Focus on Hypoglycemia

Patient Education, Disease Management, and Prevention

Dhiren K. Patel, PharmD, CDE, BC-ADM, BCACP
Michael Charkoudian, PharmD, MBA
Jennifer Goldman, PharmD, CDE, BC-ADM, FCCP
R. Rebecca Couris, PhD, RPh

Hypoglycemia can present significant physical and psychological challenges to achieving glycemic goals, for both patients with diabetes and healthcare providers. It is important to understand how diabetes disease management strategies can affect risk of hypoglycemia. The objectives of this overview are to provide a summary of the incidence of hypoglycemia and special populations at risk, identify hypoglycemia risk factors, and discuss both the prevention and proper treatment of hypoglycemia. Nutr Today. 2015;50(6):277–281

Diabetes mellitus is a disorder of insulin production, utilization, or both resulting in abnormally elevated blood glucose levels.[1] In the United States, 29.1 million people (9.3% of the population) are estimated to have diabetes. This includes 21 million who have been diagnosed with the condition and 8.1 million who are undiagnosed.[1] The total direct and indirect cost of diabetes in the United States was estimated to be $245 billion in 2012.[1] Type 1 diabetes mellitus (T1DM; previously known as insulin-dependent diabetes mellitus or juvenile-onset diabetes) is caused by an autoimmune condition that destroys pancreatic β cells responsible for producing insulin. This type of diabetes accounts for approximately 5% to 10% of all cases. Peak onset for diagnosis is in the midteens, and the condition requires exogenous insulin and is not currently

Dhiren K. Patel, PharmD, CDE, BC-ADM, BCACP, is associate professor of pharmacy practice at the School of Pharmacy–Boston, MCPHS University, Massachusetts.

Michael Charkoudian, PharmD, MBA, manager of medical information services at Sanofi US, Bridgewater, New Jersey.

Jennifer Goldman, PharmD, CDE, BC-ADM, FCCP, is professor of pharmacy practice, School of Pharmacy–Boston, MCPHS University, Massachusetts.

R. Rebecca Couris, PhD, RPh, is professor of nutrition science and pharmacy practice at the School of Pharmacy–Boston, MCPHS University, Massachusetts.

Dr. Patel is an Advisory Board Member–Diabetes at AstraZeneca; Advisory Board Member–Obesity at Novo Nordisk; and a member of the speakers' bureau at Novo Nordisk. Dr. Charkoudian is a shareholder of MannKind and Pfizer Sanofi. Dr. Goldman is a member of the speakers' bureau at Novo Nordisk and consultant at Becton Dickinson. Dr. Couris has no conflicts of interest to disclose.

Correspondence: Dhiren K. Patel, PharmD, CDE, BC-ADM, BCACP, School of Pharmacy–Boston, MCPHS University, 179 Longwood Ave, Boston, MA 02115 (dhiren.patel1@mcphs.edu).

DOI: 10.1097/NT.0000000000000127

preventable. Type 2 diabetes mellitus (T2DM; previously known as non–insulin-dependent diabetes mellitus or adult-onset diabetes) develops as insulin resistance when cells are not able to use insulin effectively. Eventually, the need for endogenous insulin production increases as the pancreas loses its ability to produce it in sufficient quantities. This type of diabetes accounts for 90% to 95% of all diagnosed cases. It is managed through administration of exogenous insulin, oral medications, and via lifestyle modification strategies. Hypoglycemia is a condition defined technically as when a patient with diabetes blood glucose level declines to less than 70 mg/dL (3.9 mmol/L). Patients may present with an array of clinical symptoms including confusion, weakness, seizures/tremors, difficulty speaking, loss of consciousness, sweating, palpitations, hunger, and paresthesias.[2] It is considered severe when the assistance of another person is required to provide treatment.[3] Hypoglycemia is a particular concern in vulnerable populations such as children and the elderly as these patients may be unable to recognize episodes as adverse events, effectively communicate their needs, or self-administer treatment. These events can lead to complications placing patients at increased risk of harm, injury, or death.

