

Received: 2016.12.08
Accepted: 2017.05.30
Published: 2017.11.28

Analysis of Risk Factors for Hypoglycemic Coma in 194 Patients with Type 2 Diabetes

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Source of support: This work was supported by the General Hospital of Tianjin Medical University

Background: The present study was conducted to analyze possible risk factors in patients with type 2 diabetes who are in hypoglycemic coma.

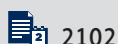
Material/Methods: A total of 194 patients with type 2 diabetic hypoglycemic coma who were admitted to our hospital between January 2010 and January 2016 were included. The patients were all in coma on admission, and their blood glucose levels were lower than 2.8 mmol/L. None of the patients had type I diabetes, specific types of diabetes, or gestational diabetes. Multiple linear regression analysis was used to determine possible factors associated with hypoglycemic coma.

Results: Among the patients, 82 were male and 112 were female (mean age, 66.88±10.62 years). In addition, 72 patients lived in urban areas and 122 lived in rural areas. Occurrence of hypoglycemic coma was correlated with difference between urban and rural residence, glycosylated hemoglobin (HbA1c) level, combined hypertension, and combined neural complications. Self-purchased drugs resulted in significantly lower blood glucose level at the onset of hypoglycemic coma than insulin, secretagogue, or non-secretagogue drugs. Blood glucose level at onset was correlated with season. Patients living in rural areas or with combined macrovascular or microvascular complications had prolonged hospital stay and poor prognosis.

Conclusions: Our results demonstrate that rural residence, higher HbA1c level, combined hypertension, and combined neural complications increase the incidence of hypoglycemic coma. Use of self-purchased drugs and colder seasons may result in lower blood glucose levels in patients with hypoglycemic coma.

MeSH Keywords: **Diabetes Mellitus, Type 2 • Hemoglobin A, Glycosylated • Hospitalization • Hypoglycemic Agents**

Full-text PDF: <https://www.medscimonit.com/abstract/index/idArt/902748>



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Background

Hypoglycemic coma is an internal medicine emergency caused by a serious reduction in blood glucose (<2.8 mmol/L) [1] and resulting in compromised basic functions of the brain and loss of consciousness, which can be life-threatening [2]. With the increased prevalence of diabetes, the incidences of hypoglycemia and hypoglycemic coma are rising, and some of these patients die due to serious illness. Analyzing and summarizing the risk factors for hypoglycemia in patients with diabetes, and intervening in hypoglycemia in the presence of various risk factors are important to alleviate hypoglycemia and hypoglycemic coma. However, many medical staff and patients with diabetes still lack awareness of hypoglycemic coma and understanding of its clinical features, risk factors, and assessment, resulting in a high incidence of hypoglycemia, as well as serious and unnecessary consequences. It is reported that the incidence rate of hypoglycemia in diabetic patients using hypoglycemic agents is 14%, among which 3% have severe hypoglycemia [2]. In the present study, we analyzed the risk factors for hypoglycemic coma in patients with type 2 diabetes.

Material and Methods

Patients

A total of 194 patients with type 2 diabetic hypoglycemic coma who were admitted to our hospital between January 2010 and January 2016 were included in the present study. Their sex, age, place of residence (urban or rural), marital status, course of diabetes, use of hypoglycemic agents, glycosylated hemoglobin (HbA1c) level, admission season, average number of hospitalization days, and complications were recorded. Patients who had taken aspirin, β -blocker, acipimox, or fibrate-type lipid-lowering drugs were excluded, because taking these drugs together with hypoglycemic agents can cause hypoglycemia. All procedures were approved by the Ethics Committee of Tianjin Medical University. Written informed consent was obtained from all patients or their families.

Inclusion and exclusion criteria

The included patients with type 2 diabetic hypoglycemic coma were all in coma on admission, and their blood glucose levels were all lower than 2.8 mmol/L. They met the diagnostic criteria for diabetes mellitus published by the World Health Organization in 1999. Any patients who had type I diabetes, specific types of diabetes, or gestational diabetes and any coma patients caused by non-hypoglycemia were excluded from the study.

Statistical analysis

Statistical analysis was performed using SPSS19.0 statistical software (IBM, Armonk, NY, USA). Measurement data are expressed as means \pm standard deviations. For data with normal or nearly normal distribution, differences between 2 groups of data were compared by *t* test, and differences among multiple groups were compared using analysis of variance. For data that did not conform to normal distribution or nearly normal distribution, differences among groups of data were compared by rank-sum test and data are expressed as medians (minimum and maximum). Correlations between 2 variables were evaluated using Pearson's test or Spearman's test. Multivariate linear regression was used in multivariate analysis. Differences with $P < 0.05$ were considered statistically significant.

