Health-related Quality of Life in Adults with Type 1 Diabetes and Severe Hypoglycemia Who Use Continuous Glucose Monitors: Results From a Cross-sectional Survey in the United States

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INTRODUCTION

- Type 1 diabetes (T1D) is an autoimmune disease characterized by endogenous insulin deficiency leading to abnormal glucose regulation.[1-2] Treatment of T1D requires lifelong exogenous insulin therapy within a therapeutic range, measured by HbA1c levels <7%.[3] Recent guidelines recommend Continuous Glucose Monitor (CGM) as part of a first line approach in the management of T1D.[4]
- Despite advances in T1D management technologies, including CGM and automated insulin delivery systems (such as hybrid closed loop systems), individuals with T1D are burdened by their condition and management options.[3-15]
  - Exogenous insulin is essential for the treatment of T1D but requires careful assessment of blood glucose due to its narrow therapeutic window.[3-4]
  - Excess insulin relative to physiologic requirements can result in hypoglycemia and experience severe hypoglycemic events (SHEs).[5-6]
  - SHEs are medical emergencies characterized by altered physical or mental status requiring the assistance of another person to treat, and can lead to seizures, cardiac arrythmias, loss of consciousness, coma, or even death.[3,7-10]
  - Repeated episodes of SHEs can lead to counterregulatory hormone responses resulting in impaired awareness of hypoglycemia (IAH).[11-12] IAH reduces the individual's ability to recognize and treat future episodes of low blood glucose,[12-14] further increasing their risk of experiencing SHE by 6-fold.[15]
- There is limited understanding of SHEs and IAH experiences and the associated impacts to health-related quality of life (HRQoL) in adult CGM users with SHE and IAH.
- Generic preference-based measures, such as the 36-Item Health Survey (SF-36)[17] and EuroQoL 5 Dimension (EQ-5D),[18-19] are frequently used to measure HRQoL. However, it is unclear how these measures perform in real-world samples of adult CGM users with SHEs and IAH.

OBJECTIVE

- To evaluate the HRQoL in individuals with T1D with SHEs and IAH in the United States using generic preference-based measures

METHODS

Study Design

- An online cross-sectional survey was administered to individuals with T1D from the T1D Exchange Registry who had previously consented to be contacted for research purposes.

Key Inclusion Criteria

- Current CGM user
- Aged ≥18 years old

Survey Design & Administration

- SHE frequency was collected through participant responses to the question, "How many times did you experience a severe hypoglycemic event in the past 12 months?"
- IAH status was determined using established cutoffs from the modified Gold measure.[16] The Gold measure is a 1-item questionnaire that asks individuals to report their experience in detecting hypoglycemic events with responses ranging from 1 (always aware) to 7 (never aware) in a Likert type scale.
  - A score of ≤2 = normal awareness (IAH-); 3 = borderline (undetermined); ≥4 suggests impaired awareness of hypoglycemia (IAH+)
- Generic preference-based measures including the RAND SF-36 and EQ-5D-5L were included to assess the impact of SHE and IAH on the HRQoL of individuals with T1D.

Cohort Definitions

- Cohorts were created based on self-reported SHE frequency and IAH status in the past 12 months.

Cohort	Definition
Recurrent SHEs with IAH	Individuals with 2+ SHEs and IAH+
Problematic SHEs	Individuals with 2+ SHEs and IAH- or 1+ SHE and IAH+
Single SHE/no-IAH	Individuals with 1 SHE and IAH-
No-SHE	Individuals with 0 SHE and IAH+; 0 SHE and IAH-

Statistical Analyses

- Descriptive analyses (mean [standard deviation (SD)]) of participant characteristics and HRQoL impacts are reported overall and by SHE/IAH cohort.
- SF-36 items were first recoded per published algorithms. The means of items were computed to create 8 subscales: Physical Functioning, Role limitations due to Physical Health; Role limitations due to Emotional Problems; Energy/Fatigue; Social Functioning; Pain; and General Health. Items are reported from 0-100 for each scale, where higher scores indicate more positive health states.[17]
- For the EQ-5D-5L, scores were calculated per scoring instructions and an index value score was calculated using the published syntax from EuroQol.[18-19] Index value numbers were calculated for all 5 dimensions of health states (Mobility, Self-Care, Usual Activities, Pain/Discomfort, Anxiety/Depression), and all 5 index values make up a value set.

