Endotext

HYPOGLYCEMIA DURING THERAPY OF DIABETES

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ABSTRACT

The major cause of hypoglycemia is iatrogenic. Treatment with an insulin secretagogue, including sulfonylureas or glinides, or insulin, particularly when coupled with compromised defenses against the resulting falling plasma glucose concentrations, is the limiting factor in the glycemic management of diabetes. It causes recurrent morbidity in most people with type 1 diabetes mellitus (T1DM) and many with advanced type 2 diabetes mellitus (T2DM) and is sometimes fatal. Low blood glucose also impairs physiological and behavioral defenses against subsequent hypoglycemia, further increasing the risk of hypoglycemia and its complications including adverse cardiovascular effects. Strategies to reduce hypoglycemia are based on the individual's age, regimen, and comorbidities. A patient-centered approach, newer insulin analogues, novel insulin delivery devices, and continuous glucose monitoring help reduce the risk of hypoglycemia and optimize glycemia.

THE CLINICAL PROBLEM OF HYPOGLYCEMIA IN DIABETES

The problem of iatrogenic hypoglycemia in diabetes has been reviewed in detail (1–6).

Glycemic Control

In the context of comprehensive treatment, including weight, blood pressure, and blood lipid control among other measures, normoglycemia makes a difference for people with diabetes. Improved glycemic control reduces microvascular complications (retinopathy, nephropathy, and neuropathy) in both type 1 diabetes mellitus (T1DM) (7) and type 2 diabetes mellitus (T2DM) (8,9). Follow-up of patients with T1DM (10) and T2DM (11) suggests that an improved earlier period of glycemic control may also reduce subsequent macrovascular complications. Thus, safe and long-term maintenance of physiologic normoglycemia is in the best interest of people with diabetes.

The Limiting Factor

Iatrogenic hypoglycemia, fundamentally but not exclusively usually results from treatment with an insulin secretagogue or insulin either alone or in combination with other glucose lowering medications, and is the major limiting factor in the goal of near normoglycemia in the management of diabetes (1). Iatrogenic hypoglycemia causes recurrent morbidity in most people with T1DM and many with advanced T2DM and is sometimes fatal (4). It impairs defenses against subsequent falling plasma glucose concentrations and results in a vicious cycle of recurrent hypoglycemia. It generally precludes maintenance of euglycemia over a lifetime of diabetes and, thus, full realization of the benefits of glycemic control.

Type 1 and Type 2 Diabetes

Iatrogenic hypoglycemia commonly occurs in the overwhelming majority of people with T1DM who must, of course, be treated with insulin. Most have untold numbers of episodes of asymptomatic hypoglycemia. These are not benign since they impair defenses against subsequent hypoglycemia (1). Individuals with T1DM suffer an average of two episodes of symptomatic hypoglycemia per week – thousands of such episodes over a lifetime of diabetes – and about one episode of disabling severe (i.e., requiring assistance) hypoglycemia per year. Hypoglycemia causes brain fuel deprivation that, if unchecked, results in functional brain failure that is typically corrected after the plasma glucose concentration is raised (12). Rarely, if low blood glucose is profound and prolonged, it can result in brain death (12). Hypoglycemia may lead to cardiac arrhythmias, especially in patients with preexisting cardiac abnormalities (13,14). Additionally, hypoglycemia has been demonstrated to be pro-coagulant and pro-atherothrombotic (15,16). Furthermore, severe hypoglycemia has been associated with increased risk of death extending many months and up to one year after the sentinel episode (17). Of concern, roughly from 2 to 10 percent of deaths of people with diabetes were the result of hypoglycemia (4,5,14,18,19). Regardless of the actual rate, the fact that there is an iatrogenic hypoglycemia mortality rate is alarming.

Overall, for a given individual, iatrogenic hypoglycemia is less frequent in T2DM (1,20,21). However, due to the greatly increased numbers of individuals with T2DM, the prevalence of hypoglycemic episodes is actually greater than in T1DM. Drugs that can cause endogenous or exogenous (insulin) hyperinsulinemia unregulated by glucose can cause hypoglycemia. On the other hand, insulin sensitizers (metformin or a thiazolidinedione), α-glucosidase inhibitors, sodium glucose cotransporter 2 inhibitors, and drugs such as dipeptidyl peptidase-IV inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1 RAs) that cause glucose-dependent hyperinsulinemia should not, and probably do not, cause hypoglycemia. They do, however, increase the risk of hypoglycemia if used with an insulin secretagogue or with insulin. Even during treatment of T2DM with insulin, hypoglycemia event rates are about one-third of those in T1DM overall (20). However, for reasons discussed shortly (see Glucose Counterregulatory Physiology and its Pathophysiology in Diabetes), the incidence of iatrogenic hypoglycemia increases over time, approaching that in T1DM, as people approach the insulin deficient end of the spectrum of T2DM (21). Because T2DM is roughly 20-fold more prevalent than T1DM and many, perhaps most, people with T2DM ultimately require treatment with insulin, most episodes of hypoglycemia, including those of severe hypoglycemia, occur in individuals with T2DM. Insulin secretagogue and insulin induced hypoglycemia can be fatal in T2DM although precise hypoglycemic mortality rates are as yet known. As many as 10% of patients with severe sulfonylurea-induced hypoglycemia die (22).

