Factors associated with hypoglycemia unawareness and severe hypoglycemia in type 1 diabetes mellitus patients

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ABSTRACT
Aims/Introduction: Several factors are associated with hypoglycemia unawareness and severe hypoglycemia, but few large studies have analyzed Japanese patients with type 1 diabetes. The aim of this study was to analyze the risk factors for hypoglycemia unawareness and severe hypoglycemia in Japanese type 1 diabetes patients.

Materials and Methods: A self-administered questionnaire investigated events, complications and treatments associated with hypoglycemia in patients with type 1 diabetes. Multiple logistic regression analysis of factors associated with hypoglycemia unawareness and severe hypoglycemia requiring medical treatment was carried out. The coefficient of variation (CV) of blood glucose levels was determined using blood samples collected at six outpatient visits.

Results: Of the 1,619 participants, 44.2% and 10.4% experienced hypoglycemia unawareness and severe hypoglycemia, respectively. Mean HbA1c levels in patients with hypoglycemia unawareness were lower than those in patients without hypoglycemia unawareness. The type 1 diabetes subtype, glycated hemoglobin (HbA1c) level, CV of blood glucose levels and history of severe hypoglycemia requiring medical treatment were significant independent variables predicting the presence of hypoglycemia unawareness. The glucose CV and a history of hypoglycemia unawareness were significant independent variables predicting severe hypoglycemia requiring medical treatment. In stratified analyses of patients divided into four groups according to glucose CV and HbA1c levels, the high-glucose-CV/low-HbA1c group had the highest odds ratios for hypoglycemia unawareness (2.60) and severe hypoglycemia requiring medical treatment (2.55).

Conclusions: The ambulant glucose CV correlated with both hypoglycemia unawareness and severe hypoglycemia. Patients with high glucose CV and low HbA1c are at high risk of such adverse events, and their treatment strategies should be reviewed.

INTRODUCTION
Strict glycemic control corrects hyperglycemia, reducing microvascular and cardiovascular complications in type 1 diabetes1,2. In contrast, trying to maintain strict glycemic control sometimes induces frequent hypoglycemia, which is also a cause of cardiovascular complications3 and lower quality of life4,5. Hypoglycemia is one of the factors that disturbs strict glycemic control in both type 1 and type 2 diabetes patients6. Some patients have hypoglycemia without symptoms, a condition called hypoglycemia unawareness. As it is rare to be completely unaware, sometimes it is called impaired awareness of
hypoglycemia, in which the threshold blood glucose level at which hypoglycemic symptoms arise is lowered or symptoms do not always appear. Some 20–25% of patients with type 1 diabetes have impaired awareness of hypoglycemia.

Severe hypoglycemia can cause lower quality of life, as well as traffic accidents. Approximately 50% of patients who experience severe hypoglycemia have impaired awareness of hypoglycemia. Impaired awareness of hypoglycemia increases the rate of severe hypoglycemia by five- to sixfold, and leads to a decrease in quality of life. Investigating the clinical characteristics of type 1 diabetes patients who have impaired awareness of hypoglycemia or severe hypoglycemia might help prevent impaired awareness of hypoglycemia and severe hypoglycemia.

Several factors have been associated with impaired awareness of hypoglycemia, such as older age, longer duration of diabetes, frequency of severe hypoglycemia and frequency of hypoglycemia. Factors reported to be associated with severe hypoglycemia include older age, longer duration of diabetes and impaired awareness of hypoglycemia. Few studies have been carried out on this topic in Japanese type 1 diabetes patients, and there are few reports examining the relationship between blood glucose level variability, which is thought to be related to hypoglycemia, and impaired awareness of hypoglycemia or severe hypoglycemia. There are also no such large-scale studies on Japanese type 1 diabetes.

The aim of the current study was to investigate the frequency of hypoglycemia unawareness and severe hypoglycemia in patients with type 1 diabetes, and to analyze the risk factors for them.

