Respective Contributions of Glycemic Variability and Mean Daily Glucose as Predictors of Hypoglycemia in Type 1 Diabetes: Are They Equivalent?

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Diabetes Care 2020;43:821–827 | https://doi.org/10.2337/dc19-1549

OBJECTIVE

To evaluate the respective contributions of short-term glycemic variability and mean daily glucose (MDG) concentration to the risk of hypoglycemia in type 1 diabetes.

RESEARCH DESIGN AND METHODS

People with type 1 diabetes ($n = 100$) investigated at the University Hospital of Montpellier (France) underwent continuous glucose monitoring (CGM) on two consecutive days, providing a total of 200 24-h glycemic profiles. The following parameters were computed: MDG concentration, within-day glycemic variability (coefficient of variation for glucose [%CV]), and risk of hypoglycemia (presented as the percentage of time spent below three glycemic thresholds: 3.9, 3.45, and 3.0 mmol/L).

RESULTS

MDG was significantly higher, and %CV significantly lower (both $P < 0.001$), when comparing the 24-h glycemic profiles according to whether no time or a certain duration of time was spent below the thresholds. Univariate regression analyses showed that MDG and %CV were the two explanatory variables that entered the model with the outcome variable (time spent below the thresholds). The classification and regression tree procedure indicated that the predominant predictor for hypoglycemia was %CV when the threshold was 3.0 mmol/L. In people with mean glucose ≤7.8 mmol/L, the time spent below 3.0 mmol/L was shortest ($P < 0.001$) when %CV was below 34%.

CONCLUSIONS

In type 1 diabetes, short-term glycemic variability relative to mean glucose (i.e., %CV) explains more hypoglycemia than does mean glucose alone when the glucose threshold is 3.0 mmol/L. Minimizing the risk of hypoglycemia requires a %CV below 34%.

It is well known that fear of hypoglycemia is a main barrier to optimizing insulin therapy in persons with type 1 diabetes (T1DM) (1,2); they prefer adhering to less stringent glycemic targets rather than experiencing severe hypoglycemic episodes that can be associated with acute and chronic cardiovascular complications (3–5). The

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Received 2 August 2019 and accepted 31 December 2019

seminal Diabetes Control and Complications Trial (DCCT) clearly demonstrated that intensive treatment in persons with T1DM resulted in higher rates of severe hypoglycemia than occurred in those with less well-controlled diabetes when expressed in terms of glycated hemoglobin (HbA_{1c}) (6). The hypothesis that abnormally high daily glucose fluctuation, between peaks and nadirs, is also associated with a higher frequency of hypoglycemic episodes (7,8) has been confirmed in both observational and interventional studies (9–14), and it has been mathematically modeled by Rodbard (15). Consequently, from a "glucocentric" viewpoint, when managing persons with T1DM, therapeutic targets should include ambient hyperglycemia, time in range (16–20), short-term glycemic variability (21–23), and the threshold for hypoglycemia (24,25). Although it is highly likely that mean daily glucose (MDG) concentration and glycemic variability are the two main explanatory factors that contribute to an increased risk of hypoglycemia, their respective contributions remain to be adequately investigated. This observational and retrospective study of subjects with T1DM who were undergoing continuous glucose monitoring (CGM) aims to determine the relative priority of MDG concentration and glycemic variability (coefficient of variation for glucose [%CV]) in determining the time spent with glucose below 3.9 and 3.0 mmol/L (17–20), levels that represent hypoglycemia.

RESEARCH DESIGN AND METHODS

Study Design and Participants

After an initial screening of 163 persons with T1DM who underwent 3 days of blinded CGM, a total of 100 persons were entered into the study, of whom 88 were receiving multiple daily insulin injections and only 12 were receiving continuous subcutaneous insulin infusion (CSII). The relatively low percentage of subjects treated with CSII is simply a result of the study being conducted between 2006 and 2012, when CSII was used less than it is today. In all patients treated with multiple insulin injections, the basal insulin was glargine U100 administered before the evening meal. Pregnant patients and those younger than 20 years of age, those who had recently experienced an illness, and those who had been treated with steroids during the 3-month period preceding the investigation were excluded. All participants (65 men and 35 women) attended the outpatient clinic of the University Hospital of Montpellier (France) for more than 3 years and had a diabetes duration of 5 years or more (mean duration of diabetes, 28 years). In addition, their respective insulin treatments were stable for a minimum of 3 months before the investigation. CGM was conducted on an ambulatory basis over 3 days. Patients were excluded from the final analysis if the glucose monitoring was unexpectedly disrupted, if an insufficient number of capillary blood tests were obtained, or if calibrations were inappropriate. As recommended by the manufacturer of the CGM technology (the second-generation MiniMed System; Medtronic, Northridge, CA), glucose was determined four times daily from capillary blood via fingersticks. An acceptable calibration was based on an accuracy criterion defined by a correlation coefficient >0.79 between paired readings. As mentioned above, all glycemic profiles were monitored on an ambulatory basis, and all CGM system sensors were inserted by trained health care professionals at the diabetes outpatient clinic. The study was conducted in accordance with the Declaration of Helsinki; each participant gave oral consent in accordance with a European directive (26). No ethics committee approval was required because of the noninterventional design of the study.

