Recognition and Management of Hypoglycemia

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"Hypoglycemia is the major limiting factor in the glycemic management of type 1 and type 2 diabetes."

—American Diabetes Association[1]

This statement by the American Diabetes Association (ADA) comes as no surprise to family physicians. People with diabetes, their families, and physicians all regularly share concerns about hypoglycemia. These concerns are well founded. More than 30% of patients with type 1 diabetes mellitus (T1D) annually experience 1 to 3 episodes of severe hypoglycemia, ie, low blood glucose characterized by altered mental and/or physical status requiring assistance.[2] For people with type 2 diabetes mellitus (T2D), approximately 50% experience hypoglycemia, and 20% have ≥1 episode of severe hypoglycemia per year.[3] In 2016, hypoglycemia was the reported cause for 235,000 emergency department (ED) visits.[4] Of these, 22.3% were admitted to the hospital and <0.1% died. Another study found that, in patients with T1D since childhood who died over 24 years of follow-up, hypoglycemia was the cause in 10%.[5]

Wider use of continuous glucose monitoring (CGM) provides for a more accurate assessment compared with relying on symptom recognition or self-monitored blood glucose and has resulted in greater insight into the true frequency of hypoglycemia.[6,7] A recent analysis of 2 trials involving 307 adults with T1D treated with multiple insulin injections per day, and with glycated hemoglobin (A1C) ≤9% to 10%, showed that patients were hypoglycemic >1 hour per day.[8] Patients spent a median of 22 minutes/day with a blood glucose <54 mg/dL, and 72 minutes/day with a blood glucose <70 mg/dL. In patients with T2D (N=108) treated with insulin and/or oral medications, a prospective evaluation showed that 49% experienced ≥1 hypoglycemic episode (mean 1.74 episodes) over a 5-day period.[9] Of these patients, 75% experienced ≥1 asymptomatic hypoglycemic episode.

Hypoglycemia may not be recognized if it occurs during the night or in patients with hypoglycemic unawareness. Similarly, episodes are likely to be missed despite periodic daily monitoring using finger sticks, especially in persons with wide glycemic variability. Moreover, the risk of severe hypoglycemia occurs similarly, across the range of A1C levels, although the reason for this is unclear. The Diabetes and Aging Study showed that the prevalence of severe hypoglycemia was 12% in persons with A1C <6%, 11% in persons with A1C 7% to 7.9%, and 14% in persons with A1C ≥9%.[10]

A wide variety of patient factors contribute to an increased risk of hypoglycemia. These include longer duration of diabetes, older age, history of recent severe hypoglycemia, chronic kidney disease, and tight glycemic control.[11-13] Medications such as sulfonylurea, meglitinide, and basal insulin, particularly at doses >0.5 units/kg per day, are common causes of hypoglycemia.[14] Lifestyle factors such as a variable eating, administering insulin after meals, drinking alcohol, and vigorous or unexpected exercise also increase the risk of hypoglycemia.[11,13]

The consequences of hypoglycemia extend well beyond ED visits and increased health care resource utilization. People feel bad when they are hypoglycemic and these spells may lead to suboptimal treatment adherence, resistance to intensifying treatment, diabetes distress and reduced quality of life among patients and families/caregivers, higher mortality rate, diminished academic performance, and possibly diminished cognition.[5,15-28] A key consequence of suboptimal treatment or scheduled adherence, as well as resistance to intensifying treatment, is that patients remain on suboptimal glucose-lowering therapy. Thus, patients are exposed

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TABLE 1. **Physiologic responses to hypoglycemia**[1,30]

Plasma glucose (mg/dL)	Physiologic response	Function in hypoglycemia
80-85	Primary: Decreased insulin secretion Secondary: Increased glucose production; decreased glucose uptake by insulin-sensitive tissues	First physiologic defense against hypoglycemia. Primary glucose regulatory factor
65-70	Primary: Increased glucagon secretion Secondary: Increased glucose production	Second physiologic defense against hypoglycemia. Primary glucose counterregulatory factor
	Primary: Increased epinephrine secretion Secondary: Increased glucose production; increased renal gluconeogenesis; decreased insulin secretion; decreased glucose uptake by insulin-sensitive tissues	Third physiologic defense against hypoglycemia. Critical when glucagon is deficient
	Primary: Increased cortisol, growth hormone secretion Secondary: decreased glucose uptake by insulin-sensitive tissues	Not critical, slower counterregulatory factor
50-55	Neurogenic symptoms	Prompt behavioral defense of food intake
<50	Neuroglycopenic symptoms	Compromised behavioral defense

to frequent postprandial hyperglycemia, prolonged basal hyperglycemia, reduced blood glucose time-in-range, and increased glucose variability that may further accelerate the dire clinical consequences of diabetes.

