FEATURE ARTICLE

Severe Hypoglycemia and the Use of Glucagon Rescue Agents: An Observational Survey in Adults With Type 1 Diabetes

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Severe hypoglycemia (SH) is the most frequent and potentially serious complication affecting individuals with type 1 diabetes and can have major clinical and psychosocial consequences. Glucagon is the only approved treatment for SH that can be administered by non–health care professionals (HCPs); however, reports on the experiences and emotions of people with type 1 diabetes associated with SH and glucagon rescue use are limited. This survey study demonstrated that an increasing number of individuals with type 1 diabetes have current and filled prescriptions for glucagon and have been educated about glucagon rescue use by an HCP. Despite this positive trend, challenges with SH remain, including a high level of health care resource utilization, considerable out-of-pocket expenses for glucagon kits, a high prevalence of hypoglycemia unawareness, and a negative emotional impact on individuals with diabetes. Nocturnal and exercise-related hypoglycemia were concerns for most survey participants.

Insulin therapy carries an increased risk of hypoglycemia, a significant and potentially fatal complication of diabetes management (1–4). The American Diabetes Association (ADA) defines level 2 hypoglycemia as a blood glucose level <54 mg/dL (3.0 mmol/L). It is associated with impaired counterregulatory mechanisms that may lead to reduced awareness of hypoglycemic events, potentially leading to a cycle of recurrent hypoglycemia (3,4). Level 3 hypoglycemia (also called severe hypoglycemia [SH]) is defined by an altered mental and/or physical status that requires assistance from another person for recovery (3). In the United States, SH results in almost 300,000 emergency department visits per year (5). Untreated SH may lead to adverse clinical outcomes that can include cognitive dysfunction, loss of consciousness, seizures, coma, and death (2,3,6).

Long-term clinical studies have shown that SH remains an ongoing challenge for people with type 1 diabetes, occurring at an average rate of 0.36–0.41 episodes per person per year (7). A history of SH is a strong indicator for the risk of subsequent SH events (7), and people with type 1 diabetes are likely to experience several SH events in their lifetime. A clinical history of SH is associated with an increased risk of all-cause mortality and cardiovascular disease (CVD) in people with type 1 diabetes (8,9), which may lead to substantial direct and indirect costs (10–12) and constitutes a significant part of the economic burden associated with diabetes (13–16). Hypoglycemia can also significantly compromise a person's emotional state and quality of life (2,3).

The potential negative impacts of SH are significant sources of distress for many individuals with type 1 diabetes and may create a strong aversion to situations in which SH might occur. This fear of hypoglycemia is prevalent among individuals with type 1 diabetes and may have substantial implications for diabetes management and subsequent health outcomes (3,17). Many

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people with diabetes who are worried about hypoglycemia maintain their blood glucose at higher than recommended levels to avoid the adverse effects of hypoglycemic episodes (18), thus contributing to the metabolic complications of hyperglycemia.

Glucagon has been the first-line emergency treatment for SH in insulin-treated people with diabetes since the 1960s (19). The ADA recommends prescribing glucagon for all individuals at an increased risk of level 2 and level 3 hypoglycemia so that it is available when needed (3). The ability to administer glucagon for the treatment of SH is not limited to health care professionals (HCPs); it can be administered by family members, caregivers, or bystanders (3). The significant burden of SH could be partially alleviated with the use of glucagon as recommended by the ADA (3). However, despite its favorable safety and efficacy profile, glucagon is underutilized as a rescue treatment for SH owing to a lack of routine prescribing of glucagon among HCPs, people with diabetes not filling their glucagon prescriptions, and caregivers not administering or not correctly administering glucagon in the event of SH (5,20–23). First-generation glucagon kits (24,25) require reconstitution of lyophilized native human glucagon before use. The complexity of this multistep process is a known barrier to the rapid and efficient administration of glucagon (21,26,27). Other barriers include lack of appropriate education and training (21,22,26,27) and reluctance to administer rescue glucagon in an emergency for fear of harming the individual with SH (21,22,27).

Over many decades, there has been an unmet need for easy-to-use glucagon products to treat SH to aid in alleviating fear related to hypoglycemia, reduce training needs, and increase overall utilization of glucagon (27). Second-generation glucagon products do not require reconstitution and have been available on the U.S. market since 2019. These products include Baqsimi (Eli Lilly and Company) (28), a native human glucagon powder for nasal administration; Gvoke (Xeris Pharmaceuticals) (29), a ready-to-use premixed solution of native human glucagon for subcutaneous injection; and Zegalogue (Zealand Pharma) (30), a ready-to-use premixed solution of the glucagon analog dasiglucagon for subcutaneous injection.

