Diabetes, Metabolic Syndrome and Obesity

Dovepress

open access to scientific and medical research

Open Access Full Text Article

REVIEW

Managing Severe Hypoglycaemia in Patients with Diabetes: Current Challenges and Emerging Therapies

Huseyin Demirbilek[1], Dogus Vuralli[1], Basma Haris[2], Khalid Hussain[2]

[1]Department of Pediatric Endocrinology, Hacettepe University Faculty of Medicine, Ankara, Turkey; [2]Department of Pediatric Endocrinology, Sidra Medicine, Doha, Qatar

Correspondence: Khalid Hussain, Sidra Medicine, OPC, C6-340, PO Box 26999, Al Luqta Street, Education City North Campus, Doha, Qatar, Tel +974-4003-7608, Email khussain@sidra.org

Abstract: Hypoglycaemia is common in patients with diabetes mellitus and is a limiting factor for achieving adequate glycaemic control. In the vast majority of cases, hypoglycaemia develops due to the imbalance between food intake and insulin injections. As recurrent hypoglycaemia leads to significant morbidity and mortality, the recognition and immediate treatment of hypoglycaemia in diabetic patients is thus important. In the last 20 years, the introduction of improved insulin analogues, insulin pump therapy, continuous glucose monitoring (CGM), and sensor-augmented pump therapy have all made significant improvements in helping to reduce and prevent hypoglycaemia. In terms of treatment, the American Diabetes Association recommends oral glucose as the first-line treatment option for all conscious patients with hypoglycaemia. The second line of treatment (or first line in unconscious patients) is the use of glucagon. Novel formulations of glucagon include the nasal form, the Gvoke HypoPen which is a ready-to-deliver auto-injector packaged formulation and finally a glucagon analogue, Dasiglucagon. The Dasiglucagon formulation has recently been approved for the treatment of severe hypoglycaemia. It is a ready-to-use, similar to endogenous glucagon and its potency is also the same as native glucagon. It does not require reconstitution before injection and therefore ensures better compliance. Thus, significant improvements including development of newer insulin analogues, insulin pump therapy, continuous glucose monitoring (CGM), sensor-augmented pump therapy and novel formulations of glucagon have all contributed to reducing and preventing hypoglycaemia in diabetic individuals. However, considerable challenges remain as not all patients have access to diabetes technologies and to the newer glucagon formulations to help reduce and prevent hypoglycaemia.

Keywords: hypoglycaemia, type 1 diabetes, type 2 diabetes, glucagon, counterregulatory hormone

Introduction

Hypoglycaemia is the most common and severe complication of type 1 diabetes mellitus (T1DM).[1] It interferes with daily activities, poses a source of fear for diabetic individuals and their families, impairs quality of life, and accounts for one of the limiting factors that affects achieving glycaemic control.[2] Avoiding severe and recurrent hypoglycemia is one of the main goals of diabetes management. Hypoglycemia can lead to acute and permanent neurological complications. Thus, addressing this severe clinical issue is paramount from the management point of the view.

Hypoglycemia is an important limiting factor in achieving glycaemic control diabetic individuals.[2] The American Diabetes Association (ADA) recommends glycosylated haemoglobin (HbA1c) target <7% for diabetic patients in all age groups, and the American Association of Clinical Endocrinologists (AACE) recommends an HbA1c <6.5% in subjects with no increased risk of hypoglycaemia.[3,4] In the Diabetes Control and Complications Trial and the United Kingdom Prospective Diabetes Trial, it has been shown that intensive glycaemic control can prevent or delay the development of microvascular complications such as retinopathy, nephropathy, and neuropathy in T1DM and type 2 diabetes (T2DM). However, there is an increased risk of hypoglycaemia with aggressive glycaemic targets.[5] Achieving tight glycaemic

Received: 10 November 2022
Accepted: 14 January 2023
Published: 27 January 2023

control to alleviate microvascular complications and yet avoiding hypoglycaemia remains a great challenge in diabetes management to the current day.

In the last 20 years, the introduction of improved insulin analogues, insulin pump therapy, continuous glucose monitoring (CGM), and sensor-augmented pump therapy to reduce and prevent hypoglycaemia have made significant improvements in the management of diabetes, especially in children. Despite these advances in diabetes technology, only a quarter of children and adolescents achieve the internationally recommended HbA1c target <7.%. However, the frequency of severe hypoglycaemia has decreased substantially in recent years as an outcome of the development in diabetes technologies.[6,7] Reducing the risk of hypoglycaemia in diabetes is the primary goal of the International Working Group on Hypoglycemia (IHSG), which can be achieved by recognizing the problem, assessing risk factors, educating families/diabetes caregivers, and applying intensive glycaemic management.[8] In this review, we first focus on defining hypoglycaemia in patients with DM, then describe the physiological mechanisms that lead to hypoglycaemia in patients with DM and then focus on describing new treatment modalities aimed at preventing and treating hypoglycaemia in patients with DM.

Definition of Hypoglycaemia in Patients with Diabetes

Hypoglycaemia can be simply defined as a plasma glucose level that is low enough to cause signs and symptoms, including impaired brain function. Glycaemic thresholds that cause symptoms of hypoglycaemia are lower in well-controlled diabetes whilst higher in poorly controlled.[9] Therefore, the signs and symptoms of hypoglycaemia may occur in the course of normal blood glucose values in diabetes patients who have poor glycemic control with high blood glucose values over the long term. Besides, patients with diabetes may have different symptoms at various glucose levels. Therefore, it is difficult to determine a numerical threshold for hypoglycaemia simply. Although a precise glucose value has not been determined to define hypoglycaemia, a glucose value <70 mg/dL has been the point of alert for the clinicians, families and diabetic patients with the risk of hypoglycaemia.[10] Overall, considering the validity of glucose measurement devices, BGM and CGM, which have a low sensitivity in the low blood glucose values, clinicians and families should avoid diagnosing and managing hypoglycaemia by simply considering the blood glucose measurements.

The ISPAD consensus panel has defined important thresholds for identifying hypoglycaemic episodes in children with T1DM.[11] The following definitions defined in the ISPAD 2018 consensus guideline are used as a guide to clinical care and are based on glucose values determined by self-blood glucose monitoring, CGM (at least 20 minutes) or laboratory measurement of glucose levels.[12]

Clinical Hypoglycaemia Alert

Blood glucose level is <70 mg/dL (3.9 mmol/L). This alert level is suggested as the threshold for recognizing hypoglycaemia and initiating treatment in diabetic children due to the potential for further reduction of glucose levels.[1,11,13]

Clinically Important or Serious Hypoglycaemia

Blood glucose level is <54 mg/dL (3.0 mmol/L). This value indicates severe, clinically significant hypoglycaemia. This low level of glucose can cause impaired hormonal counterregulation and lacking hypoglycaemia awareness. Neurogenic symptoms and cognitive dysfunction usually occur below this level followed by an increased risk of severe hypoglycaemia.[14,15] This level should be recorded and used in the monitoring of interventions to reduce hypoglycaemia and in clinical trials.[12]

Severe Hypoglycaemia

It is a blood glucose level that causes severe cognitive impairment such as coma and seizures that require the assistance of another person to correct the blood glucose, including administration of carbohydrates or glucagon or intravenous (IV) dextrose.[16–18] This definition is consistent with the definition of severe hypoglycaemia in adults according to the ADA Guidelines.[10] This will also allow full recording of events, although it may underestimate the frequency of severe hypoglycaemia in children if defined by coma or convulsions alone. This definition has also been used in previous observational studies of severe hypoglycaemia in children.[19–21] However, as young children require assistance to correct

even mild hypoglycaemia, the event requires an assessment by the caregiver and clinician for hypoglycaemia-induced cognitive dysfunction. A subgroup of severe hypoglycaemia is severe hypoglycaemic coma, defined as a severe hypoglycaemic event resulting in loss of consciousness or seizures requiring parenteral therapy to correct hypoglycaemia. Since these events are conclusive and important to the outcome, they should be recorded independently.

These blood glucose thresholds are actually arbitrary because the clinical correlations of blood glucose thresholds differ between individuals and age groups. However, these defined thresholds can be used in clinical research and also confirm the definitions recommended by an International Consensus Panel for Hypoglycemia in Adults.[12]

Incidence of Hypoglycaemia in Diabetes

The incidence of hypoglycaemia in diabetes, particularly mild or asymptomatic episodes, is often underestimated and underreported. Hypoglycaemia is more common in patients with T1DM compared to those with T2DM.[22] Patients with T1DM have an estimated 1–2 symptomatic hypoglycaemic episodes per week and one severe hypoglycaemic episode per year. Furthermore, patients with T2DM on long-term insulin therapy also have rates of hypoglycaemia comparable to patients with T1DM.[23]

While a significant improvement was observed in glycaemic control and diabetes-related complications in patients receiving intensive insulin therapy compared to conventional therapy in the Diabetes Control and Complications Trial (DCCT), the risk of severe hypoglycaemic events increased 3 times in patients receiving intensive therapy.[24] The incidence of hypoglycaemia requiring treatment was 61 per 100 patient-years in intensively treated patients versus 19 per 100 patient-years in conventionally treated patients. The incidence of coma and seizures was 16 per 100 patient-years in intensively treated patients compared to 5 per 100 patient-years in conventionally treated patients.

