Association Between Diabetic Microangiopathies and Glycemic Variability Assessed by Continuous Glucose Monitoring

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Abstract: The aim of this retrospective study was to elucidate the association between glucose profile using the continuous glucose monitoring system (CGMS) and microvascular complications in patients with type 2 diabetes mellitus (T2DM). The subjects were 160 inpatients with T2DM. The mean blood glucose (MBG) level, percentage of time in a 24-hour period spent with blood glucose level higher than 180 mg/dl (time at >180 mg/dl), standard deviation (SD), and mean amplitude of glycemic excursions (MAGE) were measured continuously over 48 hours using the CGMS. The primary outcome was the association between microvascular complications and glycemic variability. The secondary outcome was the association between microangiopathies and MBG. The SD and MAGE were not associated with presence of microangiopathies or number of complications. There were also no associations between abnormal vibratory sensation in the bilateral lower extremities, coefficient of variation of the R-R interval (CVRR), retinopathy stage, nephropathy stage, or microalbuminuria. MBG was associated, however, with retinopathy, retinopathy stage, and number of complications. Time at >180 mg/dl correlated with abnormal vibratory sensation in the bilateral lower extremities and presence or stage of retinopathy. MBG and time at >180 mg/dl were not associated with presence or stage of nephropathy. Our findings suggest that broad glycemic variability was not associated with microvascular complications, the number of which increased in patients with a high mean glucose level and long time spent with hyperglycemia. It is important, therefore, to reduce the mean glucose level and time spent with hyperglycemia to prevent future microangiopathies.

Keywords: microvascular complications, continuous glucose monitoring, fluctuations in glucose levels.

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cannot be reduced by strict treatment aimed only at improving HbA1c levels [5, 6], and strategies to control hypoglycemia and postprandial hyperglycemia [7, 8] must be implemented.

We reported previously that dysfunction of the vascular endothelium, which plays a key role in the onset and progression of arteriosclerosis, is associated with fluctuations in blood glucose levels [9], and the importance of treatment to reduce this condition has been recognized in recent years. It is not clear at this stage, however, whether microvascular complications are associated with glycemic variability, and to our knowledge, there is no information on this relationship based on the use of the continuous glucose monitoring (CGM) system.

The purpose of this retrospective study was to determine the associations among various diabetic microangiopathies, glycemic variability, and mean blood glucose level in patients with type 2 diabetes mellitus (T2DM).

**Materials and Methods**

**Patients and continuous glucose monitoring data**

We identified patients with T2DM who had been hospitalized at the Hospital of the University of Occupational and Environmental Health, Japan (or one of its affiliated hospitals) between April 2010 and April 2013 and who had worn the CGM system (CGMS® System Gold™, Medtronic Inc., Minneapolis, MN) for ≥48 hours during 7 days of hospitalization while continuing to receive the medications administered on admission. Patients receiving oral steroids, those whose treatment regimens were changed in the interval between their admission and the start of wearing the CGMS device, and patients with infections were excluded. Data on microvascular complications were collected from physical examination findings on admission and from laboratory test results, as reported in the medical charts. The CGM data collected on days 2 and 3 of monitoring were analyzed. Specifically, we analyzed the mean blood glucose level (MBG), percent time (during the 24 hours) with blood glucose level >180 mg/dl (time at >180 mg/dl), standard deviation (SD) for blood glucose, and the mean amplitude of glycemic excursions (MAGE). The mean values on days 2 and 3 were used for reporting the MBG level, time at >180 mg/dl, and the SD, and for calculation of the MAGE.