Results

Occurrence of hypoglycemic coma is correlated with difference between urban and rural residence, HbA1c level, combined hypertension, and combined neural complications

The 194 patients were admitted to the hospital Emergency Department, presenting symptoms such as unclear consciousness, somnolence, or inability to wake up. The patients were in coma for 1 hour to more than 20 hours before arriving at the hospital. Some patients had symptoms such as panic, convulsions, delirium, assaultive behavior, and mood changes before unclear consciousness and somnolence, and some patients directly fell into coma. All patients received intravenous injection of 50% glucose (doses were dependent on the conditions of the patients) on admission, and then transferred to the Department of Endocrinology, where they received rescue therapy such as 50% glucose, glucocorticoid, and elevation of blood glucose. Among all 194 patients, 191 returned to normal consciousness and 3 died due to failed rescue. Two out of the 3 dead patients had combined malignant tumors and 1 had combined respiratory failure. Among the 194 patients, possible factors associated with hypoglycemic coma included sex, urban vs. rural residence, marital status, combined neural complications, combined hypertension, other complications such as tumor and infection, age, average number of hospitalization days, course of disease, HbA1c level, use of hypoglycemic agents, and season of admission (Table 1). Multi-factor regression analysis showed that urban vs. rural residence, HbA1c level, combined hypertension, and combined neural complications were correlated with hypoglycemic coma (Table 2). The results suggest that the occurrence of hypoglycemic coma is correlated with place of residence, HbA1c level, combined hypertension, and combined neural complications.

Table 1. Analysis of related factors for hypoglycemic coma.

Variables	Gender (male/female)	Place of residence (town/village)	Marital status (married/widowed or divorced)	Neural complications (yes/no)	Macrovascular complications (yes/no)	Macrovascular complications (yes/no)	Combined hypertension (yes/no)	Other complications (yes/no)	Age (year)	Average length of stay (day)	Course of disease (year)	HbA _{1c}	Hypoglycemic agents	Admission season
No. of cases	82/112	72/122	178/16	79/115	113/81	32/162	104/90	111/83						
F/t/r	-0.891	-2.176	1.427	2.416	-0.162	1.215	2.195	2.254	-0.080	-0.033	1.127	0.158	0.024	-0.058
P	0.374	0.031*	0.155	0.017*	0.872	0.226	0.029*	0.025*	0.270	0.643	0.345	0.028*	0.740	0.418

* P<0.05.

Table 2. Multiple factor analysis of hypoglycemic coma.

Variables	β	S.E.	β (standardized)	t	P
Constants	1.042	0.225	–	4.637	<0.001
Complications (neural)	0.165	0.078	0.147	2.121	0.035*
Residence (town/village)	0.211	0.080	0.185	2.629	0.009*
Complications (hypertension)	0.200	0.078	0.181	2.566	0.011*
HbA _{1c}	0.052	0.026	0.138	1.999	0.047*

* P<0.05.

Table 3. Composition of patients treated with different drugs.

Groups	No. of cases	Percentages (%)
Self-purchased drug group	35	18.04
Insulin group	63	32.47
Secretagogue group	93	47.94
Non-secretagogue group	3	1.55
Total	194	100.00

Administration of self-purchased drugs resulted in significantly lower blood glucose level at the time of onset of hypoglycemic coma compared to administration of insulin, secretagogue, or non-secretagogue drugs

To test whether blood glucose level at the time of onset of hypoglycemic coma is correlated with hypoglycemic agents, we recorded the number of patients who used different types of drugs. The patients were divided into 4 groups according to use of different hypoglycemic agents: a self-purchased drug group (non-formal hypoglycemic drugs without drug batch number), an insulin group (various forms and types), a secretagogue group (sulfonylureas or novel non-sulfonylureas hypoglycemic agents), and a non-secretagogue group (metformin,

acarbose, and voglibose) (Table 3). The blood glucose level at the time of onset of hypoglycemic coma in the self-purchased drug group was significantly lower than in the other 3 groups (P<0.05). In addition, the blood glucose level at the time of onset of hypoglycemic coma was not significantly different among the insulin group, secretagogue group, and non-secretagogue group (P>0.05) (Table 4). The results indicate that use of self-purchased drugs resulted in significantly lower blood glucose level at the time of onset of hypoglycemic coma compared to use of insulin, secretagogue drugs, or non-secretagogue drugs.

Table 4. Blood glucose levels at the onset of hypoglycemic coma in patients treated with different drugs.