DEFINITIONS & SYMPTOMS

CASE SCENARIO

KT is a 64-year-old woman diagnosed with T2D 7 years ago. She presents today with her husband after having experienced an episode of severe hypoglycemia during the night 2 days ago that awakened her husband. She was making unusual sounds and when her husband tried to wake her, she was incoherent; her blood glucose was 50 mg/dL. She was transported to the local ED where she was treated, held for observation, then released. Her husband is worried that this may be happening more often and wonders if he should be checking her blood glucose during the night.

Hypoglycemia criteria were reclassified in 2017 by a panel of medical, patient, and charitable organizations.[29] Level 1 hypoglycemia is a blood glucose level < 70 mg/dL, and is a threshold generally recognized for the activation of neuroendocrine responses to decreasing blood glucose levels (**TABLE 1**).[30] If blood glucose levels <70 mg/dL recur, some patients with diabetes mellitus begin to experience hypoglycemia unawareness around this level. Level 2 hypoglycemia is a blood glucose <54 mg/dL, and is a threshold when neurogenic (autonomic) and neuroglycopenic symptoms may increase in severity and at which immediate treatment is required. Level 3 hypoglycemia is a severe event characterized by altered mental and/or physical functioning requiring assistance from another person, or who are unable to take fast-acting oral carbohydrate during hypoglycemia.[1,29] It is important to note that level 3 hypoglycemia is not defined by a specific blood glucose level, and it should be considered a life-threatening event that requires both prompt and definitive intervention.

Signs and symptoms of hypoglycemia are categorized as neurogenic or neuroglycopenic (**TABLE 2**).[1,29,31] Neurogenic symptoms, which largely manifest as increased sympathetic neural activity, trigger increased serum epinephrine levels and exhibit symptoms such as palpitations, anxiety, tremors, tachycardia, and behavioral defense mechanisms for hunger and immediate food ingestion. As the blood glucose further declines, neuroglycopenic symptoms such as drowsiness and cognitive dysfunction appear, which can impair behavioral defenses.

The presentations of hypoglycemia symptoms are heterogeneous and individual to patients, and are correlated only loosely with the blood glucose level. For example, older adults and patients with long-term diabetes may exhibit fewer neurogenic symptoms and instead manifest more neuroglycopenic manifestations of hypoglycemia. Longstanding diabetes and recent episodes of any hypoglycemia may attenuate the neurogenic response, which can further contribute to hypoglycemia unawareness[32-34]; in these patients the first actual sign of hypoglycemia may be the clinical presentation of severe hypoglycemia. However, hypoglycemia unawareness is generally reversible if hypoglycemia can be avoided

TABLE 2. **Signs and symptoms of hypoglycemia**[1,29,31]

Neurogenic (autonomic)	Neuroglycopenic
Sweating	Confusion
Palpitations	Drowsiness / Lethargy
Tachycardia	Slurred speech / Difficulty speaking
Tremors	Unable to follow commands / Unresponsive
Anxiety	Inappropriate behavior
Hunger	Headache
Irritability	Blurred vision
Tingling	Cool skin
	Unconsciousness
	Seizures
	Coma

for 2 to 3 weeks, as this time allows inborn mechanisms to become active again.

SELF-MANAGEMENT

Diabetes mellitus is a chronic disease, the management of which is determined by numerous decisions the patient makes daily. It is critical, therefore, that patients with T1D or T2D are educated and supported so that they are able to optimally self-manage their diabetes mellitus. In this regard, a key role for the family physician is to individualize therapy over the course of the disease to best meet the patient's health and other needs. This strategy includes balancing the benefits of glucose control while minimizing the risk of hypoglycemia.

