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Hypoglycemia in cystic fibrosis: Prevalence, impact and treatment

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ABSTRACT

Hypoglycemia is a common and feared complication of insulin therapy. As in type 1 and type 2 diabetes, people with cystic fibrosis related diabetes are also at risk for hypoglycemia related to insulin therapy. Spontaneous hypoglycemia is also common in patients with CF without diabetes, who are not on glucose lowering medications. Spontaneous hypoglycemia in CF may also occur during or after an oral glucose tolerance test. In this review, we will discuss the definition, epidemiology, pathophysiology and impact of hypoglycemia, with a focus on people with cystic fibrosis. We will also review strategies to manage and prevent hypoglycemia.

1. Background

Insulin therapy is essential for the management of cystic fibrosis related diabetes (CFRD). In patients with cystic fibrosis (CF), insulin therapy is associated with improved nutritional and pulmonary outcomes [1–4]. Iatrogenic hypoglycemia is a common and feared complication of insulin therapy. In patients with type 1 and type 2 diabetes, iatrogenic hypoglycemia is considered a limiting factor to achieving the glycemic control which has been shown to prevent microvascular complications of diabetes [5]. As in type 1 diabetes (T1D) and type 2 diabetes (T2D), patients with CFRD are also at risk for hypoglycemia related to insulin therapy. Spontaneous (reactive) and fasting hypoglycemia is also common in patients with CF, including those not on any glucose lowering therapies. However, as compared to T1Dand T2D, the literature surrounding hypoglycemia in patients with CFRD is inadequate and limits our understanding of its impact on the lives of people with CF. In this paper, we will discuss the prevalence, physiology and impact of hypoglycemia in diabetes, with a focus on hypoglycemia in CF. We will also review the general principles of management and prevention of hypoglycemia.

2. Definition of hypoglycemia

2.1. Definition of hypoglycemia in diabetes

Hypoglycemia is a condition characterized by abnormally low plasma glucose, which puts patients at risk for injury and death [6]. The glycemic thresholds which elicit symptoms and counterregulatory hormone response can be impaired in patients on insulin or an insulin secretagogue. This threshold is higher in patients with poorly controlled diabetes and low exposure to hypoglycemia and lower in patients with frequent exposure to hypoglycemia [6,7]. Therefore assigning a single threshold value of plasma glucose to define hypoglycemia would not be appropriate [6]. Previous American Diabetes Association guidelines defined iatrogenic hypoglycemia in patients with diabetes as “all episodes of an abnormally low plasma glucose concentration that expose the individual to potential harm” [6].

The International Hypoglycemia Study group (IHSG) recently published a position statement [8] on the glucose concentrations that should be used to define hypoglycemia in clinical trials (Table 1). This statement has been adopted by the American Diabetes Association and the European Association for the Study of Diabetes. The members of the IHSG argued that it is important to identify a level of hypoglycemia that needs to be avoided because of its immediate and long term risk to the individual [8]. A standard hypoglycemia value in clinical studies would allow regulators and researchers to examine and

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Table 1
Definition of hypoglycemia.

Classification of hypoglycemia [8,56]	
Level	Glycemic criteria/description
Level 1	Glucose <70 mg/dl (3.9 mmol/l) and glucose >54 mg/dl (3.0 mmol/l)
Level 2	Glucose <54 mg/dl (3.0 mmol/l)
Level 3	A severe event characterized by altered mental and/or physical status requiring assistance (often referred to as "severe hypoglycemia" in the literature)

compare the effectiveness of glucose lowering medications and other interventions in reducing hypoglycemia [8].

Classification of hypoglycemia based on IHSG recommendations is outlined in Table 1. The IHSG suggest that a glucose level of 70 mg/dl (3.9 mmol/l) or less be called an alert value (level 1) because it suggests the patient may be dropping towards a value of <54 mg/dl (3.0 mmol/l) and that actions to avoid this drop should be taken. Level 2 hypoglycemia is defined as a glucose concentration of <54 mg/dl (<3.0 mmol/l) detected by self-monitoring of plasma glucose, continuous glucose monitoring (for at least 20 min), or a laboratory measurement of plasma glucose. At a plasma glucose threshold of 54 mg/dl (3.0 mmol/l), neuroglycopenic symptoms begin to occur and immediate action is required to prevent a serious hypoglycemia event [6]. Lastly, level 3 ("severe") hypoglycemia is defined as a severe event characterized by altered mental and/or physical functioning that requires assistance.

2.2. Definition of spontaneous hypoglycemia in the absence of glucose lowering therapies

Hypoglycemic disorders are rare in people without diabetes, who are not on insulin or insulin secretagogue therapy. In the absence of diabetes and glucose lowering therapies, hypoglycemia should not be diagnosed solely on the basis of a low plasma glucose. Hypoglycemia should be diagnosed in this setting when the Whipple's triad is documented [9]. Establishing Whipple's triad requires presence of typical symptoms of hypoglycemia with low plasma glucose concentration and that the symptoms resolve when the glucose is raised [9]. Hypoglycemia in people without diabetes can be due to various causes and further workup and management is recommended in patients in whom Whipple's triad is established [9]. In patients with CF, hypoglycemia in the absence of glucose lowering therapies may be spontaneous or may be reported in the setting of an oral glucose tolerance test (OGTT), as discussed later in this review.

