Continuous glucose monitoring reveals hypoglycemia risk in elderly patients with type 2 diabetes mellitus

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ABSTRACT
Aims/Introduction: The incidence of type 2 diabetes is higher in elderly patients, in whom this disease is associated with dementia, falling, stroke and death. We utilized a continuous glucose monitoring device to analyze the relationship between hypoglycemia and diabetes treatments to identify risk factors for hypoglycemia (defined as a blood glucose level <70 mg/dL).

Materials and Methods: We classified 170 patients aged ≥65 years with type 2 diabetes who were receiving steady-state medication (29 of whom were inpatients) into hypoglycemic and non-hypoglycemic groups, and compared their glycosylated hemoglobin levels, treatment types, continuous glucose monitoring data and other parameters. We carried out univariate analyses to identify variables associated with hypoglycemia risk, followed by multivariate analyses of drug class and other factors. The accuracy of the continuous glucose monitoring data was confirmed by calibration.

Results: Hypoglycemia risk was higher in the patients using insulin (odds ratio [OR] 2.17, 95% confidence interval [CI] 1.16–4.08, P = 0.015), and lower in patients who were being treated with dipeptidyl peptidase-4 inhibitors (OR 0.47, 95% CI: 0.25–0.89, P = 0.019). Patients with lower variability in blood glucose had a significantly lower hypoglycemia risk (OR 0.87, 95% CI: 0.83–0.91, P < 0.0001), and those with a lower average blood glucose level had a significantly higher risk (OR 1.09, 95% CI: 1.06–1.12, P < 0.0001).

Conclusions: In patients aged ≥65 years with type 2 diabetes, higher glucose variability and lower average glucose levels indicate a greater hypoglycemia risk. It is therefore necessary to ensure comprehensive blood glucose control in such patients to prevent hypoglycemia.

INTRODUCTION
Global increases in life expectancy have resulted in larger elderly populations, especially in developed countries. However, the incidence of diabetes in elderly patients is also rising. Generally, the aim of treating diabetes is to maintain suitable blood glucose levels in order to prevent chronic diabetic complications and improve healthy life expectancy1,2. However, in elderly healthcare, it is more important to maintain a good quality of life and sustain current life functions as much as possible. Complications, comorbidities, activities of daily living, life expectancy and medical conditions are notably diverse in elderly populations. Therefore, achieving complication-free and good long-term prognosis while minimizing hypoglycemia and other burdens associated with blood glucose control in elderly patients with diabetes requires different levels of effort among such individuals. Some guidelines for the treatment of diabetes in the elderly have become available in recent years3–5; they recommend setting blood glucose target levels depending on elderly patients’ cognitive functions and activities of daily living.

Prevention of hypoglycemia is important in the daily lives of the elderly, especially those with chronic diabetes and associated complications who are prone to asymptomatic hypoglycemia.
Severe hypoglycemia not only impairs cognitive function, but can also result in traumatic falls, stroke, cardiovascular events and even death. However, very few studies have investigated the relationship between hypoglycemia, type of diabetes treatment and the blood glucose profile in elderly patients with type 2 diabetes as measured by continuous glucose monitoring (CGM). With CGM, it is possible to obtain continuous and accurate data, such as the occurrences of asymptomatic hypoglycemia, which are often not available with conventional self-monitoring blood glucose (SMBG).

The aim of the present study was to investigate risk factors for hypoglycemia in elderly patients with type 2 diabetes by using glycosylated hemoglobin (HbA1c) levels (which provide an indication of the average blood glucose concentration of a patient over the previous 3 months), type of diabetes treatment and CGM data.

METHODS

Participants

The present retrospective study used previously acquired CGM data from 170 elderly patients with type 2 diabetes, aged ≥65 years, who were treated at Chiba University Hospital and Kashiwado Hospital between September 2011 and July 2016. All patients were monitored while under steady-state medication; the patients’ medications were not altered during the CGM tests. Patients who were in perioperative stages were not included in the present study. We collected the following clinical data: age, sex, height, bodyweight, body mass index, type of diabetic treatment and HbA1c levels (according to the National Glycohemoglobin Standardization Program). This study was approved by the ethics committees of both hospitals.

