

## In Brief

Hypoglycemia is the limiting factor in the glycemic management of diabetes. It is a barrier to quality of life and even survival in the short term and to true glycemic control, with its established microvascular and potential macrovascular benefits, in the long term. Although it is possible to both improve glycemic control and minimize the risk of hypoglycemia in many patients with currently available regimens—by applying the principles of aggressive therapy and practicing hypoglycemia risk reduction—people with diabetes need treatment methods that provide glucose-regulated insulin secretion or replacement if euglycemia is to be maintained safely over a lifetime of diabetes.

# Negotiating the Barrier of Hypoglycemia in Diabetes

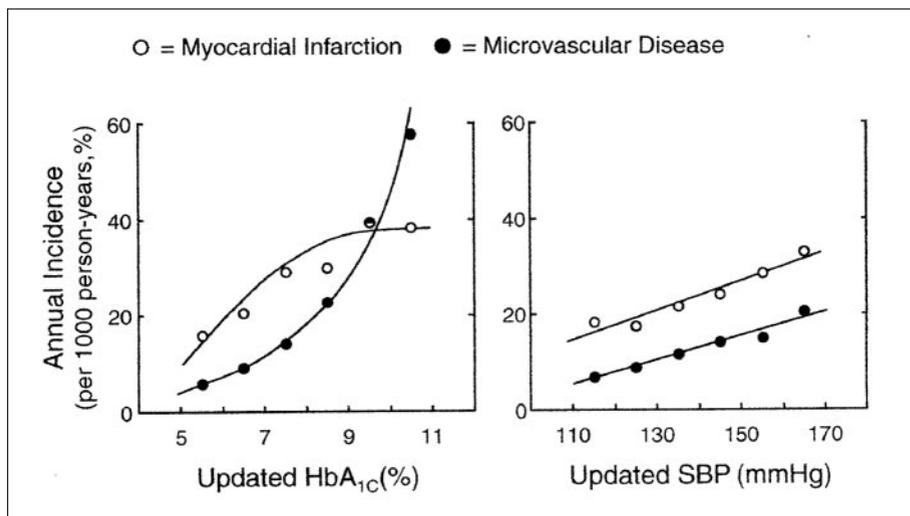
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Lowering plasma glucose concentrations to levels as close to the nondiabetic range as possible and holding them there over time is a fundamental component of comprehensive diabetes care. Glycemic control prevents or delays the microvascular complications—retinopathy, nephropathy, and neuropathy—in both type 1 diabetes mellitus (T1DM)<sup>1</sup> and type 2 diabetes mellitus (T2DM).<sup>2</sup> It may also reduce macrovascular events.<sup>1,2</sup> However, because of the pharmacokinetic imperfections of all current treatment regimens, iatrogenic hypoglycemia is the limiting factor in the glycemic management of diabetes.<sup>3-5</sup>

Were it not for the potentially devastating effects of hypoglycemia on the brain, which requires a continuous supply of glucose from the circulation, diabetes would be rather easy to treat. Enough insulin, or any effective drug, to lower plasma glucose concentrations to or below the nondiabetic range would eliminate the symptoms of hyperglycemia, prevent the acute hyperglycemic complications (ketoacidosis, hyperosmolar syndrome), almost assuredly prevent the long-term microvascular complications,<sup>1,2</sup> and likely reduce atherosclerotic risk.<sup>6,7</sup> But the effects of hypoglycemia on the brain are real, and the glycemic management of diabetes is therefore complex.

The barrier of iatrogenic hypoglycemia precludes true glycemic control, i.e., maintenance of euglycemia over time, in the vast majority of people with diabetes. As a result, complications can develop or progress despite aggressive therapy. For example, in the Diabetes Control and Complications Trial (DCCT) in T1DM, retinopathy developed or progressed in 14% of the patients treated intensively (compared with 32% of those treated conventionally).<sup>1</sup> Similarly, in the United Kingdom Prospective Diabetes Study (UKPDS) in T2DM, any microvascular endpoint was reached in 8% of the patients treated intensively (compared with 11% of those treated less intensively).<sup>2</sup>

The barrier of hypoglycemia may also explain why aggressive attempts at glycemic control have had little impact on the frequency of macrovascular events in people with diabetes.<sup>1,2</sup> It appears that the curve describing the relationship between mean glycemia (hemoglobin A<sub>1c</sub> [HbA<sub>1c</sub>]) and macrovascular events such as myocardial infarction is shifted to the left (toward lower glycemia) compared with that between mean glycemia and microvascular complications<sup>6</sup> (Figure 1). Indeed, recent prospective epidemiological data extending earlier studies based on