Hypoglycemia can be an alarming situation for patients and caregivers to experience. The resulting fear of subsequent episodes may increase antihyperglycemic medication noncompliance, limiting therapeutic goals for optimal patient management. Severe hypoglycemia can result in acute harm to the patient, impact physical and cognitive outcomes, and adversely affect long-term mortality.[3] In 2011, approximately 282 000 emergency room visits were recorded with hypoglycemia listed as a primary diagnosis in a diabetic population.[1] Fortunately, the incidence of hypoglycemia can be mitigated through education on interrelated factors including proper medication use, optimization of dietary management, physical fitness, and disease prevention.

INCIDENCE OF HYPOGLYCEMIA AND SPECIAL POPULATIONS AT RISK

Hypoglycemia occurs much more frequently in patients with T1DM than in patients with T2DM.[4] One observational study found the median rate of self-reported mild hypoglycemia to be 22.3 times higher in patients with

T1DM than in those with T2DM using insulin.[4] However, the number of patients with T2DM at risk is larger because of the greater prevalence of T2DM. Children and the elderly are special populations at risk of encountering hypoglycemia, especially when receiving therapy with insulin.[3] These populations may have difficulty recognizing signs and symptoms of hypoglycemia and communicating their needs to caregivers. Because of their variable caloric intake during meals, unpredictable snacking between meals, and fluctuating levels of physical activity, appropriate dosing of prandial insulin for children can be challenging. Designing an acceptable daily schedule of activities and feedings for children in concert with caregivers may enhance maintenance of blood glucose within the target range. In patients 65 years or greater, an epidemiological study found hypoglycemia to be the most commonly occurring metabolic problem.[5] Hypoglycemic events place elderly patients at increased risk of impaired consciousness, cognition, or dementia, interfering with daily living and blood glucose self-management activities.[3] Complications of hypoglycemia in the elderly include accidents (ie, motor vehicle), falls, and fractures, increasing morbidity and mortality. Other special populations at risk include patients who are taking therapies that can mask the signs and symptoms of hypoglycemia. For example, β-blockers modulate pulse rate and blood pressure, which otherwise signal the onset of acute hypoglycemia, precipitating hypoglycemia unawareness.[6] Therefore, it is important to review the signs and symptoms of hypoglycemia to facilitate recognition and strategies for prevention and resolution.

HYPOGLYCEMIA RISK FACTORS: PHARMACOTHERAPY, ALCOHOL, AND DIET

Pharmacotherapy

Antidiabetic agents used for the treatment of diabetes have varying risks of induction of hypoglycemia. Some agents have a significantly lower risk than others. Blood glucose–lowering agents with the lowest risk of hypoglycemia out of 12 commonly used drug classes include α-glucosidase inhibitors, bile acid sequestrants, dipeptidyl peptidase 4 (DPP-4) inhibitors, dopamine 2 agonists, glucagon-like peptide 1 agonists, metformin, sodium-glucose cotransporter 2 inhibitors, and thiazolidinediones.[7,8] Estimated risks of hypoglycemia for antidiabetic therapies used in T1 and T2DM are listed in Table 1. When the low-risk agents are used in combination with other antidiabetic therapies, the risk of hypoglycemia increases.[8] Sulfonylureas, short-acting human insulins, and basal human insulins are at the other end of the spectrum, with the highest risk of hypoglycemia. Pharmacologic therapy for individuals with T1DM requires insulin, whereas patients with T2DM may begin treatment with insulin or oral pharmacologic therapy to improve their

TABLE 1	Estimated Relative Hypoglycemia Risk for Antidiabetic Therapies Used in Types 1 and 2 Diabetes Mellitus[7–9]
Antidiabetic Therapy	**Estimate of Relative Hypoglycemia Risk**
α-Glucosidase inhibitors	Lowest
Bile acid sequestrant	Lowest
Dopamine 2 agonists	Lowest
Dipeptidyl peptidase 4 inhibitors	Lowest
Glucagon-like peptide 1 agonists	Lowest
Metformin	Lowest
Sodium-glucose cotransporter 2 inhibitors	Lowest
Thiazolidinediones	Lowest
Amylin mimetics	Moderate
Meglitinides	Moderate
Second-generation sulfonylureas	Moderate
Basal insulin analogs	High
First-generation sulfonylureas	High
Human insulin inhalation powder	High
Short-acting insulin analogs	High
Basal human insulins	Highest
Short-acting human insulins	Highest
Adapted from Oyer.[8]	

glycemic control. Where insulin therapy is indicated, rapid- and long-acting insulin analogs are recommended. These products were observed to result in less hypoglycemia than conventional injectable physiologic human insulin with equivalent HbA_{1c}-lowering results.[10,11]

