Chapter 19
Hypoglycemia in Diabetes Mellitus

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General Considerations

As indicated earlier in Chapter 2, human plasma glucose concentrations are maintained within a relatively narrow range throughout the day (usually between 55 and 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.

Hypoglycemia is to be avoided to protect the brain and prevent cognitive dysfunction. 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 several fold so that these may be used as an alternative fuel.[1]

It is generally thought that the brain cannot store or produce glucose and therefore requires a continuous supply of glucose from the circulation. Recent studies in animals, however, suggest that the brain may not contain negligible quantities of glycogen.[2] 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 has evolved to prevent or correct hypoglycemia (vide infra). Nevertheless for many patients with type 1 or type 2 diabetes, hypoglycemia is a frequent complication. Because of its possible detrimental effects on the central nervous system, hypoglycemia is considered to be the main limiting factor for achieving near-normal glycemic control.[3]

Epidemiology of Hypoglycemia

Type 1 Diabetes

The reported incidence of hypoglycemia varies considerably among studies. In general, patients with type 1 diabetes practicing conventional insulin therapy have an average of ~1 episode of symptomatic hypoglycemia per week, whereas those practicing intensive insulin therapy have ~2 such episodes per week.[4] Thus, over 40 years of type 1 diabetes, the average patient can be projected to experience 2000–4000 episodes of symptomatic hypoglycemia. The complete detection of chemical hypoglycemia (commonly defined as a capillary blood glucose concentration < 50 mg/dl[5]) would require continuous blood glucose measurements over prolonged periods.

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The few studies using this approach have generally found that the frequency and duration of hypoglycemia, especially the nocturnal hypoglycemia, is greater than what was previously thought.[6,7]

For the purpose of reporting hypoglycemia in clinical trials, the American Diabetes Association has developed five categories as outlined in Table 19.1.[8] The incidence of severe hypoglycemia has been determined more precisely since it is defined as that associated with unconsciousness or requiring external assistance. It occurs more often during intensified insulin therapy than during conventional insulin therapy. For example, during the 6.5-year follow-up in the Diabetes Control and Complication Trial (DCCT),[9] 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. This corresponds to about 60 episodes per 100 patient-years in patients being managed to achieve optimal glycemic control by intensive insulin therapy and to about 20 episodes per 100 patient-years in conventionally treated patients.[9] In a recent meta-analysis of 14 studies, which included 1028 patients on intensified insulin therapy and 1039 patients on conventional insulin therapy, the median incidence of severe hypoglycemia was 7.9 and 4.6 episodes per 100 patient-years in the two treatment groups, respectively; the combined odds ratio was 2.99 ($p < 0.0001$).[10] However the increased incidence of severe hypoglycemia in the intensified treatment group was no longer evident as soon as glycosylated hemoglobin was included in a multivariate regression analysis.[10]

Table 19.1 Hypoglycemia categories as defined by the American Diabetes Association[8]

Category	Definition
Documented symptomatic	An event during which typical symptoms of hypoglycemia are associated with a measured plasma glucose concentration ≤70 mg/dl[a]
Severe	An event requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions[b]
Asymptomatic	An event not accompanied by typical symptoms of hypoglycemia but by 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 determination but that was presumably caused by a plasma glucose concentration ≤70 mg/dl[a]
Relative	An event during which the person with diabetes reports any of the typical symptoms of hypoglycemia and interprets those as indicative of hypoglycemia, but with a measured plasma glucose concentration >70 mg/dl

[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 a sufficient evidence that the event was induced by hypoglycemia

Type 2 Diabetes

Patients with type 2 diabetes generally experience less frequent severe hypoglycemia than those with type 1 diabetes. Both the UKPDS[11] and the Kumamoto study[12] demonstrated a much lower incidence of severe hypoglycemia in insulin-treated patients with type 2 diabetes than what was reported in the DCCT[9] for patients with type 1 diabetes despite similar glycemic control. In the UKPDS, which followed 676 patients with type 2 diabetes on insulin therapy for 3 years, the incidence was 0.83 episodes per 100 patient-years. In the Kumamoto study, which followed 52 type 2 diabetic patients on intensive insulin therapy for over 6 years, no severe hypoglycemic episode was reported. However, one retrospective study, which directly compared the incidence of severe hypoglycemia in 104 insulin-treated patients with type 2 diabetes with that in 104 equally well-controlled type 1 diabetic patients, found a similar incidence of severe hypoglycemia.[13] A later study also found that hypoglycemia requiring emergency assistance was as common in patients with insulin-treated type 2 diabetes as in patients with type 1 diabetes.[14]

