Glycemic Variability in Patients With Early Type 2 Diabetes: The Impact of Improvement in β-Cell Function

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OBJECTIVE

Increased glycemic variability has been reported to be associated with the risk of hypoglycemia and possibly diabetes complications and is believed to be due to β-cell dysfunction. However, it is not known whether improvement in β-cell function can reduce glycemic variability. Because short-term intensive insulin therapy (IIT) can improve β-cell function in early type 2 diabetes (T2DM), our objective was to determine whether the β-cell functional recovery induced by this therapy is associated with decreased glycemic variability.

RESEARCH DESIGN AND METHODS

Sixty-one patients with T2DM of 3.0 years mean duration underwent 4 weeks of IIT, which consisted of basal insulin detemir and premeal insulin aspart. Glucose variability was assessed in both the first and the last week by the coefficient of variation of capillary glucose on daily 6-point self-monitoring profiles. β-Cell function before and after IIT was assessed with the Insulin Secretion-Sensitivity Index-2 (ISSI-2).

RESULTS

Between the first and the last week on IIT, 55.7% of patients had a reduction in glucose variability. Change in glucose variability was negatively correlated with the change in β-cell function (ISSI-2) ($r = -0.34$, $P = 0.008$). On multiple linear regression analyses, percentage change in ISSI-2 emerged as the only factor independently associated with the change in glucose variability (standardized $\beta = -0.42$, $P = 0.03$). Moreover, patients with an increase in ISSI-2 ≥25% experienced a reduction in glucose variability compared with their peers who had almost no change (-0.041 ± 0.06 vs. -0.0002 ± 0.04, respectively; $P = 0.006$).

CONCLUSIONS

In early T2DM, glycemic variability is a modifiable parameter that can be reduced by improving β-cell function with short-term IIT.

Diabetes Care 2014;37:1116–1123 | DOI: 10.2337/dc13-2591

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Received 5 November 2013 and accepted 21 December 2013.

This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc13-2591/-/DC1.

There is currently considerable interest and controversy regarding the impact of glycemic variability as a risk factor for diabetes complications above and beyond the mean glycemic exposure that is typically captured by hemoglobin A_{1c} (HbA_{1c}) measurement in clinical practice (1,2). Of note, previous reports suggested that acute oscillations of blood glucose have a more deleterious effect on endothelial function than constant hyperglycemia in patients with type 2 diabetes (T2DM) (3,4), which may support the concept that glycemic variability can induce oxidative stress and thereby affect the pathophysiologic pathways through which diabetes complications arise (5). However, although some studies have reported that increased glycemic variability may be associated with the incidence of diabetic retinopathy (6,7), diabetic neuropathy (8), and coronary artery calcification (9) in patients with T2DM and type 1 diabetes (T1DM), other studies have not supported this association (10–12). Nevertheless, although its relevance to vascular complications remains uncertain (13), at a given level of glycemia, increased glucose variability raises the risk of hypoglycemia (14–16) and, hence, is clinically important.

The pathophysiologic basis underlying glycemic variability in patients with diabetes is believed to be β-cell dysfunction. Specifically, cross-sectional studies in both T2DM and T1DM have reported an association between poorer β-cell function and increased glucose variability (17–19). However, it is not known whether improvement of β-cell function can reduce glycemic variability. In this context, it is of interest that short-term intensive insulin therapy (IIT) for 2–5 weeks is an intervention that can improve β-cell function early in the course of T2DM, as recently demonstrated in a meta-analysis of seven studies (20,21). Thus, in light of these data, the objective of the current study was to determine whether improvement in β-cell function induced by short-term IIT can reduce glycemic variability in patients with early T2DM.

