HHS Public Access

Author manuscript

Ann N Y Acad Sci. Author manuscript; available in PMC 2022 May 02.

Published in final edited form as:

Ann N Y Acad Sci. 2021 July ; 1495(1): 40–54. doi:10.1111/nyas.14572.

Pancreatic islet reserve in type 1 diabetes

Anneliese J. S. Flatt[1,2], **Carla J. Greenbaum**[3], **James A. M. Shaw**[1,2], **Michael R. Rickels**[4,5]

[1]Translational and Clinical Research Institute, Newcastle University, Newcastle upon Tyne, UK.

[2]Institute of Transplantation, Freeman Hospital, Newcastle upon Tyne, UK.

[3]Diabetes Program and Center for Interventional Immunology, Benaroya Research Institute, Seattle, Washington.

[4]Division of Endocrinology, Diabetes and Metabolism, Department of Medicine, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania.

[5]Institute for Diabetes, Obesity and Metabolism, University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania

Abstract

Type 1 diabetes (T1D) is a chronic autoimmune disease characterized by pancreatic islet β cell loss and dysfunction resulting in insulin deficiency and hyperglycemia. During a presymptomatic phase of established β cell autoimmunity, β cell loss may first be evident through assessment of β cell secretory capacity, a measure of functional β cell mass. Reduction in pancreatic islet β cell reserve eventually manifests as impaired first-phase insulin response to glucose and abnormal glucose tolerance, which progresses until the functional capacity for β cell secretion can no longer meet the demand for insulin to control glycemia. A functional β cell mass of ~25% of normal may be required to avoid symptomatic T1D but is already associated with dysregulated glucagon secretion. With symptomatic T1D, stimulated C-peptide levels >0.60 ng/mL (0.200 pmol/mL) indicate the presence of clinically meaningful residual β cell function for contributing to glycemic control, although even higher residual C-peptide appears necessary for evidencing glucose-dependent islet β and α cell function that may contribute to maintaining (near)normal glycemia.β cell replacement by islet transplantation can restore a physiologic reserve capacity for insulin secretion, confirming thresholds for functional β cell mass required for independence from insulin therapy.

Keywords

type 1 diabetes; pancreatic islet; β cell; α cell; insulin secretion

Address for correspondence: Michael R. Rickels, MD, MS, Institute for Diabetes, Obesity and Metabolism, University of Pennsylvania Perelman School of Medicine, 12–134 Smilow Center for Translational Research, 3400 Civic Center Boulevard, Philadelphia, PA 19104-5160. rickels@pennmedicine.upenn.edu.

Introduction

Type 1 diabetes (T1D) is a disease of insulin deficiency characterized by autoimmune destruction of pancreatic islet β cells. Now, 100 years since the discovery of insulin in 1921–1922, the clinical course of T1D has been transformed. However, insulin therapy by injection or subcutaneous infusion informed by ongoing glucose monitoring remains an unremitting daily challenge, with a continued risk of complications secondary to chronic high glucose exposure and dangerous acute episodes of hypoglycemia.[1–5]

T1D initially follows a subclinical course and presents at the point when residual β cell functional capacity can no longer meet the demand required for the maintenance of normal glucose homeostasis.[6] The subclinical course of T1D described as early as the 1980s helped to establish the Eisenbarth model of a chronic autoimmune disorder targeting the insulin-producing β cell initiated by an interaction of genetic and environmental factors and progressing at a variable rate until insufficient reserve capacity for insulin secretion results in the clinical presentation of diabetes.[7–11] As family history is associated with an increased risk of T1D, with a 1-in-20 lifetime risk in first-degree relatives compared with a 1-in-300 lifetime risk for the general U.S. population,[12] family studies have been invaluable in advancing the understanding of diabetes pathogenesis, including its subclinical course to better inform pre-clinical staging.[11,13,14] The genetic predisposition is largely mediated through human leukocyte antigen (HLA) genotype DR3/DR4-DQ8 in addition to non-HLA–related genes,[15–18] which in combination with one or more still undefined environmental factors can lead to seroconversion through the development of autoantibodies against β cell–specific antigens. These include glutamic acid decarboxylase 65 (GAD-65), the tyrosine phosphatase–related islet antigen 2 (IA-2), insulin (IAA), and zinc transporter 8 (ZnT8), with their autoantibodies representing markers of β cell autoimmunity.

Once autoimmunity is established, subclinical T1D can progress through a presymptomatic phase that can be identified clinically using biomarkers of β cell autoimmunity and dysglycemia before the development of overt, symptomatic diabetes (Table 1 and Ref. 19). During subclinical disease progression, the pancreatic islet reserve capacity for insulin secretion declines as increasing numbers of β cells are lost to autoimmune destruction. This reserve capacity for secretion normally maintains glucose homeostasis during periods of growth and times of stress, and as it becomes limited results in the appearance of glucose intolerance, and once exhausted, the development of overt diabetes. Thus, clinically, T1D may be considered a disease from the time autoimmunity is established before devel oping glucose intolerance (stage 1), progressing to glucose intolerance (stage 2), and leading to typical signs and symptoms of diabetes (stage 3).[19]

One goal of staging presymptomatic T1D is to enable early immune intervention strategies aimed at preventing or ameliorating symptomatic diabetes through the preservation of sufficient pancreatic functional β cell mass to maintain (near)normoglycemia.[20] Preservation of endogenous β cell function after clinical diagnosis is also important in facilitating optimal metabolic control. The objective of this review is to examine the physiological and clinical correlates of pancreatic islet reserve at each stage of T1D in order to aid understanding of

pancreatic islet physiology informing interventions to maintain or restore a functional β cell mass.

Islet reserve and function in health

Pancreatic islets are distributed throughout the pancreatic acinar/exocrine tissue and account for 2–3% of pancreatic mass. Human islets are composed predominantly of insulin-producing β cells and glucagon-producing α cells with the remaining 10% comprising somatostatin-producing δ cells, pancreatic polypeptide producing PP cells, and ghrelin-producing ε cells.[21] Nervous system innervation, β cell electrical activity, and intraislet paracrine signaling support glucose-dependent insulin and glucagon secretion.[22] Insulin secretion is pulsatile in nature, with pulses occurring every ~5–6 min and (in the nondiabetic state) increasing in amplitude in response to glucose.[23] In healthy individuals, insulin secretion varies by several orders of magnitude to meet the demand for control of glucose homeostasis. This is accomplished both by biphasic kinetics of insulin secretion and recruitment of additional β cells to an activated state, which provides the reserve capacity for secretion. The first-phase secretion involves rapid exocytosis of insulin granules from a readily releasable pool. Under conditions of a sustained glucose stimulus, this first phase is followed by a subsequent second, more prolonged phase of insulin release from the mobilization of granules within the reserve pool, comprising 95% of β cell insulin granules.[24] Heterogeneity of β cell functional states has long been appreciated,[25] and more recently, evidence has emerged supporting a subpopulation (<10% of β cells) that functions as a central hub, coordinating integrated β cell response to stimuli.[26] Thus, normal insulin secretion appears dependent on coordinated β cell function from intact islets.