In patients with type 2 diabetes treated with sulfonylureas, the incidence of severe hypoglycemia has been reported to be approximately 1.5 episodes per 100 patient-years.[15] Its frequency increases with the potency and

duration of action of the sulfonylurea, being greatest for second-generation sulfonylureas, glimepiride, glyburide, and glipizide averaging ~4–6%.[16]

Risk Factors for Hypoglycemia

Conventional risk factors for hypoglycemia relate to absolute or relative insulin excess. These include insulin doses that are excessive or ill timed, missed meals or snacks, lack of compensation for increased exercise, alcohol ingestion, or mistaken insulin administration. However, a thorough analysis of a large number of episodes of severe hypoglycemia in the DCCT has indicated that such conventional risk factors explained only a minority of the episodes[17,18]; indeed, mathematical models incorporating many of these factors were found to have little predictive power.[17] Instead it is now well established that impaired glucose counterregulation and hypoglycemia unawareness (vide infra) are the major risk factors for severe hypoglycemia in type 1 diabetes.[3,19] These defects are particularly common in patients with a long diabetes duration,[20,21] tight glycemic control,[20,22,23] antecedent hypoglycemia,[24,25] and autonomic neuropathy.[26–28] Hypoglycemia awareness may also be compromised by the use of β-blockers.[29] The risk of severe hypoglycemia is increased 25-fold in patients with impaired hypoglycemia counterregulation[30] and increased sixfold in those with hypoglycemia unawareness.[31] Other risk factors for severe hypoglycemia due to diabetes complications include renal insufficiency, gastroparesis which causes unpredictable and delayed food absorption, poor vision, and (rarely) insulin antibodies. In the latter condition, hypoglycemia occurs via dissociation of insulin from antibodies causing prolonged hyperinsulinemia.[21]

Despite the fact that most episodes of severe hypoglycemia in type 1 diabetes are related to impaired glucose counterregulation and hypoglycemia unawareness, one should also keep in mind that hypoglycemia can be multifactorial and could be due to several unrelated diseases. These include liver disease, malnutrition, sepsis, burns, total parenteral nutrition, malignancy, and administration of certain medications known to reduce plasma glucose concentrations (Table 19.2).[32]

Table 19.2 Drug-induced hypoglycemia

Drugs capable of causing hypoglycemia by themselves		Drugs probably causing hypoglycemia only in combination with insulin/sulfonylurea/meglitinides	
Antidiabetic drugs	Other	Antidiabetic drugs	Other
Insulin	Alcohol	Biguanides	ACE inhibitors
Sulfonylureas	Salicylates	Thiazolidinediones	Phenylbutazone
Meglitinides	Propranolol	α-Glucosidase inhibitors	Lidocaine
	Pentamidine	Exenatide[a]	Coumadin
	Sulfamethoxazole	Sitagliptin	Ranitidine, cimetidine
	Vacor	Pramlintide	Doxepin
	Quinine		Danazol
	Propoxyphene		Azapropazone
	para-Aminobenzoic acid		Oxytetracycline
	Perhexiline		Clofibrate, benzofibrate
			Colchicine
			Ketoconozole
			Chloramphenicol
			Haloperidol
			Monoamine oxidase inhibitors
			Thalidomide
			Orphenadrine
			Selegiline

[a]Combination of exenatide and a thiazolidinedione increased the incidence of hypoglycemia to 11% compared with 7% in placebo in a randomized controlled trial[161]

In principle, the same risk factors for hypoglycemia apply to patients with type 2 diabetes as to patients with type 1 diabetes, although the importance of each has been less well defined.

