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Original article

Using continuous glucose monitoring to assess contributions of premeal and postmeal glucose levels in diabetic patients treated with metformin alone

S.-D. Lin , S.-L. Su , S.-Y. Wang , S.-T. Tu , S.-R. Hsu *

Division of Endocrinology and Metabolism, Department of Internal Medicine, Changhua Christian Hospital, Changhua, Taiwan

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Abstract

Aim. – This study aimed to determine the contributions of basal excess glycaemia (BEG) and prandial excess glycaemia (PEG) to overall excess glycaemia in type 2 diabetes (T2D) patients treated with metformin alone.

Methods. – Outpatients with T2D treated with metformin alone ($n = 46$) who underwent continuous glucose monitoring (CGM) were divided into tertiles according to glycated haemoglobin (HbA_{1c}) levels. For each CGM trace, the glucose area under the curve (AUC) > 5.5 mmol/L was expressed as the $AUC_{overall}$, representing overall excess glycaemia. The sum of glucose AUCs above the premeal glucose level at 4 h after breakfast, lunch and dinner was expressed as the AUC_{peg}, representing PEG. The contribution of PEG to overall excess glycaemia was calculated as $(AUC_{peg}/AUC_{overall}) \times 100\%$. The contribution of BEG was calculated as $[(AUC_{overall} - AUC_{peg})/AUC_{overall}] \times 100\%$. Factors related to PEG contribution were also analysed.

Results. – BEG constituted more than half the overall excess glycaemia in all HbA_{1c} tertiles. The contribution of PEG was negatively correlated with HbA_{1c} and mean glucose values before each meal. Prebreakfast and predinner glucose values were the dominant factors affecting PEG contribution and was independent of HbA_{1c}.

Conclusion. – In patients treated with metformin alone, BEG was the major contributor to excess glycaemia at HbA_{1c} levels ≥ 7.7%, while PEG and BEG contributions were similar and stable below this level. For HbA_{1c} levels ≥ 7.7%, add-on therapy to metformin should preferentially target control of BEG, whereas targeting both BEG and PEG could be of equivalent importance with lower HbA_{1c} levels.

Keywords: Basal glycaemia; Continuous glucose monitoring; Metformin; Prandial glycaemia; Type 2 diabetes

1. Introduction

Metformin treatment concomitant with lifestyle modification is recommended as the first-line treatment for patients with type 2 diabetes (T2D) by numerous diabetes guidelines [1–3]. However, the progressive nature of diabetes [4] often necessitates the addition of a second-line medication to achieve or maintain optimal glycaemic control. The American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) jointly endorse a patient-centred approach for the selection of pharmacological agents that takes into consideration the patient's body weight, comorbidities and personal preferences, as well as drug efficacy, side effects and costs [1]. The American Association of Clinical Endocrinologists (AACE) guidelines preferentially recommend agents with minimal risk of hypoglycaemia and weight gain [2].

Patients who fail to achieve optimal glycaemic control might have fasting hyperglycaemia, postprandial hyperglycaemia, or both. Epidemiological studies and meta-analyses

Abbreviations: ADA, American Diabetes Association; AACE, American Association of Clinical Endocrinologist; AUC, area under the curve; BEG, basal excess glycaemia; CGM, continuous glucose monitoring; EASD, European Association for the Study of Diabetes; HbA_{1c}, glycated haemoglobin; PEG, prandial excess glycaemia; SMBG, self-monitoring of blood glucose.

* Corresponding author. Division of Endocrinology and Metabolism, Changhua Christian Hospital, 135, Nanxiao Street, 500 Changhua City, Changhua County, Taiwan. Tel.: +886 4 7238595x3239; fax: +886 4 7277982.
E-mail address: 67781@cch.org.tw (S.-R. Hsu).

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have shown that postchallenge or postprandial blood glucose levels are a better predictor of cardiovascular outcome than fasting glucose levels [5–8]. Those with predominantly postprandial hyperglycaemia may be treated with pharmacological agents that preferentially lower postprandial glucose levels, such as α-glucosidase inhibitors, glinides, rapid-acting insulin analogues, human regular insulin, glucagon-like peptide-1 derivatives and dipeptidyl peptidase-4 (DPP-4) inhibitors [2,3]. In usual practice, however, most clinicians use only glycated haemoglobin (HbA_{1c}) and the corresponding fasting blood glucose levels to guide the treatment of patients taking metformin alone. Without more intensive glucose monitoring, it is difficult for clinicians to determine whether unsatisfactory HbA_{1c} levels in their diabetic patients should be attributed to fasting hyperglycaemia or to postprandial hyperglycaemia.

