REVIEW ARTICLE

Revisiting Hypoglycemia in Diabetes

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Hypoglycemia is a common and serious complication of diabetes management. There is no uniformly accepted clinical definition of hypoglycemia. The American Diabetes Association (ADA) recommends that people with diabetes consider treating hypoglycemia when the self-monitored blood glucose (SMBG) level is ≤70 mg/dl (3.9 mmol/L). Hypoglycemia significantly affects mortality and quality of life. Normally, in people without diabetes, hypoglycemia is prevented by redundant protective counter-regulatory mechanisms. These counter-regulatory pathways become defective in people with Type 1 diabetes and those with long standing Type 2 diabetes.

Most hypoglycemic episodes in diabetes are related to the use of insulin and insulin secretagogues. The National Electronic Injury Surveillance System study in older adults found that nearly 25% of all medication induced hospitalizations were due to insulin and oral hypoglycemic agents.
The treatment of hypoglycemia will depend on the severity of the event and symptoms. When the person is conscious and able to respond, a fast acting carbohydrate is the treatment of choice. The "rule of 15" is often recommended. Severe hypoglycemia that is associated with inability to help oneself should be treated with injectable glucagon.

This paper will review the typical signs and symptoms of hypoglycemia in diabetes, its pathophysiology, classification, prevention and treatment.

INTRODUCTION

The discovery of insulin in 1922[1] was life saving for those with type1diabetes (T1DM) and many with type 2 diabetes (T2DM), but the use of exogenous insulin brought along a dramatic new problem: hypoglycemia. Hypoglycemia has become the most important limiting factor in achieving euglycemia in people with diabetes.[2]

Multiple studies such as the United Kingdom Prospective Diabetes Study (UKPDS)[3] and the Diabetes Control and Complications Trial (DCCT)[4] demonstrated that intensive glucose control reduces the microvascular complications of diabetes. However, other studies such as the Action to Control Cardiovascular Risk in Diabetes trial (ACCORD)[5], the Action in Diabetes and Vascular Disease-Preterax and Diamicron Modified Release Controlled Evaluation trial (ADVANCE)[6] and Veterans Affairs Diabetes Trial (VADT)[7] found that intensive glucose control caused a significant increase in hypoglycemia.

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MORBIDITY AND MORTALITY ASSOCIATED WITH HYPOGLYCEMIA

Hypoglycemia is a serious, life- and lifestyle-limiting condition. The National Electronic Injury Surveillance System study in older adults[8] found that nearly 25% of all medication-induced hospitalizations were due to insulin and oral hypoglycemic agents. These hospitalizations were largely preventable. Hypoglycemia burdens the economy as well: Following a severe hypoglycemic event, people with T2DM lose a mean of 3 productive work days.[9] A study estimating the economic impact of hypoglycemia among working-age patients with T2DM found the mean costs per episode of hypoglycemia were $17,564 for an inpatient admission, $1,387 for an emergency room visit, and $394 for an outpatient visit.[10]

For decades hypoglycemia mortality rates have been 2-4% for people with T1DM,[11] but recent studies show T1DM hypoglycemic mortality rates to be as high as 6%[12] to 10%.[13] Reliable hypoglycemia mortality rates in T2DM are not available. However, deaths related to sulfonylurea- induced hypoglycemia have been reported to be as high as 10%.[14]

The problems with hypoglycemia are seen both in the inpatient and outpatient setting. The ACCORD study was terminated early due to increased mortality in intensively treated patients.[5] Iatrogenic hypoglycemia was considered to be a significant contributor although it remains uncertain. The Normoglycemia in Intensive Care Evaluation–Survival Using Glucose Algorithm Regulation (NICE-SUGAR) trial

was an inpatient trial completed with hyperglycemic adults in the ICU.[15] Severe hypoglycemia was significantly higher at 6.8% with intensive glucose control as compared to 0.5% with conventional treatment. In addition, with the intensive control group, the odds ratio for death was 1.14 (95% CI, 1.02 to 1.28; P=0.02).[15]

