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Original article

Strong correlation between glycaemic variability and total glucose exposure in type 2 diabetes is limited to subjects with satisfactory glycaemic control

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Abstract

Aims. – This study investigated the relationship between markers of overall glucose exposure, postprandial glucose excursions and glycaemic variability in patients with type 2 diabetes mellitus (T2DM).

Methods. – A total of 63 patients with T2DM (mean age 56 years) were enrolled. All wore a continuous glucose monitoring system (CGMS) device for 72 h to collect data on markers of overall glucose exposure, postprandial glucose excursions and glycaemic variability parameters.

Results. – Spearman's correlation analysis revealed significant correlations between all markers of overall glucose exposure and various parameters related to glucose excursions. The percent coefficient of variation (CV) showed the strongest correlation with glycated albumin ($r = 0.470$, $P < 0.01$). In participants with HbA_{1c} levels < 7.5% ($n = 33$), almost all glycaemic markers and glycaemic variability parameters were significantly correlated with each other. Also, all postprandial glucose excursion parameters showed significant correlation with other glycaemic markers, and all markers of overall glucose exposure were significantly related to mean glucose, postprandial glucose excursions and glycaemic variability parameters (except CV). In contrast, in participants with HbA_{1c} levels ≥ 7.5% ($n = 30$), no parameters of postprandial glucose excursions and glycaemic variability were related to any markers of chronic glycaemia.

Conclusion. – Postprandial glucose excursions may explain glycaemic variability and total glucose exposures in well-controlled T2DM patients.

Keywords: HbA_{1c}; Fructosamine; Glycated albumin; 1,5-Anhydroglucitol; Continuous glucose monitoring systems

1. Introduction

Diabetes is a growing global health problem [1]. In Korea, the prevalence of diabetes has increased and its complications have become a major cause of death [2]. Control of hyperglycaemia is crucial for reducing the microvascular and macrovascular complications associated with diabetes. Activation of oxidative stress is thought to play a major role in the pathogenesis of hyperglycaemia-induced vascular damage leading to vascular complications [3]. In particular, acute glucose fluctuations have been documented as having a greater triggering effect on oxidative stress than chronic sustained hyperglycaemia [4,5]. Furthermore, the Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe (DECODE) study showed that postprandial glucose is a more potent risk factor for cardiovascular events than fasting glucose [6]. The pathophysiological element underlying the importance of glucose variability is its relationship with oxidative stress, which is itself an important risk factor for the development of cardiovascular complications of diabetes [7]. Therefore, it can be assumed that control of glucose excursions is as important as lowering fasting glucose levels in diabetic patients.

Measurement of HbA_{1c} levels is the gold standard for assessing glycaemic control and has recently been recommended for use in the diagnosis of diabetes [8]. HbA_{1c} results from the glycation of haemoglobin in erythrocytes and is indicative of

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long-term (two to three months) glycaemia. Nevertheless, as HbA_{1c} is of limited value in reflecting glucose excursions [9], it is possible that other serum markers of glycaemia, such as fructosamine (FA), glycated albumin (GA) and 1,5-anhydroglucitol (1,5-AG), may have additional clinical value. Compared with HbA_{1c}, these serum markers may be more useful for providing information on short-term (two to four weeks) glycaemic control and glycaemic excursions, as well as for monitoring glycaemic control when interpretation of HbA_{1c} is difficult (for example, in the presence of haemoglobinopathy, iron deficiency and other anaemias) [9–11]. In addition, Selvin et al. [12] reported that, after adjusting for HbA_{1c}, GA and FA were strongly associated with microvascular complications. Glucose variability had been an emerging target in the treatment of diabetes [7] and the coefficient of variation (CV) reflects glycaemic variability very well, as it is less influenced by mean glucose levels [13]. Recently, DeVries [14] recommended CV as the preferred method for assessing glucose variability.

The continuous glucose monitoring system (CGMS) was developed to evaluate daily glucose profiles. Overall glucose control, glycaemic variability and hypoglycaemic events can be evaluated using CGMS data. Previously, it had been reported that three-day continuous glucose monitoring (CGM) is useful for rapidly assessing hypoglycaemic events and glycaemic variability in type 1 diabetes mellitus (T1DM) [15]. However, few studies have evaluated the correlation of glycaemic markers with glucose parameters assessed by CGMS. Therefore, the purpose of the present study was to investigate the relationship between markers of overall glucose exposure, postprandial glucose excursions and glycaemic variability in patients with type 2 diabetes mellitus (T2DM).

