 doi:10.20944/preprints202209.0153.v1

Article

Risk of Hospitalization in Diabetic Patients with Severe Hypoglycemia: A Single-Center Study

Leonardo Pieramati [1,*], Enzo Mantovani [2], Giuseppe Lucchini [3] and Massimo Amato [1]

[1] Emergency Department, ASST Carlo Poma, Mantua, Italy
[2] Diabetology and Metabolic Diseases, ASST Carlo Poma, Mantua, Italy
[3] Biostatistical Service, ASST Carlo Poma, Mantua, Italy
* Correspondence: leonardo.pieramati@asst-mantova.it

Abstract: Background: Severe hypoglycemia is defined as having low blood glucose levels that requires assistance from another person to treat. Severe hypoglycemia is classed as a diabetic emergency and is a complication that can occur in people with diabetes that take insulin and certain antidiabetic drugs. The aim of our study was to evaluate the risk factors associated with hospitalization. Methods: The study was retrospectively conducted on the clinical records of adults with severe hypoglycemia who were admitted consecutively to the Emergency Department (ED) of the Carlo Poma Hospital from January 2021 to December 2021. Results: Overall, 50 patients were identified and most of these were elderly and had multiple comorbidities. They were treated with oral hypoglycemic drugs such as sulfonylureas or glinides (42%), insulin (46%) or both (6%). Hospitalization rates and in-hospital deaths occurred in 62% and in 4% of patients, respectively. There is a greater risk of hospitalization (15%) in favor of the group of patients aged ≥ 80 years compared to that with patients aged < 80 years. Conclusions: Severe hypoglycemia increases the risk of hospitalization particulary in elderly diabetic patients. Special care should be taken when prescribing anti-diabetic drugs in elderly patients, in accordance with recent guidelines, in order to avoid episodes of severe hypoglycemia that can lead to hospitalization.

Keywords: hypoglycemia; hospitalization; diabetes

1. Introduction

Severe hypoglycemia is defined as having low blood glucose concentrations that require assistance from another person to treat [1]. Severe hypoglycemia is the most common and feared complication by diabetic patients as it interferes with a wide range of daily activities with negative repercussions on physical and psychological well-being. In severe hypoglycemia, neuroglycopenia can cause seizures, coma, permanent neurological damage and death.

Identifying a cut-off that defines hypoglycemia is not easy since the glycemic thresholds for the onset of symptoms are influenced by chronic exposure to low glycemic levels [2]. However, in order to prevent episodes of severe hypoglycemia, a glycemic value has been defined such as to alert the patient by prompting him to recheck his blood sugar in a short time [3]. This blood glucose value was established at ≤ 3.8 mmol/L (70 mg/dL). More recently, it has been proposed that a value of 3 mmol/L (54 mg/dl) identifies clinically significant hypoglycemia, which should be reported in clinical trials in which hypoglycemic drugs are used in order to capture hypoglycemic episodes of greater clinical significance [4].

Hypoglycemia increases the risk of cardiovascular events [5], dementia [6], fractures [7] and mortality [8], reducing quality of life [9] and generating fear of hypoglycemic treatment [10] and consequently constitutes a limit to the achievement of good glycemic control. It follows that today the definition of an optimized glycemic control does not only mean reaching and maintaining an almost normal glycemia with glycated hemoglobin < 7.0% but also minimizing the risk of severe hypoglycemia.

 doi:10.20944/preprints202209.0153.v1

Episodes of severe hypoglycemia are associated with an increased consumption of resources, both for the intensification of blood glucose self-monitoring, and for access to the EDs and hospitalization [11]. Severe hypoglycemia is currently responsible for a greater recourse to hospitalization than observed for acute hyperglycemic complications [12] and represents the main cause of access to the EDs for adverse drug events, secondary only to cumarolic overdose [13]. In addition to the direct costs, hypoglycemia causes important indirect costs linked to the loss of productivity.

The choice of strategies that reduce the risk of hypoglycemia, especially in the most vulnerable patients, can represent a decisive aspect for reducing access to the EDs and hospitalization. The study aims to highlight the risk factors related to hospitalization among diabetic patients requiring ED cares for severe hypoglycemia.

2. Materials and Methods

We performed a retrospective study identifying all cases of severe hypoglycemia among patients with established diabetes, who attended the ED of Carlo Poma Hospital over the period between January 2021 and December 2021. Initially, we electronically searched for recorded blood glucose levels less than 3.8 mmol/L (70 mg/dL) at ED admission, so identifying a total of 234 patients. Patients without previously known diabetes (n = 163) and without complete data (n = 21) were excluded from statistical analysis. As a result of this selection, 50 patients (33 men and 17 women) were included in final analysis.

