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Influencing factors of glycemic variability in hospitalized type 2 diabetes patients with insulin therapy

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Ya Huang, MD, Chunni Heng, RN, Jing Wei, MD, Xiaorui Jing, MD, Xiaoguang Wang, MD, Guohong Zhao, MD, Junfeng Hou, MD, PhD, Qingquan Liu, MD, PhD, Kai Jiao, MD, PhD*

Abstract

Previous studies have shown that glucose fluctuation is closely related to oxidative stress and diabetic complications. However, only few studies have evaluated the influencing factors of glycemic variability (GV) in type 2 diabetes (T2D) patients so far.

This was a cross-sectional study design. A total of 366 cases of hospitalized patients with T2D using insulin therapy, whom received continuous glucose monitoring from January 2014 to December 2016, were enrolled for this study. The evaluation variables of GV included standard deviation of blood glucose, coefficient of variation (CV%), mean amplitude of glycemic excursion, and absolute means of daily differences.

In 366 T2D patients with insulin therapy, 148 were used multiple daily injections (MDI) insulin regimen; 144 were on premixed insulin injection; and 74 were treated with continuous subcutaneous insulin injection. Compared with MDI insulin regimen, patients on premixed insulin injection have less insulin dose per day, lower mean blood glucose, and better glycated hemoglobin (HbA1c) (all $P < .05$). Generalized linear model showed that family history of diabetes, duration of diabetes, higher HbA1c, and higher level of aspartate aminotransferase and high-density lipoprotein cholesterol were positively associated with GV parameters. Otherwise, serum levels of C-peptide, premixed insulin injection, history of cardiovascular disease, and serum concentration of uric acid were inversely associated with GV parameters.

Dysfunction of pancreatic β-cell and better insulin sensitivity were independent contributors to the fluctuation of blood glucose. Moreover, premixed insulin therapy may obtain better glucose control and lower within-day and day-to-day glucose variability for Chinese T2D patients with insulin therapy.

Abbreviations: ALT = alanine aminotransferase, AST = aspartate aminotransferase, CSII = continuous subcutaneous insulin injection, CVD = cardiovascular disease, GV = glycemic variability, HbA1c = glycated hemoglobin, HDL-c = high-density lipoprotein cholesterol, LDL-c = low-density lipoprotein cholesterol, MAGE = mean amplitude of glycemic excursion, MDI = multiple daily injections, MODD = absolute means of daily differences, SDBG = standard deviation of blood glucose (SDBG), T2D = type 2 diabetes, TC = total cholesterol, TG = total triglyceride.

Keywords: C-peptide, glycemic variability, influencing factors, type 2 diabetes

1. Introduction

Type 2 diabetes (T2D) is a chronic and progressive disease associated with multiple complications. The duration of diabetes and the level of glycemic control are major risk factors for microvascular and macrovascular complications.[1] There is no argument that improving mean level of glycemic control, assessed by glycated hemoglobin (HbA1c), reduces the risk of microvascular complications and cardiovascular disease (CVD) events in patients with T2D.[2] Chronic sustained hyperglycemia has been shown to exert deleterious effects on the β cells and the vascular endothelium.[3] However, reports from some trials have suggested that lowering HbA1c to a recommended level may not always result in improved outcomes for patients with long-standing T2D. Monnier et al[4] and Brownlee and Hirsch[5] have even emphasized that another component of dysglycemia, glycemic variability (GV), was even more important in generating oxidative stress and contributing to the development of diabetic complications. There is also compelling evidence suggesting that GV is an independent risk factor for CVD even in those without diabetes.[6]

Prolonged postprandial glucose excursions have been linked to several factors such as insulin deficiency, insulin resistance, or an abnormal release of hyperglycemic hormones.[7] However, blood glucose fluctuation in T2D appears to result from the complex interaction between pathophysiological factors and behavioral and treatment factors.[8] However, there is little and inconsistent information about the behavioral, clinical, and treatment factors

Editor: Inyang Nora Osemene.

