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Relationship between glucose variability evaluated by continuous glucose monitoring and clinical factors, including glucagon-stimulated insulin secretion in patients with type 2 diabetes

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ABSTRACT

Aims: To evaluate the clinical factors affecting daily and day-to-day glucose variability by using continuous glucose monitoring.

Methods: We performed a cross-sectional analysis of patients with type 2 diabetes mellitus (T2DM) who underwent a glucagon stimulation test (GST) with 72 h of continuous glucose monitoring. Daily glucose variability was evaluated by mean amplitude of glycemic excursions [MAGE], percentage coefficient of variation for glucose (%CV), and day-to-day glucose variability (mean of daily differences [MODD]) by using continuous glucose monitoring. Correlations of clinical factors, including insulin secretion ability by the GST with MAGE, %CV, and MODD, were analyzed.

Results: In 83 T2DM with insulin therapy, age and hemoglobin A_{1c} (HbA_{1c}) correlated with MAGE and %CV, fasting plasma glucose with MAGE and MODD, and increment of C-peptide immunoreactivity (ΔCPR) by GST correlated inversely with MAGE, %CV, and MODD. In 126 T2DM without insulin therapy, age, diastolic blood pressure, and triglycerides correlated with MODD, HbA_{1c} with MAGE and MODD, and ΔCPR inversely correlated with %CV. Use of α-glucosidase inhibitors inversely correlated with %CV, whereas that of sulfonylurea was associated with MAGE and %CV.

Conclusions: These results suggest that ΔCPR correlated with stability of glycemic control, whereas poorly controlled diabetes is associated with increase in glucose variability. α-glucosidase inhibitors may be superior to sulfonylureas in reducing the glucose variability in T2DM.

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1. Introduction

Measurement of glycated hemoglobin (HbA_{1c}) is a golden standard method to assess glycemic control. However, it does not necessarily reflect glucose variability. Short-term glucose variability can be evaluated as daily glucose variability, including hyper and hypoglycemia within a day as well as day-to-day glucose variability measured by differences of glucose levels at the same time on different days [1]. Accumulating evidence has shown that glucose variability could induce endothelial dysfunction, an initial step of atherosclerosis through oxidative stress, inflammatory and thrombotic reactions and are associated with the risk of vascular complications in diabetes [2,3]. In fact, previous clinical studies demonstrated a positive association between oxidative stress or endothelial dysfunction and daily glucose variability in patients with type 2 diabetes (T2DM) [4,5]. In addition, we have shown that daily and day-to-day glucose variability are associated with oxidative stress in T2DM in a cross-sectional study [6] and that improvements in glycemic variability reduce oxidative stress levels in these subjects [7]. Furthermore, visit to visit variability of fasting plasma glucose was correlated with the increased risk of cardiovascular disease and death in subjects with and without diabetes [8,9]. These observations suggest that glucose variability is a novel therapeutic target for preventing vascular complications in diabetes.

C-peptide immunoreactivity (CPR)-to-glucose ratio after oral glucose ingestion, but not homeostasis model assessment of β-cell function (HOMA-β) has been shown to be correlated with β-cell area in humans [10]. This suggests that fasting or unstimulated CPR and HOMA-β may not be a sensitive biomarker that reflects β–cell function in T2DM. Indeed, we have previously found that increment of CPR (ΔCPR) after intravenous glucagon injection is more reliable than fasting biomarkers for estimating individual longitudinal insulin secretion ability in T2DM [11].

Numerous studies have been conducted so far to examine the relationship between clinical factors and glucose variability in patients with diabetes [12,13]. Fasting C-peptide levels were inversely associated with higher glucose variability evaluated by standard deviation (SD) and percentage of coefficient of variation (%CV) [12]. However, it remains unclear which clinical markers, including ΔCPR after glucagon stimulation test (GST), are independently correlated with both daily and day-to-day glucose variability in insulin-treated and non-insulin-treated T2DM in a separate manner. In clinical practice, clarification of independent clinical markers associated with daily and day-to-day glucose variability would help identify high-risk T2DM and which treatment options are superior in reducing the glucose variability in those patients. Therefore, in this study, we examined the independent clinical correlates of daily and day-to-day glucose variability in T2DM.