The incidence of severe hypoglycaemia reported in two pediatric cohorts, from Western Australia[25] and Colorado,[26] was 16.6 and 19 per 100 patient-years, respectively. Lower HbA1c was found related to higher rates of severe hypoglycaemia.[24,27,28] This association between severe hypoglycaemia and HbA1c has been weakened in recent years, with the reduction in rates of severe hypoglycaemia as observed in large longitudinal cohort studies.[19,29] While a cohort from Western Australia between 2000 and 2009 showed a 12% annual reduction in severe hypoglycaemia,[30] a decrease of approximately 50% in severe hypoglycaemia was found in a nationwide cohort in Denmark between 2008 and 2013.[16] No relationship was found between glycaemic control and severe hypoglycaemia in either study. A similar rate of decline was also demonstrated between 1995 and 2009 in a study of patients younger than 20 years old in Germany and Austria, despite improved glycaemic control.[31]

Response to Hypoglycaemia in Diabetes

Hypoglycaemia is especially seen in diabetic patients using insulin, sulfonylureas or glinides. In addition to being at increased risk for hypoglycaemia, insulin-treated diabetic patients often have impaired neurohumoral responses to low blood glucose levels, with the number and severity of early hypoglycaemic symptoms decreasing over time.

Physiological responses to hypoglycaemia include increased secretion of the counterregulatory hormones glucagon, epinephrine, cortisol, and growth hormone. The counterregulatory hormone response often blunts over time in individuals with T1DM. In patients with T1DM when blood glucose levels fall, circulating insulin levels do not decrease as they do in patients with normal pancreatic beta-cell function. These patients also have impaired glucagon response to hypoglycaemia. This results in the disappearance of both the first and second lines of defense against hypoglycaemia, making diabetic individuals more prone to more frequent and severe hypoglycaemia (Figure 1). Patients with T1DM are dependent on the third line of defense to fight against hypoglycaemia. However, epinephrine fluctuation may decrease in patients with T1DM. About 30% or more of children and adolescents with well-controlled diabetes have blunted epinephrine response.[32] This is particularly likely to occur in tightly controlled patients with frequent biochemical hypoglycaemia.

Hypoglycaemia-Associated Autonomic Failure

Hypoglycaemia-associated autonomic failure (HAAF) is defined as a combination of impaired counterregulatory mechanisms and decreased hypoglycaemia awareness (Figure 2).[33,34] It is associated with recent and recurrent

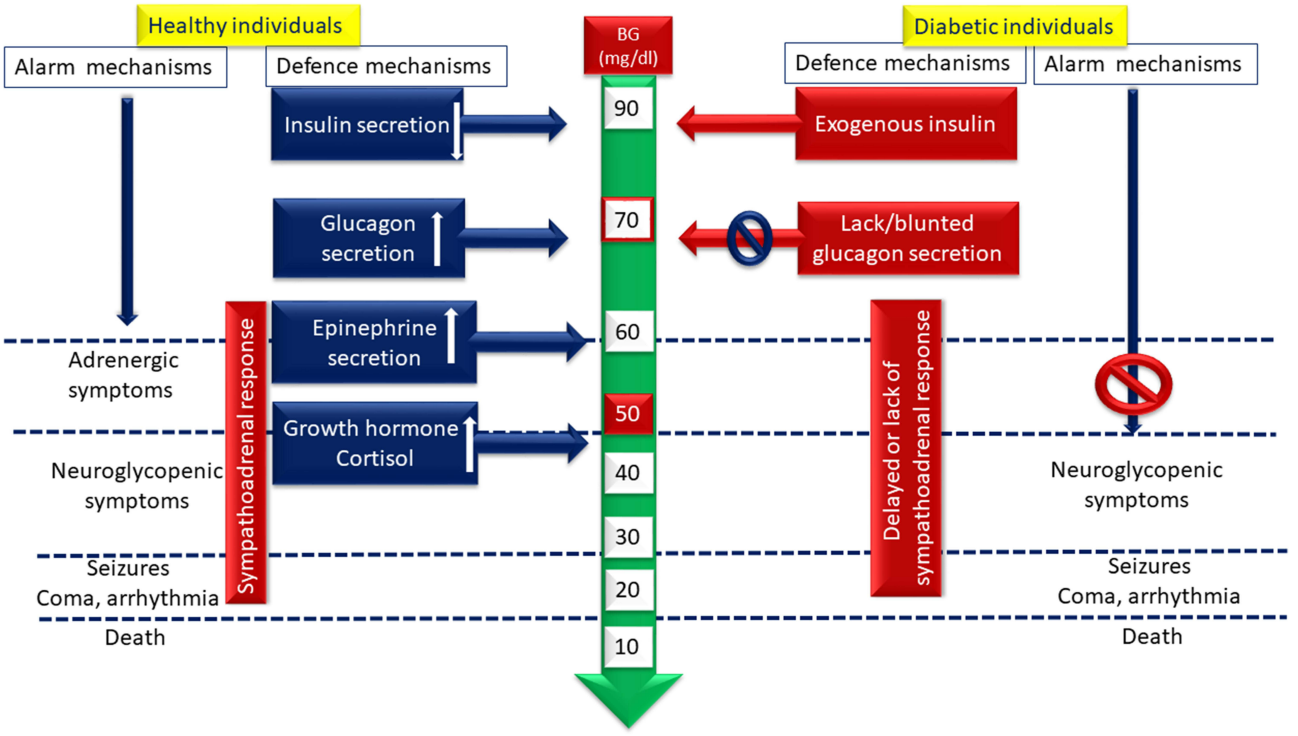

Figure 1 Response to hypoglycaemia in diabetic patients.
Notes: Physiological responses to hypoglycaemia include increased secretion of the counterregulatory hormones glucagon, epinephrine, cortisol, and growth hormone. These mechanisms account for physiological defense mechanisms. However, the counterregulatory hormone response often blunts over time in individuals with T1DM. Besides, circulating insulin levels are entirely dependent to the administered dose, individual factors, and pharmacokinetic characteristics of exogenously administered insulin types, therefore, do not decrease as they do in patients with normal pancreatic beta-cell function. These patients also have impaired glucagon and sympathoadrenal response to hypoglycaemia, which is associated with lack of adrenergic symptoms. Hence, patients may experience severe neuroglycopenic symptoms with no preceding internal alerts. This results in the disappearance of both the first and second lines of defense against hypoglycaemia, making diabetic individuals more prone to more frequent and severe hypoglycaemia. Data from Cryer.[33]

hypoglycaemia. It is seen in T1DM and in long-standing T2DM with absolute endogenous insulin deficiency. HAAF shifts the glycaemic threshold required for the sympathoadrenal response in subsequent hypoglycaemia to a lower plasma glucose level. This shift reduces epinephrine responses in the absence of insulin and glucagon responses at a given level of hypoglycaemia, resulting in defective glucose counterregulation. It also causes hypoglycaemia unawareness by reducing neurogenic symptom response. Sleep and previous exercise can cause a similar situation.[33] The risk factors identified for developing HAAF are the duration of diabetes, lack of endogenous insulin regulation, recent and frequent hypoglycaemia, and hypoglycaemia unawareness.

