Predisposing factors for hypoglycaemia in the emergency department

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Abstract

Objective: Hypoglycaemia is a common complication of diabetes mellitus. Previous studies suggest that hypoglycaemic episodes may occur with other comorbidities, influencing the outcome of recovery. Recognising the predisposing factors for hypoglycaemic episodes in the emergency department is important. Therefore, we investigated the characteristics of and predisposing factors for hypoglycaemia in the emergency department.

Methods: Data from 186 patients were retrospectively collected from a medical centre in northern Taiwan. We divided the patients into the advanced-age group (132 patients) and the younger group (54 patients). Associated data collected for statistical analysis included vital signs on arrival, first measured blood glucose level, laboratory results, related comorbidities, length of hospital stay, and survival to discharge.

Results: Hypoglycaemia was more frequently observed in women in the advanced-age group than in the younger group. Tachycardia and elevated systolic blood pressure were less predominant in the advanced-age group than younger group. More patients in the advanced-age group had concurrent infection, and more patients in the younger group had liver dysfunction, elevated liver enzymes, liver cirrhosis, and concurrent stroke.

Conclusions: Closer attention should be paid to the possibility of infection in patients of advanced age. Liver disease and stroke need to be ruled out in younger patients.

Keywords

Acute renal failure, advanced age, hypoglycaemia, liver cirrhosis, mortality rate, infection

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Introduction

Hypoglycaemia is a common complication in patients with diabetes mellitus (DM).[1] It occurs most commonly in patients with DM treated with insulin or sulfonylureas. Clinical symptoms include sweating, shakiness, anxiety, nausea, dizziness, confusion, blurred vision, headache, and lethargy.[2] Several factors are involved in the development of hypoglycaemic episodes, such as concurrent inflammatory processes, comorbidities, and inadequate food intake. Inadequate food intake is a common risk factor for hypoglycaemia but is not the major cause of death in patients with hypoglycaemia.[3] Because hypoglycaemia is a common condition among patients in the emergency department (ED), differential diagnoses such as stroke, transient ischaemic attack, and seizure disorder should be urgently and carefully ruled out. Previous studies suggest that hypoglycaemic episodes may occur with other comorbidities and influence the outcome of the patient's recovery.[4,5] Recognising the predisposing factors for hypoglycaemic episodes in the ED is important for emergency physicians. Therefore, the present study was performed to determine the characteristics of and predisposing factors for hypoglycaemia in the ED. We analysed the comorbidities associated with hypoglycaemia and their influences on patient outcomes in different age groups.

Materials and methods

Mackay Memorial Hospital is a tertiary care medical centre with 196,570 ED visits reported annually. A total of 445,321 ED visits occurred between December 2009 and February 2012. Data were collected from a retrospective review of all patients hospitalised with hypoglycaemia during this period. Hypoglycaemia was defined as a blood glucose level of <60 mg/dL measured initially in the ED before glucose administration according to the information provided by the University of Iowa (https://uihc.org/health-library/hypoglycemia-low-blood-sugar). This study was approved by the Institutional Review Board of Mackay Memorial Hospital (16MMHIS057e).

We divided the patients into two groups: the advanced-age group, which comprised patients aged >65 years, and the younger group, which comprised patients aged ≤65 years. Associated data collected for statistical analysis included vital signs on arrival, first measured blood glucose level, laboratory results, related comorbidities, length of hospital stay, and survival to discharge.

Laboratory data analysed in this study were the white blood cell (WBC) count and the C-reactive protein (CRP), glutamate oxaloacetate transaminase (GOT), creatinine (Cr), sodium (Na), and potassium (K) levels. Related comorbidities analysed among the patients were liver cirrhosis, uraemia, inadequate food intake, acute renal failure (>2-fold increase in the serum Cr level from baseline or last measurement), urinary tract infection (UTI), pneumonia, biliary tract infection, cerebrovascular accident (CVA), and cancer. The diagnosis of CVA was established according to the discharge diagnosis verified by the attending physicians in the neurology department.

We used statistical software (IBM SPSS Statistics for Windows, Version 20.0; IBM Corp., Armonk, NY, USA) for the data analyses. Both Student's *t*-test and the chi-square test, with significance set at p < 0.05, were used in the statistical analyses.