YH and CH contributed equally to this work.

Funding: This work was supported by grants of National Natural Science Foundation of China (#81502402, #30871183, and #30971122).

The authors have no conflicts of interest to disclose.

Department of Endocrinology, Tang-Du Hospital, Fourth Military Medical University, Xi'an, Shaanxi Province, China.

* Correspondence: Kai Jiao, Department of Endocrinology, Tang-Du Hospital, Fourth Military Medical University, Xi'an, Shaanxi Province, China (e-mails: tangdujk@163.com, tdjkai@fmmu.edu.cn).

Medicine (2017) 96:36(e8021)

Received: 25 April 2017 / Received in final form: 12 July 2017 / Accepted: 31 July 2017

http://dx.doi.org/10.1097/MD.0000000000008021

that contribute to this GV. A previous study conducted in T2D patients without insulin therapy have revealed that postprandial β-cell function and oral glucose-lowering drugs were independent contributors of GV, whereas insulin sensitivity, carbohydrate intake, and nonglycemic parameters failed to contribute to GV.[9] However, a recent study performed in Korea[10] has suggested that in insulin-treated T2D, fasting C-peptide level was inversely correlated with GV, whereas HbA1c and duration of diabetes were positively correlated with GV.

In recent years, with the extensive application of continuous glucose monitoring (CGM), it will be easy to detect the hyperglycemia and hypoglycemia, especially postprandial hyperglycemia and asymptomatic hypoglycemia at night, making the assessment of GV available. Given that CGM has the unique advantage in assessing of blood glucose fluctuation, in this study, we aimed to explore the association of various clinical factors and parameters of GV, including standard deviation of blood glucose (SDBG), coefficient of variation (CV%), mean amplitude of glycemic excursion (MAGE), and absolute means of daily differences (MODD) in insulin-treated patients of T2D.

2. Research design and methods

2.1. Study subjects

This was a cross-sectional study. We screened 414 hospitalized patients with T2D who treated with insulin therapy and underwent CGM between January 2014 and November 2016 at Department of Endocrinology, Tang-Du Hospital affiliated to The Fourth Military Medical University. T2D was defined as fasting plasma glucose ≥7.0 mmol/L or 2-hour oral glucose tolerance test plasma glucose ≥11.1 mmol/L or self-reported physician diagnosed diabetes according to the 1999 World Health Organization diagnostic criteria. Patients meeting the following criteria were sequentially excluded: with severe hepatic dysfunction such as hepatitis, cirrhosis, or malignancy (n=6); the estimated glomerular filtration rate <60 mL/min/1.73 m^2 (n=10); with acute diabetic complications such as diabetic ketoacidosis or hyperosmolar hyperglycemic state (n=24); with surgery, trauma, infection, or other emergency situations recently (n=4); with recently received hormone therapy or other drug that could affect glucose metabolism (n=4). Thus, 366 T2D patients were included in the final analysis. The Institutional Review Board of Tang-Du Hospital approved the study protocol. All participants have signed the written informed consent.

2.2. Clinical and laboratory measurements

Clinical data of subjects were collected by trained physicians, including clinical information, physical examination, laboratory examination, and CGM. Clinical information including age, gender, habits of tobacco smoking and alcoholic drinking, duration of diabetes, family history of diabetes, diabetic complications, history of CVD, therapeutic schedule, and dose of total insulin per day. The current smoking or drinking was defined as "yes" if the subject smoked at least 1 cigarette or consumed alcohol at least once a week in the past 6 month. Family history of diabetes was defined as "yes" if there is at least 1 first-degree relative suffering from diabetes. Diabetic nephropathy was defined as having either macroalbuminuria or end-stage renal disease. Diabetic retinopathy was diagnosed at Department of Ophthalmology and defined as the presence of ≥1 retinal microaneurysms or retinal blot hemorrhages with or without more severe lesions (hard exudates, soft exudates, intraretinal microvascular abnormalities, venous beading, retinal new vessels, preretinal and vitreous hemorrhage, and fibroproliferans). CVD was defined as "yes" if subject was diagnosed with coronary heart disease or stroke ever.

