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ORIGINAL ARTICLE

Defining the target value of the coefficient of variation by continuous glucose monitoring in Chinese people with diabetes

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ABSTRACT

Aims/Introduction: To define the target value for the percentage coefficient of variation for glucose (%CV) as a measure of glycemic variability (GV) in Chinese diabetes patients.

Materials and Methods: This retrospective study included 3,007 diabetes patients who underwent continuous glucose monitoring for 3 days. Type 2 diabetes was divided into groups according to the received treatment: group 1, non-insulinotropic agent (n = 138); group 2, insulinotropic agent (n = 761); group 3, basal insulin therapy (n = 100); group 4, premixed insulin (n = 784); and group 5, intensive insulin therapy (n = 612). Type 1 diabetes patients were included as group 6 (n = 612). %CV and percentage of time per day within, below (3.9mmol/L; $TBR_{3.9}$) and above (10.0 mmol/L) the target glucose range (3.9–10.0 mmol/L) were computed. $TBR_{3.9}$ ≥4% was defined as excessive hypoglycemia.

Results: Type 2 diabetes with a premixed or intensive insulin regimen had an increased %CV compared with those receiving oral therapy or basal insulin. The upper limit of %CV in group 1 was 33%, which was adopted as the threshold to define excessive GV. For each treatment group, the percentage of people with $TBR_{3.9}$ ≥4% was significantly greater in the subgroup with %CV >33% than ≤33% ($P < 0.001$). In participants who achieved $TBR_{3.9}$ <4%, the time per day spent within the target glucose range of 3.9–10.0 mmol/L > 70% and time per day above 10.0 mmol/L <25%, the 95th percentile of %CV was 32.70%. Further receiver operating characteristic curve analysis showed that the cut-off values of %CV for predicting $TBR_{3.9}$ ≥4% varied by the type of diabetes and glycated hemoglobin categories.

Conclusions: A %CV of 33% was set as the threshold for excess glucose variability in Chinese diabetes patients. Meanwhile, glycated hemoglobin and the type of diabetes should be considered for the goal-setting of %CV.

INTRODUCTION

As one of the three main components of 'glycemic triumvirate'[1], glycemic variability (GV) is emerging as an important glycemic target. Short-term GV is found to be associated with the development and progression of microvascular complications, and, to a lesser extent, macrovascular complications [2,3]. Notably, the availability of continuous glucose monitoring (CGM) allows clinicians to assess short-term GV accurately. Within-day GV corresponds to the distribution of glucose values around the 24 h mean glucose concentration and includes two parameters – the standard deviation (SD) and the derived percentage coefficient of variation for glucose (%CV). %CV is accepted as the widely used index for assessing within-day GV, with the main advantages being that it is easily calculated and is independent of the mean glucose concentration[4–6]. In recent years, several studies have attempted to investigate the meaningful threshold for %CV to differentiate labile from stable diabetes. Monnier *et al.*[7] regarded people with diabetes treated

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with only diet or with insulin sensitizers as the reference group and determined the %CV threshold was 36%, which was later adopted in the International Consensus on Use of Continuous Glucose Monitoring[8].

Asian people often present different glucose patterns compared with their Western counterparts[9]; therefore, whether a threshold value of 36% is appropriate for Chinese people with diabetes remains to be questionable. Previously, a national multicenter study was carried out in China to determine the reference values of CGM parameters[10,11]. However, the study was performed in a sample of healthy participants with normal glucose regulation instead of in people with diabetes. To date, there are no recommendations provided for the %CV target in Chinese people with diabetes, which the present study aims to address.

METHODS

Participants

All participants were consecutively recruited from among hospitalized patients with diabetes at the Department of Endocrinology and Metabolism of the Shanghai Jiao Tong University Affiliated Sixth People's Hospital (Shanghai, China) from 1 October 2005 to 30 September 2015. Diabetes was diagnosed according to the 1999 World Health Organization criteria[12]. Type 1 diabetes was diagnosed as positive for autoantibodies to glutamic acid decarboxylase and/or islet antigen 2. The inclusion criterion was diabetes with stable antidiabetic treatment regimens for at least 3 months preceding the recruitment. Those with acute complications, such as diabetic ketoacidosis, hyperglycemic hyperosmolar state or those who had been treated with steroids during the previous 3-month period, were excluded. Pregnant female participants were also excluded. Initially, a total of 2,989 type 2 diabetes and 612 type 1 diabetes patients were included in the study.

This was an observational study, and data were collected retrospectively. The study protocol was approved by the ethics committees of Shanghai Jiao Tong University Affiliated Sixth People's Hospital in accordance with the principles of the Helsinki Declaration. Written informed consent was obtained from each participant.