**Figure 1.** Relationship between updated systolic blood pressure (SBP), right, and updated HbA<sub>1c</sub>, left, and the incidence of microvascular complications (closed symbols) and macrovascular, specifically myocardial infarction, complications (open symbols) of T2DM in the United Kingdom Prospective Diabetes Study.<sup>6</sup>

plasma glucose concentrations indicate an increased risk of death from ischemic heart disease in individuals with glycated hemoglobin levels in the high-normal range.<sup>7</sup> Because of the barrier of iatrogenic hypoglycemia, it simply may not be practical to hold plasma glucose levels low enough long enough to prevent atherosclerotic disease in a substantial proportion of people with diabetes using current treatment regimens.

The frequency and clinical impact of iatrogenic hypoglycemia, its pathophysiology, the relationship of its pathophysiology to clinical risk factors, and the prevention and treatment of hypoglycemia in people with diabetes are reviewed in the sections that follow. The topic of hypoglycemia, including hypoglycemia in diabetes, has been reviewed in detail.<sup>4,5</sup>

Hypoglycemia is a fact of life for people with T1DM and for many with advanced T2DM. Nonetheless, it is possible to both improve glycemic control and minimize the risk of iatrogenic hypoglycemia by applying the principles of aggressive glycemic therapy and practicing hypoglycemia risk reduction.<sup>8,9</sup>

### Frequency

Hypoglycemia is a familiar event for people with established (i.e., C-peptide-negative) T1DM.<sup>4,5</sup> Those attempting to achieve some degree of glycemic control suffer untold numbers of episodes of asymptomatic hypoglycemia; plasma glucose concen-

trations may be <50 mg/dl 10% of the time. They suffer an average of two episodes of symptomatic hypoglycemia per week—thousands of such episodes over a lifetime—and episodes of severe, at least temporarily disabling, hypoglycemia approximately once a year.<sup>1,10,11</sup> Indeed, an estimated 2–4% of deaths of people with T1DM have been attributed to hypoglycemia.

Overall, the frequency of hypoglycemia is substantially lower in T2DM than in T1DM. Event rates for severe iatrogenic hypoglycemia (requiring the assistance of another individual) are roughly tenfold lower in T2DM than in T1DM, even during aggressive insulin therapy.<sup>10,12–15</sup>

The rates are undoubtedly even lower in patients with T2DM treated with oral hypoglycemic agents, although quantitative data from patients treated to near-euglycemia are limited. Over 6 years in the UKPDS, major hypoglycemia (requiring medical assistance or hospitalization) was reported in 2.4% of T2DM patients treated with metformin, 3.3% of those treated with a sulfonylurea, and 11.2% of those treated with insulin.<sup>15</sup> In comparison, severe hypoglycemia (requiring the assistance of another individual) occurred in 65% of the patients with T1DM treated intensively (with insulin) over 6.5 years in the DCCT.<sup>1</sup>

It should be recalled that, in contrast to median HbA<sub>1c</sub> levels of 7.2% in intensively treated T1DM throughout the DCCT,<sup>1</sup> median HbA<sub>1c</sub> levels

rose over time to ~8.1% in the intensively treated T2DM patients in the UKPDS.<sup>2</sup> Thus, the UKPDS data undoubtedly underestimate the frequency of iatrogenic hypoglycemia in patients with T2DM treated to glucose levels closer to the nondiabetic range. Although reliable estimates of hypoglycemic mortality rates in T2DM are not available, deaths caused by sulfonylurea-induced hypoglycemia have been well-documented.<sup>16</sup>

Among patients with T2DM, the frequency of hypoglycemia is highest in those treated with insulin.<sup>15</sup> In those using a sulfonylurea, hypoglycemia is more often reported in patients using long-acting agents such as chlorpropamide or glyburide (glibenclamide) compared with those using a shorter-acting agent such as glipizide.<sup>16,17</sup> The frequency of hypoglycemia in patients using rapid-acting insulin secretagogues such as repaglinide or nateglinide remains to be determined.

In theory, monotherapy with a biguanide, a thiazolidinedione, or an  $\alpha$ -glucosidase inhibitor should not cause hypoglycemia; endogenous insulin secretion should decline appropriately as plasma glucose levels fall. Nonetheless, hypoglycemia, including major hypoglycemia, has been reported in patients treated with metformin.<sup>15</sup> Thiazolidinediones increase the risk of hypoglycemia in patients treated with additional glucose-lowering agents, and  $\alpha$ -glucosidase inhibitors preclude oral treatment of hypoglycemia with complex carbohydrates.