DEFINITION AND CLASSIFICATION OF HYPOGLYCEMIA

The American Diabetes Association and the International Hypoglycemia Study Group (Table 1) define clinically significant hypoglycemia as a blood glucose <54 mg/dl (3.0 mmol/L) which is detected by the individual's self-monitoring blood glucose (SMBG) as well as by continuous glucose monitoring ((CGM), glucose values of <54 mg/dl (3.0 mmol/L) for at least 20 min), or laboratory measurement of plasma glucose which is sufficiently low to indicate clinically significant hypoglycemia (23,24). Blood glucose ≤70 mg/dl (3.9 mmol/L) is considered a hypoglycemia alert value, which represents an important lower glucose cutoff value for treatment with fast-acting carbohydrates and dose adjustments of antidiabetic medications. Severe hypoglycemia is defined as a low glucose value with severe cognitive impairment that requires assistance from another person in order to achieve recovery (25). Relative hypoglycemia or pseudohypoglycemia represents an event during which the person with diabetes reports any of the typical symptoms of hypoglycemia and interprets those as indicative of hypoglycemia with a measured plasma glucose concentration >70 mg/dL (>3.9 mmol/L).

Table 1. Classification of Hypoglycemia in Diabetes (23,24)

Level	**Glycemic criteria**	
Hypoglycemia alert value (level 1)	≤70 mg/dl (3.9 mmol/L)	Sufficiently low for treatment with fast acting carbohydrate and dose adjustment of glucose lowering therapy
Clinically significant hypoglycemia (level 2)	<54 mg/dl (3.0 mmol/L)	Sufficiently low to indicate serious, clinically important hypoglycemia
Severe hypoglycemia (level 3)	No specific glucose threshold	Hypoglycemia associated with severe cognitive impairment requiring external assistance for recovery

COMPLICATIONS OF HYPOGLYCEMIA

Increased mortality has been observed in randomized controlled trials during more aggressive compared with less aggressive glucose-lowering therapy in patients with T2DM (26) and in patients with hypoglycemia in intensive care units (27). In addition, intensive glycemic control has not been shown to improve cardiovascular outcomes in patients with T2DM (28). The associations between increased hypoglycemia and increased morbidity and mortality during aggressive glycemic therapy in these and other (18,29,30) trials have been thought to be multifactorial (31). A possible explanation is that aggressive reduction of blood glucose increases the risk of hypoglycemia. The latter can trigger sympathoadrenal activation with the release of catecholamines, cause abnormal cardiac repolarization, and lead to myocardial ischemia. Hypoglycemia-induced ECG changes include ST-segment depression, atrial and ventricular ectopic beats, P- and T-wave abnormalities, and QT-interval prolongation (32). Low blood glucose creates procoagulant and prothrombotic states and induces inflammation and oxidative stress (33,34).

The association of hypoglycemia with cognitive function appears to be more complicated. Among older individuals with type 2 diabetes, a history of severe hypoglycemia was associated with a greater risk of dementia (37). The ACCORD study reported that cognitive impairment at baseline and a continuing

decline in cognitive function among individuals were associated with a greater risk for dementia following hypoglycemia (35). It should be noted however that in DCCT/EDIC, which involved much younger participants, no association of severe hypoglycemia and cognitive decline was found (25, 39).

Hypoglycemic episodes can create fear of subsequent hypoglycemia and negatively affect the quality of life in T1DM as well as T2DM (36). Some of the consequences may include anxiety, shortness of breath, palpitations, tremors, symptoms of depression, and reduced ability to function.

