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Severe Hypoglycemia Is a Serious Complication and Becoming an Economic Burden in Diabetes

Won Chul Ha[1], Su Jin Oh[1], Ji Hyun Kim[2], Jung Min Lee[2], Sang Ah Chang[2], Tae Seo Sohn[1], Hyun Shik Son[1]

[1]Division of Endocrinology and Metabolism, Department of Internal Medicine, Uijeongbu St. Mary's Hospital, Uijeongbu; [2]Division of Endocrinology and Metabolism, Department of Internal Medicine, St. Paul's Hospital, The Catholic University of Korea College of Medicine, Seoul, Korea

Background: The prevalence of hypoglycemia is increasing due to the growing incidence of diabetes and the latest strict guidelines for glycated hemoglobin (HbA1c) levels under 7%. This study examined the clinical characteristics, causal factors, and medical costs of severely hypoglycemic patients in an emergency room (ER) of Uijeongbu St. Mary's Hospital.
Methods: The study consisted of a retrospective analysis of the characteristics, risk factors, and medical costs of 320 severely hypoglycemic patients with diabetes who presented to an ER of Uijeongbu St. Mary's Hospital from January 1, 2006 to December 31, 2009.
Results: Most hypoglycemic patients (87.5%, 280/320) were over 60 years old with a mean age of 69.5±10.9 years and a mean HbA1c level of 6.95±1.46%. Mean serum glucose as noted in the ER was 37.9±34.5 mg/dL. Renal function was decreased, serum creatinine was 2.0±2.1 mg/dL and estimated glomerular filtration rate (eGFR) was 48.0±33.6 mL/min/1.73 m^2. In addition, hypoglycemic patients typically were taking sulfonylureas or insulin and a variety of other medications, and had a long history of diabetes.
Conclusion: Severe hypoglycemia is frequent in older diabetic patients, subjects with low HbA1c levels, and nephropathic patients. Therefore, personalized attention is warranted, especially in long-term diabetics with multiple comorbidities who may not have been properly educated or may need re-education for hypoglycemia.

Keywords: Cost; Diabetes mellitus; Health; Hypoglycemia

INTRODUCTION

Strict blood glycemic control is necessary for the management of diabetes. The latest guidelines recommend a level of HbA1c under 7% as a target goal for glycemic control [1,2]. Many clinicians prescribe diabetic patients intensified pharmacological treatments to maintain the HbA1c target goal. This can increase the risk of hypoglycemic events. Hypoglycemia is one of the most undesirable side effects in diabetic patients and can appear unpredictably. It primarily presents as iatrogenic hyperinsulinemia by insulin secretagogues or exogenous insulin. The more episodes of hypoglycemia a diabetic experiences, the more their defense mechanism against falling serum glucose is affected, resulting in increasing cycles of recurrent hypoglycemia. This study investigated the clinical characteristics, causal factors, and economic aspects of severely hypoglycemic patients with diabetes in an emergency room (ER) of Uijeongbu St. Mary's Hospital.

METHODS

Research design and methods

Study protocol was reviewed and approved by Institutional Review Board (IRB). This study retrospectively examined 320

Corresponding author: Hyun Shik Son
Division of Endocrinology and Metabolism, Uijeongbu St. Mary's Hospital, 271 Cheonbo-ro, Uijeongbu 480-717, Korea
E-mail: sonhys@gmail.com
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hypoglycemic patients with diabetes presenting to the ER, all of whom were taking insulin or oral hypoglycemic agents. Data sources consisted of medical, pharmacy and laboratory records. Blood glucose tests were performed in all severely hypoglycemic patients in the ER. Estimated glomerular filtration rate (eGFR) was calculated using a formula based on the modification of diet in renal disease (MDRD). The medical costs of severe hypoglycemia in US dollars were determined to be the cost of hospitalization for 1 to 7 days ($46.90 to $328.30), the cost of diagnostic tests without and without brain imaging ($86.30 and $433 to $630, respectively), the cost of treatment administered ($6.60), assistance of a caregiver at the hospital for 1 to 7 days ($42.60 to $298.20), and transportation from patient's house to the hospital ($42.60 to $127.90). Severe hypoglycemia was defined as hypoglycemia that required an ER visit for treatment. Patients with an eGFR less than 60 mL/min/1.73 m^2 were considered to have stage 3 to 5 chronic kidney disease (CKD).

