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【 ORIGINAL ARTICLE 】

Risk Factors for Hypoglycemic Coma: A Study of 33 Patients on Insulin Therapy Who Were Transported to the Hospital by Ambulance

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Abstract:

Objective Patients on outpatient insulin therapy are at a high risk of severe hypoglycemia and a high incidence of hypoglycemic coma. However, only a few studies have explored the risk factors for hypoglycemic coma in such patients. We retrospectively analyzed the clinical characteristics of diabetic patients who had developed hypoglycemic coma during outpatient insulin therapy.

Methods This study included 33 diabetic patients on insulin therapy who were transported to the hospital by ambulance for severe hypoglycemia. Patients with a Japan Coma Scale score <100 were classified as the non-coma group (n=18), while those with a score ≥100 (n=15) were classified into the coma group.

Results Patients in the coma group were significantly older, with a higher proportion of elderly patients (≥ 65 years of age), than those in the non-coma group. Although no marked difference in the basal insulin dose was observed between the two groups, the bolus insulin dose was significantly higher in the coma group. However, no marked differences in the disease type or renal function were noted between the two groups.

Conclusion An advanced age and bolus insulin dose are risk factors for hypoglycemic coma in diabetic patients on insulin therapy. Bolus insulin dose minimization should be performed in order to prevent hypoglycemic coma, especially in elderly diabetic patients.

Key words: insulin, hypoglycemic coma, diabetes in the elderly

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Introduction

Strict glycemic control in patients with diabetes mellitus can prevent the onset and progression of microvascular diseases (1, 2). However, adherence to a strict glycemic control regimen increases the likelihood of severe hypoglycemia, including hypoglycemic coma (3). Previous clinical studies have indicated that the onset of severe hypoglycemia is associated with increased mortality (4, 5) and that recurrent or severe hypoglycemia may be a precipitating factor for dementia (6) or induce lethal cardiac arrhythmias or myocardial ischemia (7). In addition, hypoglycemic coma sometimes causes physical impediment or death (8). Thus, the prevention and management of hypoglycemia are important in the treatment of diabetes mellitus.

An estimated 1.8% of patients undergoing insulin therapy develop severe hypoglycemia at least once annually (9). Although insulin therapy is associated with a higher incidence of hypoglycemia than other antidiabetic therapies, only a few reports have investigated the clinical and laboratory factors associated with hypoglycemic coma in diabetic patients treated with insulin.

Therefore, the subjects in this study were limited to patients on insulin therapy. We retrospectively examined the clinical backgrounds of diabetic patients who were transported via ambulance due to hypoglycemic coma during insulin therapy.

Materials and Methods

The study included 33 diabetic patients on insulin therapy

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who developed severe hypoglycemia requiring ambulance transport to our hospital between April 1, 2006, and March 31, 2014. Severe hypoglycemia was defined as a plasma glucose level of ≤ 50 mg/dL associated with an impaired consciousness and requiring assistance from another person for hospital admission. The primary outcome was the factors that contributed to the development of hypoglycemic coma.

This study was conducted after the approval of the Human Ethics Committee of the University of Occupational and Environmental Health, Japan.

Collection of clinical information

The following clinical characteristics were assessed: age, gender, body mass index (BMI), type of diabetes mellitus, disease duration, insulin dose, plasma glucose level at the time of arrival at our hospital, glycosylated hemoglobin (HbA1c) level, and the renal function. Patients ≥65 years of age were defined as elderly patients. Based on the severity of the coma as assessed by the Japan Coma Scale (JCS) at the time of ambulance transportation, the patients were divided into two groups to analyze their clinical characteristics: the non-coma group (JCS score: <100) and the coma group (JCS score: ≥100). The JCS is widely used as a scale for evaluating the consciousness level in Japan. Disturbance of consciousness is classified into the following three categories according to the arousal level: (I) a state in which the patient is awake without any stimulus (represented in 1-digit codes); (III) a state in which the patient wakes up after stimulation (represented in 2-digit codes); and (III) a state in which the patient does not wake up even after stimulation (represented in 3-digit codes). Each category is further classified into three subcategories with codes (10).