Clinical Investigation and Laboratory Determinations

The three consecutive days of CGM avoided a weekend; the CGM sensor was inserted on day 0 (before 1200 h) and removed on day 3 at the same time of day. Chronic hyperglycemia (based on HbA_{1c}) was assessed at baseline (study day 0) by using a high-performance liquid chromatography assay (Menarini Diagnostics, Florence, Italy) (27).

Analysis of Data from CGM

The data recorded on the day the glucose sensor for GGM was inserted were excluded from the analysis in order to avoid any bias due to insufficient glucose stabilization between the sensor and the interstitial fluid during the first 24 h after insertion of the device. On the basis of two validated 24-h glycemic profiles (calculated from glucose readings obtained at 5-min intervals on study days 1 and 2), the total MDG, short-term glycemic variability (%CV), and the presence of hypoglycemia (both symptomatic and asymptomatic) were assessed, in addition to the cumulative time spent below three glycemic thresholds: 3.0, 3.45, and 3.9 mmol/L. Because 100 patients were included in this study, and because two 24-h glycemic profiles were calculated for each patient, 200 glycemic profiles were suitable for analysis. The %CV was derived from the following equation: ([SD of the 24-h mean glucose value]/[24-h mean glucose]) $\times$ 100. In accordance with our own previous findings (11), international consensus on the use of CGM has adopted the %CV as a reference to separate stable from labile diabetes (17). The %CV has the main advantage of being the simplest metric for assessing short-term within-day glucose variability, and it does not need to be adjusted for the MDG value. Because of its characteristics (28), the low blood glucose index was not used in this study because it is necessarily highly correlated with the incidence of hypoglycemia (29); thus, it is more a marker for use in evaluating the risk of hypoglycemia and less a potential causative factor for explaining the occurrence of hypoglycemic episodes. According to the recommendations of the International Hypoglycaemia Study Group (24), we considered glucose concentrations <3.0 mmol/L detected by CGM as unequivocally indicating the presence of clinical hypoglycemia. A glucose value <3.9 mmol/L from plasma venous samples, however, serves as an alert threshold (25). Because many uncertainties exist concerning the agreement between plasma venous glucose values and those recorded by CGM, we decided to determine the duration of time for which glucose was below 3.0 and 3.9 mmol/L, with an intermediate glucose threshold set at 3.45 mmol/L, to indicate the presence or absence of hypoglycemia. The time spent below the selected glucose thresholds was recorded only when the duration exceeded 15 min, that is, when three consecutive measurements, taken at 5-min intervals, indicated a glucose value below the threshold.

Statistical Analysis

For descriptive analysis, variables were expressed as the mean $\pm$ SD or the median (interquartile range [IQR]). Groups were compared by using either the

Student *t* test or the Wilcoxon-Mann-Whitney rank sum test, according to whether the data were normally distributed.

The statistical analysis was oriented toward the goodness of fit for identifying and investigating the contributions of the independent (explanatory or predictor) variables that can explain or predict the time spent below the three glucose thresholds (dependent or outcome variables). Because the time spent below the thresholds was computed over a 24-h interval, all parameters recorded throughout that period (the 24-h mean glucose concentration, within-day glucose variability, and the daily amount of insulin injected) were selected as independent variables. To this preliminary list were added two other variables: age and BMI; both can play a potential role in determining the amount of time spent below the glycemic thresholds.

A univariate analysis was conducted by calculating the simple linear regression between the dependent variables (Y) and each potential explanatory variable (X). This statistical procedure was used for removing the independent variables that did not enter the model. Statistical significance, given as a *P* value, was calculated after the time spent below glucose thresholds (normally expressed as percentage from 0 to 100%) had been converted into the arcsine of the square root of the dependent variable (30). This transformation was applied to the dependent variables to obtain an underlying distribution in agreement with the assumption of model linearity. In addition, the calculations used linear mixed-effect models because two values for the dependent variables were obtained from each patient over two consecutive days of glucose monitoring. The relationship between the independent and dependent variables was expressed as a simple linear regression function: $Y = \beta iX + \alpha$, in which each partial regression coefficient (βi) was an estimate of the relationship between the dependent variable (Y) and one given explanatory variable (X). To reflect the initial units (Y, expressed as a percentage), the βi coefficients were transformed back to proportions and then expressed as unitless standardized coefficients that provide indications of relative importance of the explanatory variables (X) in determining the value of the dependent variable (Y).

