β-Cell Glucose Sensitivity to Assess Changes in β-Cell Function in Recent-Onset Stage 3 Type 1 Diabetes

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Diabetes 2023;72:1289–1296 | https://doi.org/10.2337/db23-0196

Following a diagnosis of type 1 diabetes (T1D), persisting C-peptide secretion leads to improved glycemic control and outcomes. Residual β-cell function is often assessed with serial mixed-meal tolerance tests, but these tests do not correlate well with clinical outcomes. Herein, we instead use β-cell glucose sensitivity (βGS) to assess changes in β-cell function, incorporating insulin secretion for a given serum glucose into the assessment of β-cell function. We evaluated changes in βGS in individuals enrolled in the placebo arm of 10 T1D trials performed at diabetes onset. We found that βGS showed a more rapid decline in children, as compared with adolescents and adults. Individuals in the top quartile of βGS baseline distribution had a slower rate in loss of glycemic control time over time. Notably, half of this group were children and adolescents. Finally, to identify predictors of glycemic control throughout follow-up, we ran multivariate Cox models and found that incorporating βGS significantly improved the overall model. Taken together, these data suggest that βGS may be of great utility in predicting those more likely to have a more robust clinical remission and may be of use in design of new-onset diabetes clinical trials and in evaluating response to therapies.

ARTICLE HIGHLIGHTS

- We undertook this study to better predict β-cell loss following type 1 diabetes diagnosis.
- We set out to answer whether β-cell glucose sensitivity (βGS) improves means to evaluate β-cell function postdiagnosis and whether βGS correlates with clinical outcomes.
- We found that βGS declines faster in children, subjects in the top baseline quartile of βGS exhibit slower β-cell decline (half are children), and incorporating βGS into multivariate Cox models for glycemic improves the model.
- The implications of our findings are that βGS predicts those likely to have robust clinical remissions and may help with clinical trials design.

Type 1 diabetes (T1D) results from autoimmune-mediated destruction of insulin-producing β-cells (1). At the time of diagnosis, up to 15–40% of β-cell function may remain, and there is a variable rate of loss over time. This remnant has a significant impact on clinical outcomes, with lower glycosylated hemoglobin, lower risk for severe hypoglycemia, and lower risk for complications in those with persisting β-cell function (2). Given the limitations in reaching target glycemic control with current technologies (3), there has been renewed interest in better understanding the natural history of β-cell loss postdiagnosis and identifying safe and effective means to preserve β-cell function.

C-peptide is widely accepted as a means to track changes in β-cell function, with investigators often using stimulation with a standardized mixed-meal tolerance test (MMTT) (4–6). In analysis of these studies, the focus is usually solely on the C-peptide area under the curve (AUC) in response to MMTT, which is also the primary end point in most clinical trials testing interventions after the onset of stage 3 T1D. However, this measure provides incomplete information about β-cell function because it fails to account for the

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Received 10 March 2023 and accepted 22 June 2023
This article contains supplementary material online at https://doi.org/10.2337/figshare.23565045.

prevailing glycemia. In fact, the C-peptide AUC in response to MMTT does not correlate well with standard clinical measures, such as HbA_{1c} or exogenous insulin dose (6). We have found that when endogenous insulin secretion is analyzed relative to the concomitant glucose concentration there is better correlation with β-cell function via a measure termed β-cell glucose sensitivity (βGS) (7). Such an analysis is often used widely in those at risk for or with type 2 diabetes (7); we have found that this parameter is predictive of risk for progression to T1D (8) but has not been used widely as a measure of β-cell function postdiagnosis. Here, we report how serial βGS measurements derived from the placebo groups from a series of new-onset T1D trials may be incorporated into evaluation of change in β-cell function postdiagnosis and how this measure correlates with relevant clinical outcomes.

