

Insulin Therapy and Hypoglycemia in Type 2 Diabetes Mellitus

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ABSTRACT

Background: Iatrogenic hypoglycemia, the limiting factor in the glycemic management of diabetes mellitus (DM), is the result of therapeutic insulin excess and compromised physiological and behavioral defenses against falling plasma glucose concentrations.

Objective: The goal of this article was to review the available evidence on insulin therapy and hypoglycemia, with a focus on type 2 DM.

Methods: This review was based on the author's clinical experience, his >3 decades of translational research in the area of hypoglycemia, and his knowledge of the relevant preclinical and clinical literature.

Results: Glycemic defenses become compromised rapidly in type 1 DM but slowly in type 2 DM. As a result, the frequency of hypoglycemia increases progressively as patients approach the insulin-deficient end of the spectrum of type 2 DM. Indeed, it appears that most episodes of hypoglycemia, including those of severe hypoglycemia, occur in individuals with type 2 DM. The conventional risk factors for hypoglycemia are based on relative or absolute insulin excess. It is clear that the pathogenesis of hypoglycemia-associated autonomic failure, and thus an increased risk for iatrogenic hypoglycemia, stems fundamentally from insulin deficiency. Relevant additional risk factors include the degree of insulin deficiency, a history of severe hypoglycemia, hypoglycemia unawareness, or both, as well as recent antecedent hypoglycemia, prior exercise and sleep, and aggressive glycemic therapy per se in advanced type 2 DM, just as in type 1 DM. The prevention of hypoglycemia involves the practice of hypoglycemia risk reduction—discussion of the issue, application of the principles of aggressive therapy, and consideration of both the conventional risk factors and those relevant to compromised glycemic defenses—in advanced type 2 DM, just as in type 1 DM. With this approach, it is possible to improve glycemic control and reduce the frequency of hypoglycemia in many people with DM.

Conclusions: Pending the prevention and cure of DM, people with this disease need safe and effective therapies. Ultimately, that will require glucose-regulated insulin replacement or secretion. In the meantime, insight into the mechanisms of hypoglycemia-associated autonomic failure may lead to interventions that will further improve the lives of people affected by DM by reducing the frequency of hypoglycemia without compromising glycemic control. (*Insulin*. 2007;2:127–133) Copyright © 2007 Excerpta Medica, Inc.

Key words: insulin, hypoglycemia, type 1 diabetes mellitus, type 2 diabetes mellitus, pathophysiology.

INTRODUCTION

Iatrogenic hypoglycemia is the limiting factor in the glycemic management of diabetes mellitus (DM).¹ It causes recurrent morbidity in most people with type 1 DM and many with advanced type 2 DM, and is sometimes fatal. Furthermore, the barrier of hypoglycemia precludes maintenance of euglycemia over a lifetime of DM and thus full realization of the long-term benefits of glycemic control. Finally, even asymptomatic episodes of hypoglycemia, as well as prior exercise and sleep, further compromise defenses against subsequent falling plasma glucose concentrations and thus cause a vicious cycle of recurrent hypoglycemia. Despite steady advances in the glycemic management of DM, the problem of hypoglycemia has not been solved.

Although it is sometimes minimized even by authorities in the DM field, the problem of iatrogenic hypoglycemia during treatment of type 2 DM with insulin is real.^{2–4} The current article approached this problem from the perspective of the pathophysiology of glucose counterregulation, the physiological and behavioral mechanisms that normally prevent or rapidly correct clinical hypoglycemia. This pathophysiology was first clarified in type 1 DM and more recently extended to type 2 DM.^{1,5,6} The premise here is that the pathophysiology of glucose counterregulation is the same in type 1 and type 2 DM but, because it stems fundamentally from the loss of endogenous insulin secretion, it develops rapidly in type 1 DM but slowly in type 2 DM. Understanding the pathophysiology of glucose counterregulation therefore provides insight into the frequency of, the

risk factors for, and the prevention of iatrogenic hypoglycemia in insulin-treated type 2 DM. These are all reviewed here.