Normal insulin secretion is also dependent on the presence of sufficient reserve capacity of functional β cell mass. Functional β cell mass is best estimated from the β cell secretory capacity derived from glucose-potentiation of insulin or C-peptide release in response to injection of a nonglucose secretagogue, such as arginine or glucagon.[27] Glucose potentiation creates the condition for second-phase insulin secretion, whereby mobilization of secretory granules from the reserve pool of an increased number of activated β cells results in augmented acute insulin release in response to membrane depolarization induced by the nonglucose secretagogue. Increased islet blood flow and islet oxygenation has been demonstrated in animal models of partial pancreatectomy and gestation, suggesting the recruitment of a functional reserve capacity in response to increasing β cell demand for secretion occurs without an increase in β cell mass.[28,29] Nonetheless, the recruitment of senescent β cells and generation of new β cells from neogenesis or self-duplication of existing β cells may also contribute to increasing β cell secretory capacity for increased demand, as shown in rodent models.[30] The risk of glucose intolerance secondary to a marked reduction in pancreatic mass is evidenced in healthy hemipancreatectomy donors in whom a residual 40% β cell secretory capacity was associated with reduced first-phase insulin secretion in response to glucose, as well as the development of glucose intolerance, and long-term risk of progression to diabetes, especially in association with weight gain.[31,32] Another study involving individuals with exocrine pancreatic disease undergoing pancreatic surgery showed that diabetes was associated with a reduction in relative β cell area (assessed from sections of resected pancreatic tissue) to 30–40% of that in nondiabetic individuals.[33]

Indeed, both human and animal models suggest an islet mass of ~50% may be the threshold for maintaining sufficient β cell functional reserve for normal glucose control.[34–36] Thus, while the range is variable among individuals,[37,38] in general, with less than 50% of normal β cell secretory capacity, there may be insufficient islet reserve (including loss of first-phase insulin secretion) to meet demand. Other work reports that even mild hyperglycemia following 90% partial pancreatectomy in animal models is associated with changes in β cell–specific gene expression profiles,[39] supporting a role for β cell dysfunction in addition to absolute β cell mass loss in contributing to insulin secretory defects with potential consequences for long-term β cell health.

There exists reciprocal glucose-dependent regulation of β cell insulin secretion and α cell glucagon secretion in the normal pancreatic islet, such that increasing glucose potentiates insulin secretion and inhibits glucagon secretion in order to avoid hyperglycemia, while decreasing glucose inhibits insulin secretion and activates glucagon secretion in order to avoid hypoglycemia.[22] Hemipancreatectomy resulting in 40% of normal β cell secretory capacity is associated with 35% of normal acute glucagon response to arginine with and without glucose inhibition,[31] in keeping with equivalent reductions in both pancreatic islet β and α cell mass. Importantly, despite reduced pancreatic islet mass, the α cell glucagon secretion in response to hypoglycemia is seemingly normal,[40] and it is proposed that the remaining intact islets exhibit normal paracrine activation of glucagon secretion by the intraislet decrement in insulin secretion that occurs with the development and in defense of hypoglycemia,[41] leading to physiological secretion despite a substantial decrease in α cell mass.

Islet reserve and function at early disease stages, before clinical diagnosis

Longitudinal studies continued over several decades of follow-up have confirmed that the presence of β cell autoimmunity, as evidenced by seroconversion of two or more islet autoantibodies, almost inevitably heralds progression to the clinical diagnosis of T1D.[42–44] While considered prestage 1 disease, autoimmunity manifested by the presence of only a single autoantibody also confers risk with ~20% developing multiple antibodies within 5 years and ~15% progressing to clinical diabetes despite remaining with single autoantibody positivity.[45] The stages of the diabetes framework describe the progression of disease by changes in glycemic status and has proved to be useful for refining inclusion and outcome criteria for clinical trials aiming to slow or delay disease progression. T1D is, however, primarily a disease of β cell dysfunction and loss with the secondary consequence of glucose dysregulation. β cell secretory abnormalities are present long before clinical diagnosis;[46] but interestingly, often not well correlated with either the number of autoantibodies or glucose tolerance.

For example, Vandemeulebroucke *et al.* assessed functional β cell mass using a hyperglycemic clamp with glucagon stimulation to measure β cell secretory capacity in 17 IA-2 antibody–positive first-degree relatives followed over 5 years during which 50% were predicted to develop clinical diabetes.[47] Ten of these individuals did not develop clinical diabetes over the 5-year follow-up and had entirely normal oral glucose tolerance and β cell secretory capacity at baseline, not different from a control group with genetic risk for T1D

without antibodies.[47] The seven individuals who did progress to clinical diabetes from 3 to 63 months after baseline study had oral glucose tolerance that was initially similar to that in the group of nonprogressors and controls, but β cell secretory capacity that was <50% of normal, indicating the presence of a substantial reduction in functional β cell mass.[47] This small study suggests that the presence of two or more islet autoantibodies does not, in itself, indicate a reduction in pancreatic islet reserve, and moreover, that identification of a reduced β cell secretory capacity appears to be more sensitive than assessment of oral glucose tolerance (OGTT) for detecting those likely to progress more rapidly to overt diabetes.

β cell function in autoantibody-positive individuals is most often assessed from insulin or C-peptide levels obtained during an oral glucose tolerance test (OGTT) or from the first-phase insulin response (FPIR) during an intravenous glucose tolerance test (IVGTT). Decreased insulin secretion in individuals with early-stage T1D confers an increased risk of eventual clinical disease,[48] but strikingly, low FPIR is only moderately associated with glucose intolerance in cross-sectional studies ($r^2 = 0.114$).[49] However, a separate study in type 2 diabetes (T2D) found that once fasting glucose exceeds 115 mg/dL, FPIR is absent,[50] likely signifying the exhaustion of a reserve capacity for insulin secretion at that time. Studies by Hao *et al.* have shown significant variation in insulin secretory reserve/functional β cell mass, assessed by the acute insulin response to glucose-potentiated arginine stimulation, in antibody-positive individuals with reduced β cell function, assessed by the FPIR.[51] It has previously been shown that the insulin response to glucose is lost earlier than the response to arginine in settings of a reduced β cell mass, including both presymptomatic T1D[52] and recipients of islet transplantation,[53] groups characterized by a marked reduction in functional β cell mass, where acute insulin responses to arginine are maintained despite marked impairment of or loss of FPIR. Evidence for differences in various surrogate measures of functional β cell mass following oral or intravenous stimulatory challenges further supports underlying heterogeneity in T1D pathogenesis.[51]