The contribution of postprandial glucose increments to overall hyperglycaemia has been extensively demonstrated in several studies [9–14]. Most focused on either drug-naive patients or those variously treated with oral antidiabetic drugs, insulin, or both. One study enrolled patients treated with metformin alone, but their glycaemic profiles were derived from conventional self-monitoring of blood glucose (SMBG) data [12]. Theoretically, the use of continuous glucose monitoring (CGM) would have offered truer and more complete representations of their actual glycaemic profiles. As most patients with T2D use metformin as their initial drug treatment, the present study used CGM to investigate the contribution of postprandial glucose increments to overall excess glycaemia in patients treated with metformin alone.

2. Material and methods

2.1. Study populations

Outpatients with T2D were eligible for enrolment if they had been treated with metformin alone at a stable dosage for at least 8 weeks, and had undergone CGM between 15 March 2008 and 15 September 2015 at Changhua Christian Hospital, Taiwan. All patients gave their informed consent prior to starting CGM. A total of 87 patients were included in the study.

2.2. Continuous glucose monitoring

Either the CGMS® System Gold or iPro2 (Medtronic Inc, Minneapolis, MN, USA) glucose monitoring device was used for CGM measurements. Subjects were also instructed to check their blood glucose with a conventional glucometer three or four times a day for calibration purposes. Those who used the CGMS System Gold were asked to make a marking before beginning each meal, using the device's meal event marker. Those who used the iPro2 device were asked to record the precise time they began each meal. Each subject was required to carry the device for at least three consecutive days, during which they were advised to conduct their daily activities as usual with no deliberate changes to their lifestyles.

2.3. Measurements

CGM recordings from each subject were segmented into daily tracings at each 12 AM marking. Only those segments with complete 24-h data (from 12 AM to 12 AM of the next day) were retained. Any tracing segment with missing data during the 24-h period was discarded. The complete 24-h tracing segments were then used to calculate the respective contributions of prandial excess glycaemia (PEG) and basal excess glycaemia (BEG) to the overall excess glycaemia. The trapezoidal method was used to calculate the glucose area under the curve (AUC). Any glucose excursion > 5.5 mmol/L was considered excessive on the basis that a healthy person's normal blood glucose level should never exceed 5.5 mmol/L during the fasting basal state. Therefore, overall excess glycaemia was defined as any glucose AUC > 5.5 mmol/L, expressed as $AUC_{overall}$. Excess glycaemia due to prandial glucose excursions, expressed as AUC_{peg}, was defined as the sum of glucose AUCs, measured over the 4 h period from the beginning of each meal, that were above each respective premeal value [15], or > 5.5 mmol/L if premeal glucose levels were ≤ 5.5 mmol/L. The contributions of PEG and BEG to overall excess glycaemia were calculated as $(AUC_{peg}/AUC_{overall}) \times 100\%$ and $[(AUC_{overall} - AUC_{peg})/AUC_{overall}] \times 100\%$, respectively. The mean glucose level before each meal was the average of all glucose values recorded by the CGM device before each meal on different days in the same subject. The 24-h glucose profiles without meal markers (for those using the CGMS device) or with no documented time of meals (for those using the iPro2 device) were excluded from the analyses.

2.4. Statistical analysis

All statistical analyses were performed using SPSS software (version 14.0, Chicago, IL, USA). Data are presented as means ± standard deviation (SD). HbA_{1c} levels were divided into tertiles and the patients grouped accordingly. Differences in variables among the three groups were compared using one-way analysis of variance (ANOVA) followed by Bonferroni post-hoc tests. Categorical variables were compared using chi-square or Fisher's exact test. The Pearson correlation coefficient was used to determine the relationship between two continuous variables of measured or calculated parameters of glycaemia. Multivariable linear-regression analysis was performed to investigate factors associated with the PEG contribution to overall excess glycaemia. A value of $P < 0.05$ was considered statistically significant.

3. Results

Of the original 87 subjects (47 using CGMS and 40 using iPro2), 33 were excluded because of incomplete meal markings ($n = 23$) or missing documented mealtimes ($n = 10$), and eight patients were excluded because of incomplete 24-h data. Characteristics of the remaining 46 patients eligible for analysis are summarized in Table 1. There were no significant differences in age, gender, duration of diabetes, body weight, body mass index

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