

# Risk factors of severe hypoglycemia requiring medical assistance and neurological sequelae in patients with diabetes

## A case-control study

Ja Young Jeon, MD<sup>a</sup>, Se Ran Kim, MD<sup>b</sup>, Hae Jin Kim, MD, PhD<sup>a</sup>, Dae Jung Kim, MD<sup>a</sup>, Kwan-Woo Lee, MD, PhD<sup>a</sup>, Jung-Dong Lee, MS<sup>c</sup>, Seung Jin Han, MD, PhD<sup>a,\*</sup>

### Abstract

Hypoglycemia commonly occurs in patients who are being treated for diabetes. In some cases, these patients suffer from severe hypoglycemia that requires medical assistance and which can unfortunately result in long-term disabilities. Therefore, we investigated risk factors associated with severe hypoglycemia requiring medical assistance (HMA) and the resulting neurological sequelae in patients with diabetes. This investigation was a case-control study that assessed 129 patients with diabetes and documented hypoglycemia from a single tertiary hospital between February 2013 and May 2015. They were treated with oral hypoglycemic agents alone (54%) or with insulin with/without oral hypoglycemic agents (46%). If a patient with diabetes visited the emergency department due to hypoglycemia, this was defined as HMA. The control group was composed of patients with documented, nonsevere hypoglycemia who visited the outpatient clinic during the same period. The degree of neurological disability in the HMA patients was measured using the modified Rankin Scale. A multivariate analysis revealed that independent risk factors of HMA were associated with a lack of the self-monitoring of blood glucose (SMBG) and previous episodes of severe hypoglycemia. In the HMA group, 15 patients (22%) had neurological sequelae at the time of discharge. Patients with neurological sequelae were older than those without sequelae (74.3 years vs 65.8 years,  $P=0.006$ ) and had increased psychological evidence of disorders such as insomnia, dementia, and depression (40% vs 11%,  $P=0.017$ ). Patients with sequelae were also more likely to live in rural areas (47% vs 19%,  $P=0.04$ ) and to have a longer time from last seen normal till glucose administration (5.2 hours vs 1.6 hours,  $P=0.027$ ). In the present study, absence of SMBG and previous severe hypoglycemic episodes were independent risk factors of HMA and patients with an older age, a psychological disorder, a rural residence, and a prolonged duration of hypoglycemia had higher risks of neurological sequelae. Therefore, the present findings suggest that physicians should aim to prevent hypoglycemia in patients with a history of hypoglycemia and provide education for these patients regarding regular SMBG.

**Abbreviations:** CI = confidence interval, ED = emergency department, eGFR = estimated glomerular filtration rate, HbA1c = glycated hemoglobin, HMA = severe hypoglycemia requiring medical assistance, mRS = modified Rankin Scale, NSH = nonsevere hypoglycemia, OHA = oral hypoglycemic agent, OR = odds ratio, SMBG = self-monitoring of blood glucose.

**Keywords:** diabetes, emergency department, neurological sequelae, self-monitoring of blood glucose, severe hypoglycemia

## 1. Introduction

In patients with diabetes, uncontrolled blood glucose levels are closely associated with the development of diabetic

complications.<sup>[1,2]</sup> Conversely, strict glycaemic control may increase the risk of hypoglycemia<sup>[3,4]</sup> which, in some cases, may even offset the expected beneficial effects of good glycaemic control.<sup>[5]</sup> Therefore, hypoglycemia may be an obstacle for good glycaemic control and should be an important factor to consider when determining the optimal glycaemic target during the selection of medications. This condition is not only observed in clinical practice and tends to develop more frequently in patients with type 1 diabetes and those being treated with insulin,<sup>[6]</sup> but also reported in patients taking oral hypoglycemic agents.<sup>[7,8]</sup>

The American Diabetes Association and the Endocrine Society Workgroup on Hypoglycemia recommend the following classifications for hypoglycemia in patients with diabetes: severe hypoglycemia, documented symptomatic hypoglycemia, asymptomatic hypoglycemia, probable symptomatic hypoglycemia, and pseudohypoglycemia.<sup>[9]</sup> Severe hypoglycemia is defined as a state of low blood glucose that requires the assistance of another person<sup>[9]</sup> and this condition can lead to emergency department (ED) visits and often results in hospitalizations that incur substantial medical costs.<sup>[10]</sup> Moreover, severe hypoglycemia is strongly correlated with the increased risk of adverse clinical outcomes, such as cardiovascular events and mortality<sup>[11–13]</sup> that

Editor: Federico Bertuzzi.

The authors have no conflicts of interest to declare.

Supplemental Digital Content is available for this article.

<sup>a</sup> Department of Endocrinology and Metabolism, <sup>b</sup> Department of Nephrology,

<sup>c</sup> Office of Biostatistics, Ajou University School of Medicine, Suwon, Republic of Korea.

\* Correspondence: Seung Jin Han, Seung Jin Han: Department of Endocrinology and Metabolism, Ajou University School of Medicine, 164, World cup-ro, Yeongtong-gu, Suwon, 443-380, Republic of Korea (e-mail: hsj@aumc.ac.kr).

