Protective and risk factors of impaired awareness of hypoglycemia in patients with type 1 diabetes: a cross- sectional analysis of baseline data from the PR-IAH study

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Research Article

Keywords: impaired hypoglycemia awareness, type 1 diabetes, continuous subcutaneous insulin infusion

Posted Date: July 13th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1823400/v1

Additional Declarations: No competing interests reported.

Version of Record: A version of this preprint was published at Diabetology & Metabolic Syndrome on April 25th, 2023. See the published version at https://doi.org/10.1186/s13098-023-01024-x.

Abstract

Background

Hypoglycemia in type 1 diabetes (T1D) is associated with mortality and morbidity, especially when awareness of hypoglycemia is impaired. This study aimed to investigate the protective and risk factors for impaired awareness of hypoglycemia (IAH) in adults with T1D.

Methods

This cross-sectional study enrolled 288 adults with T1D (mean age, 50.4 ± 14.6 years; male, 36.5%; diabetes duration, 17.6 ± 11.2 years; mean HbA1c level, 7.7 ± 0.9%), who were divided into IAH and non-IAH (control) groups. A survey was conducted to assess hypoglycemia awareness using the Clarke questionnaire. Diabetes histories, complications, fear of hypoglycemia, diabetes distress, hypoglycemia problem-solving abilities, and treatment data were collected.

Results

The prevalence of IAH was 19.1%. Diabetic peripheral neuropathy was associated with an increased risk of IAH (odds ratio [OR] 2.63; 95% confidence interval [CI] 1.13–5.91; P = 0.014), while treatment with continuous subcutaneous insulin infusion and hypoglycemia problem-solving perception scores were associated with a decreased risk of IAH (OR, 0.48; 95% CI, 0.22–0.96; P = 0.030; and OR, 0.54; 95% CI, 0.37–0.78; P = 0.001, respectively). There was no difference in continuous glucose monitoring use between the groups.

Conclusions

We identified protective factors in addition to risk factors for IAH in adults with T1D. This information may help manage problematic hypoglycemia.

Trial registration:

University hospital Medical Information Network (UMIN) Center: UMIN000039475) Approval date 13 February 2020

Background

Adults with type 1 diabetes mellitus (T1D) and impaired awareness of hypoglycemia (IAH) have a reduced ability to perceive hypoglycemic symptoms and are at risk of severe hypoglycemic events

because of less than immediate appropriate corrective therapy[1]. Autonomic symptoms are typically lost before general malaise and neuroglycopenic symptoms. Therefore, individuals with IAH may plan to loosen tight glucose management and intentionally omit insulin injection to prevent severe hypoglycemia (SH). In individuals with T1D, IAH is highly prevalent with or without continuous glucose monitoring (CGM) [2]. Although recurrent hypoglycemia [3], diabetic neuropathy [4], longer diabetes duration [5], genetic factors [6], and personality traits of alexithymia and perfectionism [7] are candidate risk factors for IAH, their pathogenesis is still unclear. In individuals with IAH, counter-regulatory responses are blunted to subsequent hypoglycemic episodes due to recurrent mild to moderate hypoglycemia. This is called hypoglycemia-associated autonomic failure, which is a cellular adaptation [8]. It is also unclear which lifestyle factors are associated with the risk of IAH, although antecedent exercise, excessive drinking, psychological stress, and sleep disturbance may induce recurrent hypoglycemia[9, 10]. In contrast, diabetes treatment technologies (e.g. CGM and continuous subcutaneous insulin infusion (CSII)), and hypoglycemia-solving abilities might affect IAH status. Therefore, this study aimed to investigate the protective and risk factors of IAH in adults with T1D.

Materials And Method

This is an exploratory and cross-sectional study, using the STROBE instrument included in reports of cross-sectional studies. The study was approved by the National Hospital Organization (NHO) Central Research Ethics Committee (R2-0117002). Participants and Settings Between February 2020 and March 2022, we enrolled adults with IAH at seven NHO collaborator center in Japan. The inclusion criteria were type 1 diabetes, diabetes duration ≥ 1 year, age ≥ 20 years, and attending a collaborating center. The exclusion criteria were non-insulin therapy, anti-dementia drug use, and inappropriate cases judged by the research director or coordinators.

Diabetic complications

Treatment of diabetic retinopathy, nephropathy, and peripheral neuropathy was performed by certified diabetologists according to the treatment guidelines for diabetes 2018–2019.

