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PRACTICAL APPROACH

Practical Approaches to Diagnosing, Treating and Preventing Hypoglycemia in Diabetes

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ABSTRACT

Hypoglycemia in individuals with diabetes can increase the risk of morbidity and all-cause mortality in this patient group, particularly in the context of cardiovascular impairment, and can significantly decrease the quality of life. Hypoglycemia can present one of the most difficult aspects of diabetes management from both a patient and healthcare provider perspective. Strategies used to reduce the risk of hypoglycemia include individualizing glucose targets, selecting the appropriate medication, modifying diet and lifestyle and applying diabetes technology. Using a patient-centered care approach, the provider should work in partnership with the patient and family to prevent hypoglycemia through evidence-based management of the disease and appropriate education.

Keywords: Cardiovascular Risk Reduction; Diabetes; Diabetes Technology; Hypoglycemia

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INTRODUCTION

Hypoglycemia is both a clinical and physiologic condition that is associated with increased morbidity and all-cause mortality in individuals with both type 1 (T1DM) and type 2 diabetes (T2DM) [1]. An increasing body of evidence suggests that hypoglycemia is harmful to patients with diabetes both immediately and over time, particularly in terms of cardiovascular health [2, 3]. While hyperglycemia can cause long-term complications, hypoglycemia can be imminently life threatening and significantly decrease the quality of life. Additionally, it is often difficult for patients to achieve the recommended glucose targets due to the fear of hypoglycemia or actual hypoglycemia. For these reasons, hypoglycemia can be one of the most difficult aspects of diabetes management from both the patient's and healthcare provider's perspective. However, using a patient-centered care approach and evidence-based practice, the provider can work in partnership with the patient to reduce the risk of hypoglycemia.

Compliance with Ethics Guidelines

This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

Epidemiology

Several large-scale clinical trials have demonstrated the incidence and prevalence of hypoglycemia in patients with both T1DM and T2DM. The prevalence of hypoglycemia in patients with T1DM has been reported to range from 62 [4] to 320 [5] episodes per 100 patient-years. Individuals with T1DM may experience an average of two symptomatic hypoglycemia episodes per week and one to three disabling, potentially life-threatening episodes per year [1, 6]. The risk of hypoglycemia in individuals with T2DM is much lower and is often associated with advanced diabetes with endogenous insulin deficiency. The prevalence of hypoglycemia in T2DM ranges from 0 [7] to 73 [5] episodes per 100 patient-years. Rates of severe hypoglycemia are more common among older adults and those with chronic conditions, such as chronic kidney disease, cardiovascular disease (CVD), congestive heart failure, depression and higher glycated hemoglobin (HbA1c) levels, as well as among those who are on insulin or take secretagogues [6].

Impact

Hypoglycemia poses an economic burden to healthcare resources. Recently published studies suggest that the average cost to the healthcare provider of treating a patient—across settings and countries—is approximately US$1200 per episode, with costs increasing by up to eightfold for the treatment of severe hypoglycemia episodes that require the patient to be admitted to hospital [8, 9].

Published data also suggest that hypoglycemia directly impairs health-related quality of life in patients with T2DM and that this impairment becomes increasingly pronounced with increasing severity and frequency of the hypoglycemic episodes [10, 11]. This relationship has not been consistently shown in adult patients with T1DM [11], but it has been more clearly documented in pediatric and adolescent patients [12].

Hypoglycemia is known to contribute to morbidity and mortality in the clinical setting of diabetes [2]. This risk is primarily cardiovascular related and is seen most often in patients with diabetes who are treated with insulin [13]. Hypoglycemia causes increases in blood pressure, stroke volume, cardiac output and myocardial contractility, all of which may cause reduced cardiovascular functioning over time [14]. The results of a 2017 study of 464 patients suggested that the crude incidence rates of CVD and death were higher in persons with hypoglycemia than in those without, even after adjusting for potential confounding variables [CVD: 10.6 vs. 5.08 per 100 person-years (PY), $p < 0.001$; death: 14.3 vs. 4.5 per 100 PY, $p < 0.001$] [3]. Several large-scale studies have confirmed the strength of this relationship, such as the ACCORD trial results (action to control CVD in diabetes) which suggested that 1% of deaths in the trial were likely caused by diabetes while 9% had hypoglycemia as a contributing factor [15]. Other studies have suggested that severe hypoglycemia may contribute to the deaths of people with T1DM in up to 10% of cases [16].