**Outcome measures for complications**

The attending physicians performed neurologic examinations and confirmed the diagnosis of peripheral neuropathy in accordance with the diagnostic criteria for diabetic polyneuropathy. The vibratory sensation in both legs was examined using a C64 tuning fork for quantitative assessment of peripheral neuropathy. The diagnosis of autonomic neuropathy was confirmed by assessing the presence of clinical signs and by the coefficient of variation of the R-R interval (CVRR, %). The CVRR (%) on a 3-minute electrocardiogram at rest was used for quantitative assessment of autonomic neuropathy. Retinopathy was diagnosed as present or absent on the basis of clinical signs; its stage (normal diabetic retinopathy, simple diabetic retinopathy, preproliferative diabetic retinopathy, or proliferative diabetic retinopathy) was determined from features found at the fundus on ophthalmic examination [10]. Nephropathy was identified as present or absent and its stage was determined according to urinary albumin and estimated glomerular filtration rate (eGFR).

The primary endpoint was the associations among microvascular complications and glycemic variability. The secondary endpoint was the associations among microvascular complications and the MBG level.

**Measurement of biochemical variables**

HbA1c (%) was measured by high-performance liquid chromatography (HLC-723 G8, Tosoh Co., Kyoto, Japan). We used the HbA1c values defined by the National Glycohemoglobin Standardization Program (NGSP), which are calculated by the addition of 0.4% to the HbA1c values, as defined by the Japan Diabetes Society [11]. LDL cholesterol was measured by the selective solubilization method. Urine C-peptide was measured by electrochemiluminescence immunoassay (Kyurin Medical Laboratory, Fukuoka, Japan), and urinary albumin was measured by immunoturbidimetry (SRL Tokyo Laboratories, Inc., Tokyo, Japan). The following formulae were used to calculate eGFR in men and women, respectively: 194 × serum creatinine$^{-1.094} \times \text{age}^{-0.287}$ and 194 × serum creatinine$^{-1.094} \times \text{age}^{-0.287} \times 0.739$. 


Statistical analysis and ethical considerations

Data are expressed as mean ± SD. The SD, MAGE, the MBG level, time at >180 mg/dl, and respective outcome measures for microvascular complications were compared by Pearson’s test, Spearman’s test, the Mann-Whitney test, and the Kruskal-Wallis test. Statistical analysis was performed by SPSS Statistics version 21 software (IBM Corp., Armonk, NY). A P value < 0.05 was considered statistically significant.

The study protocol was approved by the ethics committees of the University of Occupational and Environmental Health and the participating medical centers. Informed consent was obtained from all of the subjects.

Results

Patient demographics

A total of 160 patients were recruited, with a 3:2 male:female ratio. The mean age of the patients was 61.4 ± 14.7 years, the mean duration of diabetes mellitus was 11.4 ± 10.0 years, the mean HbA1c was 8.7% ± 1.6%, and the mean fasting blood glucose was 160.1 ± 47.1 mg/dl (Table 1). On admission, 133 (83.1%) patients were on monotherapy with an oral glucose-lowering drug, insulin preparation, or glucagon-like peptide-1 mimetic. The CGM data showed that the MBG level was 166.0 ± 41.7 mg/dl and the time at >180 mg/dl was 32.9 ± 27.7%, indicating that patients had high levels of blood glucose for at least 30% of the day. The SD was 39.1 ± 14.1 mg/dl and the MAGE was 116.2 ± 39.8 mg/dl, indicating wide fluctuations in blood glucose.

The microvascular complications are shown in Table 2. Only 48 (30%) of the patients had no complications while 112 (70%) had at least one microvascular complication. Peripheral neuropathy was documented in 103 patients (64.4%), autonomic neuropathy in 53 (33.1%), retinopathy in 49 (30.6%), and nephropathy in 26 patients (16.3%).

