Severe hypoglycaemia requiring the assistance of emergency medical services – frequency, causes and symptoms

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Aims. To evaluate the incidence of severe hypoglycaemia (SH) requiring the assistance of Emergency Medical Services (EMS) in the general population of the Hradec Králové region, in a 1 year period; to describe the distribution of these events throughout the day, and to analyse the symptoms and causes.
Methods. The outcome data were obtained from special forms which were filled in by EMS medical staff. Incidence of SH was calculated and the distribution of events throughout the day was analysed using contingency tables. The relationship between blood glucose levels and the presence or absence of causes and symptoms of hypoglycaemia was evaluated using a general linear model and the regression tree technique.
Results. In all, a total of 338 events of SH were recorded in 262 patients. 150 episodes appeared in type 2 diabetic patients, 83 episodes in type 1 diabetic patients. 258 events were documented in insulin-treated patients. The incidence of SH was 2.4 and 0.4 episodes/100 patients/year for type 1 and type 2 diabetic patients, respectively. A significantly greater number of hypoglycaemic episodes was documented between 2 pm and 6 pm (P<0.001). Insulin therapy and alcohol consumption were the most dangerous causes of SH.
Conclusions. Hypoglycaemia requiring the assistance of EMS represents an essential problem, especially in type 1 diabetic patients. The percentage of SH is comparable to other frequent diagnoses requiring the assistance of EMS in the region. This study reflects the behaviour of diabetic patients and highlights information which is important in the prevention of SH.

Key words: severe hypoglycaemia, emergency medical service, regression trees, causes, symptoms, incidence

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INTRODUCTION

The incidence of progressive metabolic disease diabetes mellitus (DM) is on the rise[1]. There is substantial information available about the complications of diabetes. The importance of strict glycaemic control which can decrease the incidence of the complications of diabetes, is often highlighted. On the other hand, the maintenance of tight glycaemic control has been associated with increased incidence of hypoglycaemia[2,3]. Thus hypoglycaemia represents a limiting factor in the management of DM.

Hypoglycaemia is among the most common side effects of both insulin therapy and the use of oral antidiabetics, increasing the concentration of insulin[3]. Symptoms of hypoglycaemia depend on blood glucose levels along with the patient's perception of physiological changes associated with the hormonal counterregulation activated by hypoglycaemia[4]. Mild hypoglycaemia is characterised by unpleasant autonomic and neuroglycopenic symptoms[5]. Severe hypoglycaemia (SH) is usually defined as an episode requiring the assistance of another individual for recovery[6]. Such episodes may be accompanied by a coma or seizures, and SH can even be life threatening.

A number of studies describing the frequency of SH have been published[7-22]. However, most of these studies have been performed with a selected cohort[7,8,11-22]. The incidence of SH varied from 0.038 to 3.2 episodes of SH per patient per year in patients with DM type 1 (ref.[8-10,14-19]) and from 0.0004 to 0.96 episodes of SH per patient per year in patients with DM type 2 (ref.[8-10,13,16,20,21]). The aim of this analysis was to assess the incidence of SH and to describe the distribution of these events in the day time, and to analyse causes and symptoms of these events in the general population of the Hradec Králové region in a one year period.

MATERIAL AND METHODS

This observational, non-interventional cohort study was focused on episodes of SH experienced by patients in the region of Hradec Králové, Czech Republic during the year 2007. SH was defined as an event characterised by a low blood glucose level requiring the assistance of Emergency Medical Services (EMS). The blood glucose level was measured immediately after the arrival of EMS using a Wellion glucometer (Electa). Each single episode of SH in all tours (n=27,394) requiring the help of EMS in this region was recorded. The population of the Hradec Králové region is around 550,000 inhabitants.

The outcome data were obtained by the completion of a special form. The form was filled in by the medical staff at the time of the event. The database of EMS was checked to make sure that all hypoglycaemic events requiring the assistance of EMS were recorded. The information consisted of basic demographic data, type and treatment of DM, initial reason for calling EMS as well as parameters associated with hypoglycaemia such as blood glucose level at the time of the arrival of emergency services along with the causes, symptoms and treatment of SH and Glascow coma scale (GCS).

Statistical analysis was conducted using the SPSS software package, version 16.0. Descriptive statistics are presented as means ± standard deviation. A *P*-value <0.05 was considered statistically significant.

