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SILENT HYPOGLYCEMIA IN PATIENTS WITH DIABETES

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Abstract

Introduction. *Iatrogenic hypoglycemia increases cardiovascular morbidity sometimes even with fatalities, and also increases cognitive disorders in most people with type 1 diabetes (T1D) and type 2 diabetes (T2D). Hypoglycemia is characterized by unawareness if the sympathoadrenal response is attenuated during the night, in autonomic neuropathy or in elderly patients. Therefore, hypoglycemia is a limiting factor in the glycemic management of diabetes.*

Methods. *We aimed to analyze the hypoglycemic events and the time spent with low glucose level (glucose <3.9 mmol/l) in patients with diabetes (T1D, T2D) with insulin therapy (basal or basal-bolus), in ambulatory or hospital setting. The glucose variability was assessed via the interstitial glucose concentration, measured with a Continuous Glucose Monitoring (CGM) system over 72 hours.*

Results. *The incidence, severity and duration of hypoglycemia are not correlated with HbA1c, disease's duration and patient's age. In patients with T1D, severe hypoglycemia is more frequent in patients with a long duration of diabetes. In this analysis, the type of basal analog insulin did not influence the presence of hypoglycemia (p=0.7), but the duration of nocturnal hypoglycemia was longer with insulin glargine U100 than with insulin detemir. The basal regimen is more protective for hypoglycemia than basal-bolus insulin.*

Conclusions. *The study suggested that hypoglycemic events are common, silent and prolonged in 1/3 of patients with T1D and T2D. The CGM system is beneficial for all patients with T1D and for patients with T2D with hypoglycemic risk and complications, to adjust medication in order to prevent cardiovascular events.*

Keywords: *hypoglycemia, glucose monitoring, glycemic variability, impaired awareness hypoglycemia*

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Introduction

Maintaining glycemic values within the target range can prevent or reduce the severity of microvascular complications of diabetes, as many studies demonstrated (UKPDS, ADVANCE, VADT), but the benefits of glycemic control are rarely achieved for macrovascular complications (heart attack, stroke) and mortality[1,2,3]. Intensive glycemic control increases the frequency and severity of iatrogenic hypoglycemia. It is known that, for patients with T1D, the mortality due to hypoglycemia is as high as 10%[4]. At 25 years after the publishing of the results of Diabetes Control and Complications Trial Research Group (DCCT), the high risk of hypoglycemia in the T1D group with intensive treatment represents a challenge to clarify the mechanisms of hypoglycemia in treated patients, identifying the most reliable predictors of hypoglycemia, and also the financial and human costs[5].

Euglycemic status is maintained by the balance of insulin and glucagon; this neuroendocrine counterregulation starts when levels are lower than 70 mg/dl (3.9 mmol/l). According to ADA[6] hypoglycemia is symptomatic (palpitations, tremor, hunger and sweating), and in moderate to severe hypoglycemia neuroglycopenic symptoms occur (behavioral changes, difficulty thinking, confusion, coma, and even death); sometimes hypoglycemia may be asymptomatic due to decreased sympathoadrenal responses. These affect 30% of adults with T1D, especially when they are associated with the presence of cardiovascular autonomic neuropathy. The absence of insulin determines a failure of glucagon release, preventing glycogenolysis from the liver and increasing the risk of severe hypoglycemia[7]. Severe hypoglycemia is more frequent in T1D, with severe consequences on heart rate variability (arrhythmias, death in bed), or on the brain. In type 2 diabetes, nephropathy and macrovascular complications, especially in older patients, with cancer or hepatic disorders, predict a moderate/severe hypoglycemia[8].

During the night, *sympatho-adrenergic* symptoms are attenuated, and hypoglycemia is often prolonged for 4-8 hours[9]. The hypoglycemia has side effects on the cardiovascular system causing instability of atheromatous plaque, platelet dysfunction, hypokalemia, and catecholamine release with arrhythmias[10]. In addition, glycemic fluctuations increase the risk of endothelial dysfunction and the cardiovascular risk[11], coronary and carotid atherosclerosis in T2D patients[12,13]. A recent study demonstrated the impact of daily glucose variability, and also in successive days, on oxidative stress[14]. The risk of progression of diabetic retinopathy and cerebral atrophy with cognitive decline

caused by glucose fluctuations is well known[15].

