Hypoglycemia in Diabetes Mellitus

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Abstract

Hypoglycemia is a frequent occurrence for many patients with diabetes treated with insulin or insulin secretagogues. Episodes of hypoglycemia have significant morbidity and mortality and are the main limiting factor for achieving near optimal glycemic control. Risk factors including impaired glucose counterregulation and hypoglycemia unawareness are largely preventable and/or reversible. This chapter summarizes our current knowledge of the epidemiology, pathogenesis, risk factors, and complications of hypoglycemia in patients with diabetes and discusses prevention and treatment strategies.

Keywords

Type 1 diabetes • Type 2 diabetes • Hypoglycemia • Hypoglycemia counterregulation

Abbreviations

CKD	Chronic kidney disease
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus

Contents

General Considerations

Normally, plasma glucose concentrations are maintained within a relatively narrow range throughout the day (usually between 55 and

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L. Poretsky (ed.), *Principles of Diabetes Mellitus*,
DOI 10.1007/978-3-319-18741-9_19

165 mg/dl [~3.0 and 9.0 mM/L]) despite wide fluctuations in the delivery (e.g., meals) and removal (e.g., exercise) of glucose from the circulation. This is accomplished by a tightly linked balance between glucose production and glucose utilization regulated by complex mechanisms.

Because of limited availability of ketone bodies and amino acids and the limited transport of free fatty acids across the blood-brain barrier, glucose can be considered to be the sole source of energy for the brain except under conditions of prolonged fasting. In the latter situation ketone bodies increase severalfold so that these may be used as an alternative fuel [1].

The brain cannot store or produce glucose and therefore requires a continuous supply of glucose from the circulation. At physiological plasma glucose levels, phosphorylation of glucose is rate limiting for its utilization. However, because of the kinetics of glucose transfer across the blood-brain barrier, uptake becomes rate limiting as plasma glucose concentrations decrease below the normal range. Consequently maintenance of the plasma glucose concentration above some critical level is essential to the survival of the brain and thus the organism. It is therefore not surprising that a complex physiological mechanism exists to prevent or correct hypoglycemia (vide infra). Nevertheless for many patients with type 1 or type 2 diabetes hypoglycemia is a frequent occurrence. Because of its possible detrimental effects on the central nervous system and the fear thereof by patients and care givers, hypoglycemia is considered to be the main limiting factor for achieving near optimal glycemic control [2].

Definition and Classification of Diabetic Hypoglycemia

The American Diabetes Association and Endocrine Society workgroup on hypoglycemia defined hypoglycemia in patients with diabetes as all episodes of an abnormally low plasma glucose concentration that expose the patient to potential harm [3]. No single threshold value was assigned to define hypoglycemia since this value may differ among patients. An alert value of <70 mg/dL (<3.8 mM/L), however, was chosen to draw the attention of patients and caregivers and also for use as a cutoff value in the classification of hypoglycemia in diabetes as outlined in Table 1 [3].

Table 1 Hypoglycemia categories as defined by the American Diabetes Association and the Endocrine Society [3]

Category	Definition
Documented symptomatic	An event during which typical symptoms of hypoglycemia are associated by a measured plasma glucose concentration ≤70 mg/dl[a]
Severe	An event requiring assistance of another person to administer carbohydrate, glucagon, or other resuscitative actions[b]
Asymptomatic	An event not accompanied by typical symptoms of hypoglycemia but with a measured plasma glucose concentration ≤ 70 mg/dl[a]
Probable symptomatic	An event during which symptoms of hypoglycemia are not accompanied by a plasma glucose measurement but that was presumably caused by a plasma glucose concentration ≤ 70 mg/dl[a]
Pseudo-hypoglycemia	An event during which the person with diabetes reports any of the typical symptoms of hypoglycemia with a measured plasma glucose concentration > 70 mg/dL but approaching that level

[a]70 mg/dl equals 3.9 mmol/l

[b]If plasma glucose measurements are not available during such an event; the neurological recovery attributable to the restoration of plasma glucose to normal is considered sufficient evidence that the event was induced by hypoglycemia

Epidemiology of Hypoglycemia

The exact incidence and prevalence of hypoglycemia in patients with diabetes is difficult to define because mild to moderate hypoglycemia may go unnoticed or unreported. Additionally,

hypoglycemia unawareness (the lack of appropriate autonomic warning signals of hypoglycemia before the development of neuroglycopenia – vide infra) can be found in 25% of patients with diabetes [4, 5]. The complete detection of chemical hypoglycemia would require continuous blood glucose measurements over prolonged periods. Studies using this approach have generally found that the frequency and duration of hypoglycemia, especially nocturnal hypoglycemia, are greater than what was previously thought [6, 7]. More reliable data are available from studies reporting severe hypoglycemia that is associated with loss of consciousness or requiring external assistance [3]. In general, the frequency of hypoglycemia is lower in people with T2DM than in those with T1DM [8–11]. For example, the UK Hypoglycemia Study Group reported severe hypoglycemia rates in patients with T2DM on insulin >2 years (10 episodes per 100 patient-year) to be far less than in patients with T1DM (<5 years disease duration, 110 episodes per 100 patient-year; >15 years disease duration, 320 episodes per 100 patient-year) [9].