2. Methods

2.1. Participants

Patients were recruited consecutively from the outpatients' clinic of Samsung Medical Center in Seoul, Republic of Korea, where they had been treated for diabetes between December 2010 and October 2011. Of the 80 patients who had undergone CGM in addition to testing for all glycaemic markers, all hospitalised patients and patients with HbA_{1c} levels > 10% were excluded. Other exclusion criteria included having T1DM, severe medical illness (infection or inflammation), anaemia, renal failure (serum creatinine > 2.0 mg/dL), liver cirrhosis, thyroid disease (either hypothyroidism or hyperthyroidism), malignancy or pregnancy. Ultimately, 63 patients (36 males and 27 females) with T2DM were included in our study. The Institutional Review Board at Samsung Medical Center approved the study protocol (2010-11-036-002).

2.2. Measurements and data analysis

All participants wore a Gold^{TM} (Medtronic MiniMed, Northridge, CA, USA) CGMS device and were monitored for 78.4 ± 14.5 h consecutively for an average of 875 ± 112.4 readings after wearing the CGMS. During the study period, participants were asked to continue their usual glucose monitoring with a minimum of four capillary glucose readings per day. During the self-monitoring of blood glucose (SMBG) and CGMS periods, our study participants continued their usual therapy and were encouraged to maintain their usual lifestyle in terms of factors such as physical activity and diet. After the CGMS period, the recorded data were downloaded and analyzed by MiniMed Solutions software. Only data obtained during the middle 72 h of the study period were used for analysis, and the mean amplitude of glycaemic excursions (MAGE) was calculated using glucose values from only the middle 48 h of the CGMS data.

Mean glucose levels were measured to assess average glucose control. The area under the curve for glucose levels > 180 mg/dL (AUC_{-180}), the mean postprandial incremental area under the curve (AUC_{pp}) and mean postmeal maximum glucose (MPMG) were measured as parameters indicative of postprandial exposure to hyperglycaemia. Also determined were the incremental areas above preprandial glucose values (breakfast, lunch, dinner) in the 4-hour period starting from the beginning of each meal, using the trapezoidal rule [16]. The six incremental areas for each patient during 48 h of CGM were summed and averaged to calculate the AUC_{pp} [4]. In addition, to assess parameters of glucose variability, the standard deviation (SD), MAGE, continuous overall net glycaemic action (CONGA), mean of daily differences (MODD) and percent CV were also calculated from the CGMS data [17]. Glycaemic variability was expressed as the SD of the middle 72 h of readings during CGM as an absolute measure, even though the CV is a relative measure. CV (%) was calculated by dividing the SD by the mean of the corresponding glucose readings, while MAGE was determined by taking the arithmetic mean of blood glucose increases or decreases (from blood glucose nadirs to peaks or vice versa) when both ascending and descending changes exceeded 1 SD [18]. CONGA was calculated as the SD of the glycaemic differences between a specific point and the glucose level at exactly n h later [19]; MODD was obtained by taking the mean of the differences between the glycaemic gaps observed during the same time interval on two consecutive days [20]. MAGE and CONGA reflect same-day glucose variability, while MODD represents between-day glucose variability.

On the first day of wearing the CGMS device, levels of HbA_{1c}, FA, GA and 1,5-AG, reflecting chronic glucose exposure, were determined by the following methods. HbA_{1c} levels were measured by high-performance liquid chromatography (HPLC), using a VARIANT II TURBO analyzer (Bio-Rad Laboratories, Hercules, CA, USA). FA levels were determined using a colorimetric method (FRUC kit, Roche Diagnostics, Mannheim, Germany). The reference range for HbA_{1c} was between 4.0% and 6.0%, while that for FA was 205–285 μmol/L. Serum GA levels were measured by an enzymatic method using the Lucica GA-L kit (Asahi Kasei Pharma Corporation, Tokyo, Japan). Serum 1,5-AG levels were determined with an enzymatic method using pyranose oxidase, peroxidase and N-ethyl-N-(2-hydroxy-3-sulphopropyl)-3-methylaniline sodium dehydrate (Nippon Kayaku, Tokyo, Japan). The reference range for