Propensity score matching

Participants were then categorized into groups according to the type of diabetes and modality of therapy regimen. Out of the 2,989 type 2 diabetes, 1,206 participants with type 2 diabetes were on intensive insulin regimens, principally by multiple daily injections. Meanwhile, 612 type 1 diabetes patients were on intensive insulin regimens, including either multiple daily injections or continuous subcutaneous insulin infusion. To reduce the impact of glycated hemoglobin (HbA_{1c}) level on GV, 1,206 participants with type 2 diabetes were matched in a 1:1 ratio with 612 participants with type 1 diabetes by propensity score matching. First, 1,206 type 2 diabetes patients were extracted. Nearest neighbor matching was used as the matching algorithm. The caliper was set at the 0.001 level. A propensity score was generated by a logistic regression model. Covariate for matching was the baseline HbA_{1c} level. In the end, 612 type 2 diabetes patients were matched in a 1:1 ratio with 612 type 1 diabetes patients based on the propensity score, and there was no difference in baseline HbA_{1c} levels between these two groups (78 ± 25 mmol/mol [9.3 ± 2.3%] vs 77 ± 26 mmol/mol [9.2 ± 2.4%], $P = 0.28$). These participants with type 2 diabetes ($n = 612$) who were matched for type 1 diabetes were included into the final statistical analysis, whereas the rest of the 594 type 2 diabetes who were not successfully matched for type 1 diabetes were excluded.

Division of groups according to treatment regimen for diabetes

Next, a total of 2,395 people with type 2 diabetes were included in the final analysis, and were divided into several groups according to different categories of antidiabetic treatments: (i) monotherapy or combination oral antidiabetic drugs (OADs) therapy with only non-insulinotropic agents; that is, metformin and/or insulin sensitizers and/or alpha-glucosidase inhibitors (group 1, $n = 138$), and these people were regarded as those who had stable glucose homeostasis, as their risk of hypoglycemia is very low or even absent[13]; (ii) monotherapy or combination OADs with at least one insulinotropic agent, including sulfonylurea or glinides (group 2, $n = 761$); (iii) basal insulin treatment, including insulin glargine or insulin detemir with or without OADs (group 3, $n = 100$); (iv) premixed insulin treatment with or without OADs (group 4, $n = 784$); and (v) intensive insulin regimens with or without OADs (group 5, $n = 612$). Another 612 participants with type 1 diabetes were also included (group 6). Meanwhile, all participants were instructed to adhere to a standard medical nutrition therapy, and dietary calorie intake (kcal/day) was determined as 25 kcal/kg ideal bodyweight, with 55% of calories coming from carbohydrates, 17% from proteins and 28% from fats.

CGM parameters and the definition of hypoglycemia

All included participants had undergone blinded 72-h CGM (CGMS GOLD; Medtronic Inc., Northridge, CA, USA). The glucose sensor of the CGM system (Model MMT-7003) was inserted on day 0 and removed after 72-h, generating a daily record of 288 continuous sensor values. The equipment was calibrated against at least four capillary blood glucose measurements by a SureStep blood glucose meter (LifeScan, Milpitas, CA, USA).

CGM-derived 24-h mean glucose and intraday GV metrics were calculated based on the average values of the respective parameters taken on day 2 and 3. Intraday GV parameters included the SD and %CV (%CV = [(SD of glucose) / (mean glucose)] × 100). The CGM-derived times in glucose ranges were also calculated. The $TIR_{3.9–10}$ (%) was defined as the percentage of time spent within the target glucose range of 3.9–10.0 mmol/L. $TBR_{3.9}$ (%) and $TBR_{3.0}$ (%) were defined as the percentage of time spent below the target glucose range of 3.9 or 3.0 mmol/L. TAR_{10} (%) was defined as the percentage of time spent above the target glucose range of 10 mmol/L.

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Excessive hypoglycemia was defined as the time spent when glucose <3.9 mmol/L was >1 h per day or time spent <3.0 mmol/L was >15 min per day; that is, $TBR_{3.9}$ ≥4% or $TBR_{3.0}$ ≥1%[14]. The ideal targets of the three CGM-derived measurements were defined as $TBR_{3.9}$ <4%, $TIR_{3.9–10}$ >70% and TAR_{10} <25% according to the recent recommendation[14]. The 25th percentile, 50th percentile, 75th percentile and 95th percentile for %CV in type 2 diabetes patients who achieved all three CGM measurements targets were investigated.

Anthropometric and laboratory determinations

Each patient underwent a physical examination that included measurements of height and weight. The body mass index was calculated as weight (kg) divided by height in meters squared (m^2). Fasting venous blood sample was drawn on 6 a.m. after a 10-h overnight fast to test the laboratory examinations. Fasting plasma glucose and 2-h postprandial plasma glucose concentrations were immediately determined by the glucose oxidase method using the Hitachi 7600 autoanalyzer. HbA_{1c} was assayed using high-performance liquid chromatography (Variant II Hemoglobin A1c analyzer; Bio-Rad Laboratories, Hercules, CA, USA), with inter- and intra-assay CVs of <3.5 and <3.0%, respectively.