To estimate the respective influence of each remaining explanatory variable on the dependent variable, a sensitivity analysis was performed by using an arborescent regression (classification and regression tree [CART]) (31). The method with this approach includes all potential explanatory variables at the top of the regression tree and sequentially selects those with the best splitting in order to establish a hierarchy, allowing predictions of their role as primary or secondary key players in the expression of the dependent variable. During the first step of this top-down approach, the data for the independent variable that showed the best sensitivity were separated into two homogeneous subsamples; a cutoff (node) value served, via a pruning procedure, either to reject the data exhibiting a poor predictive value or to maintain those exhibiting a high predictive value. The latter subsample with the highest predictive value underwent the same procedure, splitting into two subsamples, which ended when the independent variable showed its lowest sensitivity.

To gain further insight into the best fit between the dependent variables and the value for each explanatory variable entering the model, the dependent variables were transformed into ln. The relationships (rearranged as increasing or decreasing simple exponential curves, as appropriate, after reverse transformation of the ordinate scale of ln) between dependent and independent variables were statistically tested by using coefficients of correlation (*r* values). The *r* values were compared after they had been converted into their corresponding Fisher *z* values.

Finally, in the subset of 24-h glycemic profiles exhibiting MDG concentrations $\leq$7.8 mmol/L, which correspond to estimated HbA_{1c} levels $<$6.5% ($<$48 mmol/mol) (32)—that is, to near-normal glycemic control (33)—the time spent below 3.0 mmol/L was divided into tertiles by using the Wilcoxon-Mann-Whitney rank sum test for unpaired, asymmetrically distributed data; these tertile values allowed for further statistical comparisons between medians and IQRs.

Analyses were performed with the R software package, version 3.5.0 (The R Foundation [www.r-project.org]).

RESULTS

Demographic, Clinical, and Laboratory Characteristics of Patients upon Enrollment in the Study

In the population considered as a whole (100 patients, 200 glycemic profiles), the mean ± SD and range for each of the main parameters are described as follows: HbA_{1c}, 8.27% ± 0.99% (67 ± 10.9 mmol/mol), 5.3–10.9% (34.3–95.9 mmol/mol) ($n = 100$); average MDG concentrations, 9.0 ± 2.4 mmol/L, 4.4–17.8 mmol/L ($n = 200$); %CV, 37.9% ± 11.5%, 82.0–94.8% ($n = 200$); daily insulin dose, 0.67 ± 0.20 units/kg/day, 0.37–1.21 units/kg/day ($n = 100$); age, 55.7 ± 13.1 years, 20.0–83.0 years ($n = 100$); BMI, 24.8 ± 3.1 kg/m^2, 19.1–34.9 kg/m^2 ($n = 100$).

Comparison of Glycemic Profiles and Clinical Characteristics According to Whether Amounts of Time Were Spent Below the Glucose Thresholds

The 200 24-h glycemic profiles recorded among the 100 participants were divided into two categories according to whether no time or a positive amount of time was spent below the selected glucose thresholds of 3.0, 3.45, and 3.9 mmol/L (Table 1). As expected, the number of glycemic profiles with no time spent below the selected thresholds was smaller when the glucose threshold was set at 3.0 mmol/L rather than 3.9 mmol/L. MDG concentration was significantly lower, and %CV significantly higher, when glycemic profiles with glucose values below the thresholds were compared with those profiles with no time spent below each of the three glucose thresholds. Daily insulin dose, age, and BMI did not differ between the groups, irrespective of whether time was spent below the glucose thresholds.

Relationships Between the Time Spent Below the Three Thresholds and the Independent Variables

When the time spent below the selected thresholds (the dependent variables [Y]) was expressed as its arcsine transformation (i.e., $\arcsin\sqrt{Y}$), the univariate mixed regression analysis showed strong positive relationships ($P < 0.001$) with the %CV and strong negative relationships ($P < 0.001$) with MDG concentration. The unitless standardized partial coefficients of regression (βi) for the thresholds (3.9, 3.45, and 3.0 mmol/L) were positive for the %CV ($\beta_1 = +1.31, +1.08$, and $+0.75$, respectively) and negative for MDG ($\beta_2 = -1.07, -0.58$, and -0.35, respectively), indicating that the time spent below the selected glucose threshold increased as %CV increased and as MDG

Table 1—Glycemic profiles that exhibited or did not exhibit a significant duration of time (>15 min) below the various glucose thresholds

	Glucose thresholds					
	3.0 mmol/L		3.45 mmol/L		3.9 mmol/L	
	No	Yes	No	Yes	No	Yes
Glycemic profiles (*n*)	120	80	100	100	71	129
Age (years)	56 ± 14	53 ± 12	56 ± 14	53 ± 12	57 ± 14	54 ± 12
BMI (kg/m^2)	24.5 ± 3.0	25.5 ± 2.9	24.6 ± 3.1	25.2 ± 2.9	24.7 ± 3.1	25.0 ± 3.0
MDG (mmol/L)	9.8 ± 2.4*	7.9 ± 2.0	10 ± 2.4*	8.0 ± 2.0	10.4 ± 2.3*	8.2 ± 2.2
%CV	33 ± 9*	44 ± 11	32 ± 9*	43 ± 11	31 ± 9*	42 ± 11
Insulin dose (units/kg/day)	0.66 ± 0.20	0.68 ± 0.19	0.66 ± 0.20	0.67 ± 0.20	0.67 ± 0.20	0.66 ± 0.20