Gastric bypass surgery is becoming more common as a treatment for morbid obesity. Many of the patients have type 2 diabetes. Hypoglycemia has been reported to occur in some patients usually in the second or third hour postprandially.[33–37] The exact mechanism is currently being investigated but is likely to be multifactorial and related to the changes that follow the surgery such as decreased caloric intake, weight loss, and a change in the nutrient composition and transit time in the gastrointestinal tract.[38–40] Studies have also shown decreased ghrelin secretion, exaggerated release of glucagon-like peptide 1 (GLP-1), and possibly other gastrointestinal hormone changes.[41–45] These hormonal changes should enhance the release of insulin and inhibit the release of pancreatic glucagon. Additionally, several severe cases of hyperinsulinemic hypoglycemia presenting as postprandial hypoglycemia after Roux-en-Y gastric bypass surgery have been published.[46–48] 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.[46,47] 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.[49] 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 in post-gastric bypass or 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.

Hypoglycemia Counterregulation

Normal Hypoglycemia Counterregulation and Hypoglycemia Awareness

Because of the importance of intact hypoglycemia counterregulation and awareness for the prevention or the correction of hypoglycemia, this shall be briefly reviewed. Glucose counterregulation refers to the sum of the body's defense mechanisms which prevent hypoglycemia from occurring and those which restore euglycemia. Hypoglycemia awareness refers to the symptomatic responses of hypoglycemia which alert the patient of declining blood glucose levels. Our knowledge of counterregulation has accumulated over the past 35 years from studies in which pharmacologic blockade of the secretion or action of individual counterregulatory hormones has been produced during standardized insulin-induced hypoglycemia.[50]

Counterregulatory mechanisms in acute hypoglycemia, i.e., induced by an intravenous insulin injection, differ markedly from those in prolonged hypoglycemia. Clinical hypoglycemia that occurs in patients with diabetes after subcutaneous insulin injection usually develops gradually and is more prolonged.[51] Therefore, in the following discussion, mainly counterregulation of prolonged hypoglycemia will be considered.

In normal postabsorptive humans, 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[52,53] and stimulates glucose uptake, exogenous insulin administration causes 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[54] (Fig. 19.1). Reduction of insulin secretion, the first in the cascade of hypoglycemia counterregulation,[3] derepresses glucose production and reduces glucose utilization. When plasma glucose levels decline to approximately 70 mg/dl, there is an increase in the secretion of counterregulatory hormones (glucagon, epinephrine, growth hormone, cortisol).[26,54–56] Glucagon and epinephrine have immediate effects on glucose kinetics, whereas the effects of growth hormone and cortisol are delayed by several hours.[57,58]

Glucagon exclusively increases hepatic glucose release, initially via glycogenolysis, later mainly via gluconeogenesis,[59] and does not affect renal glucose release or glucose utilization.[60] In contrast, catecholamines have multiorgan effects, including stimulation of hepatic and renal glucose production,[61,62] inhibition of glucose

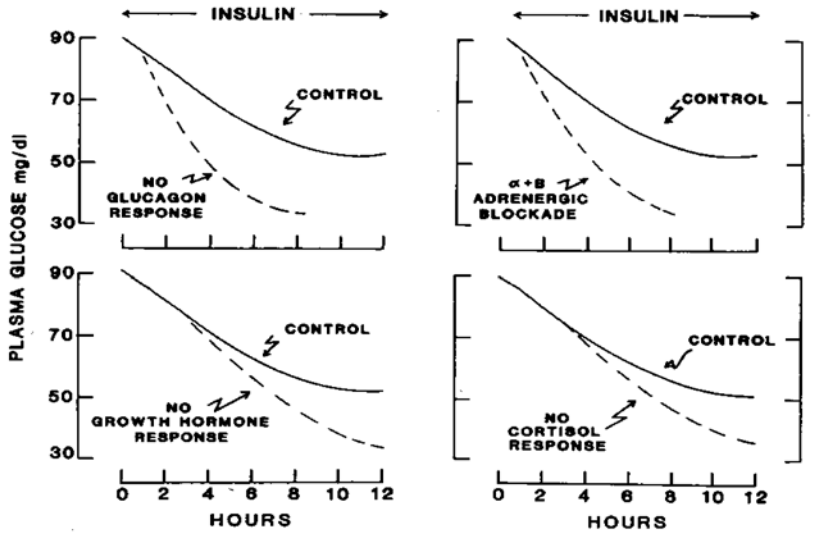

Fig. 19.1 Effect of lack of glucagon, catecholamine (α- and β-adrenergic blockade), growth hormone, and cortisol responses on insulin-induced hypoglycemia in nondiabetic volunteers studied with pituitary–adrenal–pancreatic clamp. From Gerich[50] Copyright © 1988 The American Diabetes Association. Used with permission

utilization,[63,64] stimulation of gluconeogenic substrate supply,[61,62,65] suppression of endogenous insulin secretion,[66] and stimulation of lipolysis.[66] Growth hormone and cortisol suppress insulin-mediated tissue glucose uptake and augment glucose release into the circulation.[67,68]

