# Defining Outcomes for β-Cell Replacement Therapy

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## Contents



## Abbreviations

| | |
|---|---|
| CGM | Continuous glucose monitoring |
| CIT | Clinical Islet Transplantation Consortium |
| CITR | Collaborative Islet Transplant Registry |
| CONGA4 | Continuous overlapping net glycemic action at 4 h |
| CSII | Continuous subcutaneous insulin infusion |
| CV | Coefficient of variation; GVP, glycemic variable percentage |
| $HbA_{1c}$ | Glycated hemoglobin |
| IPTR | International Pancreas Transplant Registry |
| LI | Lability index |
| MMTT | Mixed-meal tolerance test |
| SD | Standard deviation |
| SMBG | Self-monitoring blood glucose |
| TAR | Time-above-range |
| TBR | Time-below-range |
| TIR | Time-in-range |

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## Introduction

β-Cell replacement by means of whole pancreas [1] or isolated islet transplantation [2] provide complimentary approaches to the treatment of diabetes caused by severe β-cell deficiency. While most often the recipient has established type 1 diabetes with undetectable or very low levels of C-peptide [3], other candidates may have severe insulin deficient type 2 diabetes or pancreatogenic forms of diabetes that are also characterized by markedly impaired insulin secretion. Standard treatment involves intensive insulin therapy managed to achieve glycemic control targets associated with the prevention or delayed progression of micro- and macrovascular complications, while at the same time striving to avoid hypoglycemia and the occurrence of life-threatening severe hypoglycemia events. Despite increasing use of continuous subcutaneous insulin infusion (CSII or insulin pump) and continuous glucose monitoring (CGM or sensor), current specialized practice for type 1 diabetes in the U.S. achieves the American Diabetes Association recommended target of HbA1c <7.0% in <20% of adults older than 25 years, where the median $HbA_{1c}$ is >7.5% across the adult life-span, and even worse glycemic control is experienced by the majority of affected children and young adults [4]. Moreover, ~7% of adults with type 1 diabetes older than 25 years in the U.S. report experiencing a severe hypoglycemia event resulting in seizure or loss-of-consciousness in the prior 3 months [4] (see



R. W.G. Gruessner, A. C. Gruessner (eds.), *Transplantation of the Pancreas*, https://doi.org/10.1007/978-3-031-20999-4_65

Chap. 4). Thus, the primary goal for β-cell replacement therapy is to provide on-target glycemic control in the absence of severe hypoglycemia events, and secondarily to achieve this without dependence on exogenous insulin therapy (or with a clinically significant reduction in insulin requirements) with an ultimately improved quality of life.

Sensor communicating insulin pumps with automated insulin delivery are now available as the first step in realization of artificial pancreas technology capable of providing closed-loop control of glycemia and promise to provide improved glycemic control with less risk for hypoglycemia [5]. With increased availability of CGM and its integrated use with insulin pumps, assessment of glycemic control now prioritizes time spent in ranges of near-normal glycemia and the avoidance of time spent with hypoglycemia [6, 7] as well as measurement of $HbA_{1c}$ and capture of severe hypoglycemia events. In addition, novel forms of β-cell replacement therapy that include stem cell-derived and xenogeneic sources of islet tissue for transplantation have entered early phase clinical trials. In order to assess outcomes of current (whole pancreas and isolated islet) and future forms of β-cell replacement therapy, comparable metrics of glycemic control and graft function are required, and where possible should align with outcome metrics established in the field of artificial pancreas development.

## Outcome Measures of Glucose Homeostasis

Regulation of glucose homeostasis involves the maintenance and return of glucose excursions to a nondiabetic range of glycemia. Various measures of glycemic control capture average glycemia, glucose variability, and exposure to hyper- and hypoglycemia, as well as hypoglycemia awareness and severity (Table 65.1). Average glycemia is best assessed over the long term from measurement of the $HbA_{1c}$ that is dependent on the red blood cell life span, and so is affected by up to 3 months of prior glycemic exposure. Certain conditions such as marked anemia or use of dapsone [20] affect the accuracy of $HbA_{1c}$ as a measure of average glucose, and at times shorter term assessment of average glycemia may be desired. Under these circumstances, average sensor glucose can be used to provide an estimated $HbA_{1c}$, termed the glucose management indicator [10], and is most reliable when derived from 10 to 14 days of CGM data [21]. The accompanying sensor glucose standard deviation (SD) provides a measure of glucose variability that has been validated against clinic assessment of glycemic lability [16]. The glucose SD may be divided by the glucose mean to provide a coefficient of variation (CV) that is associated with both assessment of hypoglycemia severity [14] and predicted risk for hypoglycemia [17].