Groups	No. of cases	Blood glucose levels at onset (mmol/L)
Self-purchased drug group (A)	35	1.67±0.63
Insulin group (B)	63	2.05±0.55
Secretagogue group (C)	93	1.92±0.49
Non-secretagogue group (D)	3	2.40±0.44
Overall comparison: F (p)	–	4.789 (0.003)
Multiple comparison: (p)	A vs. B	0.001*
	A vs. C	0.020*
	A vs. D	0.012*
	B vs. C	0.122
	B vs. D	0.141
	C vs. D	0.103

* P<0.05.

Table 5. Composition of patients admitted in different seasons.

Groups	No. of cases	Percentages (%)
Spring	43	22.16
Summer	49	25.26
Autumn	34	17.53
Winter	68	35.05
Total	194	100.00

Blood glucose level at the onset of hypoglycemic coma is correlated with season

To examine whether blood glucose level at the onset of hypoglycemic coma was correlated with season, we recorded the number of patients admitted in different seasons (Table 5). The blood glucose level at the onset of hypoglycemic coma in patients admitted in winter or spring was significantly lower than in summer or autumn (P<0.05). In addition, the blood glucose level at the onset of hypoglycemic coma in patients admitted in summer was significantly lower than in autumn (P<0.05) (Table 6). The result suggests that blood glucose level at the onset of hypoglycemic coma is correlated with season, and patients admitted in winter have the lowest blood glucose level.

Type 2 diabetic patients with hypoglycemic coma who live in rural areas or have combined macrovascular and microvascular complications have prolonged hospital stay and poor prognosis

To study how different factors affect prognosis, we used hospitalization days to evaluate the prognosis. Single-factor regression analysis and multiple-factor stepwise regression analysis

showed that the duration of hospitalization of patients with hypoglycemic coma is related to their place of residence, as well as whether it is combined with macrovascular and microvascular complications (Tables 7, 8). The results indicate that type 2 diabetic patients with hypoglycemic coma who live in rural areas or have combined macrovascular and microvascular complications have longer hospital stay and worse prognosis.

Discussion

The prevalence of diabetes in China has increased dramatically in recent years. The prevalence of diabetes in people over the age of 18 has reached 11.6%, with a corresponding increase in the incidence of diabetes complications. Hypoglycemia is most commonest in patients with type 1 diabetes [3], and its incidence in patients with type 2 diabetes is also high [4,5]. Hypoglycemic coma may also cause serious damage to the body, or even death [6]. In the present study, the occurrence of hypoglycemic coma in patients with type 2 diabetes was shown to be related to low HbA1c. The average age of the 194 patients was 6.88±10.62 years and the average HbA1c level was (6.68±1.47)%. For patients 75–92 years old, the of HbA1c

Table 6. Blood glucose levels at the onset of hypoglycemic coma in patients admitted in different seasons.

Groups	No. of cases	Blood glucose levels at onset (mmol/L)
Spring (A)	43	1.71±0.11
Summer (B)	49	2.06±0.13
Autumn (C)	34	2.44±0.11
Winter (D)	68	1.66±0.78
Overall comparison: F (p)	–	25.528 (0.000)
Multiple comparison: (p)	A vs. B	0.000*
	A vs. C	0.000*
	A vs. D	0.995
	B vs. C	0.000*
	B vs. D	0.000*
	C vs. D	0.000*

* P<0.05.

Table 7. Single factor regression analysis of hospitalization days.

Variables	Gender (male/female)	Place of residence (town/village)	Marital status (married/widowed or divorced)	Neural complications (yes/no)	Macrovascular complications (yes/no)	Macrovascular complications (yes/no)	Combined hypertension (yes/no)	Other complications (yes/no)	Age (year)	Average length of stay (day)	Course of disease (year)	HbA _{1c}	Hypoglycemic agents	Admission season
F	0.721	28.100	0.20	4.227	11.188	11.428	0.343	4.853	1.871	3.924	1.391	0.079	0.191	1.202
P	0.391	0.000*	0.888	0.041*	0.001	0.001	0.559	0.029*	0.157	0.021*	0.239	0.971	0.826	0.310

* P<0.05.

Table 8. Multiple factor stepwise regression analysis of hospitalization days.

Variables	β	S. E.	β (standardized)	t	P
Constants	11.147	1.331	–	8.372	0.000
Complications (macrovascular)	1.364	0.686	0.315	1.990	0.048*
Tow/village	–3.221	0.694	–0.312	–4.639	0.000*
Complications (microvascular)	2.718	0.884	0.203	3.075	0.002*
HbA1c	0.052	0.026	0.138	1.999	0.047*

* P<0.05.

was only 6.63% and their mean course of disease was 8.65 years. In addition, all patients 75–92 years old had 1 or more types of combined complications, and had little awareness of hypoglycemia. Therefore, these patients are at increased risk of coma and more severe symptoms compared with younger patients and those with no complications.

