Relationships between time in range, glycemic variability including hypoglycemia and types of diabetes therapy in Japanese patients with type 2 diabetes mellitus: Hyogo Diabetes Hypoglycemia Cognition Complications study

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ABSTRACT
Aims/Introduction: Continuous glucose monitoring (CGM) metrics, such as times in range (TIR) and time below range, have been shown to be useful as clinical targets that complement glycated hemoglobin (HbA1c) for patients with type 2 diabetes mellitus. We investigated the relationships between TIR, glycemic variability and patient characteristics in patients with type 2 diabetes mellitus.

Materials and Methods: We carried out continuous glucose monitoring in 281 outpatients with type 2 diabetes mellitus who participated in a multicenter cohort (Hyogo Diabetes Hypoglycemia Cognition Complications) study.

Results: The results are shown as the median (interquartile range). The age, disease duration and HbA1c were 68 years (62–71 years), 13 years (7–23 years) and 6.9% (6.5–7.5%), respectively. TIR and standard deviation obtained by continuous glucose monitoring worsened significantly with increasing disease duration. Multiple regression analyses showed that disease duration (standard partial regression coefficient, β = -0.160, P = 0.003), diabetic peripheral neuropathy (β = -0.106, P = 0.033) and urinary albumin excretion (β = -0.100, P = 0.043) were useful explanatory factors for TIR. In contrast, HbA1c (β = -0.398, P < 0.001) and the use of antidiabetic drugs potentially associated with severe hypoglycemia (β = 0.180, P = 0.028), such as sulfonylureas, glinides and insulin, were useful explanatory factors for time below range in the elderly patients with type 2 diabetes mellitus.

Conclusions: The results of this study suggest that disease duration and diabetic complications are associated with TIR deterioration. In addition, low HbA1c levels and the use of antidiabetic drugs potentially associated with severe hypoglycemia might worsen the time below range in the elderly.

INTRODUCTION
The purpose of diabetes treatment is to maintain good glycemic control from the early stage of diabetes, and to prevent the
onset and progression of diabetic microvascular complications and arteriosclerotic diseases. In fact, the UK Prospective Diabetes Study showed that strict glycemic control can reduce diabetic complications. However, it has been reported that strict glycemic control using sulfonylureas (SU) and insulin-based regimens does not lead to suppression of cardiovascular disease, but rather, increases the risk, such as severe hypoglycemia and weight gain. Severe hypoglycemia has been shown to be associated with all-cause mortality, cardiovascular events and dementia. Therefore, it is important to control blood glucose while avoiding severe hypoglycemia.

Today, global recommendations focus on setting glycemic targets for each patient in order to effectively manage glycemic control while avoiding hypoglycemia. The number of elderly patients with diabetes is increasing in Japan due to aging. The Japan Diabetes Society (JDS)/Japan Geriatrics Society (JGS) Joint Committee on Improving Care for Elderly Patients with Diabetes has established a consensus statement for glycemic targets in the elderly. This consensus recommended that glycemic targets should be determined for each elderly patient in consideration of age, as well as disease duration, diabetic complications, risk of hypoglycemia and so on. However, due to the characteristics of Japanese individuals with low endogenous insulin secretion ability, there are many cases in which medications with a high risk of hypoglycemia, such as SU, glinides and insulin, are required.

Taking advantage of the availability of continuous glucose monitoring (CGM), this study aimed to investigate the mutual relationships between the duration of diabetes and types of diabetes therapy and the status of glycemic control in Japanese patients with type 2 diabetes mellitus. This study also aimed to investigate the current status of glycemic control and glycemic variability (GV) indices obtained by CGM after the development and implementation of the JDS/JGS Joint Committee’s consensus.

METHODS
Participants
This study is a part of a multicenter, prospective, cohort study (Hyogo Diabetes Hypoglycemia Cognition Complications [HDHCC] study), which aimed to investigate the relationship between GV indices and diabetic complications in patients who visited outpatient clinics specializing in diabetes in Japan. This study included patients with type 2 diabetes mellitus, aged between 40 and 75 years, who regularly visited outpatient hospitals or clinics. The exclusion criteria were as follows: (i) patients unable to regularly visit a hospital or clinic; (ii) those with type 1 diabetes; (iii) those diagnosed with dementia; (iv) those with severe hepatic and/or renal dysfunction; (v) those with cancer; and (vi) those deemed ineligible for this study by their physician. Among 300 eligible patients enrolled in the study between May 2018 and March 2020, 281 patients were analyzed after exclusion of 19 patients with missing CGM or blood examination data.