RESULTS

Demographic Characteristics

- The analytic cohort comprised 1,510 participants, including recurrent SHEs with IAH (n = 174), problematic SHEs (n = 201), single SHE/no-IAH (n = 102), and no-SHE (n = 1,033) cohorts. Participants' mean age was 46.4 (SD = 15.4) and most were female (66.3%) (**Table 1**).

Table 1. Demographic Characteristics

	Overall (N = 1510)	Recurrent SHEs with IAH (n = 174)	Problematic SHEs (n = 201)	Single SHE, no-IAH (n = 102)	No-SHE (n = 1033)
Age, mean (SD), years	46.4 (15.4)	50.4 (13. 9)	47.9 (15.1)	44.7 (14.8)	45.6 (15.7)
Gender, n (%)					
Male	494 (32.7)	44 (25.3)	64 (31.8)	32 (31.4)	354 (34.3)
Female	1001 (66.3)	130 (74.7)	136 (67.7)	69 (67.6)	666 (64.5)
Non-binary / genderqueer	13 (0.9)	0 (0)	1 (0.5)	1 (1.0)	11 (1.1)
Prefer to self-identify	1 (0.1)	0 (0)	0 (0)	0 (0)	1 (0.1)
Prefer not to answer	1 (0.1)	0 (0)	0 (0)	0 (0)	1 (0.1)
Race, n (%)					
White	1374 (91.0)	153 (87.9)	171 (85.1)	92 (90.2)	958 (92.7)
American Indian/Alaskan Native	8 (0.5)	1 (0.6)	2 (1.0)	0 (0)	5 (0.5)
Asian	13 (0.9)	0 (0)	1 (0.5)	2 (2.0)	10 (1.0)
Black/African-American	35 (2.3)	8 (4.6)	13 (6.5)	1 (1.0)	13 (1.3)
Native Hawaiian or Other Pacific Islander	2 (0.1)	0 (0)	1 (0.5)	0 (0)	1 (0.1)
North African/Middle-Eastern	8 (0.5)	0 (0)	1 (0.5)	0 (0)	7 (0.7)
More than 1 race	55 (3.6)	10 (5.7)	8 (4.0)	5 (4.9)	32 (3.1)
Other	15 (1.0)	2 (1.1)	4 (2.0)	2 (2.0)	7 (0.7)
Ethnicity, n (%)					
Hispanic or Latino	90 (6.0)	12 (6.9)	11 (5.5)	12 (11.8)	55 (5.3)
Employment status, n (%)					
Employed full-time (at least 32 hours per week)	867 (57.4)	70 (40.2)	102 (50.7)	60 (58.8)	635 (61.5)
Employed part-time (less than 32 hours per week)	157 (10.4)	26 (14.9)	21 (10.4)	10 (9.8)	100 (9.7)
Unemployed	75 (5.0)	9 (5.2)	15 (7.5)	6 (5.9)	45 (4.4)
Student only	40 (2.6)	4 (2.3)	3 (1.5)	2 (2.0)	31 (3.0)
Unpaid caregiver	35 (2.3)	5 (2.9)	4 (2.0)	3 (2.9)	23 (2.2)
Retired	252 (16.7)	30 (17.2)	38 (18.9)	13 (12.7)	171 (16.6)
Disabled, not able to work	84 (5.6)	30 (17.2)	18 (9.0)	8 (7.8)	28 (2.7)

Clinical Characteristics

- Overall, mean duration of T1D diagnosis was 29.4 years (SD = 15.2). Majority of participants (65.3%) used hybrid closed loop systems (HCLS)/do-it-yourself looping systems (DIY) and had CGM for ≥5 years (55.0% (**Table 2**).
- Overall, participants reported 1.9 mean SHEs (SD = 14.2) in the past 12 months and 41.1% had IAH (Gold score: ≥4). About 34.0% of participants were unable to achieve the ADA recommended glycemic targets (HbA1c <7%) (**Table 2**).
- Across SHE/IAH cohorts, higher rates of SHE were observed in the recurrent SHEs with IAH (8.6, SD = 19.4) and problematic SHEs cohorts (6.5, SD = 33.5), and 43.7 % of participants in the recurrent SHEs with IAH cohort were unable to achieve glycemic targets (HbA1c <7%) compared to the overall sample (34.0%) and no-SHE (31.3%) cohorts (**Table 2**).