For different therapeutic schedule, multiple daily injection (MDI) insulin regimen included a basal insulin (Glargine or Detemir) combined with a rapid-acting insulin (Lispro or Aspart); and premixed insulin including Humalog Mix 50/50 or Humalog Mix 70/30 or Novomix30 or Novomix50; continuous subcutaneous insulin injection (CSII) was performed using insulin pump (Medtronic MiniMed, Northridge, CA) and subcutaneous injected with Lispro.

Physical examination included body height and body weight, systolic blood pressure (SBP), and diastolic blood pressure (DBP). Body mass index (BMI) was calculated as body weight in kilograms divided by height squared in meters (kg/m^2). Blood pressure was measured in triplicate on the same day after at least ten-min rest by using an automated electronic device (OMRON Model HEM-752 FUZZY, Omron Company, Dalian, China), and the average value of the 3 measurements was used for analysis.

Laboratory tests included HbA1c, C-peptide, blood lipid, index of liver function, and renal function. Fasting serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine, total triglyceride (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-c), and low-density lipoprotein cholesterol (LDL-c) were measured by using an autoanalyser (ADVIA-1650 Chemistry System, Bayer Corporation, Germany). HbA1c was tested by high-performance liquid chromatography using the VARIANT II Hemoglobin Testing System (Bio-Rad Laboratories, CA). Fasting serum C-peptide concentrations were measured by using an electrochemiluminescence assay (Roche-Diagnostics, Switzerland).

2.3. Collection of CGMS data and assessment of GV

Eligible patients who agreed to participate were monitored by a masked CGM (Medtronic MiniMed, Northridge, CA) for a 4-day period without a change in their diabetes regimen. Patients were encouraged to record 4 SMGB (capillary blood) levels each day to calibrate the CGM. They were instructed to follow their usual diet and were advised to abstain from intense and prolonged exercise during the 4-day period.

Glucose variability was expressed as SDBG, overall glucose CV %, MAGE, and MODD. SDBG was defined as the standard deviation of all readings during the CGM. CV% was calculated by the following formula: CV%=SDBG/mean blood glucose (MBG)*100%. MAGE was defined as the average of absolute values of differences between adjacent peaks and nadirs for all differences >1 standard deviation (SD). MODD was calculated as the mean of the absolute values of the differences between any given glucose value and the value exactly (24 × d) hours later.

2.4. Statistical analysis

SAS version 9.2 (SAS Institute, Cary, NC) was used for database management and statistical analysis. Continuous variables with normal distribution were given as means ± standard deviation (SD) and those with skewed distribution were given as medians (interquartile ranges). ALT, AST, and CV% were normalized by logarithmic transformation before statistical analyses because of skewed distributions. One-way variance analysis was used to

compare continuous variables among different insulin therapy groups and Dunnett's test was used to evaluate the difference between the other 2 groups and MDI insulin regimen group. Categorical variables were shown in proportions and χ^2 test was used to estimate the difference among the 3 groups. Generalized linear model was fitted to evaluate the association of different clinical factors and parameters of GV, including SDGE, log-CV %, MAGE, and MODD. Statistical significance was set to a 2-sided P value of <0.05.

3. Results

A total of 366 T2D patients with insulin therapy were included. The average age and BMI of our study, including 294 (80.33%) men and 72 (19.67%) women, were 50.77 years and 26.39 kg/m^2. The mean of duration of diabetes was 8.20 years and range from 0 to 44 years. In this study, 148 patients were on MDI insulin regimen; 144 were used premixed insulin injection and 74 were treated with CSII. Subjects were monitored for 73.90 ± 8.63 consecutive hours averaging 886.80 ± 103.58 readings after being equipped with a CGMS device. The mean and SD of SDBG, log-CV%, MAGE, and MODD were 2.36 ± 0.55 mmol/L, 3.24 ± 0.32, 4.74 ± 0.90 mmol/L, and 2.61 ± 0.75 mmol/L, respectively.