3. Neuroendocrine responses to hypoglycemia in health and diabetes

3.1. Normal physiological response to hypoglycemia

In healthy humans, there is a hierarchy of physiological responses to lowering plasma glucose levels [10], which are initiated to restore normal glucose levels. Under normal physiology, the initial response to lowering glucose is reduction in insulin levels, followed by an increase in counterregulatory hormones including glucagon, epinephrine, cortisol and growth hormone [10]. Insulin levels begin to decline when glucose levels are falling but still within the physiological range (~80 mg/dl or 4.4 mmol/l) [11]. A further decrement in plasma glucose to ~68 mg/dl (3.8 mmol/l) elicits increased glucagon and epinephrine levels [12]. Glucagon acts on the liver to increase glycogenolysis, stimulate gluconeogenesis and inhibit hepatic glucose uptake; leading to increased plasma glucose [13]. Epinephrine increases hepatic glycogenolysis and gluconeogenesis, inhibits insulin secretion and insulin-mediated glucose uptake [14] and also increases lipolysis [15], providing an alternate source of energy. Activation of the sympathetic nervous system leading to catecholamine release also results in development of typical neurogenic symptoms of hypoglycemia. Besides the declining insulin levels, glucagon is thought to play a primary role and epinephrine a secondary in recovery from hypoglycemia [16]. If glucose continues to fall further, growth hormone is secreted at threshold of ~67 mg/dl (3.7 mmol/l) and cortisol at ~55 mg/dl (3.1 mmol/l) [12]. The effects of cortisol and growth hormone are thought to occur over several hours and they may not play a critical role in recovery from acute hypoglycemia [17].

3.2. Alterations in counterregulatory responses to hypoglycemia in diabetes and CF

The physiological defenses against hypoglycemia are altered in people with T1D and advanced T2D. Patients with diabetes treated with exogenous insulin are not able to reduce insulin levels in setting of falling glucose. In patients with T1D, the glucagon response to hypoglycemia is also compromised. The lack of an increase in glucagon in response to hypoglycemia is attributed to β cell failure, preventing normal paracrine interaction between α and β-cells in the pancreatic islet [18]. With the first two steps in the physiological defense against hypoglycemia compromised, patients with T1D and those with advanced T2D must depend on hypoglycemia-induced catecholamine secretion to prevent them from experiencing neuroglycopenia [13]. However, with repeated exposure to hypoglycemia, the glycemic threshold of hypoglycemia-induced catecholamine release is shifted to a lower glucose level and in some patients may not occur before the onset of neuroglycopenia. This attenuation of the sympathoadrenal response to hypoglycemia is thought to cause the clinical syndrome of impaired awareness of hypoglycemia [13,18].

Hypoglycemia-induced glucagon secretion has been shown to be diminished in patients with CF and exocrine pancreatic insufficiency [19]. However, subjects in this study showed normal recovery from hypoglycemia, likely due to a normal epinephrine response. Cystic fibrosis transmembrane conductance regulator (CFTR) protein may be expressed in the α cells and mutations in CFTR may contribute to the dysregulated glucagon secretion in patients with CF [20], although this is controversial [21].

3.3. Hypoglycemia in CF in the absence of diabetes and glucose lowering therapies

Spontaneous hypoglycemia in the absence of glucose lowering therapies is also common in patients with CF, and can occur both in the fasting and post-prandial state. It is frequently noted during OGTT and has also been noted on continuous glucose monitoring (CGM) [22]. The pathophysiology underlying spontaneous hypoglycemia in patients with CF is not well understood.

Fasting hypoglycemia in patients with CF has been attributed to malnutrition combined with increased energy expenditure due to underlying inflammation or acute infection [2]. Fasting hypoglycemia could also occur in the setting of adrenal insufficiency [23]. Patients with CF are at risk of iatrogenic adrenal insufficiency following withdrawal from systemic glucocorticoid therapy. However, in one study fasting hypoglycemia was associated with dysregulation of basal insulin secretion. In this study, investigators noted that in some non-diabetic patients with CF (who did have signs of malnutrition), basal insulin and c-peptide concentrations were not appropriately reduced with lower fasting plasma glucose [24].

Post-prandial or reactive hypoglycemia in CF has been attributed to delayed and extended insulin release with a blunted glucagon response. In one study, patients who developed hypoglycemia during an OGTT had a delayed insulin response to the glucose load and had a higher insulin level at 120 min compared to patients who did not develop hypoglycemia [22]. In contrast, Armaghanian et al. [25] in a recent study noted that patients who developed hypoglycemia at 120 min had lower insulin levels compared to subjects who did not.

Authors of this study speculated that in the absence of an exaggerated insulin response, abnormalities in glucose metabolism related to glucagon and incretin hormones may play a role in development of reactive hypoglycemia in CF. Glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are incretin hormones secreted from the gut in response to ingestion of meals. The primary action of incretin hormones is to stimulate insulin and to inhibit glucagon secretion is response to nutrient ingestion [26]. Dipeptidyl peptidase-4 (DPP-4) inhibitors are a class of oral antihyperglycemic agents approved for use in T2D [27]. This class of medications act by inhibiting the enzyme DPP-4, which is responsible for degradation of incretin hormones like GLP-1 and GIP. In one study, sitagliptin (a DPP-4 inhibitor) reduced symptom of reactive hypoglycemia by potentially improving the early phase of insulin secretion [28]. Future research is needed to examine if DPP-4 inhibitors could be used as a novel approach to prevent reactive hypoglycemia.