There is a syndrome described in T1DM, "dead in bed syndrome". This refers to a sudden unexpected death that occurs in young diabetes patients with no clear etiology. Hypoglycemia was correlated with cardiac events leading to sudden death.[16] Potential mechanisms for sudden death from hypoglycemia are QT prolongation and ventricular arrhythmia.[17] These sudden deaths accounted for 5-6% of all deaths in patients with diabetes below 40 years in the UK and Scandinavian countries.[16]

DEFINITION

The definitive diagnosis of hypoglycemia requires Whipple's triad: symptoms and signs consistent with hypoglycemia, documented low plasma glucose, and resolution of those symptoms and signs once glucose levels normalize.[18] The clinical presentation of hypoglycemia however, is highly variable, and there is no uniformly accepted clinical definition of hypoglycemia. Some define hypoglycemia in a physiological context as a plasma glucose value of less than 70 mg/dl (3.9 mmol/L). This is the glucose level at which the counter-regulatory responses against falling plasma glucose are activated in people without diabetes.[19] Also, precedent episodes of <70 mg/dl (3.9 mmol/L) lead to defective counter-regulatory responses to ensuing hypoglycemia.[19] Others, such as Frier[20] and Amiel et al.,[21] criticized this definition in favor of < 63 mg/dl (3.5 mmol/L) to avoid overestimation of hypoglycemia in asymptomatic patients.

The American Diabetes Association (ADA) convened a Workgroup on Hypoglycemia in June 2004 to better describe this issue. They defined hypoglycemia as all episodes of an abnormally low plasma glucose concentration, with or without symptoms, that subject a person to potential harm.[19] The workgroup recommended that people with diabetes consider treating hypoglycemia when the self-monitored blood glucose (SMBG) level is ≤70 mg/dl (3.9 mmol/L). This was updated in 2013 by the ADA and the Endocrine Society Workgroup, who recommended the following classification of hypoglycemia in diabetes[22] (Table 1: ADA Classification of Hypoglycemia).

PREVALENCE

In the DCCT study, a trial in adolescents and young adults with type 1 diabetes, the overall rate of severe hypoglycemia was three times higher in the intensive treatment group as compared to conventional treatment group, with 61.2 per 100 patient-years vs18.7 per 100 patient-years, respectively, with a relative risk increase of 3.28.[23] It has been estimated that a typical patient with T1DM has an average of two episodes of symptomatic hypoglycemia per week and an episode of severe hypoglycemia once a year.[24]

The U.K. Hypoglycemia Study Group showed that patients with T2DM treated with insulin for < 2 years had a 7% prevalence of severe hypoglycemia compared to 25% in those treated with insulin for > 5 years.[25] This suggests that with greater duration of insulin treatment, the rate of hypoglycemic events increases. Hepburn et al.[26] showed severe hypoglycemic

TABLE 1: ADA classification of Hypoglycemia

Category	Glucose value	Definition
Severe hypoglycemia	This value has arbitrarily been defined as a plasma glucose level below 50 mg/dl (2.8mmol/l) irrespective of the signs and symptoms.	An event which requires the assistance of another person to treat hypoglycemia. There may not be a plasma glucose level available at the time but return to normal neurological status with normalization of plasma glucose will suffice the fact that the event was a consequence of low plasma glucose.
Documented symptomatic hypoglycemia	≤70 mg/dl (3.9mmol/l).	An event described as having both the typical symptoms of hypoglycemia and a measured plasma glucose concentration ≤70 mg/dl (3.9mmol/l).
Asymptomatic hypoglycemia	≤70 mg/dl (3.9mmol/l)	An event with a measured plasma glucose concentration ≤70 mg/dl (3.9 mmol/l) but lacking the typical symptoms of hypoglycemia.
Probable symptomatic hypoglycemia	≤70 mg/dl (3.9 mmol/l)	An event during which symptoms typical of hypoglycemia are not accompanied by a plasma glucose value but it is presumably caused by a plasma glucose concentration ≤70 mg/dl (3.9 mmol/l).
Pseudo-hypoglycemia	>70 mg/dl (3.9 mmol/l)	An event with the typical symptoms of hypoglycemia, but with a measured plasma glucose concentration >70 mg/dl (3.9 mmol/l). This is common in patients with long standing poor glycemic control when their plasma glucose concentration starts trending towards the normal range.