The incidence of SH was calculated from data from the Institute of Health Information and Statistics of the Czech Republic[23]. The number of patients with DM type 1 and type 2 in the region of Hradec Králové as of December 31st, 2007 was 3,428 and 37,459, respectively.

The relationship between number of hypoglycaemic episodes and time of day was analysed using contingency tables. Two statistical methods, a general linear model and regression trees, were used to evaluate the dependency of blood glucose level on binary variables. These were characterised by the presence or absence of obvious causes or symptoms of hypoglycaemic events. The general linear model analysed the influence of each cause/symptom on glycaemia independently, noting whether the presence of particular cause/symptom could have been the significant predictor of blood glucose level without regard to other possible causes/symptoms. Further, the test of significance allowed assessment of the power of dependency through η^2. The regression trees assessed the influence of particular causes/symptoms on glycaemia, distinguished direct influences from indirect, and determined dangerous combinations. More details on this method have been described by Hastie et al.[24]. These methods together are an attempt to provide the whole picture regarding the dependency of blood glucose level on the presence/absence of causes and/or symptoms. A general linear model was also used to determine the influence of blood glucose level on GCS. If the blood glucose level was recorded as "low" or "immeasurable" the blood glucose level of the patient was approximated to a value of 0.5 mmol/l.

This study was performed under the approval of the local committee on medical ethics.

RESULTS

During the observed period, 1 January 2007 to 31 December 2007, there were 338 cases of SH documented in 262 patients (1.2% of all events requiring the assistance of EMS). The baseline characteristics of these cases are summarised in Table 1. Almost half the episodes occurred in patients with DM type 2; 150 episodes were experi-

Table 1. Baseline characteristics of recorded events of severe hypoglycaemia.

Baseline Characteristics		**Number of patients**	**% of all events**
Number of events of SH		338	100
Age n (mean; SD)		338 (66.2; 16.3)	
Gender	male	158	46.8
	female	180	53.3
Type of diabetes mellitus	DM type 1	83	24.6
	DM type 2	150	44.4
	non-diabetic	2	0.6
	non-specified	103	30.5
Treatment of diabetes mellitus	insulin	258	76.3
	PAD	43	12.7
	insulin+PAD	9	2.7
	no treatment	2	0.6
	non-specified	26	7.7

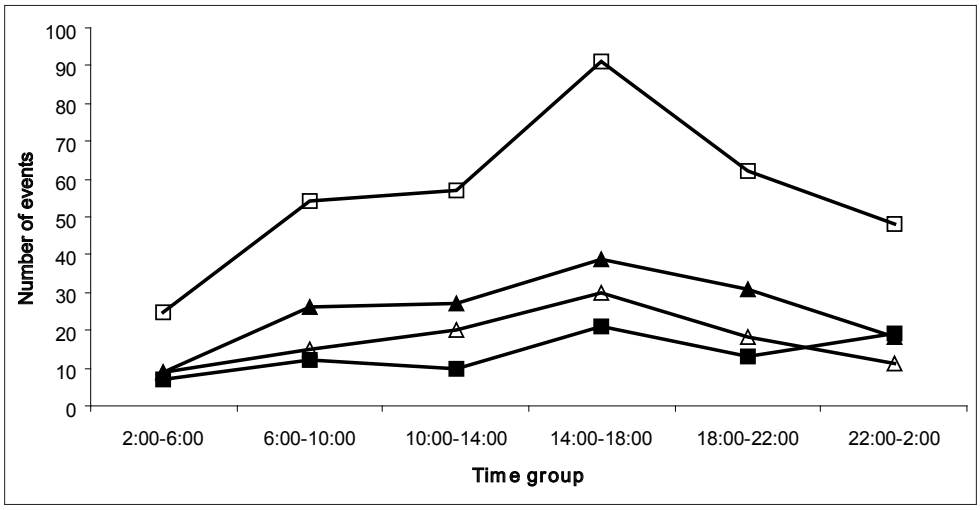

Fig. 1. Distribution of hypoglycaemic events over the day according to the type of diabetes mellitus.