To date, there has been limited research on the experiences and emotions of individuals with diabetes regarding hypoglycemia and glucagon rescue use. This dearth of research is concerning considering the potentially severe consequences that a lack of glucagon use can have for SH recovery (19). To address these questions, we surveyed adults with type 1 diabetes to gain a real-world understanding of their experiences with hypoglycemia and the use of glucagon rescue products, identify barriers to glucagon use, and determine their preferences for glucagon rescue product characteristics. The objective of this study was to provide an updated real-world perspective on how the landscape of emergency glucagon use has changed since the introduction of second-generation, ready-to-use glucagon products in 2019.

Research Design and Methods

Focus Groups Study to Inform Survey Development

The survey questions for this research were informed by focus groups conducted virtually from October to December 2020. In total, 38 adults with type 1 diabetes consented and participated. Seven focus groups with five to seven participants each were asked about their experiences with hypoglycemia and glucagon use. Participants were encouraged to interact with each other to gain robust insights. Each 90-minute session was recorded and transcribed for analysis. Each focus group participant was remunerated with a $100 Amazon gift card. The questions included in the survey for this study were developed from the key concepts that emerged during these focus groups.

Recruitment

Participants for the survey were recruited through the T1D Exchange registry (31–33), a longitudinal study collecting information on type 1 diabetes management and outcomes. To be enrolled in the registry, individuals with type 1 diabetes must either receive insulin or have had a pancreas or islet cell transplant. In May 2021, recruitment emails were sent to the adult members of the T1D Exchange registry community, and posts were set up on social media (Facebook and Twitter) containing a link directing potential participants to a brief description of the research study.

Informed Consent

An institutional review board (IRB) exemption as well as a partial waiver of the Health Insurance Portability and Accountability Act authorization signature requirement for use and disclosure of protected health information were obtained from the WCG IRB on 22 April 2021. Potential study participants from the T1D Exchange registry community were provided with a link to an electronic consent form for their review and

electronic signature. Participants who provided consent were then emailed a copy of their informed consent form for their records.

Inclusion Criteria

Participants enrolled in the study were included in the data analysis if they satisfied the following criteria: ≥18 years of age, diagnosis of type 1 diabetes for at least 1 year, at least one episode of SH defined as a low blood glucose event during which assistance was required, familiarity with current glucagon options on the market, currently residing in the United States, fluent in written and spoken English, and agreed to provide digital informed consent. Participants were excluded from the analysis if they were currently pregnant or refused to declare whether they were pregnant.

Survey

Consenting participants were directed to the online survey conducted via Alchemer (34). After completing the survey, each participant was remunerated with a $25 Amazon gift card. For the purposes of the survey, participants' experiences with hypoglycemia were classified as "mild" (blood glucose <70 mg/dL [3.9 mmol/L] to ≥54 mg/dL [3.0 mmol/L]), "moderate" (blood glucose <54 mg/dL [3.0 mmol/L]), and "severe" (an altered mental and/or physical status requiring assistance for treatment of hypoglycemia). Definitions of these classifications were provided to participants as they completed the survey. Some survey questions allowed for multiple answers to be given, resulting in an overall percentage in excess of 100%. These questions are noted in the results tables.

Statistical Analysis

All statistical analyses were performed using R software, v. 4.0.5 or later (R Core Team, Vienna, Austria). Summary statistics, including mean, SD, frequency, and percentage, were calculated for general demographic and diabetes-related health information. Bivariate statistical analyses were performed using Welch two-sample *t* tests, Pearson χ^2 tests, and Fisher exact tests to assess differences in demographic and clinical characteristics between participants who, at the time of the survey, had a current and filled glucagon prescription and those who did not and between participants who had impaired awareness of hypoglycemia and those who did not. A *P* value ≤0.05 was considered statistically significant.

Results

Participants' Demographics and Clinical Characteristics

In total, 428 individuals consented and were enrolled in the study. Of these, 316 individuals met the inclusion criteria and completed the survey. The baseline participant characteristics are shown in Table 1.

Participants had a mean ± SD age of 35.6 ± 8.9 years and a mean duration of type 1 diabetes of 17.2 ± 12.7 years since their diagnosis. Of the participants, 59.2% were female, most were White and identified as not Hispanic or Latino, and the majority were in full-time or part-time employment. Overall, 59.2% had private health insurance; 22.5% and 10.8% were enrolled in Medicare or Medicaid, respectively; 1.3% did not have health insurance of any type; and the remainder received health insurance from other sources. In terms of education, 57.5% reported having a bachelor's degree or higher, and 66.5% had an annual household income ≥$50,000.

The clinical characteristics of participants are summarized in Table 2. The most frequently used method of glucose monitoring was real-time continuous glucose monitoring (CGM; 80.4%), followed by traditional fingerstick blood glucose monitoring (BGM; 47.2%) and intermittently scanning CGM, formerly called flash CGM (FGM; 0.9%). Most participants (76.6%) reported using an insulin pump, 30.4% used injectable insulin, and 4.1% used inhalable insulin. Participants reported comorbid conditions, the most frequent of which were joint issues (27.5%), hypothyroidism (25.3%), CVD (19.3%), and retinopathy (19.3%). Overall, 69.3% were seen by an adult or pediatric endocrinologist, and 22.8% were seen by other specialized diabetes HCPs, with the remainder seen by primary care HCPs.