3.4. Symptoms of hypoglycemia

Symptoms of hypoglycemia are traditionally divided into those attributable to hypoglycemia induced activation of the autonomic nervous system (neurogenic) and those triggered by brain deprivation of glucose (neuroglycopenic) [29,30]. Neurogenic symptoms include shakiness/tremors, palpitations, anxiety, sweating, hunger and tingling [12,29] (Table 2). These symptoms are critical to perception of hypoglycemia and alert patients to take corrective action. Neuroglycopenic symptoms include warmth, weakness, difficulty thinking, drowsiness, confusion, dizziness, and blurred vision [12,29]. Severe hypoglycemia could lead to seizures, coma and rarely even death. During experimental hypoglycemia in healthy volunteers, neurogenic symptoms were shown to begin at a threshold of ~58 mg/dl (3.2 mmol/l), whereas neuroglycopenic symptoms started at lower threshold of 51 mg/dl (2.8 mmol/l) [12].

3.5. Prevalence of hypoglycemia

3.5.1. Prevalence of hypoglycemia in diabetes

A global observational study that included >27,000 insulin treated patients with diabetes found that 83% of people with T1D and 46.5% with T2D reported at least one episode of hypoglycemia over 4 weeks [31]. Other studies report that non-severe hypoglycemia occurs on average about twice weekly in people with T1D [32]. Severe hypoglycemia is also common in both T1D and insulin treated T2D and is associated with diabetes duration. In one observational study, annual prevalence of severe hypoglycemia was around 20% in patients with T2D who were on insulin for >5 years and exceeded 40% in people with T1D who had the disease for >15 years [33].

There are limited data about prevalence of hypoglycemia in patients with CFRD on insulin therapy. Tierney et al. [34], asked patients with CFRD to record episodes of low glucose in a prospective diary for one week. Twenty subjects with CFRD completed the diary and 58% of these participants reported having two or more episodes of hypoglycemia in one week. In the CFRDT trial [1], 16% of the patients on premeal aspart insulin and 23% on repaglinide reported non-severe hypoglycemia during the first 3 months, which was significantly higher compared to the placebo arm. In a 12-week trial of basal insulin (NPH or glargine) in CFRD, investigators reported that over the treatment period, non-severe hypoglycemia occurred on average 6 times in patients assigned to glargine and 5 times in those assigned to NPH. [35]. Severe hypoglycemia is thought be rare in patients with CFRD and there were no episodes of severe hypoglycemia reported in either of these trials of insulin therapy in CFRD.

Table 2
Symptoms of hypoglycemia.

Symptoms of hypoglycemia [12,29,30]	
Neurogenic	Neuroglycopenic
Shakiness/tremors	Warmth
Tremors	Weakness
Palpitations	Difficulty thinking
Anxiety	Tiredness
sweating	Dizziness
Hunger	Confusion
Tingling	Blurry vision
	Seizures
	Coma
	Death

Hypoglycemia in insulin treated patients with CFRD is also common in the inpatient setting and was found to be associated with higher rate of future readmissions [36]. In this study, 6.1% of all the measured capillary blood glucose measurements were in the hypoglycemia range (< 72 mg/dl (4 mmol/l)), with the higher proportion of low glucose readings during the nighttime. Capillary blood glucose measurements with point-of-care (POC) glucose meters can be less accurate in the hypoglycemia range [6,37]. In the inpatient and critical care settings, the accuracy of POC meters may be compromised due to variations in blood oxygen, hematocrit, changes in microcirculation and use of vasopressor therapy [6,37].

3.5.2. Prevalence of spontaneous hypoglycemia in CF

Reactive hypoglycemia is commonly noted during or after OGTT in patients with CF and is usually asymptomatic. In a systematic review, Armaghanian and colleagues reported that rates of hypoglycemia unrelated to diabetes in CF ranged between 7 and 69% in different studies [38]. The wide range in prevalence between different studies is likely due to varying definitions of hypoglycemia and differences in study design. Three hour OGTTs are more likely to lead to reactive hypoglycemia compared to standard 2 h OGTTs [38,39]. In one study, fasting hypoglycemia (blood glucose <60 mg/dl (3.9 mmol) was noted in 14% and reactive hypoglycemia (blood glucose <50 mg/dl (2.8 mmol/l)) in 15% of the OGTTs performed [24]. None of the subjects in this study reported symptoms with fasting or reactive hypoglycemia, even when blood glucose was below 50 mg/dl. However, other studies have reported symptomatic hypoglycemia during OGTT in individuals who do not have CF [38,39]. In healthy individuals undergoing OGTT, the average nadir glucose was noted to be 63 mg/dl (3.5 mmol/l) and 25% of subjects had a nadir glucose of 55 mg/dl (3 mmol/l) or less [40]. Based on these data, the frequency of hypoglycemia seen during OGTT in patients with CF does not appear to be higher than in people without CF.

Continuous glucose monitoring (CGM) has been utilized to examine the prevalence of spontaneous hypoglycemia in CF under free living conditions. In a study of children and adolescents with CF aged 5–18 years, OGTT and CGM were sequentially performed in 45 subjects [22]. In this study, the frequency of hypoglycemia was 13.3% during the 2-h OGTT, and 27.5% of individuals spent ≥3% time hypoglycemic during 3 days of CGM use. None of the subjects reported symptoms of hypoglycemia during OGTT. These data suggest that CGM may be the most sensitive method to detect spontaneous hypoglycemia in CF [41].