Results

In total, 186 hospitalised patients with hypoglycaemia were reported from December 2009 to February 2012. These 186 patients ranged in age from 26 to 98 years (mean ± standard deviation, 70.5 ± 15.3 years),

and the male:female ratio was about 1:1 (male, n = 96; female, n = 90). The advanced-age group comprised 132 patients, and the younger group comprised 54 patients. Overall, 84.9% (158/186) of the patients with hypoglycaemia had a history of DM. The blood glucose level of 97.5% (154/158) of these patients with DM was controlled by oral hypoglycaemic agents, while the blood glucose level of 2.5% (4/158) was controlled by insulin injection.

Vital signs (including body temperature, heart rate, systolic blood pressure [SBP], and diastolic blood pressure [DBP]), laboratory results (including first measured blood glucose level and CRP, GOT, Cr, Na, and K levels), and length of hospital stay were analysed. The patients in the two age groups were compared on the basis of the male:female ratio; body temperature; heart rate; SBP and DBP; WBC count; blood glucose, CRP, GOT, Cr, Na, and K levels; length of hospital stay; and mortality rate. The advanced-age group comprised significantly more women (male:female ratio, 0.76:1.00) than the younger group (male:female ratio, 2.60:1.00; $p < 0.01$). In comparison, the male:female ratio in the general population of individuals aged >65 years was 0.86:1.00. The advanced-age group included significantly fewer patients with tachycardia and elevated SBP than the younger group ($p < 0.01$). The first measured blood glucose level was 4 mg/dL lower in the younger group than advanced-age group (32.0 ± 13.7 vs. 36.1 ± 11.7 mg/dL, respectively; $p = 0.04$). A significantly higher GOT level was also noted in the younger group than advanced-age group (207 ± 552 vs. 69 ± 178 IU/L, respectively; $p < 0.02$). The GOT level was significantly higher in patients with than without liver cirrhosis (204 ± 341 vs. 99 ± 339 IU/L, respectively; $p < 0.01$). No significant differences in body temperature, DBP, WBC count, or CRP, Cr, Na, and K levels were found

between the younger and advanced-age groups (Table 1).

With respect to related comorbidities, liver cirrhosis was more prevalent in the younger group than advanced-age group (12/54, 22.2% vs. 7/132, 5.3%, respectively; $p = 0.020$). CVA was also more prevalent in the younger group than advanced-age group (3/54, 5.6% vs. 1/132, 0.8%, respectively; $p = 0.04$). The advanced-age group had a higher prevalence of infections than the younger group (81/132, 61.4% vs. 22/54, 40.7%, respectively; $p < 0.02$), especially UTI (53/132, 40.2%; $p < 0.02$). The GOT and age curves are shown in Figure 1, and the relationship between heart rate and age is shown in Figure 2.

More instances of uraemia were observed in the advanced-age group than younger group, but no statistically significant difference was found. Other conditions such as inadequate food intake, acute renal failure, pneumonia, biliary tract infection, concurrent cancer, length of hospital stay, and even mortality associated with hypoglycaemia showed no statistically significant differences.

Discussion

Sex and age

Hypoglycaemia is a commonly observed complication in the ED in daily practice, and it occurred more frequently in men than in women in our study. A report of 792 patients from Israel revealed that the mean age of patients with hypoglycaemia was 73 ± 13 years and that 51% of men had hypoglycaemia.[6] These findings are similar to those in our study of 186 patients in that the mean age was 71 ± 15 years and 51.6% of men had hypoglycaemia.

Our study revealed significant differences in several parameters between the advanced-age group and the younger group. We found that the male:female ratio was quite different between the two groups and that

Table 1. Statistical comparisons between advanced-age group and younger group using Student's t-test and chi-square test.

