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Original Research

Severe hypoglycemia in patients with known diabetes requiring emergency department care: A report from an Italian multicenter study

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ABSTRACT

Aims: To describe the characteristics and associated risk factors of patients with established diabetes who required Emergency Department (ED) care for severe hypoglycemia.
Methods: We performed an observational retrospective study to identify all cases of severe hypoglycemia among attendees at the EDs of three Italian University hospitals from January 2010 to December 2014.
Results: Overall, 520 patients with established diabetes were identified. Mean out-of-hospital blood glucose concentrations at the time of the hypoglycemic event were 2.2 ± 1.3 mmol/L. Most of these patients were frail and had multiple comorbidities. They were treated with oral hypoglycemic drugs (43.6%), insulin (42.8%), or both (13.6%). Among the oral hypoglycemic drugs, glibenclamide (54.5%) and repaglinide (25.7%) were the two most frequently used drugs, followed by glimepiride (11.3%) and gliclazide (7.5%). Hospitalization rates and in-hospital deaths occurred in 35.4% and in 2.3% of patients, respectively. Cirrhosis (odds ratio [OR] 6.76, 95% confidence interval [CI] 1.24–36.8, $p < 0.05$), chronic kidney disease (OR 2.42, 95% CI 1.11–8.69, $p < 0.05$) and center (Sapienza University OR 3.70, 95% CI 1.57–8.69, $p < 0.05$) were the strongest predictors of increased rates of hospital admission.
Conclusions: Severe hypoglycemia is a remarkable burden for patients with established diabetes and increases the risk of adverse clinical outcomes (in-hospital death and hospitalization), mainly in elderly and frail patients. This study further reinforces the notion that careful attention should be taken by health care providers when they prescribe drug therapy in elderly patients with serious comorbidities.

Introduction

Severe hypoglycemia is defined as having low blood glucose concentrations that require assistance from another person to treat and has the potential to cause accidents, injuries, coma and death [1]. Severe hypoglycemia is a relatively frequent event in patients with established diabetes that also markedly impacts on health resources [1]. It is estimated that the event rates for severe hypoglycemia range from 115 to 320 per 100 patient/years for patients with type 1 diabetes, and from 35 to 70 per 100 patient/years for those with type 2 diabetes [2,3]. Hypoglycemia may be due to multiple causes, such as the misuse of insulin therapy, the use of oral hypoglycemic drugs with a higher risk of hypoglycemia (*e.g.*, sulfonylureas and repaglinide) or the combination of multiple drugs that may interact with each other, such as antibiotics and sulfonylureas [1–6]. Importantly, Leese et al. reported that the rate of severe hypoglycemia was as common in patients with type 2 diabetes treated with insulin as in patients with type 1 diabetes [7].

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For the clinicians, reaching a tight glycemic control is often an important goal to minimize the development and progression of chronic complications in many patients with type 1 or type 2 diabetes but, as also highlighted by recent clinical trials, many doubts remain regarding the 'optimal' glycemic targets in older patients with type 2 diabetes [8–12]. Several international guidelines suggest that the targets for glucose control should be less stringent in older patients with diabetes, and promote the use of oral hypoglycemic drugs that cause less frequently hypoglycemia in this group of more vulnerable patients [13,14].

Moreover, it is also important to consider that the costs of severe hypoglycemias for public health are very high, especially if we also consider the costs arising from the use of ambulance, on-site treatment, access to emergency department and admission to the hospital [15].

Therefore, it is clinically important to identify and implement new strategies aimed at reducing the risk of severe hypoglycemias in patients with established diabetes. Presently, there is a paucity of available data on the prevalence of severe hypoglycemias in patients with established diabetes attending the emergency department (ED) [4,6].

Thus, the aim of this multicenter study was to describe the main characteristics and the associated risk factors of patients with established diabetes requiring ED care for severe hypoglycemia.

Materials and methods

Patients

We performed a retrospective multicenter study identifying all cases of severe hypoglycemia among patients with established diabetes, who attended the ED of three Italian University Hospitals ('Sapienza' University of Rome, 'Tor Vergata' University of Rome, and University and Azienda Ospedaliera Universitaria Integrata of Verona) over the period between January 2010 and December 2014. Where an individual had had multiple accesses in the ED for severe hypoglycemia during this period, only the first access with complete data was considered for the statistical analysis.