The clinical characteristics of the subjects are summarized in Table 1. Age, male sex, status of current smoking and drinking, duration of diabetes, family history of diabetes, C-peptide, proportion of diabetic retinopathy, proportion of diabetic nephropathy, history of CVD, SBP, DBP, ALT, AST, TG, TC, LDL-c, HDL-c, uric acid, and creatinine showed no significant difference among the 3 different insulin regimen groups. Compared with patients used MDI insulin regimen, those patients treated with premixed insulin showed lower level of HbA1c and MBG; and patients on CSII regimen showed higher BMI levels (all P values < 0.05). For parameters of GV, as shown in Fig. 1, patients treated with premixed insulin showed lower SDBG (panel A) and MODD (panel D) compared with patients on MDI regimen. For log-CV% (panel B) and MAGE (panel C), we did not find any significant difference among the 3 groups.

As shown in Table 2, multivariate regression analysis showed that age, C-peptide level, treatment with premixed insulin, with history of CVD, and serum uric acid concentrations were inversely associated with SDBG while longer duration of diabetes, higher HbA1c level, with family history of diabetes, and serum ALT concentrations were positively associated with SDBG. Besides, we found that with family history of diabetes, lower serum level of C-peptide, and higher concentration of serum AST and uric acid were in relation to higher log-CV%. For MAGE, we found that with family history of diabetes, lower serum level of C-peptide and higher concentration of serum HDL-c and uric acid were independent contributors. At last, for MODD, we found that longer duration of diabetes, higher level of HbA1c and higher concentration of serum AST and HDL-c were positively associated with MODD while level of C-peptide and treated with premixed insulin were inversely in relation to MODD.

Table 1

Characteristic of study participants according to different insulin treatment.

	MDI	Premixed insulin	CSII	*P* value
Number	148	144	74	–
Age, year	53.01 ± 13.65	49.01 ± 10.16	48.19 ± 10.41	.11
Male sex, n (%)	114 (77.03)	116 (80.56)	60 (81.08)	.83
BMI, kg/m^2	25.71 ± 3.78	26.20 ± 4.73	27.93 ± 4.15**	**.03**
Current smoker, n (%)	64 (43.84)	84 (59.15)	34 (45.95)	.15
Current drinker, n (%)	20 (13.70)	26 (18.31)	12 (16.22)	.57
Duration of DM, year	8.72 ± 9.13	8.20 ± 6.10	7.27 ± 6.65	.64
Family history of DM, n (%)	64 (43.24)	68 (47.89)	52 (70.27)	.06
Dose of insulin, IU/d	50.38 ± 27.12	37.99 ± 15.61**	50.16 ± 22.01	**.0008**
HbA1c, %	9.86 ± 2.16	8.51 ± 2.53**	9.22 ± 2.19	**.005**
C-peptide, ng/mL	1.37 ± 1.10	1.34 ± 1.09	1.32 ± 1.11	.65
Diabetic retinopathy, n (%)	26 (17.57)	30 (20.83)	14 (18.92)	.88
Diabetic nephropathy, n (%)	58 (39.19)	48 (33.33)	24 (32.43)	.69
History of CVD, n (%)	32 (21.62)	26 (18.06)	14 (18.92)	.86
SBP, mm Hg	124.41 ± 15.25	125.44 ± 18.22	128.49 ± 13.59	.45
DBP, mm Hg	78.04 ± 9.90	79.44 ± 10.92	80.27 ± 9.67	.51
ALT, U/L	18 (12–29)	18 (14–25)	22.5 (11.0–32.0)	.34
AST, U/L	17 (15–23)	18 (14–22)	20 (14–26)	.24
Total triglyceride, mmol/L	2.47 ± 1.20	2.05 ± 1.07	2.37 ± 1.02	.76
Total cholesterol, mmol/L	4.26 ± 1.27	4.15 ± 0.95	4.56 ± 1.50	.12
LDL-c, mmol/L	2.16 ± 0.96	2.25 ± 0.69	2.40 ± 0.85	.36
HDL-c, mmol/L	1.02 ± 0.34	0.98 ± 0.28	0.92 ± 0.22	.23
Uric acid, μmol/L	291.54 ± 103.99	310.57 ± 79.54	326.05 ± 100.15	.17
Creatinine, μmol/L	62.13 ± 22.63	61.20 ± 15.60	58.20 ± 16.11	.58
MBG, mmol/L	9.14 ± 1.97	7.97 ± 1.43**	8.99 ± 1.77	**.0002**

