

Hypoglycemia in Type 2 Diabetes—Consequences and Risk Assessment

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Abstract

Although hypoglycemia has traditionally been considered a significant complication of the treatment of type 1 diabetes, the greater incidence of type 2 diabetes compared with type 1, the intensive treatment strategies currently employed, and the longer life expectancy of patients with diabetes, give rise to a large number of type 2 patients at risk for hypoglycemia. This number is likely to rise in an aging population with the increasing use of insulin to treat diabetes. The highest incidence of hypoglycemia is seen in older patients with poor glycemic control and is associated with the use of antidiabetic agents that increase blood insulin concentrations independently of blood glucose concentration (oral antidiabetic drugs or exogenous insulin). Hypoglycemia has a substantial clinical impact in terms of mortality, morbidity, and quality of life. The economic impact of severe hypoglycemic events owing to direct hospital costs and the indirect costs of the inability to work are considerable. Furthermore, both patients' and physicians' fear of hypoglycemia reduces adherence to therapeutic regimens and limits the ability of current diabetes medications to achieve the level of glycemic control required to prevent disease progression. Newer therapies and improvements in patient education may help patients achieve improved glucose control by safely reducing glycosylated hemoglobin (HbA_{1c}) with a lower risk of hypoglycemia.

Keywords

Glycemic control, hypoglycemia, insulin, type 2 diabetes, glucagon-like peptide-1, incretin

Disclosure: Ildiko Lingvay, MD, MPH, MSCS, has received grant support and is an advisory board member for Novo Nordisk and a consultant for GI Dynamics.

Acknowledgments: Editorial assistance was provided by Sharon Cato at Touch Briefings and funded by Novo Nordisk. Dr Lingvay is supported by NIH K23 RR024470.

Received: January 4, 2012 **Accepted:** January 25, 2012 **Citation:** *US Endocrinology*, 2011;7(2):95–102 DOI: 10.17925/USE.2011.07.02.95

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Support: The publication of this article was funded by Novo Nordisk. The views and opinions expressed are those of the author and not necessarily those of Novo Nordisk.

Hypoglycemia in patients with type 2 diabetes is not often recognized as a risk with potential health consequences. Although the risk of hypoglycemia in patients with type 2 diabetes is not as great as that of patients with type 1 diabetes, the prevalence of type 2 diabetes is much greater, making it a clinically significant concern. As such, clinicians need to be aware of the hypoglycemic risk in patients with type 2 diabetes, as well as the immediate and long-term consequences of hypoglycemia. This article will review the prevalence of hypoglycemia in patients with type 2 diabetes, assess the consequences of hypoglycemia, discuss how to identify patients at risk of hypoglycemia, and provide an overview of diabetes management strategies aimed at lowering the risk of hypoglycemia.

