ORIGINAL ARTICLE

Contributions of Basal Glucose and Postprandial Glucose Concentrations to Hemoglobin A1c in the Newly Diagnosed Patients with Type 2 Diabetes—The Preliminary Study

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Abstract

Objective: The aim of this preliminary study is to investigate contributions of basal glucose (BG) and postprandial glucose (PPG) increments to overall hyperglycemia in newly diagnosed patients with type 2 diabetes mellitus (T2DM).

Research Design and Methods: We evaluated the relative contributions of BG and PPG to overall hyperglycemia in 59 newly diagnosed T2DM patients according to BG baseline value of 6.1 mmol/L and 24-h glucose profiles of normal glucose tolerance (NGT) subjects obtained by continuous glucose monitoring as baseline, respectively.

Results: When the baseline was 24-h glucose profiles of the NGT subjects, the relative contributions of PPG in the T2DM patients with hemoglobin A1c (HbA1c) levels of $\leq 7.0\%$, $7.0\text{--}9.0\%$, and $>9.0\%$ were 57.58%, 44.69%, and 21.56%, respectively. When the baseline value was equal to 6.1 mmol/L, the relative contributions of PPG in the T2DM patients with HbA1c levels of $\leq 7.0\%$, $7.0\text{--}9.0\%$, and $>9.0\%$ were 77.23%, 53.43%, and 22.78%, respectively. Compared with the 24-h glucose profiles of the NGT subjects as the baseline, the relative contribution of PPG was overestimated by about 10–20% in the T2DM patients with HbA1c levels of $\leq 9.0\%$ when 6.1 mmol/L was chosen as the baseline.

Conclusions: In the newly diagnosed T2DM patients with mild hyperglycemia, PPG is a predominant contributor, whereas the relative contributions of BG gradually increase from mild to severe hyperglycemia and obviously exceed PPG in the T2DM patients with HbA1c levels of $>9.0\%$. This finding implies that the initial pharmacotherapy may target PPG in those patients with mild hyperglycemia and target BG in those patients with severe hyperglycemia.

Introduction

ASSESSMENT OF GLUCOSE LEVELS involves hemoglobin A1c (HbA1c), basal glucose (BG), and postprandial glucose (PPG). HbA1c has been widely acknowledged as the most reliable evidence of adjusting therapeutic strategy and predicting the chronic complications in patients with diabetes.^{1,2} Hence, it is important for physicians to understand the relationship between HbA1c and the glucose levels at different levels of glycemic control in patients with diabetes.

However, results of previous studies^{3–7} about the contributions of PPG and BG to the overall hyperglycemia in patients with type 2 diabetes mellitus (T2DM) have been inconsistent; most were based on multipoint glucose measurements in treated patients with diabetes and a single baseline level (upper limit of fasting blood glucose of 5.5 or 6.1 mmol/L). In this study, we used continuous glucose monitoring (CGM) and selected 6.1 mmol/L and 24-h glucose profiles of normal glucose tolerance (NGT) subjects as the baselines separately to evaluate the relative contributions

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of BG and PPG to the overall hyperglycemia in newly diagnosed, drug-naïve T2DM patients.

Research Design and Methods

Fifty-nine newly diagnosed, drug-naïve T2DM patients and 86 NGT subjects with a body mass index of 18.5–23 kg/m² were recruited in this prospective, cross-sectional study. All of the NGT subjects (20–70 years of age) had normal hepatic and renal functions, blood pressure, and lipid profiles. Informed consent, which was approved by the Ethics Committee of West China Hospital, Sichuan University, Chengdu, Sichuan, People's Republic of China, was signed by each participant. All of the subjects received a 75-g oral glucose tolerance test and CGM. HbA1c measurement in the T2DM patients was made by using a high-performance liquid chromatography assay.

