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NOCTURNAL HYPOGLYCEMIA IN TYPE 2 DIABETES

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Abstract

Background and aims: *It is known that the majority of critical unacknowledged hypoglycemia has an increased incidence in patients with type 1 diabetes (T1DM) with a long evolution. The aim of this research is to evaluate the variability of glucose level and hypoglycemic events in patients with type 2 diabetes (T2DM) having pharmacological interventions with hypoglycemic risk. These events are sometimes asymptomatic also in T2DM: frequently in elderly, patients with autonomic neuropathy, or having a long evolution of disease.* ***Material and method:*** *This analysis includes 72 patients with T2DM, with a relative good metabolic control, and possible glucose fluctuations. Glucose variability was appreciated using continuous glucose monitoring systems (CGMS) used for more than 72 hours in hospital or ambulatory setting.* ***Results****: The incidence, duration and severity of hypoglycemia are not correlated with HbA1c value, age, disease duration or treatment. Approximately a quarter of patients had nocturnal hypoglycemia and in 37,5% of events hypoglycemia was prolonged, more 45 minutes. Clinical manifestations in diurnal hypoglycemia were presents in only 40% of the recorded events.* ***Conclusions:*** *The study suggested that CGMS is beneficial for patients with type 2 diabetes, with hypoglycemic risk and complications, to adjusted medication, education and prevention the cardiovascular events.*

key words: *hypoglycemia, continuous glucose monitoring, hypoglycemia unawareness.*

Background and aims

In most important trials for type 2 diabetes (UKPDS, ADVANCE, VADT) it was demonstrated that the maintaining a good glucose control is associated with microvascular complications reduction, but no obvious benefits in macrovascular pathology. The control of cardiovascular risk factors contributes to reduce mortality, but endothelial dysfunction due glucose fluctuations can explain the residual risk. Recent studies suggest the impact of glucose variability in physiopathology of diabetes complications, additional or independent for HbA1c [1,2]. The oxidative stress produces earl atherosclerosis and, in this way, the coronary artery diseases are frequent and severe in diabetic patients, fact not entirely explained by the HbA1c value [3].

Glucose variability may be evaluated by the mean amplitude of glycemic excursions (MAGE), a measure of postprandial hyperglycemia and hypoglycemic events. MAGE is strongly correlated with oxidative

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stress in vivo [4] and is an independent predictor for mortality [5].

In the case of type 2 diabetes (T2DM), hypoglycemia may be frequent in intensive group therapy, and usually results from the use of drugs that increased endogenous insulin levels or treatment with exogenous insulin. The glycemic variability may be decreased by using some drugs like: acarbosum or dipeptidil-peptidase inhibitors (IDPP4) which are reducing MAGE, area under curve (AUC), markers of oxidative stress, inflammation with cardioprotective effect [6,7]. Several studies demonstrated that the exenatide [8,9] and pioglitazone [10] are reducing glucose fluctuations more effectively than insulin glargine respectively glimepiride. In terms of cognitive dysfunction, glucose fluctuations contribute at cerebral atrophy and cognitive disorders in patients with T2DM [11]. Thus, the severe hypoglycemias are very important in diabetes management, for life quality and costs, both for the patients and for family or society [12,13].

In T2DM patients the hypoglycemic events are fewer than T1D, but with severe impact especially in elderly, with multiple comorbidities and a long duration of disease. It was demonstrated using CGMS that the majority of critical nocturnal hypoglycemic events (<3.1 mmol/L) remain unrecognized. During the night or in patients with autonomic neuropathy, hypoglycemia is often unrecognized because the simpathoadrenal response in attenuated. This is the reason why hypoglycemia is prolonged at 4-8 hours [14] having side effects on the cardiovascular system by hypopotassemia, instability in atheroma plaque, thrombocytes dysfunction, cardiac arrhythmias [15]. HbA1c is a valuable measure of mean plasma glucose, but without having the ability identify glucose variability. CGMS is achieved using retrospective (professional) devices or real-time, and allows to evaluate parameters of glucose control, beyond glycemic average (i.e. fluctuations in glucose levels) useful especially in T1DM, but also in T2DM with high risk for unawareness hypoglycemia, cardiovascular comorbidities or microvascular disease [16,17]. In addition, this is a good instrument in therapeutic education while for physicians is useful in evaluating the outcomes of news drugs on the overall patients management [18]. This method is beneficial in achieving glucose targets, improves quality life and helps preventing severe cardiovascular and neurologic complications in both T1DM and T2DM [19].

Material and method

Study design

This study analyzes data from adults patients with T2DM, measured in patient or ambulatory, setting between 2013 and 2017 in Department of Diabetes, Suceava County Emergency Hospital "Sf. Ioan ce Nou".

Hypoglycemia evaluation protocol – CGMS

We analyzed the hypoglycemic events in 3-5 consecutive days (72 hours- 98 hours) using CGMS (iPro2®, Medtronic MiniMed, Northridge, CA, USA), which measures interstitial glucose every 5 minutes. For sensor calibration, the patient measured blood glucose 4 times/ a day, preprandial and also during the night. Nocturnal hypoglycemia was considered an event occurring between 22:00 and 07:00.