Data are the mean ± SD unless otherwise indicated. Statistical comparisons between glycemic profiles (referenced as yes or no) were indicated only when $P < 0.001$. *$P < 0.001$.

concentrations decreased. In contrast, the remaining independent variables—daily insulin dose, age, and BMI—did not correlate with the time spent below the three glucose thresholds. When the thresholds were set at 3.9, 3.45, and 3.0 mmol/L, the respective *P* values were 0.92, 0.91, and 0.60 for daily insulin dose; 0.25, 0.16, and 0.24 for age; and 0.17, 0.13, and 0.07 for BMI. As a consequence, the latter three variables were no longer considered to be explanatory and were thus removed from the model used in statistical analysis.

CARTs

Because the %CV and MDG are both highly statistically significant ($P < 0.001$), we used the CART method to decipher whether one is more significant than the other. Different results were obtained when the three selected thresholds were tested (Fig. 1). At 3.9 mmol/L, MDG was the first explanatory variable, but when the glucose threshold was set at 3.0 or 3.45 mmol/L, the %CV appeared as the primary factor associated with a higher risk of hypoglycemia (Fig. 1). When the threshold was set at 3.0 mmol/L, the %CV was the first variable that entered the top of the regression tree. The first node of %CV for partitioning the tree was found at 47.3%. The subsample with the %CV below 47.3% was subsequently pruned from the regression tree, and in that subsample the mean terminal value of the time spent below 3.0 mmol/L was 1.7%. The subsample with a %CV ≥47.3% was retained and split further. As expected, the second explanatory variable entering the regression tree was MDG, with a splitting node at 6.8 mmol/L. The subsamples with MDG ≥6.8 mmol/L or <6.8 mmol/L ended with mean times spent below 3.0 mmol/L of 6.8 and 26.0%, respectively, as indicated at the bottom of the terminal branches.

Exponential Relationships Between the Time Spent Below 3.0 mmol/L and MDG or %CV

The exponential relationships are illustrated in Fig. 2*A* and *B*. The relationship between the percentage of time spent below 3.0 mmol/L (54 mg/dL) (dependent variable [Y]) and MDG (independent variable [X], expressed as milligrams per deciliter) was described by a simple decreasing exponential curve: $Y = 23.66\ e^{-0.009X}$ ($r = -0.358$, $P < 0.001$). When Y was plotted against the %CV (X), the relationship was represented by a simple increasing exponential curve: $Y = 0.93\ e^{0.043X}$ ($r = 0.509$, $P < 0.001$). A comparison between the two coefficients of correlation did not show any significant difference after testing the corresponding *z* values after a Fisher transformation ($z = 1.87$, $P = 0.065$), even though the *r* value for %CV seemed to be slightly better than that for MDG.

Time Spent Below 3.0 mmol/L After Dividing the %CV into Tertiles in the Subset With Mean Glucose <7.8 mmol/L

Among the 200 daily glycemic profiles, 65 exhibited mean glucose concentrations ≤7.8 mmol/L. After dividing that

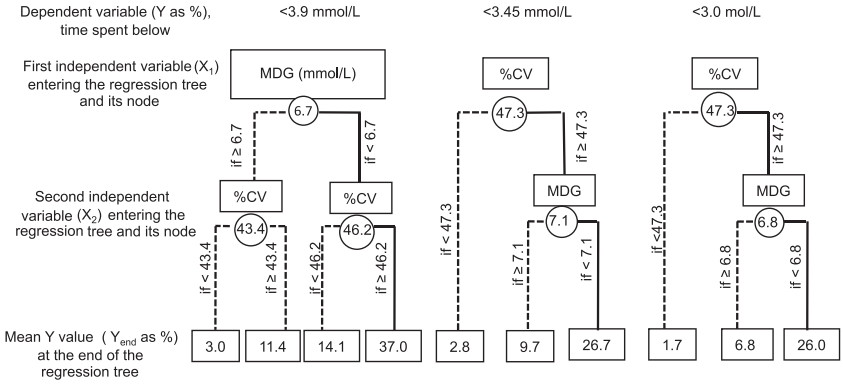


Figure 1—CART procedure. The respective influences of the potential explanatory variables (MDG concentration and the %CV) on the dependent variable (time spent below the selected thresholds [3.9, 3.45, and 3.0 mmol/L]) are estimated by using CARTs. The subsamples split from the threshold values (open circles) are considered to be the best true (right branch) or false (left branch) predictors of the risk of hypoglycemia, as assessed on the basis of the percentage of time spent with glucose below 3.9, 3.45, and 3.0 mmol/L. For instance, a Y_{end} value of 26.0 at the end of the right branch of the regression tree (threshold, <3.0 mmol/L; far right) means that after a true stepwise split that selected the first-line (%CV) and second-line (MDG) explanatory variables, the mean time spent below 3.0 mmol/L is 26.0%. When these explanatory variables are not truly selected, the final percentage is only 1.7%. In summary, the itinerary on the right side of each CART, which has selected the %CV as the first and the MDG as the second explanatory variable, at a threshold of 47.3% for %CV and 6.8 mmol/L for MDG, corresponds to the best selection with the highest sensitivity (26%).