MATERIALS AND METHODS

This invited review was based on the author's clinical experience, his >3 decades of translational research in the area of hypoglycemia, and his knowledge of the relevant preclinical and clinical literature.

THE PATHOPHYSIOLOGY OF HYPOGLYCEMIA IN DIABETES MELLITUS

Iatrogenic hypoglycemia is the result of the interplay of relative or absolute therapeutic insulin excess and compromised physiological and behavioral defenses against falling plasma glucose concentrations in type 1 DM and advanced type 2 DM.^{1,5,6}

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Insulin Excess

Relative, or even absolute, insulin excess must occur from time to time during treatment of DM with insulin or with an insulin secretagogue, such as a sulfonylurea or a glinide, because of the pharmacokinetic imperfections of these therapies. Even the most sophisticated regimens do not replicate normal endogenous insulin secretion. In nondiabetic individuals, because of the rapid onset and offset of insulin secretion and the short half-time of circulating insulin, glucose-regulated variations in circulating insulin levels occur over minutes. With the drugs, depending on the degree of endogenous insulin deficiency, insulin levels are—to a greater or lesser extent—not glucose regulated and their variations occur over hours.

Among the medications used to treat type 2 DM early in its course, biguanides (metformin), α -glucosidase inhibitors (acarbose, miglitol), thiazolidinediones (pioglitazone, rosiglitazone), glucagon-like peptide-1 (GLP-1) receptor agonists (exenatide, liraglutide), and dipeptidyl peptidase-IV (DPP-IV) inhibitors (sitagliptin, vildagliptin) should not cause hypoglycemia when used as monotherapy, although metformin has been reported to do so.⁷ To lower plasma glucose concentrations, these agents require endogenous insulin secretion, and insulin secretion decreases as plasma glucose levels decline into the physiological range. That is true even for the GLP-1 receptor agonists and the DPP-IV inhibitors that stimulate insulin secretion (among other actions) but do so in a glucose-dependent fashion. As plasma glucose levels fall into the physiological range, insulin secretion decreases appropriately. However, all of these drugs increase the risk of hypoglycemia when used with a sulfonylurea or insulin. For

example, the glucose-dependent feature of GLP-1 receptor agonist-stimulated insulin secretion is lost in the presence of a sulfonylurea, and clinical hypoglycemia can therefore occur.⁸

Insulin excess of sufficient magnitude can, of course, cause hypoglycemia. However, despite the episodes of hyperinsulinemia that must occur from time to time during sulfonylurea or insulin therapy, hypoglycemia is relatively infrequent (at least with currently recommended glycemic goals) early in the course of type 2 DM when glycemic defenses are intact, as during initial insulin therapy of patients in whom oral agents have failed to achieve adequate glycemic control.⁹

Compromised Defenses Against Falling Plasma Glucose Concentrations

Physiological defenses against falling plasma glucose concentrations include the following: (1) decrements in β -cell insulin secretion; (2) increments in α -cell glucagon secretion; and (3) absent the latter, increments in adrenomedullary epinephrine secretion.¹⁰ Insulin secretion normally decreases as plasma glucose levels decline within the physiological range; glucagon and epinephrine secretion increases as plasma glucose levels fall just below the physiological range. Low insulin and high glucagon and epinephrine levels increase glucose production, and low insulin and high epinephrine levels limit extra central nervous system (CNS) glucose utilization. If these physiological defenses fail to reverse falling plasma glucose concentrations, lower plasma glucose levels cause symptoms of hypoglycemia that prompt the behavioral defense, the ingestion of carbohydrates.¹⁰ Awareness of hypoglycemia, and thus the behavioral defense, is largely the result of the perception of neurogenic (autonomic) symptoms.¹¹ These include adrenergic symptoms, such as palpitations, tremor, and arousal/anxiety, and cholinergic symptoms, such as sweating, hunger, and paresthesias.¹¹ They are largely the result of sympathetic neural, rather than adrenomedullary, activation.¹²