RESEARCH DESIGN AND METHODS

Subjects

Data from the participants from 10 phase 2 new-onset T1D trials (Supplementary Table 1) were pooled and included in the analysis; the current study is based on the 266 patients in the placebo arms (9–18). Eligible participants were subjects aged 4–45 years at the time of screening, <100 days from diagnosis at the time of enrollment, and positive for at least one diabetes-associated autoantibody (microinsulin autoantibodies, tested only if duration of insulin therapy was <10 days, GAD, islet cell antigen-512 [ICA-512], or zinc transporter 8 [ZnT8] or islet cell autoantibodies [ICA]), with peak stimulated C-peptide of >0.2 nmol/L during an MMTT. Exclusion criteria included any serological or clinical evidence of infection; a positive purified protein derivative test; past infection with hepatitis B, C, or HIV; significant past cardiac disease; anemia, leukopenia, thrombocytopenia, or neutropenia; liver or renal dysfunction; ongoing use of diabetes medications other than insulin; vaccination with a live virus within 6 weeks before enrollment; and any other condition that might compromise study participation or confound interpretation of the results.

A total of 1,594 records were available (~6 per subject), each corresponding to an MMTT. All subjects had a baseline MMTT at study entry; thereafter, 253 were performed within 6 months from randomization, 338 between 6 and 12 months, 236 between 12 and 18 months, 205 between 18 and 24 months, 173 between 24 and 30 months, and 123 between 30 and 68 months.

Procedures

All participants received intensive diabetes management with the goal of achieving American Diabetes Association–recommended HbA_{1c} and glycemic targets. MMTTs were conducted according to standard procedures (4,12).

Laboratory Tests

Biochemical autoantibodies were assayed at the Barbara Davis Center for Diabetes (Aurora, CO) with radioimmunobinding assays, and islet cell autoantibodies were measured at the University of Florida, as previously described (12). C-peptide, HbA_{1c}, and serum chemistries were measured at the Northwest Lipid Metabolism and Diabetes Research Laboratories (Seattle, WA). All other routine laboratory measures were conducted locally.

β-Cell Function Model

β-Cell function was evaluated from MMTT glucose and C-peptide with modeling (19). The model describes the relationship between insulin secretion (expressed in pmol/min/m^2) and glucose concentration as the sum of two components. The first component represents the dependence of insulin secretion rate on glucose concentration through a dose response function. From the dose response, βGS (the mean slope) is calculated. The dose response is modulated by a potentiation factor, accounting for various mechanisms. The potentiation factor is constrained to average 1 during the test and expresses relative potentiation or inhibition of insulin secretion rate; its excursion is quantified by the ratio between the 2-h and the baseline value (potentiation ratio). The second secretory component represents the dependence of insulin secretion on the rate of change of glucose concentration and is determined by a single parameter (rate sensitivity), which is related to early insulin release (20). The model parameters were estimated from glucose and C-peptide concentrations (with use of C-peptide deconvolution [21] as previously described [19]). Basal insulin secretion rate and total insulin output during the whole test were also calculated.

Statistical Analysis

Data are presented as mean ± SD or median (interquartile range) if distribution was skewed. Baseline age was categorized as follows: <12 years old (children), ≥12 to <18 years old (adolescents), and ≥18 years old (adults). Group comparisons were performed with the Mann-Whitney *U* or Wilcoxon signed rank test (for unpaired and paired observations, respectively) and the χ^2 test for categorical variables. Linear mixed-effects models, with follow-up time as the predictor and age category as the fixed effect, were used to estimate the rate of decline of dependent variables over time. Kaplan-Meier plots were used to compare survival curves by means of the log-rank statistic. Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% CIs. The proportional hazards assumption was confirmed through examination of the log cumulative survival plots. *P* values are two sided, and $P < 0.05$ was accepted as statistically significant. All analyses were performed with JMP, version 9.0.1 (SAS Institute, Cary, NC).

Data and Resource Availability

Data and resources are available on request.

RESULTS

Baseline characteristics of the 266 participants are given in Supplementary Table 1. Age spanned four decades (4–46 years), and fasting plasma C-peptide concentrations covered a

30-fold range (43 to 1,298 pmol/L). While by selection all subjects had an MMTT-stimulated C-peptide >200 pmol/L, 18% had a fasting C-peptide ≤200 pmol/L.

β-Cell function was severely compromised in the group as a whole (Table 1). As a reference, in a group of healthy individuals (n = 213, mean age 33 years and BMI 22.7 kg/m^2) from the Relationship between Insulin Sensitivity and Cardiovascular disease (RISC) study (22), median βGS was 125 pmol/min/m^2 per mmol/L, rate sensitivity was 788 pmol/m^2 per mmol/L, the potentiation ratio was 1.86, fasting insulin secretion was 60 pmol/min/m^2, and total insulin output was 35 nmol/m^2. Thus, with the possible exception of fasting insulin secretion, all parameters of β-cell function were markedly abnormal in our participants.