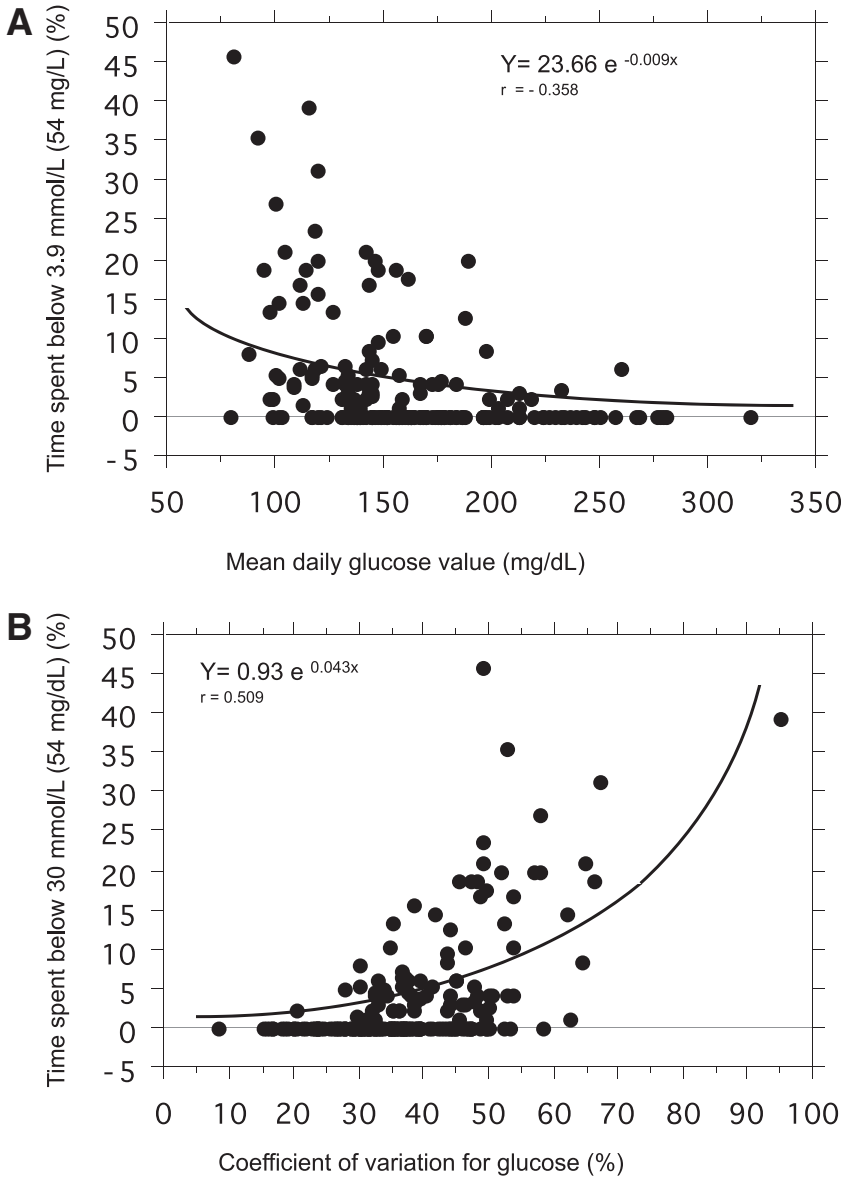


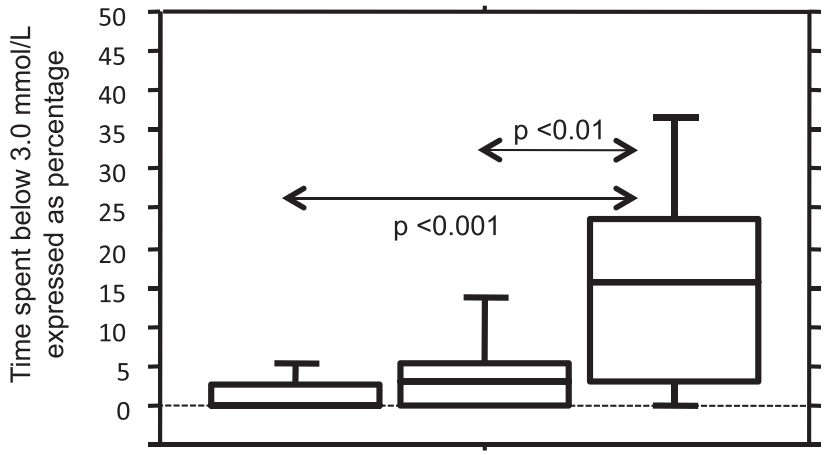
Figure 2—Simple exponential relationships. The time during which glucose is below 3.0 mmol/L (54 mg/dL) is plotted against the MDG concentration (*A*) and the %CV (*B*).