**Table 65.1** Indications and goals for measures of glucose homeostasis with β-cell replacement therapy (adapted from refs. 8 and 9)

| Metric | Indication[a] | Goal | Ideal |
|---|---|---|---|
| HbA1c, %[b] | >7.5–8.0 | <7.0 | ≤6.5 |
| Severe hypoglycemia, events per year | One or more | None | None |
| Clarke or Gold score[c] | ≥4 | <4 | 0 |
| Time <54 mg/dL (3.0 mmol/L), %[d] | ≥4 | <1 | 0 |
| Glucose SD, mg/dL (mmol/L)[e] | ≥40 (2.2) | <40 (2.2) | <30 (1.7) |
| Glucose CV, %[e] | ≥33 | <33 | <30 |
| Time <70 mg/dL (3.9 mmol/L), % | ≥10 | <4 | <4 |
| Time 70–180 mg/dL (3.9–10 mmol/L), % | <50 | >70 | >80 |
| Time >180 mg/dL (10 mmol/L), % | >50 | <25 | <15 |

*$HbA_{1c}$* glycated hemoglobin, *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] Glucose management indicator (GMI) derived from 10 to 14 days of continuously glucose monitoring may be considered as a surrogate measure of average glucose (ref. 10)

[c] Used to assess impaired awareness of hypoglycemia (refs. 11 and 12)

[d] Used to assess exposure to serious, clinically important hypoglycemia (ref. 13), which can also be defined by frequency of episodes or using the HYPO score (refs. 14 and 15)

[e] Used to assess glucose variability (refs. 16 and 17), which can also be assessed as glycemic lability using the lability index (LI), continuous overlapping net glycemic action at 4 h (CONGA4), and glycemic variability percentage (GVP) (refs. 14, 15, 18, and 19)

Temporal glucose variability accounts for time between changes in glucose and can be assessed from four times daily self-monitoring blood glucose (SMBG) over a 4-week period by the glycemic lability index (LI) that has been validated against clinic assessment of glycemic lability [15] and is highly reproducible over time [14]. CGM-based metrics of glycemic lability, including LI, continuous overlapping net glycemic action at 4 h (CONGA4), and glycemic variability percentage (GVP), are under development and require further validation [16, 18, 19]. With CGM now replacing SMBG in clinical practice [22], sensor glucose data may soon replace $HbA_{1c}$ with provision of both validated assessment of average glycemia (GMI) and glucose variability (SD, CV).

CGM data can also be used to assess glycemic control by time spent in the nondiabetic range of glycemia. The target range for sensor glucose is 70–180 mg/dL (3.9–10 mmol/L) with above range defined as >180–250 mg/dL (10–13.9 mmol/L; level 1 hyperglycemia), and >250 mg/dL (>13.9 mmol/L; level 2 hyperglycemia), and below range <70–54 mg/dL (3.9–3.0 mmol/L; level 1 hypoglycemia), and <54 mg/dL (3 mmol/L; level 2 hypoglycemia) [7]. Targets for time-in-range (TIR) have been validated against $HbA_{1c}$, whereby TIR >50% relates to $HbA_{1c}$ <8.0%, TIR >60% to $HbA_{1c}$ <7.5%, TIR >70% to $HbA_{1c}$ <7.0%, and TIR >80% to $HbA_{1c}$ ≤6.5% [23]. What is most important for assessing outcomes of β-cell replacement therapy is that the assessment

of TIR not only provides another predictor of $HbA_{1c}$, but also allows for simultaneous assessment of hypoglycemia from the time-below-range (TBR). Because exposure to biochemical hypoglycemia is related to impaired awareness of hypoglycemia, hypoglycemia severity, and risk for experiencing future severe hypoglycemia [14, 24], CGM allows for early assessment of clinically significant hypoglycemia avoidance. Moreover, evaluation of CGM metrics of average glycemia (GMI), glucose variability (SD, CV), and TIR percentages for β-cell replacement therapies allows for direct comparison of outcomes with artificial pancreas systems.