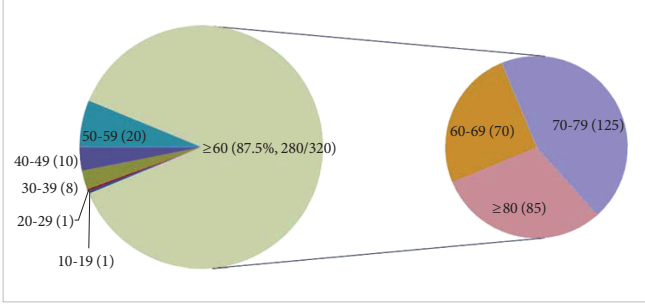

Fig. 1. Age distribution of severe hypoglycemia. The number of severe hypoglycemic event is increasing according to age.

Statistical analysis

Data are presented as the mean±standard deviation. Differences between the groups were analyzed by ANOVA. Nominal variables were analyzed by chi-square test. *P* values less than 0.05 were considered statistically significant. All analyses were performed using SPSS version 12.0 (SPSS V12.0K; SPSS Inc., Chicago, IL, USA).

RESULTS

Most hypoglycemic patients presenting to the ER were elderly, with a mean age of 69.5±10.9 years old. Patients over 60 years old comprised 87.5% of the total number of patients (280/320) (Fig. 1). Mean glycemic control levels (HbA1c 7.0±1.5%) were near the latest guidelines. Serum creatinine levels and eGFR were 2.0±2.1 mg/dL and 48.0±33.6 mg/dL, respectively. Of the 320 patients, 188 (58.8%) had stage 3 to 5 CKD. Mean serum blood glucose levels as checked in the ER were 37.9±34.5 mg/dL. The number of hypoglycemic patients appears to increase every year (Table 1).

Table 2 shows the symptoms of severe hypoglycemia. The main presenting symptom of severe hypoglycemia was a de-

Table 1. Patient characteristics

Characteristic	2006	2007	2008	2009	Total	*P* value
N	38	74	128	80	320	
M	13	33	52	35	133	
F	25	41	76	45	187	
Age, yr	70.7±10.0	71.6±10.4	67.6±11.9	70.0±11.9	69.5±10.9	0.316
HbA1c, %	6.9±1.1	6.5±1.3	7.0±1.3	7.3±1.8	7.0±1.5	0.485
Serum creatinine, mg/dL	2.0±2.1	1.9±1.8	2.2±2.3	1.8±1.8	2.0±2.1	0.770
GFR, mL/min/1.73 m^2	59.0±36.1	58.9±35.8	50.4±32.7	54.7±30.6	48.0±33.6	0.034
CKD 3-5 (GFR <60 mL/min/1.73 m^2)	21/38 (55.3)	41/74 (55.4)	81/128 (63.3)	45/80 (56.3)	188/320 (58.8)	<0.01
Duration of diabetes, yr	11.0±10.8	12.7±9.90	11.2±7.6	15.8±10.8	12.7±9.6	0.416
Serum glucose, mg/dL	37.1±14.4	36.8±13.5	34.5±2.3	35.1±15.9	37.9±34.5	<0.007
Serum AST, U/L	22.1±10.1	33.0±24.8	33.5±27.3	36.0±49.4	33.4±33.6	<0.007
Serum ALT, U/L	18.0±8.8	24.5±10.1	27.5±47.8	26.0±30.5	26.7±38.6	<0.035