Copyright © 2016 the Author(s). Published by Wolters Kluwer Health, Inc. All rights reserved.

This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

Medicine (2016) 95:47(e5365)

Received: 19 April 2016 / Received in final form: 30 September 2016 /

Accepted: 17 October 2016

<http://dx.doi.org/10.1097/MD.0000000000005365>

can lead to permanent disability, even following intensive care. Together, these conditions comprise a significant portion of the socioeconomic burden associated with diabetes.

Several studies have indicated that there are close associations between severe hypoglycemia requiring medical assistance (HMA) and advanced age, a longer duration of diabetes, higher glycosylated hemoglobin (HbA1c) levels, the presence of comorbid conditions such as depression, limited education levels, and the use of insulin or sulfonylurea.<sup>[14–17]</sup> However, risk factors for severe hypoglycemia and nonsevere hypoglycemia (NSH) may be quite disparate because these conditions are likely to occur under different circumstances.<sup>[18]</sup> A limited number of studies have investigated the associations of these conditions with the influence of self-management variables and socioeconomic status.<sup>[9,19,20]</sup> Therefore, we investigated whether diabetes self-management, education, socioeconomic status, and known risk factors for severe hypoglycemia were associated with HMA compared to NSH. We also determined the predictors of severe hypoglycemia with neurological sequelae.

## 2. Methods

### 2.1. Ethics statement

The protocol of this study was approved by the institutional review board of Ajou University Hospital and conformed to the ethical guidelines of the Declaration of Helsinki. All of the participants received and signed a statement of informed consent.

### 2.2. Study participants

The present investigation was a case–control study conducted using patients from a single tertiary hospital. If a patient with diabetes visited the ED and was subsequently diagnosed with hypoglycemia based on Whipple Triad<sup>[21]</sup> and clinical judgments, then the attending physicians in the ED diagnosed the patient with hypoglycemia and referred the individual to the endocrinology department; these cases were defined as HMA patients. Endocrinologists confirmed the diagnosis and patients were subsequently enrolled in the study after signing the consent forms.

Between February 2013 and May 2015, 69 HMA participants were identified using the above protocol and 60 control group participants, of comparable age, sex, and duration of diagnosed diabetes, with documented NSH were recruited from the diabetes outpatient clinic. Documented NSH was defined as a measured plasma glucose concentration more than 70 mg/dL or a recorded self-monitoring of blood glucose (SMBG) level less than 70 mg/dL and if the patient did not require third party medical assistance. All of the participants completed questionnaires assessing the following variables: the performance of SMBG, frequency of SMBG, history of previous hypoglycemia, previous hypoglycemia education, baseline knowledge of hypoglycemia, and socioeconomic status. If the mental status of a patient had deteriorated to the point that the researchers lacked confidence in the individual, their primary care giver completed the questionnaires.

All of the data were compiled and analyzed using a specialized case report form that included the duration of diagnosed diabetes, treatment modality, presence of diabetic complications, presence of comorbidities, and precipitating cause of hypoglycemia. The precipitating cause of hypoglycemia was assessed by a review of the patient's recent medical history by an attending physician. For cases of severe hypoglycemia, additional data regarding mode of arrival, origination of referral, time from last

seen normal till been witnessed, time from last seen normal till glucose administration, length of hospital stay, score on the modified Rankin Scale (mRS), and hospital discharge were reviewed. If the mRS score of a patient had increased at the time of discharge compared to their previous evaluation, they were diagnosed with HMA-associated neurological sequelae. All of the study participants had laboratory results measuring levels of blood and finger-stick glucose, HbA1c, and serum creatinine. The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation<sup>[22]</sup> and diabetic nephropathy was defined as albuminuria or an eGFR less than 60 mL/min/1.73 m<sup>2</sup>.

### 2.3. Statistical analyses

All data were analyzed using the SPSS statistical software package (version 22.0; SPSS Inc.; Chicago, IL) and the R software packages (R version 3.1.2; R Foundation for Statistical Computing; Vienna, Austria; <http://www.R-project.org/>). Continuous variables are presented as means  $\pm$  standard deviations (SDs) and Student *t* tests were used to compare the 2 groups. Categorical variables are presented as numbers and percentages and chi-squared ( $\chi^2$ ) tests with a Yates continuity correction was used to compare the 2 groups. To establish the independent risk factors of severe hypoglycemia, a multivariable logistic regression analysis was performed that included potential risk factors of HMA for which the *P* values in a univariate analysis were  $<0.05$ . A receiver operating characteristic curve was plotted to determine optimal models and multicollinearity between variables was detected using the variance inflation factor. The goodness of fit for the model in the multivariable logistic regression analysis was assessed with the Hosmer and Lemeshow test and 2-sided *P* values  $<0.05$  were considered statistically significant.