Under normal physiologic 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 [69,70] (hunger, anxiety, palpitations, sweating, warmth, nausea) which if interpreted correctly lead a person to eat and prevent more serious hypoglycemia. However, clues of hypoglycemia may vary considerably from person to person.[71] 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.[69,70] Further decreases can produce coma, and values below 30 mg/dl (~1.6 mM/L), if prolonged, can cause seizures, permanent neurologic 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 h without any long-term adverse effects[72] 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.[73]

Regarding the importance of each of these responses, the exact role of insulin dissipation for hypoglycemia counterregulation is controversial. Heller et al.[74] reported that dissipation of insulin is important but not critical for recovery from hypoglycemia. In contrast, De Feo et al.[75] and Sacca et al.[76] observed that no recovery from hypoglycemia occurs despite increases in counterregulatory hormones when hypoglycemia is induced by continuous low-dose insulin infusion, resulting in insulin levels lower (~25 μU/ml)[75] or similar (~40 μU/ml)[76] to those observed postprandially. On the other hand, plasma glucose concentrations stabilized and did not decrease further.

Roles of individual counterregulatory hormone responses have been delineated using the pituitary–adrenal–pancreatic (PAP) clamp technique.[77] With this technique, the spontaneous responses of counterregulatory hormones are simulated by infusions of the hormones during blockade of their secretion so that an isolated lack of response of each hormone can be examined. Studies using this technique have demonstrated that glucagon and epinephrine are the predominant counterregulatory hormones and that cortisol and growth hormone also have

major roles in glucose counterregulation (Fig. 19.1).[57,58,78] The consequences of lack of glucagon or epinephrine were quantitatively similar.[50]

These studies have also delineated the time course of action and the relative effects of each hormone on glucose production and glucose utilization.[50] As shown in Fig. 19.2, counterregulation initially involves only changes in glucose production predominantly due to glucagon and, to a lesser extent, catecholamines. Later on, changes in glucose utilization become as important as those of glucose production. At this time, cortisol and growth hormone, through their delayed effects on glucose production and glucose utilization become major hormonal factors and may be more important than catecholamines and glucagon.

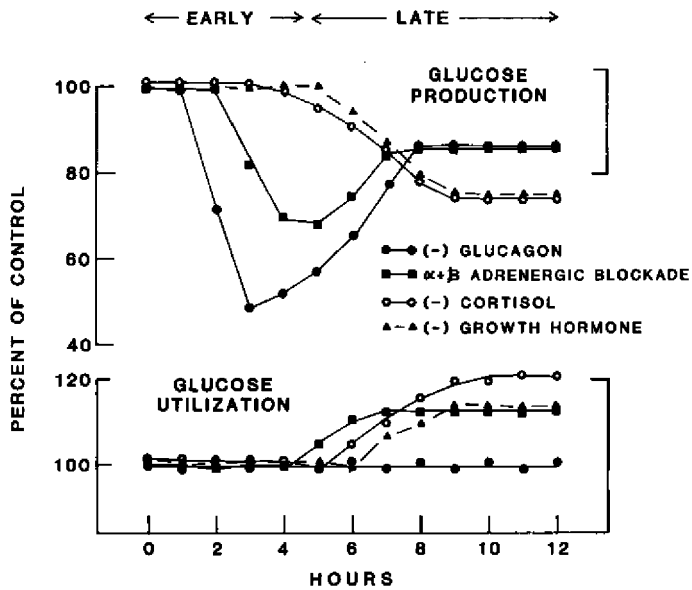

Fig. 19.2 Effect of lack of glucagon, catecholamine (α- and β-adrenergic blockade), growth hormone, and cortisol responses on counterregulatory changes in glucose production and glucose utilization in nondiabetic volunteers studied with pituitary–adrenal–pancreatic clamp. From Gerich[50] Copyright © 1988 The American Diabetes Association. Used with permission

