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The 36% coefficient of variation for glucose proposed for separating stable and labile diabetes is clinically relevant: A continuous glucose monitoring-based study in a large population of type 1 diabetes patients

The relationship between haemoglobin A_{1c} (HbA_{1c}) and risk of micro- and macrovascular complications in patients with type 1 diabetes (T1D) has been well demonstrated, particularly by the Diabetes Control and Complications Trial (DCCT) [1] and Epidemiology of Diabetes Interventions and Complications (EDIC) follow-up study [2]. Unlike the long-term glucose assessment provided by the HbA_{1c}, glycaemic variability (GV) requires a comprehensive analysis of glycaemia that includes both glucose excursions and time factors. It is well established that tight glucose control increases the risk of hypoglycaemia [1].

Now, the development of continuous glucose monitoring (CGM), which enables monitoring interstitial glucose levels almost continuously, allows subsequent analyses of short-term glucose variability to be performed. The most-used within-day and between-day variability indices with CGM are the standard deviation (SD), coefficient of variation (CV; SD/mean glucose value), mean amplitude of glycaemic excursion (MAGE) and continuous overlapping net glycaemic action (CONGA). The most-used between-day GV index is the mean of daily difference (MODD), while other indices assess the risk of hypoglycaemia or hyperglycaemia [low blood glucose index (LBGI), high blood glucose index (HBGI) or both (Average Daily Risk Range, ADRR)]. Formulas for these indices are detailed in a recent review [3].

Yet, a growing problem for clinicians is that most of these indices are complex, with many interfering factors such as timing and type of meals. A recent study by Monnier et al. [4] concluded that a CV percentage (%CV) of 36 appears to be a suitable threshold to distinguish between stable and unstable glycaemia. The authors also emphasized the idea that the %CV is a pragmatic and easy tool that can be adjusted for mean glucose values, but does not depend on glucose levels. This 36% threshold has now been adopted as the primary metric to separate stable from unstable diabetes by the International Consensus on the Use of Continuous Glucose Monitoring [5].

Thus, the present study aimed to implement this %CV cut-off value in a large population of T1D patients, each of whom wore a professional-grade CGM device as a way to determine the impact of such stratification on glycaemic parameters as well as several alternative GV indices and the risk of hypo- and/or hyperglycaemia.

Our study retrospectively included 206 T1D patients who performed professional blinded ambulatory CGM for at least 3 days and up to 7 days (iPro2 CGM, Enlite sensor; Medtronic, Minneapolis, MN, USA) between 2011 and 2017. The iPro2 recorder digitally stores the average sensor reading every 5 min, and all subjects performed at least four capillary blood glucose tests per day to calibrate the CGM system.

These patients all presented with either repeated hypoglycaemia or persistent above-target HbA_{1c} levels. Age, body mass index (BMI), type of treatment (multiple daily injections or subcutaneous insulin infusions), diabetes duration and HbA_{1c} were determined for all patients at the time of CGM recording. All investigations were routinely performed at the diabetes outpatients clinic of the University Hospital of Lyon (France), and all procedures were in accordance with the Declaration of Helsinki.

Time spent in hypoglycaemia, and in and above the glucose target, were defined as the total duration of periods with glucose levels < 70 mg/dL, 70–180 mg/dL and > 180 mg/dL, respectively. A hypoglycaemic episode was defined as at least three consecutive measures < 70 mg/dL (for at least 10 min), and the estimated HbA_{1c} was determined using mean glucose values. Evaluated GV measures included SD, %CV, MAGE, CONGA (at 1 h and at 4 h), MODD, ADRR, LBGI and HBGI, which were determined from the CGM recordings using the original methods of assessment.

Values are presented as means ± SD or percentages. Statistical tests were two-tailed; for descriptive and exploratory analyses, a significance level of $P < 0.05$ was adopted. Two-group comparisons were conducted using Student's *t* test for data with normal distribution, and the Mann–Whitney U test for data with a skewed distribution pattern; chi-squared test was used for non-parametric data; and correlations between variables were calculated using Spearman's correlation (rho). Statistical analyses were performed using SPSS version 21.0 software (SPSS Inc., Chicago, IL, USA).

A total of 206 T1D patients were retrospectively included in our study (Table 1). Mean age was 44.1 years, 45% were women, mean BMI was 25.2 kg/m^2, mean duration of diabetes was 21.0 years, 33% were treated by subcutaneous insulin pump, and mean HbA_{1c} was 8.2% ± 1.3 for the entire study population. CGM-derived glucose data and GV indices are detailed in Table 1. Mean glucose was 172 mg/dL ± 32 and estimated HbA_{1c} was 7.6% ± 1.1 for the whole of the study population.