Hypoglycemia occurs more often during intensified insulin therapy than during conventional insulin therapy. For example, during the 6.5 year follow-up in the DCCT trial [12], 35% of patients in the conventional treatment group and 65% of patients in the intensive treatment group had at least one episode of severe hypoglycemia.

Among patients with T2DM the frequency of hypoglycemia will vary by treatment modality. In patients treated with sulfonylureas the incidence of severe hypoglycemia has been reported to be approximately 1.5 episodes per 100 patient-years [13] and is more common with long-acting sulfonylureas such as glyburide [14]. Prandial insulins are associated with a greater frequency of hypoglycemia than are the long-acting so-called basal insulins [15]. Metformin, thiazolidinediones, dipeptidyl-peptidase-4 inhibitors, glucagon-like 1 mimetics, and sodium glucose cotransporter 2 inhibitors do not increase the risk of hypoglycemia when used without insulin or insulin secretagogues (sulfonylureas and meglitinides) [16].

Hypoglycemia Counterregulation

Normal Hypoglycemia Counterregulation and Hypoglycemia Awareness

Glucose counterregulation refers to the sum of the body's defense mechanisms which prevent hypoglycemia from occurring and which restore euglycemia. Hypoglycemia awareness refers to the symptomatic responses to hypoglycemia that alert the patient to the declining blood glucose levels.

In normal postabsorptive individuals, i.e., after an overnight fast, the sum of glucose release by liver and kidney nearly equals systemic glucose utilization so that plasma glucose concentrations remain relatively stable. Since insulin suppresses both hepatic and renal glucose release [17, 18] and stimulates glucose uptake, in insulin-sensitive tissues such as muscles, excessive exogenous insulin administration can cause systemic glucose utilization to exceed systemic glucose release so that plasma glucose concentrations decrease.

As the plasma glucose levels decrease there is a characteristic hierarchy of responses [19] (Fig. 1). Reduction of insulin secretion, the first in the cascade of hypoglycemia counterregulation [2, 4], derepresses glucose production and reduces glucose utilization. When plasma glucose levels decline to approximately 70 mg/dl (3.8 mM/L), there is an increase in the secretion of counterregulatory hormones (glucagon, epinephrine, growth hormone, cortisol) [19–22]. Glucagon and epinephrine have immediate effects on glucose kinetics whereas the effects of growth hormone and cortisol are delayed by several hours [23, 24] (Fig. 2).

Under normal physiological conditions, these responses prevent a further decrease in plasma glucose concentrations and restore normoglycemia. Decreases to ~60 mg/dl (3.4 mM/L) usually evoke the so-called autonomic warning symptoms [25, 26] (hunger, anxiety, palpitations, sweating, nausea) which if interpreted correctly lead a person to eat and prevent more serious hypoglycemia.

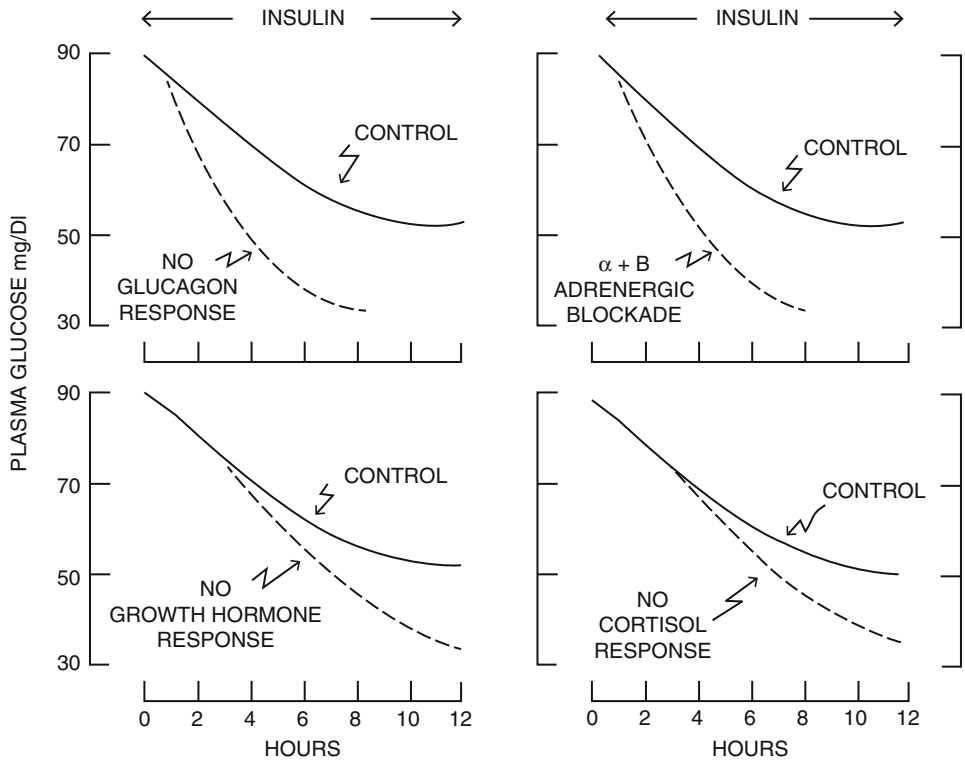

Fig. 1 Effect of lack of glucagon, catecholamine (α- and ß-adrenergic blockade), growth hormone, and cortisol responses on insulin-induced hypoglycemia in nondiabetic volunteers studied with pituitary-adrenal-pancreatic clamp (From Gerich J. Glucose counterregulation and its impact on diabetes mellitus. Diabetes 37:1608–1617, 1988. Copyright © 1988 The American Diabetes Association. Used with permission)