frequencies were similar in T1DM and T2DM when matched for the duration of insulin therapy. Thus, with longer duration of diabetes and progressive insulin deficiency in T2DM, the rate of iatrogenic hypoglycemia resembles that of T1DM.

The incidence of hypoglycemia increases with age. In an epidemiological study by Bertoni et al, the incidence rate of hypoglycemia per 1000 patient-years was 28.3, making it the most frequent metabolic complication experienced by the elderly in the U.S. with diabetes.[27] Deterioration in renal and hepatic function due to age interfering with metabolism of medications like sulfonylureas and insulin, compromised counter-regulatory hormone responses in the elderly with diabetes,[28] and age-related decrease in beta cell receptor function[29] are some of the factors responsible for susceptibility of elderly to hypoglycemia.

The overall prevalence of T2DM is 20 times greater than that of T1DM.[30] T2DM is a progressive disease and most people with T2DM will ultimately become insulin dependent. As a result, most episodes of iatrogenic hypoglycemia, including severe hypoglycemia, occur in patients with T2DM.

SYMPTOMS OF HYPOGLYCEMIA

Symptoms can be divided into 2 categories: neurogenic (related to autonomic nervous system which are triggered by the falling plasma glucose)[31] and neuroglycopenic (due to brain neuronal glucose deprivation).[11] Neurogenic symptoms can be further classified into adrenergic and cholinergic.

TABLE 2: Signs and Symptoms of Hypoglycemia

Neurogenic / Autonomic		Neuroglycopenic
Adrenergic	Cholinergic	Headache
Palpitations	Diaphoresis	Visual changes
Anxiety/Nervousness	Hunger	Dizziness
Tremors/tremulousness	Paresthesias/ tingling	Weakness
		Confusion
		Agitation
		Irritability
		Drowsiness/ Lethargy
		Seizure
		Coma

NORMAL PHYSIOLOGIC RESPONSE TO HYPOGLYCEMIA

The body initiates a cascade of events when the blood glucose starts trending downwards. (See Table 3: Physiological responses to Hypoglycemia). Counter-regulatory mechanisms begin when the plasma glucose is approximately 85-90 mg/dl (4.4-4.7 mmol/L).[25,32] The primary physiological response to declining plasma glucose concentration is a decrease in insulin secretion. With this, there is an increase in glucose production via increased gluconeogenesis and glycogenolysis by the liver and kidneys. There is also decreased insulin mediated glucose uptake by insulin-sensitive tissues such as the muscle[34, 32] due to decreased substrate availability.

The primary counter-regulatory response (second physiological defense) to a falling glucose level is an increase in glucagon release from the pancreatic alpha cells. This occurs at plasma glucose values of 65-70 mg/dl (3.6-3.9 mmol/L).[32] Glucagon stimulates hepatic glycogenolysis and gluconeogenesis thus raising blood glucose levels.

If glucose levels fail to return to normal, which is very uncommon in the absence of external causes, the next defense is the "fight or flight" response and release of stress hormones including epinephrine. Epinephrine, cortisol and growth hormone regulate glucose homeostasis in response to hypoglycemia at a plasma glucose value of 65-70 mg/dl (3.6-3.9 mmol/L).[33] Epinephrine stimulates hepatic glycogenolysis and gluconeogenesis. It mobilizes substrates for renal gluconeogenesis (lactate and amino acids from muscle and glycerol from fat), suppresses insulin secretion, and limits glucose uptake by the insulin sensitive tissues.