Laboratory tests

The HbA1c levels (%) were measured with high-performance liquid chromatography using a Tosoh HLC-723 G8 (Tosoh, Kyoto, Japan) and expressed as the National Glycohemoglobin Standardization Program (NGSP) value, which was calculated by adding 0.4% to the HbA1c levels expressed as the conventional Japanese standard substance value (Japan Diabetes Society value) (11). The renal function was assessed using the estimated glomerular filtration rate (eGFR), taking into consideration the age, gender, and serum creatinine (Cre) concentration using the revised abbreviated Modification of Diet in Renal Disease equation (12). The eGFR was calculated using the following equation: eGFR (mL/min/1.73 m^2)=0.741×175× $age^{-0.203}$ × $Cre^{-1.154}$ (×0.742 for women).

Statistical analyses

Numerical values are expressed as the mean±standard deviation. The Data of two groups were compared by Wilcoxon's signed-rank test (for normal distribution) and the Mann-Whitney *U* test (for skewed distribution). For categorical data, Fisher's exact test was performed when the expected value was 5 or less, and a χ^2 test was performed for categorical data with other expected values. Data from the coma and non-coma groups were analyzed by univariate and multivariate logistic regression analyses. The odds ratios and 95% confidence intervals (CIs) were presented for all data. A multivariate logistic regression analysis was performed with the forward selection model using factors that showed p values of <0.25 on a univariate analysis after excluding factors with multicollinearity based on a Spearman's correlation analysis. A p value <0.05 was considered to indicate statistical significance. The SPSS Statistical Software program, ver. 22.0 (SPSS, Chicago, USA), was used for the analyses.

Results

Clinical characteristics of the study participants

During the observation period, a total of 23,940 patients were transported via ambulance to our hospital. Among them, 43 patients had severe hypoglycemia, and 33 of these 43 patients were receiving insulin therapy for diabetes. The diagnoses of the remaining 10 patients were type 2 diabetes treated with SU agents (n=6), drug-induced hypoglycemia (n=1), reactive hypoglycemia (n=1), alcoholic hypoglycemia (n=1), and hepatic encephalopathy (n=1). Table 1 shows the baseline characteristics of all 33 diabetic patients on insulin therapy who required ambulance transportation to our hospital for impaired consciousness associated with severe hypoglycemia (15 men and 18 women). The mean age was 65.0± 17.4 years, with 21 (63.6%) elderly patients. Ten patients (30%) had type 1 diabetes mellitus, and the mean plasma glucose level immediately upon hospitalization was 37.8± 13.5 mg/dL.

Of the 10 patients with type 1 diabetes, 3 had slowly progressive type 1 diabetes. One of the patients with type 2 diabetes had concomitant hepatic encephalopathy due to chronic hepatitis C. No patients had pancreatic diabetes. Diabetic complications were neuropathy in 13 patients, retinopathy in 9, and nephropathy in 6 (including 1 who was on maintenance dialysis). In addition, 3 patients had cardiovascular disease, and 3 had cerebrovascular disease. No patients were taking anti-dementia drugs.

Twelve patients required intensive insulin therapy (36.3%), 1 was treated with basal insulin alone (3.0%), 10 were treated with bolus insulin alone (30.3%), and 10 were treated with biphasic insulin (30.3%). The insulin doses were 30.8±13.0 units overall, 10.4±10.4 units for basal insulin, and 20.8±12.1 units for bolus insulin. Biphasic insulin was included in the analysis of bolus and basal insulin doses with consideration of the mixed ratio. The other drugs used by the patients at the time were oral hypoglycemic agents (n=5), α-glucosidase inhibitors (n=2), pioglitazone (n=2), and biguanide (n=4). None used sulfonylurea.

The causes of hypoglycemia were failure to take a meal after insulin administration in 4 patients (12.1%), nonadherence to sick day rules of insulin dosage adjustment in

Table 1. Patient Baseline Characteristics.

Variables	Measurements
Age (years)	65.0±17.4
Gender (male/female)	15/18
Perform SMBG, n (%)	6 (18)
Solitary person, n (%)	1 (3)
Glucose intake before emergency transportation, none, n (%)	10 (30)
Alcohol intake before emergency transportation, none, n (%)	8 (24)
Body mass index (kg/m^2) (n=16)	21.6±2.8
Type 1 diabetes n (%)	10 (30)
Duration(years) (n=23)	18.7±12.3
Plasma glucose, mg/dL (n=28)	37.8±13.5
HbA1c (%) (n=25)	7.5±1.4
eGFR (mL/min/1.73 m^2)(n=32)	63.0±30.4
Oral hypoglycemic agent (n)	αGI (2), TZD (2), BG (4)

Data are presented as mean±standard deviation, SMBG: self-monitoring of blood glucose, HbA1c: glycosylated hemoglobin, eGFR: estimated glomerular filtration rate, αGI: alphaglucosidase inhibitor, TZD: thiazolidinedione, BG: biguanide

Table 2. Characteristics of Patients with Coma.

	Coma group (n=15)	Non-coma group (n=18)	p value
Age (years)	72.1±12.1	58.3±19.2	0.023
Older than 65 years (%)	83.3	40.0	0.006
Body mass index (kg/m^2) (n=16)	22.4±3.0	20.6±2.3	0.203
Type 1 diabetes, n (%)	4(26.7)	6(33.3)	0.367
Duration(years) (n=23)	25.0±14.1	13.0±6.7	0.034
Basal insulin amount (U)	7.9±8.1	12.8±12.0	0.232
Bolas insulin amount (U)	26.1±13.8	15.9±7.9	0.040
Total insulin amount (U)	34.0±12.0	27.8±13.5	0.105
Plasma glucose, mg/dL (n=28)	31.0±8.1	43.6±14.7	0.015
HbA1c (%) (n=25)	7.4±1.5	7.5±1.4	0.782
eGFR (mL/min/1.73 m^2)	62.7±30.1	63.2±31.6	0.428

Data are presented as mean±standard deviation and a p value of less than 0.05 was considered to be statistically significant. Data are results of Mann-Whitney analysis.
HbA1c: glycosylated hemoglobin, eGFR: estimated glomerular filtration rate

10 patients (30.3%), increased physical activity above usual levels in 4 patients (12.1%), the administration of an insulin dose modified according to the patients' own judgment after the onset of hyperglycemia in 3 patients (9.1%), and unknown causes in 12 patients (36.4%). Hypoglycemia occurred before a meal in 9 patients (27.3%), after a meal in 18 patients (54.5%), and during the night/sleep in 6 patients (18.1%).

Six patients were admitted to the hospital, and their mean length of stay was 12 days. In all patients, the intravenous injection of glucose solution at the Emergency Department resulted in the resolution of symptoms. None of the patients died or suffered any serious complications (e.g. cardiac arrhythmias or myocardial ischemia).

In Japan, patients with consciousness disturbance are transported by ambulance to hospitals, during which blood glucose measurements or glucose injections are not usually carried out by emergency crews. All patients in the present study were diagnosed with hypoglycemia and received intravenous glucose after arriving at the hospital. In addition, one patient received intravenous glucose and intramuscular glucagon after transportation.

Characteristics of patients with coma

The consciousness level at the time of transportation was JCS 1 in 11 patients, JCS 2 in 1, JCS 3 in 1, JCS 10 in 1, JCS 30 in 1, JCS 100 in 8, JCS 200 in 7, and JCS 300 in 3. Table 2 shows the results of a comparison of the coma (n=15) and non-coma groups (n=18). Patients in the coma group were older (age: 72.1±12.1 years) than those in the non-coma group (58.3±19.2 years) (p=0.023). The percentage of elderly patients was significantly higher in the coma group than in the non-coma group (83.3% vs. 40.0%, p=0.006). Furthermore, the disease duration (n=26) was significantly longer in the coma group than in the non-coma group (25.0±14.1 vs. 13.0±6.7 years, respectively, p=0.034).

While there was no significant difference in the basal insulin dose between the two groups, the bolus insulin dose

was significantly higher in the coma group (26.1±13.8 units) than in the non-coma group (15.9±7.9 units, p=0.040). Furthermore, the mean plasma glucose level in the coma group upon arrival at our hospital (31.0±8.1 mg/dL) was significantly lower than that in the non-coma group (43.6±14.7 mg/dL, p=0.015). However, there were no significant differences in the type of diabetes mellitus, BMI, or eGFR.

Discussion

Among diabetic patients on insulin therapy, the present study identified advanced age (≥ 65 years) and high bolus insulin dose as significant and independent risk factors associated with the development of hypoglycemic coma, regardless of the type of diabetes mellitus and HbA1c level.

The incidence of hypoglycemia increases with age (13), and the frequency of emergency transportation is several times higher in elderly diabetic patients treated with insulin than younger patients (14). One possible reason for the need for ambulance transportation is that elderly diabetic patients are likely to suffer from hypoglycemia unawareness because autonomic symptoms, such as palpitation, trembling of hands, and cold sweat, are attenuated or disappear in old age. It is also possible that the detection of hypoglycemia in elderly patients lags behind that of the younger patients due to its association with atypical symptoms, such as blurred vision, dizziness, weakness, awkward movements, and loss of motivation, which is likely to result in severe hypoglycemia (15). Furthermore, it is known that repeated episodes of hypoglycemia unawareness lower the plasma glucose threshold at which hypoglycemia-induced symptoms related to the sympathetic nervous system appear and elevate the threshold of the appearance of central nervous system symptoms (16, 17). In other words, elderly patients are likely to develop central nervous system symptoms before they become aware of hypoglycemic symptoms; consequently, elderly patients are not promptly treated for hypoglycemia and are prone to develop severe hypoglycemia. The present study also showed that advanced age (≥65 years) is a risk factor for hypoglycemic coma in diabetic patients treated with insulin.

The incidence of hypoglycemia is reported to be higher in patients treated with bolus insulin alone than in those treated with basal insulin alone (18). The present study also showed that patients receiving high bolus insulin doses were more likely to develop hypoglycemic coma. Furthermore, patients who did not take a meal after insulin administration and those who did not adhere to the sick day rules accounted for approximately 42% of the patients who received high bolus insulin doses and developed hypoglycemic coma in the present study. This suggests that both patients and their caretakers did not sufficiently understand the concept of insulin dosage adjustment and that many patients failed to take prophylactic measures against hypoglycemia. Thus, it seems important to provide thorough diabetes education including the concept of insulin dosage adjustment when insulin therapy is administered to diabetic patients, especially in elderly patients.

In the present study, failure to adhere to the sick day rules was responsible for severe hypoglycemia in approximately 30% of diabetic patients on insulin therapy. Although hypoglycemia is reported to occur most frequently between 5:00 AM and 6:00 AM in patients on insulin therapy (19), in the present study, severe hypoglycemia occurred most commonly after a meal. This finding suggests that patients with severe hypoglycemia included those who administered bolus insulin, including biphasic insulin, at the predetermined normal doses without dose reduction although less food than usual was consumed on sick days. Particularly in elderly diabetic patients, it can be expected that the amount of food consumed varies and that cognitive impairment affects judgment on sick days. Thus, in cases of elderly diabetic patients, it is important to instruct not only the patients themselves but also their caretakers on the sick day rules.

The present study has several limitations. First, this was a single-center retrospective study. Second, the sample size was relatively small. Third, 12 patients (36.4%) were not being treated with basal insulin, so the influence of basal insulin doses on coma may not have been fully assessed. Further large-sample multicenter studies are needed to confirm the results of the present study.

In conclusion, the present study identified advanced age and high bolus insulin dose as potential risk factors for hypoglycemic coma in diabetic patients on insulin therapy, regardless of the type of diabetes mellitus. In addition to diabetes education for both patients and their caretakers, the doses of bolus or biphasic insulin should be minimized in elderly diabetic patients on insulin therapy, with due consideration of possible decreases in food consumption due to sick days and other reasons.

The authors state that they have no Conflict of Interest (COI).

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