However, clues of hypoglycemia may vary considerably from person to person [27]. If, for some reason, plasma glucose levels decrease to about 55 mg/dl (~3.0 mM/L), neuroglycopenic signs/symptoms of brain dysfunction (blurred vision, slurred speech, glassy-eyed appearance, confusion, difficulty in concentrating) would occur [25, 26]. Further decreases can produce coma and values below 30 mg/dl (~1.6 mM/L), if prolonged, can cause seizures, permanent neurological deficits, and death. However, it should be pointed out that in otherwise healthy/young (<45 years) individuals, glucose levels averaging 35 mg/dl (~2.0 mM/L) have been maintained for as long as 8 hours without any known long-term adverse effects [28] and chronic levels as low as 24 mg/dl (1.3 mM/L) in insulinoma patients have been observed in association with apparently normal cerebral function [29].

Hypoglycemia Counterregulation and Hypoglycemia Awareness in T1DM

In T1DM, the defense against hypoglycemia is markedly deranged. First, as endogenous insulin secretion becomes progressively deficient over the first few years of T1DM, the appearance of insulin in the circulation becomes unregulated since it relies on absorption from subcutaneous injection sites. Consequently, as plasma glucose levels are falling, insulin levels do not decrease. Second, glucagon responses to hypoglycemia are lost early in the course of T1DM [30, 31]. This defect coincides with the loss of insulin secretion and is therefore the rule in people with T1DM [32]. Nonetheless, glucose counterregulation appears to be adequate in such patients probably due to compensatory counterregulation by epinephrine [33]. After a few more years epinephrine responses to hypoglycemia are also commonly

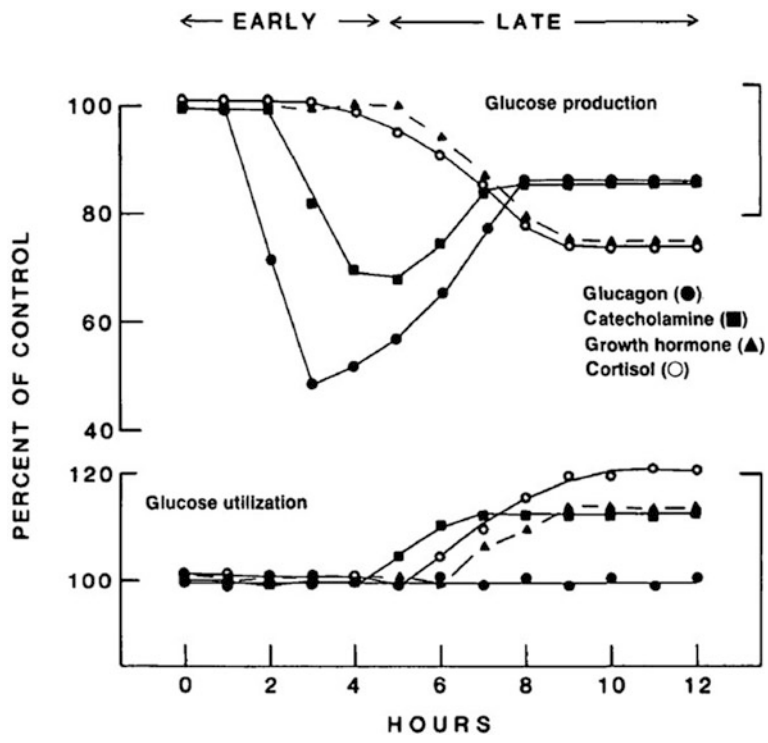

Fig. 2 Effect of lack of glucagon, catecholamine (α- and ß-adrenergic blockade), growth hormone, and cortisol responses on counterregulatory changes in glucose production and glucose utilization in nondiabetic volunteers studied with pituitary-adrenal-pancreatic clamp (From Gerich J. Glucose counterregulation and its impact on diabetes mellitus. Diabetes 37:1608–1617, 1988. Copyright © 1988 The American Diabetes Association. Used with permission)

reduced [30, 34, 35]. When compared to patients with a defective glucagon response but normal epinephrine responses, patients with a combined defect in glucagon and epinephrine responses have at least a 25-fold increased risk for severe iatrogenic hypoglycemia [36, 37]. The combined defect in glucagon and epinephrine responses is therefore considered as the syndrome of impaired hypoglycemia counterregulation [2]. This is now known to be associated with impaired glucose production in both liver and kidney [38]. Pathophysiological mechanisms might be different when only glucagon responses are impaired and epinephrine responses are intact. Since glucagon affects exclusively the liver whereas epinephrine has a temporary effect on the liver but a sustained effect on the kidney, only hepatic glucose production might be decreased under these conditions.