CGM

CGM data were obtained using either the iPro™ system version 2 (Medtronic, Inc., Minneapolis, Minnesota, USA) or CGMS System Gold™ (Medtronic, Inc.). The CGM tests were carried out for 3.7 ± 1.2 days on average. The CGM data that were documented per patient included the highest, lowest and average blood glucose levels (mg/dL), standard deviations of blood glucose levels (mg/dL) for estimating their variability, and the presence of hypoglycemia (defined as a blood glucose level <70 mg/dL) along with its duration (as a percentage of total time). The OneTouch UltraVue® device (Johnson and Johnson K.K., Tokyo, Japan) was used for SMBG measurement; each patient used the same device. SMBG measurements were carried out at least four times a day for calibration, usually before meals. In order to estimate the accuracy of the CGM results, we analyzed the average values of the mean absolute difference (MAD%) between SMBG and CGM, as well as the average correlation coefficient (R) of the relationship between SMBG and CGM.

Outcomes

We compared HbA1c levels, diabetes treatment agents, age, sex, height, bodyweight, body mass index, and CGM data between patients with and without hypoglycemia as detected by CGM. We analyzed the hypoglycemia risk by drug class and other relevant parameters, namely glucose variability, average glucose level and HbA1c, through multivariate analysis.

Statistical analysis

For the baseline variables, summary statistics were calculated using frequencies for categorical data, and the means and standard deviations for continuous variables. When comparing the hypoglycemic group with the non-hypoglycemic group, Welch’s t-test was used for continuous variables, whereas Pearson’s χ²-test was used for binary variables.

We used a multivariate logistic regression model to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for hypoglycemia risk after controlling for potential confounders. Factors subjected to the multivariate regression model were based on the results of the previously carried out univariate analyses, and were selected and analyzed according to the forward stepwise selection method. Continuous variables were not categorized for regression studies, and were assessed for multicollinearity using principal component analysis.

Outcomes were deemed significant at P-values <0.05, and all statistical analyses were carried out using the JMP Pro software, version 12 (SAS Institute, Cary, North Carolina, USA).

RESULTS

Patient demographics

Table 1 shows patient demographic information, where the average age of the patients was 74.1 ± 6.7 years, the average HbA1c level was 8.2 ± 1.8% and the average estimated glomerular filtration rate was 62.8 ± 18.2 mL/min/1.73 m². A total of 141 patients (82.9%) were outpatients, and 29 (17.1%) were inpatients. Of these patients, 42.4% were treated with dipeptidyl peptidase-4 (DPP-4) inhibitors, 55.9% were treated with insulin (long-acting and/or short-acting) and 27.1% were treated with sulfonylurea (SU). As is common practice, some patients received combinations of these treatments.

CGM outcomes and HbA1c levels in hypoglycemic vs non-hypoglycemic patients

Table 2 shows CGM outcomes and HbA1c levels in hypoglycemic patients compared with the control non-hypoglycemic group. The lowest blood glucose levels of the patients with hypoglycemia (as measured by CGM) were significantly lower than those of non-hypoglycemic patients (52.5 ± 10.7 mg/dL vs 94.5 ± 18.2 mg/dL, respectively; P < 0.0001), whereas the average glucose level was also significantly lower in the patients with hypoglycemia than that in non-hypoglycemic patients (150.3 ± 34.1 mg/dL vs 175.3 ± 34.4 mg/dL, respectively; P < 0.0001). The standard deviation of the CGM blood glucose level was significantly higher in hypoglycemic patients (53.2 ± 22.6 mg/dL vs 42.3 ± 15.8 mg/dL, P = 0.001), whereas there was no significant difference in HbA1c levels between the two groups (8.1 ± 2.1% vs 8.2 ± 1.6%). There was no
Table 1 | Total patient demographics and clinical characteristics