According to the standard Medtronic MiniMed (Northridge, CA) operating guidelines, a CGMS[®] System Gold[®] device was used to monitor subcutaneous interstitial glucose levels for 72 h consecutively. The NGT subjects and the T2DM patients were instructed to calibrate the system before each of three meals, 2 h after each of three meals, and at bedtime (seven points per day) with OneTouch[®] Ultra[®] meters (LifeScan Inc., Milpitas, CA) and Accu-Chek[®] Integra meters (Roche Diagnostics GmbH, Mannheim, Germany), respectively.

Parameters on evaluation of BG and PPG contributions to the total hyperglycemia

Baseline = 6.1 mmol/L. According to the World Health Organization standard for the upper limit of 6.1 mmol/L of fasting blood glucose in normal subjects, the area under the glucose curve (AUC) above 6.1 mmol/L during a 24-h interval was calculated to reflect the overall increments of BG and PPG. The average AUC above 6.1 mmol/L in the second and third days was defined as AUC-T1. The AUC (AUC_p) over the 4-h period after meals above the premeal levels was calculated to represent glucose response to breakfast, lunch, and dinner. The AUC_{BG} was defined as AUC-T1 – AUC_p. The relative contributions of BG and PPG to the total BG increments were calculated as $([AUC-T1 - AUC_p]/AUC-T1) \times 100\%$ and $(AUC_p/AUC-T1) \times 100\%$, respectively.

24-h glucose profiles of the NGT subjects as baseline. The AUC in the NGT subjects was defined as AUC-N.

The AUC in the T2DM patients over a 24-h interval was AUC-24h. The 24-h excess glucose increments in the T2DM patients were calculated as $AUC-T2 = AUC-24h - AUC-N$. The contributions of BG and PPG to the overall hyperglycemia were calculated as $([AUC-T2 - AUC_p]/AUC-T2) \times 100\%$ and $(AUC_p/AUC-T2) \times 100\%$, respectively.

Subgroup analysis. According to the HbA1c levels, the T2DM patients were divided into three groups: 20 cases with HbA1c $\leq 7.0\%$, 24 cases with HbA1c 7.0–9.0%, and 15 cases with HbA1c $> 9.0\%$. The contributions of BG and PPG to the overall hyperglycemia were calculated according to the above-mentioned methods, respectively.

Statistical analysis

The statistical analysis was performed using Statistical Package for the Social Sciences software (version 19.0; SPSS, Inc., Chicago, IL). Data were expressed as mean $\pm$ SE or median with quartile range. Mean values in the normally distributed data between the NGT and T2DM groups were compared by paired *t* test. Parameters of AUC among the three groups were compared by analysis of variance. Comparisons of median values in the non-normally distributed data among the three groups were performed by the Kruskal–Wallis H test and between two groups by the post hoc test. The consistency of contribution between the two methods was assessed by the Kruskal–Wallis test. $P < 0.05$ was considered significant.

Results

Fifty-nine T2DM patients (males:females, 39:20) with a mean age of 53 years (22–69 years) and 86 NGT subjects (males:females, 39:47) with a mean age of 42 years (22–69 years) were recruited for the study. Mean body mass index values of the NGT subjects and the T2DM patients were 21.44 ± 1.85 kg/m² and 24.7 ± 3.1 kg/m², respectively. HbA1c values in the NGT and T2DM groups were $5.6 \pm 0.32\%$ (4.9–6.2%) and $8.02 \pm 1.72\%$ (5.6–13.2%), respectively.