Identifying and addressing patient concerns and barriers to treatment, including hypoglycemia, is especially important. Among the various strategies that can be employed, perhaps those most important may be to build on the established and trusting relationship with the patient and to provide ongoing education and support to both the patient and the family/caregiver, eg, shared decision-making and using open-ended questions. Establishing good rapport combined with open patient provider communication, regular screening, education, and training should help ease patient (and family/caregiver) concerns and help to build the confidence needed to manage the everyday risks of hyperglycemia and hypoglycemia.

At every visit, patients should be assessed for the occurrence of symptomatic and asymptomatic hypoglycemia. In addition to asking the patient about such episodes, a review of the patient's blood glucose log is helpful—but often inadequate because episodes of hypoglycemia, particularly those occurring during sleep, may not be captured through routine blood glucose monitoring. This is especially important to consider in patients treated with daily doses of basal insulin > 0.5 units/kg (particularly when given with sulfonylureas),[14] and in patients who use continuous glucose monitoring and/or insulin pumps[35] regardless of their A1C levels.

HYPOGLYCEMIA MANAGEMENT IN CLINICAL PRACTICE

CASE SCENARIO

A 23-year-old man with T1D is being seen for a routine visit. His family physician notes that his A1C has increased over the past 11 months, rising from 6.8% to 7.2%. Upon questioning, the patient admits that he is no longer increasing his insulin dose based on his blood glucose monitoring because a friend of his was recently hospitalized after a severe hypoglycemic episode. The patient notes that he has frequently experienced symptomatic hypoglycemia through the years and is now especially fearful of a severe hypoglycemic episode. He finds hypoglycemia to be untimely and embarrassing.

The patient's growing concern about hypoglycemia emphasizes the importance of routinely assessing concerns and barriers to treatment. Partners and family members are routinely more distressed and concerned about hypoglycemia and severe hypoglycemia than the person with diabetes.[36] This emphasizes the importance of providing ongoing patient and family education and training, and the critical role for a written and executable action plan for patient self-management. A key part of the action plan is how to identify and acutely respond to adverse events such as hypoglycemia in any situation (eg, exercise, work, school, home, travel). The action plan also should include how patients can prevent hypoglycemia by adjusting medications, meals, and exercise based on blood glucose monitoring. Patient understanding and ability to follow the action plan should be assessed, particularly when changes are made.

A patient resource related to the recognition and self-management of hypoglycemia has been developed by the ADA (see https://professional.diabetes.org/sites/professional.diabetes.org/files/pel/source/sci-advisor_2018_low_blood_glucose_hypoglycemia-newb-final.pdf). For hypoglycemia that can be self-managed, the ADA recommends implementing the "15-15 rule."[37] To raise the blood glucose, 15 g of fast-acting oral carbohydrate should be ingested and the blood glucose level checked 15 minutes later. If the blood glucose remains <70 mg/dL, another 15 g of fast-acting oral carbohydrate should be ingested. These steps are repeated as necessary until the blood glucose is ≥70 mg/dL, at which time a meal or snack is to be eaten to ensure the blood glucose level does not decrease again. Carbohydrate options

TABLE 3. **Selected glucagon products for outpatient use**

	Baqsimi[40]	GlucaGen[41,42]	Gvoke[43]
Approved age group	≥4 years	Children, adults	≥2 years
Route of administration	Intranasal	IM, IV, SC	SC
Dosage form, strength	Intranasal device containing glucagon powder 3 mg	Single-dose vial containing glucagon 1 mg with 1 disposable syringe or vial containing 1 mL SWFR	Single-dose prefilled autoinjector or prefilled syringe containing glucagon 0.5 mg/1 mL or 1 mg/0.2 mL
Reconstitution needed?	No	Yes	No
Contraindications	Pheochromocytoma, insulinoma, known hypersensitivity to glucagon/excipients		
Adverse reactions	[a]Nausea, headache, vomiting, URTI	Nausea, vomiting	[a]Nausea, vomiting, injection site edema raised ≥1 mm, headache
Mean time to peak plasma glucagon level	Adults: 15 minutes Children: 15-20 minutes	12.5 minutes[b]	Adults: 50 minutes Children: 34-51 minutes
Onset of rise of plasma glucose level	<10 minutes	<10 minutes (IM)	<10 minutes
Mean time to peak plasma glucose level	NR	~30 minutes (IM) 30-45 minutes (SC)	NR
Mean maximum glucose increase from baseline	Adults: 140 mg/dL Children: 102-138 mg/dL	—	Adults: 176 mg/dL Children: 123-145 mg/dL