Participants' Experiences With Hypoglycemia

Participants' reported experiences with hypoglycemia are presented in Table 3. Participants disclosed experiencing a mean of 3.6 ± 6.0 SH events in the preceding 12 months and a mean of 15.3 ± 60.4 (median 5, range 1–1,000) SH events in total in their lifetime. Participants noticed hypoglycemia in a variety of ways, most commonly by experiencing symptoms (80.7%), but also by using the functions of their CGM system (alert [63.3%], glucose reading [49.7%], or predictive low glucose warning [48.1%]). About one-fourth of the participants also made use of fingerstick BGM.

When comparing SH events in the previous 12 months for participants who used or did not use CGM, CGM

TABLE 1 Participants' Demographics (N = 316)

Characteristic	Value
Age, years	35.6 ± 8.9
Duration of type 1 diabetes, years	17.2 ± 12.7
Gender	
Female	187 (59.2)
Male	128 (40.5)
Other	1 (0.3)
Race (multiple answers possible)	
White	290 (91.8)
Black or African American	12 (3.8)
Asian	9 (2.8)
American Indian or Alaskan Native	8 (2.5)
Native Hawaiian or other Pacific Islander	1 (0.3)
Other	4 (1.3)
Ethnicity	
Not Hispanic or Latino	302 (95.6)
Hispanic or Latino	14 (4.4)
Employment status (multiple answers possible)	
Working full time	195 (61.7)
Working part time	65 (20.6)
Student	36 (11.4)
Temporarily unemployed or on leave from work	13 (4.1)
Unemployed, looking for work	12 (3.8)
Volunteer	9 (2.8)
Disabled	8 (2.5)
Unemployed, not looking for work	6 (1.9)
Retired	2 (0.6)
Health insurance (multiple answers possible)	
Private health insurance (e.g., commercial, fee-for-service, HMO, PPO, or POS)	187 (59.2)
Medicare	71 (22.5)
Medicaid	34 (10.8)
Other government-sponsored health coverage plan	12 (3.8)
Affordable Care Act plan	8 (2.5)
Medigap	7 (2.2)
Single service plan (e.g., dental, vision, or prescriptions)	6 (1.9)
Military health care (e.g., TRICARE, CHAMPUS, CHAMPVA, or VA)	6 (1.9)
Other state-sponsored health coverage plan	5 (1.6)
No health insurance or health care coverage of any type	4 (1.3)
Not known	1 (0.3)
Education	
Bachelor's degree	111 (35.1)
Some college	77 (24.4)
Master's degree	57 (18.0)
Associate's degree	33 (10.4)
Doctoral degree	14 (4.4)
High school graduate/GED	12 (3.8)
Some high school	12 (3.8)
Annual household income	
<$30,000	44 (13.9)
$30,000 to <$50,000	41 (13.0)
$50,000 to <$75,000	85 (26.9)
$75,000 to <$100,000	53 (16.8)
$100,000 to <$200,000	54 (17.1)
≥$200,000	18 (5.7)
Do not wish to provide	12 (3.8)
Not known	9 (2.8)

Data are mean ± SD or n (%). CHAMPUS, Civilian Health and Medical Program of the Uniformed Services; CHAMPVA, Civilian Health and Medical Program of the Department of Veterans Affairs; GED, general education diploma; HMO, health maintenance organization; POS, point of service; PPO, preferred provider organization; VA, Veterans Affairs.

users experienced a mean of 3.1 ± 4.2 (median 1.0, range 0–30) SH events, and non-CGM users experienced a mean of 5.7 ± 10.6 (median 2.5, range 0–58) SH events. Excluding participants who reported having had >100 lifetime SH events (n = 3), CGM users reported a mean of 10.4 ± 17.7 (median 5.0, range 1–100) SH events in their lifetime, and non-CGM users reported a mean of 13.2 ± 21.7 (median 4.5, range 0–100) SH events in their lifetime.

Using the criteria employed by Gold et al. (35), participants' awareness of hypoglycemia was classified as "normal" (scores of 1–2) or "impaired" (scores of 4–7) on a visual analog scale. "Indeterminant" awareness (score of 3) was not included in either of these categories. Overall, 33.9% of the participants reported having normal awareness of hypoglycemia, and 44.6% reported having impaired awareness of hypoglycemia. Most participants (75.3%) considered the night or the time during or after exercise (77.2%) as the time of most concern about hypoglycemia.