Initially, we electronically searched for the terms "hypoglycemia" or "hypoglycemic event" in the discharge diagnosis from the hospital, or for recorded blood glucose levels less than 3.8 mmol/L (<70 mg/dL) at ED admission, so identifying a total of 879 patients. Patients without previously known diabetes before ED admission (n = 359) were excluded from statistical analysis. We think the relatively high prevalence of hypoglycemic events in this subgroup of patients without previously known diabetes was likely due to the following two factors. Firstly, we used a threshold of 3.8 mmol/L (<70 mg/dL) to identify any hypoglycemic events with a possible overestimation of the events. Secondly, as reported in Supplemental Table S1, there was a high prevalence of cirrhosis and cancer (*i.e.*, two diseases known to cause mild-to-moderate hypoglycemias) among patients attending the ED of Sapienza University, a hospital where many patients, who are in liver transplant list, come to get the cure.

As a result of this selection, 520 (286 men and 234 women) patients with established diabetes were included in final analysis. The diagnosis of the type of diabetes was made according to what reported on the ED's electronic records and then confirmed by the diabetes registers when available (Verona University). A flow chart of the study is summarized in Fig. 1.

The ethics committees of the three University hospitals 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.

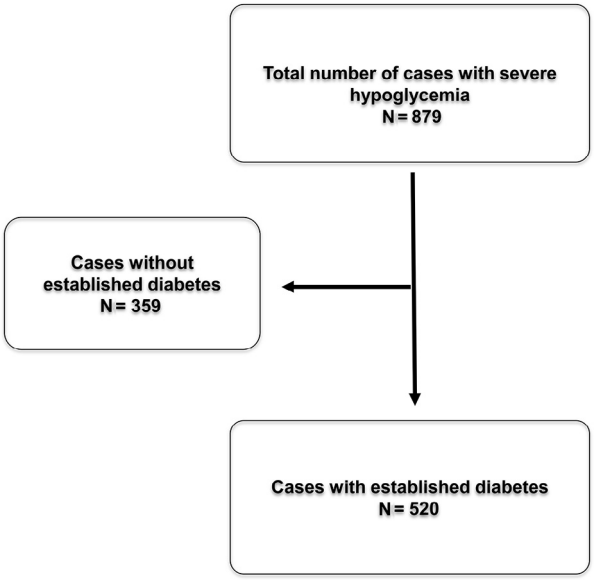

Figure 1. Details of the study design.

Data collection

Information on age, sex, type of diabetes, blood glucose concentrations at the time of the hypoglycemic event (measured at home and/or by the ambulance staff), blood glucose concentrations measured in EDs, use of any medications (including hypoglycemic drugs), alcohol abuse, emergency codes given at the triage, and rates of hospital admission and in-hospital mortality were extracted by the ED's electronic databases. Information on ambulance calls, falls and coma (using the Glasgow Coma Scale) was also extracted by the electronic databases.

Information on main comorbidities was also recorded for all patients. Presence of cardiovascular diseases was defined as a prior diagnosis of ischemic heart disease or ischemic stroke; arrhythmias included a history of any disturbance of cardiac rhythm or use of antiarrhythmic drugs; chronic kidney disease (CKD) included any diagnosis of moderate-to-severe chronic renal failure (defined as an $eGFR_{MDRD}$ <60 or <30 mL/min/1.73 m^2, respectively) and/or dialysis; chronic liver diseases were limited to a prior diagnosis of cirrhosis of any etiology; cancer included both solid and blood malignancies; finally, the presence of a prior history of dementia included any diagnosis of cognitive impairment.

Statistical analysis

Data are presented as means ± standard deviation (SD), medians (interquartile range, IQR) or percentages. Skewed variables (*i.e.*, serum creatinine and alanine aminotransferase levels) were logarithmically transformed to improve normality prior to analysis. The one-way ANOVA test (for continuous variables) and the chi-squared test (for categorical variables) were used to compare the clinical and biochemical characteristics of patients with diabetes stratified either by the type of treatment (secretagogues alone [*i.e.*, glibenclamide, glimepiride, gliclazide, repaglinide], insulin alone, or insulin plus secretagogues) or by the three participating EDs (see Fig. 3 and Supplemental Table S1, respectively). Univariate logistic regression analysis was used to examine the risk factors associated with subsequent hospital admission, which was included as the dependent variable. Subsequently, we performed a multivariate logistic regression analysis that included as covariates all significant