## 3. Results

### 3.1. Patient characteristics at baseline

Table 1 lists the demographic data and baseline characteristics of the 129 participants. Age, sex, body mass index, and duration of diagnosed diabetes were comparable between the HMA and control groups. The HMA group had lower baseline HbA1c and glucose levels compared to the control group (6.8% vs 7.3%,  $P=0.036$ ; 39.9 mg/dL vs 56.8 mg/dL;  $P<0.001$ , respectively). Fewer patients in the HMA group were treated with insulin therapy (32% vs 62%,  $P=0.001$ ), and more patients in the HMA group used oral hypoglycemia agents, especially sulfonylurea, compared with the NSH group (68% vs 38%,  $P=0.001$ ; see Table, Supplemental Content 1, <http://links.lww.com/MD/B403>).

The HMA group was less likely to perform SMBG than the NSH group (56% vs 90%,  $P<0.001$ ). In addition, the HMA group had a lower level of education than the control group ( $<9$  years of education: 62% vs 42%,  $P=0.037$ ).

When analyzing the precipitating events leading to hypoglycemia, 26% of patients in the HMA group displayed concomitant acute illnesses, such as pneumonia, influenza, acute renal failure, acute cholecystitis, gastroenteritis, and adrenal insufficiency. The HMA group also had a lower eGFR and a corresponding higher rate of nephropathy, but the difference between groups was not significant (47.6 mL/min/1.73 m<sup>2</sup> vs 56.6 mL/min/1.73 m<sup>2</sup>,  $P=0.087$ ; 77% vs 60%,  $P=0.056$ , respectively). More than half of the patients in the HMA group had experienced previous episodes of severe hypoglycemia that required third party treatment, whereas less than 10% of the NSH group had

**Table 1**  
Demographic data and baseline characteristics of the patients.

	Total (n=129)	HMA (n=69)	NSH (n=60)	P value
Age, y	66.3±10.0	67.7±10.7	64.7±9.0	0.092
Female, n, %	53 (41)	30 (44)	23 (38)	0.594
BMI, kg/m <sup>2</sup>	23.9±3.7	23.8±3.6	24.0±3.7	0.731
Duration of DM, y	14.1±8.8	13.6±8.3	14.7±9.3	0.481
HbA1c, %	7.0±1.4	6.8±1.5	7.3±1.4	0.036
Glucose, mg/dL	47.8±14.3	39.9±13.8	56.8±8.7	<0.001
eGFR, mL/min/1.73 m <sup>2</sup>	51.8±29.7	47.6±31.6	56.6±26.7	0.087
Type of treatment (insulin/OHA alone), n, %	59/70 (46/54)	22/47 (32/68)	37/23 (62/38)	0.001
SMBG, yes, n, %	91 (72)	37 (56)	54 (90)	<0.001
SMBG, freq/wk	8.3±10.2	5.4±8.6	11.0±11.0	0.003
<b>Complications</b>				
Retinopathy, n, %	52 (60)	26 (62)	26 (58)	0.827
Nephropathy, n, %	89 (69)	53 (77)	36 (60)	0.056
Neuropathy, n, %	64 (70)	36 (77)	28 (64)	0.251
<b>Precipitating cause of hypoglycemia</b>				
Diet change, n, %	79 (61)	43 (62)	35 (58)	0.719
Increased activity, n, %	7 (5)	2 (3)	5 (8)	0.249
Drug, n, %	50 (36)	19 (28)	26 (43)	0.067
Acute illness, n, %	18 (14)	18 (26)	0	<0.001
<b>Comorbidities</b>				
Hypertension, n, %	103 (80)	60 (87)	43 (72)	0.047
Psychological disease, n, %	17 (13)	12 (17)	5 (8)	0.192
<b>Socioeconomic status</b>				
Living status (alone), n, %	10 (7)	5 (7)	5 (8)	>0.99
Household income (< 850/850 to 2500/> 2500*, n, %)	39/72/18 (29/57/14)	21/39/7 (31/58/10)	15/33/11 (25/56/19)	0.263
Residence (rural), n, %	25 (19)	17 (25)	8 (13)	0.122
Education level (< 9 years), n, %	56 (51)	31 (62)	25 (42)	0.037
Previous severe hypoglycemia, n, %	42 (33)	37 (56)	5 (8)	<0.001
<b>Education for hypoglycemia</b>				
Hypoglycemia education, yes, n, %	46 (36)	26 (38)	20 (33)	0.713
Lack of knowledge on hypoglycemia, n, % <sup>†</sup>	46 (42)	26 (53)	20 (33)	0.051

BMI=body mass index, DM=diabetes mellitus, eGFR=estimated glomerular filtration rate, HbA1c=glycated hemoglobin, HMA=severe hypoglycemia requiring medical assistance, NSH=non-severe hypoglycemia, OHA=oral hypoglycemic agent, SMBG=self-monitoring of blood glucose.

\* Unit: US dollars.