All of these defenses against falling plasma glucose concentrations are typically compromised in type 1 DM and advanced (ie, insulin-deficient) type 2 DM.^{1,5,6} In established type 1 DM, circulating insulin levels cannot decrease as plasma glucose concentrations decline; in the absence of β -cells, insulin levels are a passive function of the clearance of administered insulin. Furthermore, in the absence of a β -cell signal, including a decrease in intraislet insulin,¹³ the α -cell glucagon response to hypoglycemia is also lost. In the absence of these first and second defenses, patients with type 1 DM are critically dependent on the third physiological defense, adrenomedullary epinephrine secretion. But the epinephrine response to hypoglycemia is often attenuated. Through mechanisms yet to be clearly defined but suspected to reside in the CNS,^{1,14,15} the glycemic threshold for sympathoadrenal, including adrenomedullary and sympathetic neural, activation is shifted to lower plasma glucose concentrations by recent antecedent hypoglycemia, as well as by prior exercise or sleep.^{1,14,15} In the setting of absent insulin

and glucagon responses, the attenuated epinephrine response causes the clinical syndrome of defective glucose counterregulation, which has been shown to increase the risk of severe hypoglycemia ≥ 25 -fold.¹ In addition, the attenuated sympathetic neural response causes the clinical syndrome of hypoglycemia unawareness (or impaired awareness of hypoglycemia)—impairment or even loss of the warning symptoms that previously prompted the behavioral defense, carbohydrate ingestion—which has been shown to increase the risk of severe hypoglycemia ~ 6 -fold.¹

The concept of hypoglycemia-associated autonomic failure (HAAF), first developed and documented in type 1 DM,^{1,5} posits that recent antecedent hypoglycemia (or prior exercise or sleep) causes both defective glucose counterregulation (by reducing the epinephrine response in the absence of insulin and glucagon responses) and hypoglycemia unawareness (by reducing the sympathetic neural and the resulting neurogenic symptom responses) and thus a vicious cycle of recurrent hypoglycemia. Perhaps the most compelling support for the clinical impact of HAAF in type 1 DM is the finding, in 3 independent laboratories, that as little as 2 to 3 weeks of scrupulous avoidance of hypoglycemia reverses hypoglycemia unawareness, and improves the reduced epinephrine component of defective glucose counterregulation, in most affected patients.¹

The concept of HAAF has been extended to patients with advanced (ie, insulin-deficient) type 2 DM.^{1,6} From the construct just explained, it is clear that the pathogenesis of HAAF, and thus an increased risk for iatrogenic hypoglycemia, stems fundamentally from β -cell failure. This causes loss of decrements in insulin and increments in glucagon in defense against falling plasma glucose concentrations and, in the presence of therapeutic hyperinsulinemia, episodes of hypoglycemia. Those, in turn, cause an attenuated sympathoadrenal response to subsequent hypoglycemia, the key feature of HAAF. Early in its course, type 2 DM is characterized by insulin resistance and relative hypoinsulinemia, conditions that allow decrements in insulin and increments in glucagon as plasma glucose levels fall and thus defense against hypoglycemia. Over time, however, absolute insulin deficiency develops.⁷ Thus, as patients approach the insulin-deficient end of the spectrum of type 2 DM, typically over many years, their insulin and glucagon responses to falling plasma glucose concentrations are lost.⁶ Furthermore, their glycemic thresholds for sympathoadrenal activation are shifted to lower plasma glucose concentrations by recent antecedent hypoglycemia.⁶ Thus, patients with advanced (ie, insulin-deficient) type 2 DM are also at risk for HAAF.

It is clear that the pathogenesis of hypoglycemia-associated autonomic failure, and thus an increased risk for iatrogenic hypoglycemia, stems fundamentally from β -cell failure.