Hypoglycemia is best assessed over the long term from determination of the occurrence of severe hypoglycemia, defined as an event associated with loss of consciousness, seizure, or requiring third-party assistance for recovery [25]. As discussed above, measures of glucose variability, exposure to hypoglycemia, and impaired awareness of hypoglycemia are all related to the risk for experiencing severe hypoglycemia [26], whereas measures of average glycemia are not, with an episode of severe hypoglycemia resulting in seizure or loss-of-consciousness in the past 3 months reported by 11% of those with $HbA_{1c}$ <7.0%, 7% of those with $HbA_{1c}$ 7.0 to <9.0%, and 8% of those with $HbA_{1c}$ ≥9.0% [4]. This independence of average glycemia as measured by HbA1c and the occurrence of severe hypoglycemia events with current standard implementation of intensive insulin therapy allows for considering both measures concurrently in the assessment of long-term glycemic control. Because the experience of severe hypoglycemia is relatively infrequent, in the shorter term, measurement of glucose variability, exposure to hypoglycemia, and impaired awareness of hypoglycemia provide useful surrogates for predicting the expected risk for severe hypoglycemia.

Impaired awareness of hypoglycemia is assessed by determining the glucose threshold at which hypoglycemia symptom recognition occurs. Validated questionnaires include the Clarke survey that assesses glucose thresholds at both 50 and 60 mg/dL (2.8 and 3.3 mmol/L) [11] and the Gold survey that assesses a glucose threshold of 54 mg/dL (3.0 mmol/L) [12]; both questionnaires provide a score up to 7 with scores ≥4 indicating impaired awareness of hypoglycemia that are highly correlated with each other. The HYPO score can reproducibly assess hypoglycemia severity by tabulating the frequency, associated symptoms of, and assistance required for treating a glucose level <54 mg/dL (<3.0 mmol/L) over a 4-week period [14, 15]. Due to the burden of maintaining a prospective diary in order to calculate an HYPO score, more practically, the frequency of episodes or percent time with glucose <54 mg/dL (3.0 mmol/L) can be assessed using either SMBG or CGM, which is consistent with the International Hypoglycemia Study Group recommendations to consider a glucose level <54 mg/dL (3.0 mmol/L) as sufficiently low to indicate serious, clinically important hypoglycemia [13].

## Outcome Measures of β-Cell Graft Function and Demand

Insulin requirements and levels of C-peptide both reflect the contribution of β-cell replacement therapy to the maintenance of glucose homeostasis; however, neither can provide an independent assessment of β-cell graft function and both must be interpreted with consideration of long- and near-term assessment of glucose control. Success following a pancreas or islet transplant has been judged in part by the elimination of insulin requirements (see Chaps. 66 and 84). However, insulin dosing should not be reduced or eliminated at the expense of achieving optimal glycemic control, the primary objective for both artificial and cell-based treatment of diabetes. Furthermore, insulin requirements depend upon the prevailing insulin sensitivity, which, for example, is dramatically affected by high-dose glucocorticoids that may surround the induction of immunosuppression or treatment of possible rejection episodes. When undetectable or very low prior to treatment, the post-transplant level of C-peptide can indicate the function of a β-cell graft. However, C-peptide levels are also affected by insulin sensitivity that affects demand for insulin secretion, and are further influenced by prandial state, concomitant glucose, insulin use, and renal clearance. Therefore, while it may be necessary to demonstrate a reduction in insulin requirements and/or an increase in levels of C-peptide in order to attribute a potential improvement in glycemic control outcomes to β-cell replacement therapy, it is not sufficient to claim a reduction or elimination of insulin use represents "partial" or "full" function, respectively, of a β-cell graft, or that some level of C-peptide can indicate the graft is "working" without considering the relationship to concomitant measures of glucose homeostasis.

Insulin requirements in type 1 diabetes are typically ~0.5–0.6 units/kg/day, with requirements >0.8–1.0 units/kg/day generally associated with more pronounced insulin resistance, and requirements <0.2–0.3 units/kg/day unusual in the absence of clinically significant residual islet β-cell function or an extremely insulin sensitive individual. The International Pancreas Transplant Registry (IPTR) previously defined pancreas graft function or failure by the presence of insulin-independence or the requirement for insulin therapy, respectively (Chap. 66). Recently, this definition has been revised to insulin requirements <0.5 units/kg/day or ≥0.5 units/kg/day, respectively [27], which remains, however, limited as an outcome measure without indicating an acceptable concomitant measure of glycemic control. The

Collaborative Islet Transplant Registry (CITR) also considers insulin-independence as an outcome, and further requires reporting of measures of glucose homeostasis ($HbA_{1c}$, fasting glucose, severe hypoglycemia events) and C-peptide levels, with primary outcomes defined for insulin-independence, $HbA_{1c}$ ≤6.5% (48 mmol/mol), fasting glucose 60–140 mg/dL (3.33–7.77 mmol/L), absence of severe hypoglycemia events, and C-peptide ≥0.3 ng/mL (0.10 nmol/L) [28]. Similar metrics are being collected by CITR for a registry for patients undergoing total pancreatectomy with islet autotransplantation [29].