This study was carried out in compliance with the guidelines for the Declaration of Helsinki. This study was approved by the ethics committee of Hyogo Medical University Hospital and the ethics review committee of each participating institution (Approval No. 0390). All participants provided informed consent and signed informed consent forms.

CGM
CGM was carried out using FreeStyle Libre Pro® (Abbott Japan, Tokyo, Japan). Sensor glucose (SG) data were basically collected over a 10-day period (≥70% of 14-day CGM data). As previously reported, mean SG, standard deviation (SD), coefficient of variation (CV), ratio of SG levels between 70 mg/dL and 180 mg/dL (time in range [TIR]), ratio of SG levels >180 mg/dL (time above range [TAR]), ratio of SG levels >250 mg/dL (TAR), ratio of SG levels <70 mg/dL (time below range [TBR]), ratio of SG levels <54 mg/dL (TBR), high blood glucose index and low blood glucose index (LBGI) were calculated.

Glycated hemoglobin, patients’ backgrounds and types of diabetes therapy
Glycated hemoglobin (HbA1c), estimated glomerular filtration rate (eGFR), urine albumin-to-creatinine ratio (UACR) and body mass index (BMI) were investigated at the time of attaching the CGM device. Information regarding the disease duration and medication administered were obtained from the attending physician or the patients’ medical records. Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg or treatment for hypertension. We defined dyslipidemia as the presence of low-density lipoprotein cholesterol ≥140 mg/dL, high-density lipoprotein cholesterol ≤40 mg/dL, triglyceride level ≥150 mg/dL or treatment for dyslipidemia.

The simplified diagnostic criteria of the Japanese Study Group of Diabetes Neuropathy described in the guidelines of the JDS were used for the evaluation of diabetic peripheral neuropathy (DPN). Specifically, the following two items were considered essential: (i) the presence of diabetes; (ii) the absence of peripheral neuropathy other than DPN; and a diagnosis of DPN was made when two or more of the following three items were satisfied: (i) subjective symptoms thought to be based on DPN; (ii) decrease or disappearance of bilateral Achilles tendon reflexes; and (iii) decreased vibration sense of bilateral medial malleolus. Abnormalities in at least one test (conduction velocity, amplitude and latency) in two or more nerves in nerve conduction tests were also considered as DPN. The assessment of DPN was carried out by the attending physician within 3 months of the time of wearing the CGM. The presence or absence of diabetic retinopathy (DR) was determined based on ophthalmologist records within 1 year from the time of CGM use. In the present study, DR was defined as more than simple diabetic retinopathy. Diabetic nephropathy was evaluated by measuring eGFR and UACR while wearing the CGM.
**Statistical analysis**

The results are shown as median values (interquartile range) unless otherwise stated. UACR was natural logarithm-transformed (ln) to normalize the skewed distribution. The participants were divided into quadrants based on the duration of type 2 diabetes mellitus, and the Kruskal–Wallis test and Steel’s multiple comparison test were carried out to determine the differences between the groups. The χ²-test was used to assess sex, the proportion of diabetic complications and frequency of hypoglycemic agents.

The participants were divided into two groups: those aged <65 years (non-elderly group) and those aged ≥65 years and <75 years (elderly group). In addition, the elderly group was divided into groups of users and non-users of SU, glinides or insulin (high- and low-risk groups, respectively) for comparisons. Fisher’s exact test or Mann–Whitney U-test was used for comparison between the two groups.

TIR^{70–180} and TBR^{70} were used as the objective variable, and multiple regression analysis was carried out using variables, including age, sex, disease duration, BMI, HbA1c, eGFR, ln-UACR, the presence or absence of DPN and DR, and the use of drugs with high risk for hypoglycemia, such as SU, glinide and insulin, as explanatory variables.

BellCurve software (Social Survey Research Information Co., Ltd., Tokyo, Japan) was used for all the statistical analyses.