Pathophysiology

In individuals with diabetes, hypoglycemia often results from excess insulin or the inability to raise the blood glucose (BG) level through endogenous or exogenous methods [17]. In order to understand the pathophysiology of hypoglycemia, it is imperative to understand normal glucose homeostasis. The regulation of glucose is dependent on multiple systems, including the renal, hepatic, pancreatic and neuroendocrine systems. Any deficiencies within these systems (for example end-stage renal disease or liver failure) can affect the physiologic response to hypoglycemia. Multiple hormonal interactions are also involved, as shown in Table 1.

When the BG level approaches lower physiologic levels (80–85 mg/dl), a sequence of physiologic events occurs in an attempt to maintain or restore normal glucose concentration [17]. The first counter-regulatory measure

Table 1 Hypoglycemia counter-regulatory hormones and actions [1]

Hormone	Produced from	Hypoglycemia counter-regulatory action
Insulin	Beta cells, pancreas	Suppresses hepatic glycogenolysis and hepatic gluconeogenesis; suppresses glucose production
Glucagon	Alpha cells, pancreas	Stimulates hepatic glycogenolysis and gluconeogenesis
Epinephrine/ sympathoadrenal system	Adrenal medullae (chromaffin cells)	Suppresses hepatic glycogenolysis and hepatic gluconeogenesis (more than glucagon); stimulates renal gluconeogenesis; limits glucose clearing in peripheral tissues; suppresses insulin secretion
Cortisol; growth hormone	Adrenal cortex; somatotrophic cells (anterior pituitary)	Increases glucose production; limits glucose clearance; effect is delayed for hours

is the halting of insulin production. As BG falls to 65–70 mg/dl, the alpha cells of the pancreas begin to release glucagon, an endogenous hormone that raises BG levels. At this glucose level, the body also begins to release endogenous hormones, such as epinephrine, cortisol and growth hormone, in an attempt increase BG. Finally, as the BG level drops to < 55 mg/dl, the body produces endogenous glucose from the liver to facilitate glucose recovery [1]. This chain of events is dependent on the proper functioning of the pancreatic alpha cells, liver and kidneys. The liver is responsible for 80% of gluconeogenesis while the kidneys are responsible for 20% [18]. Recurrent and frequent hypoglycemia over time can lead to hypoglycemic-associated autonomic failure (HAAF), a pathophysiologic process in which sympathoadrenal processes no longer trigger symptoms of hypoglycemia, causing potentially dangerous asymptomatic hypoglycemia [17].

Clinical Presentation and Diagnosis

In 2012, The American Diabetes Association (ADA) and the Endocrine Society assembled a workgroup to address the knowledge gaps related to the definition, implications and understanding of hypoglycemia [19]. This workgroup established parameters to define hypoglycemia and issued the statement that for individuals with diabetes "all episodes of an abnormally low plasma glucose concentration expose the individual to potential harm." [2, 19]. Due to its highly individualized presentation, the presence of hypoglycemia may be established using Whipple's Triad which includes: (1) signs/symptoms consistent with hypoglycemia, (2) a low plasma glucose level (typically < 70 mg/dl) and (3) the resolution of signs/symptoms of hypoglycemia followed an increase in plasma glucose level [1]. The workshop also determined five classifications of hypoglycemia, stating that these are important to recognize and document (Table 2) as they may guide management and patient education. Patients may present with a variety of signs or symptoms, and it is imperative that patients, together with family and friends, are educated on the spectrum of signs and symptoms that can indicate hypoglycemia (Table 3). It is important to recognize that hypoglycemia unawareness may be present 40–60% of the time, even in patients who report having hypoglycemia awareness [20, 21]. Patients with hypoglycemia unawareness may experience non-specific symptoms, such as waking up in the morning with a headache, a high blood glucose level in the morning (Somogyi effect) or nighttime sweating. Further, patients may exhibit vague symptoms (shown in Table 3) but may not associate them with the presence of hypoglycemia.