The rate of progression from autoimmunity to clinical diabetes is variable.[54] β cell glucose sensitivity, measured by the slope of insulin secretion in response to increasing plasma glucose, may be impaired several years before diagnosis and so might represent an early sign of β cell dysfunction nearing a critical threshold of insulin deficiency beyond which clinical diabetes ensues.[55] The Diabetes Prevention Trial-Type 1 risk score (DPTRS) can assess risk for future diabetes in autoantibody-positive individuals using age, body mass index, fasting C-peptide, and the 30-, 60-, 90-, and 120-min C-peptide and glucose values during a 2-h OGTT.[56] Using only the 60-min C-peptide and glucose (DPTRS60) was recently shown to predict diabetes development with similar accuracy.[57] Importantly, a 1-h OGTT glucose ≥155 mg/dL (8.6 mmol/L) had slightly greater receiver operating characteristics (sensitivity versus 1–specificity) than the standard 2-h OGTT glucose ≥140 mg/dL (7.8 mmol/L) for predicting future diabetes development.[57] The potentially greater utility of the 1-h OGTT glucose to reflect the early loss of pancreatic islet secretory reserve in T1D is similar to that observed in individuals with pancreatic insufficient cystic fibrosis, where a 1-h OGTT glucose ≥155 mg/dL (8.6 mmol/L) is associated with an already marked reduction in β cell secretory capacity.[58]

Follow-up of a cohort of individuals with autoantibody positivity and relatives with T1D by 6-monthly OGTT toward the onset of diabetes in the Diabetes Prevention Trial-Type 1 showed a progressive decline in glucose tolerance over the 2-year period preceding diagnosis, with a more rapid decline in stimulated C-peptide occurring in the last 6 months.[59] More recently, Bogun *et al.* demonstrated that this accelerated rate of fall in insulin secretion persists during and beyond the peridiagnostic period.[60] Whether this accelerated decline in β cell function prior and through the peridiagnostic period is related to ongoing immunologic destruction and/or metabolic exhaustion of β cells is unknown.

Some individuals have been reported to have disproportionately increased secretion of proinsulin relative to insulin or C-peptide during disease progression, as assessed by the elevated fasting proinsulin-to-C-peptide ratio before diagnosis.[61] Similar to observations in T2D, impaired proinsulin processing before secretion is suggestive of β cell endoplasmic reticulum stress; however, the relationship of the abnormal proinsulin-to-C-peptide ratios to either autoimmunity or glucose tolerance remains unclear. It is likely that both the dysfunction of β cells in intact islets and the loss of islet β cells due to chronic β cell destruction contribute to disease progression toward diabetes. Whether individuals with a greater dysfunctional component underlying reduced insulin secretion but relatively intact β cell secretory capacity indicating preserved β cell mass may be more likely to respond to disease-modifying therapy requires further investigation.[51]

Islet reserve and function after clinical diagnosis

Stage 3 T1D is defined by the onset of clinical disease through the presence of signs and symptoms of hyperglycemia or when asymptomatic by crossing the diagnostic glucose thresholds established by the World Health Organization/American Diabetes Association. The prospective monitoring of individuals with presymptomatic disease can enable early detection of diabetes through the confirmation of fasting glucose ≥126 mg/dL (≥7.0 mmol/L); 2-h OGTT glucose ≥200 mg/dL (≥11.1 mmol/L); and/or an HbA_{1c} ≥6.5% (48 mmol/mol) before the onset of symptoms. ≥ Individuals with early, but still asymptomatic, stage 3 T1D defined by a 2-h OGTT glucose ≥200 mg/dL (≥ 11.1 mmol/L) who are able to maintain nondiabetic levels of fasting glucose and HbA1c already exhibit markedly impaired insulin secretion in response to oral and intravenous glucose, yet preserved FPIR to the nonglucose β cell secretagogue arginine.[62] This may be explained by the potentiation of insulin release to nonglucose secretagogues by increasing fasting glucose concentration. The reduction in overall β cell secretory capacity is, however, observed by reduced insulin release in response to arginine potentiated by submaximal (AIR_{pot}) and maximal (AIR_{max}) hyperglycemic clamp conditions. Indeed, glucose-potentiated arginine testing demonstrated that the β cell secretory capacity in this cohort of individuals with asymptomatic T1D was only 25% of that in a normal control group.[62]

In another study of new-onset T1D, the median β cell secretory capacity of 80 individuals was again 25% of that measured in 20 healthy, agematched control subjects using glucose potentiation of glucagon-induced insulin release.[63] Here, individuals with β cell secretory capacity at or above the 25th percentile were more likely to experience the preservation of β cell function and a reduction in insulin requirements 18 months after receiving a 6-day

course of anti-CD3 antibody therapy.[63] Thus, a functional β cell mass of at least 25% normal may be required to avoid symptomatic T1D and may also represent a threshold that allows for the easier demonstration of protection of residual β cell function. However, it is unknown whether individuals with lower pancreatic islet reserve at clinical diagnosis have more severe and potentially treatment-resistant autoimmunity or simply greater and potentially less reversible loss of functional β cell mass. Interestingly, at a β cell secretory capacity <25% of normal adults, insulin release to nonglucose secretagogues is already maximal in the fasted state in the presence of elevated glucose concentrations, such that further glucose potentiation of insulin release to arginine under hyperglycemic clamp conditions is no longer possible (Fig. 1).

At the point when pancreatic islet reserve for β cell insulin secretion is compromised in T1D, marked abnormalities in α cell regulation of glucagon secretion are also evident. Metabolic testing through OGTT and IVGTT at the earliest identification of stage 3 T1D reveals impaired suppression of glucagon secretion in response to hyperglycemia.[62] This impaired regulation of glucagon secretion in T1D may be explained by the loss of paracrine effects of β cells on α cell function in islets, where β cells are destroyed or no longer functional due to β cell autoimmunity. The absence of suppression of glucagon during oral glucose or mixed-meal tolerance testing (MMTT) likely contributes to postprandial hyperglycemia in early T1D.[62,64]

In addition, glucagon response to hypoglycemia is already markedly impaired at diabetes onset.[65,66] Proposed underlying mechanisms include altered islet innervation, abnormal α cell glucose sensing, and reduced intraislet paracrine signaling, whereby β cell deficiency leads to an insufficient decrement of insulin in response to hypoglycemia to act as a paracrine trigger for α cell glucagon release (reviewed by Rickels[67]). Whatever the mechanism, an impaired glucagon response to hypoglycemia is observed uniformly in recent-onset diabetes regardless of the level of residual C-peptide.[66,68]