Over the 2.5 years following the baseline assessment, body weight rose ∼10 kg, and glycemic control deteriorated despite a 50% increase in exogenous insulin dose (Fig. 1); all β-cell function parameters declined markedly, including fasting and 2-h insulin secretion on MMTT, βGS, and potentiation ratio (Supplementary Fig. 1).

To gauge the effect of age on metabolic control, we divided the subjects into the three categories of children (<12 years old), adolescents (12–18 years old), and adults (>18 years old). As shown in Table 1, baseline measures of endogenous insulin secretion and β-cell function were significantly reduced in children as compared with adolescents or adults. For quantitation of the rate of functional failure by age-group over the entire follow-up, both βGS and C-peptide AUC values were normalized to the baseline value. Normalized βGS declined significantly more slowly in adults than children (P = 0.003), while the difference between adults and adolescents did not reach statistical significance (P = 0.11) (Fig. 2*A*). Using the normalized C-peptide AUC yielded a similar result, though with this measure the decline in children and adolescents was similar (Fig. 2*B*).

To assess the impact of these functional differences on the clinical course, we used survival analysis with optimal glycemic control (i.e., HbA_{1c} ≤7% [53 mmol/mol]) as the outcome. Loss of optimal glycemic control was fastest in children, slowest in adults, and intermediate in adolescents (Fig. 3*A*). Subjects with a βGS falling in the top quartile of its baseline distribution lost glycemic control at a much slower rate than the remainder of the cohort (Fig. 4). As detailed in Table 2, approximately half of these individuals were age <18 years and at baseline both indices of glycemic control and β-cell functional parameters were far better than in the remainder of the cohort, with no significant difference in insulin dose.

As HbA_{1c} is influenced by the exogenous insulin dose, we also tested the time course of a >10% loss of baseline βGS as the censor in survival analysis. The results (Fig. 3*B*) show that adolescents and adults collapse onto a single function that is statistically significantly different from that of children. For the latter group, the median time to loss of glycemic control or exceeding a 10% decline in βGS is ∼10 months. By contrast, the median time to loss of glycemic control in adolescents and adults was ∼19 and 26 months, respectively. Interestingly, using a fasting C-peptide of <200 pmol/L as

Table 1—Baseline clinical and metabolic characteristics of patients recently diagnosed with T1D by age

	<12 years	≥12 to <18 years	≥18 years	*P*
n	52	121	93	
n male/*n* female	29/23	81/40	51/42	ns
Age (years)	9.3 ± 1.8	14.5 ± 1.6	27.4 ± 7.2	<0.0001
Body weight (kg)	35 ± 11	61 ± 15	72 ± 14	<0.0001
BMI (kg/m^2)	18.0 ± 3.0	21.5 ± 4.1	23.8 ± 3.4	<0.0001
Body surface area (m^2)	1.17 ± 0.22	1.68 ± 0.25	1.87 ± 0.21	<0.0001
Fasting glucose (mmol/L)	5.8 ± 1.2	6.4 ± 1.7	6.3 ± 1.3	ns
2-h glucose (mmol/L)	10.7 ± 2.8	10.7 ± 3.2	10.9 ± 3.3	ns
HbA_{1c} (%)	6.8 ± 1.1	7.1 ± 1.2	7.2 ± 1.8	ns
HbA_{1c} (mmol/mol)	51 ± 12	54 ± 13	55 ± 20	ns
Insulin dose (units/kg/day)	0.33 ± 0.19	0.44 ± 0.24	0.30 ± 0.18	<0.0001
Fasting C-peptide (pmol/L)	264 (212)	374 (248)	314 (201)	0.0013
C-peptide AUC (nmol/L/h)	1.50 (1.53)	2.92 (1.58)	2.84 (1.26)	<0.0001
C-peptide incremental AUC (nmol/L/h)	0.68 (0.73)	1.43 (1.03)	1.68 (0.91)	<0.0001
Fasting insulin secretion rate (pmol/min/m^2)	46 (43)	58 (37)	45 (29)	0.0016
Insulin secretion AUC_{2h} (nmol/m^2)	17.6 (16.4)	28.3 (15.6)	26.3 (12.8)	<0.0001
Glucose sensitivity (pmol/min/m^2 per mmol/L)	8.3 (12.6)	13.1 (17.0)	17.4 (16.3)	0.0018
Rate sensitivity (pmol/m^2 per mmol/L)	259 (262)	314 (343)	204 (343)	0.0155
Potentiation ratio	1.17 (0.47)	1.17 (0.44)	1.21 (0.44)	ns

Data are means ± SD or median (interquartile range) unless otherwise indicated.

