Original Article

Precipitating Factors of Hypoglycemia in Diabetic Patients Undergoing Treatment in Taksin Hospital

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Background: Hypoglycemia is the most common complication and the most important obstacle to overcome to achieve good glycemic control in diabetic patients. It causes serious consequences, leading to increased morbidity and mortality.

Objective: To identify the precipitating factors of hypoglycemia in diabetic patients undergoing treatment in Taksin hospital.

Materials and Methods: A case-control study was conducted in 110 diabetic patients admitted due to hypoglycemia and 110 diabetic patients admitted for other reasons at Taksin Hospital, between October 2019 and September 2020. The sociodemographic information, clinical data, and precipitating causes of hypoglycemia were obtained from medical records. Logistic regression analysis was performed to identify the risk factor and reported as odds ratio (OR) with 95% confidence intervals (CI).

Results: The multiple logistic regression analysis showed that the precipitating factors related to hypoglycemia among diabetic patients with a significant p-value ($p<0.05$) were poor self-care knowledge of hypoglycemia prevention (adjusted OR 14.37, 95% CI 5.75 to 35.89), insulin treatment in diabetic patients (adjusted OR 13.78, 95% CI 5.43 to 34.99), and intensive glycemic control HbA1c of less than 6% (adjusted OR 3.64, 95% CI 1.70 to 7.79). Furthermore, the result from the present study showed that individual factors were statistically significant and related to hypoglycemia. The factors included the age more than 60 years, low education level, functionally dependent patients, diabetes duration more than 10 years, hypertension, dyslipidemia, diabetic retinopathy, diabetic nephropathy, diabetic neuropathy, and cognitive impairment.

Conclusion: Poor self-care knowledge of hypoglycemia prevention, insulin treatment in diabetic patients, and intensive glycemic control were strong predictors of hypoglycemia in diabetic patients undergoing treatment in Taksin Hospital. Therefore, diabetes self-management education and tailoring diabetic therapy should be provided in diabetic patients to improve treatment and prevention of hospitalization due to hypoglycemia in diabetes.

Keywords: Diabetes Mellitus; Hypoglycemia; Precipitating factor; Hospitalization

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The prevalence and incidence of type 2 diabetes mellitus (T2DM) are increasing worldwide. According to the data provided by the International Diabetes Federation, there were 463 million diabetic patients in 2019, and estimated to be 578 million by 2030[1]. In Thailand, the prevalence of diabetes as reported by the Thai National Health Examination Survey increased from 8.9% in 2014 to 9.5% in 2019 to 2020[2].

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The importance of blood glucose control and maintenance of glycated hemoglobin A1c (HbA1c) below 6.5% to 7% in preventing and reducing the progression of diabetic complications has been well established[3-5]. On the contrary, hypoglycemia is the most common complication and the most important obstacle to overcome to achieve good glycemic control in diabetic patients. It causes serious consequences, leading to increased morbidity and mortality[4,5]. The incidence of mild/moderate hypoglycemia in T2DM is 19 episodes per person-year, whereas severe hypoglycemia is 0.8 episodes per person-year[6]. Recent studies have shown that diabetic patients who develop hypoglycemia tend to be elderly, longer duration of diabetes, have the presence of comorbid diseases such as chronic kidney disease, liver disease, dementia, cardiovascular disease, low socio-economic status, and limited education level[7-11]. The precipitating factor for hypoglycemia include patients who received insulin injection, intensive

glycemic control per se as evidenced by HbA1c levels below 6%, a history of hypoglycemia, acute infection, inappropriate self-medical adjustment, and poor knowledge about presenting symptoms of hypoglycemia[9,10,12].

Studies of the precipitating factors of hypoglycemia in patients with diabetes are useful for the development of patient care approaches to prevent hypoglycemia. However, in Thailand, there are limited studies regarding the risk factors of hypoglycemia in diabetic patients. Thus, the purpose of the present study was to identify the precipitating factors of hypoglycemia in diabetic patients undergoing treatment in Taksin Hospital.