Mechanism

The exact mechanism/s of HAAF, namely the decreased sympathoadrenal response to decreased plasma glucose concentrations, is unknown.[33,34] One hypothesis suggests that changes in hypothalamic function or in any cerebral network that are caused by hypoglycaemia reduce the sympathoadrenal response to subsequent hypoglycaemia.[34] Another hypothesis in this regard suggests that the increase in cortisol during hypoglycemia causes a decreased sympathoadrenal response to subsequent hypoglycaemia. HAAF is different from classical diabetic autonomic neuropathy, which is a late complication of diabetes and results from nerve fiber loss. Besides, sympathoadrenal response to a certain level of hypoglycaemia is further reduced in patients with autonomic neuropathy.[35,36]

T1DM vs T2DM

HAAF applies to patients with T1DM as well as T2DM patients treated with intensive insulin regimens.[37,38] In T2DM, insulin secretion gradually decreases over time, and when patients with T2DM develop absolute insulin deficiency and

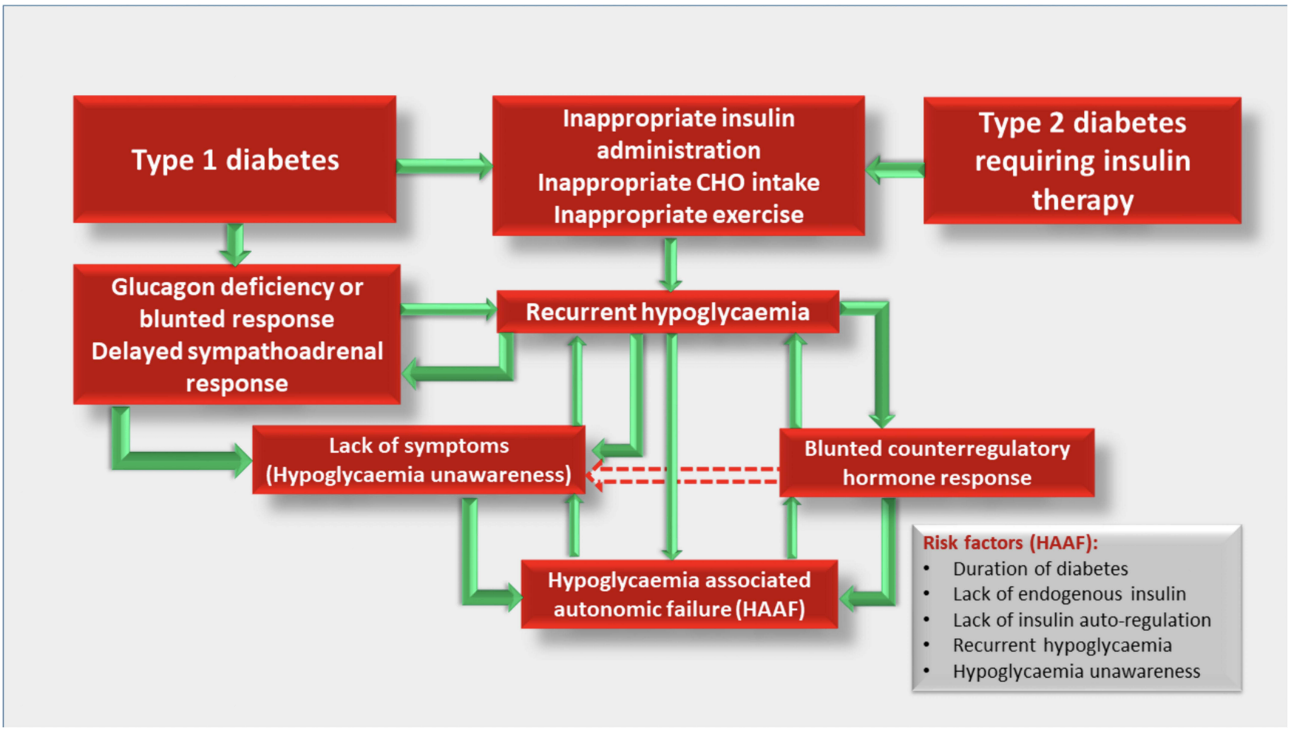

Figure 2 The vicious cycle of recurrent hypoglycaemia and HAAF.
Notes: Recurrent hypoglycaemia, in association with relevant internal and external events, leading to hypoglycaemia-associated autonomic failure (HAAF), creates a vicious cycle in diabetic individuals that complicates the management and prevention of severe hypoglycaemia and its complications. Treatment strategies should be targeting to disruption of this vicious cycle at any stage.

are treated with exogenous insulin, insulin secretion does not decrease and glucagon secretion does not increase, although plasma glucose levels decrease. In addition, prior hypoglycaemia reduces sympathoadrenal responses to subsequent low glucose levels in T2DM.[38] Features of HAAF develop later in T2DM compared to T1DM.[38] This temporal pattern of the pathophysiology of glucose counterregulation explains why iatrogenic hypoglycaemia is less likely in the early phase of T2DM, even during insulin therapy, when the glucoregulatory defenses are intact, but becomes more pronounced as patients approach the insulin-deficient part of the spectrum, in which the defenses are impaired.

Risk Factors for Hypoglycaemia

In diabetic individuals, hypoglycaemia results from increased circulating insulin levels and/or decreased defenses against hypoglycaemia. The main risk factor for hypoglycaemia is the incompatibility between the insulin administered and the food consumed. An absolute excess of insulin may result from a misunderstanding of the type and effect of insulin, or from an overdose due to accidental administration. A relative excess of insulin is seen when food intake is reduced, or meals are skipped and glucose consumption is increased such as during exercise or when endogenous glucose generation is suppressed such as after alcohol consumption.

Administration of injectable insulin, sulfonylureas, or meglitinides are medications leading to increased insulin in circulation. Other antidiabetic drugs, such as biguanides, thiazolidinediones, glucagon-like peptide 1 (GLP-1) agonists, alpha-glucosidase inhibitors, and dipeptidyl peptidase-4 (DPP-IV) inhibitors, do not directly cause hypoglycaemia. However, using these drugs in combination with high-risk hypoglycaemic agents, such as insulin, sulfonylureas, and meglitinides may increase the risk of hypoglycaemia. While GLP-1 receptor agonists and DPP-IV inhibitors stimulate insulin secretion in the course of hyperglycaemia, sulfonylureas stimulate insulin secretion independent of blood glucose levels. The factors associated with the increased risk of hypoglycaemia are displayed in Table 1.

Table 1 Risk Factors for Hypoglycaemia in Diabetic Individuals

Patient- and family-related risk factors
• Age (younger children are at highest risk)
• Lifestyle: Strenuous exercise or inappropriate management of exercise time
• Eating disorders and extremely lean habitus
• Hypoglycaemia unawareness
• Poor family/patient compliance
• Inadequate education for diabetes and hypoglycaemia management
• Feeding habitus (high fat-content diet causes postprandial hypoglycaemia and late hyperglycaemia)
• Alcohol consumption
Type of diabetes and management strategies-related risk factors
• Type of diabetes (T1DM associated with increased risk compared to T2DM)
• Tight glycaemic control (low A1c)
• Longer duration of diabetes
• Prior hypoglycaemia, recurring hypoglycaemia
• Using insulin, sulfonylureas, and meglitinides as standard care of therapy
• Methods of glucose monitoring (using CGM decreases hypoglycaemia episodes)
Concomittant diseases-related risk factors
• Adrenal insufficiency (Addison's disease)
• Renal or hepatic dysfunction
• Celiac disease
• Hypothyroidism
• Psychological disorders
• Diabetic gastroparesis

Symptoms and Signs

Symptoms of hypoglycaemia can vary between patients. Symptoms may be vague and may include nightmares, restless sleep, and headaches, confusion, or behavioural changes upon waking. Hypoglycaemic symptoms fall into two categories: neuroglycopenic and autonomic. Hypoglycaemia is often accompanied by signs and symptoms of autonomic (adrenergic) activation and/or neurological dysfunction (neuroglycopenia) resulting from insufficient glucose supply to the brain.[39] When blood glucose level decreases, the first symptoms are observed due to activation of the autonomic nervous system and include tremors, sweating, pallor, and palpitations. In non-diabetic individuals, these symptoms occur at blood glucose levels of about 3.9 mmoL/L in children and 3.2mmoL/L in adults.[40] The threshold for symptomatic hypoglycaemia is lower in individuals with well-controlled diabetes and higher in those with poorly controlled diabetes.[11] In diabetic individuals, there might be a shift of the glycaemic threshold for onset of symptoms to a higher glucose level with chronic hyperglycaemia and to a lower glucose level with chronic hypoglycaemia.[9,41–43]

Symptoms of Hypoglycaemia

Adrenergic Symptoms

Autonomic symptoms include pallor, anxiety, palpitations, tremor, and sweating. These symptoms result from sympathetic neural activation and release of epinephrine. Hypoglycaemia episodes can lower the threshold at which these symptoms occur, leading to hypoglycaemia unawareness and increasing risk of subsequent severe hypoglycaemia. Patients with mild symptoms can usually self-treat themselves.

Neuroglycopenic Symptoms

Neuroglycopenic symptoms are the results of brain glucose deprivation and include symptoms such as fatigue, lethargy, headaches, difficulty concentrating, blurred vision, difficulty in hearing, slurred speech, hunger, and more severe symptoms like drowsiness, confusion, unconsciousness, seizures, coma, and death. These symptoms result from the direct effects of hypoglycaemia on the central nervous system. Thus, the severity of neuroglycopenic symptoms is closely correlated with the severity of hypoglycaemia and glucose deprivation of the central nervous system.