The threshold for C-peptide ≥0.3 ng/mL (0.10 nmol/L) indicating the presence of β-cell graft function is based on the detectability of many standard assays for C-peptide in use at the time outcomes for clinical islet transplantation were being developed [30]. Ryan and colleagues developed a categorical β-score as a composite measure of β-cell graft function that incorporates the insulin requirement, $HbA_{1c}$, fasting glucose, and C-peptide level, and validated it against a 90-min glucose threshold of 180 mg/dL (10 mmol/L) during a standard mixed-meal tolerance test (MMTT) [30]. The β-score has been further validated against measures 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]) derived from CGM [31]. Subsequently, a β2-score was developed by modeling to produce a continuous variable based on the insulin requirement, $HbA_{1c}$, fasting glucose, and fasting C-peptide level that obviates the requirement for a test to determine the stimulated C-peptide [32]. However, stimulation of C-peptide may not be necessary for assessment of β-cell graft function, since in islet transplantation, the post-transplant ratio of fasting C-peptide-to-glucose is predictive of the 90-min MMTT glucose [33], and modeling of the fasting C-peptide and glucose concentrations can predict the peak MMTT C-peptide level [34].

Stimulated C-peptide ≥0.3 ng/mL (0.10 nmol/L) is usually associated with fasting C-peptide ≥0.1 ng/mL (0.03 nmol/L) that is detectable by current high sensitivity assays (Fig. 65.1). In type 1 diabetes with residual β-cell function, C-peptide levels ≥0.1 ng/mL (0.03 nmol/L) are associated with modest beneficial effects on glycemic control and in particular less severe hypoglycemia and incidence of retinopathy [35, 36]. More robust risk reduction for experiencing severe hypoglycemia events as well as for the development and progression of microvascular complications is observed with stimulated C-peptide >0.5 ng/mL (0.17 nmol/L) as established by the Diabetes Control and Complications Trial (DCCT) [36, 37], which is usually associated with a fasting C-peptide of at least 0.2 ng/mL (0.07 nmol/L). Nevertheless, even higher levels of stimulated C-peptide >1.2 ng/mL (0.40 nmol/L) are necessary to evidence physiologic islet β- and α-cell responsiveness to hyperglycemia and hypoglycemia, respectively, that is associated with achieving glycemic control targets for TIR [38]. Importantly, the threshold for stimulated C-peptide >0.5 ng/mL (0.17 nmol/L) is also associated with improved glycemic control and avoidance of hypoglycemia following islet transplantation for type 1 diabetes, whereas establishment of a sufficient reserve capacity for insulin secretion capable of supporting insulin-independence is not observed until a stimulated C-peptide >3.0 ng/mL (1.00 nmol/L) [39], or fasting C-peptide ≥0.9 ng/mL (0.3 nmol/L) [30]. Because C-peptide is renally cleared, end-stage kidney disease can dramatically increase measures of peripheral C-peptide that does not reflect increased secretion.