Data are presented as means ± SD, medians (interquartile ranges), or number (proportions).

P values were calculated by the one-way analysis variance for continuous variables and χ^2 for categorical variables.

ALT = alanine aminotransferase, AST = aspartate aminotransferase, BMI = body mass index, CSII = continuous subcutaneous insulin injection, CVD = cardiovascular disease, DBP = diastolic blood pressure, DM = diabetes mellitus, HbA1c = glycated hemoglobin, HDL-c = high-density lipoprotein cholesterol, LDL-c = low-density lipoprotein cholesterol, MBG = mean blood glucose, SBP = systolic blood pressure, SD = standard deviation.

** $P < .05$ compared with patients with MDI insulin regimen.

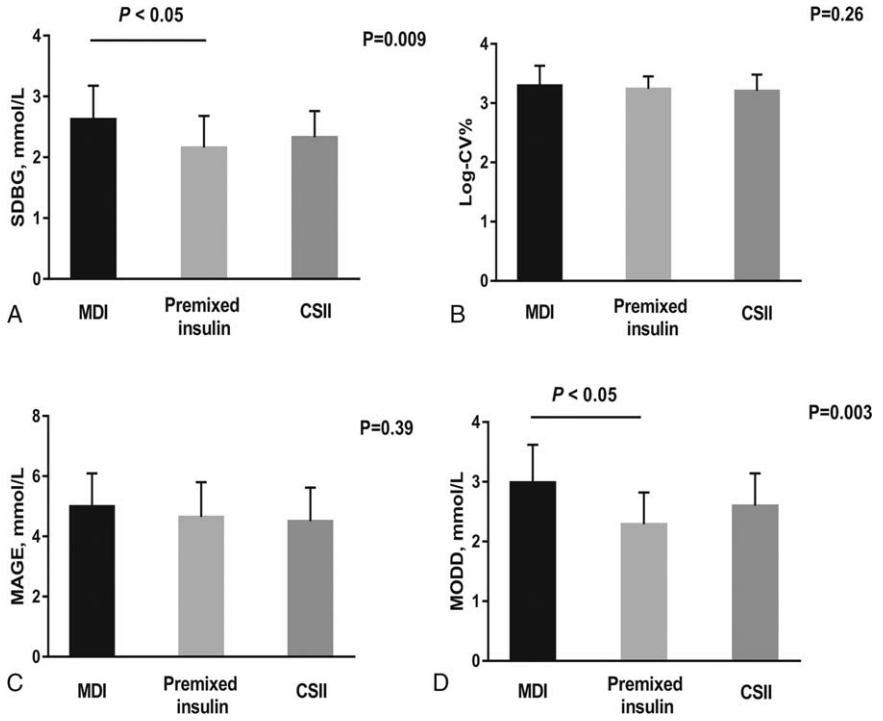

Figure 1. Levels of different parameters of glycemic variability according to different insulin regimen. Panels A, B, C, and D showed the values of SDBG, log-CV%, MAGE, and MODD according to different insulin regimen, respectively. Column represents the value of each parameter and bar represents the standard deviation. CSII = continuous subcutaneous insulin injection, CV% = coefficient of variation, MAGE = mean amplitude of glycemic excursion, MDI = multiple daily injection, MODD = absolute means of daily differences, SGBG = standard deviation of blood glucose.

