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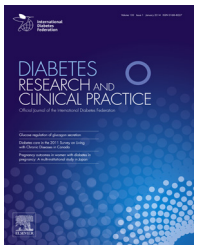

Coefficient of variation of R-R interval closely correlates with glycemic variability assessed by continuous glucose monitoring in insulin-depleted patients with type 1 diabetes

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ABSTRACT

Aims: In type 1 diabetic patients, insulin secretory capacity, meals and physical activity correlate with glycemic variability. Autonomic function associated with gastrointestinal motility and counterregulatory hormone secretion is another candidate which correlates with glucose variability. The aim of this study is to clarify a new clinical parameter associated with glycemic variability in insulin-depleted patients with type 1 diabetes.

Methods: We studied 31 inpatients with type 1 diabetes. We evaluated glycemic variability calculated by continuous glucose monitoring, clinical parameters and the coefficient of variation of R-R interval (CVR-R). Glycemic variability was also assessed during the daytime and nighttime.

Results: The CVR-R showed a significant negative correlation with the whole-day standard deviation (SD) ($r = -0.50$, $p = 0.007$), mean amplitude of glycemic excursions (MAGE) ($r = -0.47$, $p = 0.011$), M-value ($r = -0.38$, $p = 0.048$) and mean of daily differences (MODD) ($r = -0.59$, $p = 0.001$). The CVR-R also showed a significant negative correlation with the nighttime SD ($r = -0.59$, $p = 0.001$), MAGE ($r = -0.47$, $p = 0.011$), M-value ($r = -0.53$, $p = 0.004$) and MODD ($r = -0.65$, $p = 0.0003$). And furthermore, the CVR-R also showed a significant negative correlation with the daytime SD ($r = -0.44$, $p = 0.019$) and MAGE ($r = -0.50$, $p = 0.006$), but not with the daytime M-value or MODD. The nighttime SD was significantly higher in patients with diabetic polyneuropathy than in patients without it ($p = 0.016$), while the CVR-R was significantly lower in patients with polyneuropathy than in patients without it ($p = 0.009$).

Conclusions: CVR-R is closely correlated with glycemic variability, especially during nighttime, in insulin-depleted patients with type 1 diabetes. Measuring CVR-R may help us to presume the degree of glycemic variability in those patients.

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1. Introduction

Type 1 diabetes is characterized by insulin deficiency due to the loss of pancreatic beta-cells [1]. This type of diabetes is also characterized by high variability in blood glucose [2,3]. Patients with variable blood glucose readings during routine self-monitoring are at a high risk for severe hypoglycemia [4]. Patients with diabetic microvascular complications also have high glucose variability [5]. Coronary artery calcification, a predictor of coronary events [6], is associated with glucose variability in men with type 1 diabetes [7]. Thus, it is important to clarify clinical parameters that predict glycemic variability.

Insulin secretory capacity, meals and physical activity are associated with glycemic variability [8–12]. The increment of serum C-peptide (CPR) by an intravenous glucagon stimulation test negatively correlates with the standard deviation (SD) of fasting plasma glucose levels [8]. Patients with low endogenous insulin secretion have a lower *M*-value of glucose levels compared with insulin-depleted patients [9]. Blood glucose levels after a low-glycemic-index meal were significantly lower than after a high-glycemic-index meal [10]. The quantity of carbohydrate in a meal positively correlates with glycemic variability, including the mean amplitude of glycemic excursions (MAGE) and the SD, as assessed by continuous blood glucose monitoring (CGM) [11]. Post-meal physical activity decreases postprandial glucose levels and improves postprandial glycemic variability compared with post-meal inactivity [12]. All of these factors correlate with glycemic variability in insulin-depleted patients with established type 1 diabetes [1].

Autonomic dysfunction is also a candidate for predicting glycemic variability because it is associated with gastrointestinal motility [12] and counterregulatory hormone secretion [13], both of which correlate with glucose variability [14–16]. The coefficient of variation of the R-R interval (CVR-R) calculated from electrocardiographs is one of the clinical parameters representing autonomic function that are easily and quantitatively evaluated [17]. CVR-R is associated with both parasympathetic and sympathetic nervous system functions [18]. Based on these facts, we aimed to identify any additional clinical parameters associated with glycemic variability, paying particular attention to autonomic function in insulin-depleted patients with established type 1 diabetes.