Brissova *et al.* have provided cellular evidence for an inherent α cell defect in T1D, with the reduction in transcription factors associated with α cell identity and reduced expression of exocytosis and signaling-related proteins demonstrated in islets isolated from individuals with T1D.[69] Isolated islets showed the preservation of glucose-stimulated insulin secretion from the low number of β cells present; however, glucagon release to low glucose incubation was deficient despite the observation of an increased number of α cells in islets from the individuals with T1D compared with controls. Although a relative increase in α to β cells is anticipated due to β cell loss, this observation of increased numbers but the impaired function of α cells suggests an additional role for islet cell dedifferentiation in diabetes pathogenesis, a finding that is supported by pathology studies in T2D.[70] Similar data available from the Human Pancreas Analysis Program (https://hpap.pmacs.upenn.edu) demonstrate seemingly appropriate dynamics of insulin secretion in response to glucose, albeit at the markedly reduced magnitude, and paradoxically increased glucagon secretion (Fig. 2A). Interestingly, the transplantation of islets from individuals with T1D into a normoglycemic nonautoimmune environment led to partial restoration of gene expression changes toward a normal α cell phenotype.[69]

In vitro studies have demonstrated the down-regulation of key β cell transcription factors and changes in β cell phenotype associated with hyperglycemia, which, to some extent, may be reversible with normalization of glycemia.[39] However, the extent to which β cell senescence, dedifferentiation, and transdifferentiation are implicated in β cell dysfunction and loss in human T1D remains unclear.[39] Intensive insulin use at diagnosis has been associated with a period of preservation of C-peptide production[71,72] with the fasting euglycemia attained from exogenous insulin therapy, perhaps contributing to β cell "rest" and possible protection from the phenotypic and functional changes associated with β cell stress. Similar "remission" is seen with aggressive glycemic control in those with T2D. However, the failure of a randomized trial to confirm the preservation of functional β cell mass with intensive insulin therapy in recently diagnosed T1D patients,[73] as well as the failure of parenteral insulin to delay disease progression in the early stages of disease,[74] suggests that the benefit of insulin therapy on the preservation of secretion is only manifest with marked initial hyperglycemia, supporting the hypothesis that glucotoxicity plays a role in β cell dysfunction with a potentially reversible component.

Islet reserve and function in established clinical disease

Functional β cell mass continues to decline following a diagnosis such that the majority of individuals have a stimulated C-peptide <0.60 ng/mL (0.200 pmol/mL) within 5 years of symptomatic diagnosis.[75] This decline is dependent on the age at symptomatic disease onset, with individuals presenting as adults >18 years old tending to maintain residual β cell function longer than those presenting as children.[76] In the Diabetes Control and Complications Trial (DCCT), those individuals with a mixed-meal stimulated C-peptide >0.60 ng/mL (0.200 pmol/mL) within 5 years of symptomatic diagnosis had a lower incidence of retinopathy and nephropathy and a decreased prevalence of severe hypoglycemia than those with lower amounts of residual C-peptide detection regardless of treatment intensity.[77,78] These results fairly conclusively support that preservation of residual β cell function characterized by stimulated C-peptide >0.60 ng/mL (0.200 pmol/mL) is clinically meaningful and supports immunotherapy approaches toward the preservation of functional β cell mass (reviewed by Lord and Greenbaum[79]). A more recent analysis of the DCCT suggests that any level of stimulated C-peptide above the detection threshold of 0.09 ng/mL (0.03 pmol/mL) used at trial entry may be associated with better clinical outcomes.[80]

The development of highly sensitive C-peptide assays led to the detection of very low levels of C-peptide (that would have been "undetectable" in the DCCT) in the majority of individuals over the first 10 years of symptomatic T1D and in a declining minority of individuals more than a decade after clinical diagnosis.[81–83] These observations are consistent with Yu *et al.*, who identified few scattered insulin-positive cells in all individuals with T1D at autopsy.[84] Follow-up of individuals at least 5 years after diagnosis showed that circulating proinsulin may persist even in the absence of detectable C-peptide. Whether this is caused by ongoing (immunologically or metabolically mediated) β cell stress or represents an irreversible shift in β cell phenotype precluding normal proinsulin processing remains unclear.[85,86] Assessment of type 1 donor islets from pancreatic sections obtained from the Network for Pancreatic Organ Donors with Diabetes demonstrated the

reduced expression of the proinsulin processing enzymes, prohormone convertase 1/3, and carboxypeptidase, compared with nondiabetic controls, which may account for the elevated proinsulin:C-peptide ratios in individuals with the lowest detectable β cell peptides.[87]

Sustained C-peptide, >0.60 ng/mL (0.200 pmol/mL) in a random sample, has been observed in members of the Joslin Medalist group despite more than 50 years of insulin-dependent diabetes. In this cohort, sustained C-peptide was associated with a later age of diagnosis and the presence of DR3 risk alleles.[88] Postmortem examination of pancreata from nine Medalists showed significant numbers of persisting insulin-positive cells scattered as single extra-islet cells or as single cells within some islets or many cells in some islets in several lobes among many insulin-negative islets despite the long duration of diabetes.[88] Insulin-positive islets were more likely to be present in later-onset diabetes. However, even Medalists without detectable C-peptide on MMTT could have evidence of residual insulin-positive β cells present as single cells within islets.[84,88] Nevertheless, the number of residual insulin-positive cells correlated with the preceding MMTT C-peptide response such that those who experienced a physiologically significant doubling of C-peptide on stimulation had considerably more insulin-positive cells found within islets of certain lobules of the pancreas.[88] This finding suggests that physiological inducible insulin secretion may depend on the presence of residual β cells in intact islets rather than occur from scattered insulin-positive cells (Fig. 2B).

A subsequent study of 68 individuals in the Joslin Medalist cohort by Yu *et al.* identified three patterns of residual insulin staining, including scattered insulin-positive cells present in all samples; few insulin-positive cells within some islets in ~87%; and many insulin-positive cells in some islets within certain lobes of tissue present in ~20% of samples.[84] Prospective follow-up of C-peptide and autoantibody status of Medalists over 4 years showed low levels of detectable C-peptide (random sample >0.05 ng/mL (0.017 pmol/mL)) were present in ~32% of individuals. Detectable C-peptide was associated with IA2 autoantibody positivity, with GAD positivity more commonly observed in those with undetectable C-peptide. However, antibody titers and indeed C-peptide levels fluctuated over follow-up, suggestive of possible episodic autoimmune aggravation alternating with at least minimal recovery of some β cell function despite long-standing disease duration.[84] Preserved lobes containing insulin-positive islets were associated with greater C-peptide, lower HbA_{1c}, and older age at diagnosis compared with individuals with only residual scattered insulin-positive cells (within and outside islets). These findings further suggest the importance of β cell contact/islet microenvironment in the maintenance of physiological insulin secretion.[84]