RESEARCH DESIGN AND METHODS

Study Population

The study population comprised adult patients with T2DM who underwent a short course of IIT to determine eligibility for a clinical trial (clinical trial reg. no. NCT01270789, clinicaltrials.gov). The protocol for this IIT phase has been previously described in detail (22). In brief, inclusion criteria were duration of diabetes ≤7 years, treatment with zero to two oral antidiabetic medications, and baseline HbA_{1c} between 5.5 and 9.0% inclusive if on oral antidiabetic medications or between 6.0 and 10.0% inclusive if not on antidiabetic medications. Exclusion criteria were current insulin therapy, renal/hepatic dysfunction, malignancy, and chronic infection. The study protocol was approved by the Mount Sinai Hospital Research Ethics Board, and all participants provided written informed consent.

Study Design

At the start of the study, participants stopped all antidiabetic medications (metformin or sulfonylurea; no participants were taking thiazolidinediones, dipeptidyl peptidase-4 inhibitors, or glucagon-like peptide-1 agonists) for at least 36 h and underwent an overnight fast before their baseline 2-h, 75-g oral glucose tolerance test (OGTT) the next morning. After the OGTT, participants began a 4-week course of multiple daily insulin injection therapy consisting of basal insulin detemir and premeal insulin aspart with starting total daily doses of 0.2–0.4 units/kg (60% bolus insulin and 40% basal insulin). This course of IIT was extended to 5–6 weeks in 19 participants (generally because of patient scheduling issues). While on IIT, participants were asked to perform self-monitoring of capillary blood glucose (SMBG) at least four times per day, including *1*) fasting glucose daily; *2*) premeal glucose at each of breakfast, lunch, and dinner at least four times per week (each); and *3*) 2-h postprandial glucose after each of breakfast, lunch, and dinner at least four times per week (each). The pre- and postmeal SMBG was generally performed on the same day. SMBG records were sent to the study nurse at least three times per week, enabling titration of insulin doses to target fasting glucose between 4.0 and 6.0 mmol/L and 2-h postprandial glucose <8 mmol/L. Hypoglycemia was defined as capillary blood glucose ≤3.9 mmol/L and was classified as severe if it required third-party assistance and/or involved impairment of consciousness. On the final day of IIT, the last insulin dose was the bolus insulin before dinner, with no bedtime basal insulin. A 2-h OGTT was performed the day after cessation of IIT, using the same protocol as at baseline.

Assessment of Glucose Variability

Glucose variability was assessed from SMBG during the first and last weeks on IIT using the following steps:

1. For each participant, the mean of capillary glucose at each of six time points (before and 2 h after each of breakfast, lunch, and dinner) was calculated for both the first week and the last week on IIT. All participants had at least four SMBG measurements at each time point in both the first and the last weeks on IIT.
2. Based on the mean capillary glucose for each of the six time points, the glucose coefficient of variation (CV) was calculated for both the first week and the last week on IIT for each participant so that each participant had a CV for the first week and a CV for the last week. Each CV was calculated using the following equation: CV = SD/mean, where the SD is of the glucose measurements from the six time points and the mean refers to the mean of these measurements [i.e., mean = (prebreakfast capillary glucose + 2-h postbreakfast capillary glucose + prelunch capillary glucose + 2-h postlunch capillary glucose + predinner capillary glucose + 2-h postdinner capillary glucose)/6].
3. The change in glucose variability was calculated as the difference between glucose CV in the last week on IIT and glucose CV in first week on IIT (change in capillary glucose CV = $CV_{\text{last week}} - CV_{\text{first week}}$).

The measurement of CV as a method to quantify glucose variability is widely accepted (2,23) and among measures of glucose variability, is recognized as offering the advantage of adjustment for the mean level of glycemia (23). In sensitivity analyses, we also determined

the mean amplitude of glycemic excursion (MAGE) at the first and last weeks on IIT; we calculated MAGE as the average of all capillary glucose excursions that were >1 SD above or below the mean glucose level (24). In this analysis, change in glycemic variability was calculated as the difference between MAGE in the last week on IIT and MAGE in the first week on IIT. Of the 63 study participants, 61 had SMBG measurements at all the time points required for the calculation of glucose variability and were included in the current analysis.