In addition to impaired glucose counterregulation, people with T1DM often suffer from hypoglycemia unawareness. These patients no longer have autonomic warning symptoms of developing hypoglycemia which previously prompted them to take appropriate action (i.e., food intake before severe hypoglycemia with neuroglycopenia occurs). Hypoglycemia unawareness has been reported to occur in about 50% of patients with long-standing diabetes and estimated to affect 25% overall [39–42]. Hypoglycemia unawareness is associated with sixfold increased risk for severe hypoglycemia [40].

The mechanism of the loss of glucagon response is not completely understood. Recent evidence suggests that similar to insulin secretion from beta cells, glucagon secretion is influenced by ATP-regulated potassium (K_{ATP}) channels that are also present in glucagon-producing alpha cells [43, 44] and that glucose-induced closure of these channels leads to suppression of glucagon secretion. Abnormally increased channel activity found in patients with diabetes may explain the inverted glucose response and the loss of appropriate glucagon counterregulation [45]. The pathogenesis for impaired catecholamines and other hormone responses is also not entirely clear but may have been set in motion from recurrent hypoglycemia that (a) impairs glucose sensing in the ventromedial hypothalamus (a brain region that plays a

major role in controlling the counterregulatory responses to hypoglycemia) and (b) leads to cellular adaptation which contributes to hypoglycemia unawareness and reduced adrenomedullary response to subsequent hypoglycemia [46]. Additionally there is impairment of beta-adrenergic sensitivity leading to impaired responsiveness to endogenous catecholamines which in turn contributes to hypoglycemia unawareness [47–49].

Hypoglycemia Counterregulation and Hypoglycemia Awareness in T2DM

In T2DM the hormonal glucose counterregulation is usually less impaired than in T1DM [50–52]. Nevertheless defects can be seen when patients become markedly insulin deficient [53]. One important factor for the nearly intact hormonal glucose counterregulation in T2DM may be some residual albeit abnormal insulin secretion. Since antecedent hypoglycemia is one of the main factors for impaired epinephrine responses to hypoglycemia and since hypoglycemia rarely occurs in people with T2DM because of their intact glucagon response, epinephrine responses usually also remain intact. Once patients with T2DM become markedly insulin deficient, glucagon responses are commonly impaired. However, in contrast to patients with T1DM, the epinephrine responses usually remain intact and in fact may partially compensate for the reduced glucagon responses to hypoglycemia [52, 54]. This may explain the reduced risk for severe hypoglycemia in patients with T2DM compared to patients with T1DM.

Risk Factors for Hypoglycemia

Table 2 summarizes important causes and risk factors for hypoglycemia. Treatment with insulin or insulin secretagogues (sulfonylureas and meglitinides) is the main cause for hypoglycemia in patients with diabetes. Factors that lead to absolute or relative insulin excess in patients who are treated with insulin or insulin secretagogues are summarized in Table 3 [55, 56].

Table 2 Hypoglycemia causes and risk factors

Diabetes related factors
Treatment with insulin or insulin secretagogues leading to absolute or relative insulin excess (see Table 3)
Defective hypoglycemia counterregulation and hypoglycemia unawareness
Potential coexisting factors
Deficiency of hormones needed for hypoglycemia counterregulation (e.g., adrenal insufficiency and growth hormone deficiency)
Chronic kidney disease (see Table 4)
Hepatic or cardiac failure
Drugs and alcohol
Gastric bypass surgery
Extremes of age (children and elderly)
Pregnancy (usually first trimester)
Hospitalization (e.g., new NPO status, medications dispensing errors and interruption of tube feeding or parenteral nutrition)
Alimentary factors
Low body mass index
Anorexia nervosa
Malnutrition
Malabsorption (e.g., celiac disease and pancreatic exocrine insufficiency)
Critical illness (e.g., severe burns, severe infections, sepsis, mechanical ventilation)
Tumor-associated hypoglycemia
Increased insulin (insulinomas)
Decreased gluconeogenesis (e.g., advanced metastatic tumor in the liver)
Insulin-like growth factor II mediated hypoglycemia (e.g., secreting fibrosarcoma)
Autoimmune hypoglycemia
Insulin-binding antibodies
Activating insulin receptor antibodies

Impaired glucose counterregulation and hypoglycemia unawareness significantly increase the risk of hypoglycemia in patients who are treated with insulin or insulin secretagogues. The risk of severe hypoglycemia is increased 25-fold in patients with impaired hypoglycemia counterregulation [36] and increased sixfold in those with hypoglycemia unawareness [40].