**RESULTS**

**Characteristics of the study participants**

The characteristics of the participants are shown in Table 1. There were 281 participants, consisting of 107 women and 174 men. The median age was 68 years (62–71 years), the duration of type 2 diabetes mellitus was 13 years (7–23 years), BMI was 24.1 kg/m² (22.0–26.9 kg/m²) and HbA1c was 6.9% (6.5–7.5%). The mean SO obtained by CGM was 137.4 mg/dL. 119.2–159.0 mg/dL. SD was 36.7 mg/dL. 29.9–45.0 mg/dL) and CV was 26.4% (22.4–30.6%). TIR^{70–180} obtained by CGM was 78.9% (66.9–90.4%). TAR^{180} was 15.5% (6.6–30.5%) and high blood glucose index was 3.5 (2.2–5.6), both of which are indicators of hyperglycemia. For indicators of hypoglycemia, TBR^{70} was 0.3% (0.2–2.5%) and LBGI was 0.9 (0.4–2.0).

Table 1 and Figure 1 show the status of use of hypoglycemic agents. A total of 11.4% of the patients were treated without hypoglycemic agents, 21.0% of the patients were treated with a single agent, 22.4% of the patients were treated with two agents and 45.2% of the patients were treated with three or more agents. Among oral hypoglycemic agents, metformin was used most frequently in 54.1% of the patients. Dipeptidyl peptidase-4 inhibitors were used in 53.0% of the patients, followed by sodium–glucose cotransporter 2 inhibitors (25.6%), SU (19.6%), α-glucosidase inhibitors (18.5%), thiazolidines (8.2%) and glinides (8.2%). Among the SU users, all glipepicrude users received ≤2 mg (77.1% received ≤1 mg), and 90.0% of gliclazide users received ≤40 mg (and one patient each received 80 and 120 mg). Only one patient received glibenclamide (2.5 mg). In the glinide users, the use of mitiglinide was the highest, with 14 patients at ≤30 mg/day and one patient at 35 mg/day. Nateglinide was administered at ≤1.5 mg/day in seven patients and at 3.0 mg/day in one patient.

Among injectable preparations, insulin was used in 26.3% of the patients, and glucagon-like peptide-1 receptor agonists were used in 13.2%. Among the patients treated with insulin, basal insulin was used in 33.8% of patients in combination with oral hypoglycemic agents or glucagon-like peptide-1 receptor agonist, followed by premixed insulin in 29.7% of patients. Among the patients using premixed insulin, 31.8% were injected with Ryzodeg® (Novo Nordisk, Bagsvaerd, Denmark) only once daily. A total of 20.3% of patients received basal–bolus therapy (multiple daily injections), and 8.1% used bolus insulin alone. In addition, 6.7% of the patients received a combination of bolus insulin and premixed insulin, and 1.3% received a

| Table 1 | Characteristics of the study participants |
|---|---|
| n (Female : male) | 281 (107:174) |
| Age (years) | 68 (62–71) |
| Duration of diabetes (years) | 13 (7–23) |
| BMI (kg/m²) | 24.1 (22.0–26.9) |
| HbA1c (%) | 6.9 (6.5–7.5) |
| eGFR (mL/min/1.73 m²) | 71.5 (60.9–82.0) |
| UACR (mg/gCr) | 14.1 (6.1–46.2) |
| Hypertension | 177 (63.0%) |
| Dyslipidemia | 227 (80.8%) |
| CGM | 0.9 (0.4–2.0) |
| Antidiabetic drugs | 37 (13.2%) |
| Metformin | 152 (54.1%) |
| Sulfonylureas | 55 (19.6%) |
| Glinides | 23 (8.2%) |
| Thiazolidines | 23 (8.2%) |
| α-Glucosidase inhibitors | 52 (18.5%) |
| DPP-4 inhibitors | 149 (53.0%) |
| SGLT2 inhibitors | 72 (25.6%) |
| Insulin | 74 (26.3%) |
| GLP-1 receptor agonists | 37 (13.2%) |

The results are shown as the median values (interquartile range). BMI, body mass index; CGM, continuous glucose monitoring; CV, coefficient of variation; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; GLP-1, glucagon-like peptide-1; HBGI, high blood glucose index; LBGI, low blood glucose index; SD, standard deviation; SGLT2, sodium–glucose cotransporter 2; TAR, time above range; TBR, time below range; TIR, time in range; UACR, urine albumin-to-creatinine ratio.
A combination of bolus insulin once daily and basal insulin once daily. Total daily insulin doses were 0.27 units/kg/day (0.17–0.43 units/kg/day).