Hypoglycemia Counterregulation and Hypoglycemia Awareness in Type 1 Diabetes

In type 1 diabetes, the physiology of the defense against hypoglycemia is seriously deranged (Fig. 19.3). First, as endogenous insulin secretion becomes totally deficient over the first few years of type 1 diabetes, 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 type 1 diabetes.[21,79] This defect coincides with the loss of insulin secretion and is therefore the rule in people with type 1 diabetes.[80] Nonetheless, glucose counterregulation appears to be adequate in such patients probably due to compensatory counterregulation by epinephrine.[81] After a few more years, epinephrine responses to hypoglycemia are also commonly reduced.[21,82,83] 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.[30,84] The combined defect in glucagon and epinephrine responses is therefore considered as the syndrome of impaired hypoglycemia counterregulation.[3] This is now known to be associated with impaired glucose production in both liver and kidney.[85] Pathophysiologic mechanisms might be different when only glucagon responses are impaired and epinephrine responses are intact. Since glucagon affects exclusively the

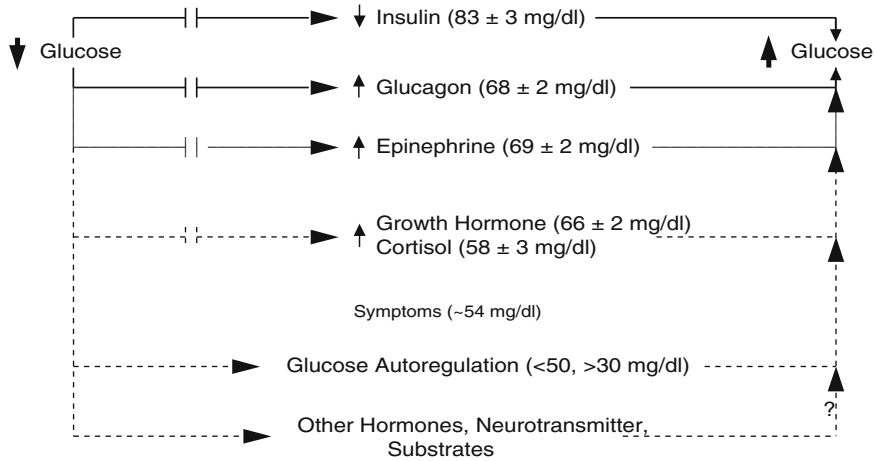

Fig. 19.3 Schematic representation of physiology of glucose counterregulation in normal humans (*arrows*) and defects in type 1 diabetes (*interrupted lines*). Mean ± SE arterialized venous glycemic thresholds for the various responses to falling blood glucose concentrations in normal humans are from Schwartz et al.[54] and Mitrakou et al.[55]

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 type 1 diabetes 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.[19,31,86,87] Hypoglycemia unawareness is associated with sixfold increased risk for severe hypoglycemia.[31]

The mechanisms of impaired hypoglycemia counterregulation and hypoglycemia unawareness are not entirely clear but several factors have been proposed. These include altered intra-islet structure and altered cell–cell interaction (reduced glucagon responses),[88,89] autonomic neuropathy (reduced catecholamine responses),[26–28] upregulation of glucose transporters in the central nervous system by antecedent hypoglycemia which prevents central hypoglycemia during subsequent hypoglycemia (reduced hormone and symptom responses),[90] and impaired β-adrenergic sensitivity to catecholamines which reduce autonomic warning symptoms of hypoglycemia.[91] Studies in animals have shown that the ventromedial hypothalamus (VMH) plays a major role in controlling the counterregulatory responses to hypoglycemia and that AMP-activated protein kinase plays a key role in the glucose sensing mechanism used by VMH neurons.[92] These studies also suggest that increased urocortin I, an endogenous type 2 corticotropin-releasing factor receptor (CRFR2) agonist in the VMH during antecedent hypoglycemia, could explain a decreased sympathoadrenal response to subsequent hypoglycemia.[93]