CKD with a GFR < 60 ml/min/1.73 m^2 is found in up to 40% of people with diabetes. It is an independent risk factor for hypoglycemia and augments the risk for hypoglycemia that is already

Table 3 Risk factors for absolute or relative insulin excess in patients with diabetes treated with insulin or insulin secretagogues

Errors and medication administration issues
Excessive doses
Lack of diabetes education (e.g., injecting insulin into lipohypertrophy or intramuscularly and patient unwilling to attend education program or use technology)
Poor adherence to regimen or distraction (e.g., miscalculated carbohydrate content or taking wrong type of insulin)
Functional neurological deficit (e.g., cognitive or visual impairment leading to incorrect dosing)
Sudden decrease in drugs that cause hyperglycemia without adjusting insulin or insulin secretagogues dose (e.g., discontinuing glucocorticosteroids or glucose infusion during hospitalization in insulin treated patients)
Mismatch between insulin or insulin secretagogues and food absorption
Ill-timed insulin doses
Missed meals
Gastroparesis
Post gastric bypass surgery
Gastrointestinal disease with malabsorption (e.g., celiac disease)
Decreased clearance (e.g., renal impairment, liver failure and hypothyroidism)
Decreased glucose production (e.g., liver or kidney disease and alcohol ingestion)
Increased glucose removal (e.g., exercise and use of sodium glucose cotransporter 2 inhibitors)
Increased insulin sensitivity (e.g., exercise, weight loss and use of insulin sensitizers)
Intentional hypoglycemia (overdose)

Table 4 Risk factors for hypoglycemia due to chronic kidney disease

Expected/presumed further impairment of counterregulation & hypoglycemia unawareness
Reduced capacity for renal glucose release due to reduced renal mass
Decreased availability of gluconeogenic substrates and reduced hepatic glycogen stores due to malnourishment and/or muscle wasting
Increased risk for hypoglycemia unawareness due to associated autonomic dysfunction
Altered Insulin degradation and clearance
Decreased renal insulin clearance
Decreased hepatic insulin metabolism
Altered drug pharmacokinetics
Decreased excretion of drugs and/or their metabolites (e.g., sulfonylureas)
Increased sensitivity to drugs bound to albumin in hypoalbuminemic states (e.g., sulfonylureas)
Caloric deprivation and substrate deficiency
Uremic anorexia and vomiting
Indigestion and decreased intestinal absorption
Intradialytic amino acid loss in patients receiving hemodialysis
Increased risk of concomitant hypoglycemic conditions
Hepatic dysfunction
CHF
Infections
Hemodialysis induced hypoglycemia
Improved insulin sensitivity
Diffusion of glucose from plasma into erythrocytes due to changes in PH from HCO_3 in dialysate
Loss of glucose, substrates (e.g., Alanine), and catecholamines into the dialysate
Interruption of usual eating and activity patterns (eating is discouraged or prohibited during dialysis)
Severe albuminuria (urinary albumin excretion rate >300 mg/24 h or albumin/creatinine >300 mg/g [>30 mg/mmol])

present in people with diabetes by adding multiple risk factors summarized in Table 3 [55].

Many nondiabetic pharmacological agents have also been implicated as a cause for hypoglycemia. Most of the evidence for that is from case reports or single cohort studies many of which have confounding factors such as concomitant use of insulin or sulfonylurea or presence of chronic kidney disease. A study that systematically reviewed the literature for reported drugs found 448 eligible studies describing nearly 2700 cases of hypoglycemia associated with 164 different drugs other than alcohol, insulin, or insulin secretagogues [57]. When taking into account the quality of evidence for the association between a particular drug and hypoglycemia (such as presence or absence of confounders, dose–response relationships, challenge/rechallenge designs, and randomized controlled trials of drug vs. placebo), none of the drugs had association supported by high-quality evidence and only seven were supported by moderate-quality evidence including cibenzoline, clinafloxacin, gatifloxacin, glucagon (when used as endoscopic premedication), indomethacin, pentamidine, and quinine. All other

drugs had low or very low evidence supporting association with hypoglycemia. The most commonly cited drugs to be associated with hypoglycemia were quinolones, pentamidine, quinine, beta blockers, and angiotensin-converting enzyme inhibitors [57].

Gastric bypass surgery is becoming more common as a treatment for morbid obesity. Many of these patients have T2DM. Hypoglycemia has been reported to occur in some patients usually in the second or third hour postprandially [58–61]. The exact mechanism is currently being investigated but could be multifactorial and related to the changes that follow surgery such as decreased caloric intake, weight loss, and a change in the nutrient composition, flora, and transit time in the gastrointestinal tract [62–64]. Studies have also shown decreased ghrelin secretion, exaggerated release of glucagon-like peptide-1 (GLP-1), and possibly other gastrointestinal hormone changes [65–69] that could enhance the release of insulin and/or inhibit the release of glucagon. Additionally, several severe cases of hyperinsulinemic hypoglycemia presenting as postprandial hypoglycemia after Roux-en-Y gastric bypass surgery have been published [70–72]. The mechanism by which this occurs is not entirely clear. Examination of pancreatic specimens obtained following partial pancreatectomy performed to treat these cases implicated nesidioblastosis or islet cell hyperplasia as a possible cause [70, 71]. A subsequent report, however, found no evidence of increased islet cell mass or neogenesis when some of these specimens were reexamined and compared with those of well-matched subjects [73]. The report suggests that hypoglycemia in these patients is related to a combination of gastric dumping and inappropriately increased insulin secretion due to either failure of beta cells to adapt to changes post gastric bypass or as an acquired phenomenon. It is also not clear whether patients with diabetes are more or less likely to suffer from post-gastric-bypass hypoglycemia when compared to other patients. Reversal of gastric bypass improved hypoglycemia in some [74, 75] but not all cases [76]. Experimentally, hypoglycemia following gastric bypass was corrected by administration of exendin-[9–39], a GLP-1 receptor antagonist [77].