Among the participants in the present study, 61.9% used antilipidemic drugs and 54.4% used antihypertensive drugs.

**Differences in medication regimen among quadrants of duration of type 2 diabetes mellitus**

Based on the duration of type 2 diabetes mellitus, the participants were divided into quadrants: 1 with the shortest and 4 with the longest diabetes duration (Table 2). The median duration of morbidity in these quadrants was 4 years, 10 years, with the longest diabetes duration (Table 2). The median duration of type 2 diabetes mellitus, the participants were divided into quadrants: 1 with the shortest and 4 with the longest diabetes duration (Table 2). The median duration of type 2 diabetes mellitus in the present study, 61.9% used antilipidemic drugs and 54.4% used antihypertensive drugs.

**Figure 1** Distribution of the numbers of medications for diabetes treatment.

The proportion of patients using SU ($P < 0.001$), glinides ($P = 0.558$), α-glucosidase inhibitors ($P = 0.769$) and sodium–glucose cotransporter 2 inhibitors ($P = 0.128$), depending on the duration of type 2 diabetes mellitus.

**Differences in GV indices and time in range among quadrants of duration of type 2 diabetes mellitus**

Figure 2 shows the results of HbA1c and CGM for each duration of type 2 diabetes mellitus. In quadrant 1, HbA1c was significantly lower in quadrant 1 than in the other groups ($P < 0.001$). The mean and SD values of SG levels were also significantly lower in quadrant 1 than in the other groups. CV was significantly higher in quadrant 4, at 28.0% (23.8–31.8%), compared with quadrant 1, at 25.6% (22.0–29.0%; $P = 0.017$).

TIR$_{70-180}$ was the highest in quadrant 1 at 87.4% (78.6–93.5%), in quadrant 2 at 82.9% (67.3–90.4%), in quadrant 3 at 77.5% (66.6–87.9%) and in quadrant 4 at 72.1% (61.3–81.7%; $P < 0.001$). The lowest TAR$_{180}$ was found in quadrant 1 at 7.3% (2.9–15.4%), in quadrant 2 at 15.1% (6.6–29.6%), in quadrant 3 at 18.6% (7.8–31.4%) and in quadrant 4 at 24.2% (12.5–35.9%; $P < 0.001$). For TBR$_{70}$, all of the groups had low values: 0.5% (0–2.7%) in quadrant 1, 0.3% (0–2.3%) in quadrant 2, 0.3% (0–2.1%) in quadrant 3 and 0.3% (0–2.6%) in quadrant 4 ($P = 0.876$).

**GV indices and time in range in the elderly**

The participants were divided into two groups: those aged <65 years (non-elderly group) and those aged ≥65 years (elderly group; Table 3a). In the elderly group, the age 70 years (68–72 years; $P < 0.001$) and the duration of type 2 diabetes mellitus 16 years (9–24 years; $P < 0.001$) were significantly higher than the non-elderly group. Although HbA1c (6.9% [6.5–7.5%]) and TIR$_{70-180}$ (78.4% [66.6–89.4%]) in the elderly group were not significantly different as compared with those in the non-elderly group, TBR$_{70}$ (0.1% [0–1.8%]) in the elderly group was significantly ($P < 0.001$) lower than that in the non-elderly group (0.9% [0.1–3.9%]). TAR$_{180}$ (17.3% [7.4–30.9%]) tended to be higher in the elderly group ($P = 0.051$). In the elderly group, 87.8% of the patients achieved TIR$_{70-180}$ of ≥50% and 68.0% of the patients achieved TBR$_{70}$ of <1%.
Table 2 | Differences in patients’ backgrounds and types of therapy for each duration of diabetes