Table 1. Patient characteristics

| Table 1. Patient characteristics |     |
|----------------------------------|-----|
| Sex, male/female n               | 94/66 |
| Age years                        | 61.4 ± 14.7 |
| Body mass index kg/m²             | 25.9 ± 4.8 |
| Duration of diabetes years       | 11.4 ± 10.0 |
| Diabetes therapy                 |     |
| Diet only n (%)                  | 27 (16.9) |
| Sulfonylurea n (%)               | 30 (18.8) |
| Glimeide n (%)                   | 1 (0.6) |
| Dipeptidyl peptidase-4 inhibitor n (%) | 64 (40.0) |
| a-glucosidase inhibitor n (%)    | 15 (3.8) |
| Pioglitazone n (%)               | 23 (14.4) |
| Metformin n (%)                  | 34 (21.3) |
| Insulin n (%)                    | 31 (19.4) |
| Glucagon like peptide-1 receptor agonist n (%) | 2 (1.3) |
| Urinary C-peptide μg/day         | 79.6 ± 59.5 |
| Systolic blood pressure mmHg     | 136.1 ± 22.1 |
| Antihypertensive therapy n (%)   | 78 (48.8) |
| eGFR ml/min/1.73 m²              | 76.2 ± 28.8 |
| Low-density lipoprotein mg/dl    | 117.9 ± 37.6 |
| HbA1c (%)                        | 8.7 ± 1.6 |
| Fasting plasma glucose mg/dl     | 160.1 ± 47.1 |
| MBG [mg/dl]³                    | 166.0 ± 41.7 |
| Time at >180 mg/ml [%]           | 32.9 ± 27.7% |
| SD [mg/dl]¹                     | 39.1 ± 14.1 |
| MAGE [mg/dl]¹                   | 116.2 ± 39.8 |

Data are mean ± SD, n, or n (%). [Measured using the continuous glucose monitoring system]. HbA1c: glycated hemoglobin, eGFR: estimated glomerular filtration rate, MBG: mean blood glucose, SD: standard deviation, MAGE: mean amplitude of glycemic excursion

Table 2. Diabetic complications

| Table 2. Diabetic complications |     |
|---------------------------------|-----|
| Peripheral neuropathy (+/-/unknown) | 103 (64.4)/56 (35.0)/1 (0.6) |
| Vibration sense                 | 4 ± 1.5 |
| Stage 1                         | 103 (64.4) |
| Stage 2                         | 49 (30.6) |
| Stage 3                         | 109 (68.1) |
| Stage 4                         | 26 (16.3) |
| Stage 5                         | 21 (13.1) |
| Microalbuminuria (mg/g Cre)     | 62.8 ± 157.6 |

Data are mean ± SD, n, or n (%), CVRR: coefficient of variation of the R-R interval, NDR: non-diabetic retinopathy, SDR: simple diabetic retinopathy, PPDR: pre-proliferative diabetic retinopathy, PDR: proliferative diabetic retinopathy
Association between complications and continuous glucose monitoring data

Abnormal vibratory sensation in the legs correlated significantly with the MBG level and time at >180 mg/dl, but not with SD and MAGE. The presence or absence of retinopathy and its severity were not associated with SD or MAGE, but were significantly associated with the MBG level and time at >180 mg/dl. The stages of retinopathy and urinary albumin levels showed no association with SD, MAGE, the MBG level, or time at >180 mg/dl. The number of microangiopathies was not associated with SD, MAGE, or time at >180 mg/dl, but was significantly associated with the MBG level (Table 3).

Discussion

This study showed that the SD and MAGE, which are two CGM markers of glycemic variability, were not associated with neuropathy, retinopathy, presence/absence of nephropathy, number of microvascular complications, vibratory sensation in the legs (as a clinical indicator of peripheral neuropathy), CVRR% (as a clinical indicator of autonomic neuropathy), stages of retinopathy and nephropathy, or urinary albumin levels (as an indicator of nephropathy).

Our finding of no significant association between the blood glucose profile on CGMS and neuropathy is consistent with that reported in a previous study from the Diabetes Control and Complications Trial [12]. However, one study demonstrated significantly high values of SD and MAGE in patients with T2DM and HbA1c < 7% who presented with peripheral diabetic neuropathy [13]. The mean HbA1c in our study was 8.7%, which was higher than that in the above study, and may explain our different findings. Therefore, there may be an association between blood glucose profile and diabetic neuropathy in patients with HbA1c < 7% and well-controlled blood glucose levels. Regarding the association between blood glucose profile and retinopathy or nephropathy, our findings using the CGM system are consistent with those of previous studies reporting that the SD and MAGE obtained by self-measurement of blood glucose do not affect the onset/progression of retinopathy or nephropathy [14, 15].