Glucagon and epinephrine are the fast-acting, counter-regulatory hormones that restore glucose levels to normal within minutes.[34] Cortisol and growth hormone[35] are slower and have an important role in prolonged hypoglycemia. Like epinephrine, they also limit glucose uptake by insulin-sensitive peripheral tissues, but their role is secondary.[34]

If plasma glucose continues to fall to 50-55 mg/dL (2.8-3.1mmol/L), the sympathoadrenal (sympathetic and adrenomedullary)[33] response is initiated, which triggers the neuroadrenergic symptoms.[27] Also, hunger initiates the defense mechanism of food ingestion.[25]

Table 3: Physiological Responses to Hypoglycemia

Plasma glucose mg/dl (mmol/l)	Response	Function in hypoglycemia
80–85 (4.4–4.7)	Decrease in Insulin	First physiological defense against hypoglycemia. Primary glucose regulatory factor
65–70 (3.6–3.9)	Increase in Glucagon	Second physiological defense against hypoglycemia. Primary glucose counter-regulatory factor
65–70 (3.6–3.9)	Increase in Epinephrine	Third physiological defense against hypoglycemia. Critical when glucagon is deficient
65–70 (3.6–3.9)	Increase in Cortisol and growth hormone	Not critical, slower counter-regulatory factor
50–55 (2.8–3.1)	Neurogenic Symptoms	Prompt behavioral defense of food intake
<50 (2.8)	Neuroglycopenic symptoms	Compromised behavioral defense

PHYSIOLOGIC CASCADE OF EVENTS DURING HYPOGLYCEMIA IN PEOPLE WITH DIABETES

People with T1DM and those with advanced T2DM no longer secrete enough insulin to meet fasting and meal time needs. This results in loss of the first (suppression of insulin) and second (glucagon secretion) physiological defenses against hypoglycemia.[36] When normal defenses to hypoglycemia are lost the body relies on epinephrine to prevent severe hypoglycemia. This is when the third physiological defense of increased adrenomedullary epinephrine secretion becomes so important.

However, with each hypoglycemic episode the body's epinephrine response becomes attenuated.[36] This defective counter-regulatory response increases the risk of subsequent hypoglycemia by 25 fold or greater.[37] This then can progress to "hypoglycemic unawareness". Here people lose the normal warning signs and symptoms of hypoglycemia.

The glycemic thresholds for the activation of counter-regulatory pathways against hypoglycemia are plastic. Patients who are relatively well controlled with lower A1C values may not perceive hypoglycemia till glucose levels drop below the physiological range for counter-regulatory mechanisms to come into play. Older adults also have a more narrow range between hypoglycemia awareness and severity of hypoglycemia, which puts them at even higher risk for adverse outcomes from hypoglycemia.

People with poorly controlled diabetes are used to higher blood glucose, and may develop symptoms at much higher glucose values when there is an attempt to intensify therapy for better glycemic control. When a person feels hypoglycemic when the glucose is normal or high, it is termed "pseudo-hypoglycemia". While this glucose level is not immediately dangerous it still may be a significant barrier to glucose control and should be addressed with patients while titrating therapy. Patients are more likely to be adherent to treatment if they understand why they develop these symptoms and are reassured that the treatment plan can be adjusted to minimize these symptoms.

IMPACT ON PEOPLE

Hypoglycemia has a blistering effect on the lives of people with diabetes and their families. Hypoglycemic symptoms can be disruptive, scary, and embarrassing. Hypoglycemia avoidance behaviors may lead to purposeful attempts at keeping blood glucose levels higher and defensive eating on part of the patients and their families, thus adversely affecting glycemic control. Further, fear of hypoglycemia in a child with diabetes can overcome parent's lives. About a third of parents reported checking their child's blood glucose level at night due to underlying fear of hypoglycemia, anxiety, and stress.[38]

PREVENTION OF HYPOGLYCEMIA

All patients should be taught to recognize the symptoms of hypoglycemia and how to treat it promptly and appropriately. Behaviors that predispose to hypoglycemia such as alcohol ingestion (by inhibiting gluconeogenesis), exercise or unusual exertion (by increasing glucose utilization by muscle), and skipped, irregular or inadequate meals, should be reviewed with the patient. Patients on insulin or insulin secretagogues as sulfonylureas/glinide drugs should be educated on the risk of hypoglycemia associated with these agents. Among oral agents for diabetes sulfonylureas pose the greatest threat and should be substituted if causing recurrent hypoglycemia.