subset on the basis of %CV, three tertiles were selected: %CV <34% (n = 21) (tertile 1); %CV between 34 and 44.1% (n = 22) (tertile 2); and %CV >44.1% (n = 22) (tertile 3). As illustrated in Fig. 3, percentages of time spent below 3.0 mmol/L (median [IQR]) were statistically significantly higher in tertile 3 (15.6% [20.5%]) than in tertile 1 (0.0% [2.7%]; $P < 0.001$) and tertile 2 (3.1% [5.5%]; $P < 0.01$). No difference was found between tertiles 1 and 2.

CONCLUSIONS

Several key messages can be drawn from this study. First, the two main factors for predicting risk of hypoglycemia in persons with T1DM are low or near-normal daily glucose levels and abnormally high glucose fluctuations from peaks to nadirs. Second, the role of these two factors was approximately equivalent across the range of glucose thresholds from 3.9 to 3.0 mmol/L, even though excessive within-day glucose fluctuations seemed to be increasingly involved in predicting the risk of hypoglycemic episodes and in precipitating their onset (with a lower glucose threshold used to define hypoglycemia). In addition, the coefficient of correlation for the exponential curve depicting the relationship between the time spent below 3.0 mmol/L and the %CV was greater than that for the MDG value (as an explanatory variable), even though the differences were not statistically significant. Similar results derived from a less sophisticated mathematical analysis were found for the %CV; these results were reported recently at the 78th Scientific Sessions of the American Diabetes Association (34). Nevertheless, all these results reinforce the opinion that, in addition to achieving near-normal glycemia for preventing the development or progression of micro- and macrovascular complications (6,35–38), it is crucial to try to reduce as much as possible the magnitude of glucose fluctuations in order to limit the risk of hypoglycemia, a main challenge for improving the quality of life of persons with T1DM (7–14).

This position is supported by two additional findings. First, in all groups, the mean %CV was below 36% (the limit that separates stable from labile diabetes [11,17]) when the patients did not spend any time below the selected thresholds—whatever the values chosen (from 3.9 to 3.0 mmol/L). By contrast, the mean %CV was always above 36% when the patients spent a positive amount of time above the aforementioned glucose thresholds. Second, the computation by tertiles of %CV in the subset with near-normal MDG values showed that the amount of time spent below 3.0 mmol/L was rarely positive when the %CV was less than 34%. Therefore, maintaining the %CV below this threshold should be a suitable recommendation for limiting the risk of hypoglycemia when the MDG concentration is stable and maintained below 7.8 mmol/L (a value that corresponds to near-normal glucose) (32,33). Even though the two thresholds of 36 and 34% are very close, they represent quite different things: a %CV above 36% is synonymous with frequent hypoglycemic episodes (labile diabetes), regardless of MDG concentration, whereas achieving a %CV below 34% ensures a very low risk of hypoglycemia when tight glycemic control is obtained in terms of overall glucose exposure. Until recently, only a few people with T1DM concomitantly attained such targets (low %CV and near-normal MDG concentration) with conventional insulin treatments consisting of either multiple injections daily or CSII through a pump (39). However, the expanded use of novel devices for CGM (17,40,41) and ceaseless progression toward the



Tertile with %CV	<34%	34- 44.1%	>44.1%
Number of profiles	21	22	22
Median	0.0	3.1	15.6
[IQR]	[2.7]	[5.5]	[20.5]
Range	0.0 – 8.0	0.0 -15.6	0.0 - 45.8

Figure 3—Percentages of time spent with glucose below 3.0 mmol/L. The %CV data were divided into tertiles for the subset of 65 daily glycemic profiles exhibiting mean glucose concentrations ≤7.8 mmol/L. Data distributions around medians are expressed as IQRs (boxes), 90th percentiles (vertical lines with upper and lower limits), and ranges (minimum to maximum).

implementation of more sophisticated systems for closed-loop insulin delivery (42) both raise promising expectations for improving glucose homeostasis in persons with T1DM. Even though it is highly likely that a reduction in short-term glycemic variability is one of the key players in reducing the incidence of hypoglycemia, the observation of a strong relationship between %CV and the time spent below various glucose thresholds does not allow us to distinguish whether glucose variability is a cause or a consequence of the time spent below the recommended target glycemic range (usually set between 3.9 and 10 mmol/L) (17,18,20). It should be noted that this study included patients who were carefully instructed to ingest moderate amounts of refined carbohydrates in order to prevent excessive glycemic rebounds after periods of hypoglycemia and thereby avoid any subsequent additional deterioration of glucose variability. Furthermore, because the patients were blinded to their CGM data throughout the entire monitoring period, all episodes of asymptomatic hypoglycemia were not corrected with therapeutic interventional measures in the absence of any warning signs. Consequently, there are many reasons to consider excessive glucose variability as more of a causative factor than a consequence of hypoglycemia.