3.6. Risk factors associated with hypoglycemia

In patients with diabetes, iatrogenic hypoglycemia is caused by treatment with insulin, sulfonylureas or glinides. Mismatch between the insulin dose and exogenous glucose intake is a frequent cause of hypoglycemia and can occur due to too much insulin (excessive, incorrectly timed or the wrong type of insulin dosed) or too little carbohydrate (missed, delayed or low carbohydrate meals or insufficient extra carbohydrate consumed during exercise). Factors that compromise a patient's defenses against falling blood glucose can also increase the risk of hypoglycemia (Table 3). Iatrogenic hypoglycemia is associated with several clinical risk factors including older age, duration of diabetes, endogenous insulin deficiency, presence of

Table 3
Factors that increase risk of Iatrogenic hypoglycemia.

Long duration of diabetes
Endogenous insulin deficiency
Strict glycemic control
Impaired aware of hypoglycemia
Alcohol consumption
Exercise
Impaired renal or hepatic function

other comorbidities like renal or liver disease and cognitive impairment [6,33]. Tight glycemic control has been associated with increased risk of severe hypoglycemia both in people with T1D and T2D [42,43]. Patients with diabetes who develop impaired awareness of hypoglycemia have 6-fold increased risk of developing severe hypoglycemia [44]. Exercise impacts glucose utilization and insulin sensitivity and can increase the risk of hypoglycemia during or even several hours after a bout of exercise. Alcohol ingestion increases the risk of hypoglycemia by reducing endogenous glucose production. Comorbidities like renal and hepatic failure can reduce the clearance of insulin [45]. Several physiological and behavioral factors associated with risk of iatrogenic hypoglycemia are listed in Table 3.

4. Consequences of hypoglycemia

4.1. Impact of iatrogenic hypoglycemia

The impact of an episode of hypoglycemia in patients with diabetes can range from development of mild symptoms to rarely seizure, coma or death. As discussed earlier, hypoglycemia can lead to development of autonomic symptoms including palpitations, tremors, anxiety, hunger and sweating. These symptoms can be bothersome and lead to interruptions in daily activities, but in addition to triggering endogenous responses to correct hypoglycemia, they alert the patient to the need to take corrective action and thus are an important safety mechanism. Neuroglycopenic symptoms include drowsiness, difficulty concentrating or confusion. The impairment of cognitive function due to hypoglycemia can limit patient's ability to perform complex tasks and increase risk of suffering physical injury as a result of falling or driving accidents. There is clear evidence that insulin induced hypoglycemia can be fatal [46]. Severe and prolonged hypoglycemia can cause brain death, but most episodes of fatal hypoglycemia are thought to be due to other mechanisms like cardiac arrhythmia [46].

Exposure to recurrent episodes of iatrogenic hypoglycemia, can lead to development of impaired awareness of hypoglycemia [18]. Counterregulatory responses to hypoglycemia are markedly reduced in subjects with impaired awareness of hypoglycemia and these individuals do not develop the typical adrenergic symptoms in response to lowering plasma glucose [6]. In these patients, the first sign of hypoglycemia can be confusion or other symptoms of neuroglycopenia. Impaired awareness of hypoglycemia is reported to be present in 20% of people with T1D [44]. Impaired awareness of hypoglycemia has not been examined in depth in CFRD but is thought to be uncommon in patients with CF [2].

Hypoglycemia and fear of hypoglycemia can negatively affect the quality of life and activities of daily living in people with diabetes [47,48]. Episodes of severe and nocturnal hypoglycemia are associated with greater worry and decreased perceived health status [48]. In one study, patients who experienced severe hypoglycemia were more affected in aspects of daily living like traveling, driving, exercising and socializing compared to patients who experienced only non-severe hypoglycemia [48]. Recurrent hypoglycemia has also been associated with mood disorders including depression and anxiety [47,49].

In a cross sectional study, Tierney et al. [34] compared patients' self-reported experiences of hypoglycemia and diabetes-specific health-related quality of life (HRQoL) measures between patients with CFRD and T1D. The authors found that diabetes in patients with CF had less of a negative impact on HRQoL compared to T1D. In this study the severity of symptoms (particularly neuroglycopenic symptoms) and not the frequency of hypoglycemia events correlated with worse HRQoL.

4.2. Does spontaneous hypoglycemia in CF predict poor clinical outcomes?

It has been hypothesized that reactive hypoglycemia seen during OGTT could be a precursor or predictor of the development of CFRD and that the mechanism of insulin dysregulation that leads to reactive hypoglycemia may lead to CFRD [50]. However, recent studies have not supported this hypothesis. Radike et al. [51] found that hypoglycemia during OGTT did not predict higher risk of development of CFRD or impaired glucose tolerance. In another recent study Mannik et al. [52], found that subjects who experienced hypoglycemia during OGTT had lower rates of progression to CFRD compared subjects with no hypoglycemia during OGTT. Reactive hypoglycemia and higher variability in glucose reading on CGM has been associated with lower FEV1 in patients with CF, independent of the nutritional status [22]. More research is needed to understand the clinical relevance of asymptomatic spontaneous low plasma glucose readings noted during OGTT or CGM monitoring in patients with CF.