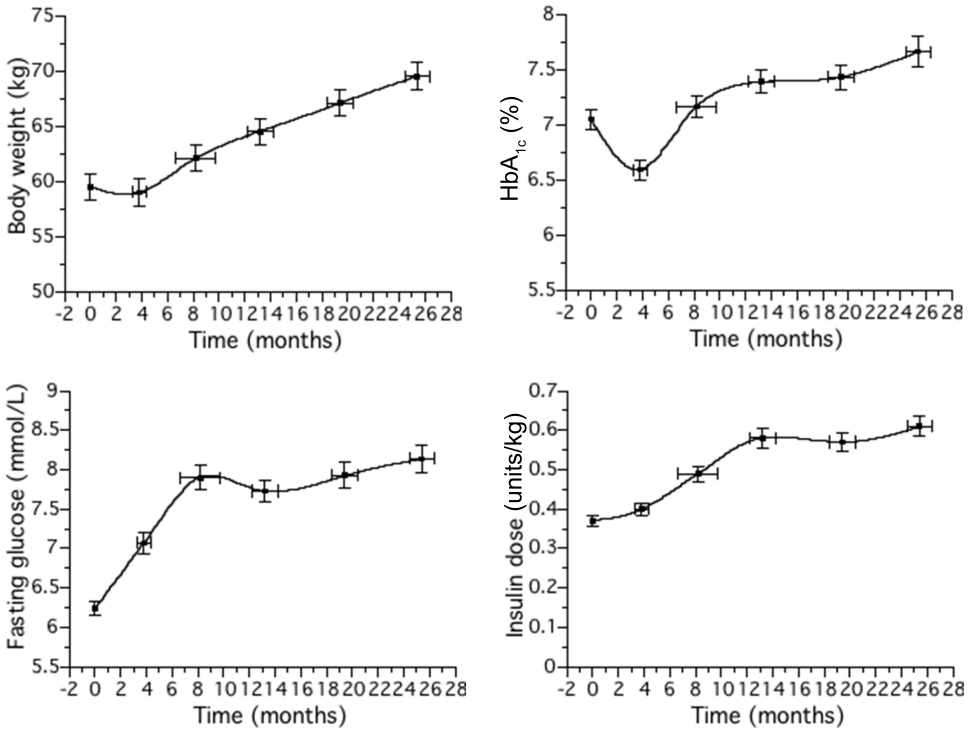

Figure 1—Time course of clinical parameters. Plots show mean ± SE (± SD for the timescale).

the discriminant was much less efficient in predicting either the clinical or the functional outcome (Supplementary Fig. 2).

To identify independent predictors of the clinical end point (i.e., $HbA_{1c} \leq 7\%$ (53 mmol/mol)), we ran multivariate Cox models using only anthropometrics and fasting measurements (plasma glucose and C-peptide [model I]) or adding conventional measurements from the MMTT (model I plus 2-h plasma glucose and the incremental area under the C-peptide response [model II]) or adding βGS (model II plus βGS [model III]). The results (Table 3) show that *1*) sex was not an independent predictor in any model; *2*) lower age, body weight, and insulin dose and higher HbA_{1c} were associated with a higher probability of HbA_{1c} exceeding the 7% (53 mmol/mol) threshold in all three models; *3*) 2-h glucose was not predictive and C-peptide incremental AUC added little to overall predictivity (as judged according to the χ^2 statistic); and *4*) βGS was an independent negative predictor of HbA_{1c} levels $\geq$7% (53 mmol/mol) and significantly improved the overall prediction.

The same three models were run to identify independent predictors of the physiologic end point (i.e., a >10% drop in normalized βGS). The results (Table 4) show that, while baseline HbA_{1c} is no longer a significant predictor, overall predictivity (as the χ^2) improves with addition of MMTT parameters to fasting parameters and is maximized when βGS is included.