<sup>†</sup> Only 109 subjects of the total 129 subjects answered this questionnaire.

previous episodes of severe hypoglycemia ( $P < 0.001$ ). Although the HMA and NSH groups did not significantly differ in terms of receiving education for hypoglycemia (38% vs 33%,  $P = 0.713$ ), the HMA group had a much larger probability of having severely lacking information or misinformation regarding symptoms, causes, and treatment of hypoglycemia compared to the NSH group (53% vs 33%,  $P = 0.051$ ).

The HMA group appeared to be more compliant than the NSH group when we analyzed the available data, excluding missing data from 18 patients in the HMA group (92% vs 77%,  $P = 0.038$ ; see Table, Supplemental Content S1, <http://links.lww.com/MD/B403>).

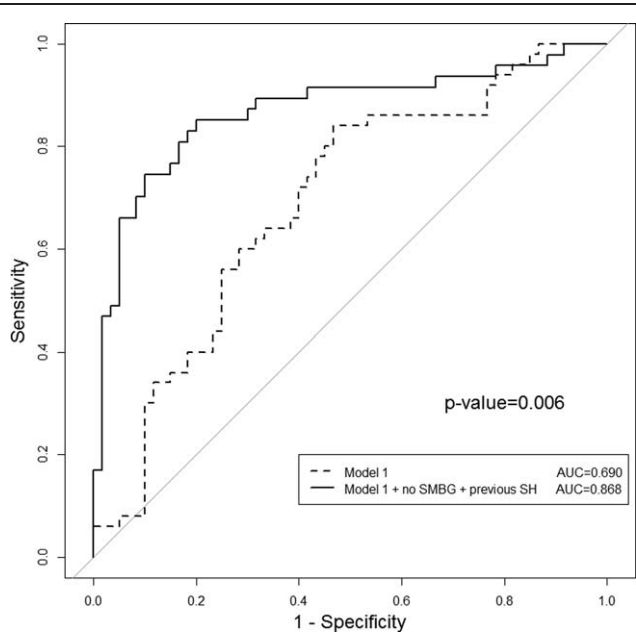
### 3.2. Risk factors for severe hypoglycemia that required medical assistance

Based on Model 2 from the multivariable logistic regression analysis, absence of SMBG and previous episodes of severe hypoglycemia were independent predictors of HMA (odds ratio [OR]: 4.43, 95% confidence interval [CI]: 1.30–15.1,  $P = 0.017$ ; OR: 22.0, 95% CI: 6.05–80.0,  $P < 0.001$ , respectively; Table 2). In addition, compared to Model 1, Model 2 showed an increased area under the receiver operating characteristic curve (0.690 vs 0.868, 95% CI: 6.08–82.4,  $P = 0.006$ ; Fig. 1) for prediction of HMA.

**Table 2**  
Multivariable logistic regression analysis of patients with severe hypoglycemia that required medical assistance.

Variables	Model 1		Model 2	
	OR (CI)	P value	OR (CI)	P value
Age	0.99 (0.94–1.04)	0.583	1.00 (0.94–1.06)	0.895
Female	0.93 (0.40–2.16)	0.472	1.47 (0.51–4.26)	0.480
HbA1c	0.88 (0.62–1.24)	0.875	1.06 (0.65–1.74)	0.806
Type of treatment (insulin)	0.40 (0.16–0.98)	0.045	0.38 (0.11–1.32)	0.127
Hypertension	1.93 (0.66–5.64)	0.228	2.92 (0.72–11.9)	0.292
Education level (> 9 years)	0.49 (0.20–1.20)	0.118	0.58 (0.17–1.97)	0.379
Not performing SMBG			4.43 (1.30–15.1)	0.017
Previous severe hypoglycemia			22.0 (6.05–80.0)	<0.001

CI=confidence interval, HbA1c=glycated hemoglobin, OR=odds ratio, SMBG=self-monitoring of blood glucose.



**Figure 1.** Receiver operating characteristic curves of models for predicting severe hypoglycemia requiring medical assistance. *P* value=0.006 between Model 1 and Model 2, SH=severe hypoglycemia, SMBG=self-monitoring of blood glucose.

**3.3. Risk factors associated with neurological sequelae**

Of the 69 patients in the HMA group, 15 (22%) had acquired neurological sequelae due to hypoglycemia at the time of discharge (Table 3). Older age, the presence of psychological diseases (eg, dementia, depression, and insomnia), residence in a rural area, and a prolonged duration of hypoglycemia were associated with the manifestation of neurological disabilities secondary to severe hypoglycemia. In the group with documented neurological sequelae, more cases were referred from other hospitals compared to the group with no sequelae (47% vs 12%, *P*=0.006). In addition, patients with sequelae were hospitalized for longer periods of time, had a higher mRS score at discharge, and were more likely to be discharged to a facility or nursing home (11.3 days vs 5.0 days, *P*=0.049; 2.9 vs 0.2, *P* < 0.001; 27% vs 8%, *P*=0.068, respectively).

**4. Discussion**

This study demonstrated that absence of SMBG and previous episodes of severe hypoglycemia were independently associated with an increased risk of HMA in patients with diabetes compared to patients with NSH. In addition, among patients who experienced HMA, those with an older age, a psychological disease, a prolonged duration of hypoglycemia, or who resided in a rural area were associated with the manifestation of neurological sequelae.