Diabetic retinopathy was assessed by an ophthalmologist using retinal photography. Retinopathy was classified as absent, simple, preproliferative, and proliferative. Diabetic nephropathy was classified as stage 1 to 5 based on the estimated glomerular filtration rate and albuminuria or hemodialysis stage[11]. Diabetic peripheral neuropathy (DPN) was considered present following the criteria after patients were diagnosed with diabetes and excluded polyneuropathy, except diabetic polyneuropathy. DPN was determined to be positive in the presence of ≥ two of the three criteria: 1) subjective neurological symptoms (pain, dysesthesia, or numbness in the bilateral lower extremities); 2) decreased or absent bilateral Achilles tendon reflexes; and 3) diminished bilateral vibratory sensation (hypesthesia) at the malleolus medialis (<10 seconds at 128 Hz using a tuning fork)[12]. Coefficient of variation of R-R intervals (CV-RR) was calculated automatically by a computed analyzer that collected 100 R-R intervals and divided the standard deviation by the mean value. CV-RR< 3% was indicative of diabetic cardiac

autonomic neuropathy (DCAN) [13]. The mean QTc interval was calculated using Bazett's formula, and a QTc >440 ms was considered prolonged[14].Hemoglobin A1c (HbA1c) level, glycated hemoglobin (GA) level, levels of liver enzymes, and lipid profiles were collected from the medical records. Furthermore, the GA/HbA1c ratio, which reflects glucose variability, was calculated by dividing the GA level by the HbA1c level [15].

Impaired awareness of hypoglycemia and hypoglycemic symptoms

The IAH was determined using the Clarke method [16] and a score ≥ 4 implies IAH. Hypoglycemic symptoms were evaluated using the Edinburgh hypoglycemia scale[17, 18]. Self-reported number of SH episodes, defined as "hypoglycemia that you were unable to treat yourself," in the preceding year was also collected.

Diabetes-related distress and hypoglycemia problem-solving abilities

Distress related diabetes management was assessed using the PAID questionnaire and high score of ≥ 40 points indicates severe distress [19, 20]. The Hypoglycemia Fear Survey (HFS) were used to have a fear of hypoglycemia [21,22]. The general utility index was calculated using the EuroQoL 5-dimension (EQ-5D)[23,24]. The hypoglycemia problem-solving scale (HPSS), which has 24 items and seven subscales, was used for hypoglycemia problem-solving ability [25].

Lifestyle factors

Self-administered questionnaires regarding lifestyle factors (exercise, dietary habits, drinking, smoking, and sleep habits) were collected [26] , and sleep debt [27] and healthy lifestyle score [28] were calculated.

Sample size

The prevalence of IAH is approximately 20%[29]. Therefore, a minimum sample size of 200 completers (40 participants with IAH and 160 participants without IAH) was needed to achieve an appropriate significance level of 5% and power of 0.8, if the prevalence of IAH of 20% and effect size of 0.5 (medium) were estimated.

Data analyses

Qualitative variables were compared using Fisher's exact test. Quantitative variables were compared using the t-test or the Mann–Whitney U test. Logistic regression was performed to estimate the odds ratio (OR) with 95% confidence interval (CI). Cronbach's alpha was calculated to assess the internal consistency. Correlation coefficients (Spearman's rho, ρ) between the HPSS and psychological distress scales was examined using Spearman's rank correlation. All P-values < 0.05 indicated significant dependencies. The analysis was conducted using R program version 4.1.2.

Results

Participants

The study was conducted on 288 adults with T1D and IAH (mean age, 50.4±14.6 years; male, 36.5%; diabetes duration, 17.6±11.2 years; mean HbA1c level, 7.7±0.9%), who were divided into control and IAH groups.

Diabetic complications, treatment, lifestyle factors, and laboratory data

DPN was more prevalent in the IAH group than in the control group. Moreover, the prescription rate of mecobalamin was higher in the IAH group than that in the control group. There was no difference in HbA1c levels and other complications, except DPN, between the groups. Treatment with CSII was less prevalent in the IAH group than in the control group, but there was no difference in CGM usage between the groups (Table 1). There was no difference in healthy lifestyle score, sleep debt, and excessive drinking rate between the groups (Table 2). There was no difference in laboratory data, including HbA1c level and GA/HbA1c ratio, between the groups (Table 3).

DPN was associated with an increased risk of IAH (OR, 2.63; 95% CI, 1.13–5.91; P = 0.014), while treatment with CSII was associated with a decreased risk of IAH (OR, 0.48; 95% CI, 0.22–0.96; P = 0.030) (Table 4). There was no difference in CGM usage, CV-RR, and QTc intervals between the groups.

