

# An evaluation of hypoglycaemia in patients with diabetes mellitus hospitalised at the Department of Gastroenterology and Metabolic Diseases, Medical University of Warsaw, Poland

## Abstract

**Background.** The aim of this retrospective study was to evaluate the incidence of hypoglycaemia and precipitating factors in patients hospitalised at the Chair and Clinic of Gastroenterology and Metabolic Disorders, Medical University of Warsaw, Poland.

**Material and methods.** We analysed 1835 hospital records of diabetic patients aged  $65.5 \pm 15.97$  years, including 243 (13.24%) patients with type 1 diabetes mellitus, 1529 (83.23%) patients with type 2 diabetes mellitus and 63 (3.43%) patients with secondary forms of diabetes mellitus. The mean duration of diabetes was  $9.57 \pm 9.58$  years.

**Results.** Episodes of hypoglycaemia were found in 108 (5.88%) patients at the mean age of  $63.58 \pm 16.03$  years,

including 79 (73.15%) women and 29 (26.85%) men. Hypoglycaemia was most common in patients managed with two injections of insulin daily (50.0%), followed by patients managed orally (16.66%), patients receiving combination treatment (20.37%) and patients on intensive insulin treatment (6.48%). The most common causes of hypoglycaemia included treatment errors (13.88%) and nutritional errors (12.03%), but in 70.37% of the cases no unequivocal cause of hypoglycaemia could be established.

**Conclusions.** Hypoglycaemia remains a frequent cause of hospitalisation in patients with diabetes mellitus and occurs least commonly in patients receiving intensive insulin therapy.

*Diabet Dośw i Klin 2008, 8, 4, 169–172*

**key words:** diabetes mellitus, hypoglycaemia, treatment

## Introduction

While the tendency in the treatment of diabetes mellitus to achieve glucose values as close as possible to values observed in healthy individuals reduces the likelihood of microvascular complications, neuropathy and macrovascular complications, it simultaneously increases the risk of hypoglycaemia. In the Diabetes Control and Complications Trial (DCCT) evaluating patients with type 1 diabetes mellitus, severe hypoglycaemia requiring intervention of other people occurred in 10% of the patients managed conventionally (two insulin injections

daily) and 26% of patients receiving intensive insulin therapy with the respective percentages for hypoglycaemic coma equalling 6% and 20%. The incidence of hypoglycaemia in patients receiving intensive insulin therapy was 0.2 episodes per patient per year and was about three times higher than that in patients receiving conventional therapy [1, 2].

The incidence of hypoglycaemia in type 2 diabetes is generally lower than that in type 1 diabetes. According to the United Kingdom Prospective Diabetes Study (UKPDS), one or more episodes of hypoglycaemia per year was experienced by 11% of the patients managed with chlorpropamide, 17.7% of the patients managed with glibenclamide and 36.5% of the patients managed with insulin with severe hypoglycaemia occurring in 0.4%, 0.6% and 2–3% of the patients. It should be noted that the number of hypoglycaemic episodes increased with the duration of diabetes, especially with the duration of insulin therapy [3–5]. Kumamoto evaluated patients with type 2 diabetes and did not observe a single episode of severe hypoglycaemia over the 8 years of follow-up [6]. The incidence of hypoglycaemia in patients

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Diabetologia Doświadczalna i Kliniczna 2008, 8, 4, 169–172  
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**Table 1.** Characteristics of the study group

Group	Number of subjects	Age (years)	Duration of diabetes
Overall	1835	65.5 ± 15.97 16–102	9.57 ± 9.58 0–55
Type 1 diabetes	243 (13.24%)		
Type 2 diabetes	1529 (83.32%)		
Other types of diabetes	63 (3.43%)		

  

Incidence of the complications of diabetes in the study group (macrovascular complications, nephropathy, retinopathy, polyneuropathy)	
Patients with hypoglycaemia (n = 108)	46 (42.59%)
Patients without hypoglycaemia (n = 1727)	816 (47.24%)

with type 2 diabetes managed with insulin increases with the duration of insulin therapy, reaching values similar to those in type 1 diabetes corrected for the duration of insulin therapy [7].