Statistical analysis

Data are expressed as the median (interquartile range [IQR]) for continuous variables with skewed distributions, mean ± SD for continuous variables with normal distributions, and numbers of cases and percentages for categorical variables. Clinical characteristics that followed a normal distribution were compared among groups using one-way analysis of variance with a post-hoc least significant difference test, whereas those with non-normal distribution were compared using the Kruskal–Wallis test followed by the Mann–Whitney *U*-test with Bonferroni correction. Spearman's correlation analysis was used to evaluate the correlation between %CV and other glycemic parameters. The area under the curve of %CV was determined as the identifier of patients with hypoglycemia, and the cut-off point was calculated from the analysis of the receiver operating characteristic curves. All *P*-values were two-sided, and a *P*-value <0.05 was considered statistically significant. Statistical analyses were carried out using SPSS version 23.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

A total of 3,007 persons with diabetes were included in the current study. Among them, 612 had type 1 diabetes and 2,395 had type 2 diabetes. People with type 2 diabetes were further divided into several groups according to the antidiabetic therapy received, as described in the Methods section. The clinical characteristics of the participants and the use of medication are presented in Table 1. Type 2 diabetes patients had the mean age of 60.6 ± 11.7 years, and type 1 diabetes patients had the mean age of 45.6 ± 19.5 years. Worsening of HbA_{1c} levels was compounded by the escalation of treatment from the group with OADs to the group with intensive insulin treatment. The fasting and 2-h C-peptide levels were significantly lower in groups with intensive insulin treatment than groups with OADs.

The quartiles of %CV were calculated in both type 1 and type 2 diabetes (Table 2). In type 1 diabetes, the quartiles (Q) were: Q1: ≤25.4%, Q2: 25.5–31.4%, Q3: 31.5–37.6% and Q4: >37.6%. Type 2 diabetes patients had the quartiles of %CV as follows: Q1: ≤19.3%, Q2: 19.4–24.4%, Q3: 24.5–30.4% and Q4: >30.4%. Type 2 diabetes receiving premixed insulin or an intensive insulin regimen had significantly increased %CV levels than those receiving oral therapy (group 1, median 19.5% [IQR 14.4–22.9%] and group 2, median 22.5% [IQR 17.4–28.1%]) or basal insulin (group 3, median 23.5% [IQR 17.1–30.8%]) although there was no difference between premixed insulin group (group 4, median 26.2% [IQR 21.0–31.8%]) and intensive insulin group (group 5, median 26.5% [IQR 21.2–32.7%]).

For each treatment group, $TBR_{3.9}$ and $TBR_{3.0}$ measurements were calculated (Table 2). None of the participants in group 1 had $TBR_{3.9}$ ≥4%. Percentages of participants with $TBR_{3.9}$ ≥4% were found to be 13.9, 10, 16.1, 14.2 and 30.7% in groups 2, 3, 4, 5 and 6, respectively. Percentages of people showing $TBR_{3.0}$ ≥1% were found to be 7.6, 7, 10.2, 9.3 and 20.1% in groups 2, 3, 4, 5 and 6. Type 1 diabetes patients (group 6) showed more time spent in hypoglycemia than other groups, as $TBR_{3.9}$ and $TBR_{3.0}$ levels in group 6 were higher than those of all the other groups. Participants in groups 2, 4, 5 and 6 had increased levels of $TBR_{3.9}$ than group 1 (all, $P < 0.001$). Patients with, but not limited to, premixed insulin (group 4) had more elevated $TBR_{3.9}$ than group 1 ($P < 0.001$), group 2 ($P = 0.003$) and group 3 ($P = 0.002$).

Group 1 was set as the reference group, as these people did not have hypoglycemia. The upper limit of the distribution of %CV was 33.2%. Therefore, 33% of %CV was adopted as the threshold to separate stable from excess GV. In the setting of our population, percentages of people showing %CVs above the threshold (33%) were found to be 10.9, 17, 20.5, 24 and 44.1% in groups 2, 3, 4, 5 and 6, respectively. Next, glucose indices were compared between subgroups with a %CV >33% or ≤33% across treatment groups 2, 3, 4, 5 and 6 (Table 3). The percentage of people with $TBR_{3.9}$ ≥4% was significantly greater in patients with a %CV >33% than in those with %CV ≤33%, as in group 2 (56.6 vs 8.7%), group 3 (35.3 vs 4.8%), group 4 (48.5 vs 7.7%), group 5 (38.1 vs 6.7%) and group 6 (55.2 vs 11.4%; all, $P < 0.001$). Similar findings were observed for the percentage of participants with $TBR_{3.0}$ ≥1%. The percentage of participants with TAR_{10} ≥25% was significantly greater in the subgroups with a %CV >33% than in the subgroups with %CV ≤33% in groups 4 (64.6 vs 49.6%, $P = 0.001$) and group 6 (74.8 vs 66.7%, $P = 0.033$). No significant differences in terms of HbA_{1c} were observed between subgroups with a %CV >33% or ≤33% across all groups.

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Table 1 | Clinical and laboratory characteristics of participants enrolled in the different treatment groups