| Age (years) | 74.1 ± 6.7 |
| Height (cm) | 157.5 ± 9.1 |
| Bodyweight (kg) | 57.3 ± 13.7 |
| BMI (kg/m²) | 23.0 ± 5.0 |
| HbA1c (%) | 8.2 ± 1.8 |
| eGFR (mL/min/1.73 m²) | 62.8 ± 18.2 |
| Inpatients (%) | 17.1 |
| CGM performed days | 3.7 ± 1.2 |
| Drug number | 2.1 ± 1.1 |
| Medication | |
| DPP-4 inhibitor (%) | 42.4 |
| Metformin (%) | 15.9 |
| a-Gl (%) | 17.7 |
| TZD (%) | 7.7 |
| GLP-1 analog (%) | 3.5 |
| SU (%) | 27.1 |
| Glinides (%) | 3.5 |
| Insulin (%) | 55.9 |
| Total amount of insulin, U/kg/day (insulin user only) | 0.44 ± 0.22 |
| Highest glucose level (mg/dL) | 297.2 ± 67.5 |
| Lowest glucose level (mg/dL) | 76.7 ± 25.9 |
| Average glucose level (mg/dL) | 164.7 ± 36.3 |
| Standard deviation (mg/dL) | 46.9 ± 19.7 |
| Rate of glucose level | |
| <70 mg/dL (%) | 2.3 ± 5.7 |
| Average MAD (%) | 9.9 ± 5.1 |
| Average correlation coefficient | 0.87 ± 0.14 |

Values expressed as mean ± standard deviation or percentages. a-Gl, alpha-glucosidase inhibitors; BMI, body mass index; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; GLP-1, glucagon-like peptide-1; HbA1c, glycosylated hemoglobin; MAD, mean absolute difference; SU, sulfonylurea; TZD, thiazolidinedione.

statistically significant difference in the standard deviations of the CGM glucose levels between outpatients and inpatients (45.9 ± 19.5 vs 51.7 ± 20.2, respectively; P = 0.164). Additionally, there was no significant difference in estimated glomerular filtration rate between patients with hypoglycemia and those without (62.1 ± 17.0 vs 63.4 ± 19.2 mL/min/1.73 m², respectively; P = 0.709).

Hypoglycemia risk by drug class

There was an increased hypoglycemia risk in patients treated with insulin (OR 2.17, 95% CI: 1.16–4.08, P = 0.015; Figure 1). Conversely, there was a significantly reduced hypoglycemia risk in patients treated with DPP-4 inhibitors (OR 0.47, 95% CI: 0.25–0.89, P = 0.019; Figure 1).

Logistic regression analysis

Based on the aforementioned results, we carried out logistic regression analysis of the variables that were associated with hypoglycemia on univariate analysis; namely, HbA1c levels, use of DPP-4 inhibitor, use of insulin, average blood glucose level and glucose variability.

Patients with reduced blood glucose variability had a significantly lower hypoglycemia risk than those with greater variability (OR 0.87, 95% CI: 0.83–0.91, P<0.0001); furthermore, those with a lower average blood glucose level had a significantly higher hypoglycemia risk (OR 1.09, 95% CI: 1.06–1.12, P < 0.0001; Table 3). Use of DPP-4 inhibitor or of insulin did not show a significant association with hypoglycemia on logistic regression analysis.

Accuracy of the CGM results

The average MAD% was 9.9 ± 5.1% (which was ≤28%), whereas the average R was 0.87 ± 0.14 (which was ≥0.79), showing that the CGM data are accurate and therefore reliable. There were no statistically significant differences in MAD% and R between patients with hypoglycemia and those without (MAD%: 9.5 ± 4.7% vs 10.3 ± 5.4%, respectively [P = 0.287]; R: 0.88 ± 0.13 vs 0.85 ± 0.15, respectively [P = 0.250]).

DISCUSSION

In elderly individuals, it is important to prevent hypoglycemia when treating diabetes, as this could lead to dementia and other adverse effects. We found that variables strongly associated with hypoglycemia were a large glucose variability (standard deviation) and a lower average blood glucose level. On multiple regression analysis, none of the diabetic drugs examined in the present study showed a strong association with hypoglycemia.