Hypoglycemia was defined as a glycemic value ≤ 70mg/dL. The specific symptoms were appreciated by patients and recorded in their journal. The collected data included: HbA1c, comorbidities, anti-hyperglycemic drugs used, duration of diabetes, age and gender. The statistics methods chosen for analysis were applied using Microsoft Excel and IBM SPSS.

Results

A total of 72 subjects, comprising 51.3% men and having in average diabetes duration of 11.7±6.64 years, and multiple comorbidities was analyzed. Hypertension was the most common comorbidity found (79.1%), followed by ischemic heart disease (29.8%). Optimal glycemic control was not achieved in the majority of patients; the average HbA1c in the studied group being 8.5±1.65%. With the exception of 5 patients treated with drugs without consecutive risk of developing hypoglycemia (metformin in combination with exenatide, dapaglifozin or IDPP-4 inhibitors), the rest had in their treatment scheme insulin (29.17% basal analog regimen, 8% premixed insulin, 26.4% basal-bolus), or sulfonylureas. Approximately 30 % of the patients had more than one episode of nocturnal hypoglycemia in 3 different nights. 37.5% of the episodes had a duration >50 minutes. A maximum of time/night spent in hypoglycemia was 69.6 minutes (max=305 minutes, min=10 min, 5 patients with duration >2 hours).

21% had diurnal hypoglycemia during in average- 42.1 minutes diurnal. (min= 10 min, max=65 min, majority <30 minutes.), only 40.9% being symptomatic and only 2 episodes being prolonged. HbA1c was not correlated with the incidence (p= 0.2), duration (p = 0.7) and severity (p= 0.3) of hypoglycemia.

The analysis between the characteristics of group with nocturnal hypoglycemic events and patients without hypoglycemic demonstrated the absence of factors with major impact in development nocturnal hypoglycemia in patients with T2DM (Table 1).

Table 1. Baseline characteristics of T2DM subjects in the two different groups

	T2DM with nocturnal hypoglycemia n=23 patients	T2DM without nocturnal hypoglycemia n=49 patients	p-value
Age (years)	61.6 +/-10.3	63.75+/-9.78	p=0.44
HbA1c (%)	7.9 +/-1.68	8.78 +/-1.56	p=0.058
DM duration (years)	11.45 +/-1.68	12.15+/-7.3	p=0.64
Macrovascular complications (%)	35	24	p=0.41
Diabetic Retinopathy (%)	65	66.6	p=0.9
Diabetic Nephropathy (%)	75	51	p=0.06
Basal insulin (%)	25	28.5	p=0.23
Basal bolus (%)	55	34	p=0.26
Sulfonylureas agents (%)	15	19	p= 0.78

The nocturnal hypoglycemia was more prevalent in patients with microvascular complications (nephropathy) and with HbA1c <8%, but the associations were not statistically significant.

Discussion

Hypoglycemia is a frequent finding resulting from an insulin imbalance of insulin concentration. The major fluctuations have stronger impact on cardiovascular diseases development than constant hyperglycemias [20]. The presence of hypoglycemic events during more than 72 hours of CGMS were reported in >38% patients with T2DM, a fact which is similar with another analysis which reported a prevalence between 24% to 60% in patients with T2DM [21]. It is possible to have more episodes because we included patients with suspicions of hypoglycemia and insulin or insulin secretor treatment. The method used (CGMS) detects more frequent hypoglycemia than classic self-

monitoring with 3 glucose tests/ day [22]. By the way, the hypoglycemic risk was reduced in patients with symptomatic hypoglycemias or with values close to targets in glucose tests for calibration, the majority of patients being hospitalized thus lacking vigurous, physical efforts during monitoring, or having reduced doses to prevent the recurrent hypoglicemia. Hypoglycemia was not observed in the two patients undergoing hemodialysis or having cognitive dysfunction.

The most common cause of death in diabetes are the cardiovascular diseases, and there exists a bulk of evidence that hypoglycemia is a major risk factor. Thus, investigations had begun to unravel the complex mechanistic relationship between hypoglycemia and cardiovascular system. DPP4- inhibiotors are safe in myocardial infarction and stroke [23] but saxagliptin was found to be associated with increased hospitalization for heart failure in SAVOR-TIMI [24].

The fluctuations of blood glucose on short term, measured by standard deviation are responsible for retinopathy progression in patients with T2DM [25]. Same studies in Japan demonstrated that it is a a relationship between postprandial hyperglycemia and end-stage renal failure [26].

A limit of this study are the errors in sensor calibrations, more frequent in outpatient settings, which did not have a complete journal. The differences between interstitial and blood glucose is lower 6%, but an accurate calibration is very important [27].

Conclusion

Hypoglycemia unawareness and nocturnal hypoglycemia are frequent in patients with T2DM treated with insulin or sulfonylureas, having thus an increased risk for of chronic complications. High glucose fluctuations may not correctly be evaluated by HbA1c. CGMS is recommended in T2DM patients to evaluate glucose variability, to identify hypoglycemic events in patients with complications, cognitive disorders, elderly and also in every patients which may need treatment adjustments.

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