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New risk and protective factors for severe hypoglycaemia in people with type 1 diabetes

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Abstract *Aims:* To evaluate risk factors for severe hypoglycaemia (SH) in patients with type 1 diabetes (T1DM).
Methods and Results: Retrospective observational and comparative study. All SH occurring between 2007 and 2014 in a German population (Lippe-Detmold) were captured. Characteristics of patients with T1DM and SH were compared with a control group being equivalent concerning age, diabetes duration, HbA1c, comorbidity, and β-blocker treatment. SH was defined as a symptomatic event requiring treatment with intravenous glucose or glucagon administration and being confirmed by a blood glucose measurement of <2.8 mmol/l. Predictive factors for SH were analysed by a multivariable regression model. As many as 405 cases of SH in T1DM occurred in 206 subjects; 50% of episodes were related to 31 patients who experienced ≥3 SH. Need for nursing care (OR 4.88), treatment with NPH (OR 3.68), and impaired hypoglycaemia awareness (OR 2.06) were the strongest risk factors for SH (all $p < 0.05$, all p_{FDR}-adjusted < 0.10; false discovery rate (FDR)). Depression (OR 0.14), treatment with CSII (OR 0.39) and short-acting insulin analogues (OR 0.31) appeared to be protective (all $p < 0.10$; FDR-adjusted). The probability of SH onset was significantly higher in patients who had previously experienced recurrent SH episodes. β-Blocker treatment did not appear to be a risk factor.
Conclusion: The complex risk for SH in people with T1DM can be reduced by treatment with CSII and short-acting analogues. Future structures of diabetes care will be challenged by the need of treating increasingly geriatric subjects with T1DM having a high risk of SH.

Introduction

Severe hypoglycaemia (SH) may increase cardiovascular and all-cause mortality in patients with long-standing and complicated diabetes [1]. Recent data indicate that self-reported SH in patients with type 1 and type 2 diabetes (T1DM, T2DM) is associated with 3.4 fold increased risk of death after a five year period [2].

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Therefore, preventing patients from SH requires better understanding of the predisposing risk factors. In this context, the occurrence of SH in randomized controlled trials (RCTs) has been predictively low as patients at high risk for SH have carefully been excluded [3].

In the current prolonged study, we characterized the clinical circumstances of SH in people with T1DM between 2007 and 2014 in an unselected German population under the conditions of real life. In order to evaluate both risk and protective factors for SH, characteristics of T1DM patients with and without SH were compared.

Methods

Study design

This retrospective population-based observational and comparative study registered the incidence of SH and its characteristics between January 1, 2007 and December 31, 2014. All patients with SH as an emergency condition were captured and treated at the medical department of the Lippe-Detmold Hospital and subsequently included in this analysis; i.e. the patients were collected consecutively. The Lippe-Detmold Hospital, a large tertiary care hospital in East Westphalia, Germany, covers all emergency patients in an urban-rural region of approximately 200,000 inhabitants. As published elsewhere [4], blood glucose testing was systematically performed in every emergency patient irrespective of the presenting condition, either in the prehospital situation at the emergency site or immediately after arrival at the emergency department.

SH was defined as an event requiring treatment with intravenous glucose or glucagon administration and being confirmed by a blood glucose measurement of $<$2.8 mmol/l.

To compare the characteristics of patients with SH and without SH, a local control group was analysed consisting of the entire 189 consecutively collected subjects with T1DM who were treated at one regional outpatient diabetes center in the period 2007–2014 and had not had any SH. These controls belonged to the same population as the cases.

Renal function was categorized according to the estimated creatinine clearance (Cockcroft–Gault equation [5]). To predict the range of comorbid conditions, the Charlson index [6] was calculated for each patient. The entire control group and subjects with SH completed the questionnaire developed by Clarke et al. [7] and also the Edinburgh Hypoglycaemia Scale [8,9] to assess previous experience of hypoglycaemia and self-estimated state of hypoglycaemic awareness. Due to partial short ambulant treatment these tests could not be performed in 17 hypoglycaemic subjects. The diagnosis of dementia was established according to the ICD-10 Classification of Mental and Behavioural Disorders (WHO 1993). In cases of newly diagnosed dementia, all respective patients underwent neurological examination and brain imaging by cerebral computer tomography or magnetic resonance tomography. All consenting inhouse-patients underwent standardized tests for dementia (Mini Mental Status Test, Montreal Cognitive Assessment Test) [10,11] as far as they were capable to complete these tests.

The protocol was approved by the Ethics Committee of the Hannover School of Medicine, Germany.

Statistical analysis

Data are presented as means with standard deviation (SD); the range is given in brackets. Data of patients was not completely excluded when single data points were missing. Standard descriptive and comparative statistics (*t*-test for two independent samples, Fisher's exact test) were used to compare clinical parameters in different groups. In order to evaluate predictive factors for SH, a logistic regression analysis adjusting for sex, BMI, diabetes duration, HbA1c and Charlson index was performed. Additionally, to address the effects of the large age-range on our analysis, we stratified the cohort by age (sub-cohort 1 $<$ 40 years $\leq$ sub-cohort 2) and also adjusted for this factor variable. Covariates were selected due to the clinical relevance regarding SH. The number of included patients for each regression model is given in the Supplementary Table 1. In the results, the confidence intervals are presented in squared brackets. All p-values for the logistic regression analysis were adjusted for multiple comparisons using the false discovery rate (FDR) by Benjamini and Hochberg. A $p_{\text{FDR-adjusted}} < 0.10$ was considered as statistical significant. For subjects with recurrent SH, the last event and the corresponding covariates were considered.

To test the hypothesis that the onset of SH is affected by previous occurrence of SH the cohort was stratified based on the number of episodes before 1st January 2012 (group 1: 0–2 SH; group 2: $>$2 SH). SH-free time was modelled and depicted by Kaplan–Meier methods and compared between groups by log-rank test. We set the 31st December 2011 as a cut-off point to provide reasonable sample sizes (n) for group 2 and a meaningful observational time span from the cut-off point till the end of the study. The time of patients who did not experience any SH after the cut-off was right-censored at 36 months (whole observation time after the cut-off). Since we had more than 50% patients with right-censored observations we used the mean instead of the median to quantify the time without an SH after the cut-off in the two groups. As confidence interval we calculated the bootstrap percentile intervals (1000 bootstraps). Furthermore, to determine a potential bias of the quantification estimates, we compared the period from the last SH before the cut-off till the cut-off between the defined groups (Wilcoxon rank sum test).

We used Cox regression to assess the hazard of SH between 2012 and 2014 from the existence of previous SH. Due to probable sample size violations regarding the number of prediction variables we used a stepwise backward model selection based on the Akaike information criterion to reduce the overall model (initially including the same covariates as for the logistic regression). This procedure resulted in holding HbA1c and diabetes duration as prediction variables. To prove the proportional hazard assumption (PH), we used Kaplan–Meier curves,