α-Glucosidase inhibitors, bile acid sequestrant, dopamine 2 agonists, DPP-4 inhibitors, glucagon-like peptide 1 agonists, metformin, sodium-glucose cotransporter 2 inhibitors, and thiazolidinediones have a relatively low risk of causing hypoglycemia. Other oral therapies, such as sulfonylureas and meglitinides, have a higher risk of hypoglycemia.[8] A review to evaluate the comparative effectiveness and safety of monotherapy and 2-drug combinations for treatment of T2DM was conducted.[12] The results showed sulfonylureas compared with metformin alone had a greater than 4-fold higher risk of mild to moderate hypoglycemia, whereas metformin plus a sulfonylurea compared with metformin

plus a thiazolidinedione had almost a 6-fold higher risk. The DPP-4 inhibitors had a lower risk of mild to moderate hypoglycemia than sulfonylureas, similar to metformin monotherapy. Another assessment of patients with T2DM was a network meta-analysis conducted on agents added to metformin. The results showed that compared with placebo the risk of hypoglycemia was increased in the sulfonylureas, glinides, basal insulin, and biphasic insulin groups.[13]

Alcohol

Alcohol intake without food should be avoided. Use of alcohol reduces endogenous glucose production, which can increase the risk of delayed hypoglycemia in patients with T2DM, especially when combined with glucose-lowering therapies.[10] Compensating for ingestion of alcohol through administration of extra insulin can also increase a patient's risk of hypoglycemia. Therefore, adults with diabetes are advised to limit their intake of alcohol to no more than 1 drink (12 oz of beer, 5 oz of wine, or 1½ oz of distilled spirits) for females or 2 drinks for males.[3] In addition, it is recommended that patients with diabetes who use alcohol should be educated to recognize and manage the signs and symptoms of delayed hypoglycemia.

Diet

The American Diabetes Association recommends patients with diabetes should receive individualized medical nutrition therapy, preferably by a registered dietitian.[3] Optimization of dietary intake involves proper food selection, including the quality and quantity of carbohydrates, proteins, and fats, which are appropriate for the patient. Meal planning strategies incorporating carbohydrate counting can ensure consistent dietary intake and meal management, which has been shown to improve glycemic control in patients with T1DM.[3] Portion control and healthy food choice planning, including reduction of caloric intake to promote weight loss, are helpful tools for the improvement of glycemic control for patients with T2DM. Weight loss is especially important for overweight or obese adults with T2DM and those at risk of diabetes because it can provide health benefits for these individuals. Limiting intake of sucrose-containing foods and drinks can also reduce the risk of weight gain in patients with or at risk of diabetes. Diets incorporating low glycemic index (GI) foods, such as lentils, beans, and oats, may contribute to improved glycemic control by providing a gradual release of glucose into the bloodstream compared with high-GI foods such as white bread.[14] A low-GI diet can stimulate lower insulin release, minimize fluctuations in blood glucose levels, and increase insulin sensitivity. A Cochrane review conducted to assess the effects of low GI, or low glycemic load, diets on glycemic control in patients with diabetes found episodes of hypoglycemia were significantly fewer with a low-GI diet compared with a high-GI diet in 1 trial (difference of −0.8 episodes per patient per month, $P < 0.01$).[14] The proportion of participants reporting more than 15 hyperglycemic episodes per month was lower in the low-GI-diet group compared with the measured carbohydrate exchange diet group in another study (35% vs 66%, respectively; $P = .006$). Poor dietary habits such as skipping or delaying meals are another factor that has been shown to result in the occurrence of hypoglycemia. In an observational study of safety net patients with T2DM, patients who were food insecure (had issues with access to sufficient, consistent, and nutritious supply of food) were twice as likely to report 4 or more episodes of severe hypoglycemia.[15] Therefore, dietary management is 1 essential modality of the diabetes treatment paradigm that can help enhance glycemic control.