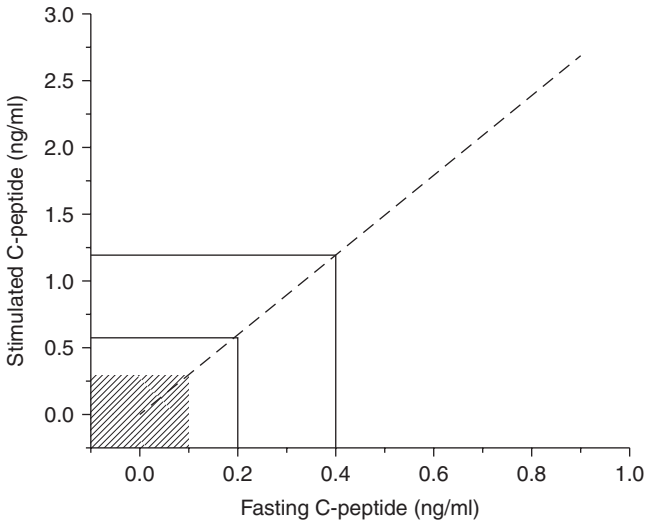


**Fig. 65.1** Relationship between fasting and stimulated measures of C-peptide derived from studies in individuals with type 1 diabetes and residual β-cell function (refs. 35–37, and 38) and following islet transplantation (refs. 30, 34, and 39). Modest benefit in glycemic control, in particular less hypoglycemia, may be observed above a stimulated C-peptide of 0.3 ng/mL that is better established above 0.6 ng/mL with physiologic islet β- and α-cell responses to glucose most evident above 1.2 ng/mL. While a reduction in insulin requirements may be observed in this higher range of stimulated C-peptide, insulin-independence is generally not observed until stimulated C-peptide is above 3.0 ng/mL. Simulated C-peptide is most often derived from 90 min or peak level achieved during a mixed-meal tolerance test standardized to the consumption of 6 mL/kg (up to 360 mL) Boost High Protein or equivalent nutritional beverage that contains ~50 g of carbohydrate. To convert C-peptide to nmol/L, divide by 3.021

Even higher levels of C-peptide may be required to maintain glucose homeostasis in the context of reduced insulin sensitivity, which is most easily assessed under fasting conditions with consideration of the concomitant glucose concentration. With impairment of insulin sensitivity, as may occur, for example, with high-dose glucocorticoid use or weight gain, insulin secretion increases to maintain normal levels of glucose as reflected by an increased C-peptide. In contrast, with impairment of β-cell graft function, as may occur, for example, with allo- or autoimmune recognition or

metabolic stress-induced cellular exhaustion, glucose levels increase without a corresponding increase in C-peptide. Finally, an increase in both fasting C-peptide and glucose may represent both an impairment of insulin sensitivity and impaired β-cell graft function with an inadequate increase of insulin secretion for the demand required to maintain glucose homeostasis. For insulin-independent individuals, a clinical measure of insulin sensitivity is most easily estimated from assessment of the fasting insulin and glucose concentrations, such as the homeostatic model assessment for insulin resistance (HOMA-IR) [40]. While fasting indices of insulin sensitivity based on measurement of insulin and glucose have been validated in chronic kidney disease [41], interpretation of HOMA-IR values in systemically drained pancreas transplant recipients should be made with caution given the presence of systemic hyperinsulinemia resulting from bypassed first-pass hepatic extraction.

More accurate assessment of the engrafted functional β-cell mass requires determination of the β-cell secretory capacity derived from glucose-potentiation of insulin or C-peptide release in response to a nonglucose insulin secretagogue, such as arginine [42, 43]. Dynamic assessment of insulin sensitivity modeled from a frequently sampled intravenous glucose tolerance or hyperinsulinemic euglycemic clamp test also provides more accurate assessment of the physiologic demand for insulin to promote glucose disposal [44, 45]. These gold-standard tests of β-cell graft function and demand are not widely available, and are generally only applied in prospective, mechanistic clinical investigation (see Chap. 51).

## Integrating Outcomes to Define β-Cell Replacement Success and Failure: The Igls Criteria

The International Pancreas and Islet Transplant Association and European Pancreas and Islet Transplantation Association held a workshop in January 2017 in Igls Austria to develop a consensus statement on the definition of function and failure of current and future forms of β-cell replacement therapy based on the achievement of goals for glycemic control and restoration of β-cell function (Table 65.2). In order to assess the goal for β-cell replacement therapy to provide on-target glycemic control in the absence of severe hypoglycemia events, successful outcomes should attain target levels of HbA1c <7.0%, and ideally near-normal HbA1c ≤6.5%, in the absence of severe hypoglycemia [47, 48]. Targeting near-normal glycemic control is important when hypoglycemia can be avoided, since even with $HbA_{1c}$ <7.0%, the residual risk for cardiovascular and all-cause mortality in patients with T1D remains more than twice that in nondiabetic individuals [49], and the lowest mortality rates are seen with $HbA_{1c}$ ≤6.5% [50]. In order to attribute the attainment of glycemic control targets to the β-cell graft, the goal for functional outcomes of β-cell replacement therapy should be to achieve a 50% reduction in insulin requirements, and ideally insulin-independence, that is associated with an increase from pretransplant measures of C-peptide [8, 9]. Because differences in insulin delivery modality and conditions of C-peptide measurement often exist between pre- and post-

