Methodology

Parsimonious Model for Blood Glucose Level Monitoring in Type 2 Diabetes patients

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To establish the parsimonious model for blood glucose monitoring in patients with type 2 diabetes receiving oral hypoglycemic agent treatment. One hundred and fifty-nine adult Chinese type 2 diabetes patients were randomized to receive rapid-acting or sustained-release gliclazide therapy for 12 weeks. Their blood glucose levels were measured at 10 time points in a 24 h period before and after treatment, and the 24 h mean blood glucose levels were measured. Contribution of blood glucose levels to the mean blood glucose level and HbA1c was assessed by multiple regression analysis. The correlation coefficients of blood glucose level measured at 10 time points to the daily MBG were 0.58-0.74 and 0.59-0.79, respectively, before and after treatment (*P*<0.0001). The multiple stepwise regression analysis showed that the blood glucose levels measured at 6 of the 10 time points could explain 95% and 97% of the changes in MBG before and after treatment. The three blood glucose levels, which were measured at fasting, 2 h after breakfast and before dinner, of the 10 time points could explain 84% and 86% of the changes in MBG before and after treatment, but could only explain 36% and 26% of the changes in HbA1c before and after treatment, and they had a poorer correlation with the HbA1c than with the 24 h MBG. The blood glucose levels measured at fasting, 2 h after breakfast and before dinner truly reflected the change 24 h blood glucose level, suggesting that they are appropriate for the self-monitoring of blood glucose levels in diabetes patients receiving oral anti-diabetes therapy.

It was reported that long-term control of blood glucose in type 2 diabetes patients can prevent micro- and macro-vascular complications[1-2]. Self-monitoring of blood glucose (SMBG) can effectively assess and control blood glucose level in diabetes patients and is used as an integral part in treatment of type 1 and type 2 diabetes patients. No relevant consensus has been reached on the SMBG in non-insulin-treated type 2 diabetes patients[3-7]. It had been shown that therapeutic interventions can reduce HbA1c more significantly in non-insulin-treated type 2 diabetes patients with structured SMBG than in those without structured SMBG[8-10]. The guidelines for type 2 diabetes management recommended by the Chinese Diabetes Society suggest that 3-6 times per week of SMBG in type 2 diabetes patients without insulin treatment can reduce the cost and control their blood glucose[11]. Blood glucose levels measured at fasting, after three meals, before bedtime and midnight are widely used in hospitalized patients on insulin therapy, but it is too inconvenient to be accepted by discharged patients at home, thus not applicable in type 2 diabetes patients on oral anti-diabetic drugs. Some experts even commented that SMBG is unbeneficial or less cost-effective for type 2 diabetes patients and even reduces their quality of life[12]. The present study as a post-hoc analysis of the registered clinical trial for the sustained-release gliclazide in China[13], aimed to find a simple, less-expensive home blood glucose monitoring pattern for type 2 diabetes patients on oral anti-diabetic drugs.

Patients Included in this study were male or female type 2 diabetes patients aged ≥35 years with their BMI of 20-35 kg/m^2 and HbA1c <8%, who were treated with gliclazide alone (80, 160, 240, or 320 mg/d) or gliclazide combined with acarbose or metformin at a stable dose for at least two months. All the participants signed their informed consent.

Methods One hundred and fifty-nine patients were randomized to receive rapid-acting gliclazide or sustained-release gliclazide therapy for 12 weeks. The dose of acarbose or metformin they used previously remained unchanged during the study period. Their HbA1c levels were determined by HPLC.

doi: 10.3967/bes2014.086

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Blood glucose levels were measured at 0:00, 2:00, 4:00, 6:00, 10:00, 12:00, 14:00, 20:00, 22:00, and 24:00 in the presence of regular 3 meals before and after treatment by GOD-PAP assay, respectively. The adverse events were observed.

Statistical Analysis Data were expressed as mean±SD. Correlation between different variables was analyzed by Pearson and Spearman correlation analysis. Contribution of individual blood glucose levels, which measured at different time point, to the 24 h mean glucose level or HbA1c were analyzed by multivariable stepwise regression analysis where the 24 h mean glucose level was used as dependent variable and the individual blood glucose levels were used as independent variables. The model with the least independent variables and the greatest R^2 from the analysis will be considered as the optimal model. All analyses were performed using the SAS statistical software package (version 9.12).