Behavioral Symptoms

Irritability, agitation, erratic behaviour, silence or tantrums account for behavioral symptoms of hypoglycaemia, which are most commonly seen in young preschool aged children. These behavioral symptoms may possibly occur due to a combination of adrenergic and neuroglycopenic responses.[44] The symptoms observed in such young age group are particularly important. There is discrepancy between reported and observed signs or symptoms at any age. The predominant symptoms of hypoglycaemia tend to differ with age with the presence of higher rate of neuroglycopenia in the young compared to autonomic symptoms.[45]

More severe symptoms, such as altered mental status, unconsciousness, seizures, and coma, require assistance from an outside person. Patients with elevated HbA1c may experience symptoms of hypoglycaemia even at normal blood glucose level due to long-term hyperglycaemia. Patients with a low HbA1c or recurrent hypoglycaemia may not experience hypoglycaemia symptoms until glucose reaches a very low level. The greater frequency of hypoglycaemia episodes, the lower threshold for the appearance of symptoms. These patients are also at increased risk of hypoglycaemia unawareness.

Hypoglycaemia Unawareness

Hypoglycaemia unawareness is characterized by the absence of warning symptoms of hypoglycaemia due to blunting of sympathetic neural activation and epinephrine response. It is more frequent in children with long-standing diabetes and increases the risk of severe and/or recurrent hypoglycaemia. Hypoglycaemia episodes can lower the glucose threshold at which adrenergic discharge and symptoms occur, and this may increase the risk of subsequent severe hypoglycaemia.

Hypoglycaemia unawareness can be reversed by allowing glucose levels to run above the target to reset the internal alarm clock to alarm when glucose levels drop. Hypoglycaemia awareness can be re-established by avoiding hypoglycaemia for 2 to 3 weeks.[46] However, this can be difficult to achieve and is not practical in a clinical setting with current treatments. Use of CGM or sensor-augmented pump therapy with suspend functions may help reduce and/or eliminate hypoglycaemia exposure.[47–49]

Management of Hypoglycaemia in Diabetic Patients

Prevention

Hypoglycaemia is a medical emergency, which can lead to brain damage and mortality. Therefore, prompt recognition and treatment as well as prevention strategies are imperative. The first step towards prevention is through identifying the risk factors and educating patients and family members. Practices reducing the risk of hypoglycaemic episodes include adequate diabetes self-management education, rigorous monitoring of blood glucose (SMBG), appropriate insulin/sulphonylurea dosage, appropriate insulin replacement and management, and lifestyle modifications such as exercise and balanced diet as well as continuous monitoring by clinicians. Educating the patient about the risks of hypoglycaemia and negative effects on health is associated with better control of this condition.[50]

Management of hypoglycaemia unawareness by self-monitoring, nocturnal snacks for nighttime hypoglycaemia as well as glucose drinks are necessary. Specific strategies to reduce the risk of hypoglycaemia and minimizing hyperglycaemia with exercise are recommended by the ADA; for example, continuous glucose monitor (CGMs) sensor technology has provided an practical method for the detection and prevention of hypoglycemia.[51] With CGM devices, the glucose level is measured every 5 minutes and provides real-time data for the patient and clinician to assess the efficacy of management and decide on medication dosage as well as identification of impending hypoglycaemia allowing early treatment.[52] When used in conjunction with SMBG, an efficacious control of morning and night hypoglycaemia as well as a more stable glucose control could be achieved.[53] Real-time CGM can also detect and reduce the frequency of hypoglycaemic events in individuals with multiple daily insulin injections or severe hypoglycaemia.[54] CGM technology in combination with automated insulin delivery systems (“closed-loop systems”) and continuous subcutaneous insulin infusion (CSII) pumps has significantly improved the detection and prevention of hypoglycaemia in patients with both type 1 and type 2 diabetes. These automated insulin delivery systems automatically suspend insulin infusion when blood glucose levels are low or predicted to be low soon, thus preventing hypoglycaemia.

The artificial pancreas models available currently are hybrid closed-loop systems that require the patient to manually add meal data so that postprandial hyperglycaemia can be controlled, thus placing a burden on the patient. The level of glucose management also depends on the patient's level of participation in recording meal information and an accurate carbohydrate count, which research has shown is not always the case. With the help of more recent technologies, algorithms for meal detection or estimation of undisclosed meals based on multitask quantile regression and neural networks will be developed, helping to further lower the danger of hypoglycemia.[55]

In the United Kingdom, the National Institute for Health and Care Excellence (NICE) has recommended all patients with T1DM should be provided with CGM technology to assist their care (either real time or intermittent).[56] This includes all adults and children above 4 years old with T1DM. NICE has also recommended that all patients with T2DM taking insulin injections more than once per day or with any disabilities should be offered CGMs.[56]

In comparison to traditional finger prick self-monitoring of blood glucose, NICE's health economic modeling revealed that both real time and flash technologies were cost-effective for children and adults with T1DM when the benefit of decreased fear of hypoglycaemia with CGM was considered.[56] In accordance with their unique preferences and needs as well as functionality of the various devices, the guidelines advise that both adults and kids be given a choice of CGM devices.[56]

However, a disadvantage of CGMs is that they are expensive and not all patients can afford to use it in some parts of the world. Some patients may also find daily calibrations to be cumbersome, thus reducing compliance and effectiveness.[57]

Other novel initiatives designed to prevent severe hypoglycaemia in patients with diabetes included a pharmacist-driven protocol.[58] Cook et al reported a study consisting of 18,297 patients with diabetes where glycaemic control protocol which was pharmacist-driven was developed and led to a reduction in the episodes of hypoglycaemia in high-risk individuals.[58] The retrospective study conducted over a 4-year period analyzed the occurrence of severe hypoglycaemic episodes (defined as blood glucose ≤40 mg/dL), before and after instituting a pharmacist-driven glycaemic control protocol. The hospitalists endorsed this procedure, which significantly decreased the number of severe hypoglycemic episodes in high-risk diabetes patient populations. It was also effective in reducing costs as well as improving the physician–pharmacist relationship.

Challenges

The challenges leading to occurrence and inappropriate management of hypoglycaemia in patients with diabetes are numerous. The most common challenges especially in the uneducated population are the lack of awareness of symptoms, risk factors and complications of hypoglycaemia. This is a problem, in particular, in children and adolescents, leading to non-compliance to glucose monitoring, carbohydrate counting and appropriate intake of insulin.

On the other end of the spectrum is the Fear of Hypoglycemia (FOH) which is an underdiagnosed problem leading to suboptimal management of blood glucose levels. Fear of the discomfort caused by the symptoms and further damage to organs causes extreme anxiety in patients and family members which precludes them from properly taking their insulin injections and leads to diminished quality of life.[59] FOH is a clinically proven entity in adult and pediatric populations and several questionnaires have been developed to assess the psycho-social condition of patients with diabetes. However, most of these are still only used on research basis and not common clinical practice. MacLean et al identified four hypoglycemia fear survey-II factors – Sought Safety, Restricted Activity, Ran High, and Worry – that were seen in subjects with high risk of hypoglycaemia.[60]

Cognitive behavioral therapy to target FOH as well as use CGM-augmented insulin pumps may be effective to alleviate the fear to some extent.[61] However, the high cost of CGM-insulin pumps makes it unavailable for a vast majority of the population.

Treatment

The ADA recommends a less stringent HbA1c goal of <8% for patients at high risk of hypoglycaemia.[62] Hypoglycaemia detected by SMBG or CGMs is most commonly of mild-to-moderate severity and could be treated by consumption of glucose tablets, juice, candy, etc by the patient. A dose of 20 g of glucose may be taken and then repeated after 15–20

minutes depending on the severity. Sometimes parenteral therapy is needed if the patient is unconscious. The usual route of delivery is subcutaneous or intramuscular; however, newer methods such as intranasal glucagon (see section on Intranasal Glucagon) have been developed recently.[63] If the hypoglycaemia is due to a drug, the patient should be admitted to the hospital for continuous glucose infusion and monitoring since the effect of the drug may continue for up to 48 hours.[64]

Another study comparing the effect of different routes of delivery of glucose in a clinically symptomatic episode of hypoglycaemia reported that sublingual administration resulted in faster rise in blood sugar level than oral administration. Delivery of glucose via buccal route or as dextrose gel did not yield a better glucose concentration than sublingual or oral routes.[65]

The use of sensor integrated insulin pumps which provide continuous subcutaneous infusion of insulin has helped tremendously with the prevention and early treatment of episodes of hypoglycaemia. Bergenstal et al reported reduced episodes of nocturnal hypoglycaemia without increasing the HbA1c with the use of sensor-augmented closed-loop insulin pump therapy.[66]

In patients with diabetes who have hypoglycaemia unawareness, further episodes of hypoglycaemia should be prevented so that the threshold for detection of hypoglycaemia can be reset, thereby the patient can eat or ask for help. This takes approximately 2–4 weeks to occur by setting higher glucose goals during this period. However, patients may experience panic to consume higher levels of glucose.[52]

The treatment for hypoglycemia is either glucagon or rapid-acting glucose. Oral glucose is advised as the first line of treatment for all aware patients with hypoglycaemia, which is indicated when blood sugar levels are below 70 mg/dL (3.9 mmol/L), according to the American Diabetes Association's (ADA) Standards of Care. However, since oral glucose tablets may not be available in some countries, diabetic patients or their families may prefer alternative whilst inappropriate methods, such as carbonated juices and chocolate. Clinicians and diabetes care providers should be aware of this and warn families to avoid using inappropriate sources instead of glucose. A prescription for glucagon should be given to people who are at risk for substantial hypoglycaemia, which is blood glucose <54 mg/dL (3.0 mmol/L), so that it is easily available on hand in case of emergency. Special attention should be paid to teaching family members, teachers, and caregivers about neuroglycopenic symptoms and management, in addition to educating the patient on the usage and administration of glucagon.