GLUCOSE COUNTERREGULATORY PHYSIOLOGY AND ITS PATHOPHYSIOLOGY IN DIABETES

Physiology

In nondiabetic individuals, there are a number of physiological defenses against falling plasma glucose concentrations. These include reductions in insulin secretion, which occur as glucose levels decline within the physiological range. This allows for increased hepatic (and renal) glucose production, and increments in glucagon and epinephrine secretion, which occur as glucose levels fall just below the physiological range and stimulate hepatic glucose production (1,2,37) (Figure 1). Increased epinephrine levels also normally mobilize gluconeogenic precursors from muscle and fat, stimulate renal glucose production, limit glucose utilization by muscle and fat, and limit insulin secretion (2). The behavioral defense against falling plasma glucose concentrations is carbohydrate ingestion prompted largely by the perception of neurogenic (autonomic) symptoms (e.g., palpitations, tremor, and anxiety/arousal which are catecholamine-mediated or adrenergic and sweating, hunger, and paresthesias which are sympatho-adrenal mediated or cholinergic) (38,39) (Figure 1). These are largely sympathetic neural, rather than adrenomedullary, in origin (39). The extent to which mild neuroglycopenic symptoms such as altered mentation or psychomotor changes contribute to the patient's recognition of hypoglycemia is unclear; awareness of hypoglycemia is largely prevented by pharmacological antagonism of neurogenic symptoms (38). Severe neuroglycopenic symptoms include frank confusion, acute focal or central neurologic deficits, seizure and/or loss of consciousness. All of these defenses can be compromised in T1DM and advanced T2DM (1,40,41).

Pathophysiology

Episodes of therapeutic hyperinsulinemia, the result of glucose unregulated delivery of endogenous (insulin secretagogue therapy) or exogenous (insulin therapy) insulin into the circulation, initiate the sequence that may, or may not, culminate in an episode of hypoglycemia (1). Absolute therapeutic insulin excess of sufficient magnitude can cause isolated episodes of hypoglycemia despite intact glucose counterregulatory defenses against hypoglycemia (Figure 2). But that is an uncommon event. Iatrogenic hypoglycemia is typically the result of the interplay of mild-moderate absolute therapeutic insulin excess, reduced glucose intake, exercise, increased insulin sensitivity, sleep, and existing or induced compromised physiological and behavioral defenses against falling plasma glucose concentrations in T1DM (1,40) and T2DM (1,41). In T1DM, because of β-cell failure, insulin levels do not decrease as glucose levels fall; the first physiological defense is lost. Furthermore, glucagon levels do not increase as glucose levels fall (42); the second physiological defense is lost. That, too, is possibly attributable to a β-cell signaling failure since a decrease in β-cell secretion, coupled with a low α-cell glucose concentration, normally signals α-cell glucagon secretion (3,43,44). Finally, the increase in epinephrine levels as glucose levels fall is also

attenuated ((1,41); and thus, the three major physiological defenses are compromised.

