

Hypoglycemia: A hard obstacle to overcome in diabetes management

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Hypoglycemia, to date, is one of the main topics for diabetes research. Defined as a fall of blood glucose that exposes a patient to potential harm, in clinical practice a value of ≤ 3.9 mmol/L (70 mg/dL) is the threshold for initiating treatment for hypoglycemia. Although the incidence of hypoglycemia is thought to decrease in recent years, the number of type 2 diabetics on insulinotropic treatment is rising; so is the problem of hypoglycemia in type 2 diabetes. An NHI survey from 2007 to 2011 reported that 1 in 49 insulin-treated seniors ≥ 65 years of age visits the emergency room because of hypoglycemia while on insulin. Among those 80 years and older, the number is 1 in 8 [1]. Hypoglycemia accounts for most endocrine emergency hospitalizations in patients especially in the very elderly [2].

As health professionals we are mainly advised on clinical aspects, and do not enquire about the emotional and psychosocial impact of hypoglycemia. Patients often have to leave employment or stay longer at home. They also feel as a burden on their families, being supervised and sometimes they react in an awkward and aggressive manner [3]. In turn, family members report being physically afraid of their relative, feeling anxious and worried about the relative's safety, neglecting their own health and well-being to take better care of their relative [4]. An analysis based on online questionnaires

revealed that 65% of type 1 diabetics and 50–59% of type 2 diabetics have rarely or never informed their general practitioner/specialist about hypoglycemia. At the same time 16% type 1 and 26% type 2 diabetics have not being asked about hypoglycemia during routine appointments [5]. Some patients do not discuss hypoglycemia with their physicians thinking that hypoglycemia is a “private issue” or a “personal failure”; others simply do not understand the importance of hypoglycemia [6]. Thus hypoglycemia is emerging as the main barrier for treatment compliance and optimal results.

Medical science is contributing a lot to the understanding of the exact mechanisms and consequences of hypoglycemia. First, the concept of hypoglycemia-associated autonomic failure as presented by P. Cryer et al. [7] is putting weight to the relative contributions of defective glucose counter-regulation and impaired hypo awareness at the brain level. The so-called intra-islet hypothesis is shows the interplay between decreasing insulin and increasing glucagon secretion while blood glucose is falling. It gives a clue to the similarities of hypoglycemia in type 1 and long-standing type 2 diabetes due to absolute beta-cell failure [8]. The news is that the “selfish brain” is contributing to the decreased awareness and counter-regulatory responses. Models of glucose-sensing mechanisms present in the brain were elucidated and different mechanisms for the altered brain metabolism and hypoglycemia detection threshold were proposed [9, 10]. Neuroimaging correlates of hypoglycemia showed less activation of stress areas and failure to deactivate the areas involved in memory, vision, or pleasure [11]. The net result is lack of internal motivation to avoid hypoglycemia. Hypoglycemia associated autonomic failure (HAAF) has become a synonym of heavily increased risk for recurrent hypoglycemia.

We know a lot about the medical consequences of hypoglycemia. An episode of serious hypoglycemia can be associated with microvascular and macrovascular events for months and years to come and even death [12]. The interplay of dementia and hypoglycemia has

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been clearly shown in the Health ABC study. Unadjusted risk for dementia was 2-fold greater in those diabetics who had experienced severe hypoglycemia [13]. Some light has been shed upon the cardiovascular mechanisms underlying the negative impact of severe hypoglycemia. An analysis of 414 cases of severe hypoglycemia (88 type 1 and 326 type 2 diabetics) in Japan found an astonishing prevalence of severe hypertension (RR \geq 180/120 mmHg in 19.8% of type 1 diabetics and 38.8% of type 2 diabetics), hypokalemia (<3.5 mEq/L in 42.4% and 36.3% respectively) and QT prolongation (50.0% and 59.9% respectively) [14]. A sophisticated study combining continuous glucose monitoring and 24-hr ECG revealed an eight-fold higher relative risk for bradycardia during nocturnal hypoglycemia [15]. This study provided a clear concept of failing glucose counter-regulation and sympato-adrenal exhaustion during night-time hypoglycemia resulting in 2–3 times longer episodes with lower blood glucose falls (by almost 1.0 mmol/l) compared to daily hypoglycemia. Recent findings also suggest that hypoglycemia is an independent risk factor for decreased renal function in patients with type 2 diabetes [16].

The growing body of knowledge has led to the publication of international recommendations and guidelines in an attempt to prevent hypoglycemia and restore hypoglycemia awareness. The American Diabetes Association published a very comprehensive and concise guide for the clinical practice [17]. Patient questionnaires and health provider checklists together with structured education are expected to help in preventing the hypoglycemia. The avoidance of iatrogenic hypoglycemia was shown to reverse the clinical syndrome of hypoglycemia unawareness with improvement of the attenuated symptomatic responses within brief periods of 2–3 weeks [10]. Restoration of self-awareness of hypoglycemia without HbA1c deterioration in adults with long-standing type 1 diabetics has been confirmed in the HypoCOMPaSS study [18]. A recent study confirmed the risk for hypoglycemia associated with omitting late-night meals, alcohol consumption and smoking [19]. Blood glucose variability is getting more and more attention in the context of hypoglycemia prevention; it is becoming a third measure of glycemia and glycemic control [20].

Hypoglycemia has become one of the rationales for new drug development or advertisement. The whole concept of incretin-based therapy as well as of insulin analogs has clear basis in the reduced risk of hypoglycemia. A great number of studies are comparing the incidence of hypoglycemia in different treatment plans. A good example is basal insulin analogs. Data from a Swedish register suggested a lower risk of first severe hypoglycemic event for insulin Detemir versus NPH (in both type 1 and 2 diabetes) or glargine (only in type 2 diabetes) [21]. However, the problem with these types of comparative studies is that results are often contradictory and cannot always be readily reproduced in the clinical setting. Promising tools for reducing the risk of hypoglycemia are continuous glucose monitoring

(CGM) and subcutaneous insulin infusions (CSII). A number of studies confirmed the ability of conventional CGM to improve glycemic control without increasing hypoglycemia [22], while the STAR-3 study showed a sustained reduction of HbA1c with no difference in severe hypoglycemia rate on real time CGM integrated CSII (sensor-augmented pump therapy) [23]. Based on the benefits of CGM and CSII a comprehensive plan for the management of recurrent hypoglycemia in type 1 diabetes patients has been proposed [24]. Structured or hypoglycemia-specific education programs are implemented in step 1. Subcutaneous insulin infusion or continuous glucose monitoring should be added as step 2. Step 3 combines sensor-augmented insulin pumps and a very frequent contact with a specialized hypoglycemia service, while islet or pancreas transplant should be considered as ultimate step 4 [24].

Having all this knowledge and clinical tools; hypoglycemia remains one of the unresolved problems in the management of diabetes. Due to its complexity no single solution can overcome this obstacle. In this context the importance of team work in medicine is being emphasized once more. The scientific work recently done in the attempt to better understand and prevent hypoglycemia is an exemplary one. Hypoglycemia can be considered as a breaking point where science meets clinical practice and still unmet patients' needs.

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Conflict of Interest

Authors declare no conflict of interest.

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