5. Management of hypoglycemia

5.1. Strategies to prevent hypoglycemia

Prevention of hypoglycemia is a key component of diabetes management. Current CFRD guidelines recommend that patients with CFRD and their care partners should receive education about symptoms, prevention and treatment of hypoglycemia [2]. Diabetes health care providers should routinely evaluate the risk of hypoglycemia in patients with CFRD on insulin therapy. Patients at risk for hypoglycemia should be asked about symptomatic and asymptomatic hypoglycemia. The treatment regimen and glycemic targets should be reevaluated in patients experiencing recurrent non-severe or one or more episodes of severe hypoglycemia.

5.1.1. Self-monitoring of blood glucose

Self-monitoring of blood glucose (SMBG) is an essential part of diabetes management to assess the response to treatment and monitor for hypoglycemia. Current guidelines recommend that patients with CFRD who are treated with insulin should perform SMBG at least three times daily. However, some patients may need to check glucose levels more frequently based on physical activity, dietary changes, illness or history of frequent hypoglycemia. Recent advances in technology have provided patients and providers with new tools for glucose monitoring and insulin delivery. CGM can not only provide real time glucose readings but also gives information about the direction and rate of change of glucose levels. CGM use has been shown to reduce both day time and nocturnal hypoglycemia in subjects with T1D [53,54]. CGM use can be considered in patients with CFRD complicated by recurrent hypoglycemia. Recently, hybrid closed loop (HCL) insulin pump/sensor systems have become available to use in patients with diabetes. In these systems, data from a CGM device are communicated to an insulin pump, which uses insulin dosing algorithms to automatically adjust the basal insulin rates. The system is “hybrid” because it is not fully automatic, as patients must still calculate and bolus for carbohydrate intake. HCL has been to shown to improve glycemic control and reduce hypoglycemia [55] (for additional details see Chan et al. [61]).

5.1.2. Management during acute illness

During acute illness or systemic glucocorticoid treatment, patients with CFRD often develop significant insulin resistance with higher

insulin needs. During recovery from illness, insulin requirements gradually return to baseline and during this period careful monitoring is needed to avoid hypoglycemia. Some patients with CFRD eat multiple small meals throughout the day (grazing meal pattern) and can be managed with single daily dose of basal insulin. These patients are at risk of developing hypoglycemia if they skip meals or have prolonged periods of fasting while usual basal insulin is on board, for example during illness with reduced appetite. Patients should receive education about factors that increase the risk of hypoglycemia, so they can anticipate situations when they may be at risk.

5.1.3. Management during exercise

Patients with CFRD are encouraged to exercise. Increased insulin sensitivity after aerobic exercise may last for several hours. Exercise-related hypoglycemia can be prevented by carefully monitoring blood glucose levels during and after exercise. Strategies to prevent exercise related hypoglycemia include a pre-exercise snack, adjustment of the insulin dose for the meals/snacks preceding and after the exercise, utilizing a temporary basal rate if on an insulin pump, or consuming an extra bedtime snack. These strategies should be individualized according to the type and intensity of exercise, the pre-exercise glucose, and patient-related risk factors of hypoglycemia.

5.2. Treatment of acute hypoglycemia

The American Diabetes Association (ADA) Standards of Care [56] recommends 15–20 g of fast acting oral glucose as the preferred treatment for a conscious individual with a glucose at or below the hypoglycemia alert level (<70 mg/dl (3.9 mmol/l)). Patient should retest after 15 min and if the glucose remains low, the treatment should be repeated. These steps could be repeated until glucose is above 70 mg/dl (3.9 mmol/l). Once glucose level recovers to normal, individual should consider eating a meal or snack to prevent the recurrence of hypoglycemia. Co-ingestion of fat could delay absorption of carbohydrates and may delay recovery from hypoglycemia. Carbohydrate sources with high protein should also be avoided in treatment of acute hypoglycemia. In patients with T2D, dietary proteins have been shown to increase the endogenous insulin response [57]. In a patient with severe hypoglycemia, who is too confused or obtunded to consume oral carbohydrate; active assistance of another person is required. In the hospital setting, hypoglycemia can be reversed quickly by administering 25 g of 50% glucose (dextrose) intravenously. In patients without intra venous (IV) access immediate administration of glucagon is indicated for the emergency treatment of severe hypoglycemia. Glucagon can be administered by subcutaneous, intra muscular or nasal route. A nasally administered formulation of glucagon was recently approved by the FDA for treatment of severe hypoglycemia in patients (4 years and above) with diabetes. The glycemic response to IV glucose or glucagon is transient. Therefore initial treatment may need to be followed by continuous glucose infusion or oral intake if patient is able to eat. Patients frequently experience nausea and vomiting after administration of glucagon. If a patient treated with ambulatory insulin pump experiences severe hypoglycemia; basal insulin delivery should be temporarily suspended until hypoglycemia is resolved.

6. Potential impact of CFTR modulation

Improved insulin secretion after oral and IV glucose tolerance testing has been shown following ivacaftor treatment in CF patients with the G551D mutation [58,59]. These pilot studies provide evidence that CFTR modulation may impact islet cell function. In a randomized double-blind, placebo controlled trial of ivacaftor, hypoglycemia was reported as an adverse effect in the treatment arm [60]. CFTR has been shown to be involved in the regulation of glucagon secretion in human and rodent α cells [20]. These data provide early evidence that treatment with CFTR modulator may impact glucose homeostasis and could potentially impact risk of hypoglycemia in CFRD. Ongoing and future studies of CFTR modulators will provide more insights into the role of CFTR in islet cell function in humans.