MATERIALS AND METHODS

Patients

The present study was carried out as a part of the Diabetes Study from the Center of Tokyo Women’s Medical University (DIACET) 2012–2018. This is a single-center observational study that carries out a questionnaire survey on diabetes treatment for patients who visit our outpatient clinic or are hospitalized, running for approximately 3 months starting around October every year. We selected type 1 diabetes patients who had participated in the study multiple times, we used the latest questionnaire data from that patient about hypoglycemia. Diagnostic criteria for type 1 diabetes and subtypes are based on those of the Japan Diabetes Society. Briefly, it classifies type 1 diabetes according to the length of time from the appearance of hyperglycemic symptoms to ketosis or ketoacidosis: fulminant type 1 diabetes mellitus (within a week), acute-onset type 1 diabetes mellitus (within 3 months) and slowly progressive insulin-dependent diabetes mellitus (>3 months). We classified fulminant type 1 diabetes mellitus and acute-onset type 1 diabetes mellitus into the acute group, and slowly progressive insulin-independent diabetes mellitus into the slow group. We excluded patients who underwent kidney transplantation or were on dialysis. We also excluded patients whose subtype of type 1 diabetes was unclear.

The total number of respondents to DIACET 2012–2018 was 12,952 (overall response rate 78.2%, the number of type 1 diabetes patients was 2,039), and the number of people analyzed in the current study was 1,619.

Questionnaire

In a self-administered questionnaire survey, we asked about hypoglycemia, complications and treatment details.

Regarding hypoglycemia, we asked about the presence and frequency of hypoglycemia within the past year, the presence and frequency of hypoglycemia unawareness within the past year, and whether they had experienced severe hypoglycemia within the past year. Hypoglycemia was defined as follows: blood glucose of ≤70 mg/dL or feeling a hypoglycemic symptom that was improved by taking carbohydrates. We asked patients “Have you experienced hypoglycemia in the past year?” If they answered “yes”, we asked them to indicate the frequency of hypoglycemia in a multiple-choice answer format.

We defined hypoglycemia unawareness as follows: blood glucose ≤70 mg/dL without symptoms or the help of a third party was required due to hypoglycemia. Patients were asked the following question to assess hypoglycemia unawareness: “Have you experienced hypoglycemia unawareness (hypoglycemia with a blood glucose level ≤70 mg/dL without experiencing symptoms or needing the help of a third party) in the past year?”. Participants could answer “yes” or “no”. If they answered “yes”, we then assessed the frequency of hypoglycemia unawareness through multiple-choice questions. Generally, severe hypoglycemia is defined as “an event requiring assistance of another person”. This includes cases where the patient is helped by people around the patient, such as their family members, and cases where the patient is taken to the hospital (severe hypoglycemia with medical treatment); the latter is presumed to be more severe than the former. In the present study, we focused on severe hypoglycemia with medical treatment. To gather this, we asked “Have you been treated at a medical institution for hypoglycemia in the past year?”. The number of hypoglycemia unawareness events per day was calculated from the responses to the multiple-choice questions. If “other” was selected, the data were excluded from the frequency analysis.

For the treatment method, information on the type and dose of insulin was asked about.