PREVENTION OF HYPOGLYCEMIA

Hypoglycemia prevention involves identification of patients who are at risk, dietary planning for optimization of nutritional intake, proper medication selection, education on proper diabetes medication use, and appropriate blood glucose monitoring. Patients who are identified to be at risk of hypoglycemia should be instructed on how to recognize the symptoms and how to manage them when they occur. Review of previous hypoglycemic episodes, including details regarding when, why, and how often they occurred, can be useful for identification of factors contributing to the events. Two methods available for assessment of blood glucose control include self-monitoring of blood glucose (SMBG), a measure of immediate blood glucose levels, and glycosylated hemoglobin (HbA_{1c}), a measure of average plasma glucose concentration over approximately 3 months. Technologies available for immediate measurement of outpatient blood glucose include capillary measurement using test strips with glucose meters and interstitial measurement with continuous glucose monitoring (CGM).[16] Appropriate SMBG testing is essential to assist in maintenance of euglycemia, especially for patients receiving multiple dose insulin or insulin pump infusion.[3] Testing should be performed routinely before meals and snacks.[3] It may also be performed after meals, before exercise or bedtime, prior to important activities requiring concentration without lapses in cognition such as driving a motor vehicle, when hypoglycemia is suspected, or following a hypoglycemic episode until a return to euglycemia is achieved.[3]

For most healthy patients using insulin, preprandial SMBG targets can be 80 to 130 mg/dL (4.4–7.2 mmol/L), whereas postprandial glucose measurements made 1 to 2 hours after starting a meal may have a target of less than 180 mg/dL (<10.0 mmol/L).[3] Targets for HbA_{1c} may be less than 7% (correlating to a mean plasma glucose of 154 mg/dL or 8.6 mmol/L) in healthy adults with diabetes. In patients with longer life expectancies and without significant hypoglycemia or adverse treatment effects, HbA_{1c} targets may be reduced to less than 6.5% (correlating to a mean

plasma glucose of 140 mg/dL or 7.8 mmol/L). However, for patients with a history of severe hypoglycemia, advanced complications, or who are encountering difficulty with control of their HbA$_{1c}$, the target may be raised to less than 8% (correlating to a mean plasma glucose of 183 mg/dL or 10.2 mmol/L). One meta-analysis concluded setting intensive glycemic control targets did not show significant differences for all-cause and cardiovascular mortality compared with conventional glycemic control while increasing the risk of hypoglycemia and serious adverse events, providing evidence that tight glycemic control does not equally benefit all patients.[17] Proper blood glucose monitoring is essential as it can identify instances of asymptomatic hypoglycemic episodes. A review of SMBG patient techniques can help identify deficiencies in the testing process and provide an opportunity to suggest recommendations for improvement, such as use of results to adjust insulin dosing. Patient-specific goals should be determined for those who suffer from issues with hypoglycemia unawareness or frequent hypoglycemia episodes. Patients may also benefit from enrollment in blood glucose awareness training programs to help them recognize early signs and symptoms of hypoglycemia and manage them before they become serious and require external intervention.[16] Patients with T1DM or T2DM 25 years or older may benefit from the use of CGM as an assistive tool to lower HbA$_{1c}$.[3,18] Individuals suffering from nocturnal hypoglycemia or issues with hypoglycemia awareness may consider use of insulin pumps using CGM combined with automatic shutoff when a set glucose threshold level is breached. It is recommended patients with T1DM receive instructions on matching carbohydrate intake with caloric needs based on planned physical activities and adjust prandial insulin calculation accordingly. When exercise is anticipated (and authorized by a healthcare provider), supplemental carbohydrates can be consumed by patients using insulin if glucose levels are less than 100mg/dL (5.6 mmol/L).[3]