	Advanced age (n = 132)	Younger (n = 54)	p value
Age (years)	78.7 ± 7.3	50.4 ± 10.6	
Male:female ratio	0.76:1.00	2.60:1.00	**<0.001**
Body temperature (°C)	36.4 ± 1.1	36.4 ± 1.4	0.93
Heart rate (beats/minute)	84.3 ± 17.7	91.8 ± 18.3	**<0.02**
Systolic blood pressure (mmHg)	144.2 ± 28.7	127.0 ± 29.4	**<0.001**
Diastolic blood pressure (mmHg)	72.3 ± 17.7	76.0 ± 19.0	0.22
White blood cell count (/μL)	11,170 ± 7675	11,353 ± 5937	0.88
Glucose level (mg/dL)	36.1 ± 11.7	32.0 ± 13.7	0.04
C-reactive protein (mg/dL)	5.5 ± 6.9	4.1 ± 5.2	0.35
GOT (U/L)	69.2 ± 177.7	207.1 ± 552.4	**<0.02**
Creatinine (mg/dL)	2.7 ± 2.6	3.0 ± 2.8	0.58
Sodium (meq/L)	133.6 ± 12.4	137.0 ± 6.9	0.11
Potassium (meq/L)	4.0 ± 1.0	4.2 ± 1.1	0.38
Length of hospital stay (days)	14.6 ± 13.4	16.6 ± 28.3	0.52
Liver cirrhosis	7 (5.3)	12 (22.2)	**0.020**
Uraemia	11 (8.3)	2 (3.7)	0.26
Concurrent infection	81 (61.4)	22 (40.7)	**<0.02**
Urinary tract infection	53 (40.2)	9 (16.7)	**<0.02**
Pneumonia	33 (25.0)	10 (18.5)	0.34
Biliary tract infection	4 (3.0)	1 (1.9)	0.65
Inadequate food intake	55 (41.7)	28 (51.9)	0.21
Acute renal failure	31 (23.5)	18 (33.3)	0.17
Concurrent cancer	10 (7.6)	6 (11.1)	0.40
Concurrent stroke	1 (0.8)	3 (5.6)	**0.04**
Mortality rate	13 (9.9)	8 (14.8)	0.33

Except for the male:female ratio, data are presented as mean ± standard deviation or n (%). GOT, glutamate oxaloacetate transaminase.
The boldface values indicate reaching statistical significance (p < .05).

hypoglycaemia was more frequently found in women in the advanced-age group. We presume that this finding is associated with the significantly higher rate of concurrent UTI in the advanced-age group than younger group (40.2% vs. 16.7%, respectively; p < 0.02).

Presentation

Hypoglycaemia is often recognised as a proarrhythmic event. Emerging evidence shows that two other changes induced by hypoglycaemia may also lead to arrhythmias: ischaemia and bradycardia.[7] Interestingly, we observed a 7.5-beats/minute slower heart rate in the advanced-age group than in the younger group (84.3 vs. 91.8 beats/minute, respectively; p < 0.02). Our study also revealed significantly lower rates of tachycardia and elevated SBP in the advanced-age group than in the younger group. No significant differences were found in body temperature or DBP between the two age groups.

Concurrent liver dysfunction

Liver function has a strong impact on hypoglycaemia because the liver is vital in
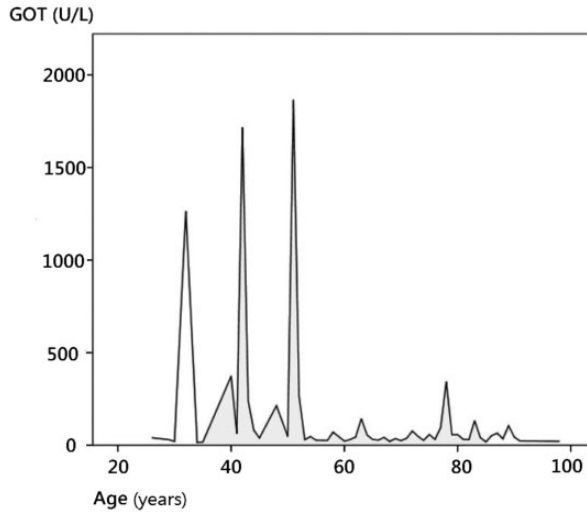
Figure 1. Curve showing association between GOT and age in patients with hypoglycaemia. GOT, glutamate oxaloacetate transaminase.
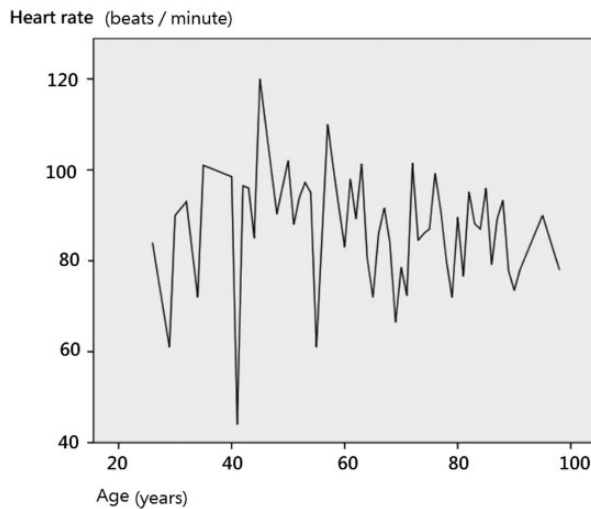
Figure 2. Curve showing association between heart rate and age in patients with hypoglycaemia.