The extent to which the frequency of iatrogenic hypoglycemia in T2DM is a function of the specific glucose-lowering drugs used to treat hyperglycemia or of the stage of the disease is not entirely clear. Is the higher frequency of hypoglycemia in patients treated with insulin<sup>15</sup> the result of the greater glucose-lowering potency of that drug—given in sufficient doses—relative to that of the other drugs and its pharmacokinetic imperfections, or is it because patients who require treatment with insulin have advanced, insulin-deficient T2DM with the associated compromised glucose counterregulation (to be discussed later)?

Hypoglycemia was found to become progressively more limiting to glycemic control over time in T2DM in the UKPDS.<sup>18</sup> Furthermore, the frequencies of severe hypoglycemia are similar in T2DM and T1DM matched

for duration of insulin therapy.<sup>19</sup> Given progressive insulin deficiency in T2DM,<sup>2,15</sup> these findings indicate that iatrogenic hypoglycemia becomes a progressively more frequent clinical problem, approaching that in T1DM, as patients approach the insulin-deficient end of the spectrum of T2DM.

### Clinical Impact

Iatrogenic hypoglycemia causes both physical morbidity (and some mortality) and psychosocial morbidity.<sup>4</sup> The physical morbidity of an episode of hypoglycemia ranges from unpleasant symptoms such as sweating, hunger, anxiety, palpitations, and tremor to neurological impairments including behavioral changes, cognitive impairments, seizures, and coma. Focal neurological deficits occur rarely. While seemingly complete neurological recovery is the rule following an episode of hypoglycemia, permanent neurological damage can occur.

At the very least, an episode of hypoglycemia is a nuisance and a distraction; it can be embarrassing and can lead to social ostracism. The psychological morbidity includes fear of hypoglycemia, guilt about that rational fear, high levels of anxiety, and low levels of overall happiness.<sup>4</sup> Fear of hypoglycemia can be an impediment to glycemic control. Thus, hypoglycemia is often a psychological, as well as a pathophysiological, barrier to glycemic control.

The performance of critical tasks such as driving is measurably impaired during hypoglycemia, as is judgment. The demands of the management of diabetes, including the prevention of both hyperglycemia and hypoglycemia, become progressively more intrusive over time in T2DM, albeit over a longer time span than in T1DM. Finally, to the extent that it precludes glycemic control, hypoglycemia limits the now well-established long-term benefits of glycemic control.<sup>1,2</sup>

### Pathophysiology: Hypoglycemia-Associated Autonomic Failure

The prevention or correction of hypoglycemia normally involves both decrements in the secretion of insulin and increments in that of glucose counterregulatory (plasma glucose-raising) hormones.<sup>4,5</sup> There are redundant glucose counterregulatory factors and a hierarchy among these.

In defense against falling plasma glucose concentrations, decrements in

insulin are normally critically important. That is the first defense against hypoglycemia. It occurs as glucose levels decline within the physiological range and favors increased hepatic (and renal) glucose production (and decreased glucose utilization by tissues other than the brain). Among the glucose counterregulatory hormones that are released as glucose levels fall just below the physiological range, increments in glucagon, which stimulates glycogenolysis and thus hepatic glucose production, play a primary role. Glucagon is the second defense against hypoglycemia. Albeit demonstrably involved, increments in epinephrine become critical only when glucagon is deficient. Epinephrine both stimulates hepatic (and renal) glucose production—both directly and by mobilizing gluconeogenic precursors—and limits glucose utilization by tissues such as muscle. Epinephrine is the third defense against hypoglycemia. Thus, insulin, glucagon, and epinephrine stand high in the hierarchy of redundant glucose counterregulatory factors.

Increments in cortisol and in growth hormone are involved in defense against slowly developing hypoglycemia, but neither is critical to recovery from even prolonged hypoglycemia or to the prevention of hypoglycemia after an overnight fast. There is evidence that glucose autoregulation—hepatic glucose production as an inverse function of ambient glucose levels independent of hormonal, neural, or other substrate gluco-regulatory factors—may be involved, albeit only during severe hypoglycemia. If other hormones, neurotransmitters, or substrates other than glucose (and nonesterified fatty acids that may mediate, at least in part, the actions of epinephrine) are involved, they play minor roles.

Iatrogenic hypoglycemia is the result of the interplay of absolute or relative insulin excess and compromised glucose counterregulation in established (C-peptide-negative) T1DM.<sup>4,5</sup> As plasma glucose levels decline, insulin levels do not decrease—they are simply a passive reflection of the absorption of exogenous insulin, and glucagon levels do not increase. The mechanism of the latter defect is not well understood, but it is tightly linked to, and possibly the result of, insulin deficiency. Thus, the first and second defenses against hypoglycemia are lost in established T1DM.