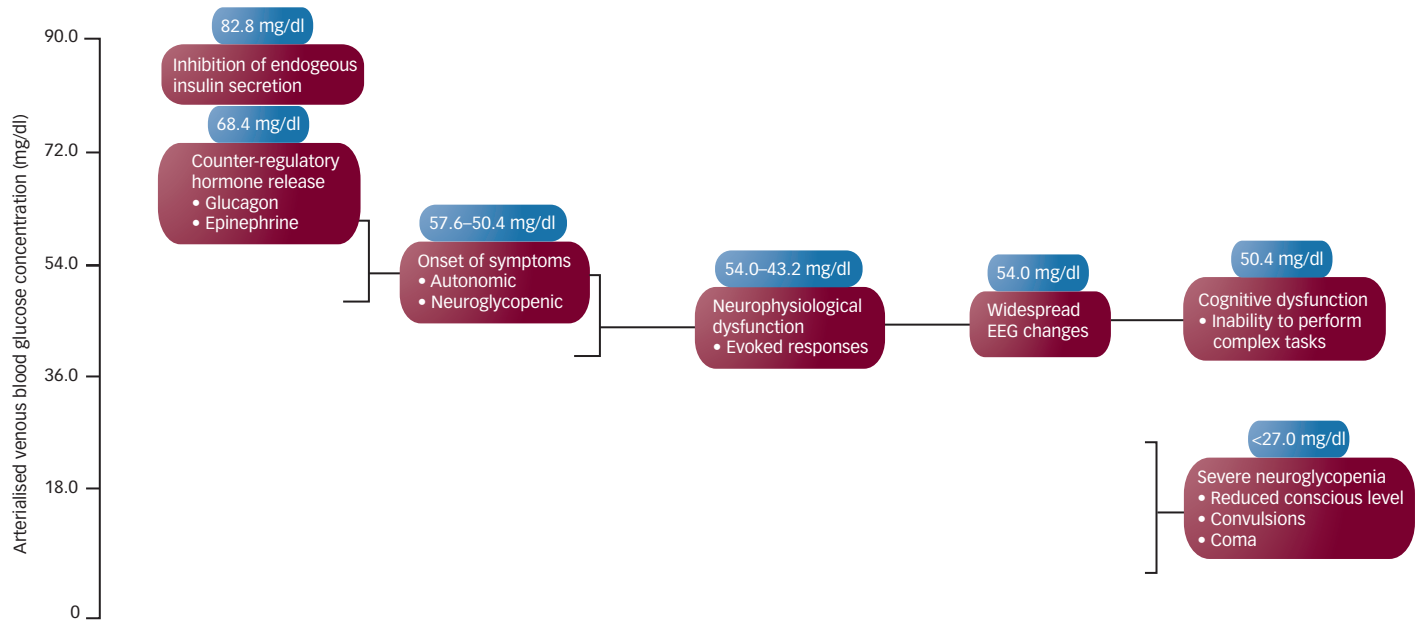
Definition of Hypoglycemia

Hypoglycemia is a frequent complication of diabetes therapy, yet there is no consensus definition. The formal definition of hypoglycemia is a condition characterized by a reduction in either plasma glucose concentration or its tissue utilization to a level that may induce symptoms or signs such as altered mental status and/or sympathetic nervous system stimulation. Criteria known as Whipple's triad are

usually used to diagnose hypoglycemia. This triad consists of low plasma glucose, presence of symptoms, and reversal of these symptoms when the plasma glucose level is restored to normal.¹

The level at which a patient becomes symptomatic differs between individuals, and thus there is great controversy when it comes to defining a clear threshold. In the last decade, the American Diabetes Association (ADA),² Canadian Diabetes Association (CDA),³ and European Agency for the Evaluation of Medicinal Products (EMA)⁴ have each set different thresholds for hypoglycemia, from <70.2 to <54.0 mg/dl. The American Association of Clinical Endocrinologists (AACE) classification states that, in general, symptoms of hypoglycemia occur when the plasma glucose level falls to 60.0 mg/dl.⁵ However, plasma glucose levels can be below these thresholds in healthy individuals, particularly women, and defining hypoglycemia as any value <70.2 mg/dl is likely to lead to overestimation of clinically significant hypoglycemia in the assessment of diabetes therapies.⁶ At the other end of the spectrum, studies in normal individuals often use a serum glucose level of >39.6 mg/dl as threshold, to avoid classifying healthy individuals with hypoglycemia.^{7,8} There is better agreement when defining hypoglycemia according to clinical

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



EEG = electroencephalogram. Reproduced from Frier and Fisher in Hypoglycaemia in Clinical Diabetes, 1999. Reproduced with permission of John Wiley & Sons Ltd.

symptoms, and it is generally accepted that a severe hypoglycemic event (HE) is one in which a patient is unable to self-treat and requires assistance,⁶ regardless of the glucose level.

Pathophysiology of Hypoglycemia

The brain primarily uses glucose as a source of energy, but is unable to synthesize or store it; hence, it is vulnerable to hypoglycemia. Physiological mechanisms that protect the brain from the effects of hypoglycemia, known as the counter-regulatory response (CRR) to hypoglycemia, involve the suppression of insulin release and activation of hormones such as glucagon and epinephrine that stimulate hepatic glucose production and inhibit peripheral glucose uptake.⁹ These usually remain functional until an advanced disease state. In non-diabetic adults, this response to a fall in blood glucose levels, along with the onset of symptoms of hypoglycemia, occur at reproducible blood glucose thresholds (see *Figure 1*). Recurrent hypoglycemia impairs the ability of the brain to detect and initiate the CRR to subsequent hypoglycemia.¹⁰

Although the physiology of the CRR is well understood, the underlying cellular mechanisms by which the brain senses hypoglycemia and initiates the CRR have only been elucidated in recent years. Absence of the glucagon response to falling plasma glucose concentrations plays a key role in the pathogenesis of hypoglycemia.¹¹ During hypoglycemia, central and peripheral glucose sensors detect declining glucose levels and initiate the CRR. Recent studies have found that impairment of the CRR is accompanied by a deficient response of ventromedial hypothalamic glucose-inhibited neurons to decreased glucose levels. Nitric oxide (NO) production in the ventromedial hypothalamus is critical for both the CRR and glucose sensing by glucose-inhibited neurons.^{11–16}

Prevalence of Hypoglycemia in Type 2 Diabetes

Since there is little consistency among diabetes studies regarding the definition of hypoglycemia, assessments of the prevalence of hypoglycemia among patients with type 2 diabetes should be interpreted with caution. A prevalence of 3.1 % was reported in a recent large sample cohort of 860,845 patients.^{17–22} Other reported prevalence data include 8.8 % in older patients (mean age 65, n=16,667);²² 34 % in self-reported patients treated with metformin and a sulfonylurea for at least six months (n=400);²¹ between 12 % using diet alone, and 30 % using insulin, in a study in which hypoglycemia was defined as typical symptoms relieved by eating and/or blood glucose level <59.4 mg/dl;¹⁹ and 63 % (46 % mild, 37 % moderate, 13 % severe, and 4 % very severe) in a study in which patients were treated with oral antihyperglycemic drugs (OADs) and episodes of hypoglycemia were self-reported.¹⁸

The wide range of the reported incidence illustrates the difficulty in assessing the prevalence of hypoglycemia. Variables include the type of hypoglycemia (for example, hypoglycemia requiring medical intervention versus mild hypoglycemia self-defined by the patient), as well as different study durations, treatment regimens, disease duration, and patient characteristics. These studies also fail to take into account nocturnal HEs, for which reported data are often sparse and imprecise.²³ Nocturnal hypoglycemia is likely to be underreported and is particularly dangerous because patients are unlikely to recognize symptoms or awaken during an episode.