TREATMENT OF HYPOGLYCEMIA

Because episodes of hypoglycemia are unpredictable, patients should be instructed to carry carbohydrates such as glucose tablets or gel on them at all times, and consideration should be given to provide a prescription for glucagon to patients who are prone to severe cases.[16] Glucose is indicated as the first-line treatment for patients with diabetes who experience hypoglycemia, are conscious, and are able to orally ingest 15 to 20 g of the simple sugar in the form of tablets (3–4 tablets) or gel (1 serving per manufacturer's instructions).[3] These and alternate sources of simple carbohydrates providing approximately 15 g of simple carbohydrates are listed in Table 2.[3,19,20]

Rebound hyperglycemia can occur with overtreatment of a hypoglycemic episode; therefore, a stepwise approach

patients can follow is known as the "rule of 15." This approach advises consumption of 15 g of simple carbohydrates when a patient's blood glucose becomes hypoglycemic.[11] Patients should retest their blood glucose every 15 minutes and if still hypoglycemic repeat the rule of 15 until blood glucose returns to normal. When SMBG returns to normal, a meal or snack should be consumed to prevent recurrence of hypoglycemia.[3] In severe cases, such as when a patient loses consciousness, a glucagon injection may be required. Family members and caregivers should be instructed on the dosage and administration of the emergency injection. Following manufacturer reconstitution instructions, administration of 0.5 mg (0.5 mL) for children weighing less than 55 lb or 1 mg (1 mL) for children and adults weighing greater than 55 lb is recommended.[21] After patients respond to treatment, oral carbohydrates should be provided to restore liver glycogen and prevent recurrence of hypoglycemia. If episodes of hypoglycemia recur and become problematic, patients may be instructed by their healthcare provider to raise blood glucose level targets in order to diminish the risk of subsequent episodes. In some cases, adjustments to pharmacologic therapy may be warranted. These adjustments may be composed of dose reduction, interchange of 1 antidiabetic agent for another with a lower relative risk of hypoglycemia (as listed in Table 1), or a combination of the two.

CONCLUSION

Expansion of knowledge regarding diabetes pathophysiology and biochemical glycemic control processes has enabled advancements in diabetes management to benefit patient care. With an ever-expanding array of therapeutic options, there is an abundance of choices for patients to select based on individualized treatment goals. It is important for patients to understand how diabetes disease management strategies can affect their risk of hypoglycemia. With a basic understanding of these principles, a

TABLE 2	Oral Hypoglycemia Treatments[3,16,17]
Glucose tablets (3–4 tablets per manufacturer's instructions)	
Glucose gel (1 serving per manufacturer's instructions)	
Sugar, honey, or corn syrup, approximately 3 teaspoons (1 tablespoon)	
Juice or regular soda with caloric sweetener (not diet), approximately 4 oz (½ cup)	
Nonfat or 1% milk, approximately 8 oz (1 cup)	
Hard candies, jellybeans, or gumdrops, 5–6 (quantity based on carbohydrate content per serving listed on package)	

collaborative foundation can be built to institute strategies for hypoglycemia risk minimization between patients, caregivers, and healthcare providers.