HAAF is a serious condition in which repeated hypoglycemic episodes fail to trigger the protective autonomic system response, leading to asymptomatic hypoglycemia. The HAAF phenomenon includes the failure of insulin levels to decrease in the presence of

Table 2 Classifications of hypoglycemia in diabetes [19]

Hypoglycemia classification	Description
Severe hypoglycemia	Requiring the assistance of another individual to increase the plasma glucose level
Documented symptomatic hypoglycemia	Typical symptoms are present and accompanied by a plasma glucose level of $\leq$ 70 mg/dl
Asymptomatic hypoglycemia	Plasma glucose concentration of $\leq$ 70 mg/dl without symptoms
Probable symptomatic hypoglycemia	Typical symptoms but not confirmed by plasma glucose determination
Relative (pseudo) hypoglycemia	Typical symptoms with a plasma glucose concentration of $>$ 70 mg/dl

Table 3 Signs and symptoms of hypoglycemia [17, 36]. Reprinted with permission of Kreider et al. [17]

Physical signs/symptoms	Neuroglycopenic signs/symptoms	Behavioral/mood signs/symptoms
Pallor	Difficulty concentration	Emotional lability including anger
Diaphoresis	Hypothermia	Giddy
Tachycardia	Weakness	Tense
Blurred vision	Warmth	Anxiety
Elevated blood pressure	Hunger	Irritability
Palpitations	Fatigue	Feeling down/teary
Paresthesias	Motor impairment	
	Slurred speech	
	Seizures	
	Loss of consciousness	

hypoglycemia, failure of glucagon secretion, and lack of epinephrine secretion [22]. HAAF is exacerbated by frequent or recent hypoglycemia as well as sleep or exercise [22]. When the regulatory system is working correctly, these systems ensure an adequate glucose supply to the brain in times of hypoglycemia. When HAAF is present, severe hypoglycemia may occur.

Management

The treatment of hypoglycemia is aimed at identifying treatable and/or modifiable causes, followed by strategies for prevention and risk reduction. Important factors to consider in prevention include patient awareness of hypoglycemia, individualized glucose targets, self-monitoring of blood glucose (SMBG), diet, exercise and medication regimen.

In patients with hypoglycemic unawareness, strict avoidance of hypoglycemia by adjusting glucose goals to higher targets on a short-term basis (2–4 weeks) can allow the symptoms of hypoglycemia to return. Many patients need reassurance for this type of approach, as some patients are fearful of high glucose levels, even over the short term, and associated diabetes complications. In the patient-centered approach to glycemic control, the ADA recommends less strict glycemic goals when the benefits of tight glycemic control outweigh the risks for hypoglycemia. The recommendation is a goal of $<$ 8.0% for patients at high risk for hypoglycemia, compared to the typical goal of $<$ 7.0% [23]. A higher HbA1c goal is reasonable for those with hypoglycemic unawareness and chronic kidney disease, the elderly and those with CVD.

There are many risk factors and precipitants of hypoglycemia (Table 4). Renal function should be monitored, as worsening renal function is associated with a decline in insulin requirements. An estimated glomerular filtration rate (eGFR) of 10–50 ml/min should prompt a 25% reduction in insulin dosage, with a dosage reduction of 50% when the eGFR drops to $<$ 10 ml/min [24].

Table 4 Precipitants for hypoglycemia [37]. Reprinted with permission of Kreider et al. [17]

Precipitants for hypoglycemia	Risk factors for hypoglycemia
Drugs	Advanced age
Insulin	Tight glucose control (HbA1c < 6.5%)
Short- and long-acting	Renal insufficiency or end-stage renal disease
Insulin secretagogues	Pregnancy
Sulfonylureas	Multiple DM medications
Glinides	Low DM knowledge
Other	T1DM
Cibenzoline	Insulin-dependent T2DM
Gatifloxacin	Previous hypoglycemia
Pentamidine	
Quinine	
Indomethacine	
Glucagon (during endoscopy)	
Physiological	
Diabetes complications	
Gastroparesis	
Malabsorption	
Celiac disease	
Pancreatic exocrine insufficiency	
Endocrinopathies	
Adrenal insufficiency	
Hypopituitarism	
Factitious	
Misuse of insulin	
Excessive alcohol consumption	
Autoimmune	
Insulin autoimmune syndrome	
Psychological/psychosocial	
Fear of both hyper- and hypoglycemia	
Denial	
Depression or other mental health illness	
Cognitive impairment	