Regarding autonomic neuropathy, we asked about the existence of orthostatic dizziness, anhidrosis, hyperhidrosis, heartburn, many belches, stomach oppression, constipation, diarrhea, repeated diarrhea and constipation, fecal incontinence, polyuria, and dysuria in a questionnaire. For men, the existence of erectile disorder and ejaculation disorder was also asked about. The number of applicable symptoms was defined as the number of autonomic neuropathies. If this number was three or more, the patient was judged to have autonomic neuropathy.
Laboratory tests
We extracted subtypes of type 1 diabetes, blood glucose value, glycated hemoglobin (HbA1c), serum creatinine, estimated glomerular filtration rate, urine albumin creatinine ratio, body mass index, dose of insulin (shown by dividing the number of units by bodyweight [kg]), whether an insulin pump or intermittently scanned continuous glucose monitoring (isCGM) was being used, age, duration of diabetes, age at onset and the status of diabetic retinopathy from medical records. In previous studies, the coefficient of variation (CV) of blood glucose levels was generally calculated from the results of continuous glucose monitoring (CGM) or self-measured blood glucose levels. However, we used blood glucose levels measured at six outpatient visits. We used data obtained at the last six outpatient visits before the questionnaire, and the CV was calculated as the standard deviation/arithmetic mean × 100 (%) of the six blood glucose levels. In our center, there were no restrictions on whether blood was collected on an empty stomach or after a meal, which is at the discretion of the patient and the attending physician. The staging of diabetic nephropathy was based on Japan Diabetes Society criteria. For patients with no uACR data available, but with negative results on the last five urinary protein tests, we treated them as having a urinary albumin creatinine ratio <30 mg/gCr. Patients who were stage 2 or higher were classified as having nephropathy. The staging of diabetic retinopathy was based on the modified Davis classification, and simple diabetic retinopathy, preproliferative diabetic retinopathy and proliferative diabetic retinopathy were classified as having retinopathy.

Statistical analysis
Welch’s test was used to compare HbA1c in patients with and without hypoglycemia unawareness, and with and without severe hypoglycemia with medical treatment. Two multiple logistic models were used to identify risk factors for hypoglycemia unawareness and severe hypoglycemia with medical treatment. In model 1, the explanatory variables included age, sex, subtype of type 1 diabetes, duration of diabetes, number of hypoglycemia episodes per year, HbA1c, severe hypoglycemia with medical treatment (only in the analysis of severe hypoglycemia with medical treatment). In model 2, the CV of the blood glucose level, presence or absence of autonomic neuropathy, diabetic nephropathy and diabetic retinopathy were included as explanatory variables, in addition to those in model 1. The significance level was set to P < 0.05. Statistical analysis was carried out with JMP Pro 16.0.0 (SAS Institute Inc., Cary, NC, USA) and SAS version 9.4 (SAS Institute Inc.). This study was approved by the ethics committee of Tokyo Women’s Medical University (approval number 2481-R3). The patients confirmed their intention to participate in the study by returning the questionnaire.

RESULTS
Baseline characteristics are shown in Table 1. Of the 1,619 participants, 68% were women. The mean duration of diabetes was 21.7 ± 12.0 years. The mean HbA1c was 7.8 ± 1.2%. The frequencies of autonomic neuropathy symptoms are shown in Table 2. The number of participants with one or more symptoms was 1,062 (65.6%), the most common was constipation (23.6%).

Table 1 | Baseline characteristics of patients

| Characteristic                              | n   | %  |
|--------------------------------------------|-----|----|
| All patients                               | 1,619|
| Male/female                                | 515/1104|
| Age (years)                                | 48 ± 15|
| Subtype (fulminant/acute/SPIDDM)           | 63/1333/223|
| Age at diagnosis, years (n = 1,618)        | 258 ± 15.5|
| Duration of diabetes, years (n = 1,618)    | 217.7 ± 12.0|
| BMI, kg/m² (n = 1,591)                     | 23.3 ± 3.6|
| Total daily dose of insulin, units/day (n = 1,458) | 26.52 ± 20.54|
| Total daily dose of insulin, units/kg/day (n = 1,453) | 0.042 ± 0.29|
| Blood glucose level, mg/dL (n = 1,618)     | 163 ± 53|
| Coefficient of variation of blood glucose level, % (n = 1,612) | 39.5 (29.4–51.3)|
| HbA1c, % (n = 1,618)                       | 7.8 ± 1.2|
| eGFR, mL/min/1.73 m² (n = 1,617)           | 81.5 ± 21.9|
| uACR, mg/gCr (n = 1,553)                   | 5.4 (3.5–10.4)|
| Aspartate aminotransferase, U/mL (n = 1,541) | 203 ± 86|
| Alanine aminotransferase, U/mL (n = 1,557) | 173 ± 96|
| γ-Glutamyltransferase, U/mL (n = 1,516)    | 24 ± 32|
| Uric acid, mg/dL (n = 1,431)               | 43.1 ± 1.2|
| Experienced hypoglycemia unawareness, n (n = 1,613) | 713 (44.2%)|
| Experienced severe hypoglycemia with medical treatment, n (n = 1,579) | 165 (10.4%)|
| Using insulin pumps, n (%)                 | 44 (2.7%)|
| Using intermittently scanned CGM, n (%)    | 385 (23.8%)|
| Using real-time CGM, n (%)                  | 11 (0.7%)|
| Retinopathy                               |     |
| No diabetic retinopathy, n (%)             | 873 (53.9%)|
| Simple diabetic retinopathy, n (%)         | 431 (26.6%)|
| Preproliferative retinopathy, n (%)        | 33 (2.0%)|
| Proliferative retinopathy, n (%)           | 207 (12.8%)|
| Unknown, n (%)                             | 75 (4.6%)|
| Nephropathy                               |     |
| Stage 1, n (%)                             | 1,396 (86.2%)|
| Stage 2, n (%)                             | 133 (8.2%)|
| Stage 3, n (%)                             | 29 (1.8%)|
| Stage 4, n (%)                             | 26 (1.6%)|
| Stage 5, n (%)                             | 0 (0.0%)|
| Unknown, n (%)                             | 35 (2.2%)|