**Table 65.2** Igls definition of functional and clinical outcomes for β-cell replacement therapy (adapted from refs. 8, 9, and 46

| β-Cell graft functional status | $HbA_{1c}$[a, b] | Severe hypoglycemia, events per year[b] | Insulin requirements[b] | C-peptide, ng/mL (nmol/L)[b, c] | Treatment success |
|---|---|---|---|---|---|
| Optimal | ≤6.5% | None | None[d] | >Baseline and >0.5 (0.17) | Yes |
| Good | <7.0% | None | <50% Baseline and <0.5 units/kg/day | >Baseline and >0.5 (0.17) | Yes |
| Marginal | Baseline or ≥7.0% | <Baseline[e] or ≥1 | ≥50% Baseline or ≥0.5 units/kg/day | >Baseline and ≥0.3 (0.10)[f] | No[g] |
| Failure | Baseline or ≥7.0% | Baseline[h] or ≥1 | Baseline or ≥0.5 units/kg/day | Baseline[i] or <0.3 (0.10)[f] | No |

$HbA_{1c}$, glycated hemoglobin. Baseline, pretransplant assessment

[a] Glucose management indicator (GMI) derived from 10 to 14 days of continuously glucose monitoring may be considered as a surrogate measure of mean glucose (ref. 10)

[b] Autologous islet transplant recipients are assessed based on threshold measures only since baseline reflects pre-pancreatectomy (ref. 46)

[c] C-peptide may be fasting or stimulated, with stimulated C-peptide values preferred for classifying a β-cell graft as failed

[d] Opitmal β-cell graft function should also not include the use of noninsulin antihyperglycemic therapy

[e] 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

[f] Modified from refs. 8 and 9 that required a stimulated C-peptide >0.5 ng/mL (0.17 nmol/L) to align with the Collaborative Islet Transplant Registry (CITR) definition for islet graft survival

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

[h] 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 65.1) may be consistent with β-cell graft failure

[i] May not be reliable in patients with end-stage kidney disease and/or in those patients with evidence of C-peptide production prior to β-cell replacement therapy

transplant, the goal for functional outcomes should also include insulin requirements <0.5 units/kg/day and C-peptide >0.5 ng/mL (0.17 nmol/L) [8, 9], targets consistent with clinically significant thresholds set by the IPTR and the DCCT, respectively. Use of these thresholds for insulin requirements and C-peptide also allows application of the Igls criteria for defining outcomes of β-cell replacement therapy to recipients of islet autografts following total pancreatectomy [46].

According to the Igls criteria [8, 9], optimal β-cell graft function is defined by near-normal glycemic control ($HbA_{1c}$ ≤6.5%) without severe hypoglycemia or requirement for insulin or other antihyperglycemic therapy, and with an increase over pretransplant measurement of C-peptide that is at least >0.5 ng/mL (0.17 nmol/L). Good β-cell graft function requires on-target glycemic control ($HbA_{1c}$ <7.0%) without severe hypoglycemia and with a significant (>50%) reduction in insulin requirements that are also <0.5 units/kg/day and restoration of clinically significant C-peptide production. Marginal β-cell graft function is defined by failure to achieve $HbA_{1c}$ <7.0%, the occurrence of any severe hypoglycemia, or less than 50% reduction in insulin requirements or dependence on ≥0.5 units/kg/day when there is restoration of clinically significant C-peptide production documented by improvement in hypoglycemia awareness/severity, or glycemic variability/lability. Treatment success is defined by the achievement of optimal and good functional outcomes. While a marginal functional outcome may be considered clinically meaningful to justify on-going support and monitoring of the β-cell graft, marginal β-cell graft function is not a treatment goal and so is not considered a treatment success. A failed β-cell graft is defined by the absence of any evidence for clinically significant C-peptide production.