	Total type 2 diabetes mellitus	Type 2 diabetes mellitus with only non-insulinotropic agent (group 1)	Type 2 diabetes mellitus with but not limited to insulinotropic agent (group 2)	Type 2 diabetes mellitus with but not limited to basal insulin (group 3)	Type 2 diabetes mellitus with but not limited to premixed insulin (group 4)	Type 2 diabetes mellitus with but not limited to intensive insulin regimens (group 5)	Type 1 diabetes mellitus (group 6)	*P*
n	2,395	138	761	100	784	612	612	
Male (%)	1,325 (55.3)	86 (62.3)**	418 (54.9)	56 (56)	435 (55.5)	330 (53.9)	295 (48.2)	0.023
Age (years)	60.6 ± 11.7	55.9 ± 11.8**	60.9 ± 10.7†**	57.8 ± 12.3**	60.7 ± 11.9†**	61.5 ± 12.1†**	45.6 ± 19.5	<0.001
BMI (kg/m^2)	25.2 ± 3.4	27.0 ± 3.6**	25.1 ± 3.3†**	25.0 ± 3.6†**	25.3 ± 3.4†**	24.8 ± 3.5†**	21.5 ± 3.3	<0.001
Diabetes duration (years)	8 (3–12)	4 (0.8–7)	6 (2–10)†**	8 (5–11) †‡**	10 (4–14.3)†‡**	10 (3.3–13.8)†‡**	4 (1–10)	<0.001
HbA_{1c} (%)	8.5 ± 2.0	7.3 ± 1.5**	7.7 ± 1.6**	8.4 ± 1.5†‡**	8.7 ± 1.9†‡§**	9.3 ± 2.3†‡§¶	9.2 ± 2.4	<0.001
HbA_{1c} (mmol/mol)	69 ± 22	57 ± 16**	61 ± 17**	68 ± 16†‡**	72 ± 21†‡§**	79 ± 25†‡§¶	77 ± 26	
FPG (mmol/L)	8.0 ± 2.6	7.4 ± 1.8**	7.3 ± 1.9**	8.5 ± 2.8†‡	8.1 ± 2.6‡**	8.8 ± 3.1†‡¶	8.6 ± 4.1	<0.001
2hPG (mmol/L)	13.4 ± 4.4	11.5 ± 3.5**	12.7 ± 3.7	13.6 ± 3.7†	13.5 ± 4.5†‡	14.7 ± 4.8†‡¶**	12.9 ± 5.5	<0.001
Fasting C–peptide (ng/mL)	1.9 (1.2–2.6)	2.5 (2.0–3.2)**	2.3 (1.8–3.0)**	2.1 (1.5–2.9)†**	1.6 (1.1–2.3)†‡§**	1.5 (0.9–2.1)†‡§¶**	0.20 (0–0.6)	<0.001
2-h C-peptide (ng/mL)	4.3 (2.7–5.8)	6.0 (4.4–7.7)**	5.5 (4.5–6.7)**	4.9 (3.6–6.3)†‡**	3.5 (2.3–5.2)†‡§**	2.9 (1.8–4.7)†‡§¶**	0.3 (0–1.1)	<0.001
Type of OADs if any, *n* (%)								
Any metformin	736 (30.7)	102 (73.9)	317 (41.7)	43 (43)	197 (25.1)	77 (12.6)	–	
Any AGI	688 (28.7)	48 (34.8)	209 (27.5)	26 (26)	180 (23.0)	225 (36.8)	–	
Any TZD	196 (8.2)	17 (12.3)	84 (11.0)	12 (12)	60 (7.7)	23 (3.8)	–	
Any sulfonylureas	687 (28.7)	–	600 (78.8)	39 (39)	42 (5.4)	6 (1.0)	–	
Any glinides	214 (8.9)	–	161 (21.2)	42 (42)	11 (1.4)	–	–	
Type of insulin regimen without OADs, *n* (%)								
Basal insulin regimen without OADs				9 (9)				
Premixed insulin regimen without OADs					395 (50.4)			
Intensive insulin regimen without OADs						291 (47.5)	612 (100)	

Data are the mean ± standard deviation, median (25th to 75th percentile) or *n* (%). †$P < 0.008$ versus group 1. ‡$P < 0.008$ versus group 2. §$P < 0.008$ versus group 3. ¶$P < 0.008$ versus group 4. **$P < 0.008$ versus group 6.

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Table 2 | Comparison of continuous glucose monitoring-derived indices of glycemic control for participants enrolled in the different treatment groups

	Total type 2 diabetes mellitus	Type 2 diabetes mellitus with only non-insulinotropic agent (group 1)	Type 2 diabetes mellitus with but not limited to insulinotropic agent (group 2)	Type 2 diabetes mellitus with but not limited to basal insulin (group 3)	Type 2 diabetes mellitus with but not limited to premixed insulin (group 4)	Type 2 diabetes mellitus with but not limited to intensive insulin regimens (group 5)	Type 1 diabetes mellitus (group 6)	*P*
n	2395	138	761	100	784	612	612	
%CV	24.4 (19.3–30.4)	19.5 (14.4–22.9)**	22.5 (17.4–28.1)†,**	23.5 (17.1–30.8)†,**	26.2 (21.0–31.8)†‡,§,**	26.5 (21.2–32.7)†‡,§,**	31.4 (25.4–37.6)	<0.001
SD (mmol/L)	2.1 (1.6–2.7)	1.5 (1.1–1.9)**	1.9 (1.4–2.3)†,**	2.1 (1.5–2.8)†,‡,**	2.3 (1.8–2.9)†,‡,**	2.5 (2.0–3.1)†,‡,§,¶,**	2.9 (2.3–3.6)	<0.001
24-h MG (mmol/L)	8.8 ± 1.8	7.8 ± 1.4**	8.2 ± 1.5†,**	9.1 ± 1.7†,‡	8.9 ± 1.7†,‡,**	9.6 ± 1.8†,‡,¶	9.5 ± 2.1	<0.001
TAR_{10} (%)	23.3 (10.2–42.7)	7.0 (1.5–17.8)**	15.5 (5.9–30.8)†,**	27.0 (15.2–47.9)†,‡,**	26.5 (12.2–42.5)†,‡,**	36.8 (21.7–54.8)†,‡,§,¶	37.7 (21.9–55.7)	<0.001
$TIR_{3.9–10}$ (%)	74.3 (56.1–87.5)	92.7 (81.6–98.1)**	82.1 (67.7–92.0)†,**	70.1 (51.4–83.6)†,‡,**	72.0 (56.0–84.9)†,‡,**	61.3 (43.7–75.7)†,‡,§,¶	57.9 (41.8–73.4)	<0.001
$TBR_{3.9}$ (%)	0 (0–1.2)	0 (0–0.2)**	0 (0–1.0)†,**	0 (0–0.2)**	0 (0–1.9)†,‡,§,**	0 (0–1.4)†,**	1.0 (0–5.4)	<0.001
$TBR_{3.0}$ (%)	0 (0–0)	0 (0–0)**	0 (0–0)†,**	0 (0–0)†,**	0 (0–0)†,**	0 (0–0)†,**	0 (0–0.3)	<0.001
%patients with $TBR_{3.9}$ ≥4%	13.7	0**	13.9†,**	10†,**	16.1†,**	14.2†,**	30.7	<0.001
%patients with $TBR_{3.0}$ ≥1%	8.4	0**	7.6†,**	7†,**	10.2†,**	9.3†,**	20.1	<0.001

