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Hypoglycemia in Elderly Type 2 Diabetes Patients

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Abstract

Hypoglycemia is a condition of reduced blood glucose level below 70 mg/dl (3.9 mmol/l). Hypoglycemic coma is a medical emergency which usually associated with glycemia around 20 mg/dl (1.1 mmol/l). Prolonged severe hypoglycemia may result in permanent neurological disorders. Hypoglycemia also has a negative impact on the cardiovascular system. Severe hypoglycemia may induce ventricular arrhythmias. Severe hypoglycemia requiring hospitalization in patients with type 2 diabetes occurred mostly in elderly. Low hemoglobin HbA1c level indicates inappropriate intensification of therapy as a main cause of severe hypoglycemia in elderly patients.

Keywords: Hypoglycemia; Type 2 diabetes; Elderly

Hypoglycemia

Hypoglycemia is a condition of reduced blood glucose levels below the normal range. According to the latest recommendations of the American Diabetes Association hypoglycemia is recognized with a decrease in blood glucose below 70 mg/dl (3.9 mmol/l). Hypoglycemia is one of the most common acute complications of diabetes therapy. Drug-induced hypoglycemia may occur in any type of diabetes as side effect of treatment with insulin or sulfonylureas. Hypoglycaemia may be associated with other diseases such as: adrenal insufficiency, hepatic parenchymal disease, or ethanol intoxication, postresection syndrome. Severe hypoglycaemia is defined in accordance with the recommendations of the Polish Diabetes Association as hypoglycemia requiring assistance of another person to provide carbohydrates, glucagon, or other activities. Recurrent severe hypoglycaemia is defined as two or more cases of severe hypoglycemia in the last 12 months [1,2].

The UKPDS severe hypoglycemia occurred in 4-6 patients with type 2 diabetes during the year per 1,000 patients treated with sulfonylureas (glibenclamide, chlorpropamide) and 23 during the year per 1000 patients treated with insulin [3]. The 5-year follow-up as part of the ADVANCE trial (11 of 140 patients with type 2 diabetes) has been shown to reduce the risk of microangiopathy among patients treated intensively with gliclazide MR. In this group, the aim of treatment was to achieve HbA1c values not exceeding 6.5%. 40.5% of patients required combined therapy with insulin to fulfill this criteria. A higher incidence of severe hypoglycemia, defined as the occurrence of transient central nervous system dysfunction requiring the help of others, has been reported in the group of patients with intensive treatment (2.7% v. 1.5%). Severe hypoglycemia was the cause of death in case of one patient in the standard control group. The average frequency of episodes of severe hypoglycemia in ADVANCE was 0.7 per 100 person-years in the group of intensive glycemic control and 0.4 per 100 person-years in the standard group [4]. Often severe hypoglycemia was observed in the ACCORD trial (the Action is Control Cardiovascular Risk in Diabetes) involving 10,251 patients with uncontrolled type 2 diabetes (HbA1c = 8.1%) and high risk or diagnosed cardiovascular disease. In the group treated intensively, in which the aim was to reduce HbA1c below 6%, severe hypoglycemia occurred in 16% of patients (3% /year). Particularly high risk for severe hypoglycemias were observed in patients with type 2 diabetes treated intensively (aim – HbA1c below 6%) in the study of the Veterans Affairs Diabetes Trail (VADT). This study included 791 patients with uncontrolled diabetes (HbA1c at baseline 9.4%). The 6-year follow-severe hypoglycemia occurred in 21% of intensively treated patients [5,6].

Clinical manifestation of hypoglycemia depends not only on current blood glucose levels but also include the rate of decrease of blood glucose, the duration and degree of metabolic control of diabetes, age of the patient, concomitant complications, previous episodes of severe hypoglycemia and the type of medication. Hypoglycemia may be associated with such manifestations like sweating, tremor, hunger, palpitations. These symptoms depend on the increased secretion of catecholamines, activation of autonomic nervous system. There may be other manifestations such as mood changes or headache. Moderate hypoglycemia is associated with dysfunction of the central nervous system. It may include: dizziness, anxiety, confusion, ataxia, blurred vision. Blood glucose levels below 45 mg/dl (2.5 mmol/l) may cause profound disturbances of Central Nervous System (CNS) with loss of consciousness and generalized convulsions. Hypoglycemic coma is a medical emergency usually associated with blood glucose level around 20 mg/dl (1.1 mmol/l). Prolonged severe hypoglycemia may result in permanent neurological disorders. Loss of consciousness may be accompanied by bilateral plantar reflex, muscle tension, hypothermia. In the course of severe hypoglycemia may also appear unusual symptoms. Recurrent hypoglycemia with generalized seizures may lead to misdiagnosis of epilepsy. Manifestation of hypoglycemia may be the cause of pseudobulbar syndrome or pseudotumor syndrome. Recurrent severe hypoglycemia may lead to the development of brain degeneration with mood disorders and impaired cognitive functions.