Laboratory Measurements

During each OGTT, venous blood samples were drawn for the measurement of glucose, insulin, and C-peptide at fasting and at 30, 60, 90, and 120 min following ingestion of the 75-g glucose load. Specific insulin levels were measured with the Roche Elecsys 1010 immunoassay analyzer and electrochemiluminescence immunoassay kit (Roche Diagnostics, Laval, QC, Canada). C-peptide was measured with the Roche Modular system and the electrochemiluminescence immunoassay kit (Roche Diagnostics).

Area under the insulin curve (AUC_{ins}) and area under the glucose curve (AUC_{gluc}) during the OGTT were calculated using the trapezoidal rule. As previously described (22), β-cell function was assessed on each OGTT with the Insulin Secretion-Sensitivity Index-2 (ISSI-2), a validated OGTT-derived measure of β-cell function that is analogous to the disposition index obtained from the intravenous glucose tolerance test (25,26). ISSI-2 has been directly validated against the disposition index from the intravenous glucose tolerance test, with which it exhibits a stronger correlation than other OGTT-derived measures of β-cell function (including insulinogenic index-based measures and the homeostasis model assessment [HOMA] of β-cell function) (26), and has been used to measure β-cell function in several previous studies, including both clinical trials and observational studies in patients with and without diabetes (22,26–31). ISSI-2 is defined as the product of *1*) insulin secretion measured by the ratio of AUC_{ins} to AUC_{gluc} and *2*) insulin sensitivity measured by the Matsuda index (25,26), such that ISSI-2 = (AUC_{ins}/AUC_{gluc}) × Matsuda index. The Matsuda index is a validated measure of whole-body insulin sensitivity calculated from plasma glucose and insulin concentrations during OGTT as follows: Matsuda index = $10{,}000/\sqrt{(MG \times MI) \times (FG \times FI)}$ where MG is mean glucose on OGTT, MI is mean insulin on OGTT, FG is fasting glucose, and FI is fasting insulin (32). HOMA of insulin resistance (HOMA-IR) was calculated as a measure of primarily hepatic insulin resistance (33). In sensitivity analyses, we also evaluated β-cell function on each OGTT as determined by (ΔC-peptide$_{0–120}$/Δglucose$_{0–120}$) × Matsuda index, calculated as described by DeFronzo et al. (34).

Statistical Analyses

All analyses were conducted using SPSS version 18.0 statistical software (IBM Corporation, Chicago, IL). Continuous variables were tested for normality of distribution, and natural log transformations of skewed variables were used where necessary. Variables with normal distribution are presented as mean ± SD, and those with nonnormal distribution are presented as median (25th–75th) (Table 1). Univariate associations between the change in glucose variability (change in glucose CV) and participant characteristics were assessed by Spearman correlation analysis (Table 2 and Fig. 1*B*). Multiple linear regression analyses of (dependent variable) change in glucose variability (change in CV glucose) were performed with a core model consisting of the following variables: age, duration of diabetes, and BMI (Table 3). Further analyses were performed with the addition of the following covariates: baseline HbA_{1c} (model 1); baseline HbA_{1c} and percentage change in HOMA-IR (model 2); baseline HbA_{1c} and percentage change in ISSI-2 (model 3); baseline HbA_{1c}, percentage change in ISSI-2, and final insulin dosage (model 4); and baseline HbA_{1c}, percentage change in ISSI-2, and change in mean glucose (model 5). As previously described (22), an increase in ISSI-2 ≥25% between the baseline and post-IIT OGTT assessments has been considered indicative of a robust improvement in β-cell function. The change in glucose CV was compared between participants with and without such an improvement by Student *t* test (Fig. 1*C*).