SH events were associated with several emergency situations, including calling an ambulance (61.7%), visiting an emergency department (58.5%), and staying for at least 1 night at the hospital (36.4%). More than half of the participants stated that they had felt either worry, anxiety, stress, fear, panic, weakness, or embarrassment during an SH episode.

Participants' Experiences With Glucagon Rescue Treatments

Participants' experiences with glucagon rescue treatments are reported in Table 4. Almost all participants

TABLE 2 Participants' Clinical Characteristics (N = 316)

Characteristic	Value
Glucose monitoring method (multiple answers possible)	
CGM	254 (80.4)
BGM	149 (47.2)
FGM	3 (0.9)
Duration of CGM use (n = 254)	
<6 months	10 (3.9)
6 months to <1 year	20 (7.9)
1 year to <3 years	105 (41.3)
3 years to <5 years	49 (19.3)
≥5 years	70 (27.6)
Blood glucose tests	
A1C, %	7.4 ± 2.5
Number of daily fingerstick blood glucose checks	2.4 ± 2.6
Number of daily glucose checks by CGM/FGM	20.7 ± 25
Insulin delivery method (multiple answers possible)	
Insulin pump	242 (76.6)
Multiple daily injections using an insulin pen	59 (18.7)
Multiple daily injections using vial/syringe	37 (11.7)
Inhalable insulin	13 (4.1)
Other	1 (0.3)
Reported diabetes-related comorbidities (multiple answers possible)	
Joint issues	87 (27.5)
Hypothyroidism	80 (25.3)
Retinopathy	61 (19.3)
CVD	61 (19.3)
Gastroparesis	51 (16.1)
Neuropathy	46 (14.6)
Sexual dysfunction	44 (13.9)
Nephropathy	22 (7.0)
Hyperthyroidism	18 (5.7)
Type of diabetes HCP	
Adult endocrinologist	203 (64.2)
Diabetes nurse practitioner	48 (15.2)
Diabetes physician assistant	24 (7.6)
Pediatric endocrinologist	16 (5.1)
Primary care physician	14 (4.4)
Primary care, nurse practitioner	7 (2.2)
Primary care, physician assistant	4 (1.3)
Frequency of visits with diabetes HCP	
Every month	9 (2.8)
Every 2–3 months	201 (63.6)
Every 6 months	92 (29.1)
Once per year	6 (1.9)
Once every 1–2 years	2 (0.6)
Other	6 (1.9)

Data are n (%) or mean ± SD.

(97.2%) had been prescribed glucagon either at the time of completing the survey or in the past, with 80.4% reporting a current glucagon prescription. Overall, 74.7% of participants had a current and filled glucagon prescription, and 25.3% did not. Participants reported a mean of 1.7 ± 5.3 uses of glucagon to treat SH in the previous 12 months.

Participants who had impaired awareness of hypoglycemia (scores 4–7, n = 141) were significantly more likely to have a current and filled glucagon prescription than those who did not have impaired awareness of hypoglycemia (scores 1–3, n = 175): 80.1% (113 of 141) versus 70.3% (123 of 175) (Pearson χ^2 test P = 0.05). There were no significant differences between those with or without a current and filled glucagon prescription in A1C (P = 0.31) or age (P = 0.19). In addition, having a current and filled glucagon prescription was not associated with a greater likelihood of receiving care from an endocrinologist (P = 0.70).

Overall, 79.4% of the participants (n = 251) reported that they currently owned a glucagon kit, with 92.0% (n = 231) owning a kit <2 years old and 8.0% (n = 20) owning a kit >2 years old. Approximately half of the participants stated that having a glucagon kit in their home made them feel safe, 40.2% felt that they were prepared for hypoglycemia, and 28.5% felt confident about hypoglycemia; however, 27.5% reported that having a glucagon kit in their home made no difference in how they felt about hypoglycemia. HCPs had provided education about glucagon use to 83.2% of the participants, but 16.8% of participants had not received education by an HCP or were unsure about whether they had received such education. Compared with other HCPs, care from an endocrinologist was not associated with better education about glucagon use (P = 0.60).

Barriers to Glucagon Use as a Rescue Treatment

Barriers to glucagon rescue use reported by the participants are included in Table 5. Importantly, the 251 participants who currently owned a glucagon kit had a mean out-of-pocket cost of $73.40 ± $85.80 (median $30, range $0–400) for their kit. When queried, 85.1% of the 316 participants reported that rescue glucagon was administered when needed. In the remaining 14.9% (n = 47) for whom glucagon was not administered when needed, the reasons were diverse, including problems with the reconstitution and administration process (n = 33), inability to locate the kit (n = 23), lack of training (n = 15), an expired kit (n = 14), the rescuing individual being unaware of the existence of the kit (n = 13), and lack of confidence of the rescuing individual (n = 7).