| Quadrant 1 | Quadrant 2 | Quadrant 3 | Quadrant 4 | P     |
|-----------|-----------|-----------|-----------|-------|
| Duration of diabetes (years) | 4 (2–5) | 10 (9–11) | 17 (15–20) | 28 (25–33) | <0.001 |
| Sex (female: male) | 37:33 | 25:38 | 29:48 | 16:55 | 0.003 |
| Age (years) | 67 (59–71) | 66 (58–69) | 69 (65–71) | 70 (67–72) | <0.001 |
| BMI (kg/m²) | 24.3 (22.9–27.1) | 24.7 (22.6–27.5) | 24.0 (21.7–26.8) | 23.7 (21.8–26.8) | 0.219 |
| HbA1c (%) | 6.7 (6.3–7.0) | 7.1 (6.6–7.7) | 7.1 (6.5–7.6) | 7.2 (6.7–7.6) | <0.001 |
| eGFR (mL/min/1.73 m²) | 72.9 (64.0–81.8) | 76.5 (65.8–85.5) | 71.0 (60.9–82.1) | 66.0 (57.9–79.0) | 0.020 |
| UACR (mg/g-Cr) | 11.1 (5.2–25.5) | 17.0 (6.3–52.7) | 17.9 (6.8–39.9) | 13.3 (6.6–71.5) | 0.258 |
| No diabetic retinopathy | 63/68 (92.6%) | 48/61 (82.5%) | 59/73 (80.8%) | 58/69 (81.7%) | 0.943 |
| Dyslipidemia | 55 (78.6%) | 52 (76.9%) | 58 (78.9%) | 56 (78.9%) | <0.001 |
| No diabetic neuropathy | 55 (78.6%) | 52 (76.9%) | 58 (78.9%) | 56 (78.9%) | <0.001 |
| BMI (kg/m²) | 24.3 (22.9–27.1) | 24.7 (22.6–27.5) | 24.0 (21.7–26.8) | 23.7 (21.8–26.8) | 0.219 |
| HbA1c (%) | 6.7 (6.3–7.0) | 7.1 (6.6–7.7) | 7.1 (6.5–7.6) | 7.2 (6.7–7.6) | <0.001 |
| eGFR (mL/min/1.73 m²) | 72.9 (64.0–81.8) | 76.5 (65.8–85.5) | 71.0 (60.9–82.1) | 66.0 (57.9–79.0) | 0.020 |
| UACR (mg/g-Cr) | 11.1 (5.2–25.5) | 17.0 (6.3–52.7) | 17.9 (6.8–39.9) | 13.3 (6.6–71.5) | 0.258 |
| No diabetic retinopathy | 63/68 (92.6%) | 48/61 (82.5%) | 59/73 (80.8%) | 58/69 (81.7%) | 0.943 |
| Dyslipidemia | 55 (78.6%) | 52 (76.9%) | 58 (78.9%) | 56 (78.9%) | <0.001 |
| No diabetic neuropathy | 55 (78.6%) | 52 (76.9%) | 58 (78.9%) | 56 (78.9%) | <0.001 |
| BMI (kg/m²) | 24.3 (22.9–27.1) | 24.7 (22.6–27.5) | 24.0 (21.7–26.8) | 23.7 (21.8–26.8) | 0.219 |
| HbA1c (%) | 6.7 (6.3–7.0) | 7.1 (6.6–7.7) | 7.1 (6.5–7.6) | 7.2 (6.7–7.6) | <0.001 |
| eGFR (mL/min/1.73 m²) | 72.9 (64.0–81.8) | 76.5 (65.8–85.5) | 71.0 (60.9–82.1) | 66.0 (57.9–79.0) | 0.020 |
| UACR (mg/g-Cr) | 11.1 (5.2–25.5) | 17.0 (6.3–52.7) | 17.9 (6.8–39.9) | 13.3 (6.6–71.5) | 0.258 |
| No diabetic retinopathy | 63/68 (92.6%) | 48/61 (82.5%) | 59/73 (80.8%) | 58/69 (81.7%) | 0.943 |
| Dyslipidemia | 55 (78.6%) | 52 (76.9%) | 58 (78.9%) | 56 (78.9%) | <0.001 |
| No diabetic neuropathy | 55 (78.6%) | 52 (76.9%) | 58 (78.9%) | 56 (78.9%) | <0.001 |

The Kruskal–Wallis test was carried out to examine the differences in individual clinical parameters among quadrants. Based on the duration of diabetes, the participants were divided into quadrants. BMI, body mass index; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; GLP-1, glucagon-like peptide-1; SGLT2, sodium–glucose cotransporter 2; UACR, urine albumin-to-creatinine ratio.