RESULTS

The study population comprised 61 participants (39 men [64%], 44 white ethnicity [72%]) with a mean age of 58.8 ± 8.3 years, duration of diabetes of 3.0 ± 2.1 years, and a median (25th–75th) HbA_{1c} of 6.6% (6.3–7.2%) (or 49 [45–55] mmol/mol). While on IIT, the median (25th–75th) rate of hypoglycemic events was 0.20 (0.0–0.62) per person-year, and there were no severe episodes. After IIT, as shown in Table 1, the study participants had significantly lower fasting glucose, HbA_{1c}, and HOMA-IR and better β-cell function (ISSI-2).

From the first week to the last week on IIT, there was an overall improvement in glucose variability as reflected by a significant decrease in capillary glucose CV (0.14 ± 0.05 vs. 0.12 ± 0.04, P = 0.05). Figure 1*A* presents the distribution of participants according to change in glucose CV, showing that 55.7% had a reduction in glucose variability in response to IIT.

On Spearman correlation analysis (Table 2), the change in glucose CV was not associated with any of the baseline characteristics of the participants or the insulin doses. However, it was negatively correlated with the change in ISSI-2 following IIT (r = −0.34, P = 0.008) and positively associated with the change in HOMA-IR (r = 0.28, P = 0.03). The relationship between change in glucose CV and change in ISSI-2 is shown in Fig. 1*B*.

We next performed multiple linear regression analyses of (dependent variable) change in glucose CV to identify independent determinants of this change (Table 3). On these analyses, percentage change in ISSI-2 emerged as the only covariate independently associated with the change in glucose variability (models 3–5). As shown in the fully adjusted model (model 4), percentage change in ISSI-2 was a negative predictor of the change in glucose CV (standardized β = −0.42, P = 0.03). Inclusion of the change in mean

Table 1—Characteristics of study population before and after short-term IIT

Characteristics	Value
No. participants	61
Baseline characteristics	
Age (years)	58.8 ± 8.3
Male sex	63.9
Ethnicity	
White	72.1
Other	27.9
Duration of diabetes (years)	3.0 ± 2.1
BMI (kg/m^2)	29.8 ± 6.3
Systolic blood pressure (mmHg)	124.7 ± 15.0
Diastolic blood pressure (mmHg)	70.8 ± 9.7
Creatinine (μmol/L)	72.2 ± 12.6
Alanine aminotransferase (IU/L)	24 (19–38)
Aspartate aminotransferase (IU/L)	24 (18–27)
Fasting plasma glucose (mmol/L)	6.7 ± 1.25
HbA_{1c} (%)	6.6 (6.3–7.2)
HbA_{1c} (mmol/mol)	49 (45–55)
HOMA-IR	3.9 (2.5–5.7)
ISSI-2	182.6 (123–235)
IIT	
Initial basal insulin dosage (units/kg)	0.08 (0.07–0.09)
Initial meal insulin dosage (units/kg)	0.10 (0.09–0.12)
Final basal insulin dosage (units/kg)	0.21 (0.13–0.40)
Final meal insulin dosage (units/kg)	0.18 (0.12–0.30)
Hypoglycemic episodes	
Any hypoglycemia (per person-year)	0.20 (0–0.62)
Number of severe episodes	0
SMBG	
Premeal glucose in first week (mmol/L)	6.5 ± 0.9
Premeal glucose in last week (mmol/L)	5.5 ± 0.5***
Postprandial glucose in first week (mmol/L)	7.8 ± 1.3
Postprandial glucose in last week (mmol/L)	6.4 ± 0.6***
After IIT	
BMI (kg/m^2)	29.4 ± 6.2**
Systolic blood pressure (mmHg)	122.8 ± 12.4
Diastolic blood pressure (mmHg)	68.9 ± 10.4
Alanine aminotransferase (IU/L)	26 (21–34)
Aspartate aminotransferase (IU/L)	25 (21–30)
Fasting plasma glucose (mmol/L)	6.2 ± 1.0*
HbA_{1c} (%)	6.2 (6.0–6.5)**
HbA_{1c} (mmol/mol)	44 (42–48)**
HOMA-IR	2.9 (1.7–4.7)**
ISSI-2	190.4 (144–291)*

Data are mean ± SD, %, or median (25th–75th), unless otherwise indicated. *$P < 0.05$ for the comparison between baseline and after IIT. **$P < 0.001$ for the comparison between baseline and after IIT. ***$P < 0.001$ for comparison of SMBG between first week and last week.

glucose did not change this association (model 5). In other words, the improvement in β-cell function induced by IIT was independently associated with reduction in glucose variability.