Data are shown as the median (25th percentile to 75th percentile) unless indicated otherwise. When urinary albumin was less than the measurement sensitivity, urinary albumin creatinine ratio (uACR) was treated as zero. The coefficient of variation of the blood glucose level was calculated from the last six outpatient visits before the questionnaire. BMI, body mass index; CGM, continuous glucose monitoring; eGFR, estimated glomerular filtration rate.
The frequencies of hypoglycemic events are shown in Table 3. Some 93.7% of participants had experienced hypoglycemia in the past year. The proportions of patients who experienced hypoglycemia unawareness and severe hypoglycemia with medical treatment were 44.2 and 10.4%, respectively. In addition, 140 (29.8%) of the patients who had experienced hypoglycemia unawareness answered that they had experienced severe hypoglycemia with medical treatment in the past year. The mean HbA1c in patients with hypoglycemia unawareness was lower than that of patients without hypoglycemia unawareness (7.6 ± 1.1 vs 7.9 ± 1.2%, P < 0.0001, Welch’s test). Between patients with and without severe hypoglycemia, no significant difference was found (7.6 ± 1.1 vs 7.8 ± 1.2%, P = 0.111, Welch’s test).

Multiple logistic regression
The results of the multiple logistic regression analyses with the presence of hypoglycemia unawareness as the dependent variable are shown in Table 4. In model 2, the subtype of type 1 diabetes (odds ratio in acute type 1.46, 95% confidence interval [CI] 1.00–2.11), HbA1c (odds ratio when changing by 1% 0.73, 95% CI 0.65–0.82), the CV of blood glucose level (odds ratio when changing by 1% 7.16, 95% CI 3.45–14.94) and history of severe hypoglycemia with medical treatment (odds ratio for patients with severe hypoglycemia 6.60, 95% CI 4.08–10.68) were significant independent variables.

In the multiple logistic regression with the presence of severe hypoglycemia with medical treatment as the dependent variable, the CV of blood glucose level (odds ratio when changing by 1% 4.36, 95% CI 1.52–12.52) and history of hypoglycemia unawareness (odds ratio for patients with hypoglycemia unawareness 6.57, 95% CI 4.06–10.64) were found to be significant independent variables in model 2 (Table 4).

Stratified analysis by CV of glucose and HbA1c
Stratified analysis of hypoglycemia unawareness and severe hypoglycemia was carried out with the patients divided into four groups according to the glucose CV and HbA1c. The threshold for the CV of glucose level was set at 36%, as this was reported as a threshold for glycemic instability by Monnier et al.26 The threshold for HbA1c was set at 7%, which is often set as a target for non-elderly, non-pregnant patients6,27. Thus, the four groups were high CV/high HbA1c, high CV/low HbA1c, low CV/high HbA1c and low CV/low HbA1c. The odds ratio of hypoglycemia unawareness and severe hypoglycemia with medical treatment was calculated using the low CV/high HbA1c group as a reference.