With all records included (n = 1,427), both MMTT insulin output and βGS were reciprocally related to insulin dose (with r values of 0.50 and 0.47, respectively); the relationships predict that, at an insulin dose of 1 unit/kg/day, insulin output averages 5.6 nmol/m^2 and βGS is 2.2 pmol/min/m^2 per mmol/L; i.e., residual β-cell function is minimal (Supplementary Fig. 3).

DISCUSSION

Accurate assessment of persisting β-cell function following T2D diagnosis holds importance for several reasons. Long-term outcome studies such as those from the Diabetes Control and Complications Trial (DCCT) demonstrate that persisting endogenous C-peptide secretion impacts clinical care, with reduction in acute risks such as severe hypoglycemia and chronic concerns from microvascular and macrovascular complications (2). Investigators now seek safe and effective means to preserve β-cell function in those at risk for or with recent-onset T1D, and accurate means of monitoring such function over time is vital to demonstrating the impact of such therapies.

There is general consensus that C-peptide serves as an important marker of endogenous β-cell function (4), and it has been incorporated into natural history and intervention studies. Responses to provocative stimuli, most often an MMTT, have proven to be more informative than fasting measures (5). However, the challenge has been that the MMTT often does not correlate well with clinical markers, such as glycemic control and exogenous insulin use (5,6). The salutary effects on clinical measures are required by regulatory agencies in the later stages of drug development as drugs are considered for clinical approval. One reason for this disconnection of C-peptide AUC from MMTTs and

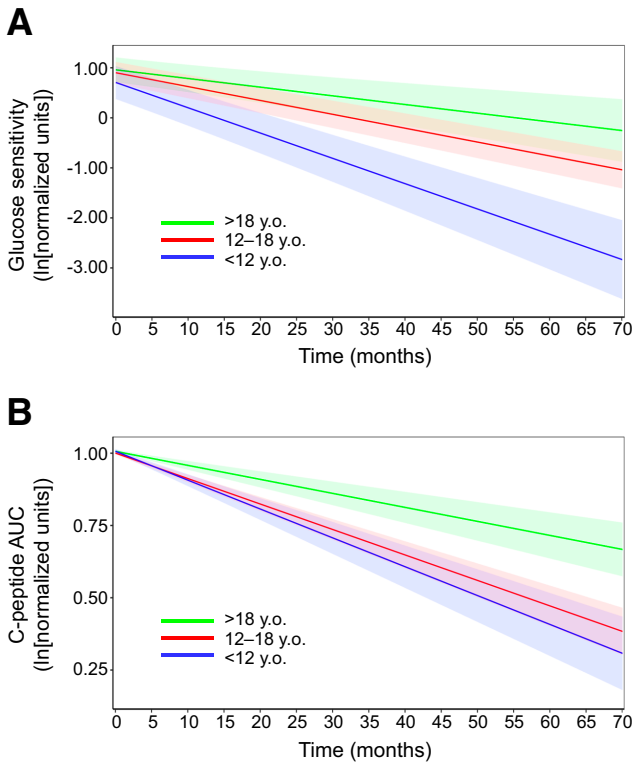

Figure 2—Decline in normalized glucose sensitivity (*A*) and normalized C-peptide AUC (*B*) by age-group. *A*: Normalized βGS declined more slowly in adults than children (P = 0.003); the difference between adults and adolescents did not reach statistical significance (P = 0.11). *B*: C-peptide AUC yielded a similar result, but the decline in children and adolescents was similar. y.o., years old.