Elderly patients with diabetes in the present study were quite prone to hypoglycemia. In another study that investigated hypoglycemia in type 2 diabetes patients (with an average age of 50.2 ± 8.2 years) for 5 days using CGM, 49.1% of participants had at least one hypoglycemic episode, whereas 75% had at least one episode of asymptomatic hypoglycemia. Hypoglycemia was more frequent in individuals taking insulin, and in those taking sulfonylureas and glinides compared with those taking non-insulin secretagogues (DPP-4 inhibitors, glucagon-like peptide receptor agonists, biguanides and thiazolidinedione). Patients on insulin showed higher glycemic variability, and insulin was found to cause hypoglycemia on univariate analysis.

There was no association between HbA1c level and the presence of hypoglycemia in type 2 diabetes patients in the present study, although HbA1c is a good indicator of blood glucose control. In a study that included both elderly and non-elderly patients with diabetes, asymptomatic hypoglycemia tended to occur more often and for a longer duration, in patients with HbA1c levels of <7%15. This was also the case for the subgroups treated with insulin. Furthermore, patients with HbA1c levels of ≥7% had higher glycemic variability. Thus, it is necessary to pay attention to hypoglycemia even in patients with HbA1c levels of ≥7%. Additionally, HbA1c measurements might not be accurate, owing to several conditions that are...
frequently observed in elderly patients; these include anemia, chronic kidney disease, chronic liver diseases and recent acute illness. Therefore, it is difficult to predict the occurrence of hypoglycemia by measuring HbA1c alone in elderly patients. CGM is useful for the detection and prevention of asymptomatic hypoglycemia. A previous study showed that many of the hypoglycemic episodes that had been confirmed by CGM were asymptomatic in nature\textsuperscript{16}. Investigators in another study

| Table 2 | Clinical characteristics and continuous glucose monitoring outcomes in hypoglycemic patients versus normoglycemic control participants |
|-----------------|-----------------|-----------------|-----------------|
| <70 mg/dL on CGM | ≥70 mg/dL on CGM | P-value |
| **Age (years)** | 74.1 ± 6.9 | 74.1 ± 6.7 | 0.955 |
| **Height (cm)** | 156.7 ± 8.2 | 158.0 ± 9.6 | 0.396 |
| **Bodyweight (kg)** | 55.7 ± 13.4 | 58.4 ± 13.9 | 0.244 |
| **BMI (kg/m\(^2\))** | 22.7 ± 4.8 | 23.3 ± 5.1 | 0.476 |
| **HbA1c (%)** | 8.1 ± 2.1 | 8.2 ± 1.6 | 0.634 |
| **eGFR (mL/min/1.73 m\(^2\))** | 62.1 ± 17.0 | 63.4 ± 19.2 | 0.709 |
| **Inpatients (%)** | 36 ± 1.1 | 38 ± 1.2 | 0.273 |
| **Drug number** | 2.1 ± 1.1 | 2.1 ± 1.1 | 0.789 |
| **Medication** | | | |
| DPP-4 inhibitor (%) | 31.9 | 50.0 | 0.019 |
| Metformin (%) | 16.7 | 15.3 | 0.811 |
| α-GI (%) | 16.7 | 18.4 | 0.774 |
| TZD (%) | 5.6 | 9.2 | 0.379 |
| GLP-1 analog (%) | 28 | 4.1 | 0.649 |
| SU (%) | 22.2 | 30.6 | 0.224 |
| Glinides (%) | 28 | 4.1 | 0.649 |
| Insulin (%) | 66.7 | 48.0 | 0.015 |
| Total amount of insulin, U/kg/day (insulin user only) | 0.45 ± 0.24 | 0.43 ± 0.20 | 0.658 |
| Highest glucose level (mg/dL) | 303.8 ± 74.8 | 292.3 ± 61.6 | 0.291 |
| Lowest glucose level (mg/dL) | 525.5 ± 10.7 | 945.6 ± 18.2 | <0.0001 |
| Average glucose level (mg/dL) | 150.3 ± 34.1 | 175.3 ± 34.4 | <0.0001 |
| Standard deviation (mg/dL) | 53.2 ± 22.6 | 42.3 ± 15.8 | 0.001 |
| Rate of glucose level | | | |
| <70 mg/dL (%) | 5.5 ± 7.7 | 0 | NA |
| Average MAD (%) | 9.5 ± 4.7 | 10.3 ± 5.4 | 0.287 |
| Average correlation coefficient | 0.88 ± 0.13 | 0.85 ± 0.15 | 0.250 |

Values are expressed as mean ± standard deviation or percentages. α-GI, alpha-glucosidase inhibitors; BMI, body mass index; CGM, continuous glucose monitoring; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; GLP-1, glucagon-like peptide-1; HbA1c, glycosylated hemoglobin; MAD, mean absolute difference; NA, not applicable; SU, sulfonylurea; TZD, thiazolidinedione.