Abbreviations: IM, intramuscular; IV, intravenous; NR, not reported; SC, subcutaneous; SWFR, sterile water for reconstitution; URTI, upper respiratory tract irritation.
[a]Incidence ≥2%
[b]Median

include glucose tablets, gel tube, hard candies, jellybeans, or gumdrops in the amount needed to provide 15 g carbohydrate. Other options include 4 ounces of juice or regular (not diet) soda; 1 tablespoonful of sugar, honey, or corn syrup; or 8 ounces of nonfat or 1% milk.

Glucagon

When a hypoglycemia episode occurs and (1) the patient is unable to take oral carbohydrate, (2) the blood glucose level has not recovered to normal levels despite using the 15-15 rule and the patient's status is deteriorating, or (3) the blood glucose level is very low (ie, <54 mg/dL), then the prompt administration of glucagon is required.

Glucagon is a hormone normally secreted by the pancreas that stimulates glycogenolysis and the release of glucose from the liver. Recent ADA guidelines recommend that glucagon should be prescribed for all individuals at increased risk of level 2 hypoglycemia, ie, blood glucose <54 mg/dL, so the medication is available should it be needed.[1] However, despite these guidelines, few patients who are eligible for a glucagon prescription, including persons who have experienced level 3 hypoglycemia, receive such a prescription.[38,39]

More than 60 glucagon products are available in the United States; several products are shown in **TABLE 3**.[40-43] Historically, glucagon products required reconstitution immediately prior to use, contributing to frequent dosing and administration errors. Now there are 2 exceptions. One is a prefilled syringe or autoinjector (Gvoke) and the other an intranasal formulation (Baqsimi).

All glucagon products provide an onset of rise of the plasma glucose level in <10 minutes. If there has been no response 15 minutes after administration, a second dose may be administered while waiting for emergency assistance. When the patient responds to glucagon treatment, oral carbohydrate should be given to restore liver glycogen and prevent the recurrence of hypoglycemia.

Glucagon administration is not limited to health care professionals; the formulation is generally administered by an individual other than the person experiencing severe hypoglycemia. Because the complexity of standard powder glucagon kits can be intimidating if the person administering them is not properly trained,[28] it is essential to educate family members, friends, and coworkers of patients at risk of hypoglycemia about the importance of glucagon, when and how to administer the glucagon product, and what to do after glucagon administration.[44] Fortunately, the newer intranasal and stable soluble glucagon formulations available in autoinjector pens make this task simpler.[1]

Gvoke PFS and Gvoke HypoPen (glucagon injection)

Gvoke is a concentrated, liquid stable glucagon for subcutaneous injection, indicated for the treatment of severe hypo-

glycemia in pediatric and adult patients with diabetes age ≥2 years. It is provided in a premixed, premeasured, and prefilled device in both adult (1 mg) and pediatric (0.5 mg) dosages.

Two phase 3, randomized, blinded, 2-way crossover trials compared a powder glucagon product available as a Glucagon Emergency Kit (GEK) requiring manual reconstitution with the liquid stable glucagon product available as a prefilled premeasured autoinjector (Gvoke HypoPen).[45] Adults with T1D (N=161) were subjected to induced level 2 hypoglycemia by intravenous administration of regular insulin, followed by treatment with a single dose of 1 of the 2 glucagon products. After a 7- to 28-day washout period, patients were crossed over to the other glucagon product. The primary outcome, increase in the plasma glucose concentration from <50 mg/dL to >70 mg/dL or ≥20 mg/dL rise in plasma glucose within 30 minutes of glucagon administration, was achieved by 99% of patients when treated with Gvoke and 100% of patients when treated with GEK.[43] The mean time to successful plasma glucose recovery was 13.8 minutes in the Gvoke group and 10 minutes in the GEK group. Comparing common adverse events between Gvoke and GEK, nausea occurred in 29.8% and 22.9% of patients, respectively, and vomiting in 16.1% and 9.6%, respectively.[43]

The safety and efficacy of the concentrated, liquid stable glucagon product has been evaluated in a phase 3 single-arm, open-label trial in children with T1D, ages 2 to <18 years (N=31).[43]

Baqsimi (glucagon nasal powder)

Baqsimi is an intranasal glucagon powder indicated for the treatment of severe hypoglycemia in patients with diabetes age ≥4 years. It is provided in a premeasured and prefilled device in a 3 mg dosage, for both adults and children.