2. Materials and methods

2.1. Subjects

We recruited 209 patients (108 in- and 101 outpatients) with T2DM who underwent the GST and a continuous glucose monitor (CGM) at Showa University Hospital between October 2013 and April 2017. Inclusion criteria were as a diagnosis of T2DM, age >20 years, and stable oral hypoglycemic and/or insulin treatment for ≥3 months before the CGM performance. Exclusion criteria were use of steroids or anti-inflammatory drugs, diabetic ketosis and coma within 3 months before the study, severe infection, severe trauma, malignancy, an estimated glomerular filtration rate (eGFR) of <30 mL/min/1.73 m^2 according to the Cockcroft–Gault formula [14], pre- and post-surgery, severe liver dysfunction, and pregnancy.

2.2. Study design

The study protocol is summarized in Fig. 1. A cross-sectional analysis was done in patients with T2DM who underwent the GST and >72 h of CGM. Glucose variability parameters, such as mean amplitude of glycemic excursions (MAGE), %CV, and mean of daily differences (MODD), were measured on days 2 and 3. GST for the assessment of residual β-cell function was done on the morning after 10 h-fasting on day 4, and then fasting C-peptide (FCPR) and ΔCPR were measured. The following clinical and laboratory parameters were measured on day 4 just before the GST: body mass index (BMI), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), eGFR, systolic (SBP) and diastolic (DBP) blood pressure, fasting plasma glucose (FPG), and HbA_{1c}. Clinical data (age, sex, and duration of diabetes in years) were retrieved from medical records.

The study protocol was approved by the ethics committee of Showa University School of Medicine. All patients provided informed consent according to the provisions of the Declaration of Helsinki.

2.3. Procedures and measurements

The CGM sensor (ipro2; Medtronic MiniMed, Northridge, CA, USA) was inserted subcutaneously on day 1 (for inpatients, admission day was day 1) and removed on day 4. Glucose vari-

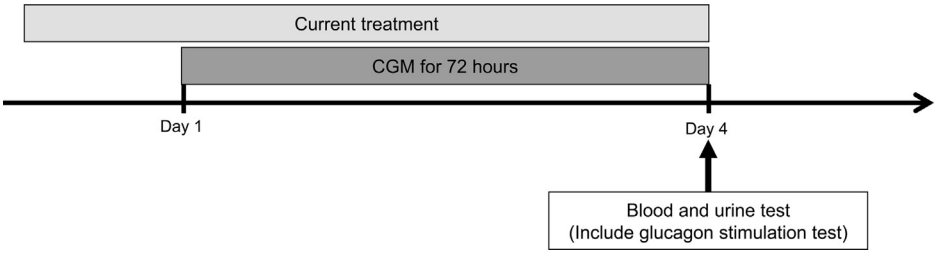

Fig. 1 – Study protocol.

ability was calculated only on days 2 and 3 for avoiding the measurement bias of CGM data. Mean glucose level (MGL) was measured from the data recorded during the CGM and was adjusted for self-monitored blood glucose. MAGE was calculated to assess the daily glucose variability [15]. MODD indicated the mean of the absolute difference between corresponding glucose values on days 2 and 3 [16]. %CV was calculated using the coefficient of variation obtained by dividing the SD by MGL and multiplying by 100 [17].

2.4. *Laboratory measurements*

Serum total cholesterol, LDL-C, HDL-C, TG, and creatinine levels were measured using an automated analyzer (BM6070; Japan Electron Optics Laboratory, Tokyo, Japan). Plasma glucose was measured with a standard glucose oxidase method, and HbA_{1c} was determined by high-performance liquid chromatography [18]. Plasma CPR concentrations were measured using an immunoenzymometric assay (ST E test Tosoh Ⅱ C-peptide; Tosoh, Tokyo, Japan).

2.5. *Statistical analysis*

Data were presented as mean ± standard deviation (SD). Simple linear correlations were calculated by determining Spearman's correlation coefficient. The Shapiro-Wilk test for normality was used to determine the appropriate statistical test for continuous variables. Multiple stepwise regression analysis was performed with MAGE, %CV, and MODD as the dependent variables, and age, duration of diabetes, BMI,

Table 1 – Baseline clinical characteristics of subjects.