Glyburide(long-acting insulin secretagogue) and sliding scale insulin are both on the 2012 Beers list, which is a list of medications that should be avoided in the elderly population to reduce their exposure to potentially inappropriate medications. [39]

Patients on intensive insulin therapy should be taught to replace insulin physiologically by taking basal/long acting insulin along with meal insulin to reduce the risk of hypoglycemia. The importance of taking meal insulin in relation to the meals should be emphasized. Patients should be encouraged to learn carb counting to enable them to "match the insulin" to their meals. Rapid-acting insulin analogs(lispro, aspart, glulisine) are preferred over regular insulin to reduce the risk of interprandial hypoglycemia as basal insulin analogs (glargine, detemir) are preferred over NPH to reduce the risk of nocturnal hypoglycemia.[22]

For exercise-related hypoglycemia, patients should be advised to check their blood glucose before, during and after exercise. The signs and symptoms of hypoglycemia (sweaty, shaky, palpitations) may be more difficult to identify in conjunction with exercise. This underscores the importance of frequent glucose monitoring. In addition, those who are participating in endurance aerobic exercise may find that they can develop hypoglycemia up to six to eight hours after the bout of exercise. Vigilance in monitoring and intake of carbohydrates should be considered.

Caloric intake is recommended before, during or after exercise to prevent hypoglycemia related to physical activity. Insulin dose should be adjusted for days of planned activity to avoid lows related to exercise. Glucose monitoring is the backbone of diabetes management, especially so in patients prone to hypoglycemia. A CGM (continuous glucose monitoring) device should be considered in patients with recurrent hypoglycemia or with hypoglycemia unawareness. Because CGM displays the direction and rate of change of blood glucose, patients can act proactively to avoid hypoglycemia.

HYPOGLYCEMIA-ASSOCIATED AUTONOMIC FAILURE (HAAF)

Initially described in 1991 in non-diabetic individuals,[40] recent antecedent hypoglycemia,[36] prior exercise, and sleep[41] can cause defective glucose counter-regulation and lead to hypoglycemia unawareness. This occurs by shifting the glycemic thresholds for the sympathoadrenal (and symptomatic) responses to subsequent hypoglycemia to lower plasma glucose concentrations. HAAF presents clinically as recurrent iatrogenic hypoglycemia. HAAF is a dynamic entity that can be reversed by absolute avoidance of hypoglycemia. Eliminating hypoglycemia for two to three weeks reverses hypoglycemia unawareness and improves the attenuated epinephrine response of defective glucose counter-regulation.[42]

TREATMENT

People with diabetes should be treated for hypoglycemia at the ADA-recommended glycemic threshold of ≤ 70 mg/dl (3.9 mmol/l).[19] When the person is conscious and able to respond, a fast acting carbohydrate (see Table 4: Examples of oral treatment for hypogycemia) is the treatment of choice. This will provide the fastest and most reliable route for glucose levels to return to normal. Consumption of snacks high in fat (such as ice cream or chocolate), or protein (cheese) may delay the absorption of carbohydrate),[43] and it will take longer for plasma glucose levels to normalize.