Health Impact of Hypoglycemia

A recent literature review highlighted the potential impact of hypoglycemia on the lives of people with type 2 diabetes, including depression, heightened anxiety, and impairment of the ability to drive,

Table 1: Productivity Loss from a Non-severe Hypoglycemic Event

| | US | UK | Germany | France | p value |
|----------------------------|------------------------------|------------------------------|-----------------------------|------------------------------|---------|
| NSHE outside working hours | \$26.43 (SD 121.26) n=307 | \$46.30 (SD 157.60) n=287 | \$15.50 (SD 67.24) n=173 | \$61.12 (SD 144.41) n=279 | <0.001 |
| NSHE at work | \$31.12 (SD 124.91) n=278 | \$57.21 (SD 140.51) n=232 | \$15.26 (SD 65.16) n=170 | \$48.33 (SD 111.58) n=283 | <0.001 |
| NSHE at sleep at night | \$55.16 (SD 184.17) n=205 | \$83.59 (SD 177.30) n=153 | \$35.58 (SD 130.27) n=88 | \$93.47 (SD 197.62) n=166 | 0.002 |

NSHE = non-severe hypoglycemic event; SD = standard deviation. Costs provided for all countries in US dollars.
Source: Brod et al., 2011.⁴²

work, and function in ways that are important for quality of life (QoL).²⁴ Mild hypoglycemia does not have serious clinical effects, other than the potential to induce defects in the CRR and impaired awareness of subsequent HEs.⁶ However, even clinically trivial events may reduce adherence to therapeutic regimens.⁶

Severe HEs have serious clinical consequences, particularly in elderly patients with diabetes. A prospective study of patients aged >80 years with well-controlled type 2 diabetes reported that hypoglycemia was responsible for 25 % of hospitalizations associated with diabetes.²⁵ It has also been associated with behavioral changes, cognitive impairment, seizures, coma, and a mortality rate estimated at between 4.9 and 9 %.^{6,18}

In addition to the immediate risks associated with HEs, recurrent HEs can have serious consequences. In a retrospective study, patients with type 2 diabetes who experienced outpatient HEs as defined by the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), were also shown to have a 79 % higher odds ratio (OR) of experiencing acute cardiovascular events (OR 1.79) than patients without HEs. Because all HEs were identified through ICD-9-CM diagnosis coding, these events were likely to have been sufficiently severe to require medical intervention. Therefore, there were likely to have been many more episodes of hypoglycemia, especially episodes that were mild in nature, that were not captured in this study.¹⁷ Severe hypoglycemia can cause neuronal cell death and may damage regions of the brain that oversee memory, particularly in brains already vulnerable due to age. A longitudinal cohort study found an association between a history of severe HEs and the risk of dementia among older patients (mean age 65 years) with type 2 diabetes: the more HEs a patient experiences, the greater the chance of developing dementia, with ≥ 3 episodes almost doubling the risk.²²

A frequently overlooked problem in type 2 diabetes is nocturnal hypoglycemia. Although underreported, it increases with more intensified glucose control and in those with greater disease duration. Almost half of all severe HEs occur at night during sleep. Undetected nocturnal hypoglycemia often contributes to hypoglycemia unawareness, anxiety, loss of vitality, physical injury, poor QoL, and possibly, neurocognitive deficits.²⁶ Nocturnal hypoglycemia can cause convulsions and coma and has been associated with cardiac arrhythmias resulting in sudden death.²⁷ Although it appears to have no immediate detrimental effect on cognitive function, mood and wellbeing may be adversely affected by disturbed sleep secondary to nocturnal hypoglycemia. Recurrent nocturnal HEs may impair cognitive function.²⁷

The increasing prevalence of hypoglycemia could pose a threat to the ability of patients with diabetes to drive. In the UK, HEs are responsible for five fatal road accidents a year and 45 serious events every month.²⁸ Although the reported data does not distinguish between types 1 and 2 diabetes, it is likely that a proportion of these road accidents occur in patients with type 2 diabetes.