Further, the epinephrine response is

typically attenuated, i.e., the glycemic threshold for the epinephrine response is shifted to lower plasma glucose concentrations. This reduction of the third defense is largely the result of recent antecedent iatrogenic hypoglycemia.

The combination of absent glucagon and attenuated epinephrine responses causes the clinical syndrome of *defective glucose counterregulation*, which, compared with absent glucagon but normal epinephrine responses, is associated with a 25-fold or greater increased risk of severe iatrogenic hypoglycemia.<sup>20,21</sup> The reduced autonomic response (including the sympathetic neural norepinephrine and acetylcholine as well as the adrenomedullary epinephrine response) causes the clinical syndrome of *hypoglycemia unawareness*—loss of the largely neurogenic warning symptoms of developing hypoglycemia. By compromising the behavioral defense (e.g., food ingestion), hypoglycemia unawareness is also associated with a high frequency of severe iatrogenic hypoglycemia.<sup>22</sup> The pathophysiology of glucose counterregulation is summarized in Table 1.

The concept of hypoglycemia-associated failure in T1DM<sup>4,5,23,24</sup> (Figure 2) posits that recent antecedent hypoglycemia causes both defective glucose counterregulation (by reducing epinephrine responses in the setting of absent glucagon responses) and hypoglycemia unawareness (by reducing autonomic and thus neurogenic symptom responses). Perhaps the most compelling support for this concept is the finding, in three independent laboratories,<sup>24–26</sup> that as little as 2–3 weeks of scrupulous avoidance of hypoglycemia reverses hypoglycemia unawareness and, at least in part, improves the epinephrine component of defective glucose counterregulation in most affected patients.

The extent to which the concept of hypoglycemia-associated autonomic failure applies to T2DM remains to be defined. Glucose counterregulatory defenses against developing hypoglycemia appear to be largely intact early in the course of T2DM. This likely explains the relatively low overall prevalence of iatrogenic hypoglycemia in T2DM despite imperfect therapies.

However, patients with advanced T2DM—selected for a relatively long-term requirement for treatment with insulin (in the absence of immunologi-

**Table 1. Pathophysiology of Glucose Counterregulation in Type 1 and Type 2 Diabetes**

Iatrogenic hypoglycemia is the result of the interplay of absolute or relative insulin excess and compromised glucose counterregulation in T1DM and in advanced T2DM.

Glucose	Insulin	Glucagon	Epinephrine
↓ Nondiabetic ↓ T1DM	↓ No ↓	↑ No ↑	↑ Attenuated ↑
• Defective glucose counterregulation (absent glucagon and attenuated epinephrine responses) • Hypoglycemia unawareness (attenuated autonomic, including epinephrine, responses)			
↓ T2DM ↓ Advanced T2DM	↓ No ↓	↑ No ↑	↑ Attenuated ↑

The concept of hypoglycemia-associated autonomic failure (Figure 2) posits that recent antecedent iatrogenic hypoglycemia causes both defective glucose counterregulation (by reducing the epinephrine response to a given level of subsequent hypoglycemia in the setting of an absent glucagon response) and hypoglycemia unawareness (by reducing the neurogenic [autonomic] symptom response to a given level of subsequent hypoglycemia).

cal evidence of late-onset T1DM) and shown to be insulin deficient as evidenced by reduced C-peptide levels—have been found to have virtually absent glucagon responses to hypoglycemia.<sup>27</sup> In addition, their epinephrine and symptomatic responses, among other responses, were shown to be shifted to lower plasma glucose concentrations following recent hypoglycemia.<sup>27</sup> Thus, hypoglycemia-associated autonomic failure may occur in advanced T2DM and may well explain the fact that iatrogenic hypoglycemia becomes progressively more limiting to glycemic control<sup>18</sup> and the high frequency of severe hypoglycemia<sup>19</sup> as T2DM patients approach insulin deficiency.