We next categorized the elderly group to two groups based on users (high-risk group) and non-users (low-risk group) of drugs potentially associated with severe hypoglycemia (SU, glinides and/or insulin) according to the JDS/JGS Joint Committee’s consensus (Table 3b). Sex and the median age (70 years) were not significantly different between the low- and high-risk groups. However, the duration of type 2 diabetes mellitus in the high-risk group (21 years [13–28 years]) was significantly (P < 0.001) longer than that in the low-risk group (11 years [5–18 years]). HbA1c in the high-risk group (7.2% [6.8–7.7%]) was significantly (P < 0.001) higher than that in the low-risk group (6.7% [6.3–7.2%]). Similarly, among parameters obtained by CGM, mean SG (P < 0.001), SD (P < 0.001), CV (P < 0.001), TAR (P < 0.001), TAR (P < 0.001) and high blood glucose index (P < 0.001) were significantly higher, whereas TIR (P < 0.001) was significantly lower in the high-risk than the low-risk group. LBGI (P = 0.016) was significantly higher in the high-risk than the low-risk group. TBR (P = 0.061) and TBR (P = 0.087) tended to be higher in the high-risk group than the low-risk group.

Factors affecting time in range and time below range

A multiple regression analysis was carried out using TIR (70–180) as the objective variable, and age, disease duration, and the presence or absence of diabetic complications as explanatory variables for 261 patients for whom all of these data were available (model 1; Table 4). The results showed that HbA1c (standard partial regression coefficient; β = −0.573, P < 0.001), disease duration (β = −0.160, P = 0.003), ln-UACR (β = −0.100, P = 0.043) and presence of DPN (β = −0.106, P = 0.033) were useful explanatory factors for TIR (70–180). Next, the participants in the elderly group (aged ≥65 to <75 years) were analyzed in model 2. Similar to model 1, HbA1c (β = −0.630, P < 0.001), disease duration (β = −0.138, P = 0.030), ln-UACR (β = −0.142, P = 0.016) and the presence of DPN (β = −0.125, P = 0.036) were useful experimental factors for TIR (70–180). Subsequently, a multiple regression analysis was carried out using TBR (70) as the objective variable. In model 1, HbA1c (β = −0.431, P < 0.001) and the use of drugs with a high risk of hypoglycemia (β = 0.147, P = 0.030) were useful explanatory factors for TBR (70). In model 2 for the elderly, BMI (β = −0.160, P = 0.027), HbA1c (β = −0.398, P < 0.001) and
the use of drugs with a high risk of hypoglycemia \( \beta = 0.180, P = 0.028 \) were useful explanatory factors for TBR.<ref>

**DISCUSSION**

The present study was part of a multicenter, prospective cohort study, which was characterized by the use of CGM in patients on an outpatient basis. In the present study, TIR\(^{70-180}\) was associated with UACR, DPN and the duration of type 2 diabetes mellitus. In addition, the investigation of the current status of the treatment of elderly Japanese patients with type 2 diabetes mellitus showed that excessive prescription of SU was avoided, and that hypoglycemic indices, such as LBGI, were lowered in many elderly patients after the formulation of the JDS/JGS Joint Committee’s consensus.

Several studies showed that worsening glycemic control and GV are associated with the onset and progression of diabetic complications. Similar to the present study, an association between TIR and albuminuria was reported. In addition, it was reported that not only diabetic microvascular complications, such as diabetic autonomic neuropathy and DR, but also vascular endothelial dysfunction, are associated with TIR deterioration. Thus, diabetic complications might be involved in the worsening of TIR.