7. Future directions

There are significant knowledge gaps in our understanding of hypoglycemia in patients with CF. Future studies are needed to better understand the rates of non-severe, nocturnal and severe hypoglycemia in CFRD. Studies are also needed to identify which patients with CF are at greater risk of hypoglycemia and how hypoglycemia may impact quality of life measures. More research is needed to better define spontaneous hypoglycemia in CF and understand its underlying mechanisms. Research is needed to examine if spontaneous hypoglycemia in CF is associated with clinically relevant outcomes. Future studies will also provide insights about the use of technology like CGM and closed loop insulin pump systems to reduce the impact of hypoglycemia and improve quality of life measures in patients with CFRD.

8. Clinical practice points

- Patients with CFRD on insulin therapy are at risk of developing hypoglycemia.
- Patients with CFRD on insulin therapy and their care partners should be educated about hypoglycemia including use of glucagon.
- Diabetes care providers should routinely ask patients about hypoglycemia during clinic visits.
- Patients should be counseled about exercise and its impact of blood glucose.
- Glycemic targets and the diabetes regimen should be modified in patients who are experiencing recurrent hypoglycemia.
- Consider use of CGM and/or insulin pump therapy as appropriate in patient with difficult to manage hypoglycemia or a history of impaired awareness of hypoglycemia.

9. Summary

Spontaneous hypoglycemia (e.g. occurring after meals or during glucose tolerance test) can occur in people with CF, but more research is needed to determine the clinical significance of this phenomenon. On the other hand, iatrogenic hypoglycemia is known to cause significant morbidity in many patients with diabetes. Several factors that increase the risk of hypoglycemia in diabetes are modifiable. To reduce the risk of hypoglycemia, it is important for the patients, their caregivers and medical providers to first recognize this problem and consider individual risk factors and modify treatment strategies and glycemic goals appropriately. Advances in the glucose monitoring and insulin delivery devices including the closed loop systems have the potential to greatly reduce and even eliminate the burden of hypoglycemia.

Declaration of Competing Interest

The authors declare no conflict of interest.

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References

[1] Moran A, Pekow P, Grover P, Zorn M, Slovis B, Pilewski J, et al. Cystic fibrosis related diabetes therapy study G. insulin therapy to improve BMI in cystic fibrosis-related diabetes without fasting hyperglycemia: results of the cystic fibrosis related diabetes therapy trial. Diabetes Care 2009;32(10):1783–8.

[2] Moran A, Brunzell C, Cohen RC, Katz M, Marshall BC, Onady G, et al. Clinical care guidelines for cystic fibrosis-related diabetes: a position statement of the American Diabetes Association and a clinical practice guideline of the Cystic Fibrosis Foundation, endorsed by the Pediatric Endocrine Society. Diabetes Care 2010;33 (12):2697–708.

[3] Moheet A, Moran A. Pharmacological management of cystic fibrosis related diabetes. Expert Rev Clin Pharmacol 2018;11(2):185–91.

[4] Mozzillo E, Franzese A, Valerio G, Sepe A, De Simone I, Mazzarella G, et al. One-year glargine treatment can improve the course of lung disease in children and adolescents with cystic fibrosis and early glucose derangements. Pediatr Diabetes 2009;10(3):162–7.

[5] Cryer PE. Hypoglycemia: still the limiting factor in the glycemic management of diabetes. Endocr Pract 2008;14(6):750–6.

[6] Seaquist ER, Anderson J, Childs B, Cryer P, Dagogo-Jack S, Fish L, et al. Hypoglycemia and diabetes: a report of a workgroup of the American Diabetes Association and the Endocrine Society. Diabetes Care 2013;36(5):1384–95.

[7] 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(23):1487–92.

[8] Group IHS. 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(1):155–7.

[9] Cryer PE, Axelrod L, Grossman AB, Heller SR, Montori VM, Seaquist ER, et al. Evaluation and management of adult hypoglycemic disorders: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2009;94(3):709–28.

[10] Cryer PE. Glucose counterregulation: prevention and correction of hypoglycemia in humans. Am J Phys 1993;264(2 Pt 1):E149–55.

[11] Fanelli C, Pampanelli S, Epifano L, Rambotti AM, Ciofetta M, Modarelli F, et al. Relative roles of insulin and hypoglycaemia on induction of neuroendocrine responses to, symptoms of, and deterioration of cognitive function in hypoglycaemia in male and female humans. Diabetologia. 1994;37(8):797–807.

[12] Mitrakou A, Ryan C, Veneman T, Mokan M, Jenssen T, Kiss I, et al. Hierarchy of glycemic thresholds for counterregulatory hormone secretion, symptoms, and cerebral dysfunction. Am J Phys 1991;260(1 Pt 1):E67–74.

[13] Stanley S, Moheet A, Seaquist ER. Central mechanisms of glucose sensing and counterregulation in defense of hypoglycemia. Endocr Rev 2019 Jun 1;40(3):768–88.