For hypoglycemia unawareness, the odds ratio was the highest, at 2.60 (95% CI 1.87–3.61, P < 0.001, Wald), in the high CV/low HbA1c group (Table 5). For severe hypoglycemia with medical treatment, the odds ratio was the highest, at 2.55 (95% CI 1.48–4.39, P < 0.001, Wald), again in the high CV/low HbA1c group (Table 5).

### Table 2 | Frequency of autonomic dysfunction

| Symptom                               | Frequency (n (%)) |
|---------------------------------------|-------------------|
| Orthostatic dizziness, n (%)          | 361 (22.3%)       |
| Anhidrosis                            | 48 (3.0%)         |
| Hyperhidrosis                         | 315 (19.5%)       |
| Heartburn                             | 142 (8.6%)        |
| Many belches                          | 104 (6.4%)        |
| Stomach oppression                    | 228 (14.1%)       |
| Constipation                          | 382 (23.6%)       |
| Diarrhea                              | 124 (7.7%)        |
| Repeated diarrhea and constipation    | 101 (6.2%)        |
| Fecal incontinence                    | 21 (1.3%)         |
| Polyuria                              | 226 (14.0%)       |
| Dysuria                               | 22 (1.4%)         |
| Erectile disorder†                    | 80 (15.5%)        |
| Ejaculation disorder†                 | 40 (7.8%)         |
| Having one or more symptoms           | 1,062 (65.6%)     |

†Percentage only in males.

### Table 3 | Frequency of hypoglycemia-related events

| Hypoglycemia | Hypoglycemia unawareness in past year | Needed medical assistance for hypoglycemia in past year |
|--------------|---------------------------------------|--------------------------------------------------------|
| Number of people who have experienced even once in the past year (%) | 1,517 (93.7%) | 713 (44.2%) | 165 (10.4%) |
| Frequency of event |                                      |                                                      |
| Approx. once per day or more | 171 (11.3%) | 44 (6.2%) | – |
| Approx. once per 2 days or more, less than above | 83 (5.5%) | 17 (2.4%) | – |
| Approx. once per week or more, less than above | 499 (32.9%) | 131 (18.4%) | – |
| Approx. once per month or more, less than above | 442 (29.1%) | 176 (24.7%) | – |
| Approx. twice per year or more, less than above | 213 (14.0%) | 192 (26.9%) | – |
| Approx. once per year | 27 (1.8%) | 102 (14.3%) | – |
| Unknown | 82 (5.4%) | 51 (7.2%) | – |
**DISCUSSION**

In the current study, we found that 93.7% of people with type 1 diabetes who used insulin experienced hypoglycemia, 44.2% of them experienced hypoglycemia unawareness and 10.4% of them experienced severe hypoglycemia with medical treatment in the past year. Factors correlated with hypoglycemia unawareness included acute-onset type 1 diabetes subtype, HbA1c, CV of glucose level and severe hypoglycemia with medical treatment. High-glucose CV and hypoglycemia unawareness were associated with severe hypoglycemia with medical treatment.

A 4-week prospective study by Khunti et al. reported that 83% of type 1 diabetes patients experienced hypoglycemia, 14% of whom had severe hypoglycemia. Approximately 20–25% of patients with type 1 diabetes have impaired awareness of hypoglycemia. The yearly prevalence of severe hypoglycemia varies from 1 to 53%, because the definition of severe hypoglycemia and the patient population differ between studies. The present