Manifestations of Hypoglycemia

Manifestations of hypoglycemia are nonspecific and can sometimes be noted by observers rather than patients themselves. They can be categorized as autonomic (mostly due sympathetic neural activation) and neuroglycopenic (due to brain glucose deprivation) (Table 5). Autonomic manifestations precede neuroglycopenic and allow patients to recognize and self-treat hypoglycemia. Patients with hypoglycemia unawareness are likely to have hypoglycemia manifesting at an advanced stage with neuroglycopenic symptoms that may prevent self-treatment. Nocturnal hypoglycemia can manifest with disturbed sleep, nightmares, and "waking in sweat." Acute severe hypoglycemia can present with a range of neurological and cardiovascular complications as detailed below.

Complications of Hypoglycemia

An episode of severe hypoglycemia can be detrimental or even fatal due to its effects on the central nervous system. At plasma glucose concentration

Table 5 Signs and symptoms of hypoglycemia

Autonomic (sympathoadrenal)
Anxiety and irritability
Fine tremor
Tachycardia
Hunger
Cold sweats
Paresthesias
Headache
Neuroglycopenic
Cognitive impairment
Mood and behavioral changes
Fatigue and weakness
Lightheadedness and dizziness
Visual changes (blurred vision, diplopia)
Slurred speech
Seizures
Coma

of ~55 mg/dl (~3 mM/L), cognitive impairment and EEG changes are demonstrable. Decreases below 40 mg/dl (~2.5 mM/L) result in sleepiness and gross behavioral (e.g., combativeness) abnormalities. Further decreases can produce coma and values below 30 mg/dl (~1.6 mM/L) if prolonged can cause seizures, permanent neurological deficits, and death [78–80] (Fig. 3). It has also been suggested that repeated episodes of severe hypoglycemia may lead to subtle permanent cognitive dysfunction [81].

Hypoglycemia also affects the cardiovascular system creating cardiac repolarization abnormalities with lengthening of the QT interval and also ST wave changes, and increasing risk of arrhythmias induced by associated catecholamines response [82, 83]. Additionally, it is found to promote inflammatory and thrombotic responses and to impair endothelial function and has therefore been implicated in precipitating myocardial infarctions and strokes [83–86]. On the other hand, there is currently a suggestion that recurrent hypoglycemia, by attenuating the catecholamines response to future severe hypoglycemia, may have a positive (adaptive) aspect by reducing risk of lethal cardiac complications that could have otherwise been induced by severe catecholamines response [87]. This suggestion is based on the data demonstrating reduced risk of lethal cardiac arrhythmias induced by severe hypoglycemia in diabetic rats previously exposed to recurrent moderate hypoglycemia [88], and also reduced risk of death in T2DM patients on intensive treatment arm who experienced more hypoglycemia in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) and the Action in Diabetes and the Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trials [89, 90].

In patients with underlying eye disease hypoglycemia has been shown to trigger retinal hemorrhages [91]. Hypoglycemia is also associated with more short-term disability and higher health care costs [92, 93]. Severe hypoglycemia has been reported to be at least a contributing factor to the cause of death in 3–13% of patients with T1DM which include motor vehicle accidents, injuries at work, etc. [94, 95]. Severe hypoglycemia due to sulfonylureas has been shown to have a mortality between 4% and 7% [96, 97].

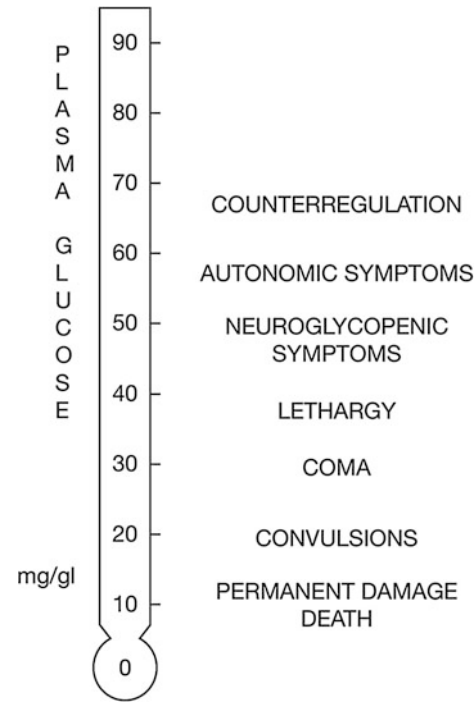

Fig. 3 Consequences of hypoglycemia (Adapted from: Gerich J. Glucose counterregulation and its impact on diabetes mellitus. Diabetes 37:1608–1617, 1988. Copyright © 1988 The American Diabetes Association. Used with permission)

In addition to its physical morbidity and mortality, recurrent hypoglycemia may be also associated with psychosocial morbidity. In fact many patients with diabetes are as much afraid of severe hypoglycemia as they are of blindness or renal failure [41].

Management of Hypoglycemia

Treatment

Treatment is aimed at restoring euglycemia, preventing recurrences and, if possible, alleviating the underlying cause.