Hypoglycemia Counterregulation and Hypoglycemia Awareness in Type 2 Diabetes

The hormonal glucose counterregulation is usually less impaired in type 2 diabetes than in type 1 diabetes.[94–96] Nevertheless defects can be seen when patients become markedly insulin deficient.[97] One important factor for the nearly intact hormonal glucose counterregulation in type 2 diabetes may be some residual albeit abnormal, insulin secretion. Normally insulin directly suppresses glucagon secretion. There is now experimental evidence to suggest that the glucagon response to hypoglycemia may depend on the decrease in insulin secretion because the latter would derepress glucagon secretion.[89] Since insulin secretion is absent in type 1 diabetes, no decrease in insulin secretion occurs during hypoglycemia. However, in type 2 diabetes, insulin secretion is usually present and decreases appropriately during hypoglycemia, which may explain the intact glucagon response

to hypoglycemia until the patient with type 2 diabetes becomes markedly insulin deficient. Since antecedent hypoglycemia is one of the main factors for impaired epinephrine responses to hypoglycemia and since hypoglycemia rarely occurs in people with type 2 diabetes because of their intact glucagon response, epinephrine responses also usually remain intact.

Once patients with type 2 diabetes become markedly insulin deficient, glucagon responses are commonly impaired. However, in contrast to patients with type 1 diabetes, the epinephrine responses usually remain intact and in fact may partially compensate for the reduced glucagon responses to hypoglycemia.[96,98] This may explain the reduced risk for severe hypoglycemia in patients with type 2 diabetes compared to patients with type 1 diabetes. Nevertheless, some studies reported that despite their increased catecholamine responses, patients with type 2 diabetes have impaired endogenous glucose production during hypoglycemia.[98,99] Recently this has been shown to be due to diminished glucose release by the liver which is partially compensated for by an increased glucose release by the kidney.[99] Factors involved in the reduced hepatic glucose release in type 2 diabetes may be diminished hepatic glycogen stores[100] and reduced glucagon activation of hepatic membrane adenylate cyclase.[101] These changes would be expected to impair hepatic glycogenolytic and gluconeogenic responses to glucagon.

Complications of Hypoglycemia

Organ Complications

As mentioned above, an episode of severe hypoglycemia can be detrimental or even fatal mostly due to its effects on the central nervous system. At a plasma glucose concentration 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 neurologic deficits, and death.

In individuals with underlying cardiovascular disease, life-threatening arrhythmias, myocardial infarction, and strokes may be precipitated.[102–110] Moreover, in patients with underlying eye disease, hypoglycemia has been shown to trigger retinal hemorrhages.[111] It has been suggested that repeated episodes of severe hypoglycemia may lead to subtle permanent cognitive dysfunction.[112] In addition to its physical morbidity and mortality, recurrent hypoglycemia may also be associated with psychosocial morbidity.[86] In fact many patients with diabetes are as much afraid of severe hypoglycemia as they are of blindness or renal failure.[86]

Severe hypoglycemia has been reported to be at least a contributing factor to the cause of death in 3–13% of patients with type 1 diabetes, which includes motor vehicle accidents, injuries at work.[113,114] Severe hypoglycemia due to sulfonylureas has been shown to have a mortality between 4 and 7%.[16,115,116]

Somogyi Phenomenon

More than 60 years ago, Somogyi postulated that secretion of counterregulatory hormones provoked by insulin-induced hypoglycemia could lead to hyperglycemia. This sequence has become known as rebound hyperglycemia or the Somogyi phenomenon. It is the result of persistent catecholamine action initially and growth hormone and cortisol action later despite return of the plasma glucose concentration to normal. These posthypoglycemia counterregulatory effects, coupled with the dissipation of insulin injected earlier to produce hypoglycemia, result in posthypoglycemic hyperglycemia in patients with type 1 diabetes. In support of this concept, Mintz et al. [117] and Frier et al. [118] have shown that hypoglycemia, even in nondiabetic individuals, could cause subsequent glucose intolerance, and several studies demonstrated that prolonged insulin resistance lasting 4–8 h occurs after hypoglycemia in type 1 diabetes.[119–121]

Despite the evidence cited above, the literature is confounded with studies that have been interpreted to question the mechanism,[122] the frequency,[123] and even the existence[124] of the Somogyi phenomenon. However, to a

large extent, study design and selection of patients (inclusion of those with impaired counterregulation[124] or type 2 diabetes[123]) can explain this controversy. It is nevertheless possible that the magnitude of the Somogyi phenomenon has been overestimated in the past. Furthermore, it is of note that the posthypoglycemia hyperglycemia in most patients is probably due to the combination of overtreatment of hypoglycemia with carbohydrate ingestion and the increase in counterregulatory hormones.