Hypoglycaemia in diabetic patients may have a plethora of causes: insufficient supply of dietary carbohydrates or omission of a meal, administration of an excessive dose of insulin or of an oral antidiabetic agent (especially tolbutamide and glibenclamide), excessive physical exercise without a preceding reduction of insulin dose or consumption of an additional portion of carbohydrates, inappropriate technique or site of insulin injection (for example, injection of insulin into the thigh before physical exercise involving running or cycling), impaired glucose absorption in malabsorption or postresection syndromes, renal failure, liver, failure, interaction with certain drugs, alcohol. Sometimes hypoglycaemia develops in the course of certain other endocrine disorders that are more prevalent among patients with diabetes, such as adrenocortical insufficiency or hypothyroidism [8].

The incidence of hypoglycaemia is higher in patients with autonomic neuropathy. Counterregulatory mechanisms in these patients are disturbed, which is manifested by impaired release of glucagon, adrenaline, growth hormone and cortisol and is accompanied by a low level of C-peptide. Also, patients with a history of hypoglycaemia are at a higher risk of hypoglycaemia in the future. Due to the fact that hypoglycaemia may be life-threatening and poses a frequent problem in everyday medical practice, various attempts to prevent hypoglycaemia are made, including the search for optimal antidiabetic therapies and the determination of factors affecting prevention [9, 10].

## Material and methods

We performed a retrospective analysis of 1835 hospital records of patients with diabetes mellitus hospita-

**Table 2.** Causes of hypoglycaemia (study group with hypoglycaemia — N = 108 patients)

Incorrect diet	13 (12.03%)
Treatment error	15 (13.88%)
Excessive exercise	2 (1.85%)
Excessive exercise and dietary error	1 (0.92%)
Unknown error	76 (70.37%)

lised between 1994 and 1998, 108 (5.4%) of whom were admitted for hypoglycaemia (Table 1).

## Results

Episodes of hypoglycaemia were found in 108 (5.88%) patients at the mean age of 63.58 ± 16.03 years, including 79 (73.15%) women and 29 (26.85%) men. Hypoglycaemia was most common in patients managed with two injections of insulin daily (50.0%), followed by patients managed orally (16.66%), patients receiving combination treatment (20.37%) and patients on intensive insulin treatment (6.48%). The most common causes of hypoglycaemia included treatment errors (13.88%) and nutritional errors (12.03%), but in 70.37% of the cases no unequivocal cause of hypoglycaemia could be established (Table 2–4).

## Discussion

The problem of hypoglycaemia in patients with diabetes mellitus arises considerable interest due to its high prevalence and clinical significance. Ginde et al. reviewed a medical registry and found that about

**Table 3.** Antidiabetic treatments in both groups

Antidiabetic treatment	Group with hypoglycaemia	Group without hypoglycaemia
Diet treatment	0 (0%)	170 (9.84%)
Oral antidiabetics	18 (16.66%)	791 (45.80%)
Combination treatment	22 (20.37%)	119 (6.89%)
Conventional insulin therapy	54 (50.0%)	484 (28.02%)
Intensive insulin therapy	7 (6.48%)	142 (8.22%)
Treatment unknown	7 (6.48%)	21 (1.21%)

**Table 4.** Patients with vs. without hypoglycaemia

	Patients with hypoglycaemia	Patients without hypoglycaemia
Number of patients	108 (5.9%)	1727 (94.1%)
Mean age $\pm$ SD	63.56 $\pm$ 16.03	65.62 $\pm$ 15.96
Age range	20–93	16–102
Mean duration of diabetes $\pm$ SD	17.05 $\pm$ 2685	9.12 $\pm$ 9.35
Females	79 (73.15%)	973 (56.34%)
Males	29 (26.85%)	754 (43.65%)
Type 1 diabetes	26 (24.07%)	217 (12.56%)
Type 2 diabetes	78 (77.22%)	1451 (84.01%)
Other forms of diabetes	4 (3.70%)	59 (3.41%)