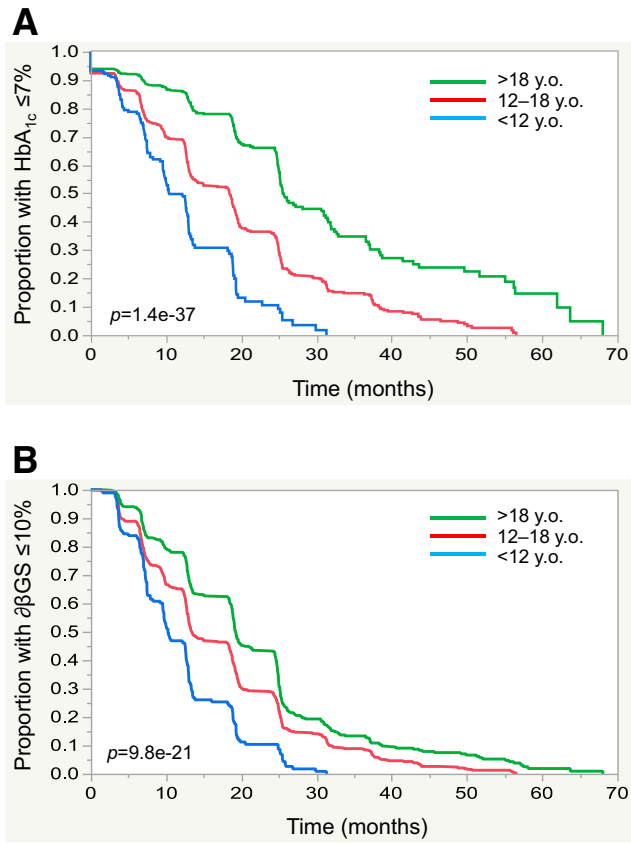

Figure 3—Probability of exceeding an HbA_{1c} value of 7% (53 mmol/mol) (*A*) or a value of βGS dropping by >10% from baseline (*B*) throughout follow-up by age-group. y.o., years old.

clinical outcomes might be that looking at the C-peptide responses does not take into account glycemic excursion and focuses solely on insulin secretion. An alternate measure that has gained traction and is used widely in assessing β-cell function in type 2 diabetes has been βGS (7). This measure is derived from data collected during an MMTT and incorporates into the assessment not only insulin secretion but also response to a given glucose. βGS proved to be an early measure predictive of progression to T1D in autoantibody-positive individuals in the Diabetes Prevention Trial–Type 1 (DPT-1), preceding changes in glucose levels, insulin secretion, or insulin sensitivity based on oral glucose tolerance test assessments (8). In the current study we evaluate the use of βGS to assess the change in β-cell function following diagnosis. The goals of this analysis were as follows: *1*) to define how βGS changed during the first 2 years postdiagnosis, *2*) to test whether patterns of change in βGS vary by age, and *3*) to relate residual β-cell function, as assessed by βGS, to the clinical outcome of maintaining HbA_{1c} ≤7% (53 mmol/mol).

As expected, all baseline measures of β-cell function in subjects with new-onset stage 3 T1D, culled from the placebo groups of 10 new-onset T1D clinical trials, were markedly abnormal and declined significantly over the ensuing months. Although change in C-peptide AUC has often been used in evaluating change in β-cell function over time, evidence showing a correlation between C-peptide AUC and glycemic control or exogenous insulin use is limited. Comparison of βGS differed from C-peptide AUC in several key aspects. In evaluation of change by age, βGS showed a more rapid decline in children, as compared with adolescents and adults, whereas C-peptide AUC demonstrated a comparable decline in both children and adolescents. We also found that

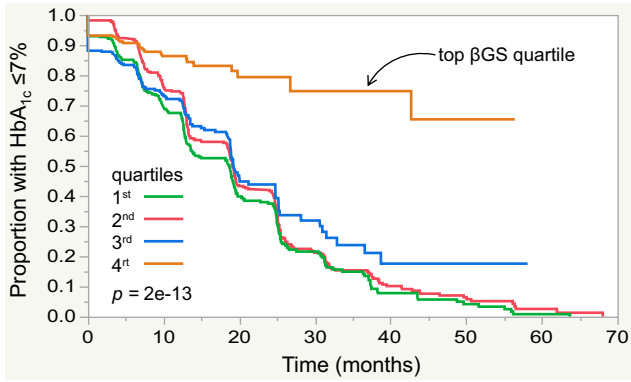

Figure 4—Probability of exceeding an HbA_{1c} value of 7% (53 mmol/mol) throughout follow-up by quartile of baseline βGS.