The most important reasons for not having a glucagon prescription stated by participants who have never

TABLE 3 Participants' Experiences With Hypoglycemia (*N* = 316)

Hypoglycemia-Related Survey Data	Value
Hypoglycemia data	
Blood glucose level at which hypoglycemia is being treated, mg/dL	70.2 ± 21.8
Number of mild hypoglycemic events per week	7.4 ± 13.2
Number of moderate hypoglycemic events per week	5.0 ± 13.3
Number of SH events in the previous 12 months	3.6 ± 6.0
Number of SH events in the lifetime	15.3 ± 60.4
How hypoglycemia is usually noticed (multiple answers possible)	
Feeling symptoms	255 (80.7)
CGM low alert	200 (63.3)
Looking at the CGM reading	157 (49.7)
CGM predictive low glucose warning	152 (48.1)
Fingerstick BGM	82 (25.9)
Other	5 (1.6)
Number of SH events	
In the previous 12 months	
CGM users (*n* = 254)	3.1 ± 4.2
Non-CGM users (*n* = 62)	5.7 ± 10.6
In the lifetime	
CGM users (*n* = 254)	15.9 ± 66.5
Non-CGM users (*n* = 62)	13.2 ± 21.7
In the lifetime, excluding those with >100 lifetime events (*n* = 3)	
CGM users (*n* = 251)	10.4 ± 16.7
Non-CGM users (*n* = 62)	13.2 ± 21.7
Awareness of hypoglycemia	
1 (always aware)	30 (9.5)
2	77 (24.4)
3	68 (21.5)
4	85 (26.9)
5	43 (13.6)
6	7 (2.2)
7 (never aware)	6 (1.9)
Times that hypoglycemia is of most concern (multiple answers possible)	
Overnight	238 (75.3)
During exercise	139 (44.0)
After exercise	105 (33.2)
During the day	87 (27.5)
Other	17 (5.4)
Occurrence of the most recent SH event	
<1 month ago	44 (13.9)
1–3 months ago	76 (24.1)
3 months to <6 months ago	51 (16.1)
6 months to 1 year ago	48 (15.2)
1–2 years ago	30 (9.5)
2–5 years ago	22 (7.0)
>5 years ago	45 (14.2)
Type of emergency resulting from SH (multiple answers possible)	
Change in mental state requiring assistance	258 (81.6)
Passing out/loss of consciousness or seizure	196 (62.0)
Calling a paramedic	195 (61.7)
Emergency department visit(s)	185 (58.5)
Requiring glucagon	181 (57.3)
Hospitalizations with at least 1 night spent in the hospital	115 (36.4)
Emotions experienced in connection with SH (multiple answers possible)	
Worry/concern	214 (67.7)
Anxiety	203 (64.2)
Stress	202 (63.9)
Fear	172 (54.4)
Panic	166 (52.5)
Weakness	159 (50.3)
Embarrassment	160 (50.6)
Anger	112 (35.4)
Guilt	106 (33.5)
Sadness	89 (28.2)
Shame	67 (21.2)

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Data are mean ± SD or *n* (%).

been prescribed glucagon (*n* = 9) were that their doctor had never discussed it with them (*n* = 6), they usually carried oral carbohydrates (*n* = 6), and their CGM device alerted them to low blood glucose levels (*n* = 5).

Participants' Preferences for Characteristics of Glucagon Rescue Products

Most participants preferred ready-to-use glucagon rescue products, with 47.8% favoring an intranasal spray and 38.0% a premixed autoinjector (Table 6). The remaining 14.2% of the participants preferred injectable glucagon that requires reconstitution before use. Valued characteristics of glucagon rescue treatments included the ease of use of ready-to-use products (76.3%), intuitive modes of administration such as a nasal spray or ready-to-use injection (55.7%), a fast onset of action (53.5%), and storage at room temperature (42.1%).

The participants also discussed various ways to improve glucagon rescue products, including greater ease of use (62.7%), reduced cost (53.5%), and more intuitive modes of administration (50.3%). The time to plasma glucose recovery was rated as a "very important" or "fairly important" characteristic of glucagon rescue products by 73.4% of the participants (Table 6).

TABLE 4 Participants' Experiences With Glucagon Rescue Treatments (*N* = 316)