Figure 1 | Hypoglycemia risk by antidiabetic drug class. The unadjusted odds ratios (ORs) and 95% confidential intervals (CIs) for hypoglycemia by antidiabetic drug class, shown as the unadjusted OR (solid circle) with 95% CIs (horizontal lines). α-GI, alpha-glucosidase inhibitors; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; HbA1c, glycosylated hemoglobin; MAD, mean absolute difference; NA, not applicable; SU, sulfonylurea; TZD, thiazolidinedione.
Insulin

DPP-4 inhibitor

HbA1c (-1 increments)

Average glucose level (-1 increments)

Glucose variability (-1 increments)

The odds ratio (OR) is for hypoglycemia. CI indicates confidence interval; DPP-4, dipeptidyl peptidase-4; HbA1c, glycosylated hemoglobin.

80 mg/dL range was 12.5 mg/dL23; with the CGM system, hypoglycemia is higher than in non-elderly patients18; therefore, DPP-4 inhibitors have been reported to decrease glucose variability. In elderly patients, the frequency of asymptomatic glycemia17. In elderly patients, the frequency of asymptomatic hypoglycemia is higher than in non-elderly patients18; therefore, DPP-4 inhibitors among our elderly patients; this was consistent with data from previous studies.

A major limitation of the present study is that it was retrospective in nature; therefore, a prospective study is now being planned. Furthermore, the present results were based on the measurement of interstitial fluid glucose levels rather than blood glucose levels. Although a high correlation between the CGM sensor and SMBG readings were shown in a previous similar study16, the accuracy and reliability of CGM remain issues of concern in the treatment of diabetes, especially in patients with hypoglycemia. With the iProTM system version 2, the MAD of the 40–80 mg/dL range was 12.5 mg/dL23; with the CGMS System Gold25, the MAD of the <70 mg/dL range was 7.34 mg/dL24. With respect to our use of ‘average daily risk range’, our glucose variability data encompassed CGM tested during all periods; that is, intra- and interday variation, as we considered both to be important. However, we did not alter medications during the CGM test; therefore, our data ought to mostly reflect intraday variation, whereas interday variation was not fully verifiable in the present study.

In conclusion, elderly patients aged ≥65 years with type 2 diabetes who show larger glucose variability and/or lower average glucose levels have a greater risk of hypoglycemia. It is difficult to determine the risk of hypoglycemia by measuring HbA1c levels alone in elderly patients with type 2 diabetes. Therefore, it will be necessary to carry out additional studies investigating optimal blood glucose control comprehensively by using HbA1c, CGM and other predictors in order to prevent hypoglycemia in elderly patients with type 2 diabetes.

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DISCLOSURE

The authors declare no conflict of interest.

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Table 3 | Hypoglycemia risk analyzed by a multiple logistic regression model

| Variable | Crude OR (95% CI) | OR (95% CI) | P-value |
|----------|------------------|-------------|---------|
| Glucose variability (-1 increments) | – | 0.87 (0.83–0.91) | <0.0001 |
| Average glucose level (-1 increments) | – | 1.09 (1.06–1.12) | <0.0001 |
| HbA1c (-1 increments) | – | 0.94 (0.73–1.18) | 0.606 |
| DPP-4 inhibitor | | | |
| Without | 1 (Reference) | 1 (Reference) | 0.673 |
| With | 0.47 (0.25–0.89) | 0.82 (0.33–2.03) | |
| Insulin | | | |
| Without | 1 (Reference) | 1 (Reference) | 0.901 |
| With | 2.17 (1.16–4.08) | 1.06 (0.44–2.59) | |

The odds ratio (OR) is for hypoglycemia. CI indicates confidence interval; DPP-4, dipeptidyl peptidase-4; HbA1c, glycosylated hemoglobin.
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