Data are the mean ± standard deviation, median (25th to 75th percentile) or %. †P < 0.008 versus group 1. ‡P < 0.008 versus group 2. §P < 0.008 versus group 3. ¶P < 0.008 versus group 4. **P < 0.008 versus group 6.

Furthermore, a total of 1,013 participants were selected by pooling all type 2 diabetes patients with achieved CGM-derived glycemic targets; that is, $TBR_{3.9}$ <4%, $TIR_{3.9–10}$ >70% and TAR_{10} <25%. These people were aged 59.2 ± 11.6 years, had HbA_{1c} 61 ± 19 mmol/mol (7.8 ± 1.7%), 24-h mean glucose 7.6 ± 0.8 mmol/L; and median $TBR_{3.9}$ 0% (IQR 0–0.5%), $TIR_{3.9–10}$ 88.9% [81.9–95.3%] and TAR_{10} 10.8% [4.3–17.7%]. The details of clinical characteristics, antidiabetic treatment and CGM-derived metrics of glycemic control of the achievers in each treatment group are presented in Table 4. Among them, 117 people received only non-insulinotropic agents; 426 received, but were not limited to, insulinotropic agents; 38 were taking basal insulin with or without OADs; 286 were taking premixed insulin with or without OADs; and 146 were on intensive insulin regimens with or without OADs. The proportions of achievers in each treatment group were significantly different, with 84.8% in group 1, 56% in group 2, 38% in group 3, 36.5% in group 4 and 23.9% in group 5 (P < 0.001). The 25th percentile, 50th percentile and 75th percentile of %CV for these achievers were 17.0, 21.5 and 25.9%, respectively. The 95th percentile of %CV was 32.7%, which was close to the upper limit of group 1 (33%).

The relationship between %CV and parameters of hypoglycemia were then explored by the Spearman correlation analysis in all participants. Significant linear correlations between %CV and $TBR_{3.9}$ were found in type 2 diabetes patients (r = 0.559, P < 0.001) and in type 1 diabetes patients (r = 0.673, P < 0.001). In type 2 diabetes patients, the values of r between %CV and $TBR_{3.9}$ were 0.542, 0.552, 0.59 and 0.581 in groups 2, 3, 4 and 5, respectively. Analysis of the receiver operating characteristic curves of %CV as an identifier of persons with the risk of $TBR_{3.9}$ ≥4% showed that the %CV yielded good areas under the curve in both type 1 and type 2 diabetes patients, both had areas under the curve >0.8 (Table 5). For all type 2 diabetes patients, the cut-off value for %CV was 28.8%, with a sensitivity of 81% and a specificity of 77%. A cut-off point of 36.7% was the optimal value for %CV for type 1 diabetes patients, with a sensitivity of 66% and a specificity of 88% at cut-point.

Type 1 or type 2 diabetes patients were then divided into groups according to ranges of HbA_{1c} from 42 mmol/mol (6%) to 86 mmol/mol (10%), and the optimal cut-off values of %CV as identifiers of people with $TBR_{3.9}$ ≥4% were determined (Table 5). In type 2 diabetes patients, the cut-off points were 27, 28.7, 27.5, 30.1 and 35.1% in groups with HbA_{1c} categories 42–52 mmol/mol (6.0–6.9%), 53–63 mmol/mol (7–7.9%), 64–74 mmol/mol (8.0–8.9%), 75–85 mmol/mol (9.0–9.9%) and ≥86 mmol/mol (≥10%), respectively. In type 1 diabetes patients, the cut-off points were 31.2, 31.7, 36.4, 37.3 and 37.2% in groups with HbA_{1c} from ≥42 mmol/mol (6%) to ≥86 mmol/mol (10%), respectively.