**Clinical Risk Factors**

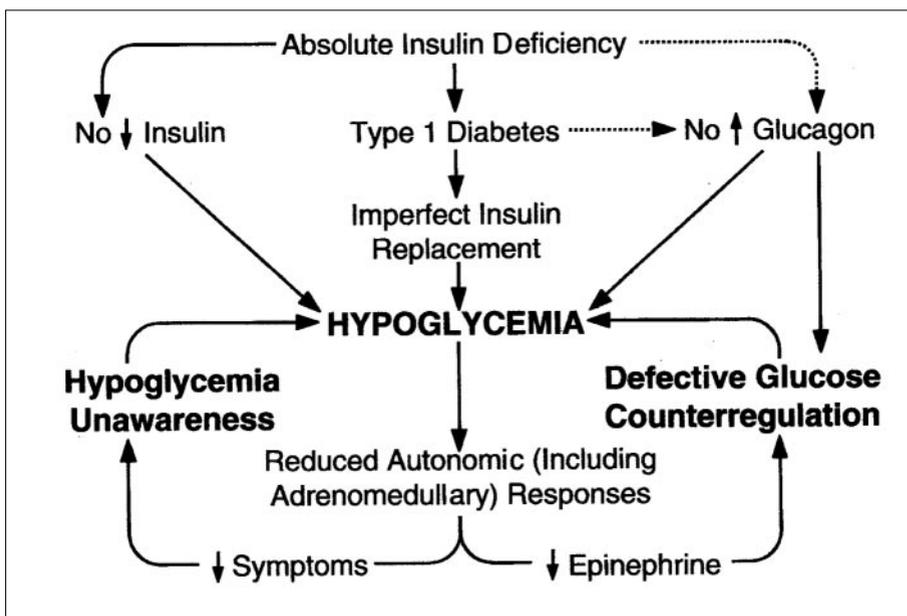
The conventional risk factors for iatrogenic hypoglycemia,<sup>4,5</sup> conceptualized in T1DM but relevant to T2DM, are based on the premise that absolute or relative insulin excess, whether injected or secreted, is the sole determinant of risk. Absolute or relative insulin excess occurs when: 1) insulin, or insulin secretagogue or sensitizer, doses are excessive, ill-timed, or of the wrong type; 2) exogenous glucose delivery is decreased (as after missed meals or snacks or during the overnight fast); 3) endogenous glucose production is decreased (as after alcohol ingestion); 4) glucose utilization is increased (as during exercise); 5) sensitivity to insulin is increased (as late

after exercise; in the middle of the night; following weight loss, increased fitness, or improved glycemic control; or during treatment with an insulin sensitizer); or 6) insulin clearance is decreased (as in renal failure). However, while they must be considered carefully, these conventional risk factors explain only a minority of episodes of severe iatrogenic hypoglycemia, at least in T1DM.<sup>28</sup>

In T1DM and advanced T2DM, iatrogenic hypoglycemia is more appropriately viewed as the result of the interplay of insulin excess and compromised glucose counterregulation rather than as absolute or relative insulin excess alone.<sup>4,5,9,27</sup> Risk factors related to compromised glucose counterregulation that are well-established in T1DM<sup>29-31</sup> and are likely relevant to advanced T2DM include: 1) insulin deficiency; 2) a history of severe hypoglycemia, hypoglycemia unawareness, or both; and 3) aggressive glycemic therapy per se as evidenced by lower HbA<sub>1c</sub> levels, glycemic goals, or both.

These are clinical surrogates of compromised glucose counterregulation. Insulin deficiency indicates that insulin levels will not decrease and predicts accurately that glucagon levels will not increase as glucose levels fall. A history of severe hypoglycemia indicates, and that of hypoglycemia unawareness or even aggressive therapy per se implies, recent antecedent hypoglycemia that compromised the autonomic (including epinephrine) and neurogenic symptom responses to falling glucose levels by shifting the glycemic thresholds for these responses to lower plasma glucose concentrations. The risk factors for iatrogenic hypoglycemia are summarized in Table 2.

An association between the angiotensin-converting enzyme (ACE) DD genotype/high serum ACE activity phenotype and severe hypoglycemia has been reported in T1DM.<sup>32</sup> However, that association was apparent only with very high serum ACE activities and was weak compared with the association of severe hypoglycemia with well-established risk factors such as C-peptide negativity, hypoglycemia unawareness, and lower HbA<sub>1c</sub> levels<sup>29-31</sup> in the same study.<sup>32</sup> Furthermore, there was no association between the ACE genotype/phenotype and symptomatic (as opposed to severe) hypoglycemia, the proportion of patients suffering severe hypoglycemia, or the frequency of hypo-



**Figure 2. Schematic diagram of the concept of hypoglycemia-associated autonomic failure and the pathogenesis of the syndromes of defective glucose counterregulation and hypoglycemia unawareness in type 1 diabetes.<sup>3</sup>**

glycemia unawareness, and a plausible mechanism is not apparent.