Rickels *et al.* assessed the physiological significance of varying levels of residual C-peptide in individuals with established T1D stratified by MMTT peak C-peptide as negative (<0.02 ng/mL (0.007 pmol/mL)), low (0.05–0.60 ng/mL (0.017–0.200 pmol/mL)), intermediate (0.60–1.20 ng/mL(0.200–0.400 pmol/mL)), and high (>1.20 ng/mL (>0.400 pmol/mL)).[89] Functional β cell mass, assessed by the acute C-peptide response to glucose-potentiated arginine, was shown to be highly associated with MMTT peak C-peptide,[89] a relationship also seen with the MMTT C-peptide area-under-the-curve (Fig. 3). Despite this continuous association between MMTT peak C-peptide and β cell secretory capacity as a measure of functional β cell mass, only the high C-peptide group showed β cell responsivity to

glucose during a hyperglycemic clamp before the injection of arginine (Fig. 4A) and α cell responsivity to insulin-induced hypoglycemia during a hyperinsulinemic hypoglycemic clamp (Fig. 4B). The increased glucagon response to hypoglycemia observed in the high C-peptide group may depend on functional β cell suppression within intact islets activating neighboring α cells. However, even with high residual C-peptide, β cell secretion of insulin in response to meal or arginine stimulation does not suppress α cell glucagon secretion.[89] This dysregulation of α cell function may be explained by the failure of glucagon suppression from the majority of diseased islets that do not contain β cells.

Importantly, individuals with high MMTT peak C-peptide who have evidence of preserved islet β and α cell responsivity to glucose also exhibit lower mean glucose and greater time in range on continuous glucose monitoring (Fig. 5A).[89] Consistent with these findings, a study investigating the glycemic effects of 45 min of aerobic exercise in T1D found that individuals with higher MMTT peak C-peptide (>0.60 ng/mL (0.200 pmol/mL)) spent more time in range on continuous glucose monitoring during the subsequent 24 h than those with low or undetectable C-peptide, and while not statistically significant given the small sample size, spent twofold less time with hypoglycemia during the postexercise period.[90] Thus, improved glycemic control in individuals with high residual C-peptide may be explained by a valuable functional reserve of preserved β and α cell responsivity to glucose, which can refine the effects of exogenous insulin, but which is less apparent with lower residual C-peptide production. Nevertheless, the Scottish Diabetes Research Network Type 1 Bioresource following over 6000 individuals with T1D has shown that after adjusting for diabetes duration, even low levels of residual C-peptide (0.09–0.60 ng/mL (0.030–0.200 pmol/mL)) in a random sample provide protection from severe hypoglycemia independent of HbA1c or insulin dose.[91]

Islet reserve and function with replacement in long-standing clinical disease

Long-standing (>10–15 years) symptomatic T1D is inextricably linked not only to decreasing prevalence of physiologically significant pancreatic islet cell reserve but also the development of progressive defects in glucose counterregulation to defend against the development of hypoglycemia. Initially, once insulin-deficient diabetes is established, the maintenance of an endogenous glucose production (EGP) response to defend against the development of low blood glucose appears most dependent on an intact epinephrine response rather than a relative increase in glucagon secretion.[89] However, it is well established that exposure to iatrogenic hypoglycemia associated with intensive insulin therapy reduces the glycemic threshold and magnitude of subsequent sympathoadrenal responses to hypoglycemia[92,93] such that with repeated hypoglycemia exposure, these may fail to reverse low blood glucose and contribute to a cycle whereby hypoglycemia begets further hypoglycemia with the development of impaired awareness and severe events.[94]

Impairment of counterregulatory epinephrine and autonomic symptom responses to hypoglycemia contributes to impaired awareness of hypoglycemia, which combined with defective glucose counterregulation (impaired EGP response), leads to the development of hypoglycemia-associated autonomic failure (HAAF), also known as hypoglycemia unawareness,[95] which increases the risk of experiencing life-threatening

severe hypoglycemia 20-fold.[96] Replacement of islet mass through allogeneic β cell transplantation in individuals with long-standing symptomatic T1D complicated by hypoglycemia unawareness restores physiologic islet cell responses to hypoglycemia that are associated with recovery of glucose counterregulation[97] and reversal of HAAF.[98] Thus, islet allotransplantation can provide additional insight into the relationship between functional islet reserve and glycemic control in T1D.

Islet allotransplantation is indicated for individuals with T1D and hypoglycemia unawareness experiencing severe hypoglycemia and/or excessive glycemic variability refractory to medical management with intensive insulin therapy. Islet allotransplantation involves the isolation of human islets from one or more deceased donor pancreata, which are transplanted by intraportal infusion during a percutaneous or minilaparotomy procedure for islet engraftment within the liver parenchyma.[99,100] Insulin independence is achieved when functional β cell mass is restored to >25–40% of normal based on measures of β cell secretory capacity derived from glucose potentiation of glucagon- or arginine-induced insulin secretion.[101,102] Lower estimates of functional β cell mass/secretory capacity following islet transplantation, while associated with ongoing insulin requirements, are related to proportionate improvement in glycemic control and variability relative to pretransplantation. Islet grafts with a functional β cell mass <5% of nondiabetic controls do not demonstrate any benefit on glycemic variability.[103] Continued islet graft function with reduction in severe hypoglycemia and glycemic variability is observed in 90% of recipients at 5 years; however, a decline in islet graft reserve capacity is often observed over time, with the majority returning to exogeneous insulin therapy by 5 years.[104] By contrast, although associated with significantly greater periprocedure morbidity, allogeneic whole pancreas transplantation more often results in insulin independence, and when transplanted simultaneously with the kidney from the same deceased donor is associated with a 5-year insulin independence rate >70%.[105] Assessment of β cell secretory capacity may require consideration for the systemic hyperinsulinemia that results from systemic venous drainage of the pancreas graft (reviewed by Rickels[106]), although functional β cell mass/secretory capacity has been shown to be normal in recipients with portal venous drainage of the pancreas graft.[107] Restoration of a normal reserve capacity for insulin secretion likely explains the more durable insulin independence experienced by recipients of the whole pancreas when compared with isolated islet transplantation.