Finally,we compared the change in glucose CV between participants with change in ISSI-2 ≥25% (n = 21) and those with change in ISSI-2 <25% (n = 40) because this threshold (25%) has been previously defined as indicative of a robust improvement in β-cell function (22). Supplementary Fig. 1 presents the mean capillary glucose levels in the first week and last week of IIT in the participants with change in ISSI-2 <25% (Supplementary Fig. 1*A*) and those with change in ISSI-2 ≥25% (Supplementary Fig. 1*B*), showing the comparatively lesser glycemic variability of the latter group in the last week. Indeed, participants who achieved the ≥25% increment in ISSI-2 had a reduction in glucose CV (−0.041 ± 0.06), whereas those who did not experience such an improvement in ISSI-2 had almost no change in glucose CV (−0.0002 ± 0.04; P = 0.006 for comparison between the groups) (Fig. 1*C*).

To evaluate the robustness of the findings, we performed a series of sensitivity analyses. First, to eliminate the effect of insulin titration, we repeated the analyses, including the change in insulin dosage from baseline to the last week as a covariate. With this approach, the improvement in β-cell function again emerged as an independent determinant of the change in glycemic variability (standardized β = −0.45, P = 0.02) (data not shown). Second, we repeated all the analyses using MAGE and confirmed that the findings were unchanged. Specifically, *1*) MAGE decreased from the first week to the last week (1.91 ± 0.9 vs. 1.29 ± 0.64 mmol/L, $P < 0.001$), *2*) the change in MAGE over this time was inversely and significantly associated with the change in ISSI-2 (r = −0.40, P = 0.001), *3*) change in ISSI-2 was an independent predictor of the change in MAGE from the first to the last week (standardized β = −0.38, P = 0.04), and *4*) there was a reduction in MAGE in participants who had an increment in ISSI-2 ≥25% compared with those without such an improvement in β-cell function (−1.07 ± 0.9 vs. −0.38 ± 0.9 mmol/L, respectively; P = 0.01). Finally, we repeated the analyses using (ΔC-peptide$_{0–120}$/Δglucose$_{0–120}$) × Matsuda index as an alternate measure of β-cell function. With this measure of β-cell function, the results were unchanged. Specifically, *1*) the change in glycemic CV between the first and last weeks was inversely and significantly associated with the change in (ΔC-peptide$_{0–120}$/Δglucose$_{0–120}$) × Matsuda index (r = −0.33, P = 0.007), and *2*) the percentage change in (ΔC-peptide$_{0–120}$/Δglucose$_{0–120}$) × Matsuda index was an independent predictor of the change in glycemic CV from the first to the last week (standardized β = −0.27, P = 0.04).

CONCLUSIONS

In this study, we demonstrate that in patients with early T2DM, glycemic variability can be significantly improved