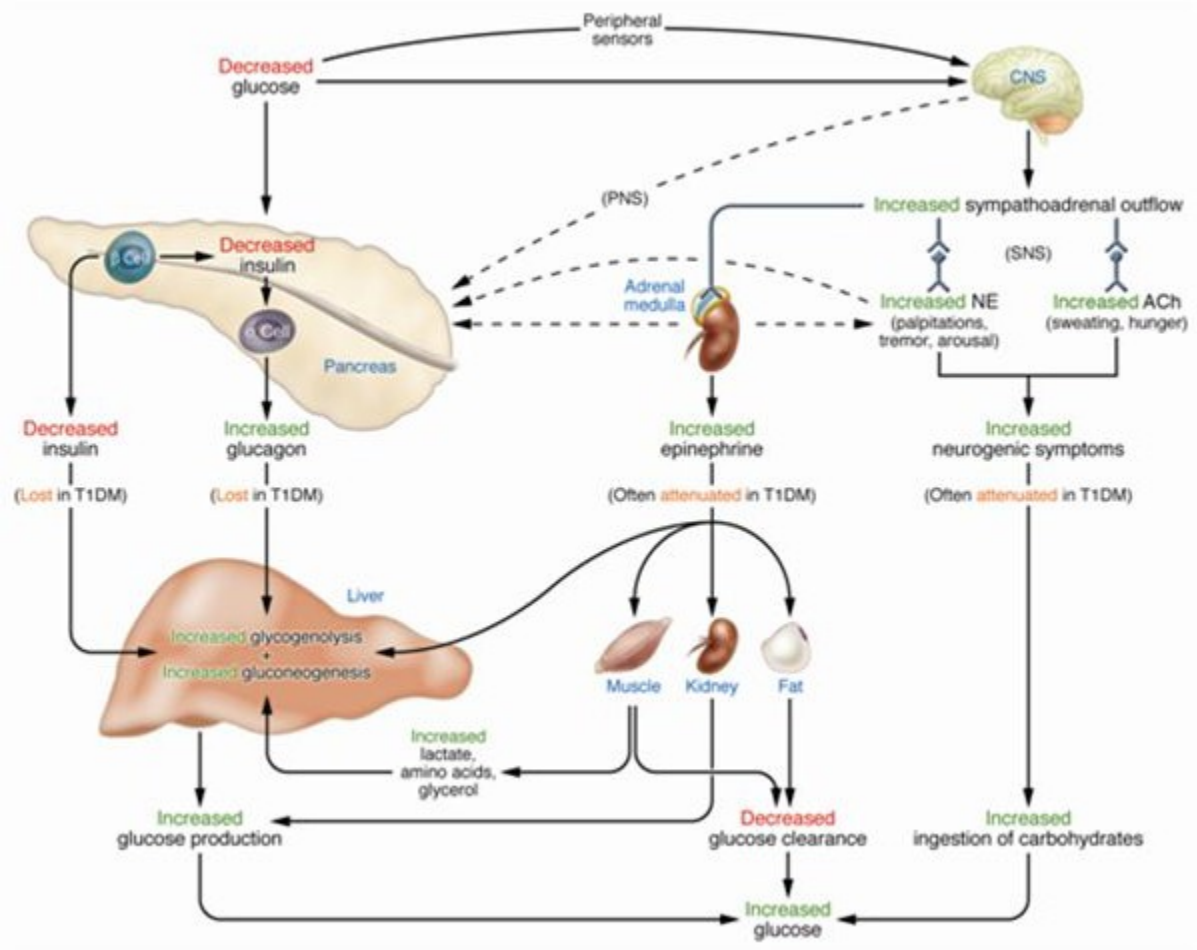

Figure 1. Physiological and Behavioral Defenses Against Hypoglycemia in Humans. ACH, acetylcholine; NE, norepinephrine; PNS, parasympathetic nervous system; SNS, sympathetic nervous system. From reference (45).

Although it is often caused by recent antecedent hypoglycemia (40,46) or by prior exercise (47) or sleep (48–50), the mechanism of the attenuated sympathoadrenal response to falling glucose levels is unknown (3). Nonetheless, the attenuated epinephrine response is a marker of an attenuated sympathetic neural response (39) and the latter largely results in the reduction of the symptoms of hypoglycemia causing hypoglycemia unawareness (or impaired awareness of hypoglycemia) and thus loss of the behavioral defense, i.e., carbohydrate ingestion. In the setting of therapeutic hyperinsulinemia, falling plasma glucose concentrations, absent decrements in insulin, absent increments in glucagon, and attenuated increases in epinephrine cause the clinical syndrome of defective glucose counter-regulation (1,40), which is associated with a 25-fold (51) or greater (52) increased risk of iatrogenic hypoglycemia. The attenuated sympathoadrenal, particularly the attenuated sympathetic neural response, causes the clinical syndrome of hypoglycemia unawareness (1)

which is associated with a 6-fold increased risk of iatrogenic hypoglycemia (53).

The pathophysiology of glucose counter-regulation is the same in T1DM and T2DM albeit with different time courses. β-cell failure, and therefore loss of the insulin and glucagon responses to falling plasma glucose concentrations, develops early in T1DM but more gradually in T2DM. Thus, iatrogenic hypoglycemia, becomes a common problem early in T1DM and later in T2DM.

The concept of hypoglycemia-associated autonomic failure (HAAF) in diabetes (1,3,5,40,41) (Figure 2) posits that recent antecedent hypoglycemia, as well as prior moderate exercise or sleep, causes both defective glucose counter-regulation (by reducing increments in epinephrine in the setting of absent decrements in insulin and absent increments in glucagon during subsequent hypoglycemia) and hypoglycemia unawareness (by reducing sympathoadrenal and resulting neurogenic symptom responses during subsequent hypoglycemia) and, therefore, a vicious cycle of recurrent hypoglycemia. Supporting this concept is the finding, that as little as 2-3 weeks of scrupulous avoidance of hypoglycemia reverses hypoglycemia unawareness and improves the attenuated epinephrine component of defective glucose counter-regulation in most affected patients. (54–57).