Controlling HbA1c level below standard values is the common goal of patients and doctors. However, different HbA1c standard values are required for different groups of patients,

such as those with different ages, different degrees of complication severity, and different education levels. In addition, HbA1c standard values need to be explained to patients. Some patients with diabetes try to control blood glucose level to even lower values, eventually leading to hypoglycemic coma [1]. Older age [7] and complications [8] increase the incidence of hypoglycemic coma. Hypoglycemic coma can cause permanent injury of brain tissue in patients with diabetes [9]. The ACCORD study showed that excessively low blood glucose level increases the risk of death in patients with diabetes [6].

Therefore, it is necessary to make the patients aware of the hazards of high blood glucose, as well as the danger of hypoglycemia. Individualized blood glucose control objectives should be made according to the specific circumstances of each patient, and the occurrence of hypoglycemia and hypoglycemic coma should be avoided.

In treating diabetes, continuous monitoring of blood sugar, administration of drugs, and monitoring complications are needed. The present study shows that the incidence of hypoglycemic coma in rural patients is significantly higher than that in urban patients, the blood glucose level at the onset of hypoglycemic coma in rural patients is significantly lower than in urban patients, and rural patients have longer hospital stays than urban patients. The prevalence rate of diabetes in rural areas of China is increasing, but there has not been adequate investigation of hypoglycemia in rural. Therefore, more economic and educational support should be given to rural diabetic patients.

All 194 patients in the present study had used hypoglycemic agents. Studies show that use of hypoglycemic agents increases the incidence of hypoglycemic coma in comparison to controlling of blood glucose by lifestyle modification [10,11]. All cases in the present study were hypoglycemic coma patients with high levels of hypoglycemia. Therefore, we did not include cases in which blood sugar was controlled by lifestyle modification. Of note, the percentage of diabetic patients who had used self-purchased drugs was 22.16%, and these patients had lower blood glucose levels at the onset of hypoglycemic coma compared with patients who used regular commercial hypoglycemic agents. Self-purchased drugs have unknown compositions and non-standardized dosages, leading to increased risks for hypoglycemia. However, these self-purchased drugs are still a hypoglycemic treatment widely used by many diabetes patients. In addition, the incidence of hypoglycemia for patients who use self-purchased drugs is higher and more difficult to control. Therefore, we included this type of treatment to remind clinicians to pay attention to this means of hypoglycemic control. Strengthening standardized management of diabetic patients and making the patients aware of the adverse effects of hypoglycemic agents are difficult for clinicians. The present study also shows that the blood glucose levels of patients with

hypoglycemic coma are affected by admission season. Blood glucose levels of patients with hypoglycemic coma who are admitted in colder seasons (winter and spring) were significantly lower. Some hypoglycemic episodes in winter are more severe compared to other seasons because it is harder to get to the hospital in winter. However, some patients with adrenocortical insufficiency may have more deficient secretion of hyperglycemic hormone at low temperatures, leading to severe hypoglycemia events. This suggests that patients with diabetes need to pay more attention to the occurrence of hypoglycemic coma in the colder seasons.

Conclusions

Our study also shows that type 2 diabetes combined with macrovascular and microvascular complications leads to prolonged hospital stay. Macrovascular lesions lead to low blood glucose levels, which are likely to induce coma and other nervous system symptoms. In addition, microvascular lesions, especially renal lesions, reduce the metabolism of hypoglycemic agents and prolong the hypoglycemic effects. Therefore, patients with type 2 diabetes should be more alert to the risk of hypoglycemic coma if they are combined with macrovascular and microvascular complications. Moreover, diabetic patients with neuropathy often have less response to hypoglycemia. Subtle symptoms of hypoglycemia can result in increased incidence of severe hypoglycemia and hypoglycemic coma. In conclusion, hypoglycemic coma, as a serious complication of diabetes, needs to receive more attention. Patients with diabetes should be correctly educated not to blindly pursue excessively low blood glucose. More attention should be paid to the effects of age, macrovascular complications, microvascular complications, neural complications, economic status, cultural conditions, and compensatory glucose hormones on the occurrence of hypoglycemic coma. Importantly, further follow-up studies should be carried out to understand the long-term prognosis of patients with hypoglycemic coma.

Conflict of interest

None.

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