Hypoglycemia in Type 2 Diabetes

Philip E. Cryer

CONTENTS

Hypoglycemia in Diabetes: The Clinical Problem
Frequency of Hypoglycemia
Physiology and Pathophysiology of Glucose Counterregulation
Risk Factors for Hypoglycemia
Prevention of Hypoglycemia: Risk Factor Reduction
Treatment of Hypoglycemia
Perspective
Acknowledgments
References

Summary

Iatrogenic hypoglycemia is the limiting factor in the glycemic management of diabetes. It can be caused by sulfonylureas or other insulin secretagogues, and perhaps by metformin, as well as by insulin. Hypoglycemia is less frequent overall in type 2 diabetes (T2DM), compared with type 1 diabetes (T1DM). However, it becomes a progressively more frequent problem, ultimately approaching that in T1DM, in advanced (i.e., insulin deficient) T2DM because of compromised glucose counterregulation—the syndromes of defective glucose counterregulation and hypoglycemia unawareness, the components of hypoglycemia-associated autonomic failure—alphanumeric to that which develops early in the course of T1DM. Clearly, prevention of hypoglycemia is preferable to its treatment. By practicing hypoglycemia risk reduction—addressing the issue, applying the principles of aggressive glycemic therapy and considering both the conventional risk factors and those indicative of compromised glucose counterregulation—the therapeutic goal is to reduce mean glycemia as much as can be accomplished safely in a given patient at a given stage of T2DM. Particularly in view of the growing array of glucose-lowering drugs that can be used to optimize therapy, hypoglycemia should not be used as an excuse for poor glycemic control. Nonetheless, better methods, such as those that would provide plasma glucose regulated insulin secretion or replacement, are needed for people with T2DM, as well as those with T1DM, if euglycemia is to be maintained over a lifetime of diabetes.

Key Words: Hypoglycemia; barrier to glycemic control; therapy with sulfonylureas; therapy with metformin; therapy with insulin; insulin analogues; glucagon; epinephrine; defective glucose counterregulation; hypoglycemia unawareness; hypoglycemia-associated autonomic; failure.

Hypoglycemia in Diabetes: The Clinical Problem

Iatrogenic hypoglycemia is the limiting factor in the glycemic management of diabetes (1–3). It causes recurrent morbidity in most people with type 1 diabetes (T1DM) and many with type 2 diabetes (T2DM), and is sometimes fatal. The barrier of hypoglycemia—its reality and its possibility—precludes maintenance of euglycemia over a lifetime of diabetes and thus full realization of the vascular benefits of glycemic control (4–6). Importantly, episodes of hypoglycemia, even asymptomatic episodes, impair physiological and behavioral defenses against subsequent hypoglycemia by causing hypoglycemia-associated autonomic failure (the clinical syndromes of defective glucose counterregulation and hypoglycemia unawareness) and thus a vicious cycle of recurrent hypoglycemia (1–3).
Episodes of iatrogenic hypoglycemia cause both physical and psychological morbidity. The physical morbidity ranges from unpleasant neurogenic symptoms (e.g., sweating, hunger, anxiety, palpitations, and tremor) and neuroglycopenic manifestations (e.g., behavioral changes and cognitive impairment) to expressions of severe neuroglycopenia such as seizure and coma. Transient focal neurological deficits sometimes occur. Although seemingly complete neurological recovery is the rule, severe, prolonged hypoglycemia can result in permanent neurological damage, and even death (7). At the very least, an episode of hypoglycemia is a nuisance and a distraction. It can be embarrassing and lead to social ostracism. The additional psychological morbidity includes fear of hypoglycemia, guilt about that rational fear and high levels of anxiety that can be an impediment to glycemic control. The performance of critical tasks, such as driving, is measurably impaired, as is judgement.

Because the glycemic thresholds for the manifestations of hypoglycemia are dynamic—they shift to higher than normal plasma glucose concentrations in poorly controlled diabetes and to lower than normal plasma glucose concentrations in well controlled diabetes, as discussed later—it is not possible to specify a plasma glucose concentration that defines hypoglycemia in people with diabetes. The diagnosis is made most convincingly by documentation of Whipple’s Triad: symptoms consistent with hypoglycemia, a low plasma glucose concentration, and relief of those symptoms after the plasma glucose concentration is raised to (or above) normal. Nonetheless, the American Diabetes Association Workgroup on Hypoglycemia (8) recommended that people with diabetes should become concerned, and consider defensive actions, at a plasma glucose concentration ≤ 70 mg/dL (3.9 mmol/L). That plasma glucose level approximates the lower limit of the postabsorptive plasma glucose concentration range and the glycemic threshold for activation of glucose counterregulatory (plasma glucose-raising) systems, as well as the upper level at which an antecedent low plasma glucose concentration results in reduced glucose counterregulatory responses to subsequent hypoglycemia, in nondiabetic individuals. The Workgroup also recommended a classification of hypoglycemia in people with diabetes (Table 1). On this background of the clinical problem of hypoglycemia in diabetes, the incidence and pathophysiology of, and risk factors for, hypoglycemia in T2DM and clinical approaches to its prevention and treatment are discussed in this chapter. The premises are that iatrogenic hypoglycemia becomes progressively more limiting to glycemic control as patients approach the insulin deficient end of the spectrum of T2DM, that the pathophysiology of glucose counterregulation becomes similar to that in T1DM as patients progress across that spectrum, and that it is possible to both improve glycemic control and reduce the risk of hypoglycemia even in advanced, insulin deficient T2DM, just as it is in T1DM (1–3).

**FREQUENCY OF HYPOGLYCEMIA**

During aggressive glycemic therapy, the average patient with T1DM suffers plasma glucose concentrations <50 mg/dL (2.8 mmol/L) approx 10% of the time, symptomatic hypoglycemia about twice a week and severe, at least temporarily disabling, hypoglycemia about once a year (1). Valid estimates of the frequencies of these hypoglycemia (i.e., those based on controlled studies designed to include treatment to near euglycemia) during aggressive glycemic therapy of T2DM are limited (1). Ascertainment of hypoglycemia in T2DM is a

---

**Table 1**

American Diabetes Association Workgroup on Hypoglycemia recommended classification of hypoglycemia in people with diabetes (8)

<table>
<thead>
<tr>
<th>Classification</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Severe Hypoglycemia</strong></td>
<td>An episode requiring the assistance of another person to raise the plasma glucose concentration resulting in resolution of symptoms, with or without a measured low plasma glucose concentration.</td>
</tr>
<tr>
<td><strong>Documented Symptomatic Hypoglycemia</strong></td>
<td>Symptoms consistent with hypoglycemia with a measured plasma glucose concentration ≤ 70 mg/dL (3.9 mmol/L).</td>
</tr>
<tr>
<td><strong>Asymptomatic Hypoglycemia</strong></td>
<td>A measured plasma glucose concentration ≤ 70 mg/dL (3.9 mmol/L) in the absence of symptoms.</td>
</tr>
<tr>
<td><strong>Probable Symptomatic Hypoglycemia</strong></td>
<td>Typical symptoms of hypoglycemia without a measured plasma glucose concentration.</td>
</tr>
<tr>
<td><strong>Relative Hypoglycemia</strong></td>
<td>Typical symptoms of hypoglycemia with a measured plasma glucose concentration &gt;70 mg/dL (3.9 mmol/L) but approaching that level. (Such episodes occur in people with poorly controlled diabetes.)</td>
</tr>
</tbody>
</table>