Hypoglycemia also has a negative impact on the cardiovascular system. Hypoglycemia may exacerbate myocardial ischemia. This phenomenon is particularly disadvantageous to patients with diabetes. Severe and moderate hypoglycemia may be associated with the induction of ventricular arrhythmias (QT prolongation). Hypoglycemia can lead to injuries, falls with fractures, traffic accidents. Severe hypoglycemia is a complication with psychological and social consequences to the patients and their families [7,8].

The aim of the treatment of patients with type 2 diabetes is to prevent late complications of diabetes – diabetic angiopathy and neuropathy. To achieve this goal it is necessary to obtain long-term good control of diabetes, nearly normoglycemia and thus HbA1c below 7% [9]. Good metabolic control is almost always associated with

a risk of hypoglycemia. Hypoglycemia usually is accompanied by clinical symptoms. Severe hypoglycemia is a medical emergency. Analysis of cases of patients with type 2 diabetes who were hospitalized due to severe hypoglycemia pointing out that it affects mostly patients above 65 years old - 96.6% (29 of 30 patients) [10]. Also those who developed severe hypoglycemia were characterized by low HbA1c. This indicates chronic mean blood glucose levels below 140 mg / dl. These values were lower than those recommended by the American Diabetes Association. According to the recommendations of ADA 2016 in patients with type 2 diabetes, in 1 general good metabolic control is characterized by A1c ≤ 7% (≤53 mmol/mol). In the case of short-term type 2 diabetes, target of HbA1c is ≤ 6.5% (≤48 mmol/mol). In the group with severe hypoglycemia mean duration of diabetes was 12.0 ± 9.82 years. In the case of patients aged over 70 years with longstanding diabetes (>20 years), who co-exist with a significant macrovascular complications (myocardial infarction and/or stroke) satisfactory metabolic control is considered when HbA1c is equal or below 8.0% (≤64 mmol/mol). The mean age of the patients in our study group was 76.0 ± 11.1 years, at 54.5% of cases ischemic heart disease was diagnosed. 24.2% patients underwent myocardial infarction. Characteristics of this group of patients indicate the need for using not too strict criteria for metabolic control. An important observation is that severe hypoglycemia occurred in 81.3% of those who were on intensive hypoglycemic therapy and achieved glucose and HbA1c values lower than recommended by the American Diabetes Association [10]. According to ADA those treated with multiple insulin injections algorithm (i.e. at least three times per day) should monitor glucose at least 4 times a day. Patients with type 2 diabetes treated with fixed doses of insulin daily require blood glucose self-monitoring 1-2 times a day and once a week they also should perform glucose profile (fasting measurements and after main meals), and once a month the full profile of blood glucose. In patients taking oral anti diabetic drugs glucose self-monitoring is recommended once a week, fasting and after main meals and one measurement at different times of the day. Severe hypoglycemia requiring hospitalization was related not only to the treatment with insulin but also with sulphonylureas (40%). There were no patients with severe hypoglycemia treated on monotherapy with metformin, acarbose, dapagliflozin, gliptines or GLP-1 agonists [10].

The risk of hypoglycemia in patients treated with sulfonylureas depends on the affinity to SUR 1 receptor, half-life, and the presence of active metabolites. The risk of hypoglycemia after sulfonylurea increased in patients with impaired renal function. The GUIDE Study which assessed the risk of hypoglycemia associated with the treatment of modified release gliclazide or glimepiride revealed lower incidence of hypoglycemia in patients treated with gliclazide at a comparable level of diabetes control [11,12]. The risk of hypoglycemia during the therapy of sulfonylureas may increase the interaction with other drugs e.g. phenylbutazone, oxyphenbutazone, sulfonamides, acenocumarol, fluconazole, miconazole, clarithromycin, ciprofloxacin, doxycycline [13,14].