Glucagon-Related Survey Data	Value
Current prescription for glucagon	
Yes, currently have a glucagon prescription and have filled it	236 (74.7)
Yes, have been prescribed glucagon in the past but not recently	53 (16.8)
Yes, currently have a glucagon prescription but have not filled it	18 (5.7)
No, have never had a glucagon prescription	9 (2.8)
Number of times glucagon was used to treat SH in the previous 12 months	1.7 ± 5.3
Likelihood of having a current and filled glucagon prescription	
Impaired awareness of hypoglycemia (scores 4–7; *n* = 141)	
Having a current and filled glucagon prescription	113 (80.1)
Not having a current and filled glucagon prescription	28 (19.9)
Not having impaired awareness of hypoglycemia (scores 1–3; *n* = 175)	
Having a current and filled glucagon prescription	123 (70.3)
Not having a current and filled glucagon prescription	52 (29.7)
Current ownership of a glucagon kit	
Yes	251 (79.4)
No	62 (19.6)
Unsure	3 (0.9)
Age of glucagon kit if currently owning one (*n* = 251)	
<1 year old	114 (45.4)
1–2 years old	117 (46.6)
>2 years old	20 (8.0)
Feelings associated with having a glucagon kit at home (*n* = 316; multiple answers possible)	
Safe	151 (47.8)
Prepared for hypoglycemia	127 (40.2)
Confident about hypoglycemia	90 (28.5)
The same as not having it in my home	87 (27.5)
Educated by an HCP about glucagon use	
Yes	263 (83.2)
No	47 (14.9)
Unsure	6 (1.9)

Data are *n* (%) or mean ± SD.

Discussion

The burden of SH remains a challenge throughout the lives of people with type 1 diabetes and has a substantial impact on their emotional well-being, diabetes management, and health outcomes (17,27). Although previous studies have examined the emotional impact of SH and glucagon rescue treatment on caregivers of individuals with type 1 diabetes (36–38), literature is limited about the views and emotions connected with hypoglycemia and glucagon rescue use of people with type 1 diabetes themselves (19). For this reason, the objective of this research study was to provide an updated real-world perspective on emergency glucagon use of individuals with type 1 diabetes, as available glucagon products have become more diversified with the introduction of second-generation, ready-to-use rescue products.

The surveyed sample of individuals with type 1 diabetes had a mean age of 35.6 ± 8.9 years and a mean diabetes duration of 17.2 ± 12.7 years since diagnosis. Participants experienced a mean of 7.4 mild and 5.0 moderate hypoglycemic events per week and a mean of 3.6 SH events in the past year and 15.3 SH events (median 5 SH events) in their lifetime. Approximately half of the most recent SH events occurred in the 6 months immediately before the survey, emphasizing the relative frequency with which SH episodes occurred in the surveyed sample. The data on SH events in the 12 months before survey completion align with recent surveys of individuals with type 1 diabetes in other countries that reported means of 1.5–4.2 SH events in the previous 12 months (39,40). Importantly, CGM users among the surveyed sample continued to experience SH events, albeit fewer than non-CGM users. The reasons for this observation may be manifold, including lack of functional data because of system warm-up time, early termination, transmitter or receiver failure, or, more commonly, insufficient supply as a result of insurance problems.

Of note, the majority of participants in this study had received care from a paramedic (61.7%) or had an emergency department visit (58.5%), and more than one-third of participants (36.4%) had experienced a hospital stay of at least 1 night as a result of an SH event. These data illustrate the high level of health resource utilization as a direct consequence of SH, which is associated with significant costs to the U.S. health care system.

Importantly, the survey highlighted the emotional burden of SH on those affected, showing a considerable proportion of participants expressing worry or concern (67.7%), fear (54.4%), panic (52.5%), embarrassment (50.6%), and shame (21.2%) in connection with SH events. These findings are reflective of the findings of other recent survey studies on the negative emotional impact of SH on individuals with type 1 diabetes (39–43).

Participants reported being aware of their hypoglycemia episodes primarily by experiencing symptoms and through the use of CGM; however, a substantial proportion (44.6%) reported impaired awareness of hypoglycemia.

TABLE 5 Barriers to Using Glucagon Rescue Treatment

Barrier-Related Survey Data	Value
Out-of-pocket cost for a glucagon kit, $ (n = 251)	73.40 (85.80)
Ability to have available glucagon administered (n = 316)	
Able	269 (85.1)
Unable	47 (14.9)
Reasons for inability to have available glucagon administered (n = 47; multiple answers possible)	
The rescuing individual was not able to locate the glucagon kit.	23 (48.9)
The rescuing individual was not trained to use the glucagon kit.	15 (31.9)
The glucagon was expired.	14 (29.8)
The rescuing individual was not aware of the glucagon kit.	13 (27.7)
There was a problem with mixing.	11 (23.4)
The rescuing individual was not able to use the glucagon kit correctly.	10 (21.3)
The rescuing individual was not comfortable administering the glucagon.	7 (14.9)
The rescuing individual who delivered glucagon broke the needle.	7 (14.9)
The process was too complex.	5 (10.6)
Other	3 (6.4)
Reasons for not currently having a glucagon prescription (n = 9; multiple answers possible)	
My doctor has never discussed glucagon with me.	6 (66.7)
I carry other supplies instead (glucose tablets, juice, etc.).	6 (66.7)
My CGM device gives me alerts before my blood glucose gets too low.	5 (55.6)
I don't need it.	1 (11.1)
I am worried about temperature changes affecting the kit.	1 (11.1)
It costs too much to fill the prescription.	1 (11.1)
The kit has too many steps to be useful.	1 (11.1)
There is nobody to administer the glucagon (e.g., living alone).	1 (11.1)
Those around me would call 911 if I became severely hypoglycemic.	1 (11.1)
Other	1 (11.1)

Data are n (%).