Table 2—Spearman correlations between change in glucose CV and patient characteristics at baseline and after short-term IIT

	r	*P* value
Baseline		
Age	0.02	0.90
Duration of diabetes	0.07	0.62
BMI	0.04	0.78
Systolic blood pressure	0.01	0.96
Diastolic blood pressure	−0.15	0.24
Creatinine	0.03	0.80
Alanine aminotransferase	−0.10	0.44
Aspartate aminotransferase	−0.02	0.89
Fasting plasma glucose	−0.01	0.92
HbA_{1c}	−0.23	0.08
HOMA-IR	0.12	0.36
ISSI-2	0.13	0.33
Insulin therapy		
Initial basal insulin dosage per kg	−0.17	0.19
Initial meal insulin dosage per kg	−0.08	0.55
Final basal insulin dosage per kg	0.02	0.87
Final meal insulin dosage per kg	0.09	0.50
Rate of hypoglycemia	0.12	0.37
After IIT		
Change in BMI	0.04	0.74
Change in systolic blood pressure	−0.21	0.10
Change in diastolic blood pressure	−0.17	0.18
Change in alanine aminotransferase	0.02	0.87
Change in aspartate aminotransferase	0.02	0.88
Change in fasting plasma glucose	0.16	0.23
Change in HbA_{1c}	0.19	0.14
Change in mean glucose	0.13	0.33
Change in HOMA-IR	**0.28**	**0.03**
Change in ISSI-2	**−0.34**	**0.008**

Boldface type indicates significance at $P < 0.05$.

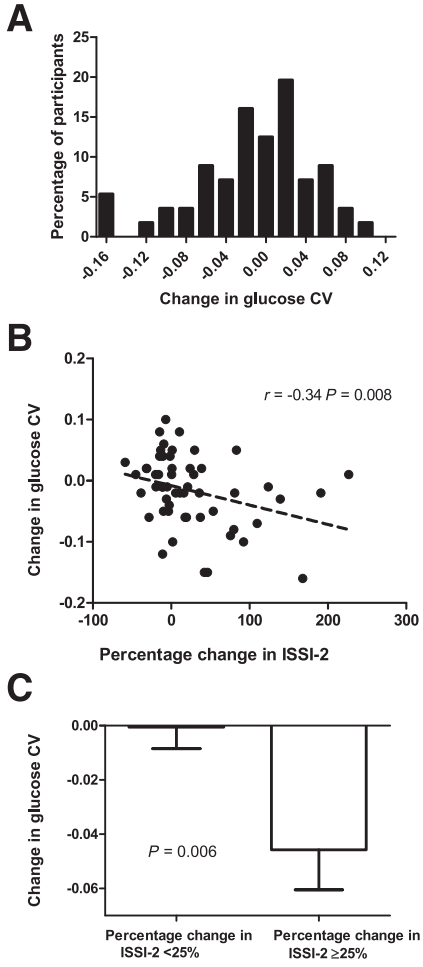

Figure 1—Changes in glucose CV and β-cell function (ISSI-2) in response to a short course of IIT. *A*: Distribution of change in glucose CV. *B*: Association of change in glucose CV and percentage change in ISSI-2. *C*: Change in glucose CV in participants with percentage change in ISSI-2 ≥25% and <25%.

(reduced) by a short course of treatment with IIT. Additionally, improvement in β-cell function emerged as the sole independent determinant of the reduction in glucose variability induced by this therapy. Thus, glucose variability is a modifiable parameter in early T2DM, a concept that may be relevant to strategies for the mitigation of risk of hypoglycemia and possibly complications in patients with diabetes.

A series of cross-sectional studies suggested that the increased glycemic variability observed in diabetes is a reflection of β-cell dysfunction. In 42 patients with C-peptide–negative T1DM who received intraportal implantation of cultured islet cell grafts, Gillard et al. (18) reported that greater functional β-cell mass of the implant (assessed by glucose clamp) was associated with a reduction in glycemic oscillation, as assessed by the CV of fasting glucose. Moreover, in a study of 59 patients with T2DM who underwent continuous glucose monitoring, postprandial β-cell function (measured by a model-based method during a mixed-meal test) was found to be an independent determinant of glycemic variability on multiple linear regression analyses (17). Similarly, poorer β-cell function on OGTT was associated with increased glycemic variability in participants spanning the spectrum of glucose tolerance from normal to prediabetes to T2DM (19). Finally, this relationship is further supported by evidence that increased glycemic variability (rather than the absolute level of glycemia) may be an important determinant of the risk of hypoglycemia, implicating diminished capacity of the β-cells (or islets) to regulate glucose levels from straying either above or below the normal range (14–16). Against this background, the current study extends this literature by demonstrating that glycemic variability in early T2DM is modifiable and can be reduced by improving β-cell function with short-term IIT.