In previous studies that investigated severe hypoglycemia, subjects were primarily limited to insulin-treated patients,<sup>[23,24]</sup> and some were controlled clinical trials, which makes it difficult to apply the findings to clinical practice.<sup>[17,18]</sup> Moreover, other studies were based on data collected from large-scale databases and did not include information regarding the self-management or education of hypoglycemia.<sup>[6,14,16,25]</sup> Thus, due to the massive socioeconomic burden associated with HMA, the present study attempted to identify additional HMA-related risk factors using patients with NSH as control subjects, which is in significant contrast to previous studies that used nonhypoglycemic patients as control subjects.<sup>[6,15,16]</sup> As mentioned above, the control group in this study included patients who visited outpatient diabetic clinics during the same time period as when the HMA patients were recruited and were confirmed as having NSH based on SMBG reports. Furthermore, we assessed information regarding socioeconomic status and laboratory results at the time of hypoglycemia.

Since the first glucometer for the self-monitoring of capillary blood glucose was released in the early 1990s, SMBG has been widely recommended as a useful component of patient self-care practice. SMBG aids patients in the evaluation of their individual response to therapy and allows them to assess whether glycemic targets are being achieved. Thus, it is a tool for guiding the actions of the patient and physician with respect to changes in diet, physical activity, and the use of antihyperglycemic medications. In addition, SMBG helps to detect and prevent hypoglycemia.<sup>[26]</sup> In the present study, absence of SMBG was identified as an independent and modifiable risk factor of HMA. On the other hand, Tschope et al<sup>[27]</sup> showed that SMBG was a predictor of hypoglycemia in a prospective German registry. The authors explained that this was most likely due to an increased awareness of the condition in patients that were asymptomatic. Taken together, these findings suggest that SMBG aids in the detection of NSH and, therefore, is useful for the prevention of HMA.

**Table 3**

**Clinical characteristics and outcomes of the patients according to the neurological sequelae associated with hypoglycemia.**

	Total (n=69)	Sequelae (n=15)	No sequelae (n=54)	<i>P</i> value
Age, y	67.7 ± 10.7	74.3 ± 8.2	65.8 ± 10.7	0.006
Glucose, mg/dL	39.9 ± 13.8	37.8 ± 17.1	40.5 ± 12.8	0.500
Psychological disease	12 (17)	6 (40)	6 (11)	0.017
Residence (rural)	17 (25)	7 (47)	10 (19)	0.040
Mode of arrival (ambulance), n, %	45 (67)	12 (80)	33 (64)	0.351
Referral from other hospital, n, %	13 (19)	7 (47)	6 (12)	0.006
Time from last seen normal till been witnessed, h	1.8 ± 3.3	3.5 ± 4.6	1.4 ± 2.7	0.098
Time from last seen normal till glucose administration, h	2.4 ± 3.6	5.2 ± 5.2	1.6 ± 2.6	0.027
Hospital stay, d	6.4 ± 7.3	11.3 ± 11.1	5.0 ± 5.1	0.049
mRS score at discharge	0.7 ± 1.5	2.9 ± 1.6	0.2 ± 0.8	< 0.001
Discharge to facility, n, %	8 (12)	4 (27)	4 (8)	0.068

mRS=modified Rankin scale.

We also found that previous episodes of severe hypoglycemia were a strong determinant of future severe hypoglycemic episodes. This is consistent with previous studies that employed various study designs, subjects, and definitions of hypoglycemia.<sup>[16,17,23,28]</sup> Although we did not evaluate autonomic warning symptoms of hypoglycemia, it is likely that prior episodes of severe hypoglycemia impair neuroendocrine defense mechanisms.<sup>[29]</sup> This suggests that proper treatment is needed for high-risk patients to prevent severe episodes of hypoglycemia.

Although SMBG and hypoglycemia are vital parts of diabetes self-management education, only 36% of patients in this study had received education about hypoglycemia. The percentages of patients that received education about hypoglycemia were similar in both groups, but the HMA group tended to have a higher percentage of patients who lacked basic knowledge or had misinformation regarding the definition of hypoglycemia, its symptoms, causes and the corresponding treatments. It is likely that the HMA group had an overall lower level of education. In addition, the HMA group appears to be more compliant than the NSH group. After evaluating each case individually, many patients in the HMA group took medications as prescribed without adjusting their medications upon changes in their condition or experiencing hypoglycemia. Based on these results, it appears that there is a considerable knowledge gap between health-care providers and patients, which indicates that patients should be regularly provided with comprehensive information about the management of hypoglycemia.<sup>[9,30]</sup> From a socio-economic perspective, the Korean National Health Service does not reimburse costs for diabetes self-management education or home supplies, such as lancets, needles, and blood glucose test strips and this barrier may hinder diabetic patients from performing SMBG or receiving diabetes self-management training.

