Hypoglycemia—The Major Barrier to Good Glycemic Control

a report by
Stephen N Davis, MD, FRCP, *and* **Julia P Dunn, MD**

Division of Diabetes, Endocrinology and Metabolism, Vanderbilt University Medical Center, Nashville Veterans Affairs Medical Center

DOI: 10.17925/USE.2006.00.1.33

Approximately 20.8 million Americans (14.6 million diagnosed and 6.2 million undiagnosed) have diabetes mellitus (DM) and in 2002 it was the sixth leading cause of death, emphasizing the need for improved treatment. However, iatrogenic hypoglycemia precludes reaching and maintaining euglycemia. During the Diabetes Control and Complications Trial (DCCT) and United Kingdom Prospective Diabetes Study (UKPDS), outcomes of diabetes improved while hypoglycemia worsened with intensive therapy. The consequence was that hypoglycemia became the major obstacle to achieving the stated glycemic targets in these studies. As a result, hypoglycemia becomes a major barrier in improving outcomes in type 1 and type 2 DM. This has considerable financial implications as at least US$40 billion is spent each year in the US on complications of diabetes. Understanding the mechanisms and impact of hypoglycemia in diabetes is vital so that it can be addressed clinically. Furthermore, newer pharmacologic agents offer the clinician options to reduce iatrogenic hypoglycemia.

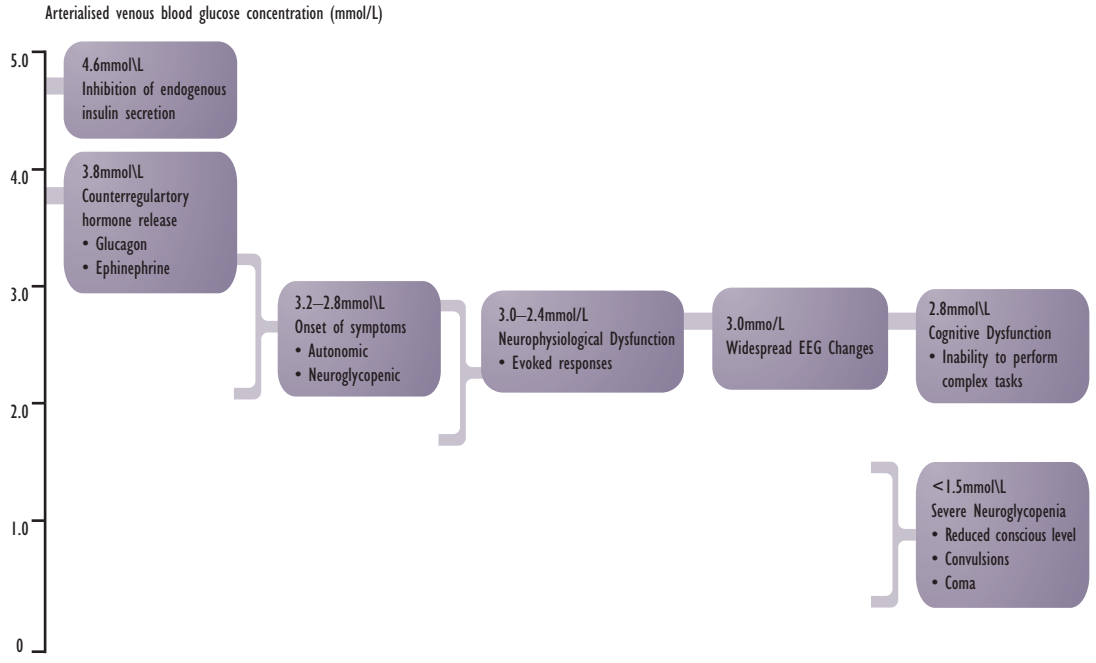
Risk factors have been identified for iatrogenic hypoglycemia, and physiologic studies have revealed the mechanisms of many of these risk factors. Predictors of severe (requiring assistance) hypoglycemia identified through the DCCT include prior history of severe hypoglycemia, longer duration of diabetes, higher baseline glycosylated hemoglobin (HbA1c), and lower treatment HbA1c in type 1 DM. The strongest predictor of future episodes of hypoglycemia was the number of prior episodes. In type 2 DM, the risk of hypoglycemia increases with disease duration and duration of insulin therapy. Counter-regulatory responses to hypoglycemia are the physiologic changes that occur to increase blood glucose and protect the body and brain from severe hypoglycemia. These responses become altered in diabetics and the pathophysiologic changes add to the above identified risk factors.