Materials and Methods

Study design and population

A retrospective case-control study was conducted between October 2019 and September 2020 among diabetic patients undergoing treatment in Taksin Hospital, a tertiary public hospital located in Bangkok, Thailand. The present study had been approved for the ethics from the Bangkok Metropolitan Administration Ethics Committee for Human Research, Approval No. S005h/64_EXP.

The inclusion criteria were diabetic patients aged 15 years or older admitted to the hospital. The exclusion criteria were diabetic patients who were pregnant. The sample size for an unmatched case-control study was calculated using the formula with correction factor by Fleiss et al[13]. The co-morbidities were used to estimate the required sample size. The proportion of diabetic patients without hypoglycemia who had co-morbidities was 0.93, reported in a previous study in Thailand[10]. The odds ratio (OR) for hypoglycemia was 3.58 among diabetic patients who had co-morbidities relative to diabetic patients who did not have co-morbidities. The case-to-control ratio had been established at 1:1. Therefore, 220 participants were needed to give a power of β=0.8 and a confidence level of 95% for the present study. The participants were classified into two groups, 110 participants were diabetic patients hospitalized due to hypoglycemia, and 110 control participants were diabetic patients admitted for other reasons. Studied cases and control participants were selected for the present study by using simple random sampling.

Hypoglycemia was defined as having blood glucose below or equal to 70 mg/dL in addition to the presence of symptoms consistent with hypoglycemia such as sweating, shaking, or palpitation, which was resolved with ingestion of sugar, food, or sugary drinks[7].

Data collection

The sociodemographic information, clinical data, and precipitating causes of hypoglycemia were obtained from medical records. BMI was calculated as weight in kilograms divided by height in meter, squared. Dependent functional status was defined as the patient requiring assistance from another person for activities of daily living. Education was classified as low education level as never attended or attended only elementary school and high education level as attended higher than elementary school. Cardiovascular disease was defined as the patient had coronary artery disease or heart failure. Cerebrovascular disease was defined as the patient having a stroke. Cognitive impairment was defined as the patient having cognitive deficiency by using Mini-Mental State Examination[14]. Diabetic retinopathy was diagnosed by an ophthalmologist. Diabetic nephropathy was defined by a clinical diagnosis made based on the presence of albuminuria and/or reduced eGFR in the absence of signs or symptoms of other primary causes of kidney damage[15]. Diabetic neuropathy was diagnosed using 10-g monofilament, pinprick sensations, and ankle reflexes[15]. Self-care knowledge of hypoglycemia prevention was defined as the patient learned about hypoglycemia prevention in Diabetes Self-Management Program (DSMP) from Diabetes and Metabolic care Center, Taksin Hospital. DSMP included an overview of diabetes, dietary recommendation, physical activity, and stress management that the nurse would provide to the patient at each hospital visit. Intensive glycemic control was defined as the patient having HbA1c level below 6%[16]. The estimated glomerular filtration rate (eGFR) was estimated by age, sex, race, and the most recent creatinine using the Chronic Kidney Disease Epidemiology Collaboration equation[17].

Statistical analysis

All statistical analyses were conducted using IBM SPSS Statistics, version 26.0 (IBM Corp., Armonk, NY, USA). The categorical variables were reported as a number with percentages. The continuous variables were reported as median (interquartile range, IQR). Chi-square or Fisher's exact test was used to analyze the differences in categorical variables between the study groups. A Mann-Whitney U test was used to analyze the differences of continuous variables between the groups studied. The logistic regression analysis was performed to determine the risk factor

Table 1. Sociodemographic characteristics and clinical baseline data of study participants