Initially 15-20 grams of carbohydrate should be sufficient to raise blood glucose level without causing hyperglycemia.[45] Therefore the "rule of 15" is often recommended. Ingest 15 grams of glucose, and check plasma glucose after 15 minutes to make sure that the level is rising. If the glucose level is still low, then another 15-20 grams of carbohydrate should be ingested. The glycemic response to oral glucose is usually transient and lasts less than 2 hours if hypoglycemia is secondary to insulin.[44]

Once the person is out of immediate danger from hypoglycemia after treatment with rapid acting carbohydrates, there should be some determination of the likelihood of recurrent symptoms. If the next meal is more than 2 hours away or if the symptoms occurred in the middle of the night it is recommended that the person have a long-acting carbohydrate with mixed nutrients such as milk, nuts, whole grains or fruits after the initial treatment to prevent recurrent symptoms.[45] Patients on alpha glucosidase inhibitors(acarbose, miglitol, voglibose) should be treated with pure glucose (dextrose) because these medications slow the digestion of other carbohydrates thereby decreasing their efficacy to raise blood sugar effectively.

With severe hypoglycemia, when the patient is incapable of ingesting glucose, injectable glucagon is the treatment of choice.[45] It is important for the friends/family to be able to recognize the signs of hypoglycemia and to administer glucagon. A glucagon injection increases blood glucose levels by stimulating hepatic glycogenolysis and gluconeogenesis. Dosing for children less than 20 kg is 0.5 mg or 20-30 mcg/kg/dose and for larger children and adults is 1 mg. It can be given intramuscularly (IM), subcutaneously (SQ) or intravenously (IV). It can be repeated in 20 minutes if needed but there is a high incidence of nausea and vomiting with rapid administration of high doses, especially via IV route.[45] All patients who are on insulin or who are at high risk for hypoglycemia should have a glucagon kit available. It is like the "epipen" of diabetes. The emergency medical system should always be contacted for severe hypoglycemia.

If the patient remains unresponsive or when medical personnel arrive, the standard therapy is 25 g of 50% glucose (D50W), if IV access is available.[45] In a hospital setting the standard parenteral therapy for hypoglycemia is IV glucose as 25 g of 50% glucose (dextrose).The glycemic response to IV glucose is transient and a subsequent glucose infusion is often required. Food should be given as soon as it is deemed safe for the patient to eat.

TABLE 4: Examples of oral treatment for hypoglycemia

15 g Food Choices
3 or 4 glucose tablets
1 tube of glucose gel
4 oz (1/2 cup) of fruit juice or regular soda
8 oz (1 cup) of skim milk
4 or 5 saltine crackers
1 tablespoon of honey or corn syrup
4 teaspoons of table sugar

TABLE 5: SORT evidence of key clinical recommendations

Key clincial recommendation	Strength of recommendation	References
Hypoglycemia is a serious complication of diabetes treatments	A	15,6,7
Hypoglycemia contributes to substantial health care system costs	B	8,10
The rule of 15 should be used for hypoglycemia that can be self treated	C	45
Severe hypoglycemia that is associated with inability to help oneself should be treated with injectable glucagon	C	45

IF THERE IS NO GLUCAGON OR IV DEXTROSE AVAILABLE FOR AN UNCONSCIOUS PATIENT WITH DIABETES

If there is no means to measure blood glucose in a comatose patient with diabetes, empirical treatment for hypoglycemia should be initiated. There is no efficacy or safety data for such a scenario. Some experts suggest applying glucose gel to the buccal mucosa. However, Gunning et.al,[46] found minimal buccal absorption of glucose. Others advocate sprinkling table sugar sublingually as sublingual sugar was well tolerated.[47]

CONCLUSION

Hypoglycemia is a serious complication of diabetes management. It is underestimated and unrecognized, especially if asymptomatic. It is not only detrimental to the patient but is also expensive to the health care system. Increased awareness is needed regarding hypoglycemia by promoting SMBG, advocating interactions during clinic visits directed towards identifying hypoglycemia by the health care providers and individualizing treatment regimens. By eliminating or decreasing the frequency of hypoglycemia, we may be able to take away the fear associated with hypoglycemia and improve the quality of life of our patients with diabetes. The rule of 15 should be used for hypoglycemia that can be self treated. Severe hypoglycemia that is associated with inability to help oneself should be treated with injectable glucagon.

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