	Insulin-treated T2DM (n = 83)	T2DM without insulin therapy (n = 126)
Age (years)	63.7 ± 11.5	62.1 ± 13.3
Sex (male)	48 (57.8)	80 (63.5)
BMI (kg/m^2)	25.6 ± 4.4	26.2 ± 4.8
Duration of diabetes (years)	15.8 ± 10.4	10.9 ± 8.4
Hypertension	65 (78.3)	79 (62.7)
Dyslipidemia	63 (75.9)	98 (77.8)
Blood pressure (mm Hg)		
SBP	130 ± 19	127 ± 20
DBP	74 ± 13	75 ± 12
LDL-C (mg/dL)	92 ± 28	101 ± 37
HDL-C (mg/dL)	50 ± 15	47 ± 16
TG (mg/dL)	129 ± 68	133 ± 67
eGFR (ml/min/1.73 m^2)	74.4 ± 24.6	79.3 ± 21.5
FPG (mg/dL)	130 ± 36	140 ± 36
HbA_{1c} (%; mmol/mol)	7.5 ± 1.4 (58.7 ± 14.8)	8.1 ± 1.6 (64.9 ± 17.0)
MGL (mg/dL)	148 ± 37	169 ± 42
Markers of glucose variability		
MAGE (mg/dL)	111 ± 45	111 ± 38
%CV	25 ± 7	22 ± 6
MODD (mg/dL)	34 ± 17	27 ± 10
FCPR (ng/mL)	1.5 ± 0.9	2.3 ± 1.0
ΔCPR (ng/mL)	1.4 ± 0.8	1.9 ± 1.5
Diabetes therapy		
Diet alone	0 (0.0)	18 (14.3)
The number of oral hypoglycemic agents	1.3 ± 1.1	1.7 ± 1.3
Metformin	29 (34.9)	48 (38.1)
SUs	3 (3.6)	49 (38.9)
Glinides	3 (3.6)	8 (6.3)
α-GIs	21 (25.3)	28 (22.2)
Thiazolidine	12 (14.5)	15 (11.9)
SGLT-2 inhibitors	4 (4.8)	6 (4.8)
DPP-4 inhibitors	34 (41.0)	59 (46.8)
GLP-1 receptor agonists	16 (19.3)	29 (23.0)
Insulin		
The number of insulin injections	2.8	N/A
Insulin dose (U/kg)	0.34 ± 0.24	N/A
Statin therapy	53 (63.9)	31 (46.3)

SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL, Low-density lipoprotein; HDL, High-density lipoprotein; TG, triglycerides; eGFR, Estimated glomerular filtration rate; FPG, fasting plasma glucose; HbA_{1c}, hemoglobin A_{1c}; MGL, mean glucose level over 24 h; MAGE, mean amplitude of glycemic excursions.

%CV, percentage coefficient of variation for glucose.

MODD, mean of daily difference of blood glucose.

SUs, Sulfonylureas; α-GIs, α-glucosidase inhibitors; SGLT-2, Sodium glucose cotransporter 2; DPP-4, Dipeptidyl peptidase 4; GLP-1, Glucose-like peptide 1.

FPG, HbA_{1c}, FCPR, ΔCPR, eGFR, HDL-C, LDL-C, TG, SBP, DBP, use of glucose-like peptide 1 receptor agonists (GLP-1RA), dipeptidyl peptidase 4 (DPP IV) inhibitors, SUs, glinides, α-glucosidase inhibitors (α-GI), metformin, thiazolidine, or sodium glucose cotransporter 2 (SGLT2) inhibitors, dose of insulin or SUs, and number of insulin injections as the independent variables.

$P < 0.05$ was considered significant (two-tailed). Analyses were performed using IBM SPSS, Version 22, for Windows (IBM Corp., Armonk, NY, USA).

3. Results

Baseline clinical characteristics of the 209 patients are shown in Table1. Table 2 shows the correlations between various parameters and glucose variability. In subjects with T2DM with and without insulin therapy, MAGE and MODD were correlated with FPG and HbA_{1c}, %CV with age, and MODD with durations of diabetes. In subjects with insulin-treated T2DM, MAGE, %CV, and MODD were inversely correlated with ΔCPR, whereas MAGE were positively associated with age. %CV was positively and inversely correlated with HbA_{1c} and DBP, respectively. In T2DM subjects without insulin therapy, MAGE was correlated with LDL-C and TG, while MODD with age.