Previous studies have reported that HbA1c deteriorates with increased disease duration, despite the complexity of diabetes treatment. The results of the present study indicate that disease duration is an independent explanatory factor for TIR. Our results suggest that pancreatic \(\beta\)-cell function worsens as the duration of type 2 diabetes mellitus increases, leading to an increase in insulin users, and worsening of TIR and GV. Conversely, glycemic targets should be set in consideration of age, as well as disease duration, diabetic complications and risk of hypoglycemia. It is possible that the deterioration of TIR and GV was caused by the setting of high target blood glucose levels in patients with long disease duration and advanced diabetic complications. In the future, a detailed study including endogenous insulin secretory capacity might be necessary.

Severe hypoglycemia is associated with various complications, such as cardiovascular disease and dementia. Therefore, it is important to maintain good glycemic control while avoiding severe hypoglycemia. The JDS/JGS Joint Committee’s consensus recommends that glycemic targets should be individualized based on patient characteristics. Among the antidiabetic drugs, patients taking SU, glinides and insulin, in particular, are at risk of developing severe hypoglycemia. Therefore, these types of antidiabetic drugs are used with caution.

![Figure 2](http://wileyonlinelibrary.com/journal/jdi)

Figure 2 | Comparisons of glycated hemoglobin (HbA1c) levels and continuous glucose monitoring data among quadrants of type 2 diabetes mellitus duration. (a) HbA1c, (b) mean sensor glucose (SG), (c) standard deviation (SD), (d) coefficient of variation (CV), (e) time in range 70–180 mg/dL (TIR\(^{70-180}\)), (f) time above range >180 mg/dL (TAR\(^{>180}\)), (g) time above range >250 mg/dL (TAR\(^{>250}\)) and (h) time below range <70 mg/dL (TBR\(^{<70}\)). Data are shown in box and whisker plots using the Tukey method. Outlier. Compared with quadrant 1 using Steel’s multiple comparison test. *P < 0.05, **P < 0.001. Q1, quadrant 1; Q2, quadrant 2; Q3, quadrant 3; Q4, quadrant 4.
Table 3 | Comparison of clinical parameters between the elderly and non-elderly patients. Comparison of clinical parameters between the high- and low-risk groups in the elderly

| Parameter | Non-elderly (aged < 65 years) | Elderly (aged ≥ 65 and < 75 years) | P |
|-----------|-----------------------------|-------------------------------|---|
| Female: Male | 35: 56 | 68: 113 | 0.860 |
| Age (years) | 58 (53–62) | 70 (68–72) | < 0.001 |
| Duration (years) | 10 (5–17) | 16 (9–24) | < 0.001 |
| BMI (kg/m²) | 25.4 (22.9–29.0) | 25.5 (13.7–24.0) | 0.928 |
| HbA1c (%) | 6.9 (6.5–7.6) | 6.9 (6.5–7.5) | 0.804 |
| eGFR (mL/min/1.73 m²) | 77.9 (65.7–86.0) | 78.4 (66.6–89.4) | 0.341 |
| UACR (mg/g-Cr) | 142.4 (53.5–453.3) | 139.6 (63.4–425.2) | 0.696 |
| Mean SG (mg/dL) | 129.6 (114.1–158.5) | 142.3 (123.2–162.6) | 0.026 |
| SD (mg/dL) | 35.4 (28.3–44.3) | 37.4 (30.8–45.2) | 0.136 |
| CV (%) | 26.3 (22.2–30.1) | 26.5 (22.4–30.6) | 0.928 |
| TIR<70-90 (%) | 80.8 (68.0–91.5) | 78.4 (66.6–89.4) | 0.341 |
| TAR<80 (%) | 13.0 (3.5–28.5) | 17.3 (7.4–30.9) | 0.051 |
| TBR<80 (%) | 0.6 (0–4.1) | 0.9 (0–4.8) | 0.152 |
| TBR<54 (%) | 0.9 (0–3.9) | 0.1 (0–1.8) | < 0.001 |
| HbGI | 0 (0–0) | 0.1 (0–1.8) | 0.026 |
| LBGI | 3.3 (1.7–5.6) | 3.8 (2.4–5.6) | 0.101 |
| TBGI | 1.2 (0.5–2.4) | 0.7 (0.3–1.7) | 0.011 |