The pathophysiology of defense against hypoglycemia is the same in type 1 and type 2 DM, but it develops rapidly in patients with type 1 DM (who become absolutely insulin deficient rapidly) but slowly in those with type 2 DM (who become absolutely insulin deficient slowly). This difference in the time course of the evolution of HAAF plausibly explains the relatively low frequency of iatrogenic hypoglycemia early in type 2 DM and the high frequency of iatrogenic hypoglycemia (approaching that in type 1 DM) later in type 2 DM, as discussed below.

THE FREQUENCY OF HYPOGLYCEMIA IN DIABETES MELLITUS

Hypoglycemia is a fact of life for most people with type 1 DM.¹ Plasma glucose concentrations may be < 50 mg/dL (2.8 mmol/L) as much as 10% of the time during aggressive glycemetic therapy of type 1 DM. The average patient suffers 2 episodes of symptomatic hypoglycemia a week—thousands of such episodes over a lifetime of DM—and 1 episode of severe hypoglycemia (ie, the assistance of another individual is required), often with seizure or coma, a year. An estimated 2% to 4% of people with type 1 DM die from hypoglycemia.¹

Overall, iatrogenic hypoglycemia is less frequent in type 2 DM than in type 1 DM.¹ However, hypoglycemia becomes progressively more frequent, and therefore more limiting to glycemetic control,¹⁶ in more advanced type 2 DM. Indeed, the frequency of hypoglycemia is reportedly similar in patients with type 2 DM and type 1 DM matched for duration of insulin therapy.¹⁷

Overall, iatrogenic hypoglycemia is less frequent in type 2 DM than in type 1 DM. However, hypoglycemia becomes progressively more frequent, and therefore more limiting to glycemetic control, in more advanced type 2 DM.

Ascertaining the incidence of hypoglycemia is a challenge. Asymptomatic episodes will be missed unless they are incidentally detected by routine self-monitoring of blood glucose (SMBG) (or reliable continuous interstitial glucose sensing). Because the symptoms of hypoglycemia are non-specific, symptomatic episodes may not be recognized as such. Even if these are recognized, they are not long remembered and therefore may not be reported at periodic clinic visits. Episodes of severe hypoglycemia are more dramatic events that are more likely to be recalled (by the patient or by an associate). Therefore, although they represent only a small fraction of the total hypoglycemic experience, estimates of the event rates of severe hypoglycemia are more reliable. Hypoglycemia event rates determined prospectively should be the most reliable.

It has been suggested that estimates of the frequency of iatrogenic hypoglycemia in type 2 DM, as well as in type 1 DM, are best determined from randomized clinical trials.⁴ However, there are limitations to that approach. First, hypo-

glycemia is not a primary outcome variable of clinical trials designed to assess the efficacy of a treatment regimen; therefore, the extent of the collection of hypoglycemia data varies. For example, detailed information about hypoglycemia was obtained in the Diabetes Control and Complications Trial in type 1 DM,¹⁸ but the hypoglycemia event rates in the United Kingdom Prospective Diabetes Study in type 2 DM are not known.¹⁹ Second, many clinical trials of insulin therapy in type 2 DM are conducted in patients who have recently failed to respond to therapy with oral agents and who are naive to insulin therapy. Enrollment of these patients is often part of a clinically relevant experimental design, but such patients are at low risk for iatrogenic hypoglycemia and not representative of those with advanced type 2 DM. Third, if used exclusively, this approach excludes evidence from clinical experience in DM specialist clinics^{20,21} and data from population-based, prospective studies.^{22–24}

The population-based, prospective study of Donnelly et al²² indicates that the hypoglycemia event rates in insulin-treated type 2 DM are about one third of those in type 1 DM (Table I). The severe hypoglycemia event rates were 115 per 100 patient-years in type 1 DM and 35 per 100 patient-years in insulin-treated type 2 DM. Furthermore, in population-based studies in hospital regions with known populations and incidences of type 2 DM and type 1 DM, the event rates for severe hypoglycemia requiring emergency medical treatment in type 2 DM were ~40%²³ and ~100%²⁴ of those in type 1 DM (Table I). Because the prevalence of type 2 DM is ~20-fold greater than that of type 1 DM, and since most

people with type 2 DM ultimately require treatment with insulin, these data suggest that the majority of episodes of iatrogenic hypoglycemia, including those of severe hypoglycemia, occur in people with type 2 DM. Clearly, the clinical impact of hypoglycemia in type 2 DM should not be underestimated.