Using Spearman's correlation, it was determined that the indices that correlated well with time spent in hypoglycaemia were the %CV (rho = 0.678) and LBGI (rho = 0.977), whereas the indices that correlated well with time spent in hyperglycaemia were SD (rho = 0.539), MODD (rho = 0.474), MAGE (rho = 0.448) and HBGI (rho = 0.946; Table S1; see supplementary materials associated with this article online).

Using the %CV cut-off of 36, the population was split into two subgroups (Table 1). Those with a %CV ≤ 36 (n = 49) were significantly older (48.8 ± 16) than those with a %CV > 36 (42.6 ± 14 years). Gender ratio, BMI and diabetes duration did not differ between the two subgroups. The proportion of patients treated by insulin pump was not significantly larger in the group with the lower %CV (38.7% *vs* 31.2%; P = 0.235), nor was the HbA_{1c} value (8.5 ± 1.4% *vs* 8.1 ± 1.4%; P = 0.07). Concerning glucose homoeostasis, the mean glucose value, estimated HbA_{1c} and time (%) spent in hyperglycaemia tended to be higher in the low %CV group, although statistical significance was not reached. The amount (%) of time spent on target (glucose 70–180 mg/L) was the same in both subgroups, whereas the amount (%) of time spent in hypoglycaemia and number of hypoglycaemic episodes were both significantly lower in the group with a %CV ≤ 36. All GV indices were significantly lower in the low %CV group except for HBGI. The proportion of time spent in

Table 1
Patients' clinicobiological characteristics, parameters of continuous glucose monitoring (CGM) and indices of glucose variability.

	Entire study population ($n = 206$)	Patients with %CV ≤ 36 ($n = 49$)	Patients with %CV > 36 ($n = 157$)	*P*
Age (years)	44.1 ± 14	48.8 ± 16	42.6 ± 14	0.018
Gender ratio: female/male (*n*)	94/112	21/28	73/84	NS
Body mass index (kg/m^2)	25.2 ± 4.2	25.4 ± 4.0	25.2 ± 4.2	0.810
Subcutaneous pump therapy (%)	33 ($n = 68$)	39 ($n = 19$)	31 ($n = 49$)	0.235
Duration of diabetes (years)	21.0 ± 12	21.0 ± 13	21.1 ± 12	0.978
HbA_{1c} at time of CGM (%)	8.2 ± 1.3	8.5 ± 1.4	8.1 ± 1.3	0.072
Mean glucose (mg/dL)	172 ± 32	179.83 ± 39	170.12 ± 30	0.116
Estimated HbA_{1c} (%)	7.6 ± 1.1	7.8 ± 1.3	7.5 ± 1.1	0.117
Time (%) spent at target glucose (70–180 mg/dL)	51.3 ± 15.2	51.8 ± 23.0	51.1 ± 11.8	0.837
Time (%) spent in hypoglycaemia (< 70 mg/dL)	7.3 ± 6.9	2.4 ± 3.2	8.9 ± 7.1	< 0.0001
Time (%) spent in hyperglycaemia (> 180 mg/dL)	41.1 ± 17.8	45.7 ± 24.8	39.7 ± 14.8	0.113
Hypoglycaemic events/day (*n*)	1.2 ± 0.8	0.6 ± 0.6	1.4 ± 0.8	< 0.0001
Standard deviation	72 ± 16	58 ± 12	76 ± 15	< 0.0001
% Coefficient of variation	42.1 ± 7.8	32.6 ± 4.1	45.2 ± 6.1	< 0.0001
MAGE	139 ± 34	110 ± 24	148 ± 32	< 0.0001
MODD	4.1 ± 1.0	3.3 ± 0.8	4.3 ± 0.9	< 0.0001
$CONGA_1$	1.7 ± 0.4	1.4 ± 0.3	1.8 ± 0.4	< 0.0001
$CONGA_4$	3.3 ± 0.9	2.7 ± 0.9	3.4 ± 0.9	< 0.0001
HBGI	10.4 ± 5.5	10.7 ± 6.6	10.3 ± 5.1	0.722
LBGI	1.9 ± 1.8	0.6 ± 0.6	2.2 ± 1.9	< 0.0001
ADRR	54.6 ± 13.6	41.8 ± 12.0	58.7 ± 11.5	< 0.0001

MAGE: mean amplitude of glycaemic excursion; MODD: mean of daily difference; $CONGA_{1/4}$: continuous overlapping net glycaemic action at 1h/4h; HBGI/LBGI: high/low blood glucose index; ADRR: Average Daily Risk Range.

hypoglycaemia as a function of the %CV (36%) is graphically illustrated in Fig. 1 for the entire study population.

