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Mini Review

Hypoglycemia-a Difficult Problem for Both Patients with Diabetes and the Diabetes Team

Mihail A Boyanov

Department of Internal Medicine, University Hospital Alexandrovska, Clinic of Endocrinology and Metabolism, Medical University Sofia, Bulgaria

*Corresponding author: Mihail Boyanov, Professor of Endocrinology, Clinic of Endocrinology and Metabolism, University Hospital Alexandrovska, Department of Internal Medicine, Medical University Sofia, Bulgaria, Tel: +3592 9230 784; Fax: +3592 9230 779; E-mail: mihailboyanov@yahoo.com

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Abstract

Hypoglycemia is a common problem in the everyday life of patients with both type 1 and type 2 diabetes. This problem is the focus of intensive clinical and basic investigations. New therapeutic strategies are developed and implemented in an attempt to keep both good glycemic control and to prevent micro- and more importantly macro-vascular complications without increasing risk of hypoglycemia. Many obstacles have to be overcome. Hypoglycemia is often neglected by both patients and their diabetologists. The fear of hypoglycemia is one of the main reasons for low compliance with the diabetes treatment plan and may lead to deteriorated glycemic control. It represents an important psychological and emotional burden and affects the normal functioning of the diabetes patients at home or in a social environment.

Keywords: Diabetes Mellitus; Hypoglycemia; Hypoglycemia-Associated Autonomic Failure; Education; Treatment

Review

Hypoglycemic events are an integral part of a life with diabetes – in both type 1 and type 2. Most diabetes patients have at least 1-2 symptomatic episodes of low blood glucose weekly but unfortunately they are unaware of them in the majority of cases [1]. Although the rate of hypoglycemia in type 2 diabetes patients is decreasing in the late decade due to the development of very sophisticated anti-hyperglycemic drugs, the number of type 2 diabetes patients is sharply increasing and therefore – the absolute number of such events. A study by the NIH covering the time period between 2007 and 2011 showed that 1 of every 49 elderly diabetes patients on insulin (aged > 65 years) visit the emergency unit at least once a year [2]. Among those aged above 80 years this proportion was 1 of 8. Hypoglycemia is the leading cause for emergency hospitalization in the setting of endocrine disease, particularly in the oldest patient groups [3]. Of particular importance is the occurrence of severe hypoglycemia necessitating the need for assistance by another person [4]. Severe hypoglycemia is an acute life-threatening condition occurring in about 30-50 % of type 1 diabetes patients every year [5]. It can lead to loss of consciousness, seizures, coma and even death. In clinical practice blood glucose values ≤ 3.9mmol/l are an alarming signal for preventive measures [4]. This threshold has been adopted by the American Diabetes Association based on the assumption that under physiological conditions the first counter-regulatory responses to falling blood glucose are triggered at that point [6]. In non-diabetic subjects the first reaction of defense is the inhibition of insulin secretion and the increase of glucagon secretion, leading to increased glycogenolysis and gluconeogenesis. Physiologically a sympato-adrenal response follows with increasing plasma epinephrine and generation of symptoms of hypoglycemia [5,7]. One of the difficulties in the clinical setting is to differentiate sympato-adrenal from the more severe neuroglucopenic symptoms [8]. The latter are seen when blood glucose is below 3.0 mmol/l: behavioral changes, dizziness, cognitive impairment, and with levels below 1.5 mmol/l -loss of consciousness and possibly death [9]. The first line of defense is seriously damaged in the case of an insulinopenic diabetes patient. The insulin secretion is so low that it cannot decrease further [10]. This is why type 1 and long-standing type 2, requiring insulin treatment, are so similar in their clinical course. The second line of defense-the sympato-adrenal response is also

compromised in the first decades of diabetes. This phenomenon decreases the patient's awareness of hypoglycemia becoming very close to the threshold of behavioral and cognitive impairment.