2. Materials and methods

2.1. Subjects

We studied 31 inpatients (13 males and 18 females) with type 1 diabetes at Osaka University hospital between April 2010 and November 2013. Type 1 diabetes was diagnosed according to the criteria of the Japan Diabetes Society [19].

The patients displayed the following characteristics (mean ± SD): 47.2 ± 16.4 years of age, 18.6 ± 12.8 years duration of the disease, 22.4 ± 3.7 kg/m^2 body mass index (BMI), and 8.0 ± 1.5% (63 ± 17 mmol/mol) hemoglobin A1c (HbA1c). The fasting CPR levels, evaluated by CLEIA, were <0.03 nmol/l (0.1 ng/ml) in 28 patients, 0.1 nmol/l (0.3 ng/ml) in one patient and 0.07 nmol/l (0.2 ng/ml) in two patients. Multiple daily insulin injections (MDI) were provided to 20 patients, and continuous subcutaneous insulin infusion (CSII) was used to treat 11 patients. During CGM, the basal insulin dosage remained constant in 27 patients, decreased in three patients because of hypoglycemia, and increased in one patient because of hyperglycemia. According to their urinary albumin/creatinine ratio (ACR), the subjects were classified into the following three groups of diabetic nephropathy: normoalbuminuria (ACR < 30 mg/g creatinine), microalbuminuria (30 ≤ ACR < 300 mg/g creatinine) and macroalbuminuria (300 mg/g creatinine ≤ ACR). Ophthalmologists assessed the presence of retinopathy through a dilated eye exam. Seventeen patients were classified as having no evidence of diabetic retinopathy (NDR), three patients had simple diabetic retinopathy (SDR), one patient had pre-proliferative retinopathy (pre-PDR), and ten patients had proliferative diabetic retinopathy (PDR) (Table 1). Diabetic polyneuropathy was assessed according to the criteria of the Diabetic Neuropathy Study Group in Japan [20] and was positive for 13 patients. Five patients were treated for hypertension with angiotensin-converting enzyme (ACE) inhibitor or beta blocker, which could affect autonomic function [21,22]. One patient had a history of angina pectoris, and another had that of silent myocardial ischemia. Twelve patients were aware of hypoglycemia, while remaining 19 patients were unaware of it (Table 1).

2.2. Methods

This study was performed in hospitalized patients. Patients woke up at approximately 7:00 and went to bed at approximately 22:00. Alcohol drinking and smoking, which could

Table 1 – Clinical characteristics of the patients.

Characteristics	Patients
Sex (M/F) (*n*)	13/18
Age (years)	47.2 ± 16.4
Body-mass index (kg/m^2)	22.4 ± 3.7
Duration of diabetes (years)	18.6 ± 12.8
HbA1c (%) (mmol/mol)	8.0 ± 1.5 (63 ± 17)
Fasting serum C-peptide (nmol/l) (*n*)	<0.03 (28), 0.07 (2), 0.1 (1)
Coefficient variation of R-R interval (%) (*n*)	2.96 ± 1.70 (28)
Schellong test (negative/positive) (*n*)	17/6
MDI/CSII (*n*)	20/11
Nephropathy (normoalbuminuria/microalbuminuria/macroalbuminuria) (*n*)	23/1/7
Retinopathy (NDR/SDR/Pre-PDR/PDR) (*n*)	17/3/1/10
Neuropathy (negative/positive) (*n*)	18/13
Hypoglycemia (unaware/aware) (*n*)	19/12
Cardiovascular complications* (none/AP/SMI) (*n*)	29/1/1

Data are means ± standard deviation. MDI, multiple daily insulin injection; CSII, continuous subcutaneous insulin injection; NDR, no evidence of diabetic retinopathy; SDR, simple diabetic retinopathy; Pre-PDR, pre-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy.
* AP, angina pectoris; SMI, silent myocardial ischemia.

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