[14] Sherwin RS, Shamoon H, Hendler R, Saccà L, Eigler N, Walesky M. Epinephrine and the regulation of glucose metabolism: effect of diabetes and hormonal interactions. Metabolism. 1980;29(11 Suppl 1):1146–54.

[15] Hoffman RP. Antecedent hypoglycemia does not alter increased epinephrine-induced lipolysis in type 1 diabetes mellitus. Metabolism. 2006;55(3):371–80.

[16] Gerich J, Davis J, Lorenzi M, Rizza R, Bohannon N, Karam J, et al. Hormonal mechanisms of recovery from insulin-induced hypoglycemia in man. Am J Phys 1979;236(4):E380–5.

[17] Rizza RA, Cryer PE, Gerich JE. Role of glucagon, catecholamines, and growth hormone in human glucose counterregulation. Effects of somatostatin and combined alpha- and beta-adrenergic blockade on plasma glucose recovery and glucose flux rates after insulin-induced hypoglycemia. J Clin Invest 1979;64(1):62–71.

[18] Cryer PE. Mechanisms of hypoglycemia-associated autonomic failure in diabetes. N Engl J Med 2013;369(4):362–72.

[19] Moran A, Diem P, Klein DJ, Levitt MD, Robertson RP. Pancreatic endocrine function in cystic fibrosis. J Pediatr 1991;118(5):715–23.

[20] Edlund A, Pedersen MG, Lindqvist A, Wierup N, Flodström-Tullberg M, Eliasson L. CFTR is involved in the regulation of glucagon secretion in human and rodent alpha cells. Sci Rep 2017;7(1):90.

[21] Hart NJ, Aramandla R, Poffenberger G, Fayolle C, Thames AH, Bautista A, et al. Cystic fibrosis-related diabetes is caused by islet loss and inflammation. JCI Insight 2018;3(8).

[22] Haliloglu B, Gokdemir Y, Atay Z, Abali S, Guran T, Karakoc F, et al. Hypoglycemia is common in children with cystic fibrosis and seen predominantly in females. Pediatr Diabetes 2017;18(7):607–13.

[23] Kelly A, Moran A. Update on cystic fibrosis-related diabetes. J Cyst Fibros 2013;12 (4):318–31.

[24] Battezzati A, Battezzati PM, Costantini D, Seia M, Zazzeron L, Russo MC, et al. Spontaneous hypoglycemia in patients with cystic fibrosis. Eur J Endocrinol 2007;156(3):369–76.

[25] Armaghanian N, Markovic TP, Brand-Miller JC, Bye PTP, Moriarty CP, Steinbeck KS. Hypoglycaemia in cystic fibrosis: an analysis of a single Centre adult cystic fibrosis clinic. J Cyst Fibros 2018;17(4):542–7.

[26] Holst JJ. The physiology of glucagon-like peptide 1. Physiol Rev 2007;87(4):1409–39.

[27] Association AD. 9. Pharmacologic approaches to glycemic treatment. Diabetes Care 2019;42(Suppl. 1):S90–S102.

[28] Cuevas-Ramos D, Almeda-Valdés P, Meza-Arana CE, Brito-Córdova G, Ruiz-Gómez DG, Razo C, et al. Sitaglitpin phosphate treatment in patients with reactive hypoglycemia secondary to dysinsulinism. Controlled, randomized, double-blind study. Gac Med Mex 2017;153:S51–9 Supl. 2.

[29] Towler DA, Havlin CE, Craft S, Cryer P. Mechanism of awareness of hypoglycemia - perception of neurogenic (predominantly cholinergic) rather than neuroglycopenic symptoms. Diabetes 1993;42(12):1791–8.

[30] Tesfaye N, Seaquist ER. Neuroendocrine responses to hypoglycemia. Ann N Y Acad Sci 2010;1212:12–28.

[31] Khunti K, Alsifri S, Aronson R, Cigrovski Berković M, Enters-Weijnen C, Forsén T, et al. Rates and predictors of hypoglycaemia in 27 585 people from 24 countries with insulin-treated type 1 and type 2 diabetes: the global HAT study. Diabetes Obes Metab 2016;18(9):907–15.

[32] Östenson CG, Geelhoed-Duijvestijn P, Lahtela J, Weitgasser R, Markert Jensen M, Pedersen-Bjergaard U. Self-reported non-severe hypoglycaemic events in Europe. Diabet Med 2014;31(1):92–101.

[33] Group UHS. Risk of hypoglycaemia in types 1 and 2 diabetes: effects of treatment modalities and their duration. Diabetologia 2007;50(6):1140–7.

[34] Tierney S, Webb K, Jones A, Dodd M, McKenna D, Rowe R, et al. Living with cystic fibrosis-related diabetes or type 1 diabetes mellitus: a comparative study exploring health-related quality of life and patients' reported experiences of hypoglycaemia. Chron Illn 2008;4(4):278–88.

[35] Grover P, Thomas W, Moran A. Glargine versus NPH insulin in cystic fibrosis related diabetes. J Cyst Fibros 2008;7(2):134–6.

[36] Jones GC, Chong ZM, Gilmour J, Matheson C, MacGregor G, Sainsbury CA. Patterns and impact of hypoglycemia, hyperglycemia, and glucose variability on inpatients with insulin-treated cystic fibrosis-related diabetes. Diabetes Ther 2016;7(3):575–82.

[37] Rebel A, Rice MA, Fahy BG. Accuracy of point-of-care glucose measurements. J Diabetes Sci Technol 2012;6(2):396–411.

