Original article

Hypoglycaemia requiring medical assistance in patients with diabetes: A prospective multicentre survey in tertiary hospitals

S. Liatis [a,*], M. Mylona [a], S. Kalopita [b], A. Papazafiropoulou [c], S. Karamagkiolis [d], A. Melidonis [e], A. Xilomenos [f], I. Ioannidis [g], G. Kaltsas [h], L. Lanaras [b], S. Papas [c], C. Basagiannis [a], A. Kokkinos [a]

[a] First Department of Internal Medicine, Diabetes Centre, Athens University Medical School, Laiko Hospital, Athens, Greece
[b] Department of Internal Medicine, General Hospital of Lamia, Lamia, Greece
[c] Third Department of Internal Medicine and Diabetes Centre, Nikaia General Hospital, Piraeus, Greece
[d] Department of Internal Medicine, General Hospital of Larissa, Larissa, Greece
[e] Diabetes Centre, Tzaneio Hospital, Piraeus, Greece
[f] Department of Internal Medicine, General Hospital of Agrinio, Agrinio, Greece
[g] Diabetes Centre, Department of Internal Medicine, Konstantopouleio Hospital, Athens, Greece
[h] Endocrinology Unit, Department of Pathophysiology, Athens University Medical School, Laiko Hospital, Athens, Greece

Abstract

Aim. – Hypoglycaemia is considered a factor contributing to morbidity and mortality in patients with diabetes. The aim of the present study was to examine the frequency, clinical characteristics, predisposing factors and outcomes of iatrogenic hypoglycaemia requiring medical assistance.

Methods. – Eight hospitals participated in this prospective survey of documented iatrogenic hypoglycaemia at their emergency departments. Cases with type 2 diabetes (T2D) were compared with a control group, consisting of patients visiting the outpatients' diabetes clinics of the same hospitals during the same time period.

Results. – Median survey duration was 16.5 months, and 295 episodes of iatrogenic hypoglycaemia were recorded. Frequency varied across centres from 0.25 to 0.78 cases per 100 presenting patients. Most cases (90.8%) were observed in patients with T2D (mean age: 76.7 ± 10.1 years), while 8.1% of events were recorded in patients with type 1 diabetes (mean age: 42.7 ± 18.3 years). Total in-hospital mortality was 3.4%, and all involved patients with T2D. In T2D patients, advanced age (OR: 1.3 [1.20–1.45] for 5-year increase), use of sulphonylureas (OR: 4.0 [2.5–6.36]), use of insulin (OR: 2.35 [1.42–3.95]), lower estimated GFR (OR: 1.15 [1.07–1.23] at 10 mL/min) and number of comorbidities (OR: 1.74 [1.34–2.27]) were each independently associated with hypoglycaemia requiring medical assistance.

Conclusion. – Hypoglycaemia requiring medical assistance in patients with diabetes is a moderately common condition seen in emergency departments and has a mortality rate of 3.4%. The majority of cases involve elderly individuals with T2D who are suffering from serious comorbidities and treated with insulin and/or sulphonylureas.
© 2014 Elsevier Masson SAS. All rights reserved.

Keywords: Hypoglycaemia; Type 1 diabetes; Type 2 diabetes

1. Introduction

Hypoglycaemia in patients with diabetes usually results as a consequence of treatment aiming to correct hyperglycaemia and, thus, is referred to as "iatrogenic hypoglycaemia". Severe

hypoglycaemia is defined as any hypoglycaemic episode that the patient is unable to self-treat and so requires the assistance of another person. A low blood glucose measurement is not necessary, as recovery following the administration of carbohydrates and/or glucagon is considered sufficient evidence. A subgroup of this patient category concerns cases requiring medical assistance [1].

Hypoglycaemia is a frequent medical condition associated with the treatment of patients with diabetes. It is by far more

commonly seen in type 1 diabetes (T1D) than in type 2 diabetes (T2D) although, in the latter, the prevalence of hypoglycaemia increases in relation to the duration of diabetes and severity of insulin deficiency. This is substantiated by the fact that, in such cases, more aggressive therapy is introduced, including exogenous insulin administration [2]. In large clinical trials performed in patients with T2D, rates of severe hypoglycaemia (especially in patients included in the intensive-treatment arm of the trials) were high, but varied considerably [3–6]. It has to be emphasized, however, that the data obtained in clinical trials are not usually representative of the general diabetic population, as study treatments are applied according to strict protocols and the reporting of hypoglycaemic episodes follows specific rules.