One hundred and fifty-six patients completed the study. No significant differences were found in their HbA1c levels before and after treatment (6.85%±0.63% *vs* 6.80%±0.82%, 51±6.9 mmol/mol *vs* 51±9.0 mmol/mol), indicating that their blood glucose was well controlled (Table 1). The blood glucose levels measured at each time point were significantly correlated with the daily MBG. The correlation coefficients of blood glucose level measured at each time point to the daily MBG were 0.58-0.74 and 0.59-0.79 respectively before and after treatment (P<0.0001, Table 2). Multivariable stepwise regression analysis showed that the blood glucose levels measured at 6 of the 10 time points could explain 95% and 97% of the changes in the daily mean blood glucose level before and after treatment (R^2=0.955, R^2=0.974, P<0.0001, Table 3). However, the blood glucose levels measured at 2 of the 10 time points (fasting and 2 h after breakfast) could explain 73% and 75% of the changes in the 24 h MBG before and after treatment (R^2=0.73, R^2= 0.755, P<0.0001, Table 3), and these explained changes were increased to 84% and 86% respectively when the blood glucose level before dinner was also included as an independent variable in the analysis (R^2=0.84, R^2=0.86, Table 3). In contrast, the blood glucose levels measured at 21:30, 19:30, 3:30 before treatment and 3:30, 11:30, 19:30 after the treatment could only explain about 10% of the changes in the 24 h MBG (Table 3). The 24 h MBG was weakly associated with HbA1c. The blood glucose levels measured at different time points throughout the 24 h were not strongly correlated to HbA1c compared to the 24 h MBG (Table 2). The blood glucose levels measured at fasting, 2 h after breakfast and before dinner could only explain 36% and 26% of the changes in HbA1c before and after treatment (Table 4).

Adverse Events Of the 23 hypoglycemia patients, 7 (4 occurred before and 3 after treatment) were diagnosed by blood glucose monitoring. Hypoglycemia was related to the strict control of blood glucose. Two patients were unwilling to continue their participation in the study. Another patient was excluded because he had a history of viral hepatitis and his ALT level was 3-fold higher than the upper limit of normal level.

The Chinese Guidelines for Type 2 Diabetes Patients addressed that self blood glucose monitoring is not only the easiest and most reliable monitoring regimen but also an important tool for the better blood glucose control and the reduction of hypoglycemia and recommended that pre- and postprandial blood glucose should be tested 2-4 times per week in diabetes patients on oral hypoglycemic agents and lifestyle intervention[11]. However, the guidelines from IDF on SMBG indicate that no evidence-based regimens are available for maintaining their optimal SMBG[14]. The Chinese Guideline on the Continuous Glucose Monitoring System also emphasizes that clinicians would not be able to improve their treatment behavior based on the data of SMBG in non-insulin-treated type 2 diabetes in case of insufficient training[15]. Poor

Table 1. Variables in Type 2 Diabetes Patients before and after Treatment

Variables	Before Treatment (n=159)	After Treatment (n=156)
	Mean±SD	Mean±SD
HbA1c mmol/mol (%)	51±6.9 (6.85±0.63)	51±9.0 (6.80±0.82)
PG0 (mmol/L) 7:30	7.78±2.07	8.04±2.02
PG2 (mmol/L) 9:30	11.88±3.45	12.40±3.50
PG4 (mmol/L) 11:30	6.59±2.53	6.58±2.64
PG6 (mmol/L) 13:30	8.87±2.65	9.11±2.85
PG10 (mmol/L) 17:30	7.20±2.71	7.61±2.77
PG12 (mmol/L) 19:30	11.90±3.46	12.78±3.49
PG14 (mmol/L) 21:30	8.08±3.01	8.58±3.44
PG20 (mmol/L) 3:30	5.58±1.46	5.83±1.59
PG22 (mmol/L) 5:30	6.57±2.41	6.74±2.41
PG24 (mmol/L) 7:30	7.26±1.79	7.46±1.80
Mean (mmol/L) of 24 h	8.15±1.63	8.51±1.90

Table 2. Correlation between MBG, HbA1c, and Blood Glucose Levels Measured at Different Time Points before and after Treatment

Items		PG0	PG2	PG4	PG6	PG10	PG12	PG14	PG20	PG22	PG24
Before Treatment (*n*=159)											
MBG	*r*	0.71	0.70	0.73	0.65	0.57	0.66	0.61	0.62	0.68	0.70
	P	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
HbA1c	*r*	0.45	0.46	0.45	0.40	0.31	0.37	0.27	0.36	0.39	0.47
	P	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	0.0007	<0.0001	<0.0001	<0.0001
After Treatment (*n*=156)											
MBG	*r*	0.76	0.72	0.79	0.60	0.59	0.75	0.77	0.64	0.64	0.69
	P	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
HbA1c	*r*	0.50	0.43	0.41	0.24	0.36	0.39	0.35	0.31	0.30	0.45
	P	<0.0001	<0.0001	<0.0001	0.0023	<0.0001	<0.0001	<0.0001	0.0001	0.0002	<0.0001

Table 3. Contribution of Blood Glucose Levels to MBG before and after Treatment

Varables	Partial R^2	Model R^2	*P*
Before Treatment (*n*=159)			
PG24 (At fasting)	0.528	0.528	<0.0001
PG2 (After breakfast)	0.204	0.732	<0.0001
PG10 (Before dinner)	0.109	0.841	<0.0001
PG14 (Before bedtime)	0.057	0.898	<0.0001
PG12 (After dinner)	0.038	0.936	<0.0001
PG20 (At night 3:30)	0.020	0.955	<0.0001
After Treatment (*n*=156)			
PG24 (At fasting)	0.538	0.538	<0.0001
PG2 (After breakfast)	0.217	0.755	<0.0001
PG10 (Before dinner)	0.110	0.865	<0.0001
PG20 (At night 3:30)	0.055	0.919	<0.0001
PG4 (Before lunch)	0.032	0.951	<0.0001
PG12 (After dinner)	0.022	0.974	<0.0001

Note. Other variables did not enter the model at $P<0.05$ level in the stepwise regression analysis.