HbA1c is a measure for the median glycemic level, but is not adequate to identify hypoglycemia and postprandial hyperglycemia. The goal of 7% for HbA1c is not a good indicator of the absence of glycemic excursions[16]. Kilpatrick *et al*. demonstrated that in DCCT the glycemic variability measured by SD (standard deviation) and MAGE are independent predictive factors for hypoglycemia[17].

Material and methods

This study analyzed data from 74 adults with T1D and T2D, in hospital or ambulatory care, between 2013 and 2017, in the Department of Diabetes of the "Sf. Ioan cel Nou" County Emergency Hospital, Suceava, Romania.
We analyzed the hypoglycemic events on 3-5 consecutive days (72 hours - 98 hours) with a Continuous Glucose Monitoring (CGM) system, with an iPro-2 professional CGM evaluation, which measures interstitial glucose every 5 minutes. For sensor calibration, the patient measured the capillary glycemia 4 times/day, preprandially and at night. Nocturnal hypoglycemia was considered between 22:00h and 07:00h.
Hypoglycemia was defined by a glycemic value <70 mg/dl. Our data includes the day with highest variability. In this study the parameters analyzed were: HbA1c, comorbidities, antihyperglycemic agents, duration of diabetes and hypoglycemic events. The statistic methods used were EXCEL and SPSS.

Results

A total of 74 subjects were included, comprising 47.3% men, 44,6% T1D, with complications - diabetic neuropathy (93.1%), retinopathy (48.2%), and nephropathy (21,8%, 5 patients with hemodialysis). Hypertension was the most common comorbidity, and ischemic heart disease (48.3%) was also prevalent.
89.5% of the patients with type 1 diabetes and 38% with type 2 diabetes had more than 1 episode of hypoglycemia in 3 days, half with moderate hypoglycemia. The proportion of patients with symptoms was only 40.9% for T2D, and 38.4% for T1D. The maximum time/day spent with hypoglycemia was on average 166.6 minutes for T1D (max=531 minutes, min=10 minutes), and 72.7 minutes/day for T2D.
About 65.5% of patients with type 1 diabetes and 32.7% patients with T2D had hypoglycemia, for an average of 124 minutes and 6 minutes/night, respectively, usually asymptomatic (Table 1). The patients with type 1 diabetes spent more time with glucose concentrations less than 70 mg/dl (3.9 mmol/l) during 24 hours and at night (p=0.00002, p=0.0007).
Mild hypoglycemic episodes frequently precede severe hypoglycemia, 43% of hypoglycemic events were moderate to severe, without values below 40 mg/dl measured with CGM. 32 patients had treatment with insulin detemir (11 patients with T1D), 31 patients with insulin glargine 100 U/ml, and 11 patients with insulin glargine 300 U/ml (22 patients with T1D). The incidence of hypoglycemia was similar, but the prolonged hypoglycemia at night was more frequent in patients treated with Lantus in the nocturnal period (p =0.03).
Treatment with basal-bolus insulin was associated with a high risk of hypoglycemia, especially for diurnal hypoglycemia.
The prevalence of hypoglycemia and the duration of hypoglycemia are not correlated

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with HbA1c, duration of the disease and age in either type 2 diabetes or in type 1 diabetes (Table 2). In patients with type 1 diabetes, severe hypoglycemia is more frequent in patients with a long duration of diabetes.

Discussion

For cardiovascular complications in type 2 diabetes, glucose fluctuations (hypo-/hyperglycemia) have a stronger impact than constant hyperglycemia[12], and also increase inflammation with endothelial dysfunction in diabetic adolescents[18].

Hypoglycemic events were reported by 24% to 60% patients with diabetes, three times more frequently in T1D and T2D with a long duration, on average 0.35 events/ year/ patient[19].

In this study we recorded a higher number of hypoglycemic events than in other prospective studies because we investigated patients treated with insulin with high risk for hypoglycemia. In patients with symptoms or hypoglycemia documented by self-monitoring, the treatment was adjusted for the next days, and that was the reason for the decrease of hypoglycemic events in the following days.

The hypoglycemia occurs at variable times/day in type 1 diabetes, frequently missed by the 3-4 glycemic monitorings/day. This is demonstrated by the monitoring of type 1 diabetes in pregnant women, who spent 10-12 hours/day with hyperglycemia (>140 mg/dl) and 2-3 hours/day with values <70 mg/dl[20]. Our data demonstrated the same risk for T1D. The risk for prolonged hypoglycemia was higher among female patients with type 1 diabetes and older patients with several comorbidities, including cardiovascular disease, cerebrovascular disease, and chronic kidney disease.