The mechanism(s) of the attenuated sympathoadrenal response to falling glucose levels, the key feature of HAAF, is not known (3). It must involve the central nervous system or the afferent or efferent components of the sympathoadrenal system. Theories include increased blood-to-brain transport of a metabolic fuel, effects of a systemic mediator such as cortisol on the brain, altered hypothalamic mechanisms, and activation of an inhibitory cerebral network mediated through the thalamus (3)

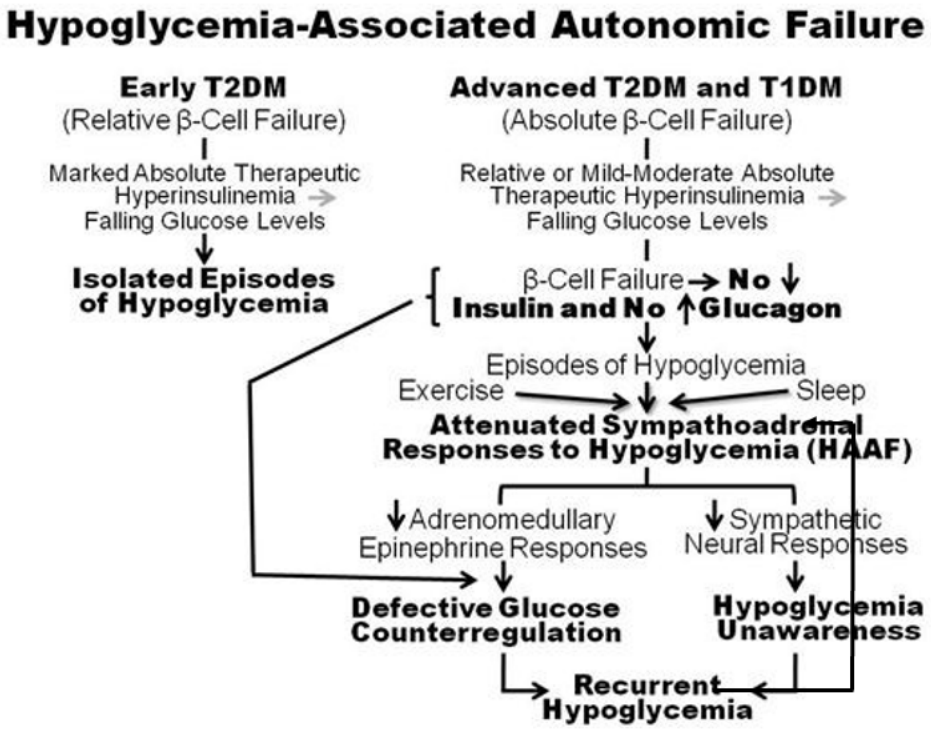

Figure 2. Schematic Diagram of HAAF in Diabetes. From reference (45).

RISK FACTORS FOR HYPOGLYCEMIA IN DIABETES

Conventional Risk Factors

The conventional risk factors are based on the premise that relative to low rates of glucose delivery into the circulation, high rates of glucose efflux out of the circulation, or both, or absolute therapeutic hyperinsulinemia is the sole determinant of risk (1). They include (but are not limited to):

1. Insulin (or insulin secretagogue) doses are excessive, ill-timed, or of the wrong type.
2. Exogenous glucose delivery is decreased (as following missed meals and during the overnight fast, with gastroparesis or celiac disease).
3. Glucose utilization and sensitivity to insulin are increased (as during and shortly after exercise, in the middle of the night, following weight loss, or improved glycemic control).
4. Endogenous glucose production is decreased (as following alcohol ingestion or in liver failure).
5. Insulin clearance is decreased (as in renal failure).
6. Classical diabetic autonomic neuropathy.

Patients with diabetes and their caregivers must consider each of these risk factors carefully whenever hypoglycemia is a problem (58).

Risk Factors Indicative of Hypoglycemia-Associated Autonomic Failure (HAAF)

These risk factors stem directly from the pathophysiology of glucose counter-regulation and the concept of HAAF in diabetes (1,40,41). They include:

1. The degree of absolute endogenous insulin deficiency. This determines the extent to which insulin levels will not decrease and glucagon levels will not increase as plasma glucose concentrations fall in response to therapeutic hyperinsulinemia. It is in part a function of the duration of diabetes.
2. A history of severe hypoglycemia, hypoglycemia unawareness, or both as well as recent antecedent hypoglycemia, prior exercise or sleep.
3. Aggressive glycemic therapy per se (lower A1C levels, lower glycemic goals). Studies with a control group treated to higher mean glycemia consistently document higher rates of hypoglycemia in individuals treated to lower mean glycemia (e.g. (4)). Mean glycemia is a risk factor for hypoglycemia. However, severe hypoglycemia can occur in individuals with any A1C level, and the fact that mean glycemia is a risk factor does not mean that one cannot both lower mean glycemia and reduce the risk of hypoglycemia in individual patients (6).