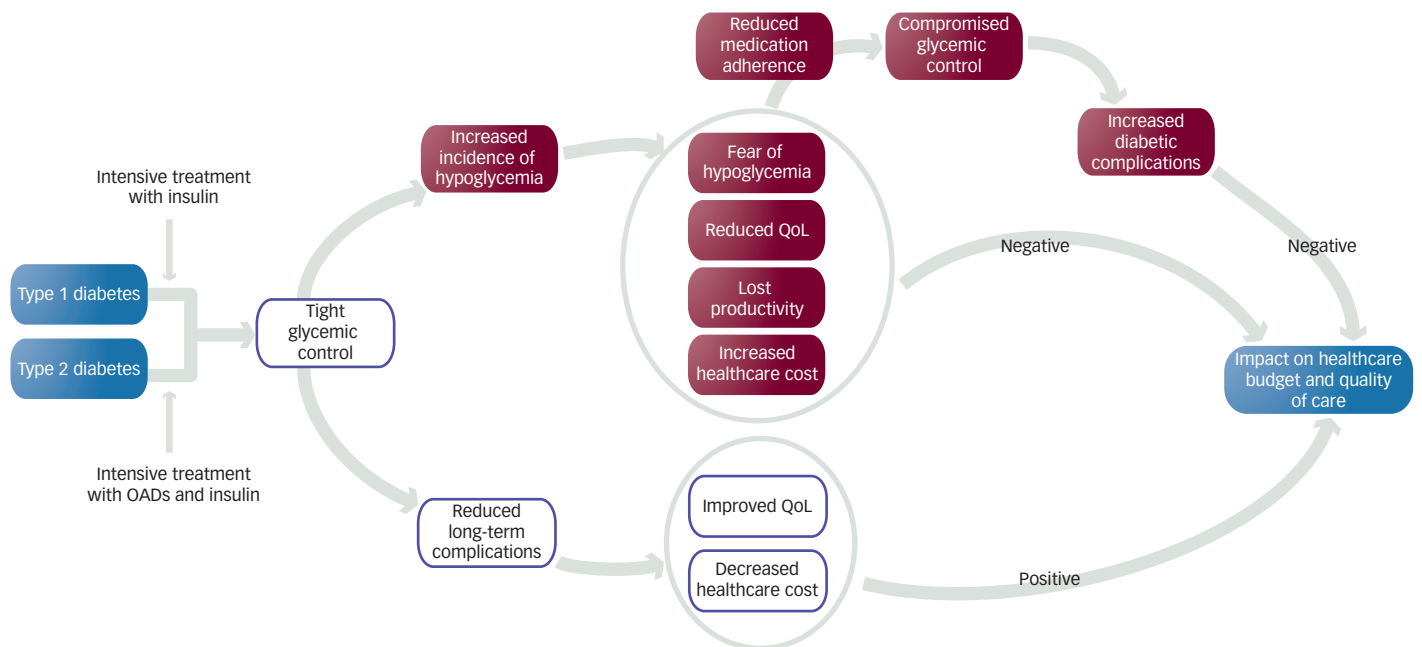
Hypoglycemia in individuals with type 2 diabetes may be associated with increased symptoms of chest pain and electrocardiographic abnormalities, and may account for sudden mortality.^{29–31} A case-control study evaluating the effect of hypoglycemia in patients with type 2 diabetes demonstrated a 65 % increase in the odds of myocardial infarction (MI) with hypoglycemia within the previous two weeks, even following adjustment for possible confounding cofactors. It was also noted that the risk of MI remained elevated (by approximately 20 %) for up to six months following a hypoglycemic event.³²

Social Impact of Hypoglycemia

Hypoglycemia in patients with type 2 diabetes is associated with significant reductions in QoL. The impact of hypoglycemia on QoL has been demonstrated in numerous surveys regardless of the measure of QoL.^{20,33–36} Patients who reported symptoms of hypoglycemia (n=286, 13.78 %) were significantly more likely to have a lower QoL in several parameters, including increased limitations on mobility (OR=1.93, $p<0.0001$) and usual activities (OR=1.78, $p<0.0001$), increased pain/discomfort (OR=2.00, $p<0.0001$), and anxiety/depression (OR=2.31, $p<0.0001$).³⁶ Even relatively minor hypoglycemia symptoms (e.g., sweating, hunger, anxiety) can reduce QoL.^{37,38}

Fear of hypoglycemia imposes an additional psychological burden. A US study assessed QoL according to the US-weighted summary score (utility) and worry subscale of the Hypoglycemia Fear Survey (HFS). The subscale comprises 18 questions that measure degree of patient fear in the past six months, and is scaled from 0 to 72 (from least to most worry). The EuroQoL-5D Questionnaire, a non-disease-specific instrument for assessing health-related QoL, was also administered. The unweighted summary scores were transformed into US preference-weighted index scores, -0.038–1.0, for the purposes of this study. Patients who reported HEs had a significantly lower mean utility score (0.78 versus 0.86, $p<0.0001$) and significantly higher mean HFS score (17.5 versus 6.2, $p<0.0001$) than those who did not report HEs. Differences in mean scores between those with and without HEs increased with the level of severity.³⁵ The magnitude of fear of hypoglycemia is associated with the severity and frequency of HEs.³⁹

Figure 2: Impact of Hypoglycemia on Patients and the Healthcare System



OAD = oral antihyperglycemic drug; QoL = quality of life.
 Source: adapted from Fidler et al., 2011.⁴⁰