The local ethics committees approved the study protocol. The informed consent requirement for the study was exempted by the ethics committee, because researchers only accessed retrospectively a de-identified database for analysis purposes.

Information on age, sex, type of diabetes, blood glucose concentrations measured in ED, use of hypoglycemic drugs, emergency codes given at the triage, rates of hospital admission and in-hospital mortality were extracted by the ED's electronic databases. Information on the main comorbidities and the clinical symptoms presented was also recorded for all patients.

3. Statistical Analysis

Continuous variables were reported as mean (standard deviation), while categorical data are reported as numbers and percentage. Comparisons between groups were carried out with an independent t-test for continuous variables and chi-squared test for categorical variables. All statistical tests were two-sided, and associations were considered statistically significant when the values were below a nominal level of 0.05 ($p < 0.05$). Calculations were performed with IBM SPSS Statistics software version 27.

4. Results

Of the 50 patients included in the study, 46 (92%) patients had type 2 diabetes, 3 (6%) had type 1 diabetes and the remaining patient had steroid diabetes. Overall, 33 (66%) were male and their mean age was 76 years. Blood glucose concentrations measured in the ED's laboratories were 2.25 ± 0.77 mmol/L (41 ± 14 mg/dL).

Table 1 show patient characteristics. Most patients had one or more comorbidities, such as hypertension (occurring in 78% of cases), ischemic heart disease (42%), atrial fibrillation (38%), chronic kidney disease (54%), previous ischemic stroke (26%) or respiratory disease (20%). SARS-CoV-2 infection was present in 1 patient (2%). We found that 42% of patients were treated with oral hypoglycemic drugs alone (sulfonylureas or glinides), 46% with insulin therapy and the remaining 6% with combined therapy.

With regard to the clinical symptoms, 40% presented autonomic symptoms, 8% dizziness, 20% and 60% presented respectively neurological deficits and alterated consciousness up to coma . These last two conditions made the clinician suspect acute neurological

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 13 September 2022 doi:10.20944/preprints202209.0153.v1

events, in particular ischemic stroke, for which CT examinations and specialist consultations were required, which could be avoided if a simple blood glucose control was performed.

Severe hypoglycemias were associated with falls at home in 22% of cases, with a patient who reported a fracture. At the medical triage, the most frequently emergency code assigned was the red code (52%), which identifies the most urgent treatment needed.

Hospitalization rates occurred in 62% of patients, whereas in-hospital deaths occurred in 4% of cases. One patient died in the emergency room, it was a polypathological elderly man who presented with an extremely low blood glucose value equal to 0.56 mmol/L (10 mg/dL), while the other patient, suffering from progressing cancer, died in the ward after a 4-day hospital stay. The average length of hospital stay was 17.06 ± 10.09 days.

No risk factor was shown to be statistically significantly correlated with the risk of hospitalization, however we observed a greater probability of hospitalization (15%) in patients aged 80 years or older compared to those with a lower age.

Table 1. Patient characteristics.

	N = 50
Age, years, median	80.78
Sex, Female, n (%)	17 (34)
Glycemia, mmol/L, median	3.1
Hypertension, n (%)	39 (78)
Dyslipidemia, n (%)	23 (46)
Chronic kidney disease, n (%)	27 (54)
Respiratory disease, n (%)	10 (20)
Malignancy, n (%)	8 (16)
Atrial fibrillation, n (%)	19 (38)
Coronary artery disease, n (%)	21 (42)
Previous ischemic stroke, n (%)	13 (26)
Infection in progress, n (%)	17 (34)
Antidiabetic drugs	
Sulfonylureas or glinides, n (%)	21 (42)
Insulin therapy, n (%)	23 (46)
Combined therapy, n (%)	3 (6)
Autonomic symptoms, n (%)	20 (40)
Dizziness, n (%)	4 (8)
Neurological deficits, n (%)	10 (20)
Altered consciousness, n (%)	30 (60)

5. Discussion

In this single-center study, we identified a total of 50 cases of severe hypoglycemias over a period of 1 year in diabetic patients requiring ED cares. However, since the patients themselves usually treat most of their mild or moderate hypoglycemic events without any assistance from another person, it is important to underline that our results represent only a little part of a serious clinical health problem. Therefore, it is plausible to assume that our results may largely underestimate the prevalence of symptomatic hypoglycemias in people with established diabetes.