A high prevalence of hypoglycemia unawareness, even in those using CGM, has previously been reported; yet, the result from this survey was slightly higher than the rates noted in people with type 1 diabetes in other studies (39,40,42,44,45).

Nocturnal hypoglycemia and hypoglycemia during or after exercise were concerns for approximately three-fourths of the participants. Although we did not measure how often participants experienced nocturnal or exercise-related hypoglycemia, current research supports our participants' concerns, indicating that 28.7–51.4% of participants' most recent SH events occurred during the night (39,40,42). Both nocturnal hypoglycemia and exercise-related hypoglycemia are associated with immediate clinical consequences (46,47). Moreover, nocturnal hypoglycemia has a long-term impact on glucose counterregulatory mechanisms that may lead to cognitive impairment, reduced hypoglycemia awareness, and autonomic failure (47).

Importantly, this research study showed encouraging results, with 83.2% of the participants receiving education from their HCP pertaining to glucagon rescue use, although receiving care from an endocrinologist compared with other HCPs was not associated with perceived better education about glucagon use. However, this is an increase from the 71.0% of adults with type 1 diabetes who reported being educated by an HCP on this topic in a 2019 U.S. survey (21). Furthermore, almost all of the participants in the current study (97.2%) had been prescribed a glucagon rescue product at the time of the survey or in the past, 80.4% had a current prescription for glucagon, and 74.7% had a current prescription and had filled it. Participants with hypoglycemia unawareness were significantly more likely to have a current and filled glucagon prescription than those who had normal awareness of hypoglycemia. A possible explanation is that those with hypoglycemia unawareness may be more vigilant about having glucagon at their disposal because they are conscious of their own difficulty in recognizing symptoms of an oncoming SH episode. Those with a normal awareness of SH may be reassured that they can recognize symptoms of an oncoming SH episode and take evasive action (e.g., consuming oral carbohydrates) and thus may feel less reliant on glucagon.

TABLE 6 Participants' Preferences for Characteristics of Glucagon Products (N = 316)

Preference-Related Survey Data	Value
Preferred method of glucagon administration	
Intranasal—spray in the nose	151 (47.8)
Premixed autoinjector—already reconstituted	120 (38.0)
Injection—needs to be reconstituted	45 (14.2)
Preferred characteristics of glucagon rescue treatments (multiple answers possible)	
Ease of use (ready-to-use treatment)	241 (76.3)
The way it is administered (nasal spray, ready-to-use injection)	176 (55.7)
How fast the glucagon works compared with others on the market	169 (53.5)
Treatment that can be carried at room temperature (vs. stored in a refrigerator)	133 (42.1)
Having multiple kits available	102 (32.3)
Main improvements to be made in glucagon rescue treatments (multiple answers possible)	
Ease of use (premixed dosing)	198 (62.7)
Cost	169 (53.5)
Administration type (nasal, syringe)	159 (50.3)
Storage options	122 (38.6)
Time to physical recovery	126 (39.9)
Fewer steps in the instructions	96 (30.4)
Size of kit	99 (31.3)
All of the above	39 (12.3)
Other	3 (0.9)
Importance of time to plasma glucose recovery in glucagon rescue treatments	
Very important	148 (46.8)
Fairly important	84 (26.6)
Important	57 (18.0)
Slightly important	26 (8.2)
Not at all important	1 (0.3)

Data are n (%).

The U.S. survey by Haymond et al. (21) noted that 85.2% (n = 225 of 264) of participating adults with type 1 diabetes had been prescribed glucagon and that 58.3% (n = 154 of 264) had a current glucagon prescription (21); 51% of those participants who had experienced an SH event in the past had not been able to have glucagon administered to them when needed, even if the kit was close by. In contrast, 14.9% of the participants in the present survey were unable to have glucagon administered to them when required. Thus, in addition to an increased number of people with type 1 diabetes being prescribed glucagon rescue therapy since 2019, the proportion of people who have been administered rescue glucagon when required has improved substantially. Nonetheless, this survey showed that known obstacles to the appropriate use of rescue glucagon (21,22,27) continue to pose challenges, including problems with the reconstitution and administration process, unawareness of the existence of the kit or inability to locate it, lack of training, kit expiration, and lack of confidence of the rescuing individual.

Participants who had never received a glucagon prescription (n = 9) stated that the main reasons for this were that their doctor had never discussed it with them, they carried oral carbohydrates with them, or they relied on CGM. A global survey report suggests differences among countries regarding the proportion of individuals with type 1 diabetes who were unable to have glucagon administered during an SH event because they did not have a glucagon prescription or it was not filled (39,40,42), ranging from 25.0% in a French cohort (42) to 68.8% in a Japanese cohort (39).