Emerging Therapies – Novel Technologies and Medications

Advances in GCMs and insulin pumps are developing rapidly to maintain optimal blood glucose levels and one of the most promising novel technologies for the treatment of diabetes is a CGM-augmented pump that can infuse both insulin and glucagon. Currently, this can function as an 'artificial pancreas' and some are in clinical trials. Haider et al conducted a randomized open-label study to analyze the effectiveness of dual hormone closed-loop delivery of insulin and glucagon in their subjects.[67] They reported reduced variability of plasma glucose concentration, more time spent in the target range of blood glucose during the night and reduced hypoglycaemia risk in comparison with conventional insulin infusion. However, a clinically significant number of hypoglycaemic episodes were still reported in their group of 15 subjects. Further studies on this technology will be beneficial for all people with diabetes.[67] Table 2 compares the novel glucagon formulations with comparison with traditional glucagon kits.

Another study investigated the effectiveness of CGM equipped with hypo- and hypoglycaemia alarms when compared to standard flash monitoring in controlling the blood glucose levels in subjects with T1DM. They reported an increased time in the normal range of glucose concentration in addition to better treatment satisfaction and lesser fear of hypoglycaemia in the subjects.[68]

Parcericas et al adopted a machine-learning approach to predict the occurrence of nocturnal hypoglycaemic events in patients taking multiple daily insulin injections.[69] The study reports that this tool helps to reduce the incidence of nocturnal hypoglycaemia by 33%, thereby assisting physicians to make better and safer choices as well as providing confidence to the patient for self-management of the disease in their everyday life.[69]

The current formulation of glucagon is not stable in the liquid state. The package contains glucagon powder in a vial that needs to be reconstituted with a diluent provided in a prefilled syringe just before administration. In an emergency

Table 2 Novel Glucagon Formulations in Comparison with Traditional Glucagon Emergency Kits

	Glucagon (Intranasal)[72,73]	**Glucagon (Subcutaneous *Gvoke HypoPen*)**[74]	**Dasiglucagon (Subcutaneous)**[75]	**Standard Glucagon Emergency Kits (*GlucaGen Hypokit*) (Intramuscular/ Subcutaneous)**[80]
Form	Dry powder	Non-aqueous solution	Aqueous solution	Aqueous solution (to be reconstituted)
Half-life (min)	38	32	30	26
Dose (mg)	Adults – 3 Children 3	Adults – 1 Children (>2 yrs) – 0.5	Adults – 0.6 Children (>6 yrs) – 0.6	Adults – 1 Children (wt. <20kg) – 0.5
Time to affect BG (min)	5	9	6–10	6–10
Sustained increase in blood glucose for (hrs)	>1.5	>1.5	>1.5	>1.5
Indication	Severe hypoglycaemia	Severe hypoglycaemia	Severe hypoglycaemia	Severe hypoglycaemia
FDA approved for severe hypoglycaemia since	2019	2020	2021	1998
Side effects	Blurred vision, increased lacrimation, puffy eyes, headache	Nausea, vomiting, headache, irritation and swelling at injection site	Nausea, vomiting, headache, pain at injection site	Nausea, vomiting, headache, pain and swelling at injection site

(such as the patient having hypoglycaemic seizures or in coma) for a non-medical person, the reconstitution and injection process will be cumbersome and difficult and likely to result in mistakes. Thus, better formulations of glucagon are required that are readily injectable and do not require reconstitution.

Intranasal Glucagon

In 1983, it was shown that intranasal glucagon is effective in raising blood glucose levels in healthy subjects and that both the powder and solution were equally effective.[70] However, it was only in 2010 that development of glucagon for intranasal administration was started. Intranasal glucagon (as glucagon powder) is now available for the management of severe hypoglycaemia in children and adults with T1DM with studies demonstrating safety, efficacy, and ease-of-use.[71] A study from Spain reports that the usage of intranasal glucagon was associated with better compliance since no professional help was needed in comparison to injectable glucagon as well as reduced expense for the health-care system.[72]

A recent systematic meta-analysis (using controlled randomized studies) compared the effectiveness of intranasal glucagon with injected intramuscular/subcutaneous glucagon for the management of hypoglycaemia in patients with T1DM. This meta-analysis indicated that in patients with T1DM intranasal as well as intramuscular/subcutaneous glucagon were equally effective in resolving hypoglycaemia.[73]

Gvoke HypoPen (Glucagon Injection)

This glucagon formulation is ready to use and is stable at room temperature. The medication is delivered in a ready-to-use auto-injector that resembles the epinephrine rescue pens administered for anaphylaxis. In comparison to only 6–31% of the patients who were able to successfully provide the full dose of the standard glucagon formulation, 99% of the subjects were successfully able to use the Gvoke HypoPen to administer the complete amount.[74]

Dasiglucagon

Dasiglucagon is a glucagon analog which was approved by the Food and Drug Administration (FDA) for the management of severe hypoglycaemia in 2021. It is a ready-to-use formulation and is composed of 29 amino acids much like endogenous glucagon with a similar potency of native glucagon. There is no need to reconstitute the aqueous formulation before injection and therefore ensures better compliance.[75]

In a single-centre, randomized control trial of 58 patients with T1DM, Hovelmann et al compared the pharmacodynamic and pharmacokinetic characteristics, safety and tolerability of various doses of dasiglucagon (0.1, 0.3, 0.6, or 1.0 mg), with full doses of GlucaGen (0.5–1 mg) in insulin-induced hypoglycaemia.[76] Dasiglucagon showed a dose-dependent and quick increase in plasma glucose concentrations in this study. Similar to GlucaGen, dasiglucagon elevated plasma glucose rapidly, increasing it from 20 mg/dL (9–14 min) to 70 mg/dL (within 6–10 min). However, dasiglucagon's effect on plasma glucose lasted longer and was more significant. Dasiglucagon has a comparable safety profile to GlucaGen and was well tolerated.

In T1DM patients who experienced hypoglycemia, Laugesen et al evaluated the effectiveness of low-dosage subcutaneous dasiglucagon in comparison with oral glucose.[77] The study group comprised 20 subjects on multiple daily insulin injections or insulin pump in a Phase 2 randomized three-arm crossover study. An individualized subcutaneous insulin bolus was administered to the patient on each visit to achieve various degrees of hypoglycaemia, and patients were treated with either 80 µg dasiglucagon, 5 g oral glucose from dextrose tablets or 120 µg dasiglucagon. The study showed that the degree and time spent in hypoglycaemia was less in those patients who received 80 or the 120 µg dasiglucagon as compared to those who were given oral dextrose tablets. The results of this study demonstrated that low-dose dasiglucagon had a faster glucose-raising profile than oral glucose and could safely and efficiently avert insulin-induced hypoglycemia.

In another randomized, double-blind clinical trial (193) involving 170 adults with T1DM (who were randomly assigned to receive either a single subcutaneous dose of 0.6 mg dasiglucagon, 1 mg reconstituted glucagon (2:1:1 randomization) or a placebo during insulin-induced hypoglycaemia) it was shown that Dasiglucagon provided quick and effectual reversal of hypoglycaemia, with a similar tolerability and safety profile as reconstituted glucagon injection.

Dasiglucagon has also been shown to be effective in treating hypoglycaemia in children and adolescents with T1DM.[78] A double-blind randomized clinical trial assessed the safety and effectiveness of dasiglucagon in 42 pediatric patients (between the ages of 6 and 17 years) with T1DM. In this study, dasiglucagon, with a safety profile similar to glucagon, successfully and rapidly normalized blood glucose levels after insulin-induced hypoglycemia in children with T1DM.