No patient was being treated with new antidiabetic drugs, while they were taking sulfonylureas or glinides, insulin or both. The insulin-releasing action of these drugs can be persistent at low glucose levels, which would lead to the development of hypoglycemia, making these drugs an undesirable choice for older diabetic patients [14].

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 13 September 2022 doi:10.20944/preprints202209.0153.v1

The average length of hospital stay was 17.06 ± 10.09 days and this emphasizes the cost that severe hypoglycemic episodes in diabetic patients entail for the healthcare system. Costs that could be reduced with greater attention on the part of clinicians in prescribing the most modern antidiabetic drugs, avoiding excessive control of the glycemic profile particulary in the elderly.

In our study we observed a greater risk of hospitalization in patients aged ≥ 80 years, frail individuals especially in relation to the high number of comorbidities. Hypoglycemia, severe or not, is a common problem in older people with diabetes. Aging changes the cognitive and symptomatic responses to hypoglycemia, increasing the risk of unawareness or severe episodes of hypoglycaemia. Although hypoglycemia in the elderly is the most common complication of tight glycemic control, multiple comorbidities such as chronic kidney failure, heart disease, malnutrition and polypharmacy can increase the risk of this complication.

Our work had some limitations. The retrospective nature of the study affected the numerical non-uniformity and baseline characteristics of the two comparison groups. Some data were not available for analysis, as they could not be obtained from the consulted sources. Changes in patterns of presentations to EDs have been reported during COVID-19 lockdowns, including reduced numbers of patients with certain high acuity conditions, such as acute coronary syndrome (ACS) and stroke [15]. Therefore, we cannot exclude that the same phenomenon affects cases of severe hypoglycemia, leading to underestimation the prevalence of symptomatic hypoglycemias.

Table 2. Baseline patient characteristics.

Variable	Hospitalization		OR	OR IC 95%	Chi square	p value
	No = 19	Yes = 31				
Sex						
Male	14 (42.4%)	19 (57.6%)	0.485	0.506 - 6.179	0.806	0.369
Female						
Age (years)						
Mean	72.7	80.4			-1.915*	0.126
< 80	11 (45.8%)	13 (54.2%)	1.904	0.599 - 6.054	1.202	0.273
≥ 80	8 (30.8%)	18 (69.2%)				
Kidney failure						
No	9 (39.1%)	14 (60.9%)	1.093	0.348 - 3.435	0.023	0.879
Yes	10 (37.0%)	17 (63.0%)				
Glycemia (mmol/L)						
< 3.1	9 (37.5%)	15 (62.5%)	0.960	0.306 - 3.012	0.005	0.944
≥ 3.1	10 (38.5%)	16 (61.5%)				
Autonomic symptoms						
No	14 (46.7%)	16 (53.3%)	2.625	0.759 - 9.076	2.391	0.122
Yes	5 (25.0%)	15 (75.0%)				
Dizziness						
No	16 (34.8%)	30 (62.5%)	0.178	0.017 - 1.851	2.526	0.112
Yes	3 (75%)	1 (25%)				
Neurological deficit						
No	17 (42.5%)	23 (57.5%)	2.957	0.556 - 15.729	1.719	0.190
Yes	2 (20.0%)	8 (80.0%)				
Altered consciousness						
No	9 (45.0%)	11 (55.0%)	1.636	0.512 - 5.325	0.693	0.405
Yes	10 (33.3%)	20 (66.7%)				
Fall						
No	13 (33.3%)	26 (66.7%)	0.417	0.107 - 1.625	1.639	0.201
Yes	6 (54.5%)	5 (45.5%)				
Triage category						
Semi-urgent	0 (0.00%)	1 (100%)			4.369	0.224
Urgent	5 (71.4%)	2 (28.6%)				
Very urgent	5 (31.3%)	11 (68.7%)				
Emergency	9 (34.6%)	17 (65.4%)				
Observation Unit						

 doi:10.20944/preprints202209.0153.v1

No	14 (40.0%)	21 (60.0%)	1.333	0.375 - 4.742	0.198	0.656
Yes	5 (33.3%)	10 (66.7%)				
Death						
No	17 (36.2%)	30 (63.8%)	0.567	0.033 - 9.650	0.158	0.691
Yes	1 (50.0%)	1 (50.0%)				

* Student's t

6. Conclusions

Our single-center study shows that severe hypoglycemia due to insulin treatment or oral hypoglycemic drugs (sulfonylureas and glinides) is an important acute event for diabetic patients, increasing the risk of adverse clinical outcomes, mostly in elderly individuals. Management goals for elderly patients should be an individualized process and must include a number of considerations. Special care should be taken when prescribing anti-diabetic drugs in elderly patients, in accordance with recent guidelines, in order to avoid episodes of severe hypoglycemia that can lead to hospitalization. Patient training and treatment of the early symptoms of hypoglycemia may prevent the occurrence of further severe hypoglycemia and decrease the rate of hospitalization that directly affects the independence and functionality of older persons.