Table 2

Multivariate analysis of clinical factors associated with parameters of glycemic variability.

	SDBG		Log-CV%		MAGE		MODD	
Clinical factors	**β (SE)**	***P* value**	**β (SE)**	***P* value**	**β (SE)**	***P* value**	**β (SE)**	***P* value**
Age, year	−0.016 (0.008)	.04	−0.003 (0.003)	.22	0.006 (0.017)	.70	−0.023 (0.011)	.03
Sex, female vs male	−0.020 (0.215)	.93	−0.049 (0.076)	.52	0.082 (0.449)	.86	−0.339 (0.291)	.25
BMI, kg/m^2	0.005 (0.018)	.77	0.0004 (0.006)	.95	0.001 (0.037)	.98	0.034 (0.023)	.14
Current smoking, yes vs no	−0.237 (0.162)	.15	−0.061 (0.057)	.29	−0.418 (0.251)	.24	−0.317 (0.224)	.16
Current drinking, yes vs no	0.178 (0.189)	.35	0.076 (0.067)	.25	−0.003 (0.400)	.99	−0.077 (0.257)	.76
Duration of DM, year	0.036 (0.011)	.0008	0.006 (0.004)	.14	0.015 (0.023)	.52	0.036 (0.015)	.02
Family history of diabetes, yes vs no	0.489 (0.142)	.0008	0.126 (0.050)	.01	0.878 (0.308)	.005	0.218 (0.197)	.27
HbA1c, %	0.113 (0.033)	.0007	0.019 (0.011)	.09	0.302 (0.337)	.37	0.198 (0.045)	<.0001
C-peptide, ng/mL	−0.754 (0.287)	.002	−0.394 (0.059)	<.0001	−0.852 (0.346)	.005	−0.276 (0.095)	.0007
Insulin therapy								
Premix insulin vs MDI	−0.277 (0.140)	.03	−0.296 (0.056)	.61	0.136 (0.469)	.77	−0.427 (0.207)	.02
CSII vs MDI	−0.032 (0.197)	.87	−0.030 (0.069)	.66	−0.150 (0.423)	.72	−0.106 (0.268)	.69
Dose of insulin, IU/d	0.005 (0.003)	.13	0.002 (0.001)	.11	0.013 (0.007)	.07	0.007 (0.005)	.11
History of CVD, yes vs no	−0.419 (0.183)	.02	−0.156 (0.064)	.01	−0.795 (0.398)	.048	−0.585 (0.254)	.02
SBP, mm Hg	−0.003 (0.006)	.67	0.0004 (0.002)	.87	−0.004 (0.013)	.78	−0.007 (0.081)	.94
DBP, mm Hg	0.004 (0.010)	.68	−0.002 (0.004)	.49	−0.017 (0.021)	.42	0.010 (0.014)	.48
Log-ALT, U/L	−0.311 (0.223)	.17	−0.125 (0.079)	.11	−0.146 (0.249)	.76	−0.577 (0.300)	.06
Log-AST, U/L	0.769 (0.352)	.03	0.275 (0.124)	.03	0.742 (0.741)	.32	1.076 (0.467)	.02
TG, mmol/L	−0.004 (0.029)	.89	−0.009 (0.010)	.38	0.089 (0.061)	.15	−0.048 (0.038)	.21
LDL-c, mmol/L	−0.080 (0.085)	.35	−0.032 (0.020)	.29	−0.064 (0.185)	.73	−0.136 (0.118)	.25
HDL-c, mmol/L	0.304 (0.261)	.25	0.104 (0.092)	.26	1.423 (0.567)	.01	0.835 (0.364)	.02
Uric acid, per 100 μmol/L	−0.311 (0.095)	.001	−0.075 (0.034)	.03	−0.628 (0.207)	.003	−0.134 (0.135)	.32
Creatinine, per 10 μmol/L	0.0004 (0.045)	.99	−0.004 (0.016)	.79	−0.022 (0.094)	.81	0.022 (0.061)	.71
MBG, mmol/L	0.272 (0.035)	<.0001	–	–	0.404 (0.084)	<.0001	0.361 (0.050)	<.0001

Data are presented as regression coefficient (β) and SE estimated by generalized linear model. All the analyses were adjusted all the clinical factors listed in the above table.