The safety and efficacy of the intranasal glucagon product (Baqsimi) was compared with intramuscular (IM) administration of glucagon in a randomized, crossover, non-inferiority study involving adults with T1D (N=75).[46] Hypoglycemia was induced by intravenous insulin, followed by treatment with a single dose of 1 of the 2 glucagon products. After a 7- to 28-day washout period, patients were crossed over to the other glucagon product. The primary outcome, increase in the plasma glucose concentration from the nadir (mean 48-49 mg/dL) to >70 mg/dL within 30 minutes of glucagon administration, was achieved by 100% of patients when treated with the IM product and 98.7% of patients when treated with the intranasal product. The mean time to success was 13 minutes and 16 minutes for the IM and intranasal products, respectively. Nausea with or without vomiting occurred during 38% and 35% of visits, respectively. Head/facial discomfort was reported during 9% and 25% of IM and intranasal visits, respectively.

The safety and efficacy of the intranasal glucagon product have been shown to be similar to an IM product in children with T1D, ages 4 to <17 years (N=48).[47]

SUMMARY

Hypoglycemia is serious and a common experience among patients with diabetes mellitus, yet the condition is often underscreened, unrecognized, and underreported. Although hypoglycemia serves as a common barrier to optimal diabetes treatment, particularly in patients who use insulin, most patients do not receive the regular ongoing screening, education, and training support needed to prevent and self-manage hypoglycemia when it occurs.

The ADA recommends that all patients with diabetes who are at increased risk of clinically important hypoglycemia should have glucagon prescribed. To support this practice, family physicians should provide applicable screening, education, and training for both patients and caregivers on a regular basis. While most glucagon products are in powder form and require manual reconstitution immediately prior to injection, 2 exceptions improve the simplicity of glucagon administration. One is a prefilled syringe or autoinjector and the other is an intranasal product. The safety and efficacy of these 2 glucagon products are similar to products requiring manual reconstitution. ●

REFERENCES

1. American Diabetes Association. 6. Glycemic targets: standards of medical care in diabetes-2020. *Diabetes Care.* 2020;43(Suppl 1):S66-S76.
2. International Hypoglycaemia Study Group. Minimizing hypoglycemia in diabetes. *Diabetes Care.* 2015;38(8):1583-1591.
3. Edridge CL, Dunkley AJ, Bodicoat DH, et al. Prevalence and incidence of hypoglycaemia in 532,542 people with type 2 diabetes on oral therapies and insulin: A systematic review and meta-analysis of population based studies. *PLoS One.* 2015;10(6):e0126427.
4. Centers for Disease Control and Prevention. N*ational Diabetes Statistics Report 2020.* Published 2020. https://www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pdf. Accessed February 26, 2020.
5. Skrivarhaug T, Bangstad HJ, Stene LC, Sandvik L, Hanssen KF, Joner G. Long-term mortality in a nationwide cohort of childhood-onset type 1 diabetic patients in Norway. *Diabetologia.* 2006;49(2):298-305.
6. Lin YK, Groat D, Chan O, et al. Associations between the time in hypoglycemia and hypoglycemia awareness status in type 1 diabetes patients using continuous glucose monitoring systems. *Diabetes Technol Ther.* 2020;doi:10.1089/dia.2020.0016.
7. Gomez-Peralta F, Dunn T, Landuyt K, Xu Y, Merino-Torres JF. Flash glucose monitoring reduces glycemic variability and hypoglycemia: real-world data from Spain. *BMJ Open Diabetes Res Care.* 2020;8(1).
8. Oliver N, Gimenez M, Calhoun P, et al. Continuous glucose monitoring in people with type 1 diabetes on multiple-dose injection therapy: the relationship between glycemic control and hypoglycemia. *Diabetes Care.* 2020;43(1):53-58.
9. Gehlaut RR, Dogbey GY, Schwartz FL, Marling CR, Shubrook JH. Hypoglycemia in type 2 diabetes--more common than you think: a continuous glucose monitoring study. *J Diabetes Sci Technol.* 2015;9(5):999-1005.
10. Lipska KJ, Warton EM, Huang ES, et al. HbA1c and risk of severe hypoglycemia in type 2 diabetes: the Diabetes and Aging Study. *Diabetes Care.* 2013;36(11):3535-3542.
11. 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.
12. Patel A, MacMahon S, Chalmers J, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med.* 2008;358(24):2560-2572.
13. American Diabetes Association. 4. Comprehensive medical evaluation and assessment of comorbidities: standards of medical care in diabetes-2020. *Diabetes Care.* 2020;43(Suppl 1):S37-S47.
14. Reid T, Gao L, Gill J, et al. How much is too much? Outcomes in patients using high-dose insulin glargine. *Int J Clin Pract.* 2016;70(1):56-65.
15. Idris I, Gulati K, Perez-Nieves M, et al. Associated factors that influenced persistence