The brilliant hypothesis by P. Cryer et al. introduced the concept of Hypoglycemia-Aassociated Autonomic Failure (HAAF) and combined the defective glucose counter-regulation with the impaired brain response to falling blood glucose [11]. Repeated hypoglycemia lowers the threshold at which the brain starts a reaction by multiple mechanisms. This can lead to a scenario when cognitive deterioration precedes hypoglycemia awareness [12]. Paradoxically, physical activity and sleep can further suppress the brain response and the start of counter-regulatory defense mechanisms. A very interesting study by Chow et al. described the line of events during nocturnal hypoglycemia [13]. Nocturnal hypoglycemia was much more pronounced and with longer duration than those during daytime. The fall in blood glucose reached 1.0 mmol/l with a 2-3-fold longer duration. Only 3 of 34 episodes lead to the perception of symptoms [13]. On the other hand, HAAF may also have an adaptive function. Cognitive impairment during hypoglycemia is much less pronounced in patients with HAAF, and the restoration of normal cognition is faster once euglycemia has been reached [14]. However, the presence of HAAF is associated with a very increased risk of repeated severe hypoglycemia, as well as with increased morbidity and mortality [15]. Neuroimaging studies aided the understanding of brain processes during hypoglycemia and in HAAF [16]. Hypoglycemia was associated with an impaired activation of the stress areas together with an impaired deactivation of zones, connected with memory, vision and pleasure. The net result could be described as lack of internal motivation to take measures and avoid hypoglycemia [16].

Up-to-date the knowledge about the medical consequences of hypoglycemia is still incomplete. One single episode of severe hypoglycemia can be associated with cardio-vascular morbidity and mortality in the 4-5 years to follow [17]. The ACCORD study (Action to Control Cardiovascular Risk in Diabetes) was terminated prematurely because of increased mortality in patients on intensive treatment (increased incidence of micro- and macro vascular events, and death) [18]. However, much more is now known about the cardio-vascular mechanisms underlying those clinical observations. The roles of sympato-adrenal overstimulation and of hypokalemia have been elucidated. A Japanese analysis based on 414 cases of severe hypoglycemia (88 in type 1 and 326 in type 2 diabetes) revealed an unexpected high prevalence of associated severe hypertension (blood pressure > 180/120 mmHgin 19.8% of type 1and 38.8% of type 2), hypokalemia (<3.5 mmol/l in 42.4% and 36.3% respectively), as well as QT-prolongation in the ECG (50.0% and 59.9% respectively) [19]. A sophisticated study combining continuous blood glucose monitoring (CBGM) and 24-hour ECG, showed an 8-fold increase in the risk of bradycardia during nocturnal hypoglycemia [13].

New data from the VADT study (Veteran Affairs Diabetes Trial) predicts a more rapid progression of atherosclerosis in patients with severe hypoglycemic episodes, particularly in type 2 diabetes with bad glycemic control (HbA1c >7.5%) [20]. Despite the higher rate of hypoglycemia in the intensively treated patients (74 % versus 21 %), the progression of the calcium artery score was more rapid in the subgroup on conventional therapy (11.15 mm3 и 5.4 mm3 respectively) [20]. A possible explanation might be the increased oxidative stress and endothelial dysfunction following abrupt blood glucose changes, leading subsequently to a progression of atherosclerosis. Recurrent hypoglycemia in type 1 diabetes has been associated with increased surrogates of subclinical atherosclerosis such as increased IMT (intima-media thickness) of the carotid and femoral arteries. An episode of hypoglycemia may also lead to an increase in pro-inflammatory cytokines which are able to destabilize the atherosclerotic plaques.

A relatively new topic of interest is the association of hypoglycemia and dementia. In the Health ABC study the risk of dementia was two-fold higher in diabetes patients with history of severe hypoglycemia than in those without such events (34% versus 18%) [21]. An interesting line of investigation is the link between hypoglycemia and kidney function. Hypoglycemia emerged as an independent risk factor for reduced glomerular filtration rate in type 2 diabetes patients, together with higher baseline serum creatinine levels, lower HbA1c and longer disease duration [22].

Members of the diabetes team are usually very well trained to address the clinical problems of their patients, but very little attention is paid to the emotional and psychosocial impact of hypoglycemia. A detailed study gives an emotional report based on the everyday patient's perception and fears due to hypoglycemic events: the need to stay at home or to reduce their professional activities, the fear of becoming a burden to their family and relatives [23]. The other side of this problem has also been explored– the concerns of the family members such as fear for the life of their relative, fear from his changing or aggressive behavior and many others [24]. An alarming signal comes from a study based on online questionnaires and revealing that 65 % of all type 1 and 50-59 % of type 2 diabetes patients had rarely or never reported freely the occurrence of hypoglycemia to their GPs [25]. In turn, the GPs had never asked about hypoglycemia in 16 %, respectively 26 %, of all interviews. Several patients view hypoglycemia as a personal or a therapy failure and chose not to mention it during medical interviews. The patient's fears and prejudices are of great importance as they often lead to impaired compliance, changes in the insulin regimen and treatment plans, including missing insulin

applications or preventive feeding [26]. Hypoglycemia, therefore, becomes the main obstacle for optimal cooperation of the patient and the diabetes team.