PREVENTION OF HYPOGLYCEMIA IN DIABETES

The prevention of hypoglycemia can be viewed as a process with four steps (1,6). The first step is acknowledging the problem; the second - considering the conventional risk factors in diabetes; the third – considering the risk factors indicative of HAAF in diabetes; and the fourth - application of the relevant principles of intensive glycemic therapy of diabetes.

Acknowledge the Problem

The issue of hypoglycemia should be addressed at every contact with a patient treated with an insulin secretagogue or with insulin (6). In addition to the patient's comments and review of the individual's SMBG data (as well as any CGM data) we find it especially helpful to inquire what is the glucose level when each patient can detect hypoglycemia and what

are the symptoms and signs at various hypoglycemic levels. It is also often helpful to question close associates of the patient since they may have observed clues to episodes of hypoglycemia. Patient concerns about the reality, or even the possibility, of hypoglycemia can be a barrier to glycemic control (59,60). Their concerns need to be discussed and addressed if hypoglycemia is a real or perceived problem.

Consider the Conventional Risk Factors for Hypoglycemia in Diabetes

Each of the risk factors that result in relative or absolute therapeutic hyperinsulinemia, as just discussed, should be considered carefully in any patient with iatrogenic hypoglycemia. Those include the dose, timing, and type of the insulin secretagogue or insulin preparations(s) used, and conditions in which exogenous glucose delivery or endogenous glucose production is decreased, glucose utilization or insulin sensitivity is increased or insulin clearance is decreased.

Consider the Risk Factors Indicative of HAAF in Diabetes

As detailed earlier, the risk factors indicative of HAAF include the degree of absolute endogenous insulin deficiency, a history of severe hypoglycemia, impaired awareness of hypoglycemia, or both as well as any relationship between iatrogenic hypoglycemia and recent antecedent hypoglycemia, prior exercise or sleep, and lower glycemic goals. A history of severe hypoglycemia is a clinical red flag. Without a fundamental adjustment of the treatment regimen, the likelihood of another episode is high (7,61).

Apply the Relevant Principles of Intensive Glycemic Therapy

The principles of intensive glycemic therapy relevant to minimizing the risk of iatrogenic hypoglycemia in diabetes include drug selection, selective application of diabetes treatment technologies, individualized glycemic goals, structured patient education, and short-term scrupulous avoidance of hypoglycemia (6). Based on the premise that the risk of hypoglycemia is modifiable, the International Hypoglycemia Study Group recommended that people with diabetes treated with a sulfonylurea, a glinide, or insulin should be educated about hypoglycemia, should treat self-monitored plasma glucose (SMPG) <70 mg/dL (<3.9 mmol/L) to avoid progression to clinical iatrogenic hypoglycemia, and should regularly be queried about hypoglycemia, including the glucose level at which symptoms develop (6).

Drug selection relevant to minimizing the risk of hypoglycemia includes avoidance, if possible, of sulfonylureas or glinides, the use of more physiological insulin regimens (62), and the use of long-acting or even ultra-long-acting daily basal insulin analogues and rapid-acting prandial insulin analogues in lieu of human insulins (63–66). Insulin analogues reduce the frequency of at least nocturnal hypoglycemia (63–65) including severe nocturnal hypoglycemia (65) compared to human insulins. In insulin-requiring T2DM, basal insulins are associated with less hypoglycemia than prandial insulin regimens. Furthermore, the combination of a long-acting basal insulin with a glucose-lowering drug with low hypoglycemic potential (e.g., a GLP-1 receptor agonist) may result in less hypoglycemia than with the use of basal-bolus insulin therapy (67).