While many GV indices have been described, assessing simple tools is crucial in a context of democratization of CGM in many countries. In fact, the present study has confirmed the clinical relevance of using the %CV at a cut-off value > 36 in a large T1D population by identifying subjects at high risk of hypoglycaemia, and has also linked short-term glucose variability with clinical outcomes. Also, the subgroup with a low %CV had other GV index values that were significantly lower (except for HBGI). Thus, adding the %CV at this cut-off (36%) to HbA_{1c} values should help clinicians to phenotype the glycaemic profiles of patients.

Our study had several strengths. Analyses were performed in a large population of T1D patients, and all of them wore the same CGM device, which blinded values. Such a system is the best approach for exploring GV, as subjects cannot adapt their insulin doses during CGM-wearing periods when they have no access to their glucose patterns and tendencies.

The total study population had a mean %CV of 42 ± 7.8%, and 76% of them had a %CV > 36. However, our inclusion criteria explain this high proportion of subjects with a high %CV.

Some other data certainly drew our attention. The estimated HbA_{1c} based on CGM data largely underestimated HbA_{1c} at the time of CGM (7.6 ± 1.1% *vs* 8.2 ± 1.3%) for the whole of the study population. This may be explained by short-term modifications of lifestyle habits during monitoring or better adaptation of insulin doses following patients' education and/or improved motivation. Also, it is difficult to extrapolate our present results to the general population of patients with T1D. Indeed, the use of CGM in our study was justified by their specific symptoms or metabolic values, which are usually associated with high GV profiles. However, it is not clear whether our present conclusions would apply to asymptomatic patients or the use of other CGM systems.

In addition, BMI, previously shown to be a factor inversely correlated with GV [6,7], was not protective in our study. However, it must be emphasized that only a minority of patients were overweight or obese.

Patients with a %CV ≤ 36 were significantly older, but shared the same diabetes duration as those with a %CV > 36, suggesting that the age of T1D diagnosis is an important contributing factor for GV. This observation confirms previous reports that the proportion of residual beta cells increases when diabetes arises after puberty [8], thereby underscoring the clinical heterogeneity of the disease.

Unlike the CONGA or MODD indices, the %CV does not determine the periodic characteristics of blood glucose. A recent editorial by Cobelli and Facchinetti [9] highlighted the importance of assessing not only the amplitude, but also the timing, of components of GV. However, most of the indices described here reflect amplitude components of GV, and our present findings confirm that the %CV is a useful index for identifying subjects at risk of hypoglycaemia; nevertheless, this index was never intended to assess hyperglycaemia risk over time, which explains why the HBGI did not correlate with the %CV (Table S1; see supplementary materials associated with this article online).

Prospective analyses examining the effects of short-term GV on micro- and/or macrovascular complications are needed. In our opinion, and as developed in a recent review by Monnier et al. [10], complementary indices to assess short-term between-day variability (such as the MODD, which integrates both amplitude and temporal dimensions of GV) should be added to the %CV when analyzing GV in these types of studies.

In conclusion, a %CV of 36 is an appropriate cut-off value for identifying patients at risk of hypoglycaemia and those with unstable glycaemia in clinical practice.

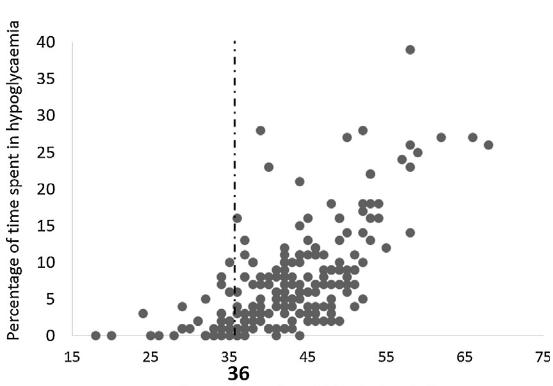

Fig. 1. Amount of time (%) spent in hypoglycaemia as a function of the percent coefficient of variation (%CV) cut-off value of 36.

Disclosure of interest

The authors declare that they have no competing interest.

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Appendix A. Supplementary data

Supplementary data (Table S1) associated with this article can be found, in the online version, at https://doi.org/10.1016/j.diabet.2018.05.009.

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