In the present study, hypoglycemic events occurred in all patients that had been treated with insulin or sulfonylurea, except for 2. Patients treated with insulin and sulfonylurea more frequently develop hypoglycemia than those treated with other hypoglycemic medications.<sup>[26]</sup> Physicians prefer to prescribe hypoglycemic agents that are less associated with hypoglycemia when treating patients with diabetes.<sup>[26]</sup> Although it is expected that hypoglycemic episodes are less likely to occur with the use of newly developed antidiabetic medications, such as dipeptidyl peptidase-4 inhibitors, glucagon-like peptide 1 receptor agonists, and sodium-glucose cotransporter 2 inhibitors, hypoglycemia remains a serious problem facing patients receiving diabetes treatment. Even if the American Diabetes Association recommendation of an HbA1c level less than 7% is applied,<sup>[31,32]</sup> only approximately half of diabetic patients is under adequate glycemic control, while the other half requires additional interventions, including additional hypoglycemic agents, to reach target glucose levels. However, as diabetes progresses, antidiabetic medications that increase the risk of hypoglycemia will be needed, and therefore, many patients with diabetes will still have taken sulfonylurea or received insulin treatment.<sup>[31,33]</sup> Although the rate of insulin treatment among total patients with hypoglycemic events in the present study was high considering the overall antidiabetic prescriptions patterns in Korea,<sup>[31]</sup> more than two-thirds of the HMA patients were treated with only oral medications and not insulin. Even so, the type of medication (insulin vs oral medications) is not an independent risk factor of HMA. In population-based studies, the incidence of severe hypoglycemia is consistently higher in insulin-treated patients than in those treated with oral medications alone.<sup>[6,14,16]</sup> Among

the patients who developed hypoglycemia, the proportion using insulin might be smaller than that using oral medications, because the proportion was correlated with the prescription frequency. Some studies reported a lower usage rate of insulin than oral medications alone in the HMA group.<sup>[15,41–43]</sup> The development of severe hypoglycemia as a result of sulfonylurea use may occur frequently because sulfonylurea, an oral hypoglycemic agent that can cause severe hypoglycemia, is prescribed more often than is insulin.<sup>[31,44–46]</sup> Based on our results, it is necessary to test for hypoglycemia in sulfonylurea-treated patients. Insulin-treated patients who perform SMBG properly can minimize the development of severe hypoglycemia.

Profound and prolonged hypoglycemia may cause transient or persistent neurological deficits.<sup>[34]</sup> Hypoglycemic encephalopathy or hypoglycemia-induced brain injury is a clinical syndrome with a broad clinical course and diverse outcomes.<sup>[35]</sup> Because of the lack of a generally acceptable clinical picture, only a few small-scale studies have attempted to identify predictors of neurological outcomes such as magnetic resonance imaging findings, initial glucose levels, and the duration of hypoglycemia.<sup>[35–38]</sup> In this study, the mRS, which is a validated clinical outcome scale,<sup>[39]</sup> was used to determine the degree of neurological disability in patients with severe hypoglycemia. This scale is useful because a patient's ability to perform daily activities corresponds to the socioeconomic burden of the disease.<sup>[40]</sup> Among patients with severe hypoglycemia in the present study, 22% did not recover their previous levels of daily activity despite the inpatient care for a mean time of 11.3 days. Furthermore, more than half of these patients had a mRS score more than 3, and therefore, required assistance with daily activities. In addition, older age, the presence of a psychological disease, residence in a rural area, and a prolonged duration of hypoglycemia were associated with poor HMA outcomes. Hospitalization due to severe hypoglycemia results in direct measurable medical costs, with the range of total medical costs per severe hypoglycemia episode reported to be from \$135.5 to \$1391.<sup>[41]</sup> However, these numbers do not take into account the hidden costs associated with permanent neurological sequelae that are related to increased disability and adjusted life-years of diabetes mellitus.

This study had several limitations. First, this was a case–control study in which the subjects were enrolled from a single tertiary center, which may have resulted in selection bias, and thus the results may not be generalizable to all patients with diabetes. Although we adjusted for a wide range of variables to identify risk factors for HMA in 2 groups that were comparable in terms of age, sex, and duration of diagnosed diabetes, the results may still be confounded by unmeasured factors. Second, because we designated the NSH group as patients with documented hypoglycemia, this group might include more individuals diagnosed via SMBG compared with the HMA group. Some of the patients with sequelae due to severe hypoglycemia did not revisit the hospital following their discharge, and thus, their long-term sequelae could not be evaluated. Finally, we defined HMA using only visits to ED due to hypoglycemia, and therefore, more severe cases that resulted in death before hospital visitation might have been missed.

## 5. Conclusions

Previous episodes of severe hypoglycemia and absence of SMBG were independent risk factors of HMA. In addition, older age, the presence of a psychological disease, residence in a rural area, and

a longer duration of diagnosed hypoglycemia were associated with poor neurological outcomes associated with severe hypoglycemia. These findings indicate that physicians should increase their efforts to educate patients on the importance of performing SMBG for the prevention of hypoglycemia as well as for maintaining glycemic control. Furthermore, patients who have experienced severe hypoglycemia and their families should receive supplemental education regarding hypoglycemia and the current treatment regimen of the patient should be reevaluated to prevent future hypoglycemic emergencies.