Mini-Dose Glucagon for Treating Hypoglycaemia

Mini-dose glucagon involves the subcutaneous administration of small doses (between 20 and 150 ug) of glucagon. It can be administered at home to manage episodes of mild-to-moderate hypoglycaemia, especially during times of illness such as gastroenteritis or when oral intake is limited. The patient/caregiver first has to reconstitute the glucagon powder with sterile water as in the standard glucagon kit (as for emergency administration). Subsequently, the required dose can be subcutaneously injected with the remaining reconstituted glucagon being stored (refrigerated) for usage within 24 hours. These smaller doses are associated with less side effects and have clear advantages in terms of reducing admissions to hospital, relieving parental anxiety about hypoglycaemia and in preventing severe hypoglycaemia.

Mini-doses of glucagon were first described in children and adolescents with T1DM for the management of hypoglycaemia when they have an intercurrent illness (such as gastroenteritis) or poor oral intake of carbohydrates by Haymond et al.[79] In these patients with T1DM small doses of glucagon (20–150ug) resulted in average increments of blood glucose between 3.33–5 mmol/L after 30 minutes of administration and the effect lasted for about 60 minutes. Some of the patients required a second small dose of glucagon with no significant worsening of nausea. The blood glucose was maintained within a reasonable range over the peak action times of the administered insulin in all patients. It has now been used in adults with T1DM to treat non-severe hypoglycaemia.[80] In addition, mini-doses of glucagon are now used for the management of hypoglycaemia following repeated, prolonged fasting in T1DM during Ramadan, as well as preventing exercise-induced hypoglycaemia.[81,82]

Future Targeted Therapies

Although the exact mechanism behind the lack of counterregulation of insulin-induced hypoglycaemia in diabetic individuals is yet to be elucidated, somatostatin receptor 2 stimulation is believed to suppress glucagon secretion. Therefore, somatostatin receptor 2 antagonism (SSTR2a) has been hypothesized to be able to restore glucagon counterregulation and delay the onset of insulin-induced hypoglycemia. Furthermore, in preclinical trials, SSTR2a has been shown to restore glucagon counterregulation in response to hypoglycaemia.[83–85] Recently, a group has published the results of Phase 1 clinical trial for a novel SSTR2a, ZT01.[86] In this study, intraperitoneal and subcutaneous administration of ZT01 was shown to increase in glucagon response and delay in the development of hypoglycaemia. It was therefore suggested that this novel SSTR2a, ZT01, may be effective in restoring glucagon responses and preventing/delaying the onset of hypoglycaemia in patients with T1DM.[86]

Conclusions and Future Directions

The prompt recognition and management of hypoglycaemia in patients with diabetes is imperative as hypoglycaemia leads to increased morbidity and mortality. It is also the key rate-limiting factor that hinders the achievement of adequate glycaemic control. Significant improvements in newer insulin analogues, insulin pump therapy, continuous glucose monitoring (CGM), and sensor-augmented pump therapy have all contributed to reducing and preventing hypoglycaemia. Novel formulations of glucagon are now available which can be used in all patients with diabetes. These have significant advantages in terms of ease of use for patient and caregiver, flexibility, and efficacy. However, considerable challenges still remain as not all patients have access to diabetes technology and the newer glucagon formulations to help reduce and prevent hypoglycaemia. Thus, making diabetes technology and glucagon preparations cheaper and available for all patients will help in tackling hypoglycemia in diabetes patients. Restoring endogenous glucagon secretion could be an important step in the development of new treatments for hypoglycaemia in T1DM patients. Hence, the recent observations of restoring endogenous glucagon secretion by somatostatin receptor 2 antagonism and by activation of AMPA/kainate receptor function are exciting. These interesting observations or similar future implications will need to be translated into clinical practice to push hypoglycaemia out as a life-threatening complication and a barrier to better glycaemic control.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Ly TT, Maahs DM, Rewers A, et al. ISPAD clinical practice consensus guidelines 2014. Assessment and management of hypoglycemia in children and adolescents with diabetes. *Pediatr Diabetes*. 2014;15(Suppl 20):180–192.
2. Johnson SR, Cooper MN, Davis EA, Jones TW. Hypoglycaemia, fear of hypoglycaemia and quality of life in children with Type 1 diabetes and their parents. *Diabet Med*. 2013;30:1126–1131. doi:10.1111/dme.12247
3. Handelsman Y, Bloomgarden ZT, Grunberger G, et al. American Association of Clinical Endocrinologists and American College of Endocrinology - clinical practice guidelines for developing a diabetes mellitus comprehensive care plan - 2015. *Endocr Pract*. 2015;21(Suppl 1):1–87.
4. Marathe PH, Gao HX, Close KL. American Diabetes Association Standards of Medical Care in Diabetes 2017. *J Diabetes*. 2017;9:320–324. doi:10.1111/1753-0407.12524
5. Nathan DM; Group DER. The diabetes control and complications trial/epidemiology of diabetes interventions and complications study at 30 years: overview. *Diabetes Care*. 2014;37:9–16. doi:10.2337/dc13-2112
6. Rewers MJ, Pillay K, de Beaufort C, et al. ISPAD clinical practice consensus guidelines 2014. Assessment and monitoring of glycemic control in children and adolescents with diabetes. *Pediatr Diabetes*. 2014;15(Suppl 20):102–114. doi:10.1111/pedi.12190
7. Phelan H, Clapin H, Bruns L, et al. The Australasian Diabetes Data Network: first national audit of children and adolescents with type 1 diabetes. *Med J Aust*. 2017;206:121–125. doi:10.5694/mja16.00737
8. International Hypoglycaemia Study G. Minimizing hypoglycemia in diabetes. *Diabetes Care*. 2015;38:1583–1591. doi:10.2337/dc15-0279
9. Amiel SA, Sherwin RS, Simonson DC, Tamborlane WV. Effect of intensive insulin therapy on glycemic thresholds for counterregulatory hormone release. *Diabetes*. 1988;37:901–907. doi:10.2337/diab.37.7.901
10. Seaquist ER, Anderson J, Childs B, et al. Hypoglycemia and diabetes: a report of a workgroup of the American Diabetes Association and the Endocrine Society. *Diabetes Care*. 2013;36:1384–1395. doi:10.2337/dc12-2480
11. Jones TW; Group IHGW. Defining relevant hypoglycemia measures in children and adolescents with type 1 diabetes. *Pediatr Diabetes*. 2018;19:354–355. doi:10.1111/pedi.12600