### Table 4 | Multivariate logistic regression analyses

| Independent variable | Hypoglycemia unawareness | Experienced severe hypoglycemia with medical treatment |
|----------------------|--------------------------|------------------------------------------------------|
|                      | Model 1 | Model 2 | Model 1 | Model 2 |
|                      | Odds ratio (95% CI) | P | Odds ratio (95% CI) | P | Odds ratio (95% CI) | P | Odds ratio (95% CI) | P |
| Age                  | 1.00 (1.00–1.01) | 0.343 | 1.01 (1.00–1.02) | 0.203 | 1.00 (0.99–1.01) | 0.919 | 1.00 (0.99–1.02) | 0.943 |
| Male sex             | 0.82 (0.64–1.04) | 0.102 | 0.82 (0.64–1.07) | 0.142 | 1.50 (1.03–2.19) | 0.035 | 1.42 (0.95–2.11) | 0.085 |
| Acute onset (fulminant or acute) | 1.52 (1.07–2.17) | 0.020 | 1.46 (1.00–2.11) | 0.047 | 1.22 (0.65–2.28) | 0.534 | 1.05 (0.55–1.98) | 0.883 |
| Duration of diabetes | 1.01 (1.00–1.02) | 0.029 | 1.01 (1.00–1.02) | 0.149 | 1.02 (1.00–1.03) | 0.028 | 1.02 (1.00–1.04) | 0.077 |
| HbA1c                | 0.78 (0.71–0.87) | <0.0001 | 0.73 (0.65–0.82) | <0.0001 | 0.98 (0.83–1.15) | 0.796 | 0.95 (0.79–1.14) | 0.609 |
| Frequency of hypoglycemia | 1.02 (0.82–1.26) | 0.863 | 0.96 (0.77–1.20) | 0.742 | 1.06 (0.77–1.46) | 0.733 | 1.09 (0.77–1.49) | 0.622 |
| Experienced severe hypoglycemia per day | 7.41 (4.66–11.78) | <0.0001 | 6.60 (4.08–10.68) | <0.0001 |
| Hypoglycemia unawareness | ref. | | 7.41 (4.66–11.78) | <0.0001 | 6.57 (4.06–10.64) | <0.0001 |
| CV of blood glucose level | 7.16 (3.47–14.94) | <0.0001 |
| Autonomic neuropathy (yes) | 1.23 (0.90–1.67) | 0.194 | 1.11 (0.69–1.78) | 0.677 |
| Retinopathy (yes) | 1.10 (0.75–1.64) | 0.618 | 1.14 (0.65–2.01) | 0.646 |
| Nephropathy (yes) | 0.93 (0.71–1.24) | 0.637 | 1.16 (0.75–1.79) | 0.516 |

For continuous variables, the odds ratio shows the value when the independent variable changed by 1 unit. Model 1: Adjusted for age, sex, subtype of type 1 diabetes, duration of diabetes, glycated hemoglobin (HbA1c), frequency of hypoglycemia per day, experience of severe hypoglycemia with medical treatment (only in analysis of hypoglycemia unawareness) and hypoglycemia unawareness (only in analysis of severe hypoglycemia needing medical treatment). Model 2: Model 1 + CV of blood glucose level, presence or absence of autonomic neuropathy, diabetic nephropathy, and diabetic retinopathy. CV, coefficient of variation.

### Table 5 | Odds ratio of hypoglycemia-related events stratified by the coefficient of variation of blood glucose and the glycated hemoglobin concentration

| Hypoglycemia unawareness | Severe hypoglycemia with medical treatment |
|--------------------------|------------------------------------------------|
|                          | Odds ratio (95% CI) | P-value | Odds ratio (95% CI) | P-value |
| Low CV, high HbA1c | ref. | | ref. | |
| Low CV, low HbA1c | 1.28 (0.90–1.82) | 0.167 | 1.21 (0.61–2.39) | 0.582 |
| High CV, high HbA1c | 1.51 (1.19–1.91) | <0.001 | 2.27 (1.46–3.52) | <0.001 |
| High CV, low HbA1c | 2.60 (1.87–3.61) | <0.001 | 2.55 (1.48–4.39) | <0.001 |

We defined a coefficient of variation (CV) of blood glucose ≥0.36 as high and <0.36 as low, and glycated hemoglobin (HbA1c) ≥7% as high and <7% as low. The low-CV/high-HbA1c group was used as a reference.
study had a higher proportion of patients who reported having hypoglycemia unawareness than previous studies investigating impaired awareness of hypoglycemia. Many previous studies have used the questionnaire by Clarke et al.¹⁰ or the questionnaire by Gold et al.⁹ to determine whether a participant had impaired awareness of hypoglycemia. The presence or absence of hypoglycemia unawareness or impaired awareness of hypoglycemia is not clearly divided, so the judgment might differ depending on the questions asked.