β-Cell dysfunction in T2DM comprises both a presumed irreversible component (e.g., loss of β-cell mass through apoptosis) and a reversible component resulting from the deleterious effect of hyperglycemia on β-cell secretory capacity (i.e., glucotoxicity) (35). Early in the course of T2DM, this dysfunction can be improved with short-term IIT, likely through alleviation of its reversible component (20). Indeed, although IIT can cause several beneficial metabolic changes (including the lowering of insulin resistance), it is the beneficial effect on β-cell function that has been linked to the subsequent glycemic remission that this therapy can induce (36), whereupon

Table 3—Multiple linear regression models of (dependent variable) change in glucose CV

	Standardized β	*P* value
Core model		
Age	0.07	0.59
Duration of diabetes	0.03	0.81
BMI	0.06	0.64
Model 1: core model + baseline HbA_{1c}		
Age	0.06	0.69
Duration of diabetes	0.06	0.65
BMI	0.05	0.70
Baseline HbA_{1c}	−0.13	0.35
Model 2: model 1 + percentage change in HOMA-IR		
Age	0.04	0.79
Duration of diabetes	0.06	0.67
BMI	0.07	0.63
Baseline HbA_{1c}	−0.10	0.45
Percentage change in HOMA-IR	0.14	0.30
Model 3: model 1 + percentage change in ISSI-2		
Age	−0.011	0.94
Duration of diabetes	0.026	0.20
BMI	0.034	0.26
Baseline HbA_{1c}	0.013	0.18
Percentage change in ISSI-2	**−0.44**	**0.02**
Model 4: model 3 + final insulin dosage		
Age	0.050	0.74
Duration of diabetes	0.001	0.99
BMI	0.032	0.80
Baseline HbA_{1c}	0.090	0.66
Percentage change in ISSI-2	**−0.42**	**0.03**
Final insulin dosage	0.16	0.33
Model 5: model 3 + change in mean glucose		
Age	−0.014	0.92
Duration of diabetes	0.003	0.98
BMI	0.04	0.77
Baseline HbA_{1c}	0.19	0.30
Percentage change in ISSI-2	**−0.66**	**0.01**
Change in mean glucose	−0.26	0.21

Estimates (β and *P* value) shown for each covariate. Boldface type indicates significance at $P < 0.05$.

patients can maintain euglycemia without antidiabetic medications for varying lengths of time after cessation of IIT (20). Similarly, in the current study, although IIT improved several other metabolic parameters (BMI, fasting glucose, HbA_{1c}, HOMA-IR), only the change in β-cell function was independently associated with the change in glycemic variability. Moreover, the methodological independence of their respective measures (β-cell function was measured by ISSI-2 on OGTT, whereas glycemic variability was assessed by capillary glucose CV) further supports the biologic relevance of this relationship.

Because the target-driven titration of insulin doses should in itself decrease glycemic excursion, we performed analyses to ensure that this was not the basis for the observed relationship between improvement of β-cell function and reduction of glycemic variability. First, it should be noted that neither insulin dosage nor the level of glycemia was associated with the change in glucose CV (Tables 2 and 3). Second, recognizing the impact of insulin dose titration, we confirmed that the change in β-cell function was also an independent predictor of the change in glycemic variability when change in insulin dosage was included in the model. Thus, insulin titration per se does not appear to be the explanation for the observed relationship.