Table 2. Clinical Characteristics

	Overall (N = 1510)	Recurrent SHEs with IAH (n = 174)	Problematic SHEs (N=201)	Single SHE no IAH (N=102)	No-SHE (N=1033)
Duration of T1D, mean (SD), years	29.4 (15.2)	32.6 (16.0)	31.3 (16.0)	28.3 (14.3)	28.6 (14.8)
Number of SHE in past 12 months					
Mean (SD)	1.9 (14.2)	8.6 (19.4)	6.5 (33.5)	1.0 (0.0)	0.0 (0.0)
Median (Min, Max)	0 (0, 360)	3 (2, 150)	1 (1, 360)	1 (1, 1)	0 (0, 0)
Impaired Awareness of Hypoglycemia, n (%)					
IAH-	889 (58.9)	0 (0)	98 (48.8)	102 (100)	689 (66.7)
IAH+	621 (41.1)	174 (100)	103 (51.2)	0 (0)	344 (33.3)
Diabetes technology subtypes, n (%)					
HCLS/DIY	986 (65.3)	90 (51.7)	119 (59.2)	64 (62.7)	713 (69.0)
PLGS	97 (6.4)	16 (9.2)	17 (8.5)	9 (8.8)	55 (5.3)
Pump no AID	182 (12.1)	31 (17.8)	21 (10.4)	11 (10.8)	119 (11.5)
MDI	245 (16.2)	37 (21.3)	44 (21.9)	18 (17.6)	146 (14.1)
Length of CGM use, n (%)					
Less than 3 months	17 (1.1)	3 (1.7)	1 (0.5)	4 (3.9)	9 (0.9)
At least 3 months but less than 1 year	43 (2.8)	13 (7.5)	8 (4.0)	6 (5.9)	16 (1.5)
At least 1 year but less than 3 years	249 (16.5)	34 (19.5)	42 (20.9)	17 (16.7)	156 (15.1)
At least 3 years but less than 5 years	370 (24.5)	44 (25.3)	55 (27.4)	28 (27.5)	243 (23.5)
5 or more years	831 (55.0)	80 (46.0)	95 (47.3)	47 (46.1)	609 (59.0)
Most recent HbA1c					
Mean (SD)	6.69 (0.95)	6.94 (1.10)	6.84 (1.12)	6.59 (1.04)	6.63 (0.87)
Median (Min, Max)	6.6 (4, 14.2)	6.9 (5.2, 12.2)	6.7 (4.9, 12)	6.45 (4, 11.4)	6.5 (4.3, 14.2)
Did not achieve glycemic target (HbA1c <7%), n (%)	514 (34.0)	76 (43.7)	83 (41.3)	32 (31.4)	323 (31.3)

Abbreviations: T1D, Type 1 Diabetes; SD, Standard Deviation; SHEs, Severe Hypogelycemic Events; IAH, Impaired Awareness of Hypoglycemia; HCLS, Hybrid Closed Loop System; DIY, Do-it-yourself looping system; PLGS, predictive low glucose suspend systems; AID, Automated Insulin Delivery; MDI, multiple daily injections of insulin; CGM, Continuous Glucose Monitor; HbA1c, Hemoglobin A1C

RAND SF-36 Results

- Across SHE/IAH cohorts, the recurrent SHES with IAH cohort reported the lowest HRQoL as measured by the RAND SF-36, compared to other SHE/IAH cohorts and to the overall sample (**Table 3**).