Elderly: Low risk Elderly: High risk

| Parameter | Elderly: Low risk | Elderly: High risk | P |
|-----------|-----------------|------------------|---|
| Female: Male | 36: 54 | 32: 59 | 0.593 |
| Age (years) | 70 (68–71) | 70 (68–72) | 0.853 |
| Duration (years) | 11 (5–18) | 21 (13–28) | < 0.001 |
| BMI (kg/m²) | 24.0 (22.1–25.5) | 23.7 (21.7–26.6) | 0.969 |
| HbA1c (%) | 6.7 (6.3–7.2) | 7.2 (6.8–7.7) | < 0.001 |
| eGFR (mL/min/1.73 m²) | 70.0 (61.2–78.8) | 67.9 (57.4–81.8) | 0.750 |
| UACR (mg/g-Cr) | 11.5 (6.0–33.5) | 14.1 (8.6–67.6) | 0.396 |
| Mean SG (mg/dL) | 133.4 (116.6–154.3) | 152.3 (128.4–168.2) | < 0.001 |
| SD (mg/dL) | 33.5 (28.1–38.0) | 43.3 (36.0–51.0) | < 0.001 |
| CV (%) | 24.0 (21.6–28.6) | 28.2 (24.3–31.5) | < 0.001 |
| TIR<70-90 (%) | 85.9 (74.7–92.6) | 72.1 (60.1–83.3) | < 0.001 |
| TAR<80 (%) | 12.1 (4.0–24.1) | 24.0 (13.7–36.4) | < 0.001 |
| TBR<80 (%) | 0.4 (0–1.7) | 2.7 (0.5–8.0) | < 0.001 |
| TBR<54 (%) | 0 (0–0) | 0.3 (0–2.2) | 0.061 |
| HbGI | 2.9 (1.8–4.3) | 4.7 (3.0–7.5) | < 0.001 |
| LBGI | 0.6 (0.3–1.3) | 1.0 (0.4–2.0) | 0.016 |

Sulfonylureas, glinides, and insulin users were defined as high-risk. Fisher’s exact test or Mann-Whitney U test was used for comparison between two groups. BMI; Body mass index, eGFR; estimated glomerular filtration rate, UACR; urine albumin-creatinine ratio, SG; sensor glucose, SD; Standard deviation, CV; coefficient of variation, TIR; Time in range TAR; Time above range, TBR; Time below range, HbGI; High blood glucose index, LBGI; Low blood glucose index.

cautions in the elderly. In fact, just two patients used a higher dose of SU (gliclazide 80 mg and 120 mg) in the present study. Thus, low LBGI in this study could be attributed to wide recognition of this recommendation, which resulted in avoidance of the use of excessive SU.

Advanced Technologies & Treatments for Diabetes recommends focusing on reducing TBR<70 and preventing excessive hyperglycemia in the elderly. The results of the present study showed that 87.8% of the elderly patients achieved TIR<70-90 ≥50%, whereas 32.0% of the elderly patients had TBR<70 ≥1.0%. It has been reported that CGM might overestimate hypoglycemia. In fact, 41.4% of the patients with TBR<70 ≥1% were not prescribed SU, glinides or insulin. Therefore, the target value of TBR<70 might require further consideration. Although the hypoglycemic indices could have been overestimated, the present study showed that low HbA1c and the use of drugs with a high risk of hypoglycemia were associated with TBR<70 deterioration. Thus, it was perceived that care should be taken not to lower HbA1c level excessively, especially when using drugs with a high risk of hypoglycemia in the elderly.
The present study had several limitations. First, this study included only Japanese patients with type 2 diabetes mellitus who were controlled by a diabetologist. In the future, a larger-scale investigation, including general physicians, is warranted. Second, there might be a problem of CGM measurement accuracy in detecting hypoglycemia. Third, in the present study, information regarding the disease duration was obtained from the attending physician or the patients’ medical records. However, unlike type 1 diabetes, it is often difficult to accurately assess the duration of type 2 diabetes mellitus.

In conclusion, we found that TIR70–180 was associated with UACR and DPN, as well as the duration of diabetes. We investigated the current status of diabetes treatment in Japan and found that the excessive use of SU was avoided. In addition, we found that low HbA1c levels and the use of antidiabetic drugs with a high risk of hypoglycemia might worsen TBR in elderly patients with type 2 diabetes mellitus.

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DISCLOSURE
The authors declare no conflict of interest.

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