Legend: –□– all hypoglycaemic events; –■– hypoglycaemic events in patients with DM type 1; –▲– hypoglycaemic events in patients with DM type 2; –Δ– hypoglycaemic events in patients with non-specified type of DM.

enced by 125 type 2 diabetic patients. 83 episodes were documented in 42 patients with DM type 1, non-diabetic patients experienced 2 events and the others were recorded in patients with a non-specified type of DM. More than three-quarters of the hypoglycaemic episodes were recorded in insulin-treated patients.

Regarding the number of type 1 and type 2 diabetic patients, the incidence of SH was 2.4 episodes of SH per 100 patients per year and 0.4 episodes of SH per 100 patients per year, respectively.

The distribution of hypoglycaemic events during the day according to the type of DM is shown in Fig. 1. The distribution of all events and events experienced by patients with DM type 2 was significantly different from a uniform distribution, with the peak recorded in the afternoon between 2 pm and 6 pm (P<0.001). Patients with DM type 1 experienced the most episodes in the afternoon between 2 pm and 6 pm as well. However, this increased incidence was not as pronounced as in patients with DM type 2. In addition, patients with DM type 1 also experienced more episodes at night between 10 pm and 2 am.

Statistically significant correlations between blood glucose level and causes of SH according to the type of DM are illustrated in Fig. 2, 3. The causes of SH with a statistically significant relation to the glycaemia in all observed events were alcohol, physical activity and insulin therapy (results not shown).

Fig. 4, 5 show symptoms significantly associated with blood glucose level. The lowest glycaemia was recorded in those patients with DM type 1 who experienced unconsciousness along with severe perspiration. Symptoms significantly associated with blood glucose level in all documented episodes of SH were unconsciousness or impaired consciousness (results not shown).

Causes and symptoms were also analysed separately using the general linear model, which showed that alcohol, insulin therapy and physical activity were statistically significant causes of SH in all documented events (P=0.002; P=0.039 and P=0.040, respectively). However, based on Cohen's convention the association reached only small effect size (η^2=0.030; η^2=0.014 and η^2=0.014, respectively). The statistically significant symptoms of SH recorded in all observed events were unconsciousness and impaired consciousness (P<0.001 and P=0.048, respec-

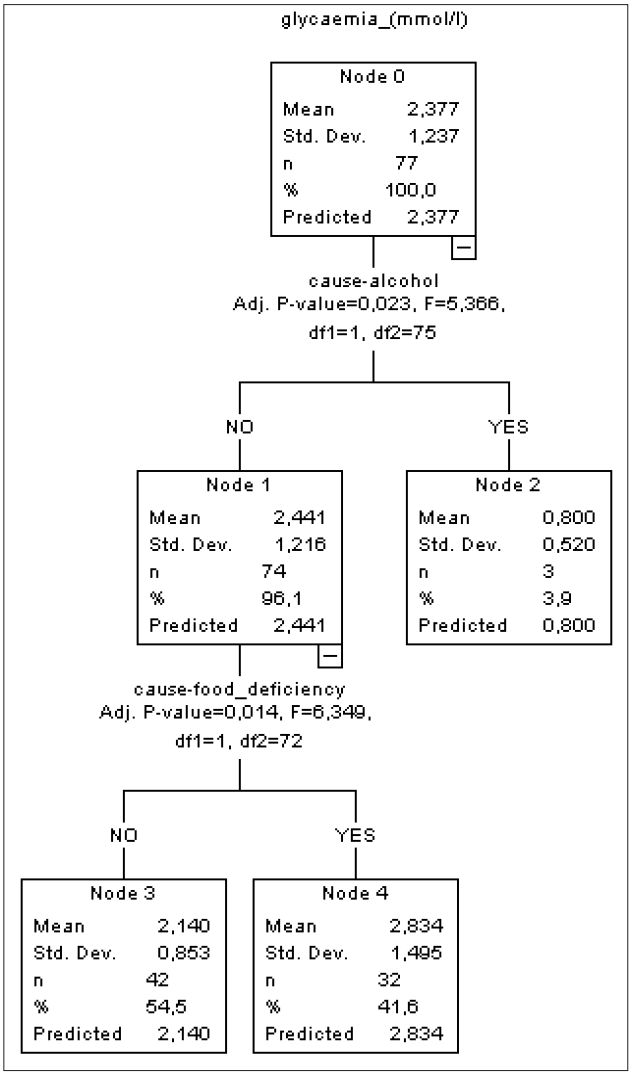

Fig. 2. Significant causes of severe hypoglycaemia in patients with diabetes mellitus type 1.