THE RISK FACTORS FOR HYPOGLYCEMIA IN DIABETES MELLITUS

Conventional Risk Factors

The conventional risk factors for hypoglycemia in DM^{1,25} (Table II) are based on the premise that relative or absolute insulin excess is the sole determinant of risk. They include insulin or insulin secretagogue doses that are excessive, ill-timed or of the wrong type, and conditions in which exogenous glucose delivery or endogenous glucose production is decreased, glucose utilization is increased, sensitivity to insulin is increased, or insulin clearance is decreased. However, while each of these factors must be considered carefully, they explain only a minority of episodes of iatrogenic hypoglycemia in DM.²⁶

Risk Factors Indicative of Hypoglycemia-Associated Autonomic Failure

As discussed earlier, iatrogenic hypoglycemia in DM is the result of the interplay of relative or absolute therapeutic insulin excess and compromised physiological and behavioral defenses against falling plasma glucose concentrations—HAAF in DM.^{1,5,6} Risk factors indicative of HAAF^{1,25} (Table II) include the following: the degree of absolute insulin deficiency, which 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; and a history of severe hypoglycemia or of hypoglycemia unawareness, which indicate or imply, respectively, recent antecedent hypoglycemia that causes an attenuated sympathoadrenal response to subsequent hypoglycemia, the key feature of HAAF. Recent antecedent hypoglycemia, prior exercise, or sleep produce HAAF. Another risk factor for HAAF is aggressive glycemic therapy per se as evidenced by lower glycosylated hemoglobin (A1C) levels, lower glycemic goals, or both. As documented in controlled clinical trials,^{27,28} all other factors being equal, patients treated to lower A1C levels are at higher risk for hypoglycemia. That does not, of course, mean that one cannot both improve glycemic control and minimize the risk of hypoglycemia in individual patients (as discussed below).

THE PREVENTION OF HYPOGLYCEMIA IN DIABETES MELLITUS

It is possible to improve glycemic control and to reduce the frequency of hypoglycemia in many patients with inadequately controlled DM, recurrent hypoglycemia, or both. The prevention of hypoglycemia requires the practice of hypoglycemia risk factor reduction.^{1,25} This reduction practice includes 4 steps.

Table I. Population-based estimates of the incidence of hypoglycemia in type 1 diabetes mellitus (DM) and type 2 DM. The event rates in type 2 DM as a percentage of those in type 1 DM are also shown.

	Episodes/100 Patient-Years	
	Any	Severe
Hypoglycemia		
Type 1 DM ²²	4300	115
Type 2 DM, insulin treated ²²	1600 (37%)	35 (30%)
Hypoglycemia requiring emergency medical treatment		
Type 1 DM ²³	–	3.8
Type 2 DM, insulin treated ²³	–	1.5 (39%)
Type 2 DM, all ²³	–	0.4 (11%)
Type 1 DM ²⁴	–	11.5
Type 2 DM, insulin treated ²⁴	–	11.8 (103%)

Table II. Risk factors for hypoglycemia in diabetes mellitus.^{1,25}

Conventional risk factors—absolute or relative insulin excess

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

Risk factors for hypoglycemia-associated autonomic failure

1. Absolute insulin deficiency
2. A history of severe hypoglycemia, hypoglycemia unawareness, or both, as well as recent antecedent hypoglycemia, prior exercise, and sleep
3. Aggressive glycemic therapy per se (as evidenced by lower glycosylated hemoglobin levels, lower glycemic goals, or both)