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Table 3 | Comparisons of glycated hemoglobin and selected continuous glucose monitoring parameters in patients stratified by treatment received and percentage coefficient of variation for glucose

	Type 2 diabetes mellitus with but not limited to insulinotropic agent (group 2)			Type 2 diabetes mellitus with but not limited to basal insulin (group 3)			Type 2 diabetes mellitus with but not limited to premixed insulin (group 4)			Type 2 diabetes mellitus with but not limited to intensive insulin regimens (group 5)			Type 1 diabetes mellitus (group 6)		
	%CV ≤ 33%	%CV > 33%	*P*	%CV ≤ 33%	%CV > 33%	*P*	%CV ≤ 33%	%CV> 33%	*P*	%CV ≤ 33%	%CV> 33%	*P*	%CV ≤ 33%	%CV> 33%	*P*
n	678	83		83	17		623	161		465	147		342	270	
HbA_{1c} (%)	7.8 ± 1.6	7.6 ± 1.5	0.271	8.3 ± 1.4	8.6 ± 1.9	0.521	8.7 ± 1.9	8.8 ± 1.7	0.654	9.2 ± 2.2	9.6 ± 2.5	0.118	9.3 ± 2.5	9.1 ± 2.2	0.478
HbA_{1c} (mmol/mol)	62 ± 17	60 ± 16		67 ± 15	70 ± 21		72 ± 21	73 ± 19		77 ± 24	81 ± 27		78 ± 27	76 ± 24	
24-h MG (mmol/L)	8.3 ± 1.6	7.8 ± 1.2	0.001	9.2 ± 1.7	8.7 ± 1.2	0.247	8.9 ± 1.7	8.6 ± 1.5	0.063	9.8 ± 1.9	9.1 ± 1.5	<0.001	9.7 ± 2.3	9.2 ± 1.8	0.009
%Patients with $TAR_{10} \geq 25\%$	30.8	38.6	0.169	53	64.7	0.432	49.6	64.6	0.001	67.5	74.8	0.101	66.7	74.8	0.033
%Patients with $TBR_{3,9} \geq 4\%$	8.7	56.6	<0.001	4.8	35.3	<0.001	7.7	48.4	<0.001	6.7	38.1	<0.001	11.4	55.2	<0.001
%Patients with $TBR_{3,0} \geq 1\%$	4.3	34.9	<0.001	4.8	17.7	0.093	4.0	34.2	<0.001	3.9	26.5	<0.001	6.1	37.8	<0.001

Data are the mean ± standard deviation or %. 24-h MG, 24-h mean glucose; TAR_{10}, percentage of time spent above target glucose range of 10 mmol/L; $TBR_{3,9}$, percentage of time spent below target glucose range of 3.9 mmol/L; $TBR_{3,0}$, percentage of time spent below target glucose range of 3.0 mmol/L.

DISCUSSION

We found that a threshold for %CV of 33% permits discrimination between those with stable or unstable glucose homeostasis in Chinese people with diabetes. More importantly, the % CV target should be individualized according to different types of diabetes or HbA_{1c} ranges.

As one of the main features of dysglycemia, excess GV has been found to be an independent predictor of diabetes complications[15,16]. Several studies have shown that GV could induce oxidative stress and endothelial dysfunction[17,18]. Increased GV, often accompanied with hypoglycemia, exerted a severe burden on cardiovascular events and mortality in persons with diabetes[19,20]. There are a few measures to describe GV, and some of them are sophisticated indices, such as the mean amplitude of glycemic excursion, mean of daily differences and continuous overlapping net glycemic action, and most measures of GV are highly correlated with each other[21,22]. With the principle of giving precedence to simplicity, %CV has been regarded as the metric of choice, as it is easily accessible and computable, and the calculation does not depend on the average glucose level[4,6]. Hence, %CV was used as the specific assessment of GV for a pragmatic purpose in the present study.

Defining glucose control targets for people with diabetes has always been an intrinsic part of clinical practice. Multiple methods to determine the %CV target for people with diabetes were reported. Hirsch proposed a %CV of 33% as the threshold value derived by multiplying the SD by three and dividing by the mean glucose value based on personal observations[23]. Rodbard *et al.*[6] suggested that measures of GV can be set in terms of excellent, good, fair or poor by stratifying the quartile of the distribution. Accordingly, the quartiles of %CV for type 2 diabetes patients in the present study were as follows: excellent, (Q1): ≤19.3%; good, (Q2): 19.4–24.4%; fair, (Q3): 24.5–30.4%; and poor, (Q4): >30.4%. It should be noted, however, that the 'excellent' and 'good' quartile levels were difficult to achieve in clinical practice. Monnier *et al.*[7] suggested that the upper limit of %CV in participants treated with non-insulinotropic agents could be served to distinguish high and low GV, with the cut-point set at 36%. In the present population, participants treated with non-insulin secretory agents had the upper limit %CV of 33%. The difference between our target and that of Monnier *et al.* could be attributed to the fact that 48 out of 138 patients in the reference group in the present study received alpha-glucosidase inhibitors, which is more commonly used in Asian people with diabetes than in western people. Alpha-glucosidase inhibitor decreases the postprandial glucose concentration by modifying the intestinal absorption of carbohydrates, therefore decreasing GV as well[24]. In addition, the definition of hypoglycemia was not the same in the two studies. The racial difference between Asian and white people might also be an important explanation, which involves different characteristics in the pathophysiology of diabetes and underlying responses to OADs.