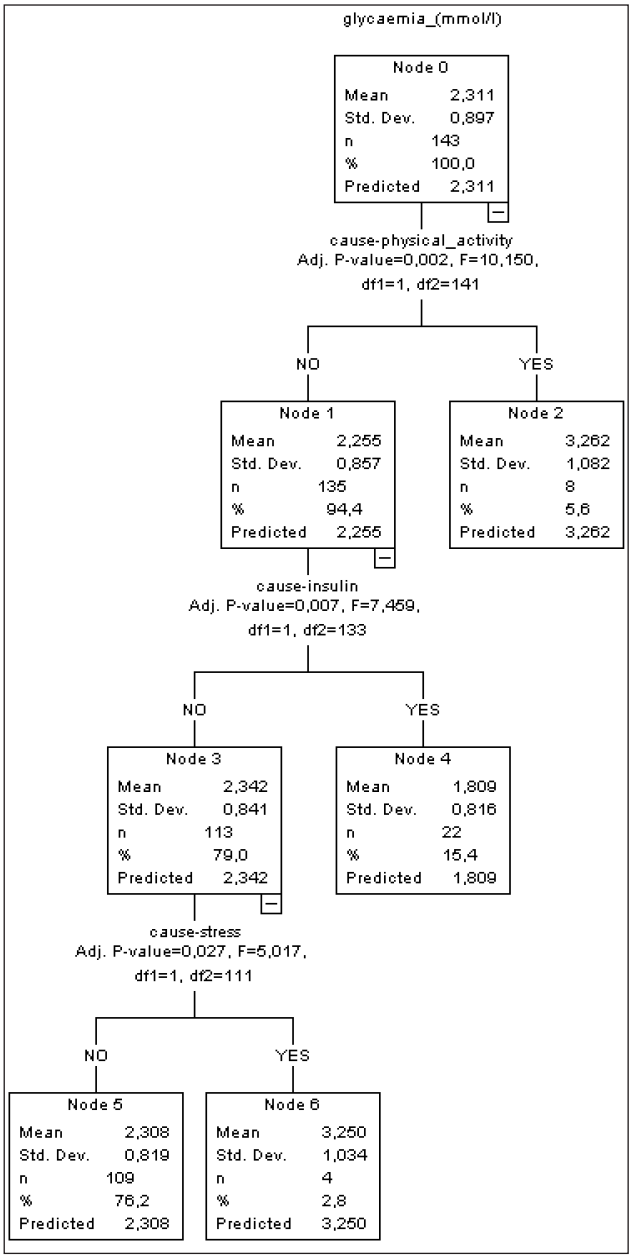

Fig. 3. Significant causes of severe hypoglycaemia in patients with diabetes mellitus type 2.