12. International Hypoglycaemia Study G. Glucose concentrations of less than 3.0 mmol/L (54 mg/dL) should be reported in clinical trials: a joint position statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care*. 2017;40:155–157. doi:10.2337/dc16-2215
13. Workgroup on Hypoglycemia ADA. Defining and reporting hypoglycemia in diabetes: a report from the American Diabetes Association Workgroup on Hypoglycemia. *Diabetes Care*. 2005;28:1245–1249. doi:10.2337/diacare.28.5.1245
14. Mitrakou A, Ryan C, Veneman T, et al. Hierarchy of glycemic thresholds for counterregulatory hormone secretion, symptoms, and cerebral dysfunction. *Am J Physiol*. 1991;260:E67–E74. doi:10.1152/ajpendo.1991.260.1.E67
15. Schwartz NS, Clutter WE, Shah SD, Cryer PE. Glycemic thresholds for activation of glucose counterregulatory systems are higher than the threshold for symptoms. *J Clin Invest*. 1987;79:777–781. doi:10.1172/JCI112884
16. Fredheim S, Johansen A, Thorsen SU, et al. Nationwide reduction in the frequency of severe hypoglycemia by half. *Acta Diabetol*. 2015;52:591–599. doi:10.1007/s00592-014-0697-5
17. Cooper MN, O'Connell SM, Davis EA, Jones TW. A population-based study of risk factors for severe hypoglycaemia in a contemporary cohort of childhood-onset type 1 diabetes. *Diabetologia*. 2013;56:2164–2170. doi:10.1007/s00125-013-2982-1
18. Johansen A, Kanijo B, Fredheim S, et al. Prevalence and predictors of severe hypoglycemia in Danish children and adolescents with diabetes. *Pediatr Diabetes*. 2015;16:354–360. doi:10.1111/pedi.12171
19. Karges B, Rosenbauer J, Kapellen T, et al. Hemoglobin A1c Levels and risk of severe hypoglycemia in children and young adults with type 1 diabetes from Germany and Austria: a trend analysis in a cohort of 37,539 patients between 1995 and 2012. *PLoS Med*. 2014;11:e1001742. doi:10.1371/journal.pmed.1001742
20. Katz ML, Volkening LK, Anderson BJ, Laffel LM. Contemporary rates of severe hypoglycaemia in youth with type 1 diabetes: variability by insulin regimen. *Diabet Med*. 2012;29:926–932. doi:10.1111/j.1464-5491.2012.03646.x
21. Svoren BM, Volkening LK, Butler DA, Moreland EC, Anderson BJ, Laffel LM. Temporal trends in the treatment of pediatric type 1 diabetes and impact on acute outcomes. *J Pediatr*. 2007;150:279–285. doi:10.1016/j.jpeds.2006.12.009
22. Frier BM. Hypoglycaemia in diabetes mellitus: epidemiology and clinical implications. *Nat Rev Endocrinol*. 2014;10:711–722. doi:10.1038/nrendo.2014.170
23. Group UKHS. Risk of hypoglycaemia in types 1 and 2 diabetes: effects of treatment modalities and their duration. *Diabetologia*. 2007;50:1140–1147. doi:10.1007/s00125-007-0599-y
24. Hypoglycemia in the Diabetes Control and Complications Trial. The diabetes control and complications trial research group. *Diabetes*. 1997;46:271–286. doi:10.2337/diab.46.2.271
25. Bulsara MK, Holman CD, Davis EA, Jones TW. The impact of a decade of changing treatment on rates of severe hypoglycemia in a population-based cohort of children with type 1 diabetes. *Diabetes Care*. 2004;27:2293–2298. doi:10.2337/diacare.27.10.2293
26. Rewers A, Chase HP, Mackenzie T, et al. Predictors of acute complications in children with type 1 diabetes. *JAMA*. 2002;287:2511–2518. doi:10.1001/jama.287.19.2511
27. Davis EA, Keating B, Byrne GC, Russell M, Jones TW. Hypoglycemia: incidence and clinical predictors in a large population-based sample of children and adolescents with IDDM. *Diabetes Care*. 1997;20:22–25. doi:10.2337/diacare.20.1.22
28. Mortensen HB, Hougaard P. Comparison of metabolic control in a cross-sectional study of 2873 children and adolescents with IDDM from 18 countries. The Hvidore Study Group on Childhood Diabetes. *Diabetes Care*. 1997;20:714–720. doi:10.2337/diacare.20.5.714
29. Karges B, Kapellen T, Wagner VM, et al. Glycated hemoglobin A1c as a risk factor for severe hypoglycemia in pediatric type 1 diabetes. *Pediatr Diabetes*. 2017;18:51–58. doi:10.1111/pedi.12348
30. O'Connell SM, Cooper MN, Bulsara MK, Davis EA, Jones TW. Reducing rates of severe hypoglycemia in a population-based cohort of children and adolescents with type 1 diabetes over the decade 2000–2009. *Diabetes Care*. 2011;34:2379–2380. doi:10.2337/dc11-0748
31. Rosenbauer J, Dost A, Karges B, et al. Improved metabolic control in children and adolescents with type 1 diabetes: a trend analysis using prospective multicenter data from Germany and Austria. *Diabetes Care*. 2012;35:80–86. doi:10.2337/dc11-0993
32. Tsalikian E, Tamborlane W, Xing D, et al.; Diabetes Research in Children Network Study G. Blunted counterregulatory hormone responses to hypoglycemia in young children and adolescents with well-controlled type 1 diabetes. *Diabetes Care*. 2009;32:1954–1959.
33. Cryer PE. The barrier of hypoglycemia in diabetes. *Diabetes*. 2008;57:3169–3176. doi:10.2337/db08-1084
34. Cryer PE. Mechanisms of hypoglycemia-associated autonomic failure in diabetes. *N Engl J Med*. 2013;369:362–372. doi:10.1056/NEJMra1215228
35. Bottini P, Boschetti E, Pampanelli S, et al. Contribution of autonomic neuropathy to reduced plasma Adrenaline responses to hypoglycemia in IDDM: evidence for a nonselective defect. *Diabetes*. 1997;46:814–823. doi:10.2337/diab.46.5.814
36. Meyer C, Grossmann R, Mitrakou A, et al. Effects of autonomic neuropathy on counterregulation and awareness of hypoglycemia in type 1 diabetic patients. *Diabetes Care*. 1998;21:1960–1966. doi:10.2337/diacare.21.11.1960
37. Dagogo-Jack SE, Craft S, Cryer PE. Hypoglycemia-associated autonomic failure in insulin-dependent diabetes mellitus. Recent antecedent hypoglycemia reduces autonomic responses to, symptoms of, and defense against subsequent hypoglycemia. *J Clin Invest*. 1993;91:819–828. doi:10.1172/JCI116302
38. Segel SA, Paramore DS, Cryer PE. Hypoglycemia-associated autonomic failure in advanced type 2 diabetes. *Diabetes*. 2002;51:724–733. doi:10.2337/diabetes.51.3.724
39. Cryer PE. Symptoms of hypoglycemia, thresholds for their occurrence, and hypoglycemia unawareness. *Endocrinol Metab Clin North Am*. 1999;28(495–500):v–vi. doi:10.1016/S0889-8529(05)70084-0
40. Jones TW, Boulware SD, Kraemer DT, Caprio S, Sherwin RS, Tamborlane WV. Independent effects of youth and poor diabetes control on responses to hypoglycemia in children. *Diabetes*. 1991;40:358–363. doi:10.2337/diab.40.3.358
41. Boyle PJ, Schwartz NS, Shah SD, Clutter WE, Cryer PE. Plasma glucose concentrations at the onset of hypoglycemic symptoms in patients with poorly controlled diabetes and in nondiabetics. *N Engl J Med*. 1988;318:1487–1492. doi:10.1056/NEJM198806093182302
42. Hepburn DA, Patrick AW, Brash HM, Thomson I, Frier BM. Hypoglycaemia unawareness in type 1 diabetes: a lower plasma glucose is required to stimulate sympatho-adrenal activation. *Diabet Med*. 1991;8:934–945. doi:10.1111/j.1464-5491.1991.tb01533.x
43. Jones TW, Borg WP, Borg MA, et al. Resistance to neuroglycopenia: an adaptive response during intensive insulin treatment of diabetes. *J Clin Endocrinol Metab*. 1997;82:1713–1718. doi:10.1210/jcem.82.6.3993