glycogenesis, glycogenolysis, and gluconeogenesis. In the present study, an elevated GOT level and the presence of liver cirrhosis were significantly associated with hypoglycaemia, even in patients without a history of DM (28/186, 15%). However, the prevalence of an elevated GOT level and liver cirrhosis was lower in the advanced-age group. Liver cirrhosis was 4.2-fold more common in the younger group than advanced-age group. One study showed that among patients with hypoglycaemia, the risk of mortality was 4.4-fold higher among those with than without concurrent liver cirrhosis.[8] Another study showed that among patients with

decompensated liver cirrhosis, the rate of admission to the intensive care unit was significantly higher among those with than without hypoglycaemia.[9]

Concurrent stroke

The prevalence of concurrent stroke was 7-fold higher in the younger group than advanced-age group (5.6% vs. 0.8%, respectively; $p < 0.05$). We considered that this result was influenced by the actions of calling for help and contributed to the different blood glucose levels measured initially in the ED between the two age groups. Among patients with hypoglycaemia in a previous study, the risk of mortality was 2.3-fold higher among patients with than without concurrent stroke.[8]

Concurrent infection

The advanced-age group had a higher incidence of concurrent infection than the younger group (61.4% vs. 40.7%, respectively; $p < 0.02$). UTI was the most prevalent type of infection (53/132, 40.2%) compared with other types of infection such as pneumonia and biliary tract infection. Concurrent infections were 1.5-fold more common and concurrent UTI was 2.4-fold more common in the advanced-age group than in the younger group. Among patients with hypoglycaemia in a previous study, the risk of mortality was 1.6-fold higher in patients with than without concurrent infection.[8] Another study showed that in the clinical management of hypoglycaemia, about one-third of patients had intractable or recurrent hypoglycaemia, and infection was related to this occurrence. Infusion of dextrose-containing intravenous fluid and administration of antibiotics were mandatory in patients with hypoglycaemia and concurrent infection.[10]

Concurrent UTI

Previous research has shown that hypoglycaemia with concurrent UTI is commonly observed in women (male:female ratio, 0.44:1.00).[8] In that same study, patients with hypoglycaemia and concurrent UTI had a 1.2-fold higher risk of mortality than those with no UTI.[8] In our study, the prevalence of concurrent UTI was 2.4-fold higher in the advanced-age group than younger group (40.2% vs. 16.7%, respectively; $p < 0.02$). For this reason, appropriate management of older patients in the ED requires routine examination of their urine to rule out the possibility of UTI.

Concurrent renal insufficiency

In patients with renal insufficiency, hypoglycaemia may result from decreased renal gluconeogenesis, insufficient gluconeogenic substrates with inadequate food intake or malnutrition that often accompanies renal failure, decreased renal degradation and clearance of insulin, and impaired counter-regulatory hormonal responses. A study that examined the risk of hypoglycaemic episodes after discharge proved a 27% increased risk of hypoglycaemia in patients with DM and acute kidney injury.[11] However, ageing may not be a significant contributor because in the present study, the associations between uraemia/acute renal failure and hypoglycaemia showed no significant differences in the younger and advanced-age groups (8.3% vs. 3.7%, respectively). A national cohort study revealed that patients with uraemia who experienced a hypoglycaemic episode had a 15% higher risk of death than those with no hypoglycaemic episodes.[12] Patients with hypoglycaemia and concurrent uraemia had a 1.4-fold higher risk of mortality than those with no uraemia.[8]