### Risk Reduction

Reducing the risk of iatrogenic hypoglycemia while attempting to keep plasma glucose levels as close to the nondiabetic range as can be done safely involves three steps.<sup>5,9</sup>

First, health care providers need to address the issue of hypoglycemia in every contact with patients with drug-treated diabetes. Are these patients having hypoglycemic episodes, and, if so, are they aware of hypoglycemia? When do the episodes occur? Are they severe? What is their temporal relation to drug administration, meals and snacks, alcohol use, and exercise? Are there low values in patients' self-monitoring of blood glucose (SMBG) logs? Do patients' family members think episodes are occurring that are not recognized by the patients themselves? To what extent are patients worried about actual or possible hypoglycemia? Hypoglycemia is more likely to be a problem in patients with T1DM and in those with advanced T2DM and during aggressive glycemic

therapy. Obviously, it can occur in other circumstances.

If hypoglycemia is a problem, as is often the case, the next step is to review the extent to which the principles of aggressive therapy—patient education and empowerment, frequent SMBG, flexible drug regimens, rational individualized glycemic goals, and ongoing professional guidance and support—are being applied. Health care providers must listen to people with diabetes and their families in order to identify the steps that need to be taken to reduce the likelihood of future hypoglycemia. Lack of understanding of the drug regimen is often a contributing factor.

Education concerning the time actions of specific insulin preparations or oral hypoglycemic agents and self-management skills is often helpful. The latter include the treatment of both hyperglycemia and hypoglycemia. In either case, excessive treatment can be detrimental. They also include the use of pattern recognition to refine the regimen. It is fundamentally important for people suffering hypoglycemic episodes to monitor their blood glucose before performing critical tasks such as driving. Finally, and particularly in older individuals with T2DM, it is often useful to consider factors such as drug interactions, renal insufficiency, and poor nutrition.

The third step in hypoglycemia risk reduction<sup>9</sup> is consideration of both the conventional risk factors for iatrogenic hypoglycemia that lead to episodes of relative or absolute therapeutic insulin excess—insulin or other drug doses, timing, and type; patterns of food ingestion and of exercise; interactions with alcohol or other drugs; and altered insulin sensitivity to, or clearance of, insulin—and the risk factors for compromised glucose counterregulation that impair physiological and behavioral defenses against developing hypoglycemia (Table 2). The principle is that iatrogenic hypoglycemia is the result of the interplay of insulin excess and compromised glucose counterregulation, rather than insulin excess alone, in T1DM and advanced T2DM.

The clinical surrogates of risk attributable to compromised glucose counterregulation include insulin deficiency and a history of recurrent hypoglycemia, or absent that, lower glycemic goals, lower HbA<sub>1c</sub> levels, or both.<sup>29-31</sup> Insulin deficiency may be apparent from a history of ketosis-

prone diabetes requiring insulin therapy from the time of diagnosis, although it is now recognized that absolute insulin deficiency can sometimes develop more gradually in T1DM and T2DM.

It is possible to test for defective glucose counterregulation (with a low-dose insulin infusion test<sup>20,21</sup>), but that is generally neither practical nor useful given the dynamic nature of the glycemic thresholds for autonomic and symptomatic responses to falling glucose levels. On the other hand, a diagnosis of hypoglycemia unawareness can usually be made from the history. Clinical hypoglycemia unawareness, which also implies defective glucose counterregulation, is a strong clue to recurrent antecedent hypoglycemia, regardless of whether the latter has been documented.

Obviously, with a history of recurrent hypoglycemia, one should identify when it occurs and adjust the treatment regimen accordingly. With a basal-bolus insulin regimen, morning fasting hypoglycemia implicates the long- or intermediate-acting insulin; daytime hypoglycemia implicates the rapid- or short-acting insulin; and nocturnal hypoglycemia may implicate either, all in the context of the other risk factors for insulin excess. Notably, substitution of preprandial rapid-acting insulin (e.g., lispro or aspart) for short-acting (regular) insulin reduces the frequency of nocturnal hypoglycemia.<sup>33-35</sup> Substitution of a long-acting insulin analog (e.g., glargine or detemir) for intermediate-acting insulin (NPH or ultralente) may also reduce the frequency of nocturnal hypoglycemia.<sup>36-38</sup> With a continuous subcutaneous insulin infusion regimen using a rapid-acting insulin such as lispro, nocturnal and morning fasting hypoglycemia implicate the basal insulin infusion rate, whereas daytime hypoglycemia may implicate the preprandial insulin bolus doses, the basal insulin infusion rate, or both. Pragmatic approaches to the glycemic management of T1DM have been reviewed by Bolli.<sup>8</sup>

As previously noted, glucose counterregulatory mechanisms are largely intact in early T2DM. The normal rapid cessation of endogenous insulin secretion as plasma glucose concentrations fall merits emphasis because of its relevance to the risk of hypoglycemia during drug treatment. Many factors in addition to the risk of iatrogenic hypoglycemia—such as effi-