Variable	Case group (n=110)	Control group (n=110)	p-value
Age (years); median (IQR)	69.5 (61.75 to 76.25)	67.0 (54.0 to 75.0)	0.059[a]
Sex (female); n (%)	71 (64.5)	66 (60.0)	0.578[b]
BMI (kg/m^2); median (IQR)	23.42 (20.31 to 26.01)	24.22 (21.59 to 29.31)	0.138[a]
Education; n (%)			<0.001[c]
No education	22 (20.0)	16 (14.5)	
Elementary school	73 (66.4)	33 (30.0)	
Secondary school	12 (10.9)	56 (50.9)	
Bachelor degree	3 (2.7)	5 (4.5)	
Functional status; n (%)			0.036[c]
Dependent	26 (23.6)	14 (12.7)	
Independent	84 (76.4)	96 (87.3)	
Alcohol drinking; n (%)	4 (3.6)	4 (3.6)	1.0[c]
Duration of diabetes (years); median (IQR)	15 (10 to 20)	10 (5 to 12)	<0.001[a]
Type of DM; n (%)			0.077[c]
DM type 1	5 (4.5)	0 (0.0)	
DM type 2	105 (95.5)	110 (100)	
Co-morbidities; n (%)			
Hypertension	105 (95.5)	96 (87.3)	0.031[c]
Dyslipidemia	105 (95.5)	79 (71.8)	<0.001[c]
Cardiovascular disease	27 (24.5)	22 (20.0)	0.517[b]
Cerebrovascular disease	24 (21.8)	19 (17.3)	0.497[b]
Liver disease	4 (3.6)	5 (4.5)	0.734[c]
Cognitive impairment; n (%)	21 (19.1)	7 (6.4)	0.005[c]
Complication of diabetes; n (%)			
Diabetic nephropathy	76 (69.1)	55 (50.0)	0.006[b]
Diabetic retinopathy	49 (47.1)	25 (32.9)	0.001[b]
Diabetic neuropathy	34 (33.7)	13 (17.8)	0.001[b]
Sulfonylurea treatment; n (%)	51 (46.4)	50 (45.5)	1.0[b]
Insulin treatment; n (%)	59 (53.6)	28 (25.5)	<0.001[c]
HbA1c (%); median (IQR)	6.6 (5.7 to 8.0)	7.2 (6.3 to 8.9)	0.007[a]
eGFR (mL/minute/1.73 m^2); median (IQR)	37.05 (20.36 to 77.12)	50.13 (17.22 to 87.70)	0.225[a]

BMI=body mass index; DM=diabetes mellitus; HbA1c=glycated hemoglobin; eGFR=estimated glomerular infiltration rate; IQR=interquartile range

[a] Mann-Whitney U test, [b] Fisher's exact test, [c] Pearson chi-square

and presented as OR with 95% confidence intervals (CI). A p-value of less than 0.05 was considered statistically significant.

Results

The characteristics of the study population

One thousand four hundred fifty-four diabetic patients admitted to Taksin Hospital were identified based on the International Statistical Classification of Diseases and Related Health Problems Tenth Revision (ICD-10) for diabetes mellitus (E100-E119). One hundred ten cases and 110 control participants were selected for the present study by using simple random sampling (Figure 1). The 110 case participants had severe hypoglycemia with an altered mental status.

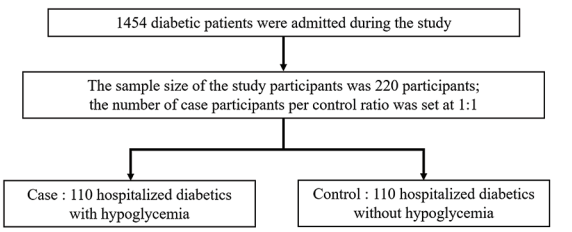

Figure 1. Participants of the study.

The sociodemographic characteristics and clinical baseline data are shown in Table 1. The median age was 69.5 years in the case study group and 67 years in the control group. A majority of the participants were female and had type 2 diabetes in

Table 2. Logistic regression analysis of individual and precipitating factors of hypoglycemia