First, the issue of hypoglycemia should be addressed in every patient contact. People with DM are often reluctant to volunteer their experience with—or fear of—hypoglycemia. They should be given the opportunity to express their concerns freely so the problem can be dealt with if it exists. Obviously, patient concerns about hypoglycemia can be a barrier to glycemic control; that barrier should be recognized. It is often helpful to obtain input from a close associate who may have observed clues to episodes of hypoglycemia not recognized by the patient. Even if no concerns are expressed, examination of the SMBG record may disclose that hypoglycemia is a problem.

Second, if hypoglycemia is a problem, the principles of aggressive glycemic therapy should be considered and applied. These include patient education and empowerment, frequent SMBG, flexible insulin (or other drug) regimens, individualized glycemic goals, and ongoing professional guidance and support. The first principle, patient education, is fundamentally important. As the therapeutic regimen becomes progressively more complex—early in type 1 DM and later in type 2 DM—the success of glycemic management becomes progressively more dependent on the management decisions and skills of a well-informed patient. Frequent SMBG data (supplemented in some instances with reliable continuous interstitial glucose sensing) can reasonably be expected to provide insight, leading to rational modifications of the therapeutic regimen. SMBG becomes more key to short-term treatment decisions as the regimen becomes more complex. In advanced type 2 DM, as in type 1 DM, the use of long-acting basal and rapid-acting prandial

insulin analogues can minimize, at least, the risk of nocturnal hypoglycemia.^{9,29} Among the commonly used sulfonylureas, glyburide (glibenclamide) is most frequently associated with hypoglycemia.³⁰ Although the generic goal is an A1C level as low as can be safely accomplished, there is a substantial long-term benefit from reducing an A1C from high to lower—albeit still above desirable—levels.^{27,28} Thus, glycemic goals should be individualized. Finally, since the glycemic management of DM in a given individual is empirical, caregivers should work with the individual patient to try a variety of approaches to glycemic control.

Third, the conventional risk factors for hypoglycemia (**Table II**) should be considered carefully, and the regimen adjusted accordingly.

Fourth, the risk factors indicative of HAAF in DM (**Table II**) should be considered. A history of severe hypoglycemia is a warning sign. Unless the cause of such an episode is easily remediable, a fundamental change in the therapeutic regimen is needed. Otherwise, the risk of a subsequent episode is high.¹⁸ Given a history of hypoglycemia unawareness, a 2- to 3-week period of scrupulous avoidance of hypoglycemia is advisable since that can be expected to restore awareness.¹ Thus, glycemic goals may need to be raised in the short term. A history of late postexercise hypoglycemia, nocturnal hypoglycemia, or both should prompt appropriately timed regimen adjustments (generally less insulin, more carbohydrate ingestion, or both) or, failing those, a pharmacologic bedtime treatment.³¹

CONCLUSIONS

In many people with DM, including those with advanced type 2 DM, it is possible to both improve glycemic control and to minimize the frequency of hypoglycemia. Nonetheless, it is not currently possible to maintain euglycemia and eliminate hypoglycemia over a lifetime of DM in the vast majority of affected people. Achievement of these goals will require safe and effective glucose-regulated insulin replacement (eg, closed-loop insulin replacement) or glucose-

It is possible to improve glycemic control and to reduce the frequency of hypoglycemia in many patients with inadequately controlled DM, recurrent hypoglycemia, or both. The prevention of hypoglycemia requires the practice of hypoglycemia risk factor reduction.

regulated insulin secretion (eg, implantation of insulin-secreting tissue). Pending the prevention and cure of DM, people with this disease need safe and effective therapies. In the meantime, insight into the mechanisms of HAAF may lead to interventions that will further improve the lives of people affected by DM by reducing the frequency of hypoglycemia without compromising glycemic control.

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