This study has some limitations. It has an observational design and a short duration, although all CGM was conducted on an ambulatory basis. Finally, the CGM sensors may have been inaccurate when glucose values were within the lower range.

In conclusion, to address the question raised in the title of this article, it seems that excess short-term glycemic variability, as assessed on the basis of the within-day %CV, is at least as important as—and perhaps slightly more important than—the MDG level in preventing the risk of hypoglycemia, especially when the threshold of hypoglycemia is set at the lowest level (3.0 mmol/L). In addition, striving to achieve a %CV below 34% in patients who already have satisfactory glycemic control in terms of chronic glucose exposure (MDG concentration ≤7.8 mmol/L) should be one of the main objectives in the management of T1DM.

Funding. This study was conducted with the help of academic funds provided by the University of Montpellier.

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

Author Contributions. L.M. designed the study, collected and interpreted data, and wrote the manuscript. A.W., C.C., E.R., and D.O. designed the study, interpreted data, and critically revised the manuscript. N.M. carried out the statistical analysis. L.M. 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.

References

1. Cryer PE. Individualized glycemic goals and an expanded classification of severe hypoglycemia in diabetes. Diabetes Care 2017;40:1641–1643
2. Cryer PE. Glycemic goals in diabetes: trade-off between glycemic control and iatrogenic hypoglycemia. Diabetes 2014;63:2188–2195
3. Gill GV, Woodward A, Casson IF, Weston PJ. Cardiac arrhythmia and nocturnal hypoglycaemia in type 1 diabetes: the "dead in bed" syndrome revisited. Diabetologia 2009;52:42–45
4. Zoungas S, Patel A, Chalmers J, et al.; ADVANCE Collaborative Group. Severe hypoglycemia and risks of vascular events and death. N Engl J Med 2010;363:1410–1418
5. Davis SN, Duckworth W, Emanuele N, et al.; Investigators of the Veterans Affairs Diabetes Trial. Effects of severe hypoglycemia on cardiovascular outcomes and death in the Veterans Affairs Diabetes Trial. Diabetes Care 2019;42:157–163
6. Nathan DM, Genuth S, Lachin J, et al.; Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993;329:977–986
7. Kilpatrick ES, Rigby AS, Goode K, Atkin SL. Relating mean blood glucose and glucose variability to the risk of multiple episodes of hypoglycaemia in type 1 diabetes. Diabetologia 2007;50:2553–2561
8. Cox DJ, Kovatchev BP, Julian DM, et al. Frequency of severe hypoglycemia in insulin-dependent diabetes mellitus can be predicted from self-monitoring blood glucose data. J Clin Endocrinol Metab 1994;79:1659–1662
9. Monnier L, Wojtusciszyn A, Colette C, Owens D. The contribution of glucose variability to asymptomatic hypoglycemia in persons with type 2 diabetes. Diabetes Technol Ther 2011;13:813–818
10. Kovatchev B, Cobelli C. Glucose variability: timing, risk analysis, and relationship to hypoglycemia in diabetes. Diabetes Care 2016;39:502–510
11. Monnier L, Colette C, Wojtusciszyn A, et al. Toward defining the threshold between low and high glucose variability in diabetes. Diabetes Care 2017;40:832–838
12. Monnier L, Colette C, Owens DR. The application of simple metrics in the assessment of glycaemic variability. Diabetes Metab 2018;44:313–319
13. Ceriello A, Monnier L, Owens D. Glycaemic variability in diabetes: clinical and therapeutic implications. Lancet Diabetes Endocrinol 2019;7:221–230
14. Beck RW, Riddlesworth T, Ruedy K, et al.; DIAMOND Study Group. Effect of continuous glucose monitoring on glycemic control in adults with type 1 diabetes using insulin injections: the DIAMOND randomized clinical trial. JAMA 2017;317:371–378

