same variables but requires only the fasting C-peptide and provides a continuous rather than categorical metric.[26] The β-score was initially validated against the 90-minute glucose derived from the MMTT and has also been shown to relate to CGM metrics of mean glucose, glucose variability, time spent with serious, clinically important hypoglycemia (<54 mg/dl [3.0 mmol/l]), and time spent with hyperglycemia (>180 mg/dl [10 mmol/l]).[27] While helpful for longitudinal monitoring, the β-score remains limited by its summative derivation and absence of including a direct measure of hypoglycemia. The β2-score may have potential utility as a continuous variable rather than the categorical quantification provided by the β-score.

The goal, then, for functional outcomes of β-cell replacement therapies should be at a minimum to achieve a 50% reduction in insulin requirements (and which should be <0.5 units

per kg body weight per day), assuming adequate glycemic control (HbA_{1c} <7.0% [53 mmol/mol]), that is associated with an increase from pre-transplant measures of C-peptide (and which should be at least >0.5 ng/ml [>0.17 nmol/l]) interpreted with a concomitant glucose level. More accurate assessment of functional β-cell mass requires determination of glucose-potentiation of insulin or C-peptide release in response to a non-glucose insulin secretagogue such as arginine or glucagon;[22,28,29] however, this gold-standard testing of β-cell secretory capacity is not widely available.

Outcome Measures of Immunologic Mechanisms

While the success of β-cell replacement therapy ultimately depends on the prevention of alloimmune rejection and autoimmune recurrence, and which themselves depend on the source of tissue for transplantation and whether the initial cause of β-cell failure was type 1 (autoimmune) diabetes, the assessment of immune markers was not felt directly relevant to the definition of outcomes, but rather to the understanding of unsuccessful outcomes or declining functional status.

CONCLUSION

Defining Successful Outcomes

There was consensus that categorizing β-cell graft function would not be synonymous with defining the clinical success of a β-cell replacement therapy. A β-cell graft that provides some function but without clinical benefit relative to the indication for treatment should be considered a failure. On the other hand, a marginal β-cell graft associated with clear evidence of improvement in hypoglycemia or glycemic variability/lability even in the absence of achieving target glycemic control may be clinically important, but such an outcome would not be considered a success in terms of function since the overall treatment goals were not accomplished. This is an important distinction from a functionally failed β-cell graft where in the absence of any evidence for clinically significant C-peptide production consideration should be made to abandoning further monitoring and support of the failed graft. In particular, continuation of immunosuppression may no longer be indicated unless to support another allograft (e.g. a transplanted kidney) or to prevent possible sensitization to HLA antigens expressed by the β-cell graft in the case that another transplant is being considered. Thus, we

sought to define the functional status and clinical success of a β-cell graft separately, but using the same components of assessment: the HbA_{1c}, severe hypoglycemic events, insulin requirements, and C-peptide. We did not define a duration required for correction of HbA_{1c}, protection from hypoglycemia, restoration of C-peptide, or insulin-independence as these measures are fluid, and should each be evaluated together at any time of post-transplant graft functional assessment. Any reported change in glycemic control noted by SMBG and/or CGM should prompt such an assessment in order to identify a functionally stressed or declining graft.

We propose that functional and clinical outcomes can be assigned using a 4 tiered system as outlined in Table 3. Optimal β-cell graft function is defined by the presence of near-normal glycemic control assessed by non-diabetic HbA_{1c} ≤6.5% (48 mmol/mol), the absence of any severe hypoglycemia, the absence of any requirement for exogenous insulin or other antihyperglycemic therapy, and documentation of an increase over pre-transplant measurement of C-peptide. Good β-cell graft function is defined by the presence of on-target glycemic control assessed by an HbA_{1c} <7.0% (53 mmol/mol), the absence of any severe hypoglycemia, a reduction by more than 50% from baseline in insulin requirements or the use of non-insulin antihyperglycemic agents, and documentation of an increase over pre-transplant measurement of C-peptide. Both optimal and good functional outcomes are considered successful clinical outcomes. Marginal β-cell graft function is defined by the failure to achieve an HbA_{1c} <7.0% (53 mmol/mol), the occurrence of any severe hypoglycemia, or less than 50% reduction in insulin requirements when there is documentation of an increase over pre-transplant measurement of C-peptide. If documented impairment in hypoglycemia awareness, frequent occurrence or exposure to SH, or marked glycemic variability/lability is convincingly improved, then it may be appropriate to consider that the β-cell graft is clinically impactful. In the absence of any evidence for a clinical impact, reassessment of the C-peptide status is warranted as clinically insignificant levels, even if quantifiably higher than before transplant, should be considered β-cell graft failure. Neither a marginal β-cell graft nor a failed β-cell graft is considered a clinically successful. Finally, the ultimate success for a β-cell replacement therapy in any individual patient requires the functional clinical benefits to outweigh any potential harm from the transplantation procedure or adverse effects of any required immunosuppression.

In conclusion, to be deemed successful β-cell replacement therapies should require the HbA_{1c} <7.0% (53 mmol/mol) in the absence of severe hypoglycemia associated with a

significant >50% reduction in insulin requirements and restoration of clinically significant C-peptide production (>0.5 ng/ml or >0.17 nmol/l). Baseline assessment of hypoglycemia awareness, hypoglycemia severity, and glycemic variability/lability is helpful for monitoring whether a marginally functioning graft is continuing to provide any clinical impact. This proposed classification of function and clinical outcomes for β-cell replacement therapies is a work in progress and should be validated and further refined based on results from implementation in future prospective investigation.