The characteristic physiologic counter-regulatory response to hypoglycemia has been described in detail elsewhere and will be briefly explained here. Hypoglycemia occurs when an imbalance of insulin and energy consumption and output (exercise) exists. As plasma glucose (pg) declines, the first counter-regulatory response is for insulin secretion to decrease. As pg continues to decline, glucagon, epinephrine, cortisol, norepinephrine and growth hormone secretion increases. Epinephrine and glucagon are the two primary counter-regulatory hormones, and their metabolic effects are seen within minutes, increasing available glucose, decreasing glucose utilization and contributing to suppression of insulin secretion. Cortisol, norepinephrine and growth hormone do not play a role in the acute defense against hypoglycemia. These later hormones only have metabolic effects during very prolonged hypoglycemia (hours) and then only one-quarter to one-fifth of the counter-regulatory actions of epinephrine and glucagon. If pg falls further, autonomic (neurogenic) symptoms (e.g. tremor, palpitations, anxiety, hunger) develop, prompting an individual to take in food. Lower pg will cause neuroglycopenic symptoms (e.g. confusion, fatigue, weakness) to develop and can be severe, including seizures or loss of consciousness. However, the more severe symptoms should not occur if the counter-regulatory system is intact and the individual increases food intake (see *Figure 1*).

Historically, a relative excess of exogenous insulin was considered to be the only cause of hypoglycemia in type 1 diabetes. However, our understanding of the mechanisms of counter-regulatory responses to hypoglycemia has improved significantly over the last two decades. It has been demonstrated that type 1 DM sufferers lose the ability to secrete glucagon in response to hypoglycemia after a few years of disease. The mechanism(s) responsible for this finding are currently a subject for intense investigation. Current plausible explanations include a lack of 'switch-off signal' for falling endogenous insulin levels to activate alpha-cell secretion of glucagon and/or sympathetic autonomic neuropathy. In intensively treated type 1 DM, the epinephrine response is suppressed for a given level of hypoglycemia and the glycemic threshold for a response is decreased. (Glycemic threshold is the pg level that

Stephen N Davis, MD, FRCP, is the Rudolph Kampmeier Professor of Medicine and Professor of Molecular Physiology and Biophysics at the Vanderbilt University School of Medicine in Nashville, TN. He is also Chief of the Division of Diabetes, Endocrinology and Metabolism and is the Associate Director of two National Institutes of Health (NIH)-funded programs at Vanderbilt – the Diabetes Research and Training Center and the General Clinical Research Center. Dr Davis received his medical training at London University, UK. He completed a fellowship in diabetes at Vanderbilt in 1991 and is a Fellow of the Royal College of Physicians (RCP). His research includes studies of hypoglycemic counter-regulatory dysfunction, exercise physiology, autonomic nervous system control of metabolism, and new therapies for type 1 and type 2 diabetes. He has authored over 127 original articles and book chapters and is widely recognized for his contributions to the physiology of counter-regulatory responses to hypoglycemia and exercise. Dr Davis has received numerous awards. He is a regular peer reviewer for many prestigious journals in the areas of diabetes, endocrinology, and metabolism, including *Diabetes Care*, *Diabetes*, *Journal of Clinical Investigation*, and *Endocrinology*. He is a member of the American Diabetes Association (ADA), American Society for Clinical Investigation (ASCI), and the American Association of Clinical Endocrinologists (AACE), among others.

Figure 1: Glycemic Thresholds for Secretion of Counter-regulatory Hormones and Onset of Physiological, Symptomatic, and Cognitive Changes in Response to Hypoglycemia in the Non-diabetic Human



Reproduced from Frier and Fisher, Hypoglycaemia in Clinical Diabetes. From: Zammitt and Frier.[28]

activates a counter-regulatory response.) The combination of absent glucagon and reduced epinephrine responses in type 1 DM increases the risk of severe hypoglycemia up to 25 fold. Downward shifts of glycemic thresholds are also contributors to the development of the syndrome of hypoglycemia unawareness (HU). Insulin-dependent diabetics with HU do not develop symptoms (either autonomic or neuroglycopenic) until their pg is close to a level where loss of consciousness may occur.

Hypoglycemia-associated autonomic failure (HAAF) is a syndrome consisting of defective glucose counter-regulation (particularly of the critical counter regulatory hormone epinephrine) with HU, resulting from antecedent hypoglycemia. The role of antecedent hypoglycemia as the cause of HAAF is supported by numerous studies in non-diabetics and type 1 and type 2 DM; however, there is still considerable debate as to the mechanisms by which recent hypoglycemia causes HAAF. Several studies have demonstrated that strict avoidance of hypoglycemia in type 1 DM can reverse HU. Several studies have also reported a recovery of epinephrine secretion, but this has not been an undisputed finding. Exercise can also result in HAAF, as antecedent exercise blunts counter-regulatory responses to hypoglycemia and antecedent hypoglycemia blunts counter-regulatory responses to exercise. This new knowledge allows clinicians to modulate insulin dosage (reduce) and carbohydrate intake (increase) to prevent exercise-associated hypoglycemia. Additionally, the role sleep plays in hypoglycemic counter-regulatory failure has recently been elucidated. Type 1 DM patients are less likely to be awakened by hypoglycemia and have reduced levels of epinephrine when hypoglycemic during sleep. Even though precise mechanisms of HAAF are still under investigation, this concept needs to be incorporated into clinical approaches when addressing recurrent episodes of hypoglycemia.