Individual factors	Case group; n (%)	Control group; n (%)	Odd ratio	95% CI		p-value
				Lower	Upper	
Sex						
Female	71 (64.5)	66 (60.0)	1.21	0.70	2.09	0.487
Male	39 (35.5)	44 (40.0)	1			
Age						
≥60 years	89 (80.9)	74 (67.3)	2.06	1.11	3.83	0.002*
<60 years	21 (19.1)	36 (32.7)	1			
BMI						
<25 kg/m^2	70 (63.6)	61 (55.5)	1.40	0.82	2.41	0.217
≥25 kg/m^2	40 (36.4)	50 (44.5)	1			
Education						
Low education level	95 (86.4)	49 (44.5)	7.88	4.07	15.29	<0.001*
High education level	15 (13.6)	61 (55.5)	1			
Functional status						
Dependent patients	26 (23.6)	14 (12.7)	2.12	1.04	4.33	0.038*
Independent patients	84 (76.4)	96 (87.3)	1			
Duration of DM						
≥10 years	96 (87.3)	62 (56.4)	5.31	2.70	10.43	<0.001*
<10 years	14 (12.7)	48 (43.6)	1			
Diabetic medication						
Insulin injection	59 (53.6)	28 (25.5)	3.39	1.92	5.99	<0.001*
Oral medication	51 (46.4)	82 (74.5)	1			
HbA1c						
<6%	42 (38.2)	18 (16.4)	3.16	1.67	5.96	<0.001*
≥6%	68 (61.8)	92 (83.6)	1			
eGFR						
<60 mL/minute/1.73 m^2	70 (63.6)	58 (52.7)	1.57	0.92	2.69	0.102
≥60 mL/minute/1.73 m^2	40 (36.4)	52 (47.3)	1			
HT						
Yes	105 (95.5)	96 (87.3)	3.06	1.06	8.82	0.038*
No	5 (4.5)	14 (12.7)	1			
DLP						
Yes	105 (95.5)	79 (71.8)	8.24	3.07	22.15	<0.001*
No	5 (95.5)	31 (28.2)	1			
Cardiovascular disease						
Yes	27 (24.5)	22 (20.0)	1.30	0.69	2.46	0.418
No	83 (75.5)	88 (80.0)	1			
Cerebrovascular disease						
Yes	24 (21.8)	19 (17.3)	1.34	0.68	2.61	0.396
No	86 (78.2)	91 (82.7)	1			
Liver disease						
Yes	4 (3.6)	5 (4.5)	0.79	0.21	3.03	0.734
No	106 (96.4)	105 (95.5)	1			
Cognitive impairment						
Yes	21 (19.1)	7 (6.4)	3.47	1.41	8.55	0.007*
No	89 (80.9)	103 (93.6)	1			
Diabetic retinopathy						
Yes	49 (47.1)	25 (32.9)	2.73	1.52	4.89	0.001*
No	61 (52.9)	85 (67.1)	1			
Diabetic nephropathy						
Yes	76 (69.1)	55 (50.0)	2.24	1.29	3.88	0.004*
No	34 (30.9)	55 (50.0)	1			
Diabetic neuropathy						
Yes	34 (33.7)	13 (17.8)	3.34	1.65	6.76	0.001*
No	76 (66.3)	97 (82.2)	1			
Self-care knowledge of hypoglycemia prevention						
Poor	86 (78.2)	43 (39.1)	5.58	3.09	10.10	<0.001*
Good	24 (21.8)	67 (60.9)	1			

BMI=body mass index; DM=diabetes mellitus; HbA1c=glycated hemoglobin; eGFR=estimated glomerular infiltration rate; HT=hypertension; DLP=dyslipidemia; CI=confidence interval

* Statistical significance

Table 3. Multiple logistic regression analysis of precipitating factors of hospitalization due to hypoglycemia

Precipitating factors	Case group; n (%)	Control group; n (%)	COR	AOR	Beta coefficient	95% CI for AOR		p-value
						Lower	Upper	
Self-care knowledge of hypoglycemia prevention								
Poor	86 (78.2)	43 (39.1)	5.58	14.37	2.67	5.752	35.880	<0.001
Good	24 (21.8)	67 (60.9)	1	1				
Insulin treatment								
Yes	59 (53.6)	28 (25.5)	3.39	13.78	2.62	5.425	34.989	<0.001
No	51 (46.4)	82 (74.5)	1	1				
Intensive glycemic control								
HbA1c <6%	42 (38.2)	18 (16.4)	3.16	3.64	1.29	1.703	7.787	0.01
HbA1c ≥6%	68 (61.8)	92 (83.6)	1	1				

HbA1c=glycated hemoglobin; COR=crude odd ratio; AOR=adjusted odd ratio; CI=confidence interval

both groups. More functionally dependent patients were included in case group at 23.6% versus 12.7% (p=0.036). Most participants in the case study group attended elementary school at 66.4%, whereas most participants in the control group attended secondary school at 50.9%. The number of participants using insulin therapy was higher in the case study group at 53.6% versus 25.5% (p≤0.001). Co-morbid such as hypertension, dyslipidemia, cognitive impairment, diabetic retinopathy, diabetic nephropathy, or diabetic neuropathy was significantly higher in the case study group.