On the other hand, the MBG level measured by the CGM system was associated with retinopathy and the number of microvascular complications, but not with nephropathy. The time at >180 mg/dl (representing long duration at high blood glucose levels) correlated with indexes of peripheral neuropathy and retinopathy, but not with nephropathy. These results are consistent with those of previous studies showing that improvement in HbA1c level (an indicator of chronic hyperglycemia) contributed to significant suppression of the onset/progression of microvascular complications of diabetes mellitus [1-5], although in our study the MBG level and time at >180 mg/dl were not associated with nephropathy. These results are different from those reported by Katayama et al. [16] for neuropathy and retinopathy in the Japan Diabetes Complications

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Table 3. Association between complications and continuous glucose monitoring data

| Variable                  | MBG    | Time at >180 mg/dl | SD       | MAGE     |
|---------------------------|--------|--------------------|----------|----------|
|                           | \( r \) | \( p \)            | \( r \)  | \( p \)  | \( r \)  | \( p \)  |
| Vibration                 | -0.165 | 0.047*             | -0.165  | 0.049*   | -0.180  | 0.225   | -0.152  | 0.221   |
| CVRR                      | -0.161 | 0.047*             | -0.135  | 0.096    | -0.029  | 0.723   | 0.018   | 0.822   |
| Diabetic retinopathy      | -0.186 | 0.027*             | -0.168  | 0.036*   | -0.108  | 0.178   | -0.077  | 0.333   |
| Stage of diabetic retinopathy | 0.202  | 0.027*             | 0.183   | 0.031*   | 0.038   | 0.076   | 0.117   | 0.115   |
| Stage of nephropathy      | 0.021  | 0.965              | 0.033   | 0.694    | 0.068   | 0.913   | 0.033   | 0.802   |
| Microalbuminuria          | 0.090  | 0.282              | 0.097   | 0.244    | 0.056   | 0.504   | 0.035   | 0.671   |
| Number of microangiopathies | 0.108  | 0.040*             | 0.114   | 0.088    | 0.107   | 0.493   | 0.070   | 0.712   |

Data are \( P \)-value by Pearson correlation analysis for normally distributed variables and Spearman rank correlation for variables with skewed distribution patterns; categorical values were tested by Mann-Whitney \( U \) test and Kruskal-Wallis test. \(^*\): \( P < 0.05 \), MBG: mean blood glucose, SD: standard deviation, MAGE: mean amplitude of glycemic excursion, CVRR: coefficient of variation of the R-R interval.
Study, where factors other than blood glucose (e.g., microalbuminuria, hypertension, and smoking) were associated with the onset and progression of nephropathy. It has also been reported previously that inhibitors of the renin-angiotensin system can suppress the onset of diabetic nephropathy independent of their glucose-lowering effects [17,18]. In our study, the MBG level and time at >180 mg/dl were not associated with the presence/absence of nephropathy or its stages. One possible reason for this finding is that patients with hypertension as comorbidity, smokers, and those treated with a renin-angiotensin system inhibitor were not excluded from our study, because the study was designed to include patients similar to those seen in routine clinical practice. Further study excluding such patients is needed to investigate the direct association between nephropathy and blood glucose profile on CGM.