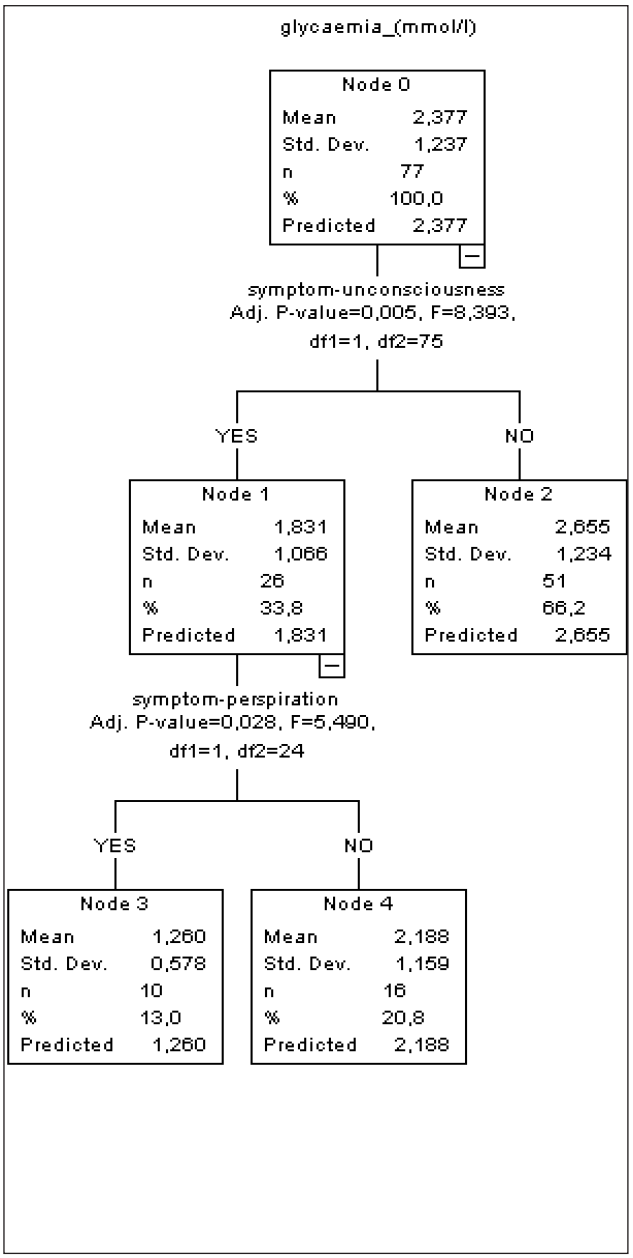

Fig. 4. Significant symptoms of severe hypoglycaemia in patients with diabetes mellitus type 1.

tively). The effect size was small (η^2=0.048 and η^2=0.013, respectively).

The general linear model also showed a significant relationship between blood glucose level and patients' consciousness as measured by GCS (P<0.001). Glycaemia influenced a 12.5% variability of GCS.

DISCUSSION

This study analysed the incidence, causes and symptoms of hypoglycaemic events requiring the assistance of EMS and their distribution throughout the day. Data for analysis were obtained by forms filled out by medical staff during or after EMS tours. All patients requiring the help of EMS due to hypoglycaemia from January 2007 to December 2007 in the region of Hradec Králové, Czech Republic, were included in this study. There were no exclusion criteria such as age, type or treatment of DM, concomitant disease or concomitant therapy. Thus these results provide information about SH in the "real-life" of a non-selected population of the region of Hradec Králové.

One limitation of this study is a number of missing responses. This could be related to the limited level of patients' knowledge about their disease. Another explanation could be the fact that EMS staff were not paid for filling in the forms. Another limitation of this study may also be that some risk factors of hypoglycaemia, such as duration of DM, duration of insulin therapy and concomitant therapy were not included in the analysis. At

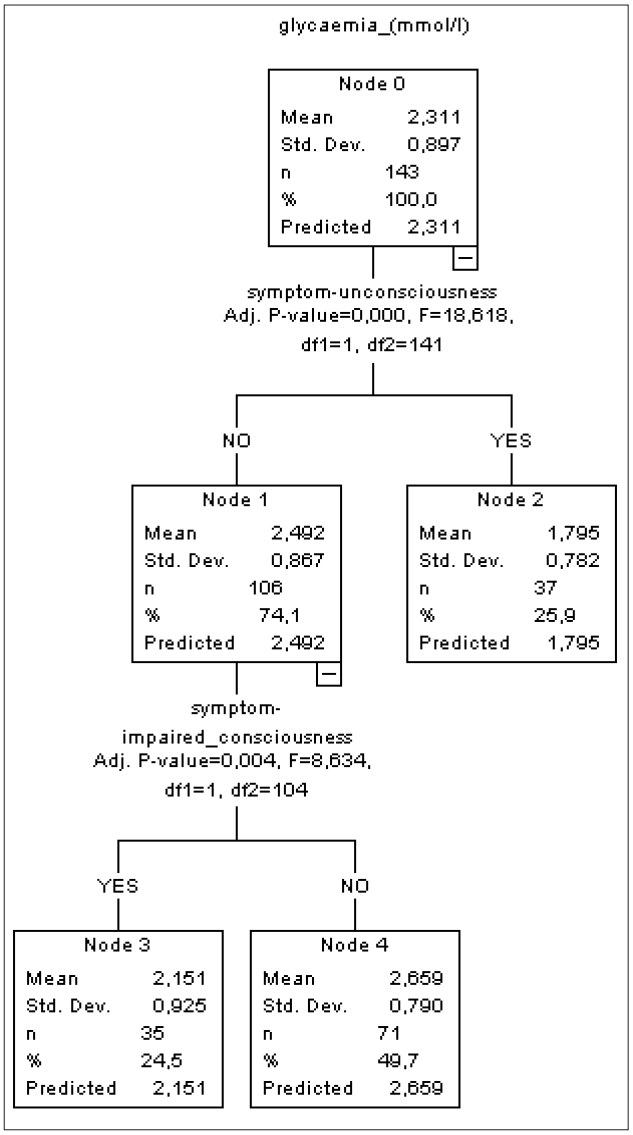

Fig. 5. Significant symptoms of severe hypoglycaemia in patients with diabetes mellitus type 2.