Table 2—Clinical and metabolic characteristics of patients recently diagnosed with T1D by baseline glucose sensitivity

	Top quartile	Lower quartiles	*P*
Glucose sensitivity (pmol/min/m^2 per mmol/L)	35.5 (32.3)	8.1 (10.6)	<0.0001
n male/*n* female	42/24	119/81	ns
Age (years)	20.3 ± 9.4	17.2 ± 8.0	0.0132
Children/adolescents/adults (%)	12/39/48	22/34/45	ns
BMI (kg/m^2)	23.7 ± 4.5	20.9 ± 3.8	<0.0001
Fasting glucose (mmol/L)	5.48 ± 0.74	6.50 ± 1.50	<0.0001
2-h glucose (mmol/L)	7.69 ± 1.80	11.8 ± 2.82	<0.0001
HbA_{1c} (%)	6.5 ± 1.3	7.2 ± 1.4	<0.0001
HbA_{1c} (mmol/mol)	48 ± 14	55 ± 15	<0.0001
Insulin dose (units/kg/day)	0.30 (0.25)	0.35 (0.28)	ns
Fasting C-peptide (pmol/L)	473 (291)	297 (195)	<0.0001
C-peptide AUC (nmol/L/h)	2.11 (1.06)	1.22 (0.69)	<0.0001
C-peptide incremental AUC (nmol/L/h)	1.16 (0.72)	0.61 (0.40)	<0.0001
Fasting insulin secretion rate (pmol/min/m^2)	69 (43)	46 (32)	<0.0001
Insulin secretion AUC_{2h} (nmol/m^2)	22.7 (11.0)	13.7 (7.1)	<0.0001
Rate sensitivity (pmol/m^2 per mmol/L)	438 (565)	241 (258)	0.0001
Potentiation ratio	1.33 (0.41)	1.14 (0.41)	0.0015

Data are mean ± SDs or median (interquartile range) unless otherwise indicated.

children showed a faster loss of >10% baseline βGS, with adolescents and adults declining at a slower and comparable rate. In further analysis, we noted that for the cohort of children, the median time to 10% loss in βGS and time to HbA_{1c} >7% (53 mmol/mol) was ∼10 months. The clinical importance of βGS is highlighted in evaluation of the top quartile of baseline distribution for this measure, with such subjects exhibiting a much slower rate in loss of glycemic control time over time, with loss defined by HbA_{1c} >7% (53 mmol/mol). Prior analysis of changes in β-cell function and metabolic control would suggest that this group would be largely adults, and yet almost half of this group was comprised of children and adolescents. These data suggest that more precise baseline measures of β-cell function, rather than reliance on demographic features such as age, could be leveraged to stratify individuals most likely to benefit from intervention with disease-modifying therapies.

Finally, to identify predictors of the clinical end point of HbA_{1c} <7% (53 mmol/mol), we ran multivariate Cox models and found that incorporating βGS into anthropometrics and fasting measurements, along with MMTT measures, significantly improved the overall model. Similarly, the models to predict a physiological end point, >10% drop in βGS, were maximized with use of baseline βGS. Thus, we have

Table 3—Probability of HbA_{1c} ≥7% (53 mmol/mol) throughout the follow-up

	Model I: fasting parameters only	Model II: model I + MMTT parameters	Model III: model II + glucose sensitivity
Male/female	1.02 (0.86–1.21)	1.00 (0.84–1.19)	0.99 (0.83–1.18)
Age (10 years)	**0.57 (0.47–0.67)**	**0.57 (0.47–0.70)**	**0.60 (0.50–0.71)**
Body weight (10 kg)	**0.87 (0.82–0.93)**	**0.88 (0.834–0.93)**	**0.87 (0.82–0.92)**
Baseline HbA_{1c} (1% or 10.9 mmol/mol)	**1.34 (1.28–1.39)**	**1.33 (1.27–1.39)**	**1.33 (1.27–1.39)**
Insulin dose (0.2 units/kg/day)	**0.90 (0.85–0.96)**	**0.90 (0.84–0.95)**	**0.91 (0.85–0.96)**
Fasting glucose (1 mmol/L)	1.02 (0.99–1.06)	1.02 (0.97–1.06)	1.02 (0.98–1.07)
Fasting C-peptide (100 pmol/L)	**1.09 (1.05–1.14)**	**1.15 (1.06–1.24)**	1.03 (0.91–1.14)
2-h glucose (2 mmol/L)		1.00 (0.93–1.07)	0.95 (0.88–1.02)
C-peptide incremental AUC (1 nmol/L/h)		0.82 (0.62–1.10)	**1.65 (1.07–2.60)**
Glucose sensitivity (5 pmol/min/m^2 per mmol/L)			**0.81 (0.73–0.90)**
χ^2	346	348	368

Data are HR (95% CI) from multivariate Cox models. The χ^2 for glucose sensitivity alone is 68. Values in bold indicate where the 95% CI does not cross 1.