The accumulated knowledge led to the development of international guidelines for the prevention of hypoglycemia and HAAF, e.g. the one issued by the American Diabetes Association [4]. Much stress is put on the patients' structured education. The diabetes patient and the diabetologist, as a team, have to address the problem of hypoglycemia and actively seek the predisposing factors, such as flaws in the insulin injection technique, missed meals, vigorous physical activity, and several drugs. The gluconeogenesis is impaired in the presence of kidney or liver failure, alcohol abuse; while the insulin clearance – in chronic kidney failure. Elucidating all possible contributing and predisposing factors is crucial for the proper strategy changes. The structured education should be offered to all family members also.

The strict avoidance of hypoglycemia might allow restoration of normal hypoglycemia awareness and adequate counter-regulatory responses. This can be achieved for a relatively short period of time-3-4 weeks free of hypoglycemia [4]. The HypoCOMPASS study proved the restoration of normal responses to hypoglycemia in long-standing type 1 diabetes without deterioration of glycated hemoglobin A1C [27]. A key step is the frequent blood glucose self-monitoring, particularly while on insulin or sulphonylurea treatment. According to the ADA Workgroup this should happen 6-8 times daily to allow for active preventive measures [4]. Further promising steps in the prevention of hypoglycemia are the continuous glucose monitoring (CGM) and the insulin pump therapy. The alarm-equipped CGM devices allow early detection of subclinical and nocturnal hypoglycemia and therefore – timely prevention. This approach was tested in adolescents with type 1 diabetes and lead to the restoration of epinephrine and sympato-adrenergic responses. The CGM can really allow optimization of glycemic control without compromising it by increased hypoglycemia. However, the sensitivity and specificity of different blood glucose thresholds for triggering the alarm signal is around 70-80 % only; and secondly, the interstitial fluid reflects changes in the blood glucose with some slight delay (5-15 minutes) [16]. This can lead to false alarm or missed genuine hypoglycemia. CGM can function best in combination with Continuous Subcutaneous Insulin Infusion (CSII)-insulin pumps [16]. Studies comparing CSII with classical basal-bolus insulin regimens produced conflicting results. Some of them did not find any particular advantages, while others registered two-threefold decrease in the rate of hypoglycemia compared to basal-bolus insulin regimes [16]. E.g. the STAR-3 study achieved improvement of glycated hemoglobin but failed to decrease the rate of severe hypoglycemia compared to basal-bolus insulin [28].

Hypoglycemia is one of the driving forces for new drug development. The whole concept of incretin-based therapy and insulin analogs aims at a decrease in the rate of hypoglycemia. There are plenty of studies showing the benefits of newer and safer diabetes drugs and treatment strategies. An analysis based on data from the Swedish Diabetes Registry confirmed a lower risk for the occurrence of first severe hypoglycemia with insulin detemir compared with classical NPH insulin (both in type 1 and type 2 diabetes) and insulin glargine (in type 2 diabetes only) [29].The problem of all these comparative studies is that they often produce ambiguous results and cannot be reproduced readily in every day clinical practice. This problem led to the development of the "treat-to-target" concept. A final solution for prevention of hypoglycemia lies in the transplantation of a pancreas or isolated beta-cells. However, there is a risk for graft disease as well as a need for lifelong immunosuppressive therapy. The surgical procedure is not without consequences and 1-year mortality rates may attain 3-5 % [16]. Despite this the initial results are encouraging. In studies based on beta-cell transplantation normal graft function was found in around 70 % of all patients during the first year [16]. Even if the graft function is gradually lost, a restoration of hypoglycemia awareness and detection is always seen. An advantage of the surgical approach is that it allows for simultaneous kidney transplantation, leading to improved pancreatic graft survival - > 85 % versus 55-75 % in case of isolated pancreas transplantation [30].

A comprehensive step-wise approach for the prevention of hypoglycemia in type 1 diabetes is suggested by P. Choudhary et al. [30]. The first step is based on structured education addressing specifically hypoglycemia. The second step suggests introduction of insulin pump and/or CGM. Step 3 is a combination of sensor-equipped insulin pump and close contact with a specialized diabetes team with pancreas or beta-cell transplantation remaining the fourth and final step [30].

In conclusion, despite all clinical and basic knowledge and implemented strategies, hypoglycemia remains a partially solved problem in the diabetes management. The team approach is the best option for complex prevention. Ongoing research is expected to improve our understanding and help in fulfilling the unmet diabetes patients' needs for effective and safe treatment strategies and plans.

Conflict of interest

The author declares no conflict of interest for this article.

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