Concurrent malignancy

Concurrent cancer was another risk factor that we considered may lead to hypoglycaemia. According to a report in 2015, 8.6% of patients with hypoglycaemia had concomitant malignancy. Of these patients, cancer of the gastrointestinal system (hypopharyngeal, oesophageal, stomach, hepatocellular, cholangiocarcinoma, and rectal cancers) accounted for 5.4% of all cancers, followed by lung cancer at 2.2%.[13] Other sites of origin included the breast and bladder.[13] Cachexia secondary to a reduced appetite in patients with cancer involving the gastrointestinal system results in hypoglycaemia. However, we found no significant difference in this association between the advanced-age group and younger group (7.6% vs. 11.1%, respectively). Despite the lack of a significant difference in hypoglycaemia and concurrent malignancy between the two age groups, patients with hypoglycaemia and concurrent cancer had an ominous 9.7-fold higher risk of mortality than those with no cancer in a previous study.[8]

Prognosis

Many studies have revealed the impact of hypoglycaemia on patients' outcomes with respect to the length of hospital stay and mortality. Patients' prognosis largely depends on their comorbidities. The use of palliative care to treat hypoglycaemia in patients without DM mainly results in multiorgan failure (or severe liver, renal, or heart failure), sepsis, a state of exhaustion due to prolonged inadequate food and water intake, or cancer cachexia.[14] Patients who are at greater risk for hypoglycaemia also include those who have recently been admitted to the ward or ED and those who are under polypharmacy, particularly patients taking more than five medications.[15] Turchin et al.[5] suggested that patients who have experienced at least one episode of hypoglycaemia should stay in the hospital 2.8 days longer than patients who have had no hypoglycaemic episodes. Moreover, the odds ratio of inpatient mortality increased 3-fold for every 10-mg/dL decrease in the lowest blood glucose level.[5] Risk factors that predict increased mortality include sepsis, a low albumin level, and malignancy.[4] However, our analysis revealed no significant differences between the two age groups. Neither the length of hospital stay nor mortality rate was significantly different between the advanced-age group and younger group (14.6 vs. 16.6 days and 9.9% vs. 14.8%, respectively). The high prevalence of DM worldwide has resulted in increased knowledge through the gathering of increasingly more data to provide better care. The high proportion of older patients with hypoglycaemia presenting to the ED is one of the challenges that clinical practitioners currently face. A report from Italy in 2018 stated that patients with a serum uric acid level of >5.43 mg/dL were more prone to death after 1 year than patients with a lower serum uric acid level. Hence, the serum uric acid level could be a useful predictor of 1-year mortality in patients with hypoglycaemia irrespective of severe comorbidities, notably increasing the risk of death in these frail patients.[16] The mean length of hospital stay was 15.2 ± 18.9 days and the overall mortality rate was 11.3% in our study; this mortality rate is lower than that in a Japan national database of in-hospital mortality (14.9%).[17]

Hypoglycaemia is always a major complication of DM, and our study is thus clinically valuable because it highlights the aetiologies of hypoglycaemia and the differences in the clinical distributions, characteristics, and comorbidities between advanced-age and younger patients. These findings will contribute to the current progress in the care of patients with hypoglycaemia. Women of advanced age were more

prone to hypoglycaemia in our study. Tachycardia and elevated SBP were less frequently observed in the advanced-age group. The patients of advanced age had poorer tolerance of hypoglycaemia and were more symptomatic when presenting to the ED. High proportions of patients with stroke, hepatitis, and cirrhosis were found in the younger group. When treating patients of advanced age with hypoglycaemia, comorbidities including infection (especially UTI) should be taken into consideration. Conversely, examination for liver or brain dysfunction is mandatory in younger patients.

Limitations

Because this was a retrospective study involving review and analysis of previously collected data, each risk factor/variable could not be more specifically categorised in detail according to its severity (e.g., the stages of concurrent liver disease and malignancy). The patients' second or even third hypoglycaemic episode during hospitalisation after initial treatment in the ED can also be taken into consideration for analysis in further studies.

Conclusion

Hypoglycaemia is a commonly observed complication in the ED in daily practice. We found that hypoglycaemia was predominantly observed in women of advanced age and that they frequently had concurrent infection, especially UTI. However, younger patients predominantly had liver dysfunction, elevated liver enzymes, liver cirrhosis, and concurrent stroke. The results of our study suggest that closer attention should be paid to workup for infection, especially UTI, in patients of advanced age. Liver diseases and stroke need to be ruled out in younger patients.

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