ALT = alanine aminotransferase, AST = aspartate aminotransferase, BMI = body mass index, CSII = continuous subcutaneous insulin injection, CVD = cardiovascular disease, DBP = diastolic blood pressure, DM = diabetes mellitus, HbA1c = glycated hemoglobin, HDL-c = high-density lipoprotein cholesterol, LDL-c = low-density lipoprotein cholesterol, MAGE = mean amplitude of glycemic excursion, MBG = mean blood glucose, MDI = multiple daily injection, MODD = absolute means of daily differences, SBP = systolic blood pressure, SE = standard error, SGBG = standard deviation of blood glucose, TG = triglyceride.

4. Discussion

The main finding of this study is that for 366 T2D patients with insulin therapy, family history of diabetes, duration of diabetes, higher HbA1c, and higher level of AST were positively associated with GV parameters. On the other way, C-peptide, premixed insulin treatment, history of CVD, serum concentrations of HDL-c, and uric acid were inversely associated with GV parameters.

More than 20 parameters have been described to measure GV,[11] but no gold standard exists. SDBG is the most widely used parameter to assess GV, which represented the dispersion of blood glucose while cannot distinguish major and minor fluctuations in blood glucose. Since SDBG is also positively associated with MBG, the coefficient of variance (CV; SDBG divided by mean $\times$ 100%) is also used to assess GV and is a measure independent of the mean.[12] MAGE, considered as the "gold standard" of GV, was calculated as described by Service et al[13] and was found to be closely related to oxidative stress[5] and occurrence of diabetes complications. MAGE reflects relatively large glycemic excursions, but the measurement may be subjective in terms of definition of large glycemic excursions. MODD is the absolute value of the difference between the measured values in the 2 consecutive days and does not depend on within-day fluctuations in blood glucose. Thus, MODD is considered as an accurate method to evaluate day-to-day blood glucose fluctuation.[8] In this study, we chose the representative 4 parameters as makers of GV to explore the influencing factors of GV in T2D with insulin therapy.

To date, only few studies have evaluated clinical factors associated with GV.[10,14,15] In a SMBG-based study conducted in insulin-treated T2D, the authors revealed that longer duration of insulin therapy was associated with higher GV.[14] However, another study conducted in T2D using either oral hypoglycemic agents or diet alone has found that postprandial β-cell function and oral glucose-lowering drugs were independent contributors to GV, which were estimated by MAGE, whereas clinical factors such as age, sex, duration of diabetes, insulin sensitivity, and carbohydrate intake failed to contribute to GV.[15] A recent study performed in Korea[10] has showed that in insulin-treated T2D, fasting C-peptide level was inversely correlated with GV while HbA1c and duration of diabetes positively correlated with GV. Their research have also revealed that in T2D without insulin therapy, age, BMI, HbA1c, HDL-c, TG levels, and use of sulfonylurea positively associated with GV and LDL-c levels inversely correlated with GV. Consistent with previous studies, we have found that pancreatic β-cell dysfunction, measured as lower level of fating serum C-peptide, was associated with both with-day and day-to-day GV. Similarity, we have also found that longer duration of diabetes and higher level of HbA1c were related to higher GV in T2D patients treated with insulin injection.