Incremental improvements in MMTT-stimulated C-peptide following islet allotransplantation are associated with a progressive reduction in glycemic variability and increasing time spent in the target glucose range by continuous glucose monitoring.[108] A continuous relationship was seen between stimulated C-peptide and all continuous glucose monitoring parameters, with a 0.100-pmol/mL increment in C-peptide associated with a 5% reduction in glucose standard deviation and a 2.5% reduction in interstitial glucose. Improved glycemic control (HbA1c) with a simultaneous reduction in exogenous insulin requirement was also observed across C-peptide groupings. Low levels (<0.6 ng/mL (<0.200 pmol/mL)) of MMTT-stimulated C-peptide following islet allotransplantation were associated with poor glycemic control and excessive glucose variability, with time in the range of 54–180 mg/dL (3–10 mmol/L) improving with moderate (0.6–1.5 ng/mL (0.200–0.500 pmol/mL)) and more significantly with good (1.5–3.0 ng/mL (0.500–1.000 pmol/

mL)) levels (Fig. 5B). MMTT-stimulated C-peptide (>3.0 ng/mL (>1.000 pmol/mL)) was associated with 95% of the time within the 54–180 mg/dL glucose range and attainment of insulin independence.[108] Importantly, the restoration of only moderate levels of MMTT-stimulated C-peptide above the DCCT threshold of 0.6 ng/mL (0.200 pmol/mL) was associated in this high-risk cohort with absolute prevention of biochemical hypoglycemia (glucose <54 mg/dL).[108] Thus, the goal for interventions targeting preservation or restoration of β cell function in T1D should consider aiming for a stimulated C-peptide level of at least 0.6 ng/mL (0.200 pmol/mL) as suggested by recent consensus guidelines for defining outcomes of β cell replacement therapies.[109]

Conclusions

Abnormalities in pancreatic islet β cell function and secretory capacity can be detected before the clinical presentation of T1D and progress over the years following diagnosis. It is now clear that residual islet β cells may persist for many decades with evidence in some cases of physiologic islet β cell function and that individuals with high residual C-peptide production may benefit from reduced glucose variability and improved overall glycemic control. Effective approaches to both preserve and restore pancreatic islet reserve before or at diabetes onset and sustain or replace the functional β cell mass in established diabetes are likely to lead to reduced diabetes-related complications with direct implications for quality of life.[110] Transplant studies have shown that even partial restoration of functional islet β cell mass can enable insulin independence, setting a target mass to attain through nontrans-plant approaches designed to maintain or regenerate endogenous pancreatic islet reserve.

Acknowledgments

The authors thank Henry T. Bahnson and Alyssa Ylescupidez of the Benaroya Research Institute for help with the creation of Figure 3. M.R.R. is supported in part by Public Health Services Research Grants R01 DK091331 and UC4 DK112217 (Human Pancreas Analysis Program). This manuscript used data for Figure 2 acquired from the Human Pancreas Analysis Program (HPAP-RRID:SCR_016202) Database (https://hpap.pmacs.upenn.edu), a Human Islet Research Network (RRID:SCR_014393) consortium (UC4-DK-112217, U01-DK-123594, UC4-DK-112232, and U01-DK-123716).[111]

Competing interests

M.R.R. has received consulting honoraria from Semma Therapeutics and Sernova Corp., and has received research support from Xeris Pharmaceuticals.

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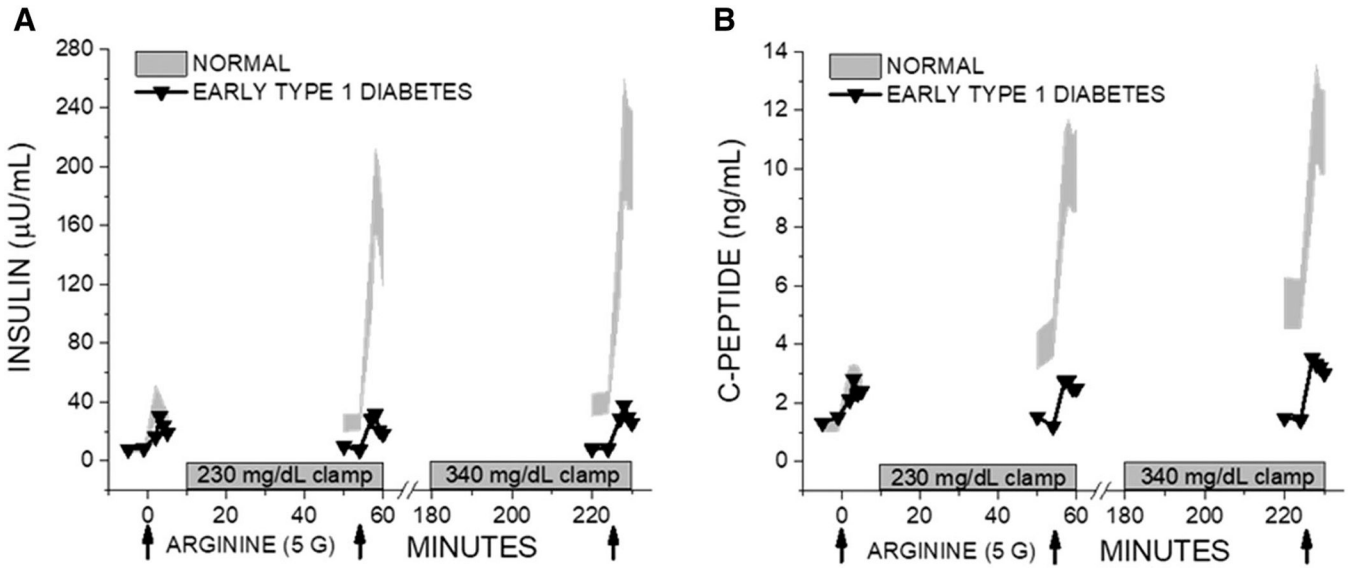

Figure 1.

β cell secretory capacity data from an individual with adult-onset T1D, initially diagnosed with T2D and at the time of glucose-potentiated arginine testing before initiating insulin therapy. Under fasting conditions, the acute insulin (A) or C-peptide (B) response to arginine appear “normal” (although not when considering the fasting glucose was elevated at 162.5 mg/dL (not shown)), and further elevation of the glucose cannot further potentiate insulin release as the entire reserve capacity for secretion (~15% of normal) is already engaged under the fasting condition. The normal data are 95% CI based on 28 nondiabetic individuals.