with basal analog insulin therapy among people with type 2 diabetes: an exploratory analysis from a UK real-world sample. *Prim Care Diabetes.* 2019;13(2):106-112.
16. Polonsky WH, Henry RR. Poor medication adherence in type 2 diabetes: recognizing the scope of the problem and its key contributors. *Patient Prefer Adherence.* 2016;10:1299-1307.
17. McCoy RG, Lipska KJ, Van Houten HK, Shah ND. Association of cumulative multimorbidity, glycemic control, and medication use with hypoglycemia-related emergency department visits and hospitalizations among adults with diabetes. *JAMA Netw Open.* 2020;3(1):e1919099.
18. Hendrieckx C, Ivory N, Singh H, Frier BM, Speight J. Impact of severe hypoglycaemia on psychological outcomes in adults with type 2 diabetes: a systematic review. *Diabet Med.* 2019;36(9):1082-1091.
19. Pawaskar M, Iglay K, Witt EA, Engel SS, Rajpathak S. Impact of the severity of hypoglycemia on health-related quality of life, productivity, resource use, and costs among US patients with type 2 diabetes. *J Diabetes Complications.* 2018;32(5):451-457.
20. Strandberg RB, Graue M, Wentzel-Larsen T, Peyrot M, Wahl AK, Rokne B. The relationships among fear of hypoglycaemia, diabetes-related quality of life and psychological well-being in Norwegian adults with type 1 diabetes. *Diabetes Res Clin Pract.* 2017;124:11-19.
21. Standl E, Stevens SR, Lokhnygina Y, et al. Confirming the bidirectional nature of the association between severe hypoglycemic and cardiovascular events in type 2 diabetes: Insights from EXSCEL. *Diabetes Care.* 2020;43(3):643-652.
22. Nathan DM. The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications study at 30 years: overview. *Diabetes Care.* 2014;37(1):9-16.
23. Lacy ME, Gilsanz P, Eng C, Beeri MS, Karter AJ, Whitmer RA. Severe hypoglycemia and cognitive function in older adults with type 1 diabetes: the Study of Longevity in Diabetes (SOLID). *Diabetes Care.* 2020;43(3):541-548.
24. Pilgaard KA, Breinegaard N, Johannesen J, et al. Episodes of severe hypoglycemia is associated with a progressive increase in hemoglobin A1c in children and adolescents with type 1 diabetes. *Pediatr Diabetes.* 2020;21(5):808-813.
25. Knight MF, Perfect MM. Glycemic control influences on academic performance in youth with Type 1 diabetes. *Sch Psychol.* 2019;34(6):646-655.
26. Jensen MH, Dethlefsen C, Hejlesen O, Vestergaard P. Association of severe hypoglycemia with mortality for people with diabetes mellitus during a 20-year follow-up in Denmark: a cohort study. *Acta Diabetol.* 2020;57(5):549-558.
27. Rossi MC, Nicolucci A, Ozzello A, et al. Impact of severe and symptomatic hypoglycemia on quality of life and fear of hypoglycemia in type 1 and type 2 diabetes. Results of the Hypos-1 observational study. *Nutr Metab Cardiovasc Dis.* 2019;29(7):736-743.
28. Haymond MW, Liu J, Bispham J, Hickey A, McAuliffe-Fogarty AH. Use of glucagon in patients with type 1 diabetes. *Clin Diabetes.* 2019;37(2):162-166.