the beginning of this study, we tried to collect this information, however due to inadequate completion of this type of information in the forms, we decided to exclude it. The main reason was that patients often did not know this information. Another reason could be the fact that EMS medical staff did not have enough time to obtain the information. The effect of HbA1c value was not analysed, as this value is not obtained during EMS tours.

Hypoglycaemic episodes represent 1.2% of all EMS tours in the region of Hradec Králové. This is not an insignificant percentage in comparison to other frequently occuring diagnoses requiring the assistance of EMS in the same region, e.g. the number is similar to that for asthma. Less than 2% of the tours are related to cerebrovascular stroke and around 4% to acute coronary syndrome (based on the internal data of EMS).

The total number of hypoglycaemic events recorded within the year was similar to that published by Leese et al.[10]. Among the 552,212 people living in the Hradec Králové region, 338 episodes of SH were recorded in 262 patients, compared to 244 episodes of SH identified in 160 patients of the population of Tayside (total number of Tayside residents was 367,051). With regard to population, the frequencies of hypoglycaemic episodes were very similar, even if the inclusion criteria were different. In addition Leese et al. also focused on events requiring emergency treatment by primary care, ambulance, and accident or hospital services, as well as with blood glucose level <3.5 mmol/l, which was associated with the need for treatment with glucagon or intravenous glucose. Thus a larger range of patients was included. On the other hand in our study, some patients (n=32) required the assistance of EMS despite the fact that their blood glucose level was higher than 3.5 mmol/l. Counterregulatory mechanisms of blood glucose level are changed individually in patients with DM. It has been found that in patients with DM type 2 and poorly controlled DM type 1 glucose counterregulation is generally activated within higher plasma glucose level, thus hypoglycaemic symptoms can appear in higher plasma glucose concentrations[4].

Regarding the incidence of SH, we found that the rate of SH in patients with type 2 DM was the same as reported in a prospective population-based study (0.4 episodes of SH per 100 patients per year) (ref.[25]). However, the rate of SH observed in patients with DM type 1 was lower than the incidence published in the study performed by Holstein (2.4 episodes per 100 patients per year versus 3.8 episodes per 100 patients per year). The lower rate found in our study could be explained by a significant number of events being experienced by patients with a non-specified type of DM (30%). Those events were not included for calculating the incidence. Although the same criteria were used by Holstein, only 4% of events were reported by patients with non-classified insulin-treated DM. The rate of SH in patients with type 1 DM may also be under-reported, as the informed family or friends of patients were able to administer the glucagon and thus the SH incident was resolved without the help of EMS. According to Jørgensen et al.[26], 58% of patients observed and 51% of their cohabitants were familiar with the use of glucagon and 34% had glucagon at home. The results of this survey also showed the significant positive relationship between the rate of SH and cohabitants' involvement in their friend's or family member's disease[26]. In comparison to other studies, the incidence of SH was lower in our study[16-21]. However, studies of various incidences of hypoglycaemia cannot be compared without difficulty as differences in population, study design, medication regimens, and even varying definitions of hypoglycaemia emerge as problems.

A graph illustrating the distribution of hypoglycaemic events throughout the day shows that most episodes were experienced by patients between 2 pm and 6 pm. As this period includes mealtime, this pattern could be explained by the fact that food deficiency was the most frequently identified cause of SH. Murata et al.[27] found that an omitted meal led to the highest number of hypoglycaemic episodes at 5 pm. Another reason could be the

finding that the lowest glycaemia during the course of the day is just before the evening meal[21]. Furthermore, many people have free time in the afternoon when they partake in different activities such as sport. Therefore, this could be another explanation of why patients experienced the most events at the above mentioned time, as physical activity was the third most frequently reported cause of SH. Patients with DM type 1 experienced the most episodes in the afternoon as well. However, nocturnal hypoglycaemia (10 pm-2 am) was also quite frequent, suggesting that patients with type 1 DM are more prone to this condition. Holstein et al.[9] have found that the most critical period for patients with DM type 1 on intensified treatment was during nighttime hours (10 pm-6 am).