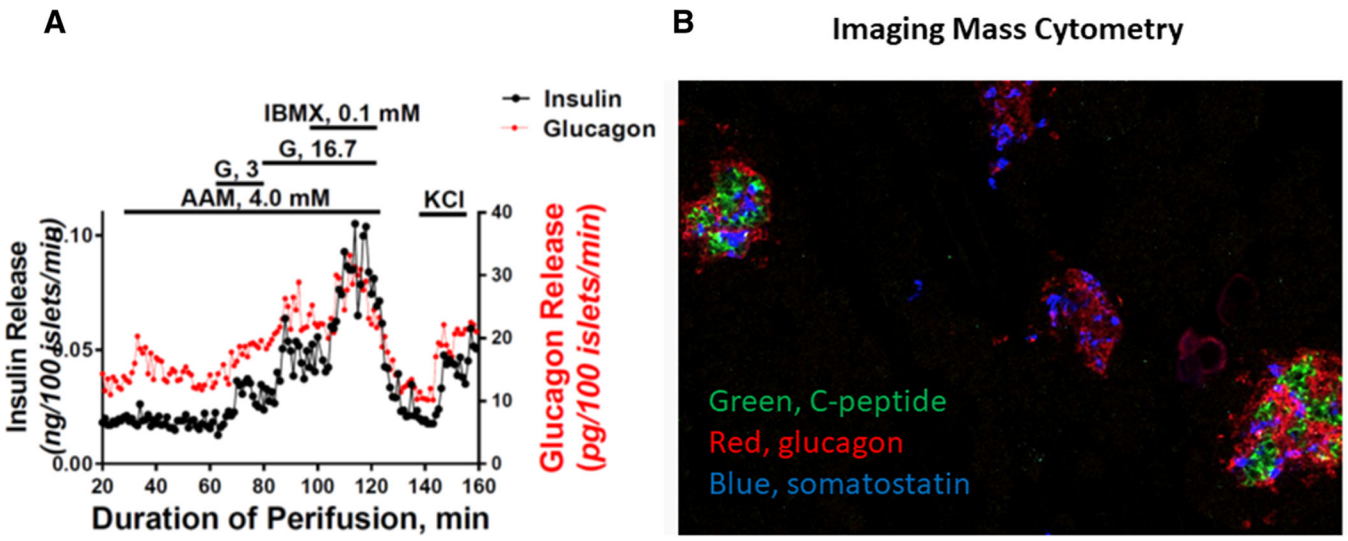

Figure 2.

(A) The perifusion of islets isolated from a deceased donor with a 5-year duration of T1D. Insulin release is appropriate in response to change from low glucose (G; 3 mM) to high glucose (G; 16.7 mM), and to phosphodiesterase inhibition with 3-isobutyl-1-methylxanthine (IBMX, 0.1 mM) and membrane depolarization with KCl, albeit at the markedly reduced magnitude. Glucagon release is appropriate in response to amino acid mixture (AAM, 4.0 mM), IBMX, and KCl, but paradoxically increased (failed suppression) in response to change from low to high glucose. (B) Imaging mass cytometry of pancreatic sections from the same deceased donor demonstrates the presence of few islets with normal numbers of β cells (green) and more representative islets containing α (red) and δ (blue) but no β cells. Data are available at https://hpap.pmacs.upenn.edu.

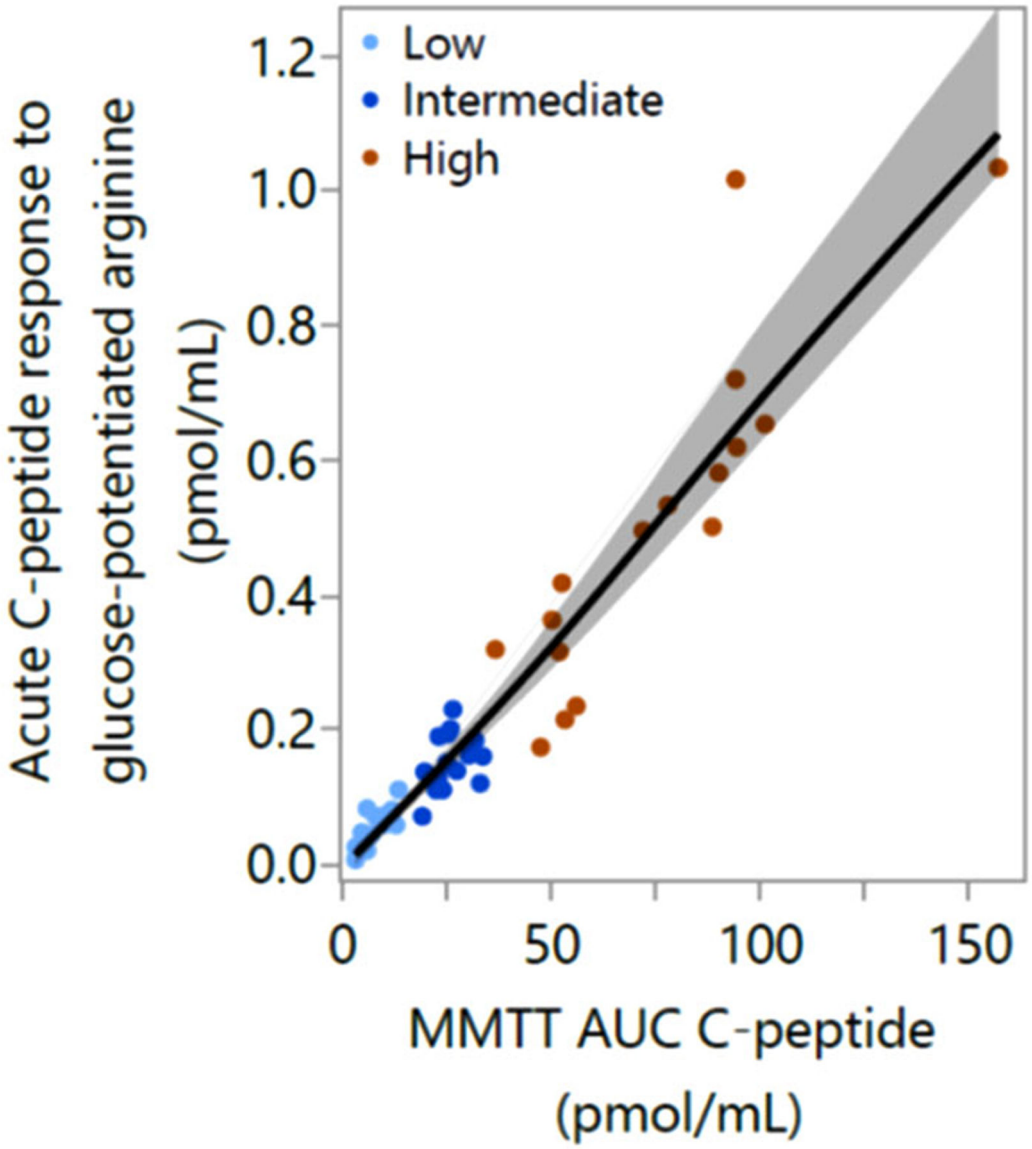

Figure 3.

Relationship between β cell secretory capacity measured from the acute C-peptide response to glucose-potentiated arginine and the mixed-meal tolerance test (MMTT) area-under-the-curve (AUC) C-peptide response over 120 min in individuals with MMTT peak C-peptide defined as: low, 0.05–0.60 ng/mL (0.17–0.20 pmol/mL); intermediate, >0.60–1.20 ng/mL (0.20–0.40 pmol/mL); or high, >1.20 ng/mL(>0.40 pmol/mL). Data are from Ref. 89.

