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Relationship between daily and day-to-day glycemic variability and increased oxidative stress in type 2 diabetes

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ABSTRACT

Aims: To determine the association of daily and day-to-day glucose variability with oxidative stress.

Methods: This was a cross-sectional analysis of 68 patients with type 2 diabetes mellitus (T2DM) over 72 h of continuous glucose monitoring. Fasting plasma glucose (FPG) and hemoglobin A1c (HbA1c) were measured before breakfast on day 1. Glucose variability, mean glucose level (MGL), mean amplitude of glycemic excursions (MAGE), mean of daily differences (MODD) in glucose levels and area under the postprandial plasma glucose curve (AUC_{PP}) were measured on days 2 and 3. Plasma oxidant capacity against N,N-diethylpara phenylenediamine was measured with the diacron-reactive oxygen metabolites (d-ROMs) test on day 1.

Results: Overall, 66.2% males with the mean age of 63.2 ± 12.6 years, diabetes duration of 12.9 ± 10.4 years, and HbA1c level of 8.1 ± 1.6% (65 ± 17 mmol/mol) were included. MGL ($r = 0.330$), HbA1c ($r = 0.326$), MAGE ($r = 0.565$), MODD ($r = 0.488$), and AUC_{PP} ($r = 0.254$) exhibited significant correlations with d-ROMs and not FPG; these correlations remained significant after adjustment for clinical factors (sex, age, duration of diabetes, smoking habit, insulin use, statin use, angiotensin II receptor blocker use, BMI, LDL-C, HDL-C, TG, eGFR, and systolic blood pressure) ($R^2 = 0.268$, $R^2 = 0.268$, $R^2 = 0.417$, $R^2 = 0.314$, and $R^2 = 0.347$, respectively). MAGE was significantly correlated with MODD ($r = 0.708$) and MAGE and MODD were independently correlated with d-ROMs by multivariate analysis.

Conclusions: Therefore, oxidative stress is associated with daily and day-to-day glucose variability in patients with T2DM.

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1. Introduction

The United Kingdom Prospective Diabetes Study (UKPDS) demonstrated that chronic hyperglycemia, as measured by glycated hemoglobin (HbA1c), is the main risk factor for diabetes-related complications [1]. However, HbA1c does not inform us about short-term glycemic variability, which refers to swings in blood glucose levels throughout the day, including the possibilities of hypoglycemic and hyperglycemic periods within and between days. Recently, continuous glucose monitoring (CGM) has become increasingly relevant when evaluating such variability and can detect glucose variability in greater detail than conventional self-monitoring methods.

Various studies have been conducted on the relationship between glucose variability and diabetic complications. Postprandial plasma glucose (PPG) is more closely related to cardiovascular disease than fasting plasma glucose (FPG) [2], with glucose variability considered important in patients with type 2 diabetes mellitus (T2DM) [3]. In addition, FPG variability is reportedly associated with the 10-year survival of this patient group [4], with both intra-day glucose variability and HbA1c variability being independent risk factors for microangiopathy [5,6]. Therefore, glucose variability may be an additional risk factor for diabetic complications, independent of hyperglycemia [7]. On the other hand, HbA1c and mean blood glucose are related to cardiovascular disease in addition to PPG and glucose variability [8]. Furthermore, a decrease in glucose variability dose does not reduce the risk of cardiovascular disease in patients with T2DM after acute myocardial infarction [9]. Furthermore, HbA1c variability is not associated with microvascular complications in type 1 diabetes [10]. Based on the abovementioned findings, the relationship between glucose variability and diabetic complication is controversial.

Oxidative stress appears important in the development and progression of diabetic complications [11]. Hyperglycemic damage results from reactive oxygen species (ROS)-induced activation of polyol, hexosamine, protein kinase C, and the advanced glycation end-product pathway [12]. Because atherosclerosis can result when acute glucose variability induces endothelial dysfunction through oxidative stress [13], the activation of oxidative stress could be a risk factor for diabetic complications. There are various markers of oxidative stress [14], but 8-hydroxydeoxyguanosine (8-OHdG) and 8-iso-prostaglandin F2α (8-iso-PGF2α) are particularly useful in diabetes: 8-OHdG has often been used as a biomarker of oxidative DNA damage [15], whereas 8-iso-PGF2α is a major product of the peroxidation of unsaturated fatty acids and can predict oxidative stress [16].

Direct measurement of ROS and free radicals is difficult in a standard laboratory owing to their biochemical instability, which requires that the oxidation products of biological components be used as markers of oxidative stress. However, such assays are complex and unsuitable when analyzing a large number of subjects. Recently, a method of measuring reactive oxygen metabolites (ROMs) in the blood has been developed that uses diacron (i.e., the d-ROMs test) [17]. This photometric test measures the total oxidant capacity of serum or plasma against the chromogenic substrate N,N-diethylparaphenylenediamine. ROMs mainly comprise organic hydroperoxide; despite its moderate oxidative power, serum levels are detectable because of its relative stability compared with other free radicals. Not only is the d-ROMs test quick and inexpensive for use in clinical settings, it is also predictive of morbidity and mortality [18,19]. Moreover, the test correlates positively with plasma glucose and HbA1c levels [20], and levels reduce after antioxidant supplementation in patients with T2DM [21].

Therefore, we aimed to determine whether daily and day-to-day glucose variability measured by CGM were associated with plasma oxidative stress measured by d-ROMs in patients with T2DM.

2. Subjects, materials and methods

2.1. Subjects

We recruited 68 patients (45 inpatients and 23 outpatients) with T2DM among those treated at Showa University Hospital (from October 2013 to May 2015) and Nippon Medical School (from March 2012 to December 2012). The reasons for hospital admission were to achieve glycemic control because of poor control or to evaluate for glucose variability. The inclusion criteria were a diagnosis of T2DM and stable oral hypoglycemic and/or insulin treatment, both for $\geqslant$3 months before the study. The exclusion criteria were the use of steroids or anti-inflammatory drugs, any febrile illnesses within 3 months before the study, and an estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2 according to the Cockcroft–Gault formula [22].

2.2. Study design

This was a cross-sectional analysis of patients with T2DM over a 72-h period of (CGM).

The following clinical and laboratory parameters were measured before breakfast on day 1: body mass index, low-density lipoprotein cholesterol (LDLc), high-density lipoprotein cholesterol (HDLc), triglycerides, eGFR, blood pressure, FPG, and HbA1c. Plasma oxidant capacity against N,N-diethyl paraphenylenediamine was also measured using the d-ROMs test on day 1. Glucose variability, mean glucose level (MGL), mean amplitude of glycemic excursions (MAGE), mean of daily differences (MODD) in glucose levels, and area under the PPG curve (AUC_{PP}) were measured on days 2 and 3. Clinical data (age, sex, smoking, and duration of diabetes in years) were retrieved from medical records.

The study protocol was approved by the ethics committee of the Showa University School of Medicine. Informed consent was obtained from all subjects after receiving a clear explanation of the study protocol. The study was designed in compliance with the Declaration of Helsinki.

2.3. Procedures and measurements

The CGM sensor (CGMS System Gold; Medtronic MiniMed, Northridge, CA, USA or ipro2; Medtronic MiniMed, Northridge, CA) was inserted subcutaneously on day 1 and removed on

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