According to current recommendations of EASD and ADA metformin is the drug of choice in all patients with newly diagnosed type 2 diabetes (after exclusion of contraindications). It is also recommended the use of metformin in the next stages of treatment as part of combination therapy. Metformin is particularly effective in reducing the risk of cardiovascular complications in patients with type 2 diabetes. Metformin results not only in normoglycemic effect, but also in many pleiotropic effects. An important advantage of metformin treatment is low, at the level of the placebo, risk of hypoglycemia. Also it has been shown to reduce the risk of hypoglycemia in patients treated with insulin and metformin compared with insulin therapy alone with the similar improvement of metabolic control [15-17].

Acarbose – inhibitor of intestinal alpha-glucosidase, alone does not cause hypoglycemia. From a practical point of view, it is important that in the case of hypoglycemia in the course of combine therapy with sulfonylurea or insulin, glucose should be used to the prevent severe hypoglycemia (no polysaccharide) [18].

Gliflozins are inhibitors of sodium-glucose cotransporter (SGLT2). SGLT2 is responsible for reabsorption of approx. 80% primary urine glucose. Gliflozin mechanism of action is an inhibition of this process. This leads to a reduction in the renal threshold (physiologically approx. 175 mg/dl) and consequently increases the excretion with urine, even with normal glucose values above 75-90 mg%. Gliflozin therapy is associated with a reduction in blood glucose and glycosylated hemoglobin (HbA1c). In the case of combine therapy with insulin and gliflozin improvement can be achieved with reduced metabolic insulin dose and reduced risk of hypoglycemia. An additional advantage of gliflozin therapy is a weight loss in people with overweight and obesity. There was a reduction in body weight in obese type 2 diabetes, approximately 2 kg at 24 weeks of therapy. The risk of hypoglycemia in case of monotherapy with gliflozin is comparable to placebo. This is particularly important in elderly patients [19,20].

The treatment with bromocritine is safe in terms of the risk of hypoglycemic episodes [21,22]. Pharmacotherapy with inhibitor of dipeptidyl peptidase (DPP-4), for example: vildagliptin, sitagliptin, saxagliptin or linagliptin is associated with a low risk of hypoglycemia. This is due to the mechanism of action – glucose depended stimulation of insulin secretion. Inhibitors of DDP-4 simultaneously decrease glucagon secretion but this action is not presented under the condition of insulin-induced hypoglycemia [23-25].

In recent years there is increasing used of the agonists of the GLP-1 receptor for the treatment of type 2 diabetes. These include exenatide and liraglutide, lixisenatide.

Exenatide is, eliminated primarily by the kidneys with half-life about 4 hour. Its biological effect is presented for 8 hours following subcutaneous administration. Exenatide exhibits a series of actions of GLP-1 - increases secretion of insulin by pancreatic β-cells depending on the blood glucose, inhibits glucagon secretion, slows down gastric emptying, reduce glucose levels on both the meal and fasting. The side effects of exenatide therapy include: nausea 57%, vomiting 17% [26,27]. There is a form of exenatide as a depot action (Exenatide LAR), used 1 time per week. Lixisenatide is an agonist of the GLP-1 receptor. It may be used alone or in combination with metformin, a sulphonylurea or a long-acting insulin. Lixisenatide treatment is associated with improved metabolic control and the reduction of body weight. As in the case of exenatide it may cause nausea and vomiting. Liraglutide is a long-acting GLP-1 analogue. Its half-life in plasma is 13 hours. Liraglutide is recommended for the treatment of type 2 diabetes in adults in order to improve glycemic control in combination with: metformin or a sulphonylurea. Liraglutide may be used also in combination with metformin and a thiazolidinedione. Age of the patient is not a contraindication for treatment with liraglutide. Significant benefits of such therapy can be obtained in patients over 65 years of age with type 2 diabetes and obesity. The advantage of liraglutide therapy is a low risk of hypoglycemia [28-31].

Severe hypoglycemia can be induced by ethanol abuse. Specific risk is present from 6 to 36 hours after acute intoxication. In addition,

alcohol consumption may mask the symptoms of drug-induced hypoglycemia and cause significant delay in the aid.

Conclusion

Severe hypoglycemia requiring hospitalization in patients with type 2 diabetes affects mostly elderly patients. Severe hypoglycemia is mostly related to insulin or sulfonylureas. In elderly people with type 2 diabetes who are hospitalized due to severe hypoglycemia low HbA1c values below 6.5% are usually revealed. Most elderly patients do not conduct proper blood glucose self-monitoring. Inappropriate intensification of therapy is a main cause of severe hypoglycemia in elderly patients.

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