## Continuous Glucose Monitoring Targets for β-Cell Replacement Therapy

Where CGM is available (Fig. 65.2), an analogous goal for β-cell replacement therapy is to provide on-target glycemic control while avoiding hypoglycemia that includes TIR >70%, and ideally >80%, with TBR <4%. In the international consensus on TIR targets [7], two situations were distinguished: for adults with type 1 or type 2 diabetes, TIR should be greater than 70%, TBR less than 4%, and TAR less than 25%. For older or high-risk patients, avoidance of hypoglycemia is prioritized, such that the goal is first aimed at limiting TBR to less than 1%, and decreasing the requirement of TIR to greater than 50% with TAR less than 50%. While such a

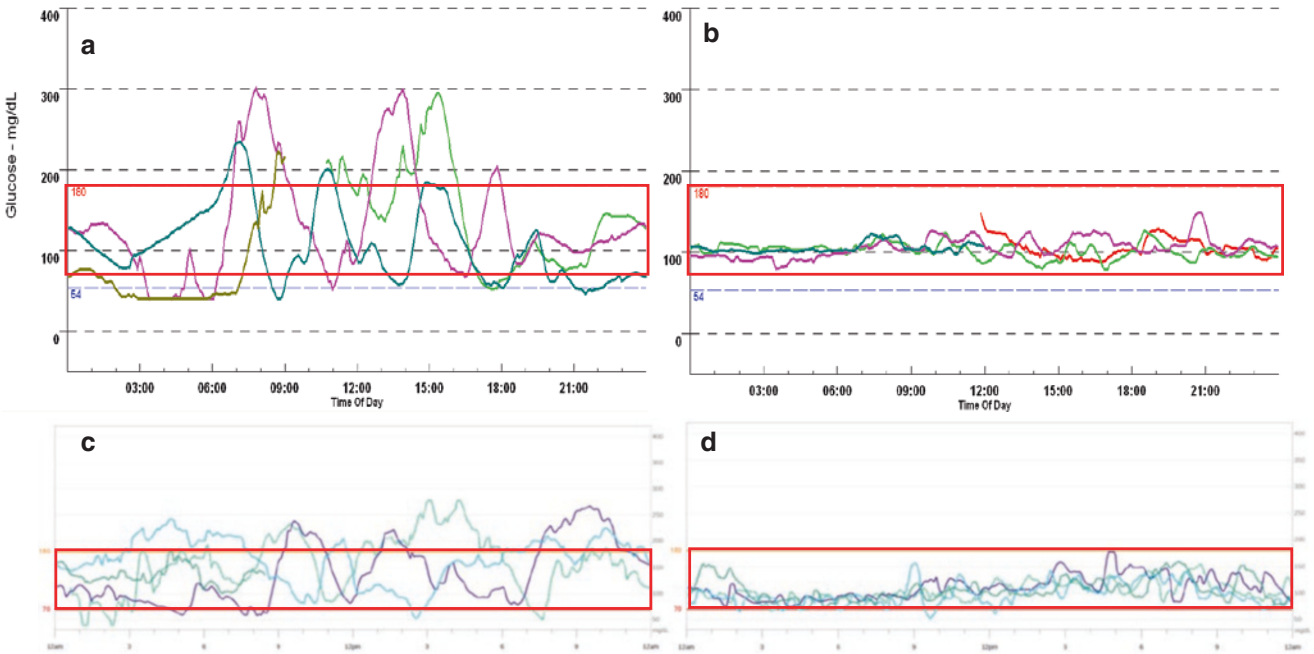


**Fig. 65.2** Daily overlay plots of continuous glucose monitoring data that provide an interstitial sensor glucose value every 5 min. (**a**, **b**) Sensor glucose data from a patient with type 1 diabetes and hypoglycemia unawareness before (**a**) and 12 months after (**b**) undergoing isolated islet transplantation (data are from ref. 51). (**c**, **d**) Sensor glucose data from a patient with type 1 diabetes and hypoglycemia unawareness before (**c**) and 12 months after (**d**) undergoing whole pancreas transplantation (data are from author's clinical practice). The red boxes give the target range of 70–180 mg/dL (3.9–10 mmol/L). Both patients exhibit limited time-in-range, marked glycemic lability, and significant time-below-range, including with clinically important, serious hypoglycemia <54 mg/dL (3.0 mmol/L) before transplantation (**a**, **c**), and almost all time spent in the target range with limited glucose variability and no hypoglycemia after receiving β-cell replacement therapy (**c**, **d**)

compromise in glycemic control is appropriate when hypoglycemia is a significant risk, the objective of β-cell replacement therapy to eliminate hypoglycemia should allow for the achievement of TIR >70–80% even for high-risk individuals such as those with hypoglycemia unawareness or having already undergone kidney transplantation. Thus, with β-cell replacement therapy spending <4% TBR is acceptable even for high-risk patients as long as time spent with clinically important, serious hypoglycemia <54 mg/dL (3.0 mmol/L) is negligible (<1%). Healthy, nondiabetic individuals may also spend <4% TBR as measured by CGM [52].