HbA1c Glycated hemoglobin, *DM* diabetes mellitus, *T1/T2 DM* type1/type 2 DM

Beta (β) blockers are commonly used in people with diabetes. The authors of a recent study noted that the incidence of severe hypoglycemia (confirmed BG level < 50 mg/dl) was significantly higher in those on β-blockers than those not on β-blockers [25, 26]. Moreover, β-blockers are associated with an increased risk of hypoglycemia unawareness due to the β-blockade that blunts symptoms of hypoglycemia in addition to lowering blood pressure [27]. For patients at high risk of hypoglycemia, it may be prudent to change anti-hypertensive agents.

A visit to a certified diabetes educator to review glucose logs along with diet and activity logs can help discern important glucose trends and hypoglycemia triggers. For those patients who are working on losing weight, a 24-h diet recall should be included to assess whether insulin mealtime doses should be altered. Weight loss improves insulin sensitivity and may lead to a necessary reduction in insulin doses.

A new exercise routine or a change in type or intensity of activity will increase insulin sensitivity, glucose utilization and the "lag effect" during which muscle glucose stores are replenished after exercise. This creates a glucose utilization/insulin dose mismatch and can increase the risk for hypoglycemia. Lowering the insulin dose or increasing food intake for the meal before the planned exercise are strategies to prevent hypoglycemia, and both interventions may be necessary [28]. For patients engaged in lifestyle modifications, such as increased physical activity and dietary changes, it may be necessary to reduce the insulin dose by 10–20%. Guidelines for carbohydrate intake related to exercise for people with diabetes are shown in Table 5.

Many of the new agents to treat diabetes are less likely to cause hypoglycemia than the older classes of medications. In addition to metformin, glucagon-like peptide-1 (GLP-1) agonists, dipeptidyl peptidase-4 (DPP-IV) inhibitors and sodium–glucose cotransporter 2 (SGLT-2) inhibitors are all excellent choices for people who are at risk of hypoglycemia. Older medication classes, such as sulfonylureas and meglitinides, should generally be avoided by patients who are at high risk for hypoglycemia.

Table 5 Recommended carbohydrate intake with exercise [22]

Type of activity/duration	CHO intake	Insulin adjustments[a]
Low-intensity, short-duration activity (e.g. 30 min of walking)	15 gm CHO if longer than 1–2 h after meal	Usually not needed
Moderate-intensity, intermediate-duration activity (e.g. competitive sports, running) for 30–60 min)	15 gm CHO with 7–8 gm protein before exercise	Reduction in mealtime insulin pre-exercise by ≥ 30% and based on glucose readings
High-intensity, relatively long-duration activity (e.g. hiking for several hours, cross-country skiing for ≥ 60 min)	Snacks of 15–20 gm CHO with 7–8 gm protein every 60 min	Reduction in mealtime insulin by 50–100% and based on glucose readings
Regular water intake for any activity		

CHO Carbohydrate

[a] Responses are individualized. Monitoring blood glucose levels before and after exercise and every 60 min during a long bout of exercise will help identify trends in glucose levels

An understanding of the pharmacokinetic profiles of the various insulin preparations is important when the aim is to modify insulin dosing to prevent hypoglycemia. In addition, there are insulins that are associated with less frequent hypoglycemia, and thus a change in insulin preparation may help reduce the frequency of low glucose readings. The pharmacokinetics of common insulin types is shown in Table 6 [29]. Most notably, the intermediate-action insulin isophane, also known as NPH, and regular insulin are associated with more frequent hypoglycemic episodes than the long-acting glargine, detemir and degludec insulins, particularly at night. The authors of a