Multivariate analyses were used to assess the effects of different clinical variables on daily and day-to-day glucose variability (Table 3). In insulin-treated T2DM patients, MAGE was correlated with age, FPG, and HbA_{1c}, and inversely associated with ΔCPR ($R^2 = 0.346$). %CV was correlated with age, HbA_{1c} and the number of insulin injections, while inversely associated with ΔCPR ($R^2 = 0.246$). MODD was positively and inversely correlated with FPG and ΔCPR, respectively ($R^2 = 0.213$). In T2DM patients without insulin therapy, MAGE was correlated with HbA_{1c} and use of SUs ($R^2 = 0.384$). %CV was positively associated with use of SUs, while inversely with ΔCPR and use of α-GIs ($R^2 = 0.161$). In addition, MODD was correlated with age, DBP, TG, and HbA_{1c} ($R^2 = 0.240$). Furthermore, MAGE was independently correlated with dose of SUs. Fig. 2 shows the relationship between MAGE and dose of glimepiride.

4. Discussion

To the best of our knowledge, there is no comprehensive study to examine which clinical factors, including ΔCPR—a marker of insulin secretion ability evoked by glucagon, are independently correlated with both daily and day-to-day glucose variability in insulin-treated and non-insulin-treated T2DM separately. The present study demonstrated that ΔCPR after glucagon injection was associated with stability of glycemic control in insulin-treated T2DM, whereas poor glycemic control was correlated with higher glucose variability in T2DM. In addition, SU therapy showed worse daily glucose variability in T2DM without insulin therapy. Because glucose variability could induce endothelial dysfunction through oxidative stress and is associated with vascular complications and death as atherosclerosis progresses in T2DM [19], the present findings suggest that ΔCPR after GST, but not fasting CPR is a more reliable marker for insulin secretion ability in insulin-treated T2DM and one of the key factors that may determine the glucose variability, thereby predicting future vascular events in these patients.

Since glucose variability indexes, such as MAGE and SD, are greatly influenced by MGL, these values would theoretically increase as the MGL increases. Therefore, in this study, we evaluated the glucose variability using a CV obtained by dividing the SD by the MGL and multiplying by 100 [20]. Previous studies have reported that daily glucose variability could influence glycemic control, such as HbA_{1c} levels [12,21] and

Table 2 – Correlation between glycemic variability and clinical factors.

	Insulin-treated T2DM ($n = 83$)			T2DM without insulin therapy ($n = 126$)		
	MAGE	%CV	MODD	MAGE	%CV	MODD
Age (years)	0.355**	0.311**	0.195	0.155	0.222*	0.262*
BMI (kg/m^2)	−0.045	−0.004	−0.045	0.141	0.126	0.116
Duration of diabetes (years)	0.198	0.160	0.225*	0.130	0.158	0.244*
Blood pressure (mm Hg)						
SBP	0.031	−0.020	0.140	−0.017	−0.061	0.070
DBP	−0.202	−0.272*	−0.033	−0.008	−0.070	0.089
LDL-C (mg/dL)	0.037	−0.018	0.095	0.227*	−0.011	0.099
HDL-C (mg/dL)	0.090	0.097	0.134	0.065	0.096	−0.050
TG (mg/dL)	−0.092	−0.149	−0.027	0.317*	0.150	0.197
eGFR (mL/min/1.73 m^2)	−0.038	−0.103	−0.151	−0.049	−0.138	0.026
FPG (mg/dL)	0.370**	0.070	0.443**	0.461**	−0.036	0.322**
HbA_{1c} (%; mmol/mol)	0.546**	0.362**	0.351**	0.609**	0.165	0.346**
Fasting CPR (ng/mL)	−0.091	−0.205	−0.004	0.122	0.087	0.048
ΔCPR (ng/mL)	−0.736**	−0.326**	−0.277*	−0.014	−0.089	−0.068

Values represent Spearman's correlation coefficients.

SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL, Low-density lipoprotein; HDL, High-density lipoprotein; TG, triglycerides; eGFR, Estimated glomerular filtration rate; FPG, fasting plasma glucose; HbA_{1c}, hemoglobin A_{1c}; MAGE, mean amplitude of glycemic excursions; %CV, percentage coefficient of variation for glucose; MODD, mean of daily difference of blood glucose.

* $P < 0.05$.

** $P < 0.01$.

Table 3 – Multivariate analysis of clinical factors associated with glycemic variability.

	Insulin-treated T2DM (n = 83)			T2DM without insulin therapy (n = 126)		
	MAGE (R^2 = 0.346)	%CV (R^2 = 0.246)	MODD (R^2 = 0.213)	MAGE (R^2 = 0.384)	%CV (R^2 = 0.161)	MODD (R^2 = 0.240)
Age (years)	0.227*	0.270*				0.406**
DBP (mm Hg)						0.281**
TG (mg/dL)						0.238**
FPG (mg/dL)	0.287**		0.413**			
HbA_{1c} (%)	0.266**	0.232*		0.501**		0.303**
ΔCPR (ng/mL)	−0.223*	−0.235*	−0.275**		−0.175*	
The number of insulin injections		0.282**				
Use of α-GIs					−0.231**	
Use of SUs				0.308**	0.327**	

Multiple stepwise regression analysis was performed with MAGE, %CV, and MODD as the dependent variables, and age, duration of diabetes, BMI, FPG, HbA_{1c}, FCPR, ΔCPR, eGFR, HDL-C, LDL-C, TG, SBP, DBP, use of glucose-like peptide 1 receptor agonist use, dipeptidyl peptidase 4 inhibitor, sulfonylurea, glinide, α-glucosidase inhibitor, metformin, thiazolidine, sodium glucose cotransporter 2 inhibitor, dose of insulin or sulfonylurea, and number of insulin injections as the independent variables.

DBP, diastolic blood pressure; TG, triglycerides; FPG, fasting plasma glucose; HbA_{1c}, hemoglobin A_{1c}; α-GIs, α-glucosidase inhibitors; SUs, Sulfonylureas; MAGE, mean amplitude of glycemic excursions; %CV, percentage coefficient of variation for glucose; MODD, mean of daily difference of blood glucose.

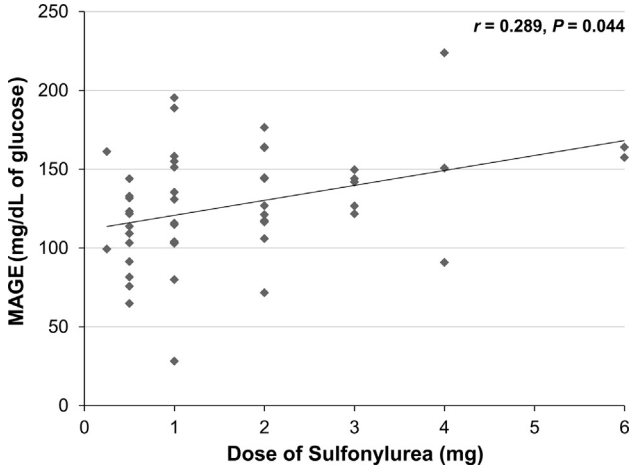

Fig. 2 – Relationship between MAGE and dose of SUs. Values represent the Spearman's correlation coefficients. MAGE, mean amplitude of glycemic excursions; Gliclazide 40 mg was calculated to correspond to glimepiride 1 mg.

MGL [22], whereas day-to-day glucose variability also affected the HbA_{1c} values [13]. In accordance with the previous studies, we found here that HbA_{1c} was positively associated with daily glucose variability evaluated by MAGE and %CV in insulin-treated T2DM, while it was correlated with MAGE and MODD in T2DM without insulin therapy. These observations suggest that improvement of chronic hyperglycemia as well as amelioration of postprandial hyperglycemia without hypoglycemia may be crucial for reducing the glucose variability in T2DM. Since we have previously shown that improvement of MAGE, MODD, and FPG, but not %CV, an indicator of glucose variability divided by MGL are associated with the reduction of oxidative stress marker [7], control of both chronic hyperglycemia and postprandial hyperglycemia may be a therapeutic target for reducing the oxidative stress in T2DM.