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, 12–18 g oral carbohydrate every 30 min until the blood glucose is above 80 constitutes adequate treatment.[125,126] In a patient with more severe hypoglycemia resulting in obtundation, where oral administration of carbohydrate might result in aspiration, 1 mg 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/hr) for as long as necessary for the insulin or sulfonylurea to wear off. 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 30 min and subsequently at 1–2 h intervals. Rarely diazoxide or a somatostatin analogue may be needed to inhibit insulin secretion.[127] 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.

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. 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 as to how to treat the affected patients.

The principles of intensive therapy – patient education, blood glucose self-monitoring, 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.[128,129]

Although therapy of type 1 and type 2 diabetes is discussed in detail in other chapters, several suggestions for prevention of hypoglycemia may be useful.

In patients treated with insulin, hypoglycemia can be most successfully prevented by continuous subcutaneous insulin infusion (CSII) by means of a minipump. This has been reported to reduce the frequency of severe hypoglycemia by 50–75% [130,131] despite the fact that glycemic control actually improved. If CSII is not feasible, substitution of preprandial short-acting (regular) insulin for rapid insulin (e.g., lispro or aspart) may reduce the frequency of hypoglycemic episodes by reducing prolonged postprandial hyperinsulinemia. In a recent meta-analysis of eight studies comparing 2327 patients treated with insulin lispro with 2339 patients treated with regular insulin, the frequency of hypoglycemia was approximately 20% less in those who received lispro despite virtually identical glycemic control.[132] 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.[133–138]

In patients with type 2 diabetes on oral hypoglycemic agents, substitution of a long-acting sulfonylurea for a short-acting sulfonylurea or a meglitinide (nateglinide, repaglinide) may be useful, especially in patients with chronic renal insufficiency since most of these agents are cleared by the kidney.[139,140]

If these measures result in strict avoidance of hypoglycemia, hypoglycemia awareness may be restored.[141] This might be due to an improvement in β-adrenergic sensitivity.[142] Although strict avoidance of hypoglycemia does not improve glucagon responses to hypoglycemia in type 1 diabetes,[141,143–146] it does increase epinephrine responses.[143,146] This however seems to be limited to patients with a diabetes duration of less than ∼15 years. In patients with type 1 diabetes of more than 15 years duration, epinephrine responses may remain markedly impaired.[141,144] 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 type 2 diabetes, it seems likely that these are similar to those in type 1 diabetes.

Pancreas/Islet Transplantation

Because of the irreversibly impaired hypoglycemia counterregulation in long-standing type 1 diabetes, pancreas or islet transplantation has been proposed as a possible treatment in patients who suffer from recurrent severe hypoglycemia despite all conventional measures.[147–149] Pancreatic transplantation is usually reserved for patients undergoing simultaneous kidney transplantation. It has been found to improve glucagon responses to hypoglycemia in most studies[150–156] and to improve or normalize epinephrine responses.[152–154,156–158] Furthermore, it has been reported to improve hypoglycemia awareness in type 1 diabetes.[156]

Experience in the effects of islet transplantation on hypoglycemia counterregulation and awareness is limited and inconsistent. It seems that glucagon responses remain impaired after islet transplantation[147,148,159] possibly because of the transplantation site.[160] However, in one study, epinephrine responses and hypoglycemia awareness were reported to improve in long-standing type 1 diabetes,[148] whereas a later larger study found no evidence of improvement in epinephrine or hypoglycemia awareness despite prolonged insulin independence and near-normal glycemic control in seven islet transplantation patients.[159]

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

Summary and Conclusions

In summary, severe hypoglycemia is a relatively common, potentially life-threatening complication of diabetic treatment more often affecting patients with type 1 than those with type 2 diabetes. Major risk factors for severe hypoglycemia are impaired hypoglycemia counterregulation and hypoglycemia unawareness, whereas conventional risk factors explain only a minority of the hypoglycemic episodes. Treatment is to be aimed at acute restoration of normoglycemia and prevention of recurrences. The latter can be accomplished by temporary

loosening of glycemic control and changes in types and times of administration of insulin in addition to education, frequent blood glucose monitoring, and ongoing professional guidance. This may restore hypoglycemia counterregulation and hypoglycemia awareness, which subsequently may allow tightening of glycemic control.

Suggested Sites for the Readers

- www.cadre-diabetes.org
- http://professional.diabetes.org

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