Type 2 DM has an array of phenotypes that can respond differently to hypoglycemia. The UKDPS clearly indicated that type 2 DM patients receiving insulin therapy have increased hypoglycemic events compared with those on oral antidiabetic agents (OADs). The study also established the progressive nature of the disease with subjects requiring increasing numbers of oral agents and insulin with time. Insight into how hypoglycemia effects type 2 diabetics at different stages of the disease has been the focus of a few recent studies. Levy et al. reported that the glucagon response to hypoglycemia is preserved in non-insulin-requiring type 2 DM. The glycemic threshold for epinephrine and norepinephrine release

increased as HbA1c increased and for each level it was greater in type 2 than in type 1 DM; conversely, the threshold decreased as HbA1c decreased.

Segel et al. compared counter-regulatory responses to hypoglycemia in both insulin-requiring and non-insulin-requiring type 2 DM. Their work supported the finding that non-insulin-requiring type 2 diabetics maintain a glucagon response to hypoglycemia but that insulin requiring type 2 diabetics have a nearly absent glucagon response similar to type 1 DM. This study also demonstrated that recent antecedent hypoglycemia lowered glycemic thresholds in type 2 DM for epinephrine, norepinephrine and autonomic symptoms. They concluded that advanced insulin-requiring type 2 diabetics are at risk of HAAF since they lack a glucagon response, and recurrent hypoglycemia attenuates epinephrine response and shifts the glycemic threshold for autonomic symptoms.

Type 1 diabetics may have asymptomatic hypoglycemia 10% of the time and have symptomatic hypoglycemia twice a week. A comparison of insulin-treated type-1 and type 2 DM reported the frequency of hypoglycemia as 43 versus 16 events per patient year and the frequency of severe hypoglycemia as 1.15 versus 0.35 per patient year, respectively. Other sources have indicated the rates of severe hypoglycemia in type 1 and insulin-requiring type 2 to be as high as 62–170 episodes per 100 patient-years and three to 73 episodes per 100 patient-years, respectively.

There are limited data on the healthcare cost of iatrogenic hypoglycemia. Analysis of healthcare claims from five large employers revealed significant differences between insulin-requiring diabetic employees with hypoglycemia and those without hypoglycemia. Of the employees with hypoglycemia, hospitalization and emergency room visits were doubled and there was an excess medical expenditure of US$3,241 per patient directly related to hypoglycemia. Furthermore, comparing the group with hypoglycemia with those without, the rates of short-term disability (work absence related to health problems) were 19.5 versus 11 days per person-year, respectively. Another claims analysis revealed that during a six-year follow-up, 16% of insulin-treated DM patients had an episode of hypoglycemia requiring medical attention with the mean cost per episode at US$1,186.

A retrospective claims analysis in Medicaid patients in California evaluated the cost differential before and after six months of glargine insulin treatment, which has a reduced hypoglycemia profile. It was reported that the glargine group had a total diabetes-related cost reduction of US$69 per person during the first six months despite an increase in pharmacy claims. The in-patient claims decreased by US$96 per patient and there was a decline in hypoglycemia-related in-patient claims from 9.5% to 3.8%. Even though there are very limited data on strategies to decrease the financial burden of hypoglycemia, this study supports that even short-term cost savings can occur with interventions that decrease hypoglycemia.

Sulfonylureas (oral insulin secretagogues) were the first class of pharmacologic agents available for type 2 DM and remain a mainstay of therapy. However, they are the oral agent class most commonly complicated by hypoglycemia. More commonly used sulfonylureas include second-generation glibenacamide (glyburide), gliclazide (not available in US), and glipizide, and third-generation glimepiride. First-generation agents, such as chlorpropamide, are now rarely initiated due to side effects including frequent hypoglycemia. Population studies based in clinical practice have indicated increased episodes of severe hypoglycemia with glyburide compared with glimepiride and gliclazide. It is well-established that older long-acting sulfonylureas, such as chlorpropamide and glyburide, increase the prevalence of hypoglycemia compared with short-acting agents, as these agents cause a greater mis-match in insulin release related to glucose availability. Randomized double-blind comparisons of glyburide to glimepiride and gliclazide demonstrated equivalent glycemic control (HbA1c) but increased hypoglycemia with glyburide. Glipizide is available in an immediate and an extended-release formulation. The extended release has been shown to offer equivalent glycemic control to glyburide. The authors did not specifically comment on differences in hypoglycemic events between the two drugs. However, extended-release glipizide dispensed in the morning did not show a significant change in fasting or 24-hour insulin unlike glyburide, which produced an increase in both. From this the authors proposed that extended-release glipizide may present a reduced risk of hypoglycemia compared with glyburide. The European GUIDE study compared once-daily monotherapy of gliclazide modified release (MR) with glimepiride. Results included equivalent glycemic control and no major hypoglycemia in either group, but there was significantly less hypoglycemia with gliclazide MR (3.7% versus 8.9%). The equivalent glycemic control with different hypoglycemic profiles offers some clinical options for managing hypoglycemia related to sulfonylurea treatment. ■

This article is continued, with references, tables and an additional graphic, in the Reference Sectiono on the website supporting this briefing (www.touchendocrinedisease.com).