In addition to assessment of time spent with serious, clinically significant hypoglycemia <54 mg/dL (3.0 mmol/L) [13], CGM assessment of glucose variability is also associated with risk for experiencing severe hypoglycemia [14]. Glucose variability has gained increasing importance as both a therapeutic target and an outcome measure in diabetes clinical trials [53], including of islet transplantation [54], where improvement in glucose variability may be related to improvements in measures of neuropathy [55]. In the phase 3 Clinical Islet Transplantation (CIT) Consortium CIT07 trial of islet alone transplantation in individuals with type 1 diabetes complicated by hypoglycemia unawareness, significant improvement in hypoglycemia awareness (measured by Clarke score) and reductions in hypoglycemia severity (measured by HYPO score) and in the number of daily episodes of serious, clinically important hypoglycemia assessed by CGM, were associated with significant reductions in both glycemic lability (measured by the LI) and glucose variability (measured as glucose SD) assessed by CGM at 1- and 2-year post-transplant [47, 51]. These outcomes were further confirmed in the phase 3 CIT06 trial of islet-after-kidney transplantation in individuals with type 1 diabetes complicated by hypoglycemia unawareness in the presence of a stable, functioning kidney graft [48]. In another trial involving patients with type 1 diabetes and hypoglycemia unawareness initially receiving intensive insulin therapy administered by multiple daily injections, transition to continuous subcutaneous insulin infusion (CSII or pump) therapy resulted in modest reduction in hypoglycemia severity (assessed by HYPO score) and glycemic lability (assessed by glucose SD and CONGA4), while subsequent islet transplantation abolished all hypoglycemia with an associated further marked reduction in glycemic lability measures [56].

CGM has also been applied to the early post-transplant evaluation of pancreas graft function [57, 58]. CGM assessment of TIR can predict post-transplant oral glucose tolerance [57], which may be clinically significant in pancreas transplantation, since abnormal oral glucose tolerance in the absence of insulin therapy within the first few weeks post-transplant is associated with increased risk for later return to insulin therapy to control hyperglycemia [59], and can be assessed earlier post-transplant by CGM than by $HbA_{1c}$. Moreover, as following islet transplantation, CGM assessment following pancreas transplantation allows for simultaneous documentation of significant reductions in both TBR and glucose variability [58].

## Conclusions

Outcomes for β-cell replacement in the treatment of diabetes should include the glycemic control attributable to β-cell graft function, with the evaluation including at a minimum measures of average glycemic control and severe hypoglycemia events in addition to insulin requirements and levels of fasting and/or stimulated C-peptide. Because the experience of severe hypoglycemia is relatively infrequent, additional assessment of the level of hypoglycemia awareness, degree of glucose variability and/or glycemic lability, and frequency of exposure to clinically important, serious hypoglycemia (<54 mg/dL [3.0 mmol/L]) is important to best understand the effect of β-cell replacement on minimizing the risk for future severe hypoglycemia events. The use of CGM metrics to evaluate glycemic control may identify changes in glycemia sooner than a change in $HbA_{1c}$, allow for simultaneous assessment of measures of average glucose, glucose variability/lability, and exposure to hypoglycemia, and enable more direct comparison of outcome measures with artificial pancreas systems such as sensor augmented insulin pumps with automated insulin delivery algorithms [60].

There exists a heavy psychological burden for implementation of intensive insulin therapy that affects disease management [61]. Clinical trials of diabetes treatments increasingly include patient-reported outcomes, which have been recognized as clinically meaningful outcomes for type 1 diabetes [6]. In the phase 3 CIT07 trial of islet transplantation alone, there were significant improvements in diabetes distress, fear of hypoglycemia, as well as patient self-assessments of personal well-being [62]. Health-related quality-of-life measures improved significantly in five of the eight SF-36 domains, and results were not significantly different between those who achieved or did not achieve insulin independence [62]. These outcomes have been further validated in the phase 3 CIT06 trial of islet-after-kidney transplantation [48], and against intensive insulin therapy for patients with type 1 diabetes experiencing either severe hypoglycemia or poor glycemic control after kidney transplantation in a randomized clinical trial [63]. Future comparison of β-cell replacement therapies and artificial pancreas technologies should also consider patient-reported outcomes, including assessment of patient satisfaction and treatment preferences.

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