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Table 4 | Clinical characteristics and indices of glycemic control of type 2 diabetes who achieved percentage of time spent below target glucose range of 3.9 mmol/L <4%, percentage of time spent within target glucose range of 3.9–10.0 mmol/L >70% and percentage of time spent above target glucose range of 10 mmol/L <25%

	Type 2 diabetes mellitus with only non-insulinotropic agent (group 1)	Type 2 diabetes mellitus with but not limited to insulinotropic agent (group 2)	Type 2 diabetes mellitus with but not limited to basal insulin (group 3)	Type 2 diabetes mellitus with but not limited to premixed insulin (group 4)	Type 2 diabetes mellitus with but not limited to intensive insulin regimens (group 5)	*P*
No. achievers	117	426	38	286	146	
Proportion of achievers in each treatment group (%)	84.8	56†	38†,‡	36.5†,‡	23.9†,‡,§,¶	<0.001
Clinical characteristics and baseline HbA_{1c}						
Male (% of achievers)	71 (60.7)	239 (56.1)	23 (60.5)	151 (52.8)	80 (54.8)	0.629
Age (years)	56.0 ± 12.3	60.0 ± 10.6†	56.5 ± 10.5	59.1 ± 12.3	60.5 ± 12.5†	0.005
BMI (kg/m^2)	26.9 ± 3.7	25.3 ± 3.3†	24.4 ± 3.3†	25.9 ± 3.4	25.1 ± 3.7†	<0.001
Diabetes duration (years)	3 (0.8–7)	6 (2.8–10)†	7 (3.5–10.5)†	8 (3–14)†,‡	8 (2–12)†	<0.001
HbA_{1c} (%)	7.0 ± 1.2	7.4 ± 1.4	7.7 ± 1.3	8.0 ± 1.7†,‡	8.9 ± 2.4†,‡,§,¶	<0.001
HbA_{1c} (mmol/mol)	53 ± 13	57 ± 16	61 ± 14	64 ± 18†,‡	74 ± 27†,‡,§,¶	
CGM-derived metrics						
%CV	18.8 (13.9–22.2)	20.4 (15.9–25.5)†	20.6 (14.5–27.9)	22.6 (18.7–26.7)†,‡	23.4 (19.9–28.1)†,‡	<0.001
SD (mmol/L)	1.3 (1.0–1.7)	1.5 (1.2–2.0)†	1.8 (1.1–2.1)	1.7 (1.4–2.1)†,‡	1.9 (1.5–2.2)†,‡	<0.001
24-h MG (mmol/L)	7.3 ± 0.8	7.6 ± 0.8†	7.9 ± 0.7†	7.7 ± 0.7†	7.9 ± 0.7†,‡,¶	<0.001
TAR_{10} (%)	5.2 (0.6–10.8)	9.9 (3.1–16.5)†	13.1 (4.4–20.4)†	11.9 (6.8–17.5)†,‡	16.0 (9.5–20.5)†,‡,¶	<0.001
$TIR_{3.9–10}$ (%)	93.9 (89.1–98.4)	89.8 (82.6–96.1)†	86.8 (79.6–95.6)†	87.4 (81.9–92.8)†,‡	83.4 (78.6–90.4)†,‡,¶	<0.001
$TBR_{3.9}$ (%)	0 (0–0.3)	0 (0–0.4)	0 (0–0)	0 (0–0.9)	0 (0–0.7)§	0.002
$TBR_{3.0}$ (%)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0.063
Type of OADs if any, *n* (% of achievers)						
Any metformin	88 (75.2)	188 (44.1)	16 (42.1)	82 (28.7)	22 (15.1)	
Any AGI	40 (34.2)	108 (25.4)	9 (23.7)	76 (26.6)	57 (39.0)	
Any TZD	15 (12.8)	41 (9.6)	3 (7.9)	16 (5.6)	9 (6.2)	
Any sulfonylurea	/	329 (77.2)	12 (31.6)	15 (5.2)	2 (1.4)	
Any glinides	/	97 (22.8)	16 (42.1)	6 (2.1)	/	
Type of insulin treatment without OADs, *n* (% of achievers)						
Basal insulin regimen without OADs			5 (13.2)	/	/	
Premixed insulin regimen without OADs			/	132 (46.2)	/	
Intensive insulin regimen without OADs			/	/	63 (43.2)	

Total *n* = 1,013. Data are the mean ± standard deviation, median (25th to 75th percentile) or *n* (%). 24-h MG, 24-h mean glucose; AGI, alpha-glucosidase inhibitors; CV, coefficient of variation for glucose; OADs, oral antidiabetic drugs; SD, standard deviation for glucose; TAR_{10}, percentage of time spent above target glucose range of 10 mmol/L; $TBR_{3.0}$, percentage of time spent below target glucose range of 3.0 mmol/L; $TBR_{3.9}$, percentage of time spent below target glucose range of 3.9 mmol/L; $TIR_{3.9–10}$, percentage of time spent within target glucose range of 3.9–10.0 mmol/L; TZD, thiazolidinediones. †$P < 0.01$ versus group 1. ‡$P < 0.01$ versus group 2. §$P < 0.01$ versus group 3. ¶$P < 0.01$ versus group 4.