[38] Armaghanian N, Brand-Miller JC, Markovic TP, Steinbeck KS. Hypoglycaemia in cystic fibrosis in the absence of diabetes: a systematic review. J Cyst Fibros 2016;15(3):274–84.

[39] Hirsch IB, Janci MM, Goss CH, Aitken ML. Hypoglycemia in adults with cystic fibrosis during oral glucose tolerance testing. Diabetes Care 2013;36(8):e121–2.

[40] Lev-Ran A. Nadirs of oral glucose tolerance tests are independent of age and sex. Diabetes Care 1983;6(4):405–8.

[41] Chan CL, Hope E, Thurston J, Vigers T, Pyle L, Zeitler PS, et al. Hemoglobin A. Diabetes Care 2018;41(7):1406–13.

[42] Nathan DM. Long-term complications of diabetes mellitus. N Engl J Med 1993;328 (23):1676–85.

[43] Seaquist ER, Miller ME, Bonds DE, Feinglos M, Goff Jr. DC, Peterson K, et al. The impact of frequent and unrecognized Hypoglycemia on mortality in the ACCORD study. Diabetes Care 2012;35(2):409–14.

[44] Geddes J, Schopman JE, Zammitt NN, Frier BM. Prevalence of impaired awareness of hypoglycaemia in adults with type 1 diabetes. Diabet Med 2008;25(4):501–4.

[45] Group IHS. Minimizing hypoglycemia in diabetes. Diabetes Care 2015;38 (8):1583–91.

[46] Cryer PE. Death during intensive glycemic therapy of diabetes: mechanisms and implications. Am J Med 2011;124(11):993–6.

[47] Barendse S, Singh H, Frier BM, Speight J. The impact of hypoglycaemia on quality of life and related patient-reported outcomes in type 2 diabetes: a narrative review. Diabet Med 2012;29(3):293–302.

[48] Harris SB, Khunti K, Landin-Olsson M, Galbo-Jørgensen CB, Bøgelund M, Chubb B, et al. Descriptions of health states associated with increasing severity and frequency of hypoglycemia: a patient-level perspective. Patient Prefer Adherence 2013;7:925–36.

[49] Gold AE, Deary IJ, Frier BM. Hypoglycaemia and non-cognitive aspects of psychological function in insulin-dependent (type 1) diabetes mellitus (IDDM). Diabet Med 1997;14(2):111–8.

[50] Moheet A, Ode KL. Hypoglycaemia in patients with cystic fibrosis- harbinger of poor outcomes or innocent bystander? J Cyst Fibros 2018;17(4):428–9.

[51] Radike K, Molz K, Holl RW, Poeter B, Hebestreit H, Ballmann M. Prognostic relevance of hypoglycemia following an oral glucose challenge for cystic fibrosis-related diabetes. Diabetes Care 2011;34(4):e43.

[52] Mannik LA, Chang KA, Annoh PQK, Sykes J, Gilmour J, Robert R, et al. Prevalence of hypoglycemia during oral glucose tolerance testing in adults with cystic fibrosis and risk of developing cystic fibrosis-related diabetes. J Cyst Fibros 2018;17(4):536–41.

[53] Beck RW, Riddlesworth T, Ruedy K, Ahmann A, Bergenstal R, Haller S, et al. Effect of continuous glucose monitoring on glycemic control in adults with type 1 diabetes using insulin injections: the DIAMOND randomized clinical trial. JAMA. 2017;317(4):371–8.

[54] Heinemann L, Freckmann G, Ehrmann D, Faber-Heinemann G, Guerra S, Waldenmaier 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(10128):1367–77.

[55] Garg SK, Weinzimer SA, Tamborlane WV, Buckingham BA, Bode BW, Bailey TS, et al. Glucose outcomes with the in-home use of a hybrid closed-loop insulin delivery system in adolescents and adults with type 1 diabetes. Diabetes Technol Ther 2017;19(3):155–63.

[56] Association AD. 6. Glycemic targets. Diabetes Care 2019;42(Suppl. 1):S61–70.

[57] Layman DK, Clifton P, Gannon MC, Krauss RM, Nuttall FQ. Protein in optimal health: heart disease and type 2 diabetes. Am J Clin Nutr 2008;87(5):1571S–5S.

[58] Bellin MD, Laguna T, Leschyshyn J, Regelmann W, Dunitz J, Billings J, et al. Insulin secretion improves in cystic fibrosis following ivacaftor correction of CFTR: a small pilot study. Pediatr Diabetes 2013;14(6):417–21.

[59] Kelly A, De Leon DD, Sheikh S, Camburn D, Kubrak C, Peleckis AJ, et al. Islet hormone and incretin secretion in cystic fibrosis following 4-months of Ivacaftor therapy. Am J Respir Crit Care Med 2019;199(3):342–51.

[60] Ramsey BW, Davies J, McElvaney NG, Tullis E, Bell SC, Dřevínek P, et al. Group V–S. a CFTR potentiator in patients with cystic fibrosis and the G551D mutation. N Engl J Med 2011;365(18):1663–72.

[61] Chan CL, Ode KL, Granados A, Moheet A, Moran A, Hameed S. Continuous glucose monitoring in cystic fibrosis - A practical guide. J Cyst Fibros 2019;18(S2):S25–31.