15. Rodbard D. Hypo- and hyperglycemia in relation to the mean, standard deviation, coefficient of variation, and nature of the glucose distribution. Diabetes Technol Ther 2012;14:868–876
16. Beck RW, Bergenstal RM, Cheng P, et al. The relationships between time in range, hyperglycemia metrics, and HbA1c. J Diabetes Sci Technol 2019;13:614–626
17. Danne T, Nimri R, Battelino T, et al. International consensus on use of continuous glucose monitoring. Diabetes Care 2017;40:1631–1640
18. Beck RW, Bergenstal RM, Riddlesworth TD, et al. Validation of time in range as an outcome measure for diabetes clinical trials. Diabetes Care 2019;42:400–405
19. Hirsch IB, Sherr JL, Hood KK. Connecting the dots: validation of time in range metrics with microvascular outcomes. Diabetes Care 2019;42:345–348
20. Battelino T, Danne T, Bergenstal RM, et al. Clinical targets for continuous glucose monitoring data interpretation: recommendations from the International Consensus on Time in Range. Diabetes Care 2019;42:1593–1603
21. Rodbard D. Clinical interpretation of indices of quality of glycemic control and glycemic variability. Postgrad Med 2011;123:107–118
22. Rodbard D. Glucose variability: a review of clinical applications and research developments. Diabetes Technol Ther 2018;20(Suppl. 2):S25–S215
23. Gómez AM, Henao DC, Imitola Madero A, et al. Defining high glycemic variability in type 1 diabetes: comparison of multiple indexes to identify patients at risk of hypoglycemia. Diabetes Technol Ther 2019;21:430–439
24. International Hypoglycaemia Study Group. Glucose concentrations of less than 3.0 mmol/L (54 mg/dL) should be reported in clinical trials: a joint position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2017;40:155–157
25. Workgroup on Hypoglycemia, American Diabetes Association. Defining and reporting hypoglycemia in diabetes: a report from the American Diabetes Association Workgroup on Hypoglycemia. Diabetes Care 2005;28:1245–1249
26. Directive 2001/20/EC of European Parliement and the council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical trials on medicinal products for human use [Internet]. Luxembourg, Official Journal of the European Communities, 2001. Available from https://www.eorct.be/services/doc/clinical-eu-directive-04-april-01.pdf. Accessed 15 December 2016
27. John WG, Braconnier F, Miedema K, Aulesa C, Piras G. Evaluation of the Menarini-Arkray HA 8140 hemoglobin A1c analyzer. Clin Chem 1997;43:968–975
28. Kovatchev BP. Metrics for glycaemic control - from HbA_{1c} to continuous glucose monitoring. Nat Rev Endocrinol 2017;13:425–436
29. Rodbard D. Metrics to evaluate quality of glycemic control: comparison of time in target, hypoglycemic, and hyperglycemic ranges with "risk indices." Diabetes Technol Ther 2018;20:325–334
30. Zar JH. Data transformations. In *Biostatistical Analysis*. 4th ed. Upper Saddle River, New Jersey, Prentice-Hall, 1999, p. 273–281
31. Breiman L, Friedman JH, Olshen RA, Stone CJ. *Classification and Regression Tree*. New York, Wadsworth Publishing Co., 1987
32. Nathan DM, Kuenen J, Borg R, Zheng H, Schoenfeld D, Heine RJ; A1c-Derived Average Glucose Study Group. Translating the A1C assay into estimated average glucose values [published correction appears in Diabetes Care 2009;32:207]. Diabetes Care 2008;31:1473–1478
33. American Diabetes Association. 6. Glycemic targets: *Standards of Medical Care in Diabetes—2019*. Diabetes Care 2019;42(Suppl. 1):S61–S70
34. Hachmann-Nielsen E, Bartholdy T, Born Djurhuus C, Kvist K. Glycemic variability associated with time spent in hypoglycemia in type 1 diabetes—explorative data in real-world, real-time continuous glucose monitoring (Abstract). Diabetes 2018;67(Suppl. 1):80-LB
35. Nathan DM, Cleary PA, Backlund JY, et al.; Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. N Engl J Med 2005;353:2643–2653
36. Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) Study Research Group. Intensive diabetes treatment and cardiovascular outcomes in type 1 diabetes: the DCCT/EDIC Study 30-year follow-up. Diabetes Care 2016;39:686–693
37. Hainsworth DP, Bebu I, Aiello LP, et al.; Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) Research Group. Risk factors for retinopathy in type 1 diabetes: the DCCT/EDIC study. Diabetes Care 2019;42:875–882
38. Perkins BA, Bebu I, de Boer IH, et al.; Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) Research Group. Risk factors for kidney disease in type 1 diabetes. Diabetes Care 2019;42:883–890
39. Pickup JC, Renard E. Long-acting insulin analogs versus insulin pump therapy for the treatment of type 1 and type 2 diabetes. Diabetes Care 2008;31(Suppl. 2):S140–S145
40. Rodbard D. Continuous glucose monitoring: a review of successes, challenges, and opportunities. Diabetes Technol Ther 2016;18(Suppl. 2):S3–S13
41. Petrie JR, Peters AL, Bergenstal RM, Holl RW, Fleming GA, Heinemann L. Improving the clinical value and utility of CGM systems: issues and recommendations: a Joint Statement of the European Association for the Study of Diabetes and the American Diabetes Association Diabetes Technology working group. Diabetes Care 2017;40:1614–1621
42. Renard E, Farret A, Kropff J, et al.; AP@home Consortium. Day-and-night closed-loop glucose control in patients with type 1 diabetes under free-living conditions: results of a single-arm 1-month experience compared with a previously reported feasibility study of evening and night at home. Diabetes Care 2016;39:1151–1160