Univariate analysis of individual and precipitating factors of hypoglycemia in diabetic patients undergoing treatment in hospital

The logistic regression analysis showed individual and precipitating factors that were statistically significant and related to hypoglycemia. The individual factors included the age more than 60 years (OR 2.06, 95% CI 1.11 to 3.83, p=0.002), low education level (OR 7.88, 95% CI 4.07 to 15.29, p≤0.001), functionally dependent patients (OR 2.12, 95% CI 1.04 to 4.33, p=0.038), diabetes duration more than 10 years (OR 5.31, 95% CI 2.70 to 10.43, p≤0.001), hypertension (OR 3.06, 95% CI 1.06 to 8.82, p=0.038), dyslipidemia (OR 8.24, 95% CI 3.07 to 22.15, p≤0.001), diabetic retinopathy (OR 2.73, 95% CI 1.52 to 4.89, p=0.001), diabetic nephropathy (OR 2.24, 95% CI 1.29 to 3.88, p=0.004), diabetic neuropathy (OR 3.34, 95% CI 1.65 to 6.76, p=0.001), and cognitive impairment (OR 3.47, 95% CI 1.41 to 8.55, p=0.007). The precipitating factors related to hypoglycemia among diabetic patients with a significant p-value were insulin treatment in diabetic patients (OR 3.39, 95% CI 1.92 to 5.99, p≤0.001), HbA1c less than 6% (OR 3.16, 95% CI 1.67 to 5.96, p≤0.001), and poor self-care knowledge of hypoglycemia prevention (OR 5.58, 95% CI 3.09 to 10.10, p≤0.001). The results are shown in Table 2.

Multiple logistic regression analysis of precipitating factors of hypoglycemia in diabetic patients undergoing treatment in hospital

The multiple logistic regression analysis was performed to identify the precipitating factors associated with a higher likelihood of hospitalization due to hypoglycemia. Poor self-care knowledge of hypoglycemia prevention was found to be the most preponderant predictor of hypoglycemia in diabetic patients undergoing treatment in hospital, with a 14-fold increased risk of hospitalization due to hypoglycemia (adjusted OR 14.37. 95% CI 5.75 to 35.89, p≤0.001). Other predictors identified in the present study were insulin treatment in diabetic patients (adjusted OR 13.78, 95% CI 5.43 to 34.99, p≤0.001), and intensive glycemic control (adjusted OR 3.64, 95% CI 1.70 to 7.79, p=0.01). The results are shown in Table 3.

Discussion

The present study aimed to identify risk factors of hypoglycemia in diabetic patients undergoing treatment in Taksin Hospital. Hypoglycemia in diabetic patients were caused by various risk factors, such as individual factors and precipitating factors. In the present study, precipitating factors that played the role in the occurrence of hypoglycemia in diabetes were poor self-care knowledge of hypoglycemia prevention, insulin treatment in diabetic patients, and intensive glycemic control.

The authors found that diabetic patients with poor self-care knowledge of hypoglycemia prevention had the highest risk of hypoglycemia compared to

diabetic patients with good self-care knowledge of hypoglycemia prevention. The present study results were similar to the other studies finding that patients who had poor knowledge about hypoglycemia symptoms had a higher risk for hospitalization due to hypoglycemia[10,11]. Diabetes with good knowledge about hypoglycemia prevention was strongly associated with hypoglycemia prevention interventions[18]. Awareness of hypoglycemia and diabetic self-care management practice are the keys to the prevention of hypoglycemia.

Insulin treatment was a significant precipitating factor of hypoglycemia consistent with the previous studies[10,11]. In trials, there was a 4.5-fold increase in the risk of hypoglycemia with insulin[19]. As well, the risk of severe hypoglycemia increased by 42% every additional year of insulin treatment[20]. Although insulin treatment was associated with severe hypoglycemia, it can be used safely and must not be avoided if there was a clinical need.