In an insulin-taking diabetic patient with mild hypoglycemia due to a skipped meal, 15–20 g oral carbohydrate every 15–20 min until the blood

glucose is above 80 mg/dl (4.5 mM/L) constitutes adequate treatment (Table 6) [98, 99]. Examples for oral carbohydrate source are presented in Table 7. In a patient with more severe hypoglycemia resulting in obtundation, where oral administration of carbohydrate might result in aspiration, 1 mg of glucagon administered subcutaneously or intramuscularly might be sufficient to raise the blood glucose and revive the patient so that oral carbohydrate may be given. Comatose patients should receive intravenous glucose (25 g bolus, followed by an infusion at an initial rate of 2 mg/kg/min, roughly 10 g/h) for as long as necessary for the insulin or sulfonylurea to wear off (Table 8). Sulfonylurea overdose can result in prolonged hypoglycemia requiring sustained intravenous glucose infusion aimed at keeping the blood glucose at ~80 mg/dl (~4.5 mM/L) to avoid hyperglycemia which would cause further stimulation of insulin secretion thus setting in motion a vicious cycle. Blood glucose levels should be monitored initially every 15–20 min and subsequently at 1–2 h intervals. Rarely diazoxide or a somatostatin analogue may be needed to inhibit insulin secretion [100]. Where other drugs may be involved, they should be discontinued if possible (i.e., sulfonamides in a patient with renal insufficiency). In other conditions, the underlying disorder should be treated (e.g., sepsis, heart failure, endocrine deficiency) and the blood glucose supported.

Table 6 Treatment of hypoglycemia in nonhospitalized patients (From Alsahli M. Gerich JE. Hypoglycemia. Endocrinology and Metabolism Clinics of North America. 42(4):657–76, 2013. Used with permission)

Patient conscious and able to swallow
1. Consume 15–20 g of rapidly absorbed carbohydrates (see Table 7 for examples)
2. Check blood glucose 15–20 min later and retreat if hypoglycemia not reversed
3. Follow successful treatment (blood glucose above 70–80 mg/dl [3.8–4.5 mM/L]) with a meal or snack within 30–60 min
Patient cannot swallow/at risk for aspiration, combative, or with decreased level of consciousness
1. Administer Glucagon 0.5–1 mg SC or IM. Glucagon may cause nausea and vomiting. Turn patient on their side during treatment to avoid aspiration
2. Check blood glucose 15–20 min later and retreat if hypoglycemia not reversed (patient may be able to take oral carbohydrates then)
3. Follow successful treatment with a meal or snack within 30–60 min

Table 7 Examples of 15–20 g oral carbohydrates for treatment of hypoglycemia

Pure glucose or dextrose (e.g., Glucose tablet, Glucose gel and glucose liquid) is the preferred choice especially for patients on alpha-glucosidase inhibitors that will slow digestion and absorption of other forms of carbohydrates
Beverages containing rapidly absorbed carbohydrates (e.g., 1/3–1/2 cup of fruit juice or regular soft drink, 1 cup of skim milk or sports drink)
Food containing carbohydrates with minimal fat, protein or fiber content (e.g., 1 tablespoon table sugar or honey, 2 tablespoons raisins, 2–3 pieces of hard candy, 3 squares graham crackers, 7 lifesavers, 7 gummy bears and 7 jelly beans)

Prevention of Recurrences

Conventional Measures

For prevention of recurrences, it is important to determine whether hypoglycemia was an isolated event or whether it has occurred before. If so, how frequently? Is there any pattern to occurrences, i.e., always at night? For how long have the hypoglycemic episodes been occurring? Are they associated with hypoglycemic warning symptoms? If so, usually at what level of glycemia is hypoglycemia recognized? Are there any precipitating factors, i.e., exercise, skipped meal, erroneous insulin injection, alcohol ingestion, recent weight loss, or other precipitating factors (see above)? Did the patient spontaneously recover? What did the patient do to prevent recurrences or relieve symptoms? What is the patient's occupation?

Obviously, if these questions reveal precipitating factors for hypoglycemia these should be eliminated (Table 9). However if careful testing does not reveal any apparent precipitating factors but reveals hypoglycemia unawareness instead, chances are relatively high that there is also impaired hypoglycemia counterregulation, especially in a patient with frequent hypoglycemic episodes. Consequently the question arises how to treat the affected patients.

Table 8 Treatment of hypoglycemia in hospitalized patients (From Alsahli M. Gerich JE. Hypoglycemia. Endocrinology and Metabolism Clinics of North America. 42(4):657–76, 2013. Used with permission)

1. Assess level of consciousness, swallowing, NPO status, and availability of venous access
Patient alert and able to swallow ➔ 15–20 g oral carbohydrates or 25 g of 50% Dextrose IV bolus
Patient alert and NPO ➔ 25 g of 50% Dextrose IV bolus
Patient with decreased level of consciousness or unable to swallow ➔ 25 g of 50% Dextrose IV bolus
Patient with decreased level of consciousness or unable to swallow or is NPO and has no venous access ➔ glucagon 1 mg SC or IM plus establish venous access for further treatment. Glucagon may cause nausea and vomiting. Turn patient on their side during treatment to avoid aspiration
2. Recheck blood glucose every 15–20 min and retreat until euglycemia is restored (blood glucose >70–80 mg/dl [3.8–4.5 mM/L])
3. Follow successful treatment with a meal or snack within 30–60 min unless the patient is NPO
4. Glucose infusion at initial rate of 2 mg/kg/min aimed at keeping the blood glucose at ~80 mg/dl (~4.5 mM/L) should be considered soon following initial treatment if patient is NPO or recurrent or prolonged hypoglycemia is expected