As shown in Table 1, AUC-T2 values were significantly higher than AUC-T1 values in the T2DM patients and the two subgroups with HbA1c $> 9.0\%$ and $\leq 7.0\%$ ($P < 0.01$). However, AUC-T2 values were significantly lower than AUC-T1 values in the patients with HbA1c 7.0–9.0% ($P < 0.01$). Furthermore, AUC_{BG} values were statistically greater than

TABLE 1. COMPARISON OF AREA UNDER THE GLUCOSE CURVE DERIVED FROM CONTINUOUS GLUCOSE MONITORING IN THE NEWLY DIAGNOSED PATIENTS WITH TYPE 2 DIABETES MELLITUS

	All T2DM patients	HbA1c		
		$\leq 7.0\%$	7.0–9.0%	$> 9.0\%$
AUC _p	1,408.24 $\pm$ 724.61	1,226.57 $\pm$ 645.91	1,387.18 $\pm$ 844.91	1,636.16 $\pm$ 591.22
AUC-T1	4,091.85 $\pm$ 3,771.03	1,699.15 $\pm$ 1,210.34	3,558.04 $\pm$ 1,885.33	9,147.19 $\pm$ 3,632.75 ^{ab}
AUC-T2	4,723.71 $\pm$ 3,771.03 ^c	2,331.01 $\pm$ 1,210.34 ^c	2,926.18 $\pm$ 1,885.33 ^c	9,779.05 $\pm$ 3,632.74 ^{a-c}
AUC _{BG}	2,746.78 $\pm$ 3,475.80	944.02 $\pm$ 704.80	2,138.99 $\pm$ 1,613.48	7,522.50 $\pm$ 3,450.78 ^{ab}
AUC _{BG-2} ^d	2,808.74 $\pm$ 3,518.34 ^c	1,070.40 $\pm$ 840.50 ^c	2,219.51 $\pm$ 1,803.48 ^c	8,142.89 $\pm$ 3,477.76 ^{a-c}

Data are mean $\pm$ SD values.

^aSignificant difference between hemoglobin A1c (HbA1c) 7.0–9.0% and HbA1c $> 9.0\%$ ($P < 0.05$).

^bSignificant difference between HbA1c $\leq 7.0\%$ and HbA1c $> 9.0\%$ ($P < 0.05$).

^cSignificant difference between the two baselines ($P < 0.01$).

^dArea under the glucose curve (AUC)_{BG-2} = AUC-T2 – AUC_p.

AUC_{BG-2} values (AUC-T2 – AUC_P) in the T2DM group and the three subgroups ($P < 0.05$). The values of AUC_P were not significantly different among the three subgroups ($P > 0.05$). The patients with HbA1c $> 9.0\%$ had greater AUC-T1, AUC-T2, and AUC-T-AUC_P values compared to the patients with HbA1c $\leq 7.0\%$ ($P < 0.001$) and $7.0\text{--}9.0\%$ ($P < 0.001$).

The relative contributions of PPG to overall hyperglycemia decreased progressively, and the contributions of BG gradually increased with elevated HbA1c levels while using either 6.1 mmol/L (Fig. 1A) or the 24-h glucose profiles of the NGT subjects (Fig. 1B) as baseline.

In the T2DM patients with HbA1c $> 9.0\%$, contributions of PPG to the total hyperglycemia were 22.78% and 20.42% according to 6.1 mmol/L and 24-h glucose profiles of the NGT subjects as baseline, respectively. In the T2DM patients with HbA1c $\leq 7.0\%$ and $7.0\text{--}9.0\%$, contributions of PPG to the total hyperglycemia were 57.58% and 44.70%, respectively, based on the 24-h glucose profiles of the NGT subjects as baseline. However, contributions of PPG to the total hyperglycemia were 77.23% in the T2DM patients with HbA1c $\leq 7.0\%$ and 53.43% in the patients with HbA1c $7.0\text{--}9.0\%$ when the baseline value was equal to 6.1 mmol/L. Compared with the 24-h glucose profiles of the NGT subjects as baseline, the contribution of PPG was overestimated by about 10–20% in the T2DM patients with HbA1c $\leq 9.0\%$ when baseline was set to 6.1 mmol/L.