Author Contributions: Conceptualization, L.P. and E.M.; data curation, G.L.; methodology, L.P.; supervision, M.A.; validation, M.A.; writing-original draft, L.P. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: This study was also approved by the local Ethics Committee (Comitato Etico Val Padana).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: Data are available on request from the corresponding author.

Conflicts of Interest: The authors declare they have no conflict of interest.

 doi:10.20944/preprints202209.0153.v1

References

1. Seaquist ER, Anderson J, Childs B, Cryer P, Dagogo-Jack S, Fish L, et al. Hypoglycemia and diabetes: a report of a workgroup of the American Diabetes Association and the Endocrine Society. Diabetes Care 2013;36:1384–95.
2. Dagogo-Jack SE, Cryer PE. Hypoglycemia-associated autonomic failure in insulin-dependent diabetes mellitus. Recent antecedent hypoglycemia reduces autonomic responses to, symptoms of, and defense against subsequent hypoglycemia. J Clin Invest 91: 819–8.
3. Workgroup on Hypoglycemia, American Diabetes Association. Defining and reporting hypoglycemia in diabetes: a report from the American Diabetes Association Workgroup on Hypoglycemia. Diabetes Care 28: 1245–1249, 2005.
4. International Hypoglycemia Study Group. Glucose concentrations of less than 3.0 mmol/L (54 mg/dL) should se seported in clinical trials: a joint position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 40: 155–157, 2017.
5. Johnston SS, Conner C, Aagren M, Smith DM, Bouchard J, Brett J. Evidence linking hypoglycemic events to an increased risk of acute cardiovascular events in patients with type 2 diabetes. Diabetes Care 34: 1164–1170, 2011.
6. Whitmer RA, Karter AJ, Yaffe K, Quesenberry CP Jr, Selby JV. Hypoglycemic episodes and risk of dementia in older patients with type 2 diabetes mellitus. JAMA 301: 1565–1572, 2009.
7. Johnston SS, Conner C, Aagren M, Ruiz K, Bouchard J. Association between hypoglycemic events and fall-related fractures in Medicare-covered patients with type 2 diabetes. Diabetes Obes Metab 14: 634–643, 2012.
8. McCoy RG, Van Houten HK, Ziegenfuss JY, Shah ND, Wermers RA, Smith SA. Increased mortality of patients with diabetes reporting severe hypoglycemia. Diabetes Care 35: 1897–1901, 2012.
9. Green AJ, Fox KM, Grandy S; SHIELD Study Group. Self-reported hypoglycemia and impact on quality of life and depression among adults with type 2 diabetes mellitus. Diabetes Res Clin Pract 96: 3.
10. Leiter LA, Yale J-F, Chiasson JL, Harris S, Kleinstiver P, Sauriol L. Assessment of the Impact of Fear of Hypoglycemic Episodes on Glycemic and Hypoglycemia Management. Canadian Journal Diabetes.
11. Shi L, Fonseca V, Childs B. Economic burden of diabetes-related hypoglycemia on patients, payors, and employers. J Diabetes Complications, 2021.
12. Lipska KJ, Ross JR, Wang Y et al (2014) National trends in US hospital admissions for hyperglycemia and hypoglycemia among medicare beneficiaries, 1999 to 2011. JAMA 174:1116–1124.
13. Budnitz DS, Lovegrove MC, Shehab N et al (2011) Emergency hospitalizations for adverse drug events in older Americans. N Engl J Med 365:2002–2012.
14. Zammitt, N.N.; Frier, B.M. Hypoglycemia in type 2 diabetes: Pathophysiology, frequency, and effects of different treatment modalities. Diabetes Care 2005, 28, 2948–2961.
15. Rosenbaum L. The untold toll: the pandemic's effects on patients without Covid-19. N Engl J Med 2020; 382: 2368–2371.