APPENDIX

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TABLE 1.

Workshop session objectives

Indications for and Approaches to β-cell Replacement Therapy
Patient candidates and available forms of β-cell replacement vary. The goal of this session was to define those patient characteristics that directly influence the type of β-cell graft and measures of glycemic control and graft function, and so lay the framework for how definitions of successful outcomes may be tailored by indication.
Outcome Measures of Glucose Homeostasis
Regulation of glucose homeostasis involves the maintenance and return of glucose excursions to a non-diabetic range of glycemia. Various measures of glycemic control capture average glycemia, glycemic variability, and exposure to hyper- and hypoglycemia, as well as hypoglycemia awareness and severity. The goal of this session was to define successful outcomes for glycemic control, and align definitions with those used in the field of artificial insulin delivery/artificial pancreas development.
Outcome Measures of β-cell Graft Function and Demand
Measures of β-cell graft function may vary by the stimulus for secretion, differences in metabolic clearance, demands for secretion imposed by differences in insulin sensitivity or the use of insulin, as well as any possible residual native β-cell function. The goal of this session was to define a meaningful reduction in insulin requirements attributable to β-cell graft function, necessary confirmatory testing, relationship to standardized measures of glucose tolerance, and differences between type 1 and type 2 diabetic recipients.
Outcome Measures of Immunologic Mechanisms
Distinguishing immunologic from metabolic mechanisms for β-cell graft dysfunction and/or failure is paramount to understanding the mechanisms underlying current graft status and implications of functional β-cell graft monitoring. The goal of this session was to define useful assays of allo- and autoimmune reactivity and when they should be employed to complement the metabolic evaluation of β-cell replacement therapies.
Defining Successful Outcomes
Clear definitions for success or failure of available β-cell replacement therapies require incorporation

of both metrics for glycemic control and β-cell graft function. The goal of this session was to establish a practical consensus definition for β-cell graft functional and efficacy outcomes for β-cell replacement therapies.

TABLE 2.

Indications and goals for beta cell replacement therapies expressed in relation to various glycemic control measures

Metric	Indication[a]	Goal	Ideal
HbA1c, % (mmol/mol)[b]	>7.5-8.0 (58-64)	<7.0 (53)	≤6.5 (48)
SH, events per yr	One or more	None	None
Clarke or Gold score[c]	≥4	<4	0
Time <54 mg/dl (3.0 mmol/l), %[d]	≥5	<1	0

Glucose SD, mg/dl (mmol/l)[e]	≥40 (2.2)	<40 (2.2)	NE
Glucose CV, %[f]	≥30	<30	NE
Time <70 mg/dl (3.9 mmol/l), %[g]	NE	<5	<5
Time 70 – 180 mg/dl (3.9 – 10 mmol/l), %[h]	NE	>70	>90
Time >180 mg/dl (10 mmol/l), %[i]	NE	<20-30	<5

HbA_{1c}, glycated hemoglobin; SH, severe hypoglycemia; SD, standard deviation; CV, coefficient of variation = mean/SD; NE, not established.

[a]Typically more than one measure is used to define indications for β-cell replacement therapy and establish a baseline prior to treatment.

[b]Mean glucose should be used to provide an estimate of the HbA_{1c} in the setting of marked anemia or administration of dapsone.[10]

[c]Used to assess impaired awareness of hypoglycemia.[14,15]

[d]Used to assess exposure to serious, clinically important hypoglycemia,[4] which can also be defined by frequency of episodes or using the HYPO score.[11]

[e]Used to assess glycemic variability,[10] which can also be assessed as glycemic lability using the lability index or LI.[11]

[f]Used for comparison to artificial pancreas systems.[3]

TABLE 3.

Igls definition of functional and clinical outcomes for β-cell replacement therapy

β-cell graft functional status	HbA_{1c}, % (mmol/mol)[a]	Severe hypoglycemia, events per yr	Insulin requirements, $U \cdot kg^{-1} \cdot d^{-1}$	C-peptide	Treatment success
Optimal	≤6.5 (48)	None	None	>Baseline[b]	Yes
Good	<7.0 (53)	None	<50% baseline[c]	>Baseline[b]	Yes
Marginal	Baseline	<Baseline[d]	≥50% baseline	>Baseline[b]	No[e]
Failure	Baseline	Baseline[f]	Baseline	Baseline[g]	No

HbA_{1c}, glycated hemoglobin. Baseline, pre-transplant assessment.

[a]Mean glucose should be used to provide an estimate of the HbA_{1c} in the setting of marked anemia or administration of dapsone.[10]

[b]Should also be >0.5 ng/ml (>0.17 nmol/l) fasting or stimulated.

[c]Should also be <0.5 $U \cdot kg^{-1} \cdot d^{-1}$; might include the use of non-insulin antihyperglycemic agents.

[d]Should severe hypoglycemia occur following treatment, then continued benefit may require assessment of hypoglycemia awareness, exposure to serious hypoglycemia (<54 mg/dl [3.0 mmol/l]), and/or glycemic variability/lability with demonstration of improvement from baseline.

[e]Clinically, benefits of maintaining and monitoring β-cell graft function may outweigh risks of maintaining immunosuppression.

[f]If severe hypoglycemia was not present before β-cell replacement therapy, then a return to baseline measures of glycemic control used as the indication for treatment (Table 2) may be consistent with β-cell graft failure.

[g]May not be reliable in uremic patients and/or in those patients with evidence of C-peptide production prior to β-cell replacement therapy.

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