Table 9 Measures to reduce hypoglycemia

Identification and management of risk factors
Education programs for patients and as needed for their family members, friends, or coworkers
Individualization of glycemic goals for both A1C and SMBG
At risk patients should carry or wear emergency medical identification
Continuous glucose monitoring for appropriate patients
Judicious management of insulin therapy
Adjusting regimen according to glycemic pattern and life style
Avoiding sliding scales and insulin stacking
Switching from regular to rapid insulin with meals and from NPH to long-acting analogues as basal insulin
Considering basal-bolus with correction scale instead of fixed-ratio regimens
Carbohydrate counting for appropriate patients
Insulin pump therapy for appropriate patients

The principles of intensive therapy – patient education, self-monitoring of blood glucose (SMBG), and an insulin regimen that provides basal insulin levels with prandial increments – still apply to the majority of patients who require insulin to control their diabetes. However, glycemic goals must be individualized according to the frequency of hypoglycemia. Since the prevention or correction of hypoglycemia normally involves dissipation of insulin and activation of counterregulatory hormones as discussed above, it follows that patients with impaired glucose counterregulation are extremely sensitive to very little insulin in excess of its requirement resulting in hypoglycemia. It is therefore generally accepted that normoglycemia is not a reasonable goal for such patients [101, 102]. American Diabetes Association most recent practice guidelines still recommend A1C goal for most adults to be <7% but also recognize that less stringent goals (such as <8%) may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced complications, and comorbid conditions [103]. Approximately 25–35 mg/dL (1.5–2.0 mM/L) upward adjustment of SMBG goals is needed to increase in A1C by one percentage point.

Diabetes education in general and programs that focus on hypoglycemia have proven to be helpful and should be implemented to involve patients and their family or friends [104–106]. Patients need to learn basic skills such as the need to check blood glucose regularly, to carry supplies for treating hypoglycemia with them all the time, to have glucagon emergency kit available, to carry or wear medical alert identification, and to plan better for exercise. Advanced skills such as insulin dose adjustments and the use of continuous glucose monitors and/or insulin pumps can also be taught for many motivated and capable patients.

Substitution of preprandial short-acting (regular) insulin for rapid insulin (lispro, aspart, glulisine) may reduce the frequency of hypoglycemic episodes by reducing prolonged postprandial hyperinsulinemia [107]. Furthermore, substitution of intermediate-acting insulin (NPH) for long-acting insulin analogue (glargine or detemir) has been shown to reduce the frequency of hypoglycemia in patients with type 1 or type 2 diabetes [108–110]. In appropriate candidates,

hypoglycemia can be reduced by insulin pump therapy despite the fact that glycemic control could actually improve with such therapy [111, 112]. Additionally, implementation of continuous glucose monitoring systems alone or in conjunction with insulin pump therapy has shown promising results in preventing hypoglycemia [113–115] and should be considered for appropriate patients.

If these measures result in strict avoidance of hypoglycemia, hypoglycemia awareness may be restored [116]. This might be due to an improvement in beta-adrenergic sensitivity [117]. Although strict avoidance of hypoglycemia does not improve glucagon responses to hypoglycemia in T1DM [116, 118–121], it does increase epinephrine responses [118, 121]. This however seems to be limited to patients with a diabetes duration of less than ~15 years. In patients with T1DM of more than 15 years' duration, epinephrine responses may remain markedly impaired [116, 119]. Thus there is unfortunately no conventional therapy available to reverse impaired hypoglycemia counterregulation in such patients. Although the effects of avoidance of hypoglycemia have not been studied in patients with T2DM, it seems likely that these are similar to those in T1DM.

Pancreas/Islet Transplantation

Because of the irreversibly impaired hypoglycemia counterregulation in long-standing T1DM, pancreas or islet transplantation has been proposed as a possible treatment in patients who suffer from recurrent severe hypoglycemia despite all conventional measures [122–124]. Both procedures have been shown to lower the risk of hypoglycemia [125, 126]. Pancreatic transplantation is usually reserved for patients undergoing simultaneous kidney transplantation. It has been found to improve glucagon responses to hypoglycemia in most studies [127–133] and to improve or normalize epinephrine responses [129–131, 133–135]. Furthermore, it has been reported to improve hypoglycemia awareness in T1DM [125, 133].

Experience in the effects of islet transplantation on hypoglycemia counterregulation and awareness is limited and inconsistent [126]. Hypoglycemia awareness was found to improve in some studies [123, 136]. It seems that glucagon responses remain impaired after islet transplantation [122, 125, 137], However, epinephrine responses were reported to improve responses in some [123] but not all studies [137].

Although pancreas transplantation and islet transplantation may be promising alternatives for some patients with recurrent severe hypoglycemia, risk-benefit ratios should be very carefully analyzed because of the invasive nature of these forms of therapy and the necessity for potent lifelong immunosuppression.

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