Insulin secretion was reported to decrease with age [23], while postprandial glucose was deteriorated with age [24]. In the present study, daily glucose variability was positively associated with age and inversely with ΔCPR in insulin-treated T2DM. These findings suggest that aging-associated endogenous β-cell deterioration may play a role in glucose variability in these subjects. In our study, insulin-treated T2DM was older with lower insulin secretion ability compared with T2DM without insulin therapy, thus supporting our speculation. In contract to our present findings, Jin et al. [12] reported that daily glucose variability was correlated with fasting CPR in insulin-treated T2DM. We did not know the exact reason of discrepant results between their study and ours. However, several reports have shown that β-cell dysfunction during the postprandial state compared with the fasting condition is more closely associated with daily glucose variability as evidenced by MAGE in T2DM [25]. Taken together, the present findings suggest that insulin secretory ability should be evaluated in both fasting and stimulated states, including postprandial condition and GST, because. CPR under the latter conditions is a more sensitive marker that reflects daily glycemic variability in T2DM.

Since insulin secretion ability is lower in Asian T2DM, such as Japanese subjects than Caucasian patients, which is characteristic feature of type 2 diabetes in the former population [26], SUs and DPP IV inhibitors that could potentiate the endogenous insulin secretion are one of the commonly used agents for the treatment of T2DM [27]. Our present study demonstrated that SU use was dose-dependently associated with higher daily glucose variability in T2DM without insulin therapy, which was extended the previous observation by Jin et al, showing that use of SU was correlated with SD and %CV in T2DM without insulin therapy [12]. Combination of metformin with SUs was associated with the increased the risk of hypoglycemia, cardiovascular events, and all-cause mortality compared to that with DPP IV inhibitors [28]. SU use may cause glucose variability, which could evoke oxidative stress

and endothelial dysfunction, thereby being involved in the development and progression of cardiovascular disease in T2DM [29]. The positive and dose-dependent association of SUs with the increased glucose variability observed here may support the speculation. Furthermore, in the present study, α-GI use was associated with the reduction in daily glucose variability irrespective of MGL. Satoh et al. [30] recently compared the effect of DPP IV inhibitor on daily glucose variability with that of α-GI using CGM. The study findings demonstrated that although both the drugs improved daily glucose variability such as MAGE and SD, α-GI was superior to DPP IV inhibitor in ameliorating the glucose variability. Because α-GI was reported to reduce oxidative stress and attenuate endothelial damage and dysfunction in T2DM [31,32], it may lead to reduction of cardiovascular disease by improvement of glycemic variability in these patients [33]. In addition, Glinide, which is used to improve postprandial blood glucose levels together with αGI, has also been reported to improve daily glucose variability and reduce oxidative stress as compared to SU [34].

Our study had several limitations. First, since we included both in- and outpatients in this study, diets and lifestyle may differ among patients, which could affect the present findings because lifestyle could influence the day-to-day glucose variability in T2DM outpatients on insulin therapy [13]. Second, in the present study, patients performed self-monitoring of blood glucose during the period of CGM, which could result in some bias.

In conclusion, we found that clinical factors associated with glucose variability differed among T2DM. ΔCPR was correlated with stability of glycemic control, whereas poorly controlled diabetes was associated with increase in glucose variability. α-glucosidase inhibitors may be superior to sulfonylureas in reducing the glucose variability in non-insulin-treated T2DM.

Availability of data and material

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

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Authors' contributions

MO contributed to study design, data acquisition, and data analysis and wrote the manuscript. TY, YM, TH, TF, and TH reviewed and edited the manuscript for intellectual content. MO and TH drafted the manuscript. MO, HN, YK, TF, SG, NS, HK, MH, TY, YM, TH, TF, SY and TH interpreted data and critically revised and completed the manuscript. All authors have read and approved the final version of the manuscript.

Declaration of Competing Interest

The authors of this manuscript have the following competing interests: T. Hirano received lecture fees from Kowa, MSD, Takeda, Astra Zeneca, Ono, Novo Nordisk, Eli Lilly, Boehringer Ingelheim. The other authors have no competing interests to declare.

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