As shown in Table 1, the final IIT doses were lower than those that would be expected for full replacement of insulin in patients with T2DM and BMI ~30 kg/m^2, thereby suggesting the contribution of endogenous insulin secretion. Similarly, the tight glycemic control that was achieved (median HbA_{1c} 6.2% post-IIT) with a very low rate of any hypoglycemia again implicates the moderating influence of endogenous insulin secretion (likely as a result of the reversal of β-cell dysfunction). Taken together with the observed effects on glucose CV, these data suggest that reduction in glycemic variability is another feature of the improvement in β-cell function that can be achieved with early IIT in T2DM.

The current demonstration that glycemic variability is a modifiable factor that can be reduced in early T2DM also potentially holds clinical implications. Specifically, the findings raise the possibility that the improvement in glycemic variability induced by short-term IIT may lower the subsequent risk of hypoglycemia and, potentially, vascular complications. Although studies of short-term IIT in T2DM have largely focused on the metabolic benefits of IIT and its induction of glycemic remission, the current data support the need for long-term studies addressing the impact of this early intervention on the future development of these adverse clinical outcomes. Furthermore, these data provide additional biologic rationale for how therapeutic strategies targeting the preservation of β-cell function in early T2DM potentially could lower future risk of these outcomes. It should also be noted, however, that ~44% of participants did not have a reduction in glycemic variability in response to IIT. The absence of improvement in glycemic variability in these participants possibly reflects the heterogeneity of the β-cell response to IIT (22). Although we have previously demonstrated a role for insulin resistance as a determinant of the β-cell response to IIT (22), clinical predictors of this response and of the anticipated effect on glycemic variability remain to be identified.

A key strength of the current study is its interventional design, which provides a model for evaluating the longitudinal relationship between improvement in

β-cell function and change in glycemic variability. A limitation is that glucose variability was assessed using SMBG rather than continuous glucose monitoring. However, although many measures have been proposed for this purpose (37), it should be noted that the evaluation of glycemic variability by capillary glucose CV from SMBG across the day has been recommended in the literature as an approach that accounts for the level of ambient glycemia, which could otherwise affect the degree of glucose fluctuation (21). Furthermore, assessment of the change in glycemic variability by either glucose CV or MAGE in the current study yielded clear and consistent findings. It should be recognized that improvement in glycemic control can be associated with improvement in β-cell function, potentially through alleviation of glucotoxicity. In this context, however, it should be noted that we found no direct association between improvement in glycemia and reduction in glycemic variability (Tables 2 and 3). Finally, hormones such as incretins and glucagon that contribute to the regulation of postprandial glycemic excursion may be relevant to glycemic variability but were not assessed in this analysis.

In conclusion, short-term IIT is an intervention that can reduce glycemic variability in patients with early T2DM. Improvement in β-cell function is the key independent determinant of the reduction in glucose variability in response to this therapy. It thus emerges that early in the course of T2DM, glucose variability is a modifiable parameter for which intervention may mitigate future risk of adverse outcomes.

Funding. C.K.K. holds a Canadian Diabetes Association Postdoctoral Fellowship Award. B.Z. holds the Sam and Judy Pencer Family Chair in Diabetes Research at Mount Sinai Hospital and the University of Toronto. R.R. holds an Ontario Ministry of Research and Innovation Early Researcher Award.

Duality of Interest. This study was funded by an investigator-initiated research grant from Novo Nordisk Canada, Inc. B.Z. and R.R. have received research funding and consulting honoraria from Novo Nordisk. No other potential conflicts of interest relevant to this article were reported.

The sponsor had no role in study design, data collection, analysis/interpretation, manuscript preparation, or submission.

Author Contributions. C.K.K. contributed to the statistical analyses, data analysis and interpretation, writing of the first draft of the manuscript, revision of the manuscript for intellectual content, and approval of the manuscript. H.C. contributed to the data collection, analysis, and interpretation; revision of the manuscript for intellectual content; and approval of the manuscript. B.Z. and R.R. contributed to the study conception and design, data analysis and interpretation, revision of the manuscript for intellectual content, and approval of the manuscript. R.R. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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