5 million patients were referred to Emergency Departments with episodes of hypoglycaemia between 1993 and 2005 in the US, 25% of whom were hospitalised. In this period the incidence of hypoglycaemia episodes was increasing year by year, which was explained by the increase in the overall number of patients suffering from diabetes, as the number of hypoglycaemic events did not change significantly in relation to this number. Hypoglycaemia was more common in young people, below 45 years of age, in elderly patients, over 75 years of age, in women and in certain ethnic groups [9]. It is difficult to estimate the actual rate of mild hypoglycaemia, as many patients do not report it to their doctors and due to the fact that there is a considerable number of patients who do not experience any clinical symptoms of hypoglycaemia. The clinical manifestations of hypoglycaemia traditionally fall into two groups: neurovegetative and neuroglycopenic manifestations. The neurovegetative manifestations result from the release of hormones antagonising insulin (glucagon, adrenaline) and most commonly include: anxiety, irritability, hyperhidrosis, tachycardia, asthenia, pallor and mydriasis. The neuroglycopenic manifestations develop in patients with markedly reduced glucose levels and most commonly affect cognitive functions and may include convulsions, plantar response, abnormal

deep tendon reflexes and even loss of consciousness and coma [8]. In one of our studies we found that severe hypoglycaemia accounted for a considerable number of hospitalisations (over 5% of all patients with diabetes hospitalised at our Clinic). The most common causes of hypoglycaemia were treatment errors (administration of excessive doses of insulin or overdose of oral antidiabetic medication). Of note is the fact that hypoglycaemic episodes were most common in patients receiving conventional insulin therapy (two injections daily) and much rarer in patients on intensive insulin therapy. It seems that this finding may be explained by a better patient education and self-monitoring among persons receiving insulin according to multiple injection regimens. Unfortunately, due to the lack of data, we did not analyse the effect of metabolic control, measured by the level of glycated haemoglobin, or the level of patient education on the incidence of hypoglycaemia. Ginde et al. did not observe any relative increase in the incidence of hypoglycaemia despite the undoubted increase in the absolute number of patients receiving intensive insulin therapy [9], which is in contrast with the DCCT trial, which demonstrated that intensive insulin therapy actually increased the risk of hypoglycaemia by a factor of three [1, 2]. In order to better understand the physiological mechanisms of the

body's responses to hypoglycaemia hypothalamic and thalamic functions were evaluated. It is postulated that recurrent hypoglycaemia may increase the activity of the GABA-ergic system in the ventromedial hypothalamus, which impairs the counterregulatory mechanisms following a previous episode of hypoglycaemia [11]. The ventromedial area of the hypothalamus plays a special role in the detection of changes in glucose levels: while some neurons become activated by elevated glucose levels (glucose-excited neurons), others become activated by reduced glucose levels (glucose-inhibited neurons). It also seems that AMP-activated protein kinase as well as the activity of neuronal glucokinase play an important role in the body's response to hypoglycaemia. Drugs that would suppress the increased activity of glucokinase in the hypothalamus in response to a previous hypoglycaemia could, hypothetically, improve the impaired counterregulatory mechanisms [12, 13]. A similar role might be played by procedures involving ablation of certain thalamic nuclei, whose increased activation is associated with impaired mechanisms of response to hypoglycaemia [14]. A considerable interest is being generated by evaluations of peakless insulin analogues (detemir, glargine) and rapid-acting analogues (aspart, lispro, Apidra) for the reduction of the incidence of hypoglycaemia. Rapid-acting analogues mimic the release of endogenous insulin in a closer manner than short-acting insulins do and their use may reduce the risk of hypoglycaemia although the results of clinical studies are equivocal in this respect [15]. A metaanalysis of over 1400 patients with type 1 diabetes mellitus demonstrated a 25% reduction in the rate of severe hypoglycaemia in patients receiving insulin lispro compared to patients managed with short-acting insulin (15%), while Garcia et al. did not demonstrate superiority of lispro in terms of the incidence of hypoglycaemia over three years of follow-up [16]. It is also recognised that long-acting and peakless analogues tend to reduce the risk of hypoglycaemia compared to intermediate-acting insulins [17]. Episodes of hypoglycaemia hinder the attempts to achieve maximum metabolic control in diabetes and may impair cognitive function, which is more pronounced in patients who do not experience hypoglycaemia [18].