Values are presented as mean±standard deviation or number (%). *P* values are obtained by ANOVA. N is the number of patients with available data per year and total.
GFR, glomerular filtration rate; CKD, chronic kidney disease; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

Table 2. Severe hypoglycemic symptoms

Hypoglycemic Sx or Sn	Decreased consciousness	Weakness	Abnormal behavior	Difficulty with speech	Dizziness	Others
N=320	276 (86.3)	21 (6.6)	7 (2.2)	5 (1.6)	1 (0.3)	10 (3.0)

Values are presented as number (% of total number). N is the number of patients with available data.
Sx, symptom; Sn, sign.

Table 3. Administered oral hypoglycemic agents and insulin

	2006	2007	2008	2009	Total	*P* value
SU	13/38 (34.2)	25/74 (33.8)	59/128 (46.1)	35/80 (43.7)	132 (41.3)	
Glimepiride	8	16	43	28	95	
Glibenclamide	1	2	10	2	15	
Gliclazide	4	5	4	2	15	<0.05
Gliquidone	0	1	1	2	4	
Glipizide	0	1	1	1	3	
Total	13	25	59	35	132	
INS	12/38 (32.0)	21/74 (28.3)	39/128 (30.5)	21/80 (26.3)	93 (29.0)	
SU or INS	24/38 (63.2)	43/74 (58.1)	91/128 (71.1)	51/80 (63.8)	209/320 (65.3)	
SU+INS	1/38 (2.6)	3/74 (4.1)	7/128 (5.4)	5/80 (6.3)	16 (5.0)	
Others[a]	12/38 (31.2)	25/74 (33.8)	23/128 (18.0)	19/80 (23.7)	79 (24.7)	

Values are presented as number/total number (%). *P* value obtained by chi-square test for trend.
SU, sulfonylurea; INS, insulin.
[a]Others are oral hypoglycemic agents, except for sulfonylureas.

creased state of consciousness (86.3%, 276/320). Seventeen of the 276 hypoglycemic patients with a change in consciousness were in a persistent coma/stupor for ≥24 hours despite normalization of blood glucose levels and were ultimately discharged or transferred to another department.

Sulfonylureas and insulin increased the risk of severe hypoglycemia. Glimepiride-related severe hypoglycemia occurred more frequently than severe hypoglycemia associated with other sulfonylureas (Table 3).

Causal factors associated with hypoglycemia as reported by the patients were as follows: poor nutrition (73.4%, 235/320), change in medication or change in dose of current medication (12.5%, 40/320), alcohol intake (11.6%, 37/320), hemodialysis (4.4%, 14/320), and exercise (9%, 3/320). The most common problem reported was poor nutrition or missed meals.

Of the 320 patients, 242 (75.6%) were experiencing polypharmacy, which is the use of many different drugs not related to diabetes in patients who might have other health problems. Of the 235 patients who had poor nutrition, 65 of them (27.7%) experienced polypharmacy.

The total average medical cost in US dollars per severely hypoglycemic event was $135.50 to $1,391. The largest costs were from hospitalization and brain imaging studies.

DISCUSSION

Several guidelines emphasize the need for strict glycemic control to reduce diabetic complications, but this raises the risk of severe hypoglycemic events.

This study examined the clinical characteristics and causal factors associated with severe hypoglycemia in diabetic patients and also analyzed economic aspects. The present study defined severe hypoglycemia as requiring medical assistance in the ER, though severe hypoglycemia is usually defined as hypoglycemia requiring any type of medical treatment.