As may have been expected, the majority of events (76%) appeared in patients treated with insulin. Many previous studies have shown that hypoglycaemia is more frequent in insulin-treated diabetic patients[9,10,29,30]. Leese et al.[10] also found a similar incidence of SH in insulin-treated type 2 diabetic patients and type 1 diabetic patients. In our study insulin was the most frequently reported causes of SH, along with food-deficiency and physical activity. This nearly correlates with results published by Holstein et al.[9], who found that skipped meals, increased physical activity, the incorrect dosing of anti-diabetic treatment, and alcohol consumption were the major causes of SH. Dietary mistakes and exercise as major factors triggering SH were also found by Gürlek et al.[8]. Decreased food intake or skipped meals as the most common cause of hypoglycaemia was also presented by Kim et al.[31]. These results suggest that patient behaviour is the most commonly specified cause of SH. However, it is important to highlight that quite often the cause is not specifically identified. In our study there were 36% of events for which the cause was not specified.

To analyse the causes and symptoms of SH we used regression trees. Characteristics of this method are mentioned in the section Materials and Methods. Regression trees demonstrate that patients who experienced alcohol as the cause of SH had uniquely significantly lower blood glucose levels than those whose episodes had different causes. This result highlights the danger of this risk factor. In our study there were not so many patients reporting alcohol as cause of SH, indicating that patients are probably aware of the danger of this risk factor and are careful in using alcohol.

In patients with DM type 2 it has been found that physical activity was a cause of SH which substantially influenced glycaemia. However the relationship was positive. Patients apply different approaches to maintain optimal blood glucose levels during exercise. Some individuals reduce the dosage of anti-diabetic treatments, some increase food intake and some do both. But even if patients use these strategies, sometimes they do not manage to avoid hypoglycaemia[32]. Taking these precautions may be why patients who reported physical activity as the cause of SH had a higher blood glucose level than those who did not.

As may have been expected, unconsciousness or impaired consciousnes were symptoms of SH which significantly influenced blood glucose level. Patients with these symptoms experienced a significantly lower blood glucose level compared to those who did not. This result has been confirmed by a statistically significant correlation between blood glucose level and GCS. Impaired consciousness or unconsciousness along with sweating and mental confusion were the four most frequently occurring symptoms. It is evident that neuroglycopenic symptoms were reported at the highest rate, which was expected as we observed SH. The frequencies of these symptoms correlate with the fact that 68% of patients were unaware of the development of their hypoglycaemia. Henderson et al.[33] found that neuroglycopenic symptoms were more evident in patients with impaired awareness of their hypoglycaemia, and such patients experienced a 9-fold higher incidence of SH compared to those with normal awareness. Similarly, Ly et al.[34] found increased incidence of SH in patients with impaired awareness in comparison with those with normal awareness.

CONCLUSIONS

This study shows that SH represents an essential problem requiring the assistance of EMS, especially in patients with type 1 DM. The percentage of hypoglycaemic episodes is comparable with other frequent diagnoses requiring the assistance of EMS in the same region, indicating the seriousness of this complication. The most critical period of the day is between 2 pm - 6 pm. Diabetic patients should be aware of the risk of alcohol consumption. To minimise the frequency of SH, the necessity of regular food intake in accordance with anti-diabetic treatment and exercise should be strongly and repeatedly emphasized. Although some results of this study could have been predicted, the findings reflect the everyday behaviour of patients and highlight vital information for diabetologists and general practitioners to remind diabetic patients of. In addition, the results of this study reflect the ongoing contribution to the treatment of SH by EMS medical staff, who could also facilitate the communication of this information to patients. Results from this analysis should be taken into account with other clinical and pharmacoepidemiological studies.

ABBREVIATIONS

DM, Diabetes mellitus; EMS, Emergency medical service; GCS, Glascow coma scale; SH, Severe hypoglycaemia; SPSS, Statistical Package for the Social Sciences.

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CONFLICT OF INTEREST STATEMENT

Author's conflict of interest disclosure: The authors stated that there are no conflicts of interest regarding the publication of this article.

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