One of the most critical barriers to the use of glucagon rescue products identified in this study was a mean out-of-pocket cost of $73.40 ± $85.80 for glucagon kits. Cost was identified by 53.5% of participants as one of the improvements they would like to see in glucagon rescue products. Financial barriers may therefore contribute to people with type 1 diabetes not filling their glucagon prescriptions or relying on other means of achieving normoglycemia.

Our survey data further demonstrated that most participants preferred ready-to-use glucagon products over first-generation glucagon products that require reconstitution because of the former's ease of use, ready-to-use administration format, fast onset of action, and storage at room temperature. Participants favored a nasal mode of administration (47.8%) and a premixed autoinjector (38.0%) over reconstituted first-generation glucagon (14.2%). When queried, at least half of the participants indicated that they would also like to see improvements in ease of use (62.7%) and more intuitive modes of administration (50.3%). This finding suggests that a large proportion of the participants may still use first-generation glucagon products that require complex reconstitution and administration steps.

Advice for Primary Care Providers

Despite the increasing use of CGM, SH and fear of SH continue to pose challenges for individuals with type 1 diabetes. Although the typical automated insulin delivery system responds by adjusting the insulin dose when an SH event occurs, this process does not obviate the immediate need for administration of counterregulatory glucagon. Thus, glucagon continues to be a necessary and potentially life-saving component of therapy for type 1 diabetes.

To provide the best possible care for individuals with type 1 diabetes, primary care providers are advised to follow the ADA's guidelines for prescribing glucagon (3) and to address the following topics with their patients.

- Ask whether the individual has a supply of glucagon at home.
  - If so, ascertain that the glucagon is not out of date.
  - If not, determine the barriers to accessing glucagon that the individual may face.
- Ask about who in the individual's support network is trained in glucagon use.
  - Ascertain whether these trusted individuals know where the glucagon is stored and are confident about administering it.
- Given that ready-to-use glucagon products are now available, determine whether these individuals need to be retrained or whether additional people can be added to the individual's circle of trusted individuals to optimize safety.

Limitations

A limitation of this study is that the surveyed sample is not representative of the overall population of people with type 1 diabetes in the United States. The survey sample was predominantly White and female and relatively young, affluent, and well-educated. The study design made use of an online survey format, and recruitment was conducted via digital media, which may have excluded people with limited computer skills or restricted computer or Internet access. The study included only adults with type 1 diabetes who had experienced at least one SH event in their lifetime and who were aware of the glucagon products on the market; therefore, the survey sample may be skewed toward people who were more aware of the available glucagon products than those who had never experienced an SH episode. In addition, the survey was conducted retrospectively, and data were self-reported, which carries the potential for misclassification of hypoglycemic events as well as recall bias, especially for the number of SH events in the participants' lifetime. It was noted that a small number of participants reported a very high number of SH events in their lifetime (up to 1,000 events), which may have skewed the mean; the median may be more representative of the overall survey sample.

Conclusion

This study highlighted several important findings about the experiences of individuals with type 1 diabetes in the United States with SH and glucagon rescue use. The survey results suggest that the majority of individuals with type 1 diabetes have a current and filled prescription for rescue glucagon and have received education about glucagon rescue use from their HCP. The proportion of individuals with type 1 diabetes who were unable to have glucagon administered to them when required has decreased substantially compared with previous surveys. These data show a promising trend toward increased utilization of rescue glucagon and improved training in its use by HCPs in the past few years.

Despite these positive findings, there are continued challenges, including a high level of costly health care resource utilization directly resulting from SH events, substantial out-of-pocket expenses for glucagon kits, and a substantial prevalence of hypoglycemia unawareness. This study also highlighted the emotional burden of SH for individuals with type 1 diabetes.

Ready-to-use glucagon products do not yet seem to be fully adopted by HCPs and the diabetes community. Greater dissemination of these products among individuals with type 1 diabetes could improve the use of glucagon for SH rescue even more in the future. Further research is needed to understand experiences with and emotional effects of hypoglycemia and glucagon rescue use in both individuals with type 1 diabetes and their caregivers to improve the health and quality of life of people with type 1 diabetes.

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AUTHOR CONTRIBUTIONS

A.S.H., K.S.C., J.L., J.B., and W.A.W. participated in the conceptualization and design of the study, enrolled the survey participants, and conducted the survey. A.S.H., K.S.C., and H.N. analyzed the survey data. H.N. conducted the correlation analysis. M.W. obtained funding for medical writing and editorial

assistance. All of the authors interpreted the data, reviewed the manuscript critically for intellectual content, provided feedback for incorporation, and approved the final version for publication. A.S.H. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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