**Table 2. Risk Factors for Iatrogenic Hypoglycemia**

#### *Absolute or Relative Insulin Excess*

1. Doses of insulin, insulin secretagogue, or insulin sensitizer are excessive, ill-timed, or of the wrong type.
2. Decreased exogenous glucose delivery
  - Missed meals or snacks, overnight fast
3. Decreased endogenous glucose production
  - Alcohol
4. Increased glucose utilization
  - Exercise
5. Increased sensitivity to insulin
  - Late after exercise
  - Improved fitness
  - Middle of the night
  - Glycemic control
  - Weight loss
  - Insulin sensitizer
6. Decreased insulin clearance
  - Renal failure

#### *Compromised Glucose Counterregulation*

1. Insulin deficiency
2. History of severe hypoglycemia, hypoglycemia unawareness, or both
3. Aggressive glycemic therapy per se
4. Lower HbA<sub>1c</sub>
5. Lower glycemic goals

cacy, side effects, ease of adherence, and cost—enter into the selection of a glucose-lowering agent for a given patient with T2DM. However, to the extent that patients with T2DM have residual insulin secretion sufficient to achieve drug-facilitated euglycemia, monotherapy with a biguanide, a thiazolidinedione, or an  $\alpha$ -glucosidase inhibitor would seem preferable from the perspective of iatrogenic hypoglycemia because these drugs should allow endogenous insulin secretion to fall as plasma glucose levels fall. (Nonetheless, iatrogenic hypoglycemia has been reported in patients with T2DM treated with the biguanide metformin,<sup>15</sup> as noted earlier.)

All insulin secretagogues, such as sulfonylureas and the rapid-acting insulin secretagogues (e.g., repaglinide, nateglinide), can produce absolute or relative insulin excess and thus hypoglycemia. An agent that would only enhance glucose-stimulated insulin secretion would be preferable. The extent to which the rapid-acting insulin secretagogues will be found to have a lower risk of iatrogenic hypoglycemia during treatment to near-euglycemia remains to be determined.

Obviously, injected insulin can also produce absolute or relative insulin excess largely because of the imperfectly regulated dosing and the flawed pharmacokinetics of injected insulin. Even with the shortest-acting insulin preparations, such as lispro and aspart, the time course of the glucose-lowering actions is much longer (hours) than those of normally secreted endogenous insulin (minutes). As mentioned earlier, with progressive insulin deficiency over time<sup>2</sup> and the associated compromised glucose counterregulation,<sup>27</sup> the glycemic management of T2DM becomes more like that of T1DM.<sup>18,19</sup>

A history of severe iatrogenic hypoglycemia (requiring assistance of another individual) is a clinical red flag. Unless it was the result of an obviously remediable factor, such as a missed meal after insulin administration or vigorous exercise without the appropriate regimen adjustment, a substantive change in the regimen must be made. If it is not, the risk of recurrent severe hypoglycemia is unacceptably high.<sup>30,31</sup>

A history of hypoglycemia unawareness implies recurrent hypoglycemia. If that is not apparent to patients or their families or from the SMBG log, it is probably occurring

during the night. Indeed, hypoglycemia, including severe hypoglycemia, occurs most commonly during the night in people with T1DM.<sup>1,31</sup> That is typically the longest interdigestive interval and time between SMBG and the time of maximal sensitivity to insulin.<sup>39</sup> Furthermore, sleep often precludes recognition of warning symptoms of developing hypoglycemia and thus the appropriate behavioral response. Sleep has also been reported to further reduce the epinephrine response to hypoglycemia<sup>40</sup> and thus further compromise the physiological defense against developing hypoglycemia.

Approaches to the problem of nocturnal hypoglycemia include regimen adjustments, including use of rapid-acting rather than regular insulin during the day and a long-acting basal insulin, as mentioned earlier, and administration of bedtime snacks, although the efficacy of the latter is largely limited to the first half of the night.<sup>41</sup> Protein snacks have been reported to be more effective than standard (or cornstarch) snacks.<sup>42</sup> However, treatment of insulin-induced hypoglycemia in a controlled setting with bread plus meat compared with bread alone was not found to provide prolonged protection against subsequent hypoglycemia.<sup>43</sup>

Experimental approaches to the prevention of nocturnal hypoglycemia include bedtime administration of the glucagon-stimulating amino acid alanine, the epinephrine-simulating  $\beta_2$ -adrenergic agonist terbutaline, or complex, slowly digested carbohydrate in the form of uncooked cornstarch. Both bedtime alanine and bedtime terbutaline have been reported to more effectively prevent nocturnal hypoglycemia than a conventional snack in patients with T1DM.<sup>41</sup> Practical limitations to the use of alanine include its limited solubility and unpleasant taste. Despite potentially detrimental metabolic (higher morning glucose, lactate, and ketone levels) and cardiovascular (slightly higher heart rates) effects, terbutaline tablets offer convenience and dosage flexibility and, in the dose used, produce no adverse effects perceivable by patients.