Discussion

Our study suggested the PPG was the greatest contributor to mild hyperglycemia with HbA1c $\leq 7.0\%$ and that the BG was the predominant contributor to severe hyperglycemia with HbA1c $> 9.0\%$ in the newly diagnosed T2DM patients. PPG and BG almost contributed equally to moderate hyperglycemia in the newly diagnosed T2DM patients with HbA1c $7.0\text{--}9.0\%$.

In fact, the contributions of BG and PPG to HbA1c remain debatable. Published studies demonstrated that mild hyperglycemia with HbA1c $< 7.3\%$ was mainly attributed to the elevation of PPG and that BG reached a 50–75% contribution to the overall hyperglycemia in poorly controlled, T2DM patients with HbA1c $> 8.0\%$ or 9.0% .^{3,8} Bonora et al.⁴

showed that HbA1c could be estimated by premeal glucose levels throughout the day. Wang et al.⁹ reported that 24-h and 4-h PPG made the major contributions in well-controlled patients with diabetes but only accounted for 10% in less well-controlled patients with diabetes. All of the results from the above-mentioned studies were not completely inconsistent with our results.

The main reason was that AUC-T was calculated based on 6.1 mmol/L^{3,10,11} or 5.5 mmol/L^{8,9} in the previous studies. Actually, these values (5.5 mmol/L and 6.1 mmol/L) are just the upper limits of fasting BG in the NGT subjects as defined by the American Diabetes Association and the World Health Organization, respectively. Only using the single value as the baseline to evaluate the BG and PPG contributions to the overall hyperglycemia was inaccurate because glucose variability was also present in the NGT subjects.¹² Furthermore, multipoint blood glucose measurements could not represent the integrated glucose fluctuations of the day. Therefore, in our study, the 24-h glucose profiles of the NGT subjects obtained from the CGM were chosen as the baseline. All of the T2DM participants received CGM, and the AUC values were calculated to reflect the diurnal and nocturnal glucose profiles. As a result, we found that the contribution of PPG to the overall hyperglycemia was overestimated by about 10–20% in the T2DM patients with HbA1c $\leq 9.0\%$ when baseline was set to 6.1 mmol/L.

Second, most of the previous studies^{3,7–11} about contributions of BG and PPG to HbA1c focused on those patients with diabetes treated with oral antihyperglycemia drugs or insulin. Our study enrolled newly diagnosed, drug-naïve T2DM patients, which could avoid the interference of the drugs. The potential implication of the study is to provide the practical guidance of initial treatment for clinicians. For the newly diagnosed T2DM patients with HbA1c $\leq 7.0\%$, initial therapy may target PPG rather than BG, which includes lifestyle intervention and oral antihyperglycemia drugs controlling PPG. The contribution of BG to the overall hyperglycemia obviously exceeds PPG in those T2DM patients with HbA1c $> 9.0\%$, and the pharmacotherapy should target BG rather than PPG.

Finally, the proportion of carbohydrate in meals influenced glucose excursions.¹³ In this study, all of the participants

FIG. 1. Relative contributions of postprandial and basal glucose to overall glucose increment in the different hemoglobin A1c (HbA1c) subgroups according to (A) fasting blood glucose = 6.1 mmol/L as baseline and (B) 24-h glucose profiles of normal glucose tolerance subjects as baseline.

were under unrestricted outpatient conditions with 30 kcal/kg/day calorie intake from three daily meals. Compared with standard meals, common Chinese foods could make the PPG difference, which could reflect the real contribution of PPG to the overall hyperglycemia.

We demonstrated that PPG mainly contributed to the overall hyperglycemia in those newly diagnosed T2DM patients with an HbA1c level of $\leq 7.0\%$. Contributions of BG to the overall hyperglycemia increased progressively with increasing level of HbA1c and exceeded 75% in those T2DM patients with an HbA1c level of $>9.0\%$. The small sample was the limitation of this study, and a large-size clinical trial is currently underway to further confirm the results.

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Author Disclosure Statement

No competing financial interests exist.

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