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Relationships among different glycemic variability indices obtained by continuous glucose monitoring

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ABSTRACT

The aim of this study was to assess the relationships among indices of glycemic variability obtained by continuous glucose monitoring (CGM). CGM was performed in 88 patients with diabetes (20 type 1 and 68 type 2 diabetes, age 59 ± 15 years) admitted to our hospital (Keio University Hospital, Tokyo, Japan) between 2010 and 2012. Mean glucose, glucose standard deviation (SDglu) and other glycemic indices such as index of glycemic control (ICG), *J*-index, mean of daily differences (MODD), continuous overlapping net glycemic action 1 (CONGA1), mean amplitude of glycemic excursions (MAGE) and *M* value were calculated from CGM data, and the correlations among these indices were assessed. There were strong correlations between SDglu and the indices MAGE, CONGA1, MODD and *M* value (all $r > 0.8$, $P < 0.05$). On the other hand, mean glucose was strongly correlated with *J* index and *M* value (both $r > 0.8$, $P < 0.05$). SDglu and other glycemic variability indices were more strongly correlated with hypoglycemia than was mean glucose, and the combination of mean glucose and SDglu was useful for predicting hypoglycemia in patients with diabetes. In this study, we demonstrated the characteristics of various glycemic variability indices in relation to mean glucose and SDglu. This information will help physicians to understand the characteristics of various glycemic variability indices and to select an appropriate index for their purpose. Our results also underpin the importance of glycemic variability in relation to risk of hypoglycemia in patients with diabetes.

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Abbreviations: CGM, continuous glucose monitoring; SMBG, self-monitoring of blood glucose; SD, standard deviation; SDglu, SD of glucose; ICG, index of glycemic control; MODD, mean of daily differences; CONGA, continuous overlapping net glycemic action; MAGE, mean amplitude of glycemic excursions; NGSP, National Glycohemoglobin Standardization Program; AUC, area under the curve; Tglu > 180, time of glucose >180 mg/dl; AUCglu > 180, AUC of glucose >180 mg/dl; Tglu < 70, time of glucose <70 mg/dl; AUCglu < 70, AUC of glucose <70 mg/dl.

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1. Introduction

Dysglycemia in patients with diabetes includes two components: sustained chronic hyperglycemia and acute glucose fluctuations [1]. Studies have shown that these two components are both associated with cardiovascular complications in patients with diabetes [2–5]. Although HbA1c is the current gold standard for glycemic control in patients with diabetes, it mainly reflects the former component and evaluation of the latter component remains difficult [1].

Since Service and colleagues introduced novel methods for assessing glycemic variability, the mean amplitude of glucose excursions (MAGE) and the mean of daily differences (MODD), in the 1970s [6,7], various indices of glycemic variability have been developed [8–11]. Furthermore, recent development of a continuous glucose monitoring system (CGM) has made it possible to evaluate glycemic variability more precisely [1,10].

While the relationships among various indices of glycemic variability calculated from CGM data have been recently evaluated in a Caucasian population [10,12], the standard deviation (SD) of glucose values appears to be the gold standard for the assessment of glycemic variability, and the application of other indices in clinical settings remains controversial [1,13]. Moreover, because SD and mean glucose were also correlated with each other [13,14], the relationships among the indices are more complicated.

In this study we aimed to characterize various indices of glycemic variability obtained from CGM data, especially in relation to SD and mean glucose, in Japanese diabetic patients. Moreover, we assessed the relationships of these indices with time and area under the curve (AUC) of hyper- and hypoglycemia, respectively.

2. Research design and methods

2.1. Subjects

A total of 88 Japanese patients (46 male and 42 female) with diabetes mellitus (20 with type 1 and 68 with type 2 diabetes) who were admitted to our hospital from April 2010 to March 2012 because of poor glycemic control participated in this study. Characteristics of the patients are described elsewhere [14] and in Table 1. Of these patients, two had liver cirrhosis and four had autoimmune thyroid disease, but none had nephrotic syndrome or end-stage renal disease, severe anemia, erythropoietin treatment or glucocorticoid treatment. During admission, the patients were treated according to the Japan Diabetes Society (JDS) guidelines for treatment of diabetes and, if necessary, medical therapy was intensified during admission to obtain optimal glycemic control (i.e., fasting plasma glucose <130 mg/dl and postprandial plasma glucose <180 mg/dl) [15].

Written informed consent was obtained during admission. This study was conducted according to the principles expressed in the Declaration of Helsinki and was approved by the ethical review committee of Keio University School of Medicine, Tokyo, Japan.

2.2. Measurements

All measurements were performed by the Department of Laboratory Medicine, Keio University School of Medicine with routine automated laboratory methods as previously described [14]. HbA1c was measured on the day of admission by HPLC and expressed as the National Glycohemoglobin Standardization Program (NGSP) value according to the JDS statement [16].

All patients received the ideal dietary calorie intake calculated from their ideal body weight (i.e., height $(m)^2 \times 22 \times 25$ kcal/kg; carbohydrate 50–60%, protein 15–20% and fat 20–25% based on a meal-exchange plan) during admission.

2.3. Continuous glucose monitoring (CGM)

CGM was performed using a CGMS Gold (Medtronic Minimed, Northridge, CA, USA), as previously reported [14]. After treating hyperglycemia during admission (i.e., usually for 7–10 days after admission), CGM was performed for 2–4 days before discharge. During CGM, among the patients with type 2 diabetes, three patients were treated with diet only, 13 with oral hypoglycemic agents (OHA) (five with sulfonylurea, six with biguanide, eight with dipeptidyl peptidase-4 inhibitor, four with α-glucosidase inhibitor and one with thiazolidinedione: six with monotherapy, four with a combination of two OHAs and three with a combination of three or more OHAs), 40 with insulin ± OHA (27 with basal-bolus therapy, six with premixed insulin, four with preprandial insulin and three with basal insulin) and 12 with a glucagon-like peptide-1 (GLP-1) receptor agonist ± OHA (eight with monotherapy and four with a combination with sulfonylurea). All patients with type 1 diabetes were treated with insulin (19 with basal-bolus therapy and one with continuous subcutaneous insulin infusion (CSII)). Patients checked their blood glucose with a Medisafe Fit Pro blood glucose meter (Terumo Corporation, Tokyo, Japan) at least four times a day (pre-meal and bedtime) and entered the readings into the CGM monitor for calibration.

2.4. Glycemic indices based on CGM

After downloading the CGM data, mean glucose, SD of glucose (SDglu), time of glucose >180 mg/dl per 24 h (Tglu > 180), AUC of glucose >180 mg/dl per 24 h (AUCglu > 180), time of glucose <70 mg/dl per 24 h (Tglu < 70), and AUC of glucose <70 mg/dl per 24 h (AUCglu < 70) were calculated. In this study, hypoglycemia was defined as plasma glucose level <70 mg/dl [17]. In addition, hyperglycemic index, hypoglycemic index, index of glycemic control (ICG) [10], *J*-index [8], MODD [7], continuous overlapping net glycemic action 1 (CONGA1) [11], MAGE [6] and *M* value [9] were calculated as previously reported. *M* value was calculated as: $\sum|10 \times \log(GR_t/100)|^3/n$, where GR_t is the glucose reading at time *t*, and *n* is the number of observations.

2.5. Statistical analysis

The association between two variables was assessed with Spearman's correlation coefficient. Multivariate regression analysis was performed to adjust for other variables. Since the

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