We found that factors associated with hypoglycemia unawareness included subtype of type 1 diabetes, HbA1c, CV of blood glucose level and severe hypoglycemia with medical treatment. Factors reported to be associated with impaired awareness of hypoglycemia include older age, longer duration of diabetes, severe hypoglycemia and frequency of hypoglycemia.⁸,¹³,¹⁵ A study of pediatric type 1 diabetes patients aged 6–19⁵¹ reported lower levels of HbA1c in patients with impaired awareness of hypoglycemia, consistent with the results of the present study. However, Geddes et al.¹³ found no significant difference in HbA1c between patients with normal awareness and impaired awareness of hypoglycemia. No report was found examining the correlation between subtypes of type 1 diabetes and impaired awareness of hypoglycemia or hypoglycemia unawareness.

Classifying type 1 diabetes into three subtypes, as the Japan Diabetes Society criteria do, is common in Japan, but not globally, so this might explain the sparseness of reports. Two studies¹⁹,³² reported that daily variation of blood glucose is a risk factor for hypoglycemia in type 1 diabetes patients. The involvement of autonomic dysfunction in impaired awareness of hypoglycemia has also been pointed out. Geddes et al.⁹ reported that patients with impaired awareness of hypoglycemia had a lower intensity of autonomic symptoms during hypoglycemia. In contrast, Olsen et al.⁴³ found no significant difference in autonomic function between patients with impaired awareness of hypoglycemia and normal awareness of hypoglycemia. Although age and duration were reported to be associated in previous studies,⁸,¹³,¹⁵ the present results did not show an association of these two variables. Possible explanations for this discrepancy include differences in patient ethnicity or criteria and overfitting. The factors associated with severe hypoglycemia with medical treatment were unawareness of hypoglycemia and the CV of blood glucose level in model 2. Impaired awareness of hypoglycemia has been associated with severe hypoglycemia in studies carried out in adults with type 2 diabetes¹⁴ and children⁵¹, consistent with the present study. Giorda et al.¹⁷ reported an association with neuropathy. We examined the association with autonomic neuropathy, but did not see a significant association. Disease duration has been associated with severe hypoglycemia¹⁷,¹⁸; this association was significant in model 1, but not significant in model 2 in the present study. We analyzed only severe hypoglycemia events that required medical treatment. This criterion was narrower than those of previous reports; thus, the difference in criteria might have produced the difference in results.

The CV value used in the current study was calculated from the blood glucose levels of patients during outpatient visits. This value is different from that of the CV of the glucose level calculated from CGM or self-monitoring of blood glucose (SMBG). The former represents glucose values mainly during the daytime on work days. The latter represents glucose values throughout the whole day. Therefore, the former value might be smaller than the latter. However, further study is required to clarify the association of these two CVs.

In our analysis of four groups defined by the thresholds of 36% CV of blood glucose level and 7.0% HbA1c, the odds ratio of hypoglycemia unawareness and the odds ratio of severe hypoglycemia with medical treatment in the high-CV/low-HbA1c group were 2.60 (95% CI 1.87–3.61, P < 0.0001, Wald) and 2.55 (95% CI 1.48–4.39, P < 0.0001, Wald), respectively. Therefore, it was possible to identify high-risk patients only by outpatient examination, without CGM. This does not mean that we do not recommend real-time CGM. In our center, >90% of patients with type 1 diabetes undergo blood glucose monitoring, including SMBG, isCGM and real-time CGM. The current study was based on DIACET carried out from 2012 to 2018, and isCGM was reimbursed in Japan in late 2017. Today, it seems that more than half of patients with type 1 diabetes use SMBG, approximately 30% use CGM and <10% use real-time CGM, including with a sensor-augmented pump. Even if medical staff propose using CGM, some patients do not want CGM for various reasons, such as medical costs, sensitive skin or the burden of wearing it all the time. Therefore, we thought it would be preferable to have a method to identify high-risk hypoglycemia unawareness and severe hypoglycemia groups without using CGM.