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Table 5 | Area under the curve of percentage coefficient of variation for glucose for percentage of time spent below target glucose range of 3.9 mmol/L ≥4% by subgroups according to six ranges of glycated hemoglobin from <6% to ≥10% in type 1 and type 2 diabetes patients

	Type 1 diabetes mellitus				Type 2 diabetes mellitus			
HbA_{1c} categories	*n*	ROC AUC	95% CI	Optimal %CV cut-off	*n*	ROC AUC	95% CI	Optimal %CV cut-off
Total	612	0.842	0.807–0.876	36.7%	2,395	0.857	0.836–0.878	28.8%
<6.0%	19	NS	NS	NS	115	0.835	0.759–0.911	23.7%
6.0–6.9%	71	0.852	0.759–0.945	31.2%	444	0.864	0.819–0.910	27.0%
7.0–7.9%	128	0.885	0.829–0.940	31.7%	569	0.889	0.853–0.924	28.7%
8.0–8.9%	119	0.860	0.780–0.940	36.4%	462	0.875	0.827–0.922	27.5%
9.0–9.9%	97	0.798	0.706–0.891	37.3%	327	0.86	0.797–0.922	30.1%
≥10%	178	0.886	0.828–0.944	37.2%	478	0.917	0.881–0.953	35.1%

AUC, area under the curve; CI, confidence interval; CV, coefficient of variation for glucose; NS, not significant; ROC, receiver operating characteristic.

Additionally, we also included those with type 2 diabetes who achieved ideal glucose control according to three key targets of time in ranges[14]; that is, $TBR_{3.9}$ <4%, $TIR_{3.9–10}$ >70% and TAR_{10} <25%. These patients showed satisfactory glucose control with both acceptable hypoglycemia and hyperglycemia. The 95% percentile of %CV in these people was calculated as the reference value[25], which was equal to 32.7% and quite close to 33%.

Other approaches have been investigated to estimate the % CV target. As increased glucose fluctuations can play a consistent role in precipitating hypoglycemia[26], Gómez *et al.*[27] estimated the cut-off point by the construction of receiver operating characteristic curves with the attempt to avoid hypoglycemia, and obtained 34% as the %CV threshold in type 2 diabetes patients. However, %CV is affected by both hypoglycemia and hyperglycemia. Instead of finding a %CV cut-off to define people at high risk for hypoglycemia, several hypoglycemia-specific glycemic indices, such as $TBR_{3.0}$, $TBR_{3.9}$, Low Blood Glucose Index, Hypoglycemia Index and $GRADE_{hypoglycemia}$, perform better in showing hypoglycemia than %CV [28].

In contrast, the potential impact of a low mean glucose level on the incidence of hypoglycemia should be considered[29]. Lipska *et al.*[30] showed that an increased risk of hypoglycemia was associated with near-normal HbA_{1c} level (HbA_{1c} <6%). In the present study, we found the %CV cut-offs increased with ascending HbA_{1c} levels (Table 5). The present study results suggest that patients who have lower HbA_{1c} levels should have stricter %CV targets to prevent hypoglycemia compared with those with higher HbA_{1c} level. Therefore, an individualized % CV target should be suggested for any given patient, with the patient's type of diabetes and HbA_{1c} level at least taken into consideration. However, none of the previous consensuses or the present study could yet properly address the extent to which %CV targets might be changed by individualization. There are people for whom the burden from acute hypoglycemia is higher than other patients, such as those who have incapacitating cardiovascular disease or those who are severely ill, or more often, living alone. These people require personal assessment of risk and burden from the disease itself, and from more aggressive treatment, with the assistance of CGM monitoring at best.

The main feature of the present study was the use of a new definition of hypoglycemia and euglycemia according to the recent consensus, and patients who achieved ideal glucose control with $TBR_{3.9}$ <4%, $TIR_{3.9–10}$ >70% and TAR_{10} <25% were investigated. Another feature was that we included a large sample of Asian type 2 diabetes patients, as CGM has been studied extensively in type 1 diabetes patients, but less well studied in type 2 diabetes patients. The study had several limitations that should be noted. First, all measurements were limited to the monitoring of 24-h glycemic profiles on two consecutive days. Although a previous study suggested that reliable assessment of CGM-derived indices can be made with two or three recording days[31], a longer period of recording, such as 14 consecutive days, with approximately 70% of data available of CGM data can provide a more accurate assessment of overall glycemic control[32]. In the future, a study using CGM with a more extended period is essential to ensure optimal analysis and decision-making. Another limitation is that we did not analyze patients with or without insulinotropic agents separately regarding groups 3, 4 and 5 of type 2 diabetes patients, as the sample sizes of patients with or without insulinotropic agents were drastically different. Finally, the study did point out that individualized %CV targets are required, but the extent to which % CV targets might be modified cannot be determined by the present retrospective study. More findings are required from large prospective investigations designed to evaluate whether lowering %CV to certain targets customized to patients' individual needs can prevent the development and progression of complications from diabetes.

In conclusion, we found the target value of 33% for %CV to discern between stable glucose homeostasis and those with increased GV in Chinese people with diabetes. Furthermore, the present study suggested that the %CV target should be individualized, or at least modified for the type of diabetes or HbA_{1c} ranges. Translation of these data into clinical practice

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might enable better glycemic control in the management of diabetes.

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DISCLOSURE

The authors declare no conflict of interest.

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