REFERENCES

1. Centers for Disease Control and Prevention. *National Diabetes Statistics Report: Estimates of Diabetes and Its Burden in the United States, 2014*. Atlanta, GA: US Department of Health and Human Services; 2014.
2. Cryer PE, Axelrod L, Grossman AB, et al. Evaluation and management of adult hypoglycemic disorders: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*. 2009;94(3):709–728.
3. American Diabetes Association. Standards of medical care in diabetes—2015. *Diabetes Care*. 2015;38(suppl 1):S1–S93.
4. UK Hypoglycaemia Study Group. Risk of hypoglycaemia in types 1 and 2 diabetes: effects of treatment modalities and their duration. *Diabetologia*. 2007;50(6):1140–1147.
5. Bertoni AG, Krop JS, Anderson GF, Brancati FL. Diabetes-related morbidity and mortality in a national sample of U.S. elders. *Diabetes Care*. 2002;25(3):471–475.
6. *Inderal LA [package insert]*. Cranford, NJ: Akrimax Pharmaceuticals; 2012. http://www.inderalla.com/IND%20Web%20PI.pdf. Accessed July 12, 2014.
7. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycaemia in type 2 diabetes: a patient-centered approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetologia*. 2012;55(6):1577–1596.
8. Oyer DS. The science of hypoglycemia in patients with diabetes. *Curr Diabetes Rev*. 2013;9(3):195–208.
9. *Briefing Document, Endocrinologic and Metabolic Drug Advisory Committee, NDA 022472 AFREZZA® (Insulin Human [rDNA origin]) Inhalation Powder. An Ultrarapid Acting Insulin Treatment to Improve Glycemic Control in Adult Patients With Diabetes Mellitus* [Internet]. Valencia, CA: Mannkind Corporation; 2014. http://www.fda.gov/downloads/advisorycommittees/committees meetingmaterials/drugs/endocrinologicandmetabolicdrugs advisorycommittee/ucm390865.pdf. Accessed July 12, 2014.
10. Yip L. Chapter 77. Ethanol. In: Nelson LS, Lewin NA, Howland M, Hoffman RS, Goldfrank LR, Flomenbaum NE, eds. *Goldfrank's Toxicologic Emergencies*. 9th ed. New York, NY: McGraw-Hill; 2011.
http://accesspharmacy.mhmedical.com.ezproxy.mcphs.edu/content. aspx?bookid=454&Sectionid=40199482. Accessed July 4, 2014.
11. Triplitt CL, Repas T, Alvarez C. Chapter 57. Diabetes mellitus. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey L. eds. *Pharmacotherapy: A Pathophysiologic Approach*. 9th ed. New York, NY: McGraw-Hill; 2014. http://accesspharmacy.mhmedical.com .ezproxy.mcphs.edu/content.aspx?bookid=689&Sectionid= 45310509. Accessed July 4, 2014.
12. Bennett WL, Maruthur NM, Singh S, et al. Comparative effectiveness and safety of medications for type 2 diabetes: an update including new drugs and 2-drug combinations. *Ann Intern Med*. 2011;154(9):602–613.
13. Liu SC, Tu YK, Chien MN, Chien KL. Effect of antidiabetic agents added to metformin on glycaemic control, hypoglycaemia and weight change in patients with type 2 diabetes: a network meta-analysis. *Diabetes Obes Metab*. 2012;14(9):810–820.
14. Thomas D, Elliott EJ. Low glycaemic index, or low glycaemic load, diets for diabetes mellitus. *Cochrane Database Syst Rev*. 2009;(1):CD006296.
15. Seligman HK, Jacobs EA, Lopez A, Sarkar U, Tschann J, Fernandez A. Food insecurity and hypoglycemia among safety net patients with diabetes. *Arch Intern Med*. 2011;171(13):1204–1206.
16. Seaquist ER, Anderson J, Childs B, et al. Hypoglycemia and diabetes: a report of a workgroup of the American Diabetes Association and the Endocrine Society. *Diabetes Care*. 2013;36(5):1384–1395.
17. Hemmingsen B, Lund SS, Gluud C, et al. Targeting intensive glycaemic control versus targeting conventional glycaemic control for type 2 diabetes mellitus. *Cochrane Database Syst Rev*. 2013; 11:CD008143.
18. Meade LT. The use of continuous glucose monitoring in patients with type 2 diabetes. *Diabetes Technol Ther*. 2012;14(2):190–195.
19. *Hypoglycemia (Low Blood Glucose)* [Internet]. Alexandria, VA: American Diabetes Association; 2014. Available at http://www .diabetes.org/living-with-diabetes/treatment-and-care/blood-glucose-control/hypoglycemia-low-blood.html. Accessed July 6, 2014.
20. American Diabetes Association. Hypoglycemia? Low blood glucose? Low blood sugar? *Clin Diabetes*. 2012;30(1):38.
21. *GlucaGen* [package insert]. Plainsboro, NJ: Novo Nordisk Inc; 2014. http://www.novonordiskmedicalinformation.com//file_ upload/GlucaGen%20HypoKit%20Prescribing%20Information, April%202014%20.pdf. Accessed July 5, 2014.

For more than 98 additional continuing education articles related to Nutrition and Diabetes topics, go to NursingCenter.com/CE.