The results of the current study are in line with our original purpose, because we were able to identify a high-risk group for impaired awareness of hypoglycemia using the blood glucose level and HbA1c level at the time of outpatient consultation. The high-CV/low-HbA1c group had low average blood glucose and wide fluctuations in blood glucose levels, suggesting that they might be experiencing frequent hypoglycemia. The frequency of preceding hypoglycemia has been reported to be associated with impaired awareness of hypoglycemia,⁸,¹⁵, and impaired awareness of hypoglycemia is associated with severe hypoglycemia.⁹,¹³,¹⁴ We speculated that type 1 diabetes patients with low HbA1c and high glucose variability might have repeated hypoglycemia, develop impaired awareness of hypoglycemia and thus suffer severe hypoglycemia. Such patients are considered to be at relatively high risk of severe hypoglycemia, so we might consider setting higher target blood glucose levels for them, starting CGM if possible, providing appropriate treatment and educating them on blood glucose levels to avoid severe hypoglycemia in the near future. As HbA1c levels and the CV of the glucose levels calculated from ambulant blood sampling can be easily extracted from medical record without importing CGM or SMBG data, we can easily identify the high-risk group to prevent severe hypoglycemia by adding an
The strength of the present study was the large number of patients. There has been no other analysis of such large-scale hypoglycemia in Japanese type 1 diabetes patients. There were several limitations to the present study. First, whether each patient had hypoglycemia awareness or severe hypoglycemia was based on their answers to the questionnaire. Only a few patients used CGM, so there might have been hypoglycemia unawareness that they did not notice. Additionally, as we asked about hypoglycemia-related events over the past year, there might have been recall bias. We did not use the popular questionnaire by Clarke et al. or Gold et al., so care must be taken when comparing the present results with others. However, the current study showed how type 1 diabetes patients feel about hypoglycemia in their everyday real life.

Second, we did not investigate concomitant medications other than insulin. Drug-induced hypoglycemia has been reported for drugs, such as beta-blockers, quinolone antibacterial agents and angiotensin-converting enzyme inhibitors. Beta-blockers can also lower the threshold for hypoglycemic symptoms, which might predispose patients to hypoglycemia unawareness. In our department, few patients with type 1 diabetes are given beta-blockers, angiotensin-converting enzyme inhibitors have been changed to angiotensin receptor blockers in most patients and no patient is taking quinolone antibiotics on a regular basis. Therefore, the impact of these drugs is considered small.

Third, to achieve a clear diagnosis of diabetic autonomic neuropathy, other neurological disorders must be excluded, which is difficult at the outpatient level. The symptoms we investigated in the questionnaire are listed in Table 2. These symptoms were significantly more frequent in diabetes patients than in non-diabetes patients. We defined patients with three or more of these symptoms as having autonomic neuropathy and analyzed them accordingly. However, the results might have been different if the diagnosis had been made on the basis of quantitative tests, such as an orthostatic test or the R-R interval of an electrocardiogram.

In conclusion, factors correlated with hypoglycemia unawareness in patients with type 1 diabetes include fulminant type 1 or acute type 1 diabetes, low HbA1c, a high CV of blood glucose level and severe hypoglycemia with medical treatment. Factors correlated with severe hypoglycemia with medical treatment include a high CV of glucose level and hypoglycemia unawareness. Patients with a high CV of glucose level might require special attention to prevent hypoglycemia unawareness and severe hypoglycemia.

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Approval of the research protocol: This study was approved by the ethics committee of Tokyo Women’s Medical University.
Informed consent: The patients confirmed their intention to participate in the study by returning the questionnaire.
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