## Acknowledgments

The authors would like to thank Jacob R. Berry, MD for proofreading the manuscript. Jacob Berry is a graduate of the Uniformed Services University, F. Edward Hébert School of Medicine, and a medical English volunteer at Ajou University Hospital, Suwon, Republic of Korea.

## References

- Nathan DM, Group DER. The diabetes control and complications trial/epidemiology of diabetes interventions and complications study at 30 years: overview. *Diabetes Care* 2014;37:9–16.
- Chalmers J, Cooper ME. UKPDS and the legacy effect. *N Engl J Med* 2008;359:1618–20.
- Hypoglycemia in the Diabetes Control, Complications TrialThe diabetes control and complications trial research group. *Diabetes* 1997;46:271–86.
- Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998;352(suppl 9131):837–53.
- McEwan P, Evans M, Kan H, et al. Understanding the inter-relationship between improved glycaemic control, hypoglycaemia and weight change within a long-term economic model. *Diabetes Obes Metab* 2010;12:431–6.
- Leese GP, Wang J, Broomhall J, et al. Frequency of severe hypoglycemia requiring emergency treatment in type 1 and type 2 diabetes: a population-based study of health service resource use. *Diabetes Care* 2003;26:1176–80.
- Monami M, Dicembrini I, Kundisova L, et al. A meta-analysis of the hypoglycaemic risk in randomized controlled trials with sulphonylureas in patients with type 2 diabetes. *Diabetes Obes Metab* 2014;16:833–40.
- Chico A, Vidal-Rios P, Subira M, et al. The continuous glucose monitoring system is useful for detecting unrecognized hypoglycemia in patients with type 1 and type 2 diabetes but is not better than frequent capillary glucose measurements for improving metabolic control. *Diabetes Care* 2003;26:1153–7.
- Sequist ER, Anderson J, Childs B, et al. Hypoglycemia and diabetes: a report of a workgroup of the American Diabetes Association and the Endocrine Society. *J Clin Endocrinol Metab* 2013;98:1845–59.
- Foos V, Varol N, Curtis BH, et al. Economic impact of severe and non-severe hypoglycemia in patients with Type 1 and Type 2 diabetes in the United States. *J Med Econ* 2015;18:420–32.
- McCoy RG, Van Houten HK, Ziegenfuss JY, et al. Increased mortality of patients with diabetes reporting severe hypoglycemia. *Diabetes Care* 2012;35:1897–901.
- Gerstein HC, Miller ME, et al. Action to Control Cardiovascular Risk in Diabetes Study GEffects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* 2008;358:2545–59.
- Zoungas S, Patel A, Chalmers J, et al. Severe hypoglycemia and risks of vascular events and death. *N Engl J Med* 2010;363:1410–8.
- Pathak RD, Schroeder EB, Seaquist ER, et al. Severe hypoglycemia requiring medical intervention in a large cohort of adults with diabetes receiving care in U.S. Integrated Health Care Delivery Systems: 2005–2011. *Diabetes Care* 2015;39:363–70.
- Liatis S, Mylona M, Kalopita S, et al. Hypoglycaemia requiring medical assistance in patients with diabetes: a prospective multicentre survey in tertiary hospitals. *Diabetes Metab* 2015;41:126–31.
- Davis TM, Brown SG, Jacobs IG, et al. Determinants of severe hypoglycemia complicating type 2 diabetes: the Fremantle diabetes study. *J Clin Endocrinol Metab* 2010;95:2240–7.
- Miller ME, Bonds DE, Gerstein HC, et al. The effects of baseline characteristics, glycaemia treatment approach, and glycated haemoglobin concentration on the risk of severe hypoglycaemia: post hoc epidemiological analysis of the ACCORD study. *BMJ* 2010;340:b5444.
- Investigators OT. Predictors of nonsevere and severe hypoglycemia during glucose-lowering treatment with insulin glargine or standard drugs in the ORIGIN trial. *Diabetes Care* 2015;38:22–8.
- Elliott J, Jacques RM, Kruger J, et al. Substantial reductions in the number of diabetic ketoacidosis and severe hypoglycaemia episodes requiring emergency treatment lead to reduced costs after structured education in adults with Type 1 diabetes. *Diabet Med* 2014;31:847–53.
- Berkowitz SA, Karter AJ, Lyles CR, et al. Low socioeconomic status is associated with increased risk for hypoglycemia in diabetes patients: the Diabetes Study of Northern California (DISTANCE). *J Health Care Poor Underserved* 2014;25:478–90.
- Cryer PE, Axelrod L, Grossman AB, et al. Evaluation and management of adult hypoglycemic disorders: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab* 2009;94:709–28.
- Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009;150:604–12.