29. Agiostratidou G, Anhalt H, Ball D, et al. Standardizing clinically meaningful outcome measures beyond HbA1c for type 1 diabetes: a consensus report of the American Association of Clinical Endocrinologists, the American Association of Diabetes Educators, the American Diabetes Association, the Endocrine Society, JDRF International, The Leona M and Harry B Helmsley Charitable Trust, the Pediatric Endocrine Society, and the T1D Exchange. *Diabetes Care.* 2017;40(12):1622-1630.
30. Gehlaut RR, Shubrook J Jr,. Revisiting hypoglycemia in diabetes. *Osteopath Fam Physician.* 2014;1:19-25.
31. Tesfaye N, Seaquist ER. Neuroendocrine responses to hypoglycemia. *Ann N Y Acad Sci.* 2010;1212:12-28.
32. Cryer PE. Mechanisms of hypoglycemia-associated autonomic failure in diabetes. *N Engl J Med.* 2013;369(4):362-372.
33. Segel SA, Paramore DS, Cryer PE. Hypoglycemia-associated autonomic failure in advanced type 2 diabetes. *Diabetes.* 2002;51(3):724-733.
34. White NH, Skor DA, Cryer PE, Levandoski LA, Bier DM, Santiago JV. Identification of type I diabetic patients at increased risk for hypoglycemia during intensive therapy. *N Engl J Med.* 1983;308(9):485-491.
35. Foster NC, Beck RW, Miller KM, et al. State of type 1 diabetes management and outcomes from the T1D Exchange in 2016-2018. *Diabetes Technol Ther.* 2019;21(2):66-72.
36. Polonsky WH, Fisher L, Hessler D, Johnson N. Emotional distress in the partners of type 1 diabetes adults: worries about hypoglycemia and other key concerns. *Diabetes Technol Ther.* 2016;18(5):292-297.
37. American Diabetes Association. Low blood glucose (hypoglycemia). Published 2020. https://professional.diabetes.org/pel/low-blood-glucose-hypoglycemia-english. Accessed April 3, 2020.
38. Fendrick AM, He X, Liu D, Buxbaum JD, Mitchell BD. Glucagon prescriptions for diabetes patients after emergency department visits for hypoglycemia. *Endocr Pract.* 2018;24(10):861-866.
39. Mitchell BD, He X, Sturdy IM, Cagle AP, Settles JA. Glucagon prescription patterns in patients with either type 1 or 2 diabetes with newly prescribed insulin. *Endocr Pract.* 2016;22(2):123-135.
40. Baqsimi [package insert]. Indianapolis, IN: Eli Lilly and Company; August 2019.
41. GlucaGen [package insert]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.; July 2018.
42. GlucaGen Hypokit [package insert]. Plainsboro, NJ: Novo Nordisk Inc.; July 2018.
43. Gvoke [package insert]. Chicago, IL: Xeris Pharmaceuticals, Inc.; March 2020.
44. Fidler C, Elmelund Christensen T, Gillard S. Hypoglycemia: an overview of fear of hypoglycemia, quality-of-life, and impact on costs. *J Med Econ.* 2011;14(5):646-655.
45. ClinicalTrials.gov. Safety and efficacy of G-Pen compared to Lilly glucagon for hypoglycemia rescue in adult type 1 diabetics (NCT02656069). Published October 30, 2018. https://clinicaltrials.gov/ct2/show/study/NCT02656069?term=NCT02656069&draw=2&rank=1. Accessed May 5, 2020.
46. Rickels MR, Ruedy KJ, Foster NC, et al. Intranasal glucagon for treatment of insulin-induced hypoglycemia in adults with type 1 diabetes: a randomized crossover noninferiority study. *Diabetes Care.* 2016;39(2):264-270.
47. Sherr JL, Ruedy KJ, Foster NC, et al. Glucagon nasal powder: a promising alternative to intramuscular glucagon in youth with type 1 diabetes. *Diabetes Care.* 2016;39(4):555-562.