Despite the use of a rather small dose of cornstarch relative to that used to prevent hypoglycemia in patients with glucose-6-phosphatase deficiency (type 1 glycogen storage disease),<sup>44–46</sup> Kaufman and colleagues<sup>47–50</sup> have consistently found

significantly fewer SMBG levels <60 mg/dl at two time points during the night (midnight or 2:00 a.m. and before breakfast) following a cornstarch snack at 11:00 p.m. in adolescents and young adults with T1DM. When compared with a bedtime snack, bedtime uncooked cornstarch did not prevent nocturnal hypoglycemia in other studies.<sup>42,51,52</sup> When compared with bedtime placebo, it reduced the number of low 3:00 a.m. blood glucose levels significantly in the outpatient setting and appeared to reduce the frequency of nocturnal hypoglycemia in the inpatient setting,<sup>54</sup> but the contrast was with placebo rather than with a conventional bedtime snack.

Given clinical hypoglycemia unawareness, a 2- to 3-week period of scrupulous avoidance of hypoglycemia is advisable and can be assessed by return of awareness of hypoglycemia. Although this can be accomplished without<sup>25,26</sup> or with<sup>24</sup> minimal compromise of glycemic control, it requires substantial involvement of health professionals. In practice, it can involve acceptance of somewhat higher glucose levels in the short term. Nonetheless, with the return of symptoms of developing hypoglycemia, empirical approaches to better glycemic control can then be tried.

## Treatment

Prevention of iatrogenic hypoglycemia is preferable to treatment of hypoglycemia. Episodes of asymptomatic hypoglycemia (detected by SMBG) and most episodes of mild-to-moderate symptomatic hypoglycemia are effectively self-treated by ingestion of glucose tablets or carbohydrate in the form of juices, soft drinks, milk, crackers, candy, or a meal.<sup>45</sup> An initial glucose dose of 20 g is reasonable.<sup>55</sup> However, the glycemic response to oral glucose is transient, typically less than 2 h.<sup>55</sup> Therefore, ingestion of a snack or meal shortly after the plasma glucose concentration is raised is generally advisable.

Parenteral treatment is necessary when hypoglycemic patients are unable or unwilling (because of neuroglycopenia) to take carbohydrate orally. While parenteral glucagon is often used by family members to treat hypoglycemia in T1DM, glucagon is less useful in T2DM because it stimulates insulin secretion as well as glycogenolysis. Intravenous glucose is

the preferable treatment of severe iatrogenic hypoglycemia. Because iatrogenic hypoglycemia, particularly that caused by a sulfonylurea, is often prolonged in T2DM, prolonged glucose infusion and frequent feedings are often required. It is crucial to establish absence of recurrent hypoglycemia unequivocally before such patients are discharged. This often requires hospitalization with prolonged medical supervision.

## Conclusions

Iatrogenic hypoglycemia is the limiting factor in the glycemic management of diabetes and a barrier to true glycemic control and its established microvascular and potential macrovascular long-term benefits. Severe hypoglycemia is less frequent overall in T2DM compared with T1DM, even during aggressive glycemic therapy, because of intact glucose counterregulatory systems early in the course of T2DM. However, iatrogenic hypoglycemia becomes a progressively more frequent clinical problem, ultimately approaching that in T1DM, in advanced T2DM because of compromised glucose counterregulation—the syndromes of defective glucose counterregulation and hypoglycemia unawareness and the concept of hypoglycemia-associated autonomic failure.

By practicing hypoglycemia risk reduction—addressing the issue, applying the principles of aggressive therapy, and considering both the conventional risk factors and those indicative of compromised glucose counterregulation—health care providers should strive to reduce mean glycemia as much as can be accomplished safely. Clearly, though, given current treatment limitations, people with diabetes need more physiological approaches to glycemic control tailored to their degree of insulin deficiency.

Hypoglycemia should not be used by providers or patients as an excuse for poor glycemic control. Nonetheless, better methods, such as those that would provide glucose-regulated insulin secretion or replacement, are clearly needed if we are to achieve and maintain euglycemia safely.

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