- Cariou B, Fontaine P, Eschwege E, et al. Frequency and predictors of confirmed hypoglycaemia in type 1 and insulin-treated type 2 diabetes mellitus patients in a real-life setting: results from the DIALOG study. *Diabetes Metab* 2015;41:116–25.
- Sonoda N, Morimoto A, Ugi S, et al. Predictors for mild and severe hypoglycemia in insulin-treated Japanese diabetic patients. *PLoS One* 2015;10:e0130584.
- Sako A, Yasunaga H, Matsui H, et al. Hospitalization for hypoglycemia in Japanese diabetic patients: a retrospective study using a national inpatient database, 2008–2012. *Medicine (Baltimore)* 2015;94:e1029.
- Association AD. Standards of medical care in diabetes. *Diabetes Care* 2015;38(supplement 1):S33–40.
- Tschope D, Bramlage P, Binz C, et al. Incidence and predictors of hypoglycaemia in type 2 diabetes—an analysis of the prospective DiaRegis registry. *BMC Endocr Disord* 2012;12:23.
- Akram K, Pedersen-Bjergaard U, Borch-Johnsen K, et al. Frequency and risk factors of severe hypoglycemia in insulin-treated type 2 diabetes: a literature survey. *J Diabetes Complications* 2006;20:402–8.
- Zammit NN, Frier BM. Hypoglycemia in type 2 diabetes: pathophysiology, frequency, and effects of different treatment modalities. *Diabetes Care* 2005;28:2948–61.
- Elliott JA, Abdulhadi NN, Al-Maniri AA, et al. Diabetes self-management and education of people living with diabetes: a survey in primary health care in Muscat Oman. *PLoS One* 2013;8:e57400.
- Ko SH, Kim DJ, Park JH, et al. Trends of antidiabetic drug use in adult type 2 diabetes in Korea in 2002–2013: Nationwide population-based cohort study. *Medicine (Baltimore)* 2016;95:e4018.
- Thorpe LE, Upadhyay UD, Chamany S, et al. Prevalence and control of diabetes and impaired fasting glucose in New York City. *Diabetes Care* 2009;32:57–62.
- Hampp C, Borders-Hemphill V, Moeny DG, et al. Use of antidiabetic drugs in the U.S., 2003–2012. *Diabetes Care* 2014;37:1367–74.
- Malouf R, Brust JC. Hypoglycemia: causes, neurological manifestations, and outcome. *Ann Neurol* 1985;17:421–30.
- Ikeda T, Takahashi T, Sato A, et al. Predictors of outcome in hypoglycemic encephalopathy. *Diabetes Res Clin Pract* 2013;101:159–63.
- Witsch J, Neugebauer H, Flechsenhar J, et al. Hypoglycemic encephalopathy: a case series and literature review on outcome determination. *J Neurol* 2012;259:2172–81.
- Ma JH, Kim YJ, Yoo WJ, et al. MR imaging of hypoglycemic encephalopathy: lesion distribution and prognosis prediction by diffusion-weighted imaging. *Neuroradiology* 2009;51:641–9.
- Johkura K, Nakae Y, Kudo Y, et al. Early diffusion MR imaging findings and short-term outcome in comatose patients with hypoglycemia. *AJNR Am J Neuroradiol* 2012;33:904–9.
- Patel N, Rao VA, Heilman-Espinoza ER, et al. Simple and reliable determination of the modified Rankin scale score in neurosurgical and neurological patients: the mRS-9Q. *Neurosurgery* 2012;71:971–5. discussion 975.
- Economic costs of diabetes in the U.S. in 2012. *Diabetes Care* 2013;36(suppl 4):1033–46.
- Ha WC, Oh SJ, Kim JH, et al. Severe hypoglycemia is a serious complication and becoming an economic burden in diabetes. *Diabetes Metab J* 2012;36:280–4. 35. Ikeda T, Takahashi T, Sato A, et al. Predictors of outcome in hypoglycemic encephalopathy. *Diabetes research and clinical practice*. 2013;101(2):159–163.

- [42] Holstein A, Patzer OM, Machalke K, et al. Substantial increase in incidence of severe hypoglycemia between 1997-2000 and 2007-2010: a German longitudinal population-based study. *Diabetes Care* 2012;35:972–5.
- [43] Hsu PF, Sung SH, Cheng HM, et al. Association of clinical symptomatic hypoglycemia with cardiovascular events and total mortality in type 2 diabetes: a nationwide population-based study. *Diabetes Care* 2013;36:894–900.
- [44] Sharma M, Nazareth I, Petersen I. Trends in incidence, prevalence and prescribing in type 2 diabetes mellitus between 2000 and 2013 in primary care: a retrospective cohort study. *BMJ Open* 2016;6:e010210.
- [45] Yanai H, Adachi H, Katsuyama H, et al. Causative anti-diabetic drugs and the underlying clinical factors for hypoglycemia in patients with diabetes. *World J Diabetes* 2015;6:30–6.
- [46] Moisan J1, Breton MC, Villeneuve J, et al. Hypoglycemia-related emergency department visits and hypoglycemia-related hospitalizations among new users of antidiabetes treatments. *Can J Diabetes* 2013;37:143–9.