The present study found that intensive glycemic control is also the significant precipitating factor of hypoglycemia. The association of HbA1c with hypoglycemic risk is complex. In some studies, hypoglycemia rates were higher in diabetic patients who achieved targets of low HbA1c with intensive glucose-lowering therapy[4,5,21]. However, other studies revealed that the risk of hypoglycemia increased when HbA1c was higher instead of lower[20,22]. According to a recent study, HbA1c's relationship with severe hypoglycemia was U-shaped. An elevated risk for hypoglycemia was associated with near-normal or poor glycemic control[23]. Therefore, treatment of diabetic patients with an individualized goal can reduce the adverse consequences of hypoglycemia.

In addition, the present study found individual factors related to hypoglycemia, similar to the previous studies. Elderly patients at age of more than 60 years, functionally dependent patients, cognitive impairment, and a longer duration of diabetes of more than 10 years are recognized as a higher risk for hypoglycemia. In elderly patients, the aging process modifies the counter-regulatory hormonal responses to become less effective in preventing hypoglycemia[24-27]. Functionally dependent patients have a reduced ability to recognize and avoid hypoglycemia by triggering appropriate responses[28]. Cognitive impairment impairs the perception of symptoms associated with hypoglycemia[24]. Patients with long-term type 2 diabetes are similar to patients with type 1 diabetes mellitus in terms of their increased risk of hypoglycemia. In addition, a longer duration of diabetes is associated with advancing beta-cell failure[4,27,29].

The authors also found low education level is associated with hypoglycemia, as a recent study showed that low education level is related to low health literacy, whereas health literacy serves as an enabling factor for safe diabetes management[30]. However, in the current study, hypoglycemia was not related to lower BMI as described in the earlier study[29].

Co-morbidities including hypertension, dyslipidemia, and complications of diabetes including diabetic retinopathy, diabetic nephropathy, and diabetic neuropathy were significant individual factors for hypoglycemia. The results are similar to the previous studies. Hypertension is associated with hypoglycemia and suggests that hypoglycemia can induce hypertension among type 2 diabetes[31]. Dyslipidemia may be a consequence of the chronic increase in blood sugar and is associated with a longer duration of diabetes[32]. Microvascular complications may be linked to the history of long-term poor glycemic control. Poor glycemic controls are usually treated with aggressive insulin therapy[27,33]. In the present study, however, cardiovascular disease, cerebrovascular disease, liver disease, renal impairment of eGFR of less than 60 mL/minute/1.73 m^2, were not related to hypoglycemia as described in the previous studies[11,27,29,34].

The present study results suggest that diabetic patients, especially those who are advanced age, have a longer duration of diabetes, and had co-morbidities, should receive diabetes self-management education. Individualized glycemic goals, frequent SMBG, flexible insulin, and other drug regimens are necessary for diabetic patients with a recent history of hypoglycemia.

There are limitations of the present study. First, due to the retrospective study design, some precipitating factors of hypoglycemia were not available. Second, the authors only assessed diabetic patients undergoing treatment in the hospital. Therefore, there is a lack of data on patients with mild hypoglycemia who were not hospitalized. Further studies are required to determine management strategies that may prevent hypoglycemia.

Conclusion

Poor self-care knowledge of hypoglycemia prevention, insulin treatment in diabetic patients, and intensive glycemic control were strong predictors of hypoglycemia in diabetic patients undergoing

treatment in Taksin Hospital. Therefore, diabetes self-management education and tailoring diabetic therapy should be provided in diabetic patients to improve treatment and prevention of hospitalization due to hypoglycemia in diabetes.

What is already known on this topic?

Studies demonstrated that advanced age, functionally dependent patients, longer duration of diabetes, low education level, and co-morbidities were associated with hypoglycemia.

What this study adds?

The precipitating factors related to hypoglycemia among diabetic patients were poor self-care knowledge of hypoglycemia prevention, insulin treatment in diabetic patients, and intensive glycemic control.

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Conflicts of interest

The authors have nothing to disclose.

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