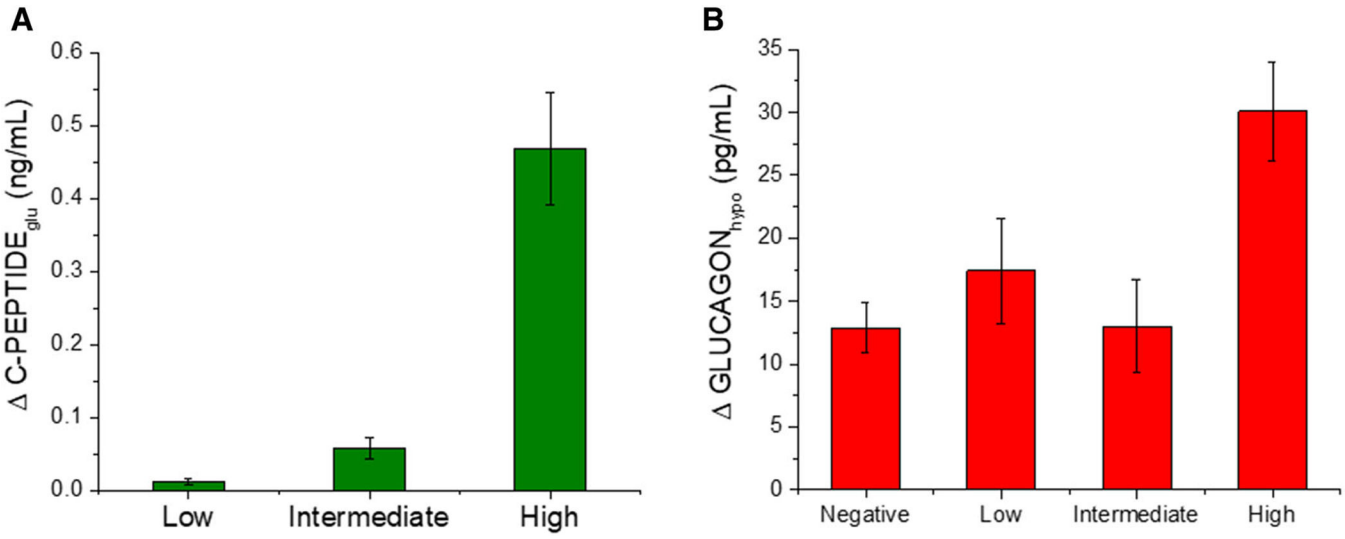

Figure 4.

(A) β cell response to an increase in glucose during a hyperglycemic clamp, and (B) α cell response to insulin-induced hypoglycemia during a hypoglycemic clamp in individuals with T1D by peak C-peptide during a mixed-meal tolerance test (negative, <0.02 ng/mL; low, 0.05–0.60 ng/mL; intermediate, >0.60–1.20 ng/mL; and high, >1.20 ng/mL). An increase in C-peptide in response to hyperglycemia and an increase in glucagon in response to hypoglycemia were observed only in the group with the highest residual C-peptide production that may represent a minimal functional islet reserve. Data are from Ref. 89.

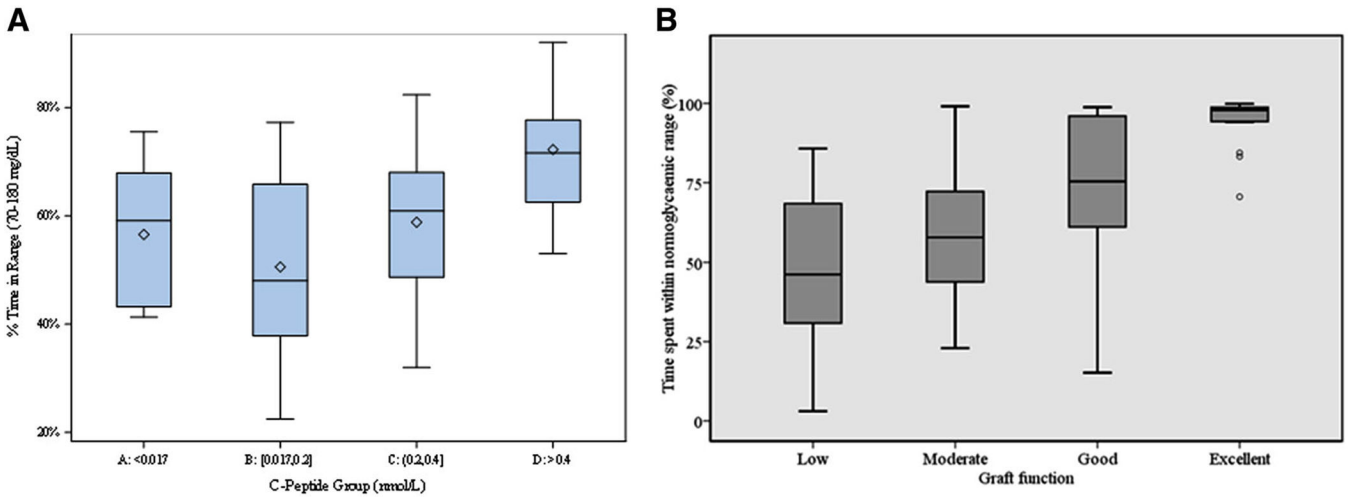

Figure 5.

(A) Relationship of residual MMTT peak C-peptide (negative, <0.02 ng/mL; low, 0.05–0.60 ng/mL; intermediate, >0.60–1.20 ng/mL; and high, >1.20 ng/mL) and time spent in glucose range 70–180 mg/dL by continuous glucose monitoring. (B) Relationship of islet transplant MMTT peak C-peptide (low, <0.60 ng/mL; moderate, 0.60–<1.50 ng/mL; good, 1.5-to–<3.0 ng/mL; and excellent, ≥3.0 ng/mL) and time spent in the glucose range of 54–180 mg/dL by continuous glucose monitoring. Data are from Refs. 89 (A) and 108 (B).

Table 1.

Stages in the pathogenesis of type 1 diabetes[19]

Nomeclature	Prestage 1	Stage 1	Stage 2	Stage 3
Natural history	Genetic and environmental susceptibility	Presymptomatic	Presymptomatic	Symptomatic
β cell autoimmunity	0–1 autoantibodies[a]	2 or more autoantibodies[b]	2 or more autoantibodies[b]	2 or more autoantibodies[b]
Glucose tolerance and glycemia	Normal, normoglycemia	Normal, normoglycemia	Impaired, dysglycemia	Diabetic, dysglycemia
First-phase insulin response	Normal	Normal to mild impairment	Impaired	Absent
β cell secretory capacity	Normal	Normal to moderate impairment	Variable impairment	Markedly impaired to absent

[a]T1D-associated autoantibodies include those against the β cell–specific antigens, glutamic acid decarboxylase 65 (GAD-65), the tyrosine phosphatase–related islet antigen 2 (IA-2), insulin (IAA), and zinc transporter 8 (ZnT8).

[b]The risk for disease progression toward diabetes is much less with a single autoantibody; however, some individuals with a single autoantibody do progress, and the clinical diagnosis of symptomatic T1D does not require the presence of multiple autoantibodies.