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

A case–control study

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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, NIS = 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.[¹,²] Conversely, strict glycemic control may increase the risk of hypoglycemia[³,⁴] which, in some cases, may even offset the expected beneficial effects of good glycemic control.[⁵] Therefore, hypoglycemia may be an obstacle for good glycemic control and should be an important factor to consider when determining the optimal glycemic 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,[⁶] but also reported in patients taking oral hypoglycemic agents.[⁷,⁸]

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.[⁹] Severe hypoglycemia is defined as a state of low blood glucose that requires the assistance of another person[⁹] and this condition can lead to emergency department (ED) visits and often results in hospitalizations that incur substantial medical costs.[¹⁰] Moreover, severe hypoglycemia is strongly correlated with the increased risk of adverse clinical outcomes, such as cardiovascular events and mortality.[¹¹–¹³]
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 glycated hemoglobin (HbA1c) levels, the presence of comorbid conditions such as depression, limited education levels, and the use of insulin or sulfonylurea.[14–17] However, risk factors for severe hypoglycemia and nonsevere hypoglycemia (NSH) may be quite disparate because these conditions are likely to occur under different circumstances.[18] A limited number of studies have investigated the associations of these conditions with the influence of self-management variables and socioeconomic status.[9,19,20] 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[21] 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[22] and diabetic nephropathy was defined as albuminuria or an eGFR less than 60 mL/min/1.73 m².

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 ± 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 (χ²) 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 m² vs 56.6 mL/min/1.73 m², 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
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: 0.68–0.824, $P = 0.006$; Fig. 1) for prediction of HMA.

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

| Variables                          | 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/m²                         | 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 m²               | 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   |

### Complications

| Variables                          | HMA (n = 69) | NSH (n = 60) | P value |
|------------------------------------|-------------|-------------|---------|
| Hypertension, n, %                 | 103 (80)    | 60 (87)     | 0.047   |
| Hypertension, n, %                 | 17 (13)     | 12 (17)     | 0.192   |

### Socioeconomic status

| Variables                          | Total (n = 129) | HMA (n = 69) | NSH (n = 60) | P value |
|------------------------------------|----------------|-------------|-------------|---------|
| Previous severe hypoglycemia       | 39/72/18 (29/57/14) | 21/39/7 (31/58/10) | 15/33/11 (25/65/19) | 0.263   |
| Education (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  |

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

| Variables                          | OR (CI) | P value |
|------------------------------------|---------|---------|
| Age                                | 0.99 (0.94–1.04) | 0.583   |
| Female                             | 0.93 (0.40–2.16) | 0.472   |
| HbA1c                              | 0.88 (0.62–1.24) | 0.875   |
| Type of treatment (insulin)        | 0.40 (0.16–0.98) | 0.045   |
| Hypertension                       | 1.93 (0.68–5.64) | 0.228   |
| Education level (> 9 years)        | 0.49 (0.20–1.20) | 0.118   |
| 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.
respectively).

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

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, and some were controlled clinical trials, which makes it difficult to apply the findings to clinical practice. 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. 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.

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.

In the present study, absence of SMBG was identified as an independent and modifiable risk factor of HMA. In the other hand, Tschope et al 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) | Sequeleae (n=15) | No sequelae (n=54) | P 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 hospital stay, 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.[16,17,23,24] Although we did not evaluate autonomic warning symptoms of hypoglycemia, it is likely that prior episodes of severe hypoglycemia impair neuroendocrine defense mechanisms.[25] 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.[9,30] From a socioeconomic 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.[26] Physicians prefer to prescribe hypoglycemic agents that are less associated with hypoglycemia when treating patients with diabetes.[26] 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,[31,32] 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.[31,33] 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,[31] 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.[6,14,16] 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.[11,41–43] 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.[31,44–46] 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.[34] Hypoglycemic encephalopathy or hypoglycemia-induced brain injury is a clinical syndrome with a broad clinical course and diverse outcomes.[35] 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.[35–38] In this study, the mRS, which is a validated clinical outcome scale,[39] 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.[40] 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.[41] 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 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.

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