Relevant diabetes treatment technologies include continuous subcutaneous insulin infusion (CSII), continuous glucose monitoring (CGM), and combinations of CSII and CGM. Although earlier meta-analyses disclosed little (68) or no (69) advantage of CSII, recent evidence suggest that CSII treatment is superior in achieving glucose control compared to multiple daily injections (70,71). CGM devices alone

have been shown to improve glycemic control and decrease duration of hypoglycemia in patients with diabetes mellitus (72,73). As their accuracy is continuously improving, several CGM systems have been approved by the FDA, and other regulatory authorities to even replace point of care blood glucose testing (74,75). Real-time CGM systems have also been found to improve hypoglycemia awareness, without a change in A1C, in a small group of patients with T1DM (76). A favorable experience with CSII has also been reported (77,78). The combination of CSII and real-time CGM – sensor augmented pump therapy, particularly that including an insulin pump programmed to stop insulin infusion for up to two hours when CGM values fall to a selected glucose level ("low glucose suspend") – has been reported to reduce the frequency of severe hypoglycemia in T1DM (79–81). Recent innovations have included cessation of insulin delivery during hypoglycemia. Several promising studies have investigated approaches for leading closed-loop insulin (or insulin and glucagon) replacement. The development of automated closed-loop insulin pumps represents an area of ongoing research and fully closed-loop insulin (82) or insulin and glucagon replacement (83) and pancreatic islet transplantation (84) will undoubtedly eliminate hypoglycemia and improve overall glycemic control. A hybrid-not fully automated -system (as only basal insulin is automatically adjusted) has received approval by the FDA (85).

Special circumstances relevant to drug selection and treatment technologies in the prevention of hypoglycemia in diabetes include exercise, the overnight period, the elderly, drivers, and pregnancy. Especially in insulin-treated patients' hypoglycemia can occur during or shortly after exercise (86) or late after exercise (87,88). Measures to avoid early-onset exercise hypoglycemia include interspersing episodes of intense exercise (which tends to raise plasma glucose concentrations), adding carbohydrate ingestion, and reducing insulin doses (89). A consistent observation since the DCCT (7) is that more than half of episodes of hypoglycemia, including severe hypoglycemia, occur during the night. That is typically the longest interval between meals and between SMPG and includes the time of maximal sensitivity to insulin. In addition to the use of insulin analogues, sensor augmented pump therapy or closed-loop insulin or insulin and glucagon replacement, all discussed earlier, approaches to the prevention of nocturnal hypoglycemia include attempts to produce sustained delivery of exogenous carbohydrate or sustained endogenous glucose production (90). With respect to the former approach, a conventional bedtime snack or bedtime administration of uncooked cornstarch have not been found to be consistently effective (90). With respect to the latter approach an experimental treatment is bedtime administration of a β2-adrenergic agonist such as terbutaline (90–92). In addition to HAAF, comorbidities including renal insufficiency, polypharmacy, and impaired cognition are more relevant to the development of hypoglycemia in older individuals (93). Drivers with diabetes and a history of recurrent hypoglycemia-related driving mishaps have been found to have greater driving simulator impairments (94). Finally, up to 45% of pregnant women with type 1 diabetes experience severe hypoglycemia especially in the first trimester (95).

Individualized Glycemic Goal

Glycemic goals should be individualized in patients with diabetes (4,96). The selection of a glycemic goal in a person with diabetes is a trade-off between the benefits of glycemic control – partial prevention or delay of microvascular complications – and the risk of recurrent morbidity, and potential mortality, of hypoglycemia (4). A reasonable individualized glycemic goal is the lowest A1C that does not cause severe hypoglycemia and preserves awareness of hypoglycemia, preferably with little or no symptomatic or even asymptomatic hypoglycemia, at a given stage in the evolution of the individual's diabetes (4). Thus, the glycemic goal should be linked not only to the level of glycemic control (i.e., the A1C) but also to the risk

of hypoglycemia, specifically the drugs used (a sulfonylurea, a glinide, or insulin), the degree of endogenous insulin deficiency, and the anticipated benefit of the targeted level of glycemic control. A nondiabetic A1C would be reasonable in a patient with early T2DM treated effectively with lifestyle changes and/or drugs that do not cause hypoglycemia. For the majority of non-pregnant adults, a reasonable goal for an A1C is <7% (53 mmol/mol). For selected individuals with long life expectancy, without significant comorbidities (especially cardiovascular disease), stringent A1c goals (<6.5% (48 mmol/mol)) should be targeted, if this can be achieved without significant hypoglycemia (23). For children and adolescents, an A1C of <7.5% (58 mmol/mol) should be the goal, although a lower target (<7% (53 mmol/mol)) should be reasonable if it can be achieved without excessive hypoglycemia (97). However much higher levels of A1C (7.5%-8.0% (58-64 mmol/mol)) may be appropriate in elderly patients where hypoglycemia may be harmful. Even higher targets (A1C<8.5% (69 mmol/mol)) may be appropriate in individuals with very limited life expectancy (93).