Table 6 Pharmacokinetics of common insulin types [29]

Insulin	Onset of action	Peak	Duration of action
Lispro, aspart, glulisine	5–15 min	45–75 min	2–4 h
Regular	30 min	2–4 h	3–5 h
NPH	1–2 h	4–10 h	14 + hours
Glargine	90 min	None	24 h
Detemir	3–4 h	3–9 h (relatively flat)	20–24 h
Degludec	2 h	None	approx. 40 h

NPH Isophane insulin, an intermediate–acting insulin

2017 study comparing degludec insulin (a once-daily ultra-long-acting insulin) to glargine insulin in over 7000 patients at high risk for CVD reported that compared to patients using glargine, patients on degludec showed a 40% reduction in severe hypoglycemia and a 53% reduction in nocturnal hypoglycemia ($p < 0.001$) [23].

Continuous glucose monitors (CGMs) have revolutionized the treatment and prevention of hypoglycemia. These monitors measure interstitial glucose levels every 5 min, thereby providing real time data for patient use. CGMs are not meant to replace SMBG, and most models need to be calibrated twice daily with SMBG to assure accuracy. CGMs also identify important glucose trends, such impending hypoglycemia, that allow for early treatment and prevention of hypoglycemia. CGM data can be downloaded and reviewed online or in a clinic setting to help providers identify trends to allow for more accurate medication modification. The CGMs also alarm at night, alerting patients and families to hypoglycemia. There is a strong body of evidence noting that the use of CGM results in less frequent hypoglycemic episodes when compared to conventional SMBG, while improving and stabilizing overall glycemic control [30].

Patients find that CGM can help improve their quality of life and self-efficacy in managing hypoglycemia. However, CGMs are less

accurate during times of rapid glucose excursions (such as right after a meal) [30]. Patients may find the false alarms and need for calibration to be annoying (alarm fatigue), and the cost of a CGM may be prohibitive for some patients [31]. Patients likely to benefit from CGMs include individuals with required manual dexterity to insert and operate the sensor system and individuals with multiple risk factors for hypoglycemia (older age, chronic kidney disease, autonomic neuropathy, CVD). Starting in 2017, Medicare in the USA will cover CGMs for selected patients [32].

Insulin pumps (continuous subcutaneous insulin infusion) have long been recognized as a tool that can decrease hypoglycemia while improving glycemic control. CGMs are also integrated into insulin pump technology and include an alarm and automatic 2-h suspension of the insulin infusion for hypoglycemia, which is particularly helpful at night. The sensor-augmented pumps can reduce the frequency of hypoglycemic episodes while maintaining good glucose control [33]. Results from the initial closed-loop trial (the Pivatol trial) of 124 patients with T1DM suggested that the MiniMed 670G/Enlite 3 system (Medtronic, Dublin, Ireland) kept the participants within the target range 72% of the time (compared to 67% for those not using the system) and was associated with a 44% reduction in time spent with low BG (< 70 mg/dl) and a 40% decline in severe low BG (< 50 mg/dl) [34]. Other strategies for preventing hypoglycemia include a CGM-augmented pump that infuses both insulin and glucagon [35]. This type of integrated system would be one step closer to creating the much desired "artificial pancreas."

CONCLUSION

Hypoglycemia causes harm to people with diabetes, creating cardiovascular impairment and an increased risk of cardiovascular morbidity and all-cause mortality [19]. Further, hypoglycemia significantly impacts the quality of life of patients with diabetes and can limit optimal glucose control. A patient-centered approach is imperative to achieve optimal glucose control while avoiding hypoglycemia and its harmful effects. A patient-centered approach is one that is based on shared medical decision-making among the patient, family and healthcare provider and uses individualized approaches to problem solving and diabetes management planning. Education aimed at recognizing the signs and symptoms of hypoglycemia is imperative for both patients and families. Appropriate teaching includes individual risk factors, prevention, and treatment of hypoglycemia. In addition, healthcare providers must work diligently with patients and families to identify and eradicate hypoglycemia by using appropriate glucose targets and medications and modifying lifestyle.

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