In patients with insulin-treated T2D, we found that serum fasting C-peptide level was independent factor associated with all the 4 parameters of GV, indicating the importance of endogenous β-cell function in stabilization of blood glucose. The results of this study suggested that fasting C-peptide level would be a simple independent indicator of GV. As well as known, the worse the β-cell function, the worse the blood glucose controls. In this study, we also found that higher MBG, longer duration of diabetes, and higher levels of HbA1c were also independent factors associated with SDBG and MODD. Otherwise, in this study we have also yielded that family history of diabetes was positively associated with SDBG, CV%, and MAGE. At present, most of the genetic loci of T2D found in GWAS are related to the function of beta-cell dysfunction[16] and higher genetic susceptibility of T2D was associated with the worse function of β-cells. Using 34 T2D-related SNPs, a recent research[17] conducted in China has constructed a T2D genetic risk score and revealed that higher T2D genetic risk score was associated with lower HOMA-β, a marker of pancreatic β-cell function. Thus, the potential relationship between the family history of diabetes and GV are likely to represent the true relationship between β-cell function and GV.

Premixed insulin formulations, containing both basal and prandial insulin, are often prescribed because they are superior to long- or intermediate-acting insulin in obtaining good metabolic control.[18] In addition, they are considered as an attractive alternative to classical MDI therapy as fewer daily injections are required.[19] Postprandial hyperglycemia is the main feature of blood glucose spectrum in Chinese T2D patients. Previous epidemiological results[20] have showed that >80% newly diagnosed Chinese T2D patients are accompanied with postprandial hyperglycemia, which may be associated with a more pronounced decline in β-cell early secretory function, a carbohydrate based diet, and a higher response to postprandial glycemia. Interestingly, our study found that compared with patients who used MDI regimen, patients on premixed insulin showed lower SDBG and MODD, which suggested that premixed insulin is more conductive to reduce GV and maintain day-to-day glucose stability. However, those patients with premixed insulin injection in our study had lower HbA1c and MBG, which showed great contribution for GV. Thus, the smaller glucose fluctuation showed by premixed insulin therapy patients may be mediated by better glycemic control. Or it can be said that premix insulin analogs with advantages of excellent pharmacokinetic characteristics and flexible and convenient administration may provide a comprehensive solution for Chinese T2DM patients to effectively control postprandial glucose and reduce blood glucose fluctuation.[21] However, the real relationship and detail mechanisms need to be confirmed by larger sample population or basic experiments in the future.

Dysfunction of β-cell was an independent contributor to GV; on the other hand, insulin sensitivity may also play an important role in blood glucose fluctuations, for the reason that small changes in insulin dosing would largely affect the glycemic fluctuation. Serum uric acid has been considered as a marker for inflammation and was positively associated with insulin resistance in several studies.[22,23] Given that insulin resistance had been confirmed playing an important role in the pathogenesis of CVD,[24] patients with history of CVD may represent the possible status of insulin resistance. Besides, a previous study had also proved that in patients with insulin resistance, peripheral hyperinsulinism increases the HDL-c level by suppression of a cholesteryl ester transfer protein) and putative acitivation of hepatic lipoprotein lipase through the portal circulation.[25] Therefore, elevated HDL-c level may also be a marker of peripheral hyperinsulinism and insulin resistance. In this study, we found that with a history of CVD, higher serum levels of HDL-c and uric acid were inversely in relation to parameters of GV, which may indicate that lower insulin sensitivity would reduce the GV.

Several limitations of this study should be discussed. Firstly, our study was a cross-sectional and observational study, thus it was not appropriate to infer casualty. Besides, the sample size in this study was relatively small and we involved many clinical factors in the generalized linear model, and it was very likely to see the false positive results in this setting. Therefore, future larger

scale and prospective studies are needed to confirm these results in the future. Secondly, because CGM was performed for clinical reasons and not at random, the typical subjects in this study had inadequate glucose control. Thus, the results of this study cannot be extrapolated to general diabetes patients.

In conclusion, dysfunction of pancreatic β-cell and better insulin sensitivity were independent contributors to the fluctuation of blood glucose. Moreover, premixed insulin therapy may acquire better glucose control and lower within-day and day-to-day glucose variability for insulin-treated Chinese T2D patients.

Acknowledgment

The present study would not have been possible without the participation of the participants.

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