Table 3. RAND SF-36 Results

	Overall (N = 1510)	Recurrent SHEs with IAH (n = 174)	Problematic SHEs (n = 201)	Single SHE, no-IAH (n = 102)	No-SHE (n = 1033)
SF-36 Domains, mean (SD)					
Physical Functioning	84.1 (19.9)	74.9 (24.2)	79.8 (22.3)	83.6 (20.0)	86.5 (18.0)
Role Functioning/Physical	64.3 (39.5)	42.2 (39.8)	54.5 (41.6)	63.0 (39.9)	70.0 (37.3)
Role Functioning/Emotional	66.1 (39.5)	53.3 (41.3)	60.7 (39.8)	54.6 (42.9)	70.4 (38.0)
Energy/Fatigue	46.4 (22.9)	38.1 (23.9)	45.0 (23.0)	42.5 (22.8)	48.4 (22.3)
Emotional Well-being	68.6 (19.7)	61.6 (21.9)	67.3 (20.5)	67.7 (19.5)	70.1 (18.8)
Social Functioning	77.9 (23.7)	64.9 (26.0)	72.6 (25.6)	73.2 (26.6)	81.5 (21.6)
Pain	73.6 (23.1)	59.9 (25.3)	67.4 (26.5)	74.9 (22.1)	77.0 (20.9)
SF-36 General Health, mean (SD)	54.1 (21.7)	44.9 (22.3)	50.4 (22.5)	51.1 (21.6)	56.7 (20.9)
SF-36 Health Change, mean (SD)	57.2 (22.2)	53.3 (23.7)	59.8 (23.7)	57.4 (21.3)	57.4 (21.6)

EQ-5D-5L Results

- Participants rated their general health relatively positively (EQ-5D-5L Index, mean = 0.8); however, there was some variability in observed means between SHE/IAH cohorts (**Table 4**).
- In general, participants in the recurrent SHEs with IAH cohort reported the worst observed health impacts, followed by the problematic SHEs cohort, then the single SHE/no-IAH and finally, the no-SHE cohorts.

Table 4. EQ-5D-5L Results

	Overall (N = 1510)	Recurrent SHEs with IAH (n = 174)	Problematic SHEs (n = 201)	Single SHE, no-IAH (n = 102)	No-SHE (n = 1033)
EQ-5D-5L Domains, mean (SD)					
Mobility	1.3 (0.7)	1.6 (0.9)	1.4 (0.8)	1.3 (0.7)	1.3 (0.6)
Self-care	1.1 (0.4)	1.3 (0.6)	1.1 (0.4)	1.1 (0.4)	1.1 (0.3)
Usual Activities	1.4 (0.7)	1.8 (0.9)	1.5 (0.8)	1.5 (0.8)	1.3 (0.6)
Pain/Discomfort	1.9 (0.9)	2.4 (0.9)	2.1 (1.0)	1.9 (0.9)	1.8 (0.8)
Anxiety/Depression	1.9 (1.0)	2.3 (1.2)	2.0 (1.1)	2.0 (1.0)	1.8 (0.9)
EQ-5D-5L Total Scale, mean (SD)	1.5 (0.5)	1.9 (0.7)	1.6 (0.6)	1.6 (0.6)	1.5 (0.5)
EQ VAS Today Health, mean (SD)	74.2 (19.3)	64.8 (23.2)	73.0 (19.5)	74.3 (19.6)	76.1 (18.0)
EQ-5D-5L Utility Index Score, mean (SD)	0.8 (0.2)	0.7 (0.3)	0.8 (0.3)	0.8 (0.2)	0.9 (0.2)

LIMITATIONS

- Study participants were from the T1D Exchange Registry, a cohort of individuals with T1D who tend to be highly engaged, have a high degree of diabetes technology use, and have historically been shown to be more likely to achieve glycemic targets.
- Study participants were mostly White, non-Hispanic or Latino, identified as female, highly educated, were self-selected and needed access to the Internet and email, which may all impact the generalizability of these results.
- All data were self-reported; eligibility and clinical data were not verified by a clinician.

CONCLUSIONS

- Despite the high rates of diabetes technology adoption among study participants, a substantial proportion of participants with recurrent SHEs with IAH (41.3%) reported not meeting their glycemic targets, compared to other cohorts.
- On average, adult CGM users with T1D with recurrent SHEs and IAH reported experiencing ~9 SHEs in the past 12 months compared to ~2 SHEs in the overall cohort.
- Generally, HRQoL as measured by the RAND SF-36 and EQ-5D-5L worsened with increasing SHE frequency and IAH status, although some variability in specific measures were observed, highlighting the need to further investigate preference-based measures appropriate for use in the recurrent SHE with IAH subpopulation.
- Collectively, these findings demonstrate the substantial humanistic burden among those living with T1D with recurrent SHEs with IAH, and they highlight unmet need in this population.

AUTHOR DISCLOSURES

This study was sponsored by Vertex Pharmaceuticals Incorporated. ABK, PC, KC, DB and LC are employees of Vertex Pharmaceuticals Incorporated and may hold stock or stock options in the company.

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