Table 2: Treatment Options for the Management of Hypoglycemic Unawareness

| Options | Mechanism | Comment |
|------------------------------------|----------------------------------------------|-----------------------------------------------------------------------------------|
| Reducing hypoglycemia risk | Avoidance of hypoglycemia | Two-to-three weeks is sufficient to improve hypoglycemia unawareness clinically |
| Optimizing insulin treatment | Idem | Effect on counterregulation depends on effectiveness of hypoglycemia avoidance |
| Pharmacological therapy | | |
| • Alanine | Stimulation of glucagon response | Not tested in clinical trials |
| • β 2-adrenergic agents | Enhancement of adrenaline effect | Not tested in clinical trials |
| • Methylxanthine derivatives | CNS stimulation | May be efficacious, but emergence of tolerance may limit effect of long-term use |
| • KATP channel modulators | Modulation of hypoglycemia sensing | Not effective in humans, possibly due to inability to cross blood-brain barrier |
| • Fructose | Idem | Promising, but not tested in clinical trials |
| Miscellaneous | | |
| • Blood glucose awareness training | Improving accuracy of hypoglycemia detection | Intensive program that has only been found effective in the hands of its founders |
| • High-intensity exercise | Prevention of exercise-induced hypoglycemia | Single observation in a limited number of subjects |

CNS = central nervous system; KATP = adenosine triphosphate-sensitive potassium.
 Source: reproduced from de Galan et al., 2006,⁴⁶ with permission from the editor, Van Zuiden Communications BV.

Fear of hypoglycemia may promote compensatory behaviors such as decreased insulin doses, resulting in poor glycemic control and an increased risk of serious health consequences.⁴⁰

Economic Impact of Hypoglycemia

The economic impact of HEs in patients with type 2 diabetes is substantial (see Figure 2). A Swedish study estimated the direct and indirect costs of hypoglycemia in type 2 diabetes patients with hypoglycemic symptoms at between \$12.90 and \$14.10 for a one-month period.⁴¹ A recent survey (n=1,404) estimated that lost productivity

ranged from \$15.26 to \$93.47 per HE, representing 8.3–15.9 hours of lost work time per month (see Table 1). Among respondents who experienced an HE at work (n=972), 18.3 % missed work for a mean duration of 9.9 hours. Among those who had HEs outside working hours (including nocturnally), 22.7 % arrived late for work or missed a full day. Nocturnal HEs had the greatest impact on productivity loss, with an average of 14.7 working hours lost.⁴²

Hypoglycemia also represents a considerable economic burden in terms of healthcare systems. Reported costs of a severe HE varied from

approximately \$80 to \$5,000, depending on the requirement for resources, including hospitalization, emergency services, healthcare professionals, and diagnostic tests. Furthermore, because the cost of a severe HE is higher than that of a mild episode, it may be assumed to have a larger impact on the economy. However, the annual costs of non-severe HES should not be overlooked. Due to their higher frequency, non-severe HES may incur annual costs that are similar to severe HES.⁴⁰ Annual out-of-pocket costs per person attributable to the treatment of hypoglycemia have been reported to be similar for mild/moderate events and severe events.⁴³ A further cost associated with hypoglycemia is patient self-monitoring of blood glucose. Patients monitor their blood glucose more frequently following an HE; in the week following a non-severe HE, compared with usual blood glucose monitoring practices, patients performed an average of 5.6 (standard deviation 8.5) extra self-monitoring tests.⁴²

Identification of At-risk Patients

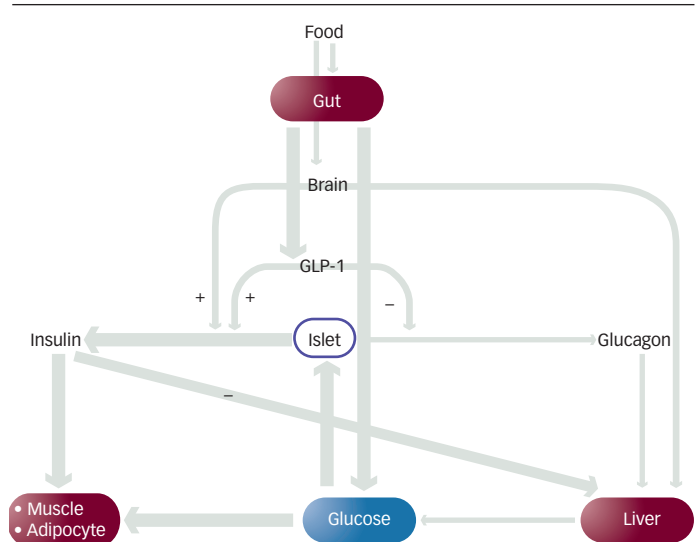
There are therapeutic, physiological, and behavioral risk factors for individual episodes of hypoglycemia in patients with type 2 diabetes.^{19,44–46} Missed or irregular meals have been identified as the most frequent behavioral factor that causes individual episodes of severe hypoglycemia.^{47,48} Incorrect use of glucose-lowering medication (dose/timing), exercise, and alcohol are other lifestyle factors.⁴⁴

The incidence of HES is highest in older patients with poor glycemic control.⁴⁹ In the UK prospective diabetes study (UKPDS), the rate of severe hypoglycemia rose once the known diabetes duration exceeded nine years.⁵⁰ Factors that may increase the likelihood of hypoglycemia include duration of diabetes, presence of other comorbidities, renal impairment, loss of residual insulin secretion, defective counter-regulation, weight gain in the last 12 months, microvascular complications, and specific cardiovascular conditions (angina, heart attack, stroke, peripheral vascular disease, or congestive heart failure).^{6,18} The UKPDS found the highest incidence of hypoglycemia in patients with type 2 diabetes who used insulin.⁵⁰ Some of these factors are interrelated, as increasing diabetes duration is invariably associated with increasing age and increasing loss of endogenous insulin secretion.