Patients with chronic kidney disease or dementia who were treated with sulpho-nylureas and insulin have a very high risk of hypoglycemia. Four of the five patients with hemodialysis had hypoglycemia in this analysis.

Our study has some limitations due to errors of self-monitoring and device calibration. It is known that the difference between plasma glucose and interstitial glucose is <6%[21]. If we introduced the 4 capillary glucose measured preprandially or 2 hours postprandially, we had an optimal calibration[22]. We will discuss the possible mechanisms which may explain the association between the type of basal insulin and the hypoglycemic events. The impact of rapid human insulin on the risk for nocturnal hypoglycemia was demonstrated[22] and in this analysis the percentage of patients with T1D treated with insulin glargine U100 is higher than of those treated with insulin detemir. The retrospective or real-time CGM

	Total	T1D	T2D	
Type of Diabetes Mellitus	74	33	41	
Age (Years)	55.6	40.8	63.13	
Male gender	35	11	24	
Duration of DM (years)	16.9	19.9	13.6	
HbA1c, mean	9.03	8.93	9.06	
Patients with nocturnal hypoglycemia	31 (41.17%)	14 (42.5%)	17(41.5%)	
Time spent with nocturnal hypoglycemia (minutes)	79.5	97.5 (61.5% >30 min 38.4% >100 min)	39.4 (40.9% >30 min 18.18% >100 min)	p=0.0007
Total time spent with hypoglycemia (minutes/day)	16	166.65 (65%>100 min)	72.7	p=0.00002
Patients with diurnal hypoglycemia	32	21	11	
Symptoms during hypoglycemic events	19	10	9	
% of prolonged hypoglycemia (>50 minutes)	43.75%	30.7%	59.09%	
Cardiovascular diseases	42	6	36	
Diabetic neuropathy	81	26	55	
Diabetic retinopathy	41	18	23	
Nephropathy (Hemodialysis- HD)	19 (5-HD)	6 (3-HD)	13 (2-HD)	

Table 2. *The prevalence of hypoglycemia and duration of hypoglycemia in correlation with HbA1c, duration of the disease and age in type 1 and type 2 diabetes*

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Type 1 diabetes	HbA1c - duration of nocturnal hypoglycemia	p=0.27
	Hb1c - duration of hypoglycemia/day	p=0.07
	Duration of the disease - duration of total time with hypoglycemia/day	p=0.13
	Duration of disease - hypoglycemic events	p=0.58
Type 2 diabetes	HbA1c - duration of nocturnal hypoglycemia	p=0.17
	Hb1c - duration of hypoglycemia/day	p=1.25
	Duration of the disease - duration of nocturnal hypoglycemia	p=0.6
	Duration of the disease - duration of total time with hypoglycemia/day	p=0.65

Table 2. *The prevalence of hypoglycemia and duration of hypoglycemia in correlation with HbA1c, duration of the disease and age in type 1 and type 2 diabetes*

systems have many benefits for the assessment and the improvement of the glycemic control in type 1 and type 2 diabetes. In type 2 diabetes, CGM is indicated for patients with treatment with hypoglycemic risk, comorbidities, older and also to assess the action of new drugs[23,24].

Silent hypoglycemia is also a manifestation of autonomic neuropathy, possibly accompanied by abnormalities in heart rate control, orthostatic hypotension, painless myocardial ischemia, or gastro-intestinal manifestations[25]. The real-time and retrospective CGM systems concomitantly used with devices for cardiovascular investigations could provide a greater insight on the mechanisms of glucose variability and the cardiovascular complications of diabetes.

Conclusions

Nocturnal and asymptomatic diurnal hypoglycemia is more frequent and severe in

patients with T1D, independent of HbA1c value, diabetes duration and age. This complication is present in over 40% patients with T1D and T2D, without symptoms in many cases. More than 1/3 of patients with T2D have minimum 1 hypoglycemic event in 3 days, often worsening cardiac and neurologic diseases and cognitive decline due to vascular damage, elevation of reactive oxygen species, hypokalemia and low-grade inflammation. The impact of severe or prolonged hypoglycemia is defining the treatment modality of older patients with T1D and T2D with comorbidities.

Conflict of interest - no conflict of interest

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