The consequences of hypoglycaemia can be divided in two main categories:

- those related to acute hypoglycaemia;
- those related to chronic/recurrent hypoglycaemia.

Acute hypoglycaemia can lead to health problems, either directly (deleterious effects of a low blood glucose supply to the brain), or indirectly usually via trauma due to loss of consciousness or seizures. Another possible mechanism of acute health damage, including sudden death, is through the induction of cardiovascular events, although this issue remains controversial [7,8].

The majority of studies evaluating the frequency and specific features of severe hypoglycaemia in patients with diabetes are mainly retrospective [9–17], and only a few had a prospective design [18–20]. The main disadvantage of examining hypoglycaemic cases retrospectively is the inability to distinguish between patients with and without diabetes, as well as between different types of diabetes. The aim of the present multicentre study was to prospectively examine the frequency of hypoglycaemia requiring medical assistance (HRMA) in adult patients with diabetes and to identify potential contributing factors predisposing to this complication.

2. Methods

Eight tertiary hospitals in five cities across Greece participated in this prospective survey. All emergency department (ED) attending physicians of the participating hospitals were informed of the aims of the present study and agreed to participate. Patients admitted to the ED and subsequently diagnosed as having hypoglycaemia were included in the study. Diagnosis of hypoglycaemia was established by the ED attending physician at each hospital on the basis of the presence of Whipple's triad: symptoms/signs compatible with low blood glucose concentrations; low plasma glucose levels (< 70 mg/dL); and resolution of symptoms after increasing blood glucose levels [2]. Only cases with a documented history of diabetes were recorded. For every hypoglycaemic case, information regarding the history and type of diabetes, presence of comorbidities, types of medication taken, time and circumstances under which the event occurred, and history of any previous serious hypoglycaemic episodes were recorded on a prespecified form, available at each participating ED. The recorded information was reported by either the patient or other witnesses after recovery from hypoglycaemia. Specific comorbidities included coronary artery disease, stroke, hepatic disease (defined as chronic hepatitis or cirrhosis), dementia and depression. Dementia was diagnosed on the basis of the patient's medical record and/or information provided by the patient's environment. The presence of depression was considered confirmed if the patient was taking antidepressant medication.

Plasma and capillary glucose values, serum creatinine and a complete blood count were measured, as these tests are routinely performed in all patients presenting with symptoms of hypoglycaemia according to our ED protocol. Estimated glomerular filtration rate (eGFR) was calculated according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula [21]. Severe chronic kidney disease (CKD) was defined as an eGFR < 30 mL/min. In cases of admission, the duration of hospitalization and final outcome (discharge from hospital or death) were also recorded. Cases of documented hypoglycaemia in patients without a previous diagnosis of diabetes were excluded.

To identify factors associated with the development of HRMA in patients with T2D, all T2D hypoglycaemic cases were compared (at a 1/2 ratio) with a control group of patients with T2D who were examined at the diabetes outpatients clinics of the same hospitals during the same time period, but who did not report severe hypoglycaemic episodes during the year prior to examination. The same information as for the recorded cases was completed by the examining physician. However, if a serum creatinine value was not available within the last 6 months of the recorded visit, then that potential control patient was excluded.

All cases and control patients signed an informed consent regarding their participation. The ethics committees of all participating institutions approved the study protocol.

Analysis of the data was performed using an SPSS statistical software package (IBM-SPSS 20.0). Categorical data were compared using the Chi^2 test. Comparisons of normally distributed data between groups (mainly between cases and controls) were performed by independent samples of Student's *t* test or by analysis of variance (ANOVA). Analysis of covariance (ANCOVA) was used to adjust the compared means for confounders. Regarding non-normally distributed data, the Mann–Whitney *U* test (two independent samples) or the Kruskal–Wallis H test was performed. Multivariable stepwise logistic-regression analysis was used to assess the independent association of different (independent) variables with the occurrence of HRMA (dependent variable). *P* values (two-tailed) < 0.05 were considered statistically significant.

3. Results

Median survey duration was 16.5 months. Hypoglycaemia frequency differed between centres, and ranged from 0.25 to 0.78 cases per 100 patients presenting at EDs. The main demographic and clinical characteristics of all patients are presented in Table 1. The majority of the recorded hypoglycaemic