Table 4. Contribution of Blood Glucose Levels to HbA1c before and after Treatment

Varables	Partial R^2	Model R^2	*P*
Before Treatment (*n*=159)			
PG24 (At fasting)	0.254	0.254	<0.0001
PG2 (After breakfast)	0.090	0.345	<0.0001
PG10 (After supper)	0.016	0.360	0.05
After Treatment (*n*=156)			
PG24 (At fasting)	0.208	0.208	<0.0001
PG2 (After breakfast)	0.034	0.243	0.0094
PG10 (After supper)	0.019	0.262	0.0487

understanding of blood glucose monitoring in inevitably leads to miss useful knowledge of blood glucose fluctuations. It was reported that patients with poorly controlled blood glucose have more complications than those with well controlled blood glucose[16]. A German study showed that the risk/hazard ratio is significantly lower in SMBG-using diabetes patients than in those not using SMBG[17]. Palmer et al reported that interventions including SMBG can improve the outcome in diabetes patients[18]. Clinicians should inform their patients that blood glucose level may more accurately reflect hypoglycemia than its symptoms[19]. SMBG can be used for adjusting medications, medical nutrition therapy and physical activity[20]. SMBG is likely to be an effective self-management tool when the results are reviewed and acted upon by healthcare providers and/or diabetes patients to actively adjust their treatment and/or modify their own behaviors[21]. Ignoring regular SMBG is the most common cause of re-hospitalization for poor glucose control and complications in China. However, it is difficult for a great many patients to use SMBG in adjusting their diet and treatment at home because of the high cost and inconvenience. Therefore, the need to improve compliance with SMBG underlines the necessity to identify a simple, practical and inexpensive glucose monitoring profile.

In the present study, the ten blood glucose levels measured at each time point in 24 h were closely related to the changes in the MBG. However, the three blood glucose levels which measured at fasting, after breakfast and before dinner could explain most of the changes in blood glucose level throughout the whole 24 h period. SMBG profile measured at these 3 time points could provide an optimal model for the daily blood glucose

monitoring. This model can reduce the number of test points, decrease the financial burden and less interfere with the daily life of patients, thus being more suitable for SMBG in these patients.

The correlation between blood glucose levels measured at different time points and HbA1c were much weaker than that between the blood glucose levels measured at different time points and the 24 h MBG. The 24 h MBG was also weakly associated with HbA1c. Multivariable stepwise regression analysis showed that the blood glucose levels measured at fasting, after breakfast and before dinner could only explain 36% and 26% of the changes in HbA1c before and after treatment.

It is well known that HbA1c monitoring every 2-3 months is necessary for long-term control of blood glucose. However, our results demonstrated that it could not replace the SMBG in terms of the usefulness for the improvement of glucose control. In some special situations it may not reflect the real status of short-term of blood glucose control since HbA1c was an integrate value of the MBG. In those patients with big fluctuation of blood glucose level, the optimization of a blood glucose management program should be based on the blood glucose levels measured at different time points throughout the day rather than on the HbA1c. In this context, SMBG should be considered as a part of ongoing diabetes self-management education. The blood glucose levels measured at 10 time points throughout the 24 h period in this study provide the opportunity to establish a parsimonious model for blood glucose monitoring in type 2 diabetics patients on oral hypoglycemic agents. Fortunately, we found there are three glucose levels greatly contributed to the change of the mean glucose in the whole day.

In conclusion, the three blood glucose levels measured at fasting, 2 h after breakfast and before dinner truly reflects the 24 h blood glucose profile suggesting they are fit for the self-monitoring of blood glucose in patients on oral anti-diabetes therapy. However, it cannot replace the regular HbA1c testing.

ACKNOWLEDGMENTS

We thank the 4 participating investigators and their staff members involved in the trial. We are indebted to Dr. AN Ya Li for his assistance to the data analysis. We express our sincere appreciation to all participants, LI Guang Wei and ZHAO Fang who contributed to research design, data analysis and writing, MA Yan Fen, WEN Jing Xiao, DU Yan Fang and LI Chun Lin who contributed to patient visits and data collection.

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Received: December 15, 2013;
Accepted: March 4, 2014

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