44. McCrimmon RJ, Gold AE, Deary IJ, Kelnar CJ, Frier BM. Symptoms of hypoglycemia in children with IDDM. *Diabetes Care*. 1995;18:858–861. doi:10.2337/diacare.18.6.858
45. Tupola S, Rajantie J. Documented symptomatic hypoglycaemia in children and adolescents using multiple daily insulin injection therapy. *Diabet Med*. 1998;15:492–496. doi:10.1002/(SICI)1096-9136(199806)15:6<492::AID-DIA600>3.0.CO;2-6
46. Cranston I, Lomas J, Maran A, Macdonald I, Amiel SA. Restoration of hypoglycaemia awareness in patients with long-duration insulin-dependent diabetes. *Lancet*. 1994;344:283–287. doi:10.1016/S0140-6736(94)91336-6
47. van Beers CA, DeVries JH, Kleijer SJ, et al. Continuous glucose monitoring for patients with type 1 diabetes and impaired awareness of hypoglycaemia (IN CONTROL): a randomised, open-label, crossover trial. *Lancet Diabetes Endocrinol*. 2016;4:893–902. doi:10.1016/S2213-8587(16)30193-0
48. Abraham MB, Nicholas JA, Smith GJ, et al. Reduction in hypoglycemia with the predictive low-glucose management system: a long-term randomized controlled trial in adolescents with type 1 diabetes. *Diabetes Care*. 2018;41:303–310. doi:10.2337/dc17-1604
49. Ly TT, Nicholas JA, Retterath A, Lim EM, Davis EA, Jones TW. Effect of sensor-augmented insulin pump therapy and automated insulin suspension vs standard insulin pump therapy on hypoglycemia in patients with type 1 diabetes: a randomized clinical trial. *JAMA*. 2013;310:1240–1247. doi:10.1001/jama.2013.277818
50. Muche EA, Mekonen BT. Hypoglycemia prevention practice and its associated factors among diabetes patients at university teaching hospital in Ethiopia: cross-sectional study. *PLoS One*. 2020;15:e0238094. doi:10.1371/journal.pone.0238094
51. 13 Children and Adolescents. Standards of Medical Care in Diabetes—2019. *Diabetes Care*. 2019;42:S148–S164. doi:10.2337/dc19-S013
52. Evans Kreider K, Pereira K, Padilla BI. Practical approaches to diagnosing, treating and preventing hypoglycemia in diabetes. *Diabetes Ther*. 2017;8:1427–1435. doi:10.1007/s13300-017-0325-9
53. Rodbard D. Continuous glucose monitoring: a review of successes, challenges, and opportunities. *Diabetes Technol Ther*. 2016;18(Suppl 2):S3–S13. doi:10.1089/dia.2015.0417
54. Heinemann L, Freckmann G, Ehrmann D, et al. Real-time continuous glucose monitoring in adults with type 1 diabetes and impaired hypoglycaemia awareness or severe hypoglycaemia treated with multiple daily insulin injections (HypoDE): a multicentre, randomised controlled trial. *Lancet*. 2018;391:1367–1377. doi:10.1016/S0140-6736(18)30297-6
55. Daniels J, Herrero P, Georgiou P. A deep learning framework for automatic meal detection and estimation in artificial pancreas systems. *Sensors*. 2022;22(2):466. doi:10.3390/s22020466
56. Iacobucci G. All patients with type 1 diabetes in England should be offered continuous glucose monitoring, says NICE. *BMJ*. 2022;376:o834. doi:10.1136/bmj.o834
57. Stone JY, Bailey TS. Benefits and limitations of continuous glucose monitoring in type 1 diabetes. *Expert Rev Endocrinol Metab*. 2020;15:41–49. doi:10.1080/17446651.2020.1706482
58. Cook CA, Vakayil V, Pribyl K, et al. A pharmacist-driven glycemic control protocol to reduce the rate of severe hypoglycemia in high-risk patients. *Hosp Pharm*. 2022;57:45–51. doi:10.1177/0018578720973891
59. Przezak A, Bielka W, Molęda P. Fear of hypoglycemia-An underestimated problem. *Brain Behav*. 2022;12:e2633. doi:10.1002/brb3.2633
60. Maclean RH, Jacob P, Choudhary P, et al. Hypoglycemia subtypes in type 1 diabetes: an exploration of the hypoglycemia fear survey-II. *Diabetes Care*. 2022;45:538–546. doi:10.2337/dc21-1120
61. Kłak A, Mańczak M, Owoc J, Olszewski R. Can continuous glucose monitoring technology reduce fear of hypoglycemia in people with type 1 diabetes? Authors' reply. *Pol Arch Intern Med*. 2022;132:16210.
62. American Diabetes Association. Glycemic targets: standards of medical care in diabetes-2019. *Diabetes Care*. 2019;42:S61–S70. doi:10.2337/dc19-S006
63. Davis HA, Spanakis EK, Cryer PE, et al. Hypoglycemia during therapy of diabetes. In: Feingold KR, Anawalt B, Boyce A, Chrousos G, de Herder WW, Dhatariya K, editors. *Endotext*. South Dartmouth (MA): MDText.com, Inc. Copyright © 2000–2022, MDText.com, Inc; 2000.
64. Forțofoiu M, Vladu IM, Forțofoiu MC, et al. New strategies of diagnostic and therapeutic approach to emergencies in the evolution of patients with diabetes mellitus (Review). *Exp Ther Med*. 2022;23:178. doi:10.3892/etm.2021.11101
65. De Buck E, Borra V, Carlson JN, Zideman DA, Singletary EM, Djärv T. First aid glucose administration routes for symptomatic hypoglycaemia. *Cochrane Database Syst Rev*. 2019;4:Cd013283. doi:10.1002/14651858.CD013283.pub2
66. Bergenstal RM, Klonoff DC, Garg SK, et al. Threshold-based insulin-pump interruption for reduction of hypoglycemia. *N Engl J Med*. 2013;369:224–232. doi:10.1056/NEJMoa1303576
67. Haidar A, Legault L, Dallaire M, et al. Glucose-responsive insulin and glucagon delivery (dual-hormone artificial pancreas) in adults with type 1 diabetes: a randomized crossover controlled trial. *Cmaj*. 2013;185:297–305. doi:10.1503/cmaj.121265
68. Boscari F, Ferretto S, Cavallin F, Fadini GP, Avogaro A, Bruttomesso D. Effectiveness of adding alarms to flash glucose monitoring in adults with type 1 diabetes under routine care. *Acta Diabetol*. 2022;59:921–928. doi:10.1007/s00592-022-01884-1
69. Parcerisas A, Contreras I, Delecourt A, et al. A machine learning approach to minimize nocturnal hypoglycemic events in type 1 diabetic patients under multiple doses of insulin. *Sensors*. 2022;22(4):1665. doi:10.3390/s22041665
70. Pontiroli AE, Alberetto M, Pozza G. Intranasal glucagon raises blood glucose concentrations in healthy volunteers. *Br Med J*. 1983;287:462–463. doi:10.1136/bmj.287.6390.462-a
71. Pontiroli AE, Ceriani V. Intranasal glucagon for hypoglycaemia in diabetic patients. An old dream is becoming reality? *Diabetes Obes Metab*. 2018;20:1812–1816. doi:10.1111/dom.13317
72. Osumili B, Artime E, Mitchell B, et al. Cost of severe hypoglycemia and budget impact with nasal glucagon in patients with diabetes in Spain. *Diabetes Ther*. 2022;13:775–794. doi:10.1007/s13300-022-01238-8
73. Pontiroli AE, Tagliabue E. Intranasal versus injectable glucagon for hypoglycemia in type 1 diabetes: systematic review and meta-analysis. *Acta Diabetol*. 2020;57:743–749. doi:10.1007/s00592-020-01483-y
74. Valentine V, Newswanger B, Prestrelski S, Andre AD, Garibaldi M. Human factors usability and validation studies of a glucagon autoinjector in a simulated severe hypoglycemia rescue situation. *Diabetes Technol Ther*. 2019;21:522–530. doi:10.1089/dia.2019.0148
75. Pieber TR, Aronson R, Hövelmann U, et al. Dasiglucagon-A next-generation glucagon analog for rapid and effective treatment of severe hypoglycemia: results of phase 3 randomized double-blind clinical trial. *Diabetes Care*. 2021;44:1361–1367. doi:10.2337/dc20-2995

76. Hövelmann U, Bysted BV, Mouritzen U, et al. Pharmacokinetic and pharmacodynamic characteristics of dasiglucagon, a novel soluble and stable glucagon analog. *Diabetes Care*. 2018;41:531–537. doi:10.2337/dc17-1402
77. Laugesen C, Ranjan AG, Schmidt S, Nørgaard K. Low-dose dasiglucagon versus oral glucose for prevention of insulin-induced hypoglycemia in people with type 1 diabetes: a phase 2, randomized, three-arm crossover study. *Diabetes Care*. 2022;45:1391–1399. doi:10.2337/dc21-2304
78. Battelino T, Tehranchi R, Bailey T, et al. Dasiglucagon, a next-generation ready-to-use glucagon analog, for treatment of severe hypoglycemia in children and adolescents with type 1 diabetes: results of a phase 3, randomized controlled trial. *Pediatr Diabetes*. 2021;22:734–741. doi:10.1111/pedi.13220
79. Haymond MW, Schreiner B. Mini-dose glucagon rescue for hypoglycemia in children with type 1 diabetes. *Diabetes Care*. 2001;24:643–645. doi:10.2337/diacare.24.4.643
80. Haymond MW, DuBose SN, Rickels MR, et al. Efficacy and safety of mini-dose glucagon for treatment of nonsevere hypoglycemia in adults with type 1 diabetes. *J Clin Endocrinol Metab*. 2017;102:2994–3001. doi:10.1210/jc.2017-00591
81. Algeffari M, Hussain S, Almogbel T, Alsharidah M, Alghadouni H, Mahmood F. Home use of mini-dose glucagon as a novel treatment for hypoglycemia following repeated, prolonged fasts in type 1 diabetes during ramadan. *Diabetes Care*. 2022;45:990–993. doi:10.2337/dc21-1655
82. Rickels MR, DuBose SN, Toschi E, et al. Mini-dose glucagon as a novel approach to prevent exercise-induced hypoglycemia in type 1 diabetes. *Diabetes Care*. 2018;41:1909–1916. doi:10.2337/dc18-0051
83. Karimian N, Qin T, Liang T, et al. Somatostatin receptor type 2 antagonism improves glucagon counterregulation in biobreeding diabetic rats. *Diabetes*. 2013;62:2968–2977. doi:10.2337/db13-0164
84. Yue JT, Burdett E, Coy DH, Giacca A, Efendic S, Vranic M. Somatostatin receptor type 2 antagonism improves glucagon and corticosterone counterregulatory responses to hypoglycemia in streptozotocin-induced diabetic rats. *Diabetes*. 2012;61:197–207. doi:10.2337/db11-0690
85. Yue JT, Riddell MC, Burdett E, Coy DH, Efendic S, Vranic M. Amelioration of hypoglycemia via somatostatin receptor type 2 antagonism in recurrently hypoglycemic diabetic rats. *Diabetes*. 2013;62:2215–2222. doi:10.2337/db12-1523
86. Farhat R, Aiken J, D'Souza NC, et al. ZT-01: a novel somatostatin receptor 2 antagonist for restoring the glucagon response to hypoglycaemia in type 1 diabetes. *Diabetes Obes Metab*. 2022;24:908–917. doi:10.1111/dom.14652