Of note, it needs to be underscored that severe hypoglycemia can and does occur at A1C levels between 8-10% (64-86 mmol/mol) or higher in either T1DM or T2DM. Thus, severe hypoglycemia is not just a consequence of “low or near normal” A1C values. Of concern are recent data that severe hypoglycemia occurring in T2DM individuals >60 years with elevated A1C may have greater serious adverse events and increased mortality compared to individuals with improved glycemic control and lower A1C values.

Thus, attempts to improve glycemic control with insulin in T2DM individuals that have been resistant or proven challenging to strategies to lower glucose levels may be at greater risk for severe hypoglycemia and associated serious adverse events (18,26,29,30).

Structured Patient Education

The core approach, applicable to virtually all patients with diabetes treated with a sulfonylurea, a glinide, or insulin in whom hypoglycemia becomes a problem, is thorough, structured patient education (often re-education) that teaches the patient how and when their drugs can cause hypoglycemia, how to adjust their medications, meal plans, and exercise to optimize glycemic control and minimize hypoglycemia, and how to recognize and treat hypoglycemia (6). Based conceptually on earlier inpatient education programs (98), there is increasing evidence that outpatient structured education programs decrease hypoglycemia, often with a decrease in A1C (99–103). For example, a structured patient education program in flexible insulin therapy led to a reduction of impaired awareness of hypoglycemia (45% of those with impaired awareness initially were aware at one year) and a reduction in severe hypoglycemia (from 1.9 to 0.6 episodes per patient-year and a small but significant decrease in A1C in patients with type 1 diabetes (101). Patient education needs to cover a broad range of information and skill training and often include a motivational element (6).

Short-Term Scrupulous Avoidance of Hypoglycemia

In patients with impaired awareness of hypoglycemia structured patient education should be combined with 2- to 3-weeks of scrupulous avoidance of hypoglycemia – which may require acceptance of somewhat higher glycemic goals in the short-term – since that can be expected to restore awareness of hypoglycemia in most affected patients (54–57).

In summary, people with diabetes treated with a sulfonylurea, a glinide, or insulin should be educated about hypoglycemia, should treat SMPG (or CGM) glucose levels <70 mg/dL (<3.9 mmol/L) to avoid progression to clinical iatrogenic hypoglycemia, and

should regularly be queried about hypoglycemia, including the SMPG (or CGM) level at which symptoms develop (6).

TREATMENT OF HYPOGLYCEMIA IN DIABETES

Most episodes of asymptomatic hypoglycemia, detected by routine SMBG or CGM, or of mild-moderate symptomatic hypoglycemia are effectively self-treated by ingestion of glucose tablets or carbohydrate containing juice, soft drinks, candy, other snacks, or a meal (1,104). A reasonable dose is 20 g of carbohydrate (104). The dose can be repeated in 15 to 20 minutes, if necessary. Since the glycemic response to oral glucose is transient – roughly two hours in the setting of ongoing hyperinsulinemia (104) – the ingestion of a more substantial snack or meal shortly after the plasma glucose level is raised is generally advisable.

When a hypoglycemic patient is unwilling (because of neuroglycopenia) or unable to take carbohydrate orally, parenteral therapy is required. That is often glucagon injected subcutaneously or intramuscularly by an associate of the patient who has been trained to recognize and treat severe hypoglycemia. The usual glucagon dose is 1.0 mg; that can be life-saving although it causes substantial, albeit transient, hyperglycemia (104) and can cause nausea, and even vomiting. Smaller doses (e.g., 150 mcg), repeated, if necessary, have been found to be effective without side effects in adolescents (105). Recent advances include 1) approval of nasal glucagon and of a device to deliver glucagon intranasally (106), that would obviate the need for parenteral injection and 2) a glucagon that is stable in solution (107), that would obviate the need to reconstitute the drug prior to administration. Because it also stimulates insulin secretion, glucagon might be less effective in patients with early T2DM. In a medical setting intravenous glucose, 25 g initially, is the standard parenteral therapy (1). The glycemic response to intravenous glucose is, of course, transient. A subsequent glucose infusion is generally needed, and food should be provided as soon as the patient is able to ingest it safely.

The duration of a hypoglycemic episode is a function of its cause. While that caused by a short-acting insulin secretagogue or a rapid-acting insulin can be measured in hours, that caused by a long-acting insulin secretagogue or insulin can last for days requiring hospitalization for prolonged therapy. The duration of secretagogue-induced hypoglycemia can be shortened by administration of octreotide (108,109).

In the UK, the Joint British Diabetes Societies for Inpatient Care have produced guidance on the management of hypoglycemia for hospital inpatients, although these can be used in the community setting as necessary (110).

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