The most common cause of hypoglycemia in type 2 diabetes is iatrogenic, occurring with the use of insulin secretagogues and insulin therapy.^{44,51} These can overwhelm the normal physiological response to a fall in plasma glucose, primarily by preventing a corresponding drop in circulating insulin. Defects in glucagon and other stress responses develop during type 2 diabetes and these are worsened by specific therapies, such as sulfonylurea drugs, which sustain intrapancreatic insulin levels during hypoglycemia.⁵²

At the University of Texas Southwestern Medical Center and its affiliated clinics, by far the most common cause of hypoglycemia is the inappropriate administration of insulin. A careful history helps identify whether the timing of meals and insulin administration is adequate. Regular human insulin should be injected 30–40 minutes prior to commencement of a meal, while rapid-acting analog insulins should be injected 5–15 minutes prior to a meal. Additionally, if mixed insulins (either premixed or self-mixed) are used, the timing of the second meal

Figure 3: Schematic View of the Control of Prandial Circulating Glucose Levels



GLP-1 = glucagon-like peptide-1.
Source: Ahren, 2009.⁷⁶

(i.e., lunch) is also critical. Patients need to be instructed that delaying this meal past the peak action of the insulin, or missing this meal altogether, will lead to hypoglycemia. I recommend that patients using mixed insulins eat their lunch no later than five hours after the morning dose and have a light evening snack about four hours after the evening insulin dose. Obtaining a diet history with timing of meals and insulin injections is critical. Often patients assume that small frequent meals and snacks are the best regimen for diabetes, but this is not the case once insulin treatment is initiated, and they have to be instructed about the proper timing of their treatment and meals.

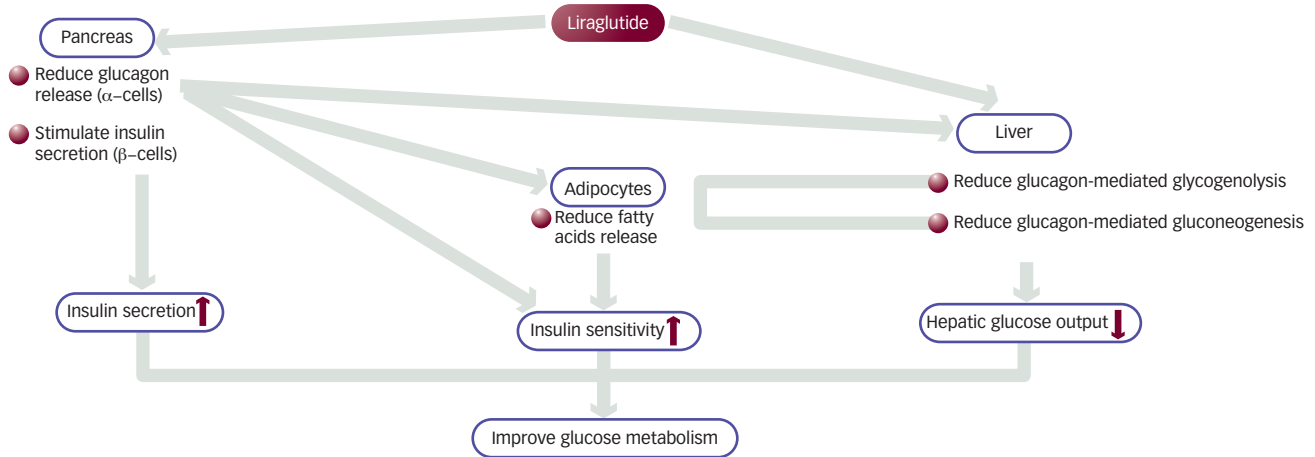
Another potential source of hypoglycemia is insulin dosing error. This can occur when patients have visual impairment or when small or uneven insulin units have to be delivered via a syringe. The smallest syringe should be used for the dose prescribed (i.e., for doses under 30 units, use a 30-unit syringe rather than a 50- or 100-unit syringe) and, whenever possible, round dosage increments should be used (prescribe 50 units rather than 48 units) to aid in the precision of the dosing. If a dosing error is still suspected, especially if the patient is insulin-sensitive and uses small amounts of insulin (in which case even a 1-unit error can have a significant impact on the glucose level), delivery via an insulin pen should be strongly considered.

Lastly, consider other comorbidities when evaluating patients with hypoglycemia. For example, a progressive worsening of renal function can lead to accumulation of insulin and increased risk of hypoglycemia.