Hypoglycemic symptoms, diabetes distress, and hypoglycemia problem-solving abilities

The mean autonomic symptom scores, except for palpitations and hunger in the IAH group compared to the control group, were significantly reduced, while the mean neuroglycopenic symptom scores were relatively lower in the control group than in the IAH group. The scores are shown in (Table 5). The average PAID and HFS-worry scores in the IAH group were significantly higher than those in the control group, and there was no difference in the PHQ-9 and HFS-behavior scores between the groups. The HPSS, composed of 24 items, demonstrated high internal consistency, as reflected by a Cronbach's alpha coefficient of 0.883. A weak positive correlation of the HPSS score with HFS-B (ρ=0.331, P<0.001) and HFS-W (ρ=0.162, P=0.006) were observed, although no significant correlation of the HPSS with age, HbA1c, PAID and PHQ-9 scores were observed. Hypoglycemia problem-solving perception score of HPSS was associated with a decreased risk of IAH (OR, 0.54; 95% CI, 0.37–0.78; P = 0.001), although there was no difference in the other six subscales between groups.

Discussion

This is the first study to identify protective factors (treatment with CSII and higher problem-solving perception) and risk factors (DPN) of IAH in Japanese adults with T1D.

DPN and IAH

Cross-sectional and observational studies have indicated that DPN, cardiac autonomic neuropathy, and gastroparesis are associated with SH[30-34]. However, Olsen et al. reported that IAH was not associated with autonomic dysfunction or DPN in adults with T1D[35]. Conversely, Flatt et al. reported that peripheral neuropathy was more prevalent in patients with SH than in patients without SH in the 24-month follow-up of the HypoCOMPASS study (39% vs. 4.7%, respectively)[36]. This discrepancy between the results is unknown. The diagnostic criteria, ethnicity, and differences in the population with diabetes may explain this. Furthermore, the mechanism by which DPN causes IAH remains unclear. CV-RR and abnormality of the QTc interval were not associated with severe hypoglycemic attacks in this study although SH attacks were independently associated with a prolonged QTc interval in 3,248 patients with T1D from the EURODIAB IDDM Complications Study [34]. DPN is associated with cognitive impairments in adults with T1D [37]. In this study, we observed deficits in autonomic symptoms in adults with T1D and IAH. Cognitive impairment may affect the perception of hypoglycemia. In addition, repeated hypoglycemia can cause DPN as reported in animal experiments. Further large and long-standing examinations are required to confirm these issues in the future.

Diabetes-related technologies

In this study, treatment with CSII was less prevalent in adults with T1D and IAH although CGM devices were not associated with an increased risk of IAH. New technologies, including CGM, aim to improve the awareness status of hypoglycemia. However, several studies have suggested that IAH persists even with CGM usage. Reddy et al. reported that rtCGM (Dexcom G5) more effectively reduces time spent in hypoglycemia at 8 weeks compared to isCGM (Abbott Freestyle Libre) in 40 adults with T1D and IAH using a multiple daily injections (MDI) regimen [38]. Moreover, rtCGM systems reduce unawareness of hypoglycemia in children, adolescents, and adults with T1D.[39] Further examinations including rtCGM and large samples are required to confirm these issues because the rtCGM usage rate was low in this study. Conversely, treatment with CSII may be useful in reducing unawareness of hypoglycemia in adults with T1D. The clinical statement for the management of problematic hypoglycemia (2015) recommended structured education, MDI with real-time CGM or CSII, a sensor-augmented pump with or without a low glucose suspension feature, and pancreatic islet transplantation [40,41]. Observational studies based on these guidelines are needed to confirm these issues in the future.

Limitation of the study

The strength of the study includes a validated self-administered questionnaire. However, our study had some limitations. This study used a cross-sectional study design to make a causal inference. DPN was estimated as presence or absence; therefore, the severity of peripheral neuropathy was not evaluated. DCAN was evaluated using the CV-RR in this study. DCAN is an underdiagnosed cardiovascular complication in individuals with diabetes. In an animal model, DCAN was evaluated using histology patterns and cardiac nerve densities. QTc intervals are affected by other factors, such as obesity, arteriosclerotic macroangiopathy, and autonomic nerve function. Nerve conduction studies and sympathetic skin responses are reliable methods in detecting DCAN. Furthermore, definite DCAN was

defined as ≥ 2 positive cardiac autonomic tests.[42] Further examination, including the definite DCAM method, is required to compare DCAN and IAH status.

Implication for practice

We adopted the Clarke method; however, the prevalence of IAH using the Clarke method is likely to be underestimated according to the CGM data. IAH is prevalent in adults with T1D. Moreover, the diagnosis of DPN is challenging.[43,44]. Careful attention should be paid to diabetes distress and fear of hypoglycemia. We identified protective factors for IAH as treatment with CSII and problem-solving perception of HPSS. We should consider CSII or structured education in adults with T1D and IAH [45]. Problem-solving, which is defined as a self-directed cognitive-behavioral process by which people attempt to cope with a difficult situation, is a behavioral strategy in diