

# Risk Factors of Hypoglycemic Encephalopathy and Prolonged Hypoglycemia in Patients With Severe Hypoglycemia

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## Abstract

**Background:** The aim of the study was to investigate risk factors of hypoglycemic encephalopathy (HE) in patients with severe hypoglycemia.

**Methods:** We retrospectively enrolled patients with severe hypoglycemia who were transported to the emergency department in an ambulance. We defined severe hypoglycemia as plasma glucose level < 60 mg/dL (or capillary levels < 50 mg/dL). HE was defined as severe hypoglycemia with altered level of consciousness (Glasgow coma scale < 12) and prolonged HE as coma or stupor lasting > 24 h after glucose administration. We compared several parameters between patients with and without HE and between prolonged and recovered patients.

**Results:** Included were 173 patients with severe hypoglycemia; of them, 94 were diagnosed with HE, with 12 of them prolonged HE. Glucose level in HE patients was lower than that in those without HE ( $P < 0.001$ ). Moreover, we noted a significant difference in glucose levels between the prolonged and recovered groups. Furthermore, body temperature was higher in prolonged versus recovered patients ( $P = 0.0017$ ).

**Conclusion:** Blood glucose level may be correlated with severity of altered level of consciousness. In addition, body temperature may be related to coma or prolonged stupor.

**Keywords:** Hypoglycemic encephalopathy; Severe hypoglycemia; Body temperature

## Introduction

Severe hypoglycemia is a common metabolic event in the emergency department (ED). It may cause irreversible altered levels of consciousness, cognitive decline, and death [1]. A case-control study examining patients' social status and self-management revealed that a previous episode of hypoglycemia and inadequate blood glucose monitoring were risk factors for severe hypoglycemia [2]. In addition, hypoglycemic encephalopathy (HE) is a critical condition with poor clinical outcome [3]. Ikeda et al revealed that higher body temperature and low lactic acid levels may be factors in predicting poor prognosis in HE [4]. On magnetic resonance imaging, early changes in the brain due to hypoglycemia were seen in the internal capsule and extended to the hemispheric white matter [5]. Understanding the risk factors for HE is useful in treating hypoglycemia and preventing HE; however, few studies have examined the risk factors for progression to HE in severe hypoglycemic patients. Therefore, the aim of this study is to elucidate: 1) The risk of clinical background and metabolic parameters of HE; and 2) The prolonged aspect of HE.

## Materials and Methods

### Study participants

This was a retrospective, single-center, observational cohort study. We enrolled patients with severe hypoglycemia who were transferred by ambulance to the ED at Jichi Medical University, Saitama Medical Center between April 2009 and March 2018. The definition of severe hypoglycemia was an event requiring the assistance of another person and a plasma glucose level < 60 mg/dL (or capillary levels < 50 mg/dL) [6]. We included patients aged > 20 years who were transported to our ED with severe hypoglycemia, and we excluded patients with glucose levels  $\geq 60$  mg/dL or those with unknown glucose levels.

### Study design

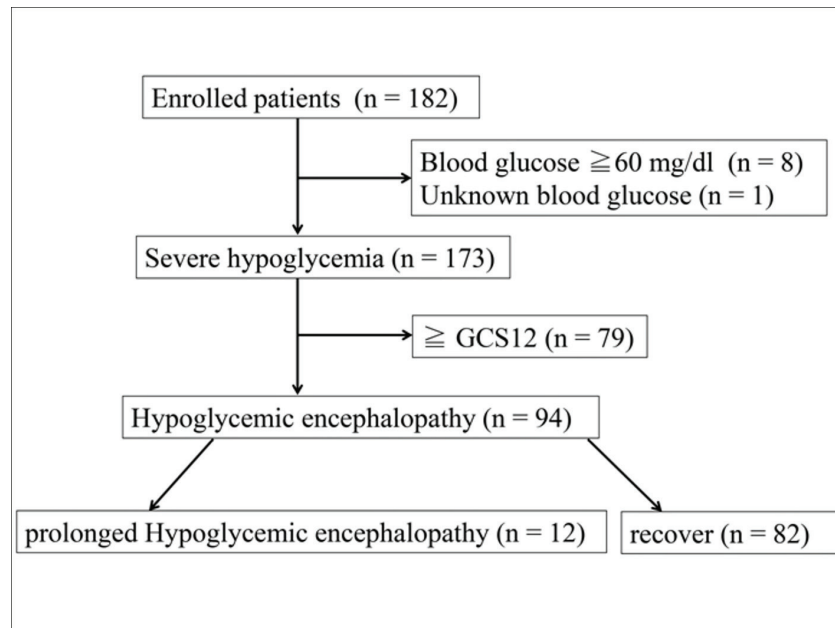
We defined HE as severe hypoglycemia with altered levels of consciousness and a score of < 12 on the Glasgow coma scale

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**Figure 1.** Flow chart of patient enrollment throughout the study.

(GCS) (scores range from 3 to 15, with lower scores suggesting reduced levels of consciousness) [7]. In addition, we defined prolonged HE as comatose cases or those in a prolonged stupor for > 24 h after glucose administration. We divided the participants into two groups of those with and without HE (GCS  $\geq$  12). Moreover, HE patients were classified into the prolonged HE group and the recovered group. Cases with episodes of emergency transport for severe hypoglycemia or those in whom HE was suspected at least once were included in the HE group.

### Data collection

We reviewed medical records and assessed the physical findings, blood tests, and clinical outcomes for all patients. Axial body temperatures were checked on arrival at the ED with an electronic thermometer. We obtained drug information and dosage for patients with diabetes mellitus.

We defined high-dose sulfonylurea as > 2 mg glimepiride, > 40 mg gliclazide, and > 1.25 mg glibenclamide.

### Ethical approval

This study was approved by the Ethics Committee of the Jichi Medical University, Saitama Medical Center (No. S16-76) and conformed to the ethical guidelines of the Declaration of Helsinki. Formal consent is not required for this retrospective type of study.

### Statistical analysis

Data were presented as mean  $\pm$  standard deviation (SD), and

skewed variables were described as median and interquartile range. We compared patient characteristics upon presentation to the ED between the two groups using the Student *t*-test or the Mann-Whitney U test. The Fisher's exact test was used to compare categorical variables. All analyses were performed with EZR (Jichi Medical University, Saitama Medical Center), a graphical user interface for R (v. 2.13.0; The R Foundation for Statistical Computing, Vienna, Austria), and a modified version of the R commander (v. 1.6-3), which was designed to add statistical functions frequently used in biostatistics research [8].  $P < 0.05$  was considered statistically significant.

## Results

### Patient characteristics

Initially, we identified 182 eligible patients; however, nine were excluded because their glucose level was  $\geq$  60 mg/dL or unknown, for a total study enrollment of 173 patients (Fig. 1). Table 1 shows the patients' basic characteristics. Severe hypoglycemia in other 168 patients was considerably caused by anti-hyperglycemic drugs. Figure 2a shows causative drugs for severe hypoglycemia in the overall patient population and Figure 2b shows those for type 2 diabetes. Insulin was the major causative agent in patients overall; however, sulfonylurea was the major agent in patients with type 2 diabetes. We itemized data for the other drugs in Supplementary Tables 1 and 2 ([www.jocmr.org](http://www.jocmr.org)). None of the 173 patients were prescribed sodium-glucose cotransporter-2 inhibitors (SGLT2is). Three patients took glucagon-like peptide-1 receptor agonist (GLP-1RA), but one patient used GLP-1RA together with glinide and two patients used it with insulin. The sulfonylurea-induced

**Table 1.** Baseline Demographic and Clinical Parameters of Participants (n = 173)

Overall clinical parameters	
Type of diabetes	
Type 1 diabetes, n (%)	33 (19.1)
Type 2 diabetes, n (%)	119 (68.8)
Others, n (%)	21 (12.1)
Age (years)	73 (64 - 81)
Male, n (%)	89 (51.4)
Duration of diabetes (years)	20.1 ± 10.5
BMI (kg/m <sup>2</sup> )	22.8 ± 4.4
eGFR (mL/min/1.73 m <sup>2</sup> )	56.8 (26.6 - 78.5)
Blood glucose (mg/dL)	32.1 ± 11.1
HbA1c (%)	7.2 (6.2 - 7.9)
Causes of hypoglycemia	
Medication, n (%)	168 (97.1)
Alcohol abuse, n	1 (0.6)
Others, n	4 (2.3)
Severe complications	
No, n (%)	162 (93.6)
Yes, n (%)	11 (6.4)
Complications, n	
Cardiovascular disease	2
Death	7
Others (fracture, subdural hemorrhage)	2
Prior history of severe hypoglycemia	
No, n (%)	130 (75.1)
Yes, n (%)	43 (24.9)

Data are expressed as mean ± standard deviation (SD), and skewed variables are described as median and interquartile range. BMI: body mass index; HbA1c: glycosylated hemoglobin; eGFR: estimated glomerular filtration rate.

hypoglycemic patients were significantly older than the insulin-induced hypoglycemic patients ( $P < 0.001$ ). No significant difference in estimated glomerular filtration rates (eGFRs) was seen between those with insulin- and sulfonylurea-induced hypoglycemia ( $P = 0.083$ ) (Table 2). Figure 3 shows the age and eGFR distribution in diabetic patients with sulfonylurea-, insulin-induced severe hypoglycemia and other hypoglycemic patients ( $n = 173$ ). Patients taking sulfonylureas were older than those taking insulin; however, we could not identify a regular tendency of distribution.

### Comparison of clinical parameters between patients with and without HE

We examined several clinical parameters between HE patients and those with severe hypoglycemia ( $GCS \geq 12$ ) (Table 3).

HE patients had significantly lower blood glucose levels before glucose administration compared with non-HE patients. No significant difference was noted between causative drugs in those with or without HE (sulfonylurea, insulin, and other anti-hyperglycemic drugs) ( $P = 0.767$ ). We reviewed the dosage of sulfonylureas (high or low dose) in patients with sulfonylurea-induced severe hypoglycemia, and the differences between high and low dosage of sulfonylurea were not significant with glimepiride ( $P = 0.554$ ) or glibenclamide ( $P = 1.000$ ). Only two patients used gliclazide and both patients had HE.

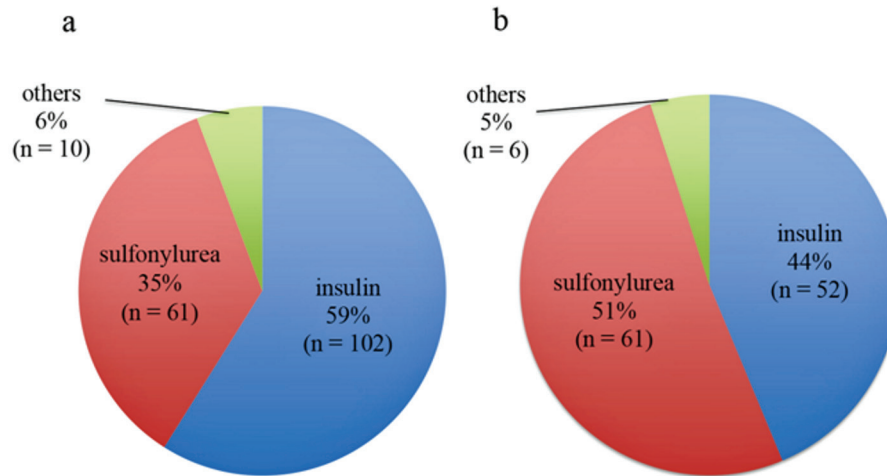
### Comparison of clinical parameters between prolonged and recovered HE

We examined the parameters between prolonged and recovered HE patients (Table 4), and found that blood glucose levels were significantly lower and body temperatures higher in prolonged HE patients with severe hypoglycemia.

## Discussion

In the present study, we showed that low blood glucose levels and higher body temperatures were predictors for HE in patients with severe hypoglycemia. In addition, almost all episodes of hypoglycemia were due to anti-hyperglycemic agents, and sulfonylureas in particular were a major causative factor in older patients with type 2 diabetes. Ikeda et al analyzed 165 HE patients and evaluated their clinical outcome, demonstrating that prolonged hypoglycemia, higher body temperature, and low levels of lactic acid were prognostic indicators of HE. In particular, hypothermia ( $< 35^\circ$ ) was observed more frequently in the patients with good outcomes compared to those with poor clinical outcomes [4]. Our results revealed that blood glucose levels and body temperature can affect HE outcome. Hypoglycemia is reported to induce neuronal death via mitochondrial dysfunction and oxidative stress [9, 10]. Ultimately, we considered hypoglycemia severity as a risk factor for HE and its progression. A retrospective study showed that hypothermia was observed in severe hypoglycemic patients and associated with lower body temperature and good GCS [11]. Hypothermia in hypoglycemia was considered to decrease energy demand [11]. Alternatively, Barbara et al reported that body temperature was not related to neurological outcome in hypoglycemic patients in an intensive care unit (ICU) [3]. These differences were due to patient background, disease severity, percentage of diabetes, and the department (ICU or ED). In addition, missing data might affect the results of retrospective studies; hence, further investigation is necessary to determine whether temperature significantly affects hypoglycemia or whether hypothermia may be a therapeutic option for HE patients.

In our causative drug analysis in patients with diabetes, use of sulfonylureas was a major risk factor for severe hypoglycemia, especially in older patients; however, there was no correlation with progression to HE. The patients with sulfonylurea-induced severe hypoglycemia were older compared



**Figure 2.** Major causative anti-hyperglycemic agents of severe hypoglycemia in the overall patient population (n = 173) (a) and those with type 2 diabetes (n = 119) (b).

**Table 2.** Comparison of Age and Renal Function Between Insulin and Sulfonylurea Users With Severe Hypoglycemia

	Insulin (n = 102)	Sulfonylurea (n = 61)	Other (n = 10)
Age (years)	69 (57.3 - 79)	77 (72.0 - 84)*	74 (68.5 - 80.8)
eGFR (mL/min/1.73 m <sup>2</sup> )	64.9 (27.4 - 86.7)	52.9 (28.3 - 67.4)	31.0 (13.6 - 55.1)

eGFR: estimated glomerular filtration rate. \*P < 0.001 vs. insulin users.

to those taking insulin, both in the overall population of severe hypoglycemic patients and the type 2 diabetes patients. Sulfonylurea dosage was not significantly associated with renal function (eGFR), suggesting that hypoglycemia severity can be associated with HE regardless of sulfonylurea dosage. Namba et al reported that in patients with type 2 diabetes, the sulfonylurea-induced group was older and their eGFRs were lower than in the insulin-induced group (Japan Diabetes Society Scientific Survey/Research Ethics Committee) [6]. This discrepancy can be attributed to the presence of dialysis patients. Our study included 12 dialysis patients and nine were

insulin users. Therefore, this could contribute to the comparatively low eGFR in the insulin-induced group. In our study, non-sulfonylurea agents (glinide, dipeptidyl peptidase-4 inhibitor, biguanide) were low risk for causing severe hypoglycemia (Supplementary Tables 1 and 2) ([www.jocmr.org](http://www.jocmr.org)), consistent with a previous multicenter survey [6].

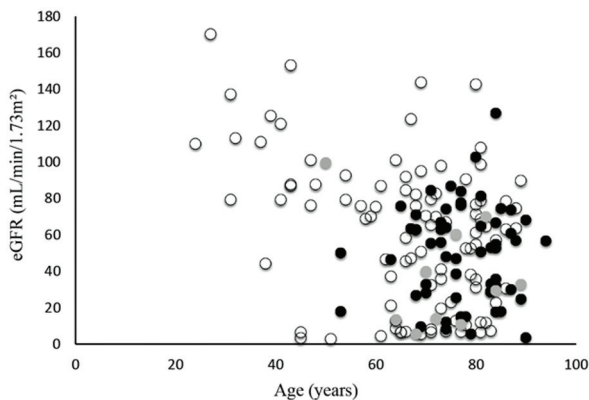
This study has several limitations that should be addressed. First, this was a single-center, retrospective cohort study; therefore, a larger number of participants are necessary. Second, we retrospectively collected data of hypoglycemic patients who were transferred to the ED; therefore, there were some missing values. In the statistical analysis, these missing data affected the result in this small number study. Finally, we only checked the axillary body temperature, and we could not investigate the air temperature at the time of arrival at the ED. The timing of transfer, whether during the day or night, and the seasons in Japan may affect the axillary body temperature.

**Conclusions**

Blood glucose levels before administration can be a clinical predictor of severity of altered levels of consciousness, and body temperature can be a risk factor for prolonged HE.

**Conflict of Interest**

The authors declare no conflict of interest.



**Figure 3.** Distribution of age and eGFR in sulfonylurea- or insulin-induced severe hypoglycemia. Black circles indicate sulfonylurea-induced hypoglycemia, white circles indicate insulin-induced hypoglycemia, and gray circles indicate other severe hypoglycemic patients.

**Table 3.** Difference Between the Hypoglycemic Encephalopathy Group and the Severe Hypoglycemic Group

Clinical parameters	HE (n = 94)	GCS $\geq$ 12 (n = 79)	P value	Presence of data (%)
Type 1 diabetes (%)	15 (16.0)	18 (22.8)	0.319	
Age (years)	73 (66.3 - 81)	72 (63.5 - 80.5)	0.364	
Sex (male, n/female, n)	49/45	40/39	0.845	
Causes of hypoglycemia				
Medication, n	91	77		
Alcohol abuse, n	1	0		
Others, n	2	2		
Causative drugs				
Insulin-induced, n (%)	53 (56.4)	49 (62.0)		
Sulfonylurea induced, n (%)	35 (37.2)	26 (32.9)		
Others, n (%)	6 (6.4)	4 (5.1)		
Time to hospital (min)	41 (31 - 49.8)	39 (31 - 52.0)	0.577	86.2/82.3
Blood glucose (mg/dL)	28.8 $\pm$ 11.3	36.0 $\pm$ 9.7	< 0.001	100/100
eGFR (mL/min/1.73 m <sup>2</sup> )	63.1 (28.75 - 79.2)	49.9 (21.1 - 74.6)	0.286	93.6/92.4
Body temperature ( $^{\circ}$ C)	35.8 (35.4 - 36.5)	36.0 (35.7 - 36.3)	0.812	78.7/78.5
Lactic acid (mmol/L)	11.8 (9.6 - 16.35)	9.5 (8.2 - 13.7)	0.176	54.3/21.5
Sodium (mEq/L)	138.5 $\pm$ 4.7	139.2 $\pm$ 4.4	0.346	97.9/94.9
Potassium (mEq/L)	3.9 $\pm$ 0.8	4.1 $\pm$ 1.0	0.226	97.9/94.9
Prior history of severe hypoglycemia, n (%)	25 (26.6)	18 (22.8)	0.563	

Data are expressed as mean  $\pm$  standard deviation (SD), and skewed variables are described as median and interquartile range. eGFR: estimated glomerular filtration rate.

**Table 4.** Difference in Clinical Parameters Between the Prolonged and Recovered Groups of Patients With Hypoglycemic Encephalopathy

Clinical parameters	Prolonged (n = 12)	Recovered (n = 82)	P value	Presence of data (%)
Type 1 diabetes, n (%)	1 (8.3)	14 (17.1)	1.000	75/90.2
Age (years)	73 (65.5 - 82.5)	73 (67.0 - 80.8)	0.883	
Sex (male, n/female, n)	6/6	43/39	1.000	
Causes of hypoglycemia				
Medication, n	10	81		
Alcohol abuse, n	1	0		
Others, n	1	1		
Causative drugs				
Insulin induced, n (%)	5 (41.7)	48 (58.5)		
Sulfonylurea induced, n (%)	4 (33.3)	31 (37.8)		
Others, n (%)	3 (25.0)	3 (3.7)		
Time to hospital (min)	54 (41.0 - 79.5)	41 (30.5 - 48.0)	0.051	91.7/86.6
Blood glucose (mg/dL)	22.2 $\pm$ 14.1	29.8 $\pm$ 10.6	0.028	100/100
eGFR (mL/min/1.73 m <sup>2</sup> )	69.7 $\pm$ 27.5	56.7 $\pm$ 37.3	0.250	100/92.7
Body temperature ( $^{\circ}$ C)	36.6 $\pm$ 1.15	35.8 $\pm$ 0.66	0.002	83.3/78.0
< 35 ( $^{\circ}$ C), n (%)	0 (0)	6 (8.8)	0.587	
Lactic acid (mmol/L)	17.2 (12.25 - 22.6)	11.3 (8.9 - 14.6)	0.084	91.7/48.8
Sodium (mEq/L)	140 (132.8 - 141.5)	140 (137.0 - 141.0)	0.820	100/97.6
Potassium (mEq/L)	4.00 $\pm$ 0.81	3.8 $\pm$ 0.76	0.574	100/97.6
Prior history of severe hypoglycemia, n (%)	3 (25)	22 (26.8)	1.000	

Data are expressed as mean  $\pm$  standard deviation (SD), and skewed variables are described as median and interquartile range. SU: sulfonylurea; eGFR: estimated glomerular filtration rate.



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