The clinical data presented in this study showed that oral glucose-lowering agents, insulin preparations, and glucagon-like peptide-1 mimetics were used in 83.1% of subjects, antihyperlipidemic drugs in 41.9%, and antihypertensive drugs in 48.8%. Accordingly, we cannot exclude the direct effect of these drugs on the microvascular complications reported in this study. Previous animal studies showed that exendin-4 improves the function of the nervous system [19] and that vildagliptin inhibits the onset and progression of peripheral neuropathy [20]. Other studies also reported a low risk of peripheral neuropathy in patients taking statins [21] and that hypertension is a risk factor for peripheral neuropathy [22, 23]. There is some evidence from research in animals that the initial changes seen in retinopathy improve following injection of exendin-4 into the vitreous body [24]. Furthermore, the risk of diabetic retinopathy is reportedly very low in patients taking statins [21], hypertension is a risk factor for retinopathy [22, 23], antihypertensive therapy protects against progression of retinopathy [25], and retinopathy can be suppressed or alleviated by angiotensin-converting inhibitors or angiotensin receptor blockers [26, 27]. With regard to nephropathy, there is some evidence that angiotensin receptor blockers may suppress the onset of microalbuminuria [28] and that Dipeptidyl peptidase-4 inhibitors can alleviate it [29, 30]. Another study showed that increased risk of complications in patients with diabetes mellitus correlated with increased blood pressure and that lowering blood pressure reduced this risk [31]. Accordingly, future research should include patients not receiving drug therapy.

To our knowledge, there are no previous studies that investigated the association between the number of microvascular complications and glycemic variability or mean blood glucose levels obtained by CGM. This is the first study to investigate such associations. Our findings suggest that microangiopathies are not associated with broad glycemic variability, but are associated with higher mean blood glucose levels and longer time spent at these high levels. As in previous studies, prevention of the onset and/or progression of microvascular complications and treatment to reduce mean blood glucose levels and shorten the duration of high glucose levels are essential.

This study has several limitations. Our present study was retrospective and cross-sectional in nature and based on a review of medical charts, and thus caution should be exercised when interpreting the results. Moreover, this study targets inpatients. Because they ate meals of calorie setting from their ideal weight, the difference in the blood glucose by quantification of meals became small, but we cannot evaluate blood glucose profiles in real life. The complications of diabetes mellitus usually develop several years after the onset of the disease; therefore, long-term blood glucose profiles and mean blood glucose levels are considered unlikely to be evaluable by continuous blood glucose monitoring. Additionally, the duration of diabetes was possibly different from the period after the onset of diabetes because it was determined based on medical history recalled by the patients. Further prospective and longitudinal studies to verify the results of this study are needed.

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Conflicts of interest

The authors declare no conflict of interest.
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Continuous Glucose Monitoring (CGM) を用いた 2型糖尿病患者の糖尿病細小血管合併症と血糖変動との関連

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要   旨: 入院中の 2型糖尿病患者で continuous glucose monitoring (CGM) による血糖変動および平均血糖と各種細小血管合併症との関連について検討した。CGM データより平均血糖, 血糖 180 mg/dl 以上の時間の割合 (Time at >180), 血糖変動 (SD: standard deviation) を測定し, 平均血糖幅 (MAGE: mean amplitude of glycemic excursions) を算出し, 細小血管合併症は入院時の身体所見と検査所見で評価した。SD と MAGE は, 細小血管合併症の存在や合併数と関連せず, 下肢振動覚低下, coefficient of variation of the R-R interval (CVR-R), 網膜症の病期, 腎症の病期, 尿中微量アルブミンのいずれとも関連していなかった。しかし, 平均血糖は網膜症の有無および病期, 細小血管合併症の合併数と相関していた。さらに, 高血糖の持続時間を示す Time at >180 は下肢振動覚低下, 網膜症の有無および病期と相関していた。平均血糖や Time at >180 は腎症の有無および病期と関連していなかった。本研究の結果からは, 血糖変動が大きいという指標が多彩な細小血管合併症と関連することなく, 平均血糖が高く高血糖持続時間が長いほど, 細小血管合併症を合併することが示唆された。やはり, 細小血管合併症の発症・進展の予防のためには, 従来から報告されている通り, 平均血糖・高血糖持続時間を小さくする治療が重要である。

キーワード: 細小血管合併症, 持続血糖モニタリング, 血糖変動。

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