Most severe hypoglycemic events (87.5%, 280/320) occurred in patients greater than 60 years old. The most common cause of hypoglycemia was poor nutrition or a missed meal. Feher et al. [3] reported that precipitating causes of hypoglycemia were a missed meal (51%), alcohol intake, excess insulin, or exercise. These results support the findings of the present study. Poor nutrition in elderly patients can be caused masticatory

problems, dysphagia, and problems preparing food due to hand tremors and visual problems [4]. Many of the patients (75.6%, 242/320) experienced polypharmacy not related to diabetes, which suggests multimorbidities. Polypharmacy in elderly multimorbid patients often includes anti-hypertensive drugs, anti-parkinsons drugs, anti-depressants and analgesics, all of which can cause decreased food intake [4]. Moreover, several anti-diabetics are associated with the decreased food intake [4]. It appears that polypharmacy due to multimorbidity has an indirect effect on severe hypoglycemia by reducing oral food intake.

The risk of hypoglycemia is particularly high in diabetic patients with renal impairment. It is estimated that 6 to 8 units of insulin are removed by the kidney daily, accounting for 25% to 40% of the removal of insulin [5]. The prevention of hypoglycemia in diabetic patients with renal failure or who are undergoing hemodialysis requires a 25% systematic reduction of exogenous insulin administration [6]. In this study, glycemic control (HbA1c 7.0±1.5%) in severely hypoglycemic patients was close to the goal established by the latest guidelines, and 58.8% (188/320) patients were stage 3 to 5 CKD. Sulfonylureas or insulin was associated with the incidence of severe hypoglycemia. Severe hypoglycemia associated with glimepiride occurred more frequently, correlating with higher doses of glimepiride. Long-acting sulfonylureas such as glimepiride and glibenclamide are associated with a higher risk of hypoglycemia in comparison to short-acting sulfonylureas. The metabolites of long-acting sulfonylureas are excreted renally, and in patients with renal impairment, even low doses of glimepiride (1 mg) can induce prolonged hypoglycemia lasting up to 64 hours [7]. Badian et al. [8] reported that the hepatic metabolites of glimepiride are hydroxyl-glimepiride, which is still associated with hypoglycemic activity, and carboxy-glimepiride. The active metabolite of hydroxyl-glimepiride (58%) is eliminated renally and carboxy-glimepiride (42%) is eliminated fecally. Thus, when treating elderly diabetic patients with renal impairment, low dose insulin or sulfonylureas should be administered to help prevent severe hypoglycemia.

Severe hypoglycemia has a significant impact on the total cost of treating diabetes. In this study, the largest average medical cost per severely hypoglycemic event was $1,385, which is approximately 1.35 times the annual treatment cost ($1,027) [9] for a diabetic patient without complications in Korea. The average medical costs per severely hypoglycemic event in other countries were $1,186 (US), €2,942 (Germany), €1,370 (Spain), €1,269 (UK), and €2806.8 (Sweden), and the cost of mild hypoglycemia was €26.0 (Sweden) [10-12]. Indirect costs that are often overlooked such as productivity and time lost should be considered when evaluating the costs of severe hypoglycemia. Patients with hypoglycemia had 77% more short-term disability days annually [13]. Reviriego et al. [14] reported that the overall mean cost of hypoglycemia is comprised of 65.4% direct costs and 34.6% indirect costs. The overall cost of hypoglycemia in 300,000 patients with type 2 diabetes in Sweden was estimated to be approximately €4,250,000 [12]. The economic burden of severe hypoglycemia in Korea might be greater than indicated in this study if indirect costs are also considered, such as missed work by the patient and by any family members who are caring for the patient.

This study is limited because it is retrospective and only included patients presenting to the ER in one health center. A nationwide survey is needed to more accurately evaluate the economic burden of diabetes, including indirect costs due to severe hypoglycemia in diabetic patients.

The incidence of severe hypoglycemia in diabetic patients is increasing due to stricter guidelines for managing diabetes. Severe hypoglycemia can impose an economic burden not only on the patients but also on the health care system. Moreover, severe hypoglycemia can induce permanent brain damage leading to a vegetative state. Therefore individualized goals for glycemic control are necessary. These goals should take into account factors such as the duration of diabetes, life expectancy, and comorbid conditions. More effective education for diabetic patients and their providers is also needed.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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