Table 4—Probability of glucose sensitivity (normalized) dropping by ≥10% throughout the follow-up

	Model I: fasting parameters only	Model II: model I + MMTT parameters	Model III: model II + glucose sensitivity
Male/female	0.91 (0.79–1.06)	0.87 (0.75–1.01)	**0.85 (0.74–0.99)**
Age (10 years)	**0.69 (0.61–0.77)**	**0.68 (0.61–0.77)**	**0.74 (0.65–0.83)**
Body weight (10 kg)	**0.92 (0.87–0.96)**	**0.93 (0.88–0.97)**	**0.91 (0.87–0.96)**
Baseline HbA_{1c} (1%)	0.98 (0.93–1.03)	0.96 (0.91–1.01)	0.96 (0.91–1.01)
Insulin dose (0.2 units/kg/day)	**0.89 (0.84–0.93)**	**0.86 (0.82–0.91)**	**0.88 (0.83–0.93)**
Fasting glucose (1 mmol/L)	1.03 (1.00–1.06)	1.01 (0.97–1.05)	1.02 (0.98–1.07)
Fasting C-peptide (100 pmol/L)	**1.03 (1.02–1.09)**	**1.16 (1.10–1.22)**	1.06 (0.99–1.13)
2-h glucose (2 mmol/L)		0.99 (0.94–1.05)	**0.92 (0.87–0.98)**
C-peptide incremental AUC (1 nmol/L/h)		**0.66 (0.54–0.81)**	1.23 (0.91–1.68)
Glucose sensitivity (5 pmol/min/m^2 per mmol/L)			**0.82 (0.76–0.89)**
χ^2	127	143	176

Data are HR (95% CI) from multivariate Cox models. The χ^2 for glucose sensitivity alone is 22. Values in bold indicate where the 95% CI does not cross 1.

identified a physiologic measure that can be used in predicting decline in β-cell function over time, rather than relying on age at diagnosis.

Improved measures to predict change in β-cell function over time may have important implications for clinical care and for the design of intervention studies. Those individuals with lower βGS may experience a shorter remission or "honeymoon" phase, thus meriting closer follow-up and potentially earlier implementation of technologies to optimize glycemic control, such as use of hybrid closed loop pump technology. For clinical trials, one challenge in designing and interpreting study results is the tremendous heterogeneity in change in β-cell function over time (5,23). By virtue of the ability to enroll subjects who are at higher risk for β-cell functional loss over time, one may be able to conduct smaller studies and more readily demonstrate a difference between placebo and a successful intervention strategy, though the generalizability of the study results would be impacted. Future studies should focus on reevaluation of the impact of various interventions on change in βGS. We had the opportunity to use βGS as a secondary end point in a new-onset T1D trial with imatinib and found that this measure readily distinguished the treatment group from the placebo group, and unlike change in C-peptide AUC, βGS correlated with lower exogenous insulin dose and improved glycemic control (14). Thus, βGS may offer a better primary end point for evaluation of therapies to preserve β-cell function in new-onset T1D trials.

The strengths of this study include the large group of participants, drawn from 10 phase 2 new-onset T1D clinical trials. These subjects were well characterized and preselected to have complete baseline measures and serial assessments over a 2-year period. The weaknesses of the study are that the subjects enrolled into clinical research trials may not be representative of a standard clinical population and may have been more carefully monitored and had more intensive diabetes management. The group was largely Caucasian and non-Hispanic and was somewhat underrepresented in the <12 years age-group relative to older groups.

In summary, βGS offers a novel means to assess change in β-cell function over time for those with new-onset T1D. This measure may be of great utility in predicting those most likely to have a more robust clinical remission and may be of use in new-onset T1D clinical trials design and in evaluating response to therapies.

Funding. This work was supported by National Institutes of Health grant R21 DK119800-01A1 (to E.F., S.E.G., and C.E.-M.).

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. S.E.G., C.E.-M., and E.F. conceived of the study, obtained funding, reviewed data analysis, and wrote the manuscript. A.G. and A.M. conducted the data analysis and edited the manuscript. S.E.G., C.E.-M., and E.F. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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