## Conclusions

Our results suggest that hypoglycaemia is a serious medical problem requiring hospitalisation of a considerable number of patients with diabetes and should be investigated further.

## References

1. The Diabetes Control and Complications Trial Research Group. Epidemiology of severe hypoglycemia in the Diabetes Control and Complications Trial. *Am J Med* 1991; 90: 450–459.
2. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993; 329: 977–986.
3. UKPDS Research Group. Overview of 6 years therapy of type 2 diabetes: a progressive disease. *Diabetes* 1993; 44: 1249–1258.
4. UKPDS Research Group. Effort of intensive blood glucose control with insulin and sulfonylureas on insulin compared with conventional treatment and risk of complication in patients with type 2 diabetes. *Lancet* 1998; 352: 837–853.
5. UK Hypoglycemia Study Group. Risk of hypoglycemia in type 1 and 2 diabetes, effects of treatment modalities and their duration. *Diabetologia* 2002; 50: 1140–1147.
6. Shichiri M, Kishikawa H, Ohkuba Y, Wake N. Long term results of the Kumamoto study on optimal diabetes control in type 2 diabetes patients. *Diabetes Care* 2000; 23: B21–B29.
7. Hepburn DA, MacLeod KM, Pell ACH, Scougal J, Frier BM. Frequency and symptoms of hypoglycemia experienced by patients with type 2 diabetes treated with insulin. *Diabet Med* 1993; 10: 231–237.
8. Sieradzki J. *Cukrzyca*. Vol. 2. Via Medica, Gdańsk 2006; 646–654.
9. Ginde A, Espinola J, Camargo C. Trends and disparities in US Emergency Department Visits for hypoglycemia 1993–2005. *Diabetes Care* 2008; 3: 511–513.
10. Cox D, Gonder-Flederick L, Ritterband L. Prediction of severe hypoglycemia. *Diabetes Care* 2007; 6: 1370–1373.
11. Chan O, Cheng H, Herzog R. Increased GABAergic tone in the Ventromedial hypothalamus contributes to suppression of counterregulatory response after antecedent hypoglycemia. *Diabetes* 2008; 5: 1363–1368.
12. Levin B, Becker T, Eiki J. Ventromedial hypothalamic glucokinase is an important mediator of the counterregulatory response to insulin-induced hypoglycemia. *Diabetes* 2008; 5: 1371–1379.
13. McCrimmon B, Shaw M, Fan X. Key role for AMP-activated protein kinase in the ventromedial hypothalamus in regulating counterregulatory hormone responses to acute hypoglycemia. *Diabetes* 2008; 2: 444–450.
14. Arbelaez A, Powers W, Videen T. Attenuation of counterregulatory responses to recurrent hypoglycemia by active thalamic inhibition. *Diabetes* 2008; 2: 470–475.
15. Brunelle BL, Llewelyn J, Anderson JH. Metaanalysis of the effect of insulin lispro on severe hypoglycemia in patients with type 1 diabetes. *Diabetes Care* 1998; 21: 1726–1731.
16. Garcia L, Lames C, Tuset MJ. Treatment with the insulin analogue lispro in children and adolescents with type 1 diabetes mellitus: evaluation over 3-year periods. *Nutr Metab* 2002; 15: 7–13.
17. Shaltin S, Phillip M. Hypoglycemia in type 1 diabetes. *Diabetes Care* 2008; 31: 5112–5124.
18. Zammit N, Warren R, Deary J. Delayed recovery of cognitive function following hypoglycemia in adults with type 1 diabetes. *Diabetes* 2008; 3: 732–736.