Diabetes Management Strategies that Mitigate Hypoglycemia

According to the ADA and European Association for the Study of Diabetes (EASD) joint consensus statement, the first approach to type 2 diabetes treatment should be intervention at the time of diagnosis with metformin in combination with lifestyle changes, followed by augmentation of therapy with additional agents as a means of achieving

Figure 4: Possible Mechanisms for the Liraglutide-mediated Improvements in Glycemic Control Suggested by Study Switching from Premixed Insulin 50/50 to Liraglutide



Source: Yanai et al., 2011.⁸⁶

and maintaining recommended levels of glycemic control.⁵³ Appropriate targeting of plasma glucose may help patients and practitioners achieve glycosylated hemoglobin (HbA_{1c}) goals, reduce excessive self-testing, and minimize the occurrence of HES.⁵⁴

Subset analyses from the Action to control cardiovascular risk in diabetes (ACCORD) trial demonstrated that the lowest risk of mortality was related to lower mean levels of HbA_{1c} with the intensive therapy strategy. Risk of death increased steadily as mean levels increased from 6 % to 9 %. The minority subgroup of patients in the intensive therapy group who had HbA_{1c} levels higher than 7 % accounted for the excess risk associated with that therapy regimen. Therefore, trying to lower the HbA_{1c} level to less than 7 % with intensive treatment in therapy-resistant individuals may be detrimental.⁵⁵⁻⁵⁷ Basically, an HbA_{1c} goal of less than 7 % remains recommended, although goals should be individualized for selected patients. Unrecognized hypoglycemia and weight gain in the ACCORD study were also likely major contributors to its adverse outcomes.⁵⁸

Earlier and more intensive intervention when a patient is not experiencing severe HES, rather than waiting for an increase in HbA_{1c} and then intensifying glucose control, may improve the glycemic profile by avoiding prolonged periods of hyperglycemia.⁵⁹ Periods of glycemic exposure may be avoided by transitioning earlier to more intensive glucose therapy, instead of waiting for a rise in HbA_{1c} and then increasing glucose control. Intensive glucose control has demonstrated advantages, such as lowering the risk of non-fatal MI; however, it may also increase the risk of severe hypoglycemia.⁶⁰⁻⁶³ A meta-analysis of the effect of intensive glucose control on cardiovascular outcomes in individuals with type 2 diabetes found that a higher proportion of patients on intensive therapy than standard treatment had a hypoglycemic episode. Severe hypoglycemia was much less frequent than non-severe hypoglycemia; however, nearly twice as many patients on intensive therapy compared with those on standard treatment had a severe HE. Additionally, patients receiving intensive therapy were a mean of 2.5 kg heavier than those on standard treatment by the end of the study.⁶⁴

A major challenge in the management of HES in patients with type 2 diabetes is hypoglycemic unawareness, which is caused by deficient epinephrine response and characterized by a progressive loss of the autonomic symptoms of hypoglycemia, such as sweating, tremor, and palpitations, together with a reduced response of glucagon and epinephrine to falling levels of blood glucose.^{15,16} As a result, patients are unaware of the problem until they have central nervous system dysfunction and may not be able to appropriately respond to the hypoglycemia. Hypoglycemic unawareness is associated with a high risk of more severe HES that may result in seizures and coma.⁶⁵ However, the condition is reversible to some extent and several strategies for managing hypoglycemic unawareness exist, such as strict avoidance of HES for two to three weeks and optimizing insulin treatment (see *Table 2*).⁶⁶

Metformin often fails to maintain glycemic control over the long term, because disease progression is accompanied by a progressive decline in insulin-secreting β -cell function, which begins early in the disease course, and an impaired incretin response. After five years, metformin has been shown to have a 21 % failure rate.⁶⁷ The ADA and EASD recommend that patients who fail to achieve glycemic control on metformin should consider alternative regimens, including concomitant treatment with a sulfonylurea or insulin.^{53,68} However, effective insulin treatment is often delayed because of perceived fear of hypoglycemia.

Insulin has traditionally been considered a last resort for patients who fail to maintain glycemic control with diet and OADs. A recent study compared insulin-based therapy with an oral therapy-based treatment regimen in patients with newly diagnosed type 2 diabetes. Insulin-based therapy was found to be equivalent to oral-based therapy in terms of efficacy, weight gain, frequency of HES, compliance, treatment satisfaction, and QoL.⁶⁹ Insulin is also thought to protect against the decline in β -cell function, therefore conferring a disease-modifying effect.⁷⁰ Recently developed insulin analogs have more predictable onsets and durations of action than human insulin formulations and more closely approximate the physiological action profile of endogenous insulin. Rapid-acting analogs have a more rapid onset

of action (5–15 minutes) compared with regular human insulin (30–60 minutes), higher peak action, and shorter duration of action, which more closely approximates endogenous mealtime insulin response, allowing more flexibility in the timing of meals and exercise and, consequently, a lower risk of HEs.⁷¹ Similarly, long-acting insulin analogs exhibit a more consistent, longer, and flatter action profile than neutral protamine Hagedorn (NPH), and demonstrate a lower risk of hypoglycemia, particularly nocturnal.^{72–74} Advances in insulin therapy continue to evolve, with newer insulins achieving a more physiological profile, ultimately resulting in a lower risk of hypoglycemia even when more intensive glycemic levels are targeted.

Recent advances in the treatment of type 2 diabetes have resulted in the development of incretin-based therapies which, through their glucose-dependent action, overcome some of the limitations of conventional treatments, including minimizing the risk of hypoglycemia and weight gain.⁷⁵ The incretin hormone, glucagon-like peptide-1 (GLP-1), is released by L-cells in the small intestine upon eating and induces glucose-dependent stimulation of insulin secretion while suppressing glucagon release. As a consequence of this glucose-dependent action, when the plasma glucose concentration is in the normal fasting range, GLP-1 no longer stimulates insulin, which minimizes the risk of hypoglycemia. GLP-1 is also associated with enhanced satiety, reduced food intake, and weight loss or neutrality; it may also preserve β -cell morphology and function. Incretin-based therapies include GLP-1 receptor agonists and dipeptidyl peptidase-IV (DPP-4) inhibitors. GLP-1 receptor agonists are resistant to degradation by DPP-4 and can be dosed to pharmacological levels. DPP-4 inhibitors block the enzyme that degrades incretin hormones, thereby increasing levels of intact, physiologically active endogenous GLP-1 and glucose-dependent insulinotropic polypeptide (GIP-1) (see *Figure 3*).⁷⁶

Two GLP-1 receptor agonists have received US Food and Drug Administration (FDA) approval for treatment of type 2 diabetes. Exenatide is a synthetic mimetic of GLP-1, derived from the saliva of the Gila monster lizard, that shares 53 % amino acid sequence homology with human GLP-1. Liraglutide is produced by a chemical modification of native human GLP-1 and has 97 % homology to the human sequence.^{77,78} *Figure 4* illustrates the possible mechanisms of action of GLP-1 analogs, using liraglutide as an example. DPP-4 inhibitors approved by the FDA for use in type 2 diabetes include sitagliptin, saxagliptin, and linagliptin.^{79,80} Both classes of medications will likely play more prominent roles in the management of type 2 diabetes as they provide effective glucose control, have a favorable weight profile (GLP-1 agonists lead to weight loss, DPP-4 inhibitors are weight-neutral), and have a low risk of hypoglycemia.⁵⁹

Although therapeutic innovations in type 2 diabetes may help address the problem of poor glycemic control, improved communication between patients and caregivers is also a powerful tool that should be

incorporated into current therapeutic approaches.⁸¹ There is a knowledge, attitude, and practice gap in type 2 diabetes. Many patients do not understand HbA_{1c} targets and how they can positively impact their long-term health. Patients struggle to meet lifestyle targets, especially those for weight control. Healthcare professionals can help patients in the self-management of diabetes by helping to create individualized approaches according to the needs, risks, and limitations of patients. Innovative strategies should be implemented that use a community-based approach to encourage diabetes self-management, and embrace new technologies that allow access to diabetes self-management education and support networks.^{82,83}

A recent study evaluated the effect of intensive interventions involving weekly clinic visits, structured self-monitoring of glucose levels, patient education, and adjustment of therapy. There was a dramatic improvement in glycemic control within six weeks as measured by a reduction in HbA_{1c} of 1.82 ± 0.16 % versus 0.66 ± 0.22 % in the control group, which was sustained until Week 12. Additionally, there were no significant changes in the frequency of hypoglycemia or weight gain.⁸⁴ Patient education should include such topics as self-monitoring blood glucose levels, and advice concerning nutrition and exercise. The routine discussion and assessment of hypoglycemia symptoms should be an important part of the regular review of patients with diabetes.⁸⁵

Achievement of glycemic goals without risk of hypoglycemia, especially in patients with advanced diabetes, can only be accomplished if there is a close relationship between the patient and the healthcare team, with significant investment and commitment on the part of both. Patients should undergo intensive diabetes education with periodic refreshers, and the healthcare team should elicit at each visit a full history regarding all aspects of care, including: diet and its timing, treatment regimen and its timing, review of injection technique, if applicable, review of medication storage conditions and expiration dates, review of comorbidities, and new treatment regimens. If a patient is unable or unwilling to adhere to more intensive lifestyle and/or treatment recommendations, a more conservative glycemic goal with a larger ‘safety net’ for hypoglycemia should be considered.

Conclusion

Hypoglycemia has serious clinical, social, and economic consequences, and its occurrence in type 2 diabetes is likely to escalate along with the increase in disease prevalence, as more patients reach the insulin-defective stage of the disease. Hypoglycemia is not just the result of insulin use; in fact, most hypoglycemia is seen in patients using OADs. Treatment selection, as well as glycemic targets, should be customized based on each patient’s individual risk of hypoglycemia. Recent advances in diabetes therapy allow for lower blood glucose levels to be more intensively and successfully targeted, while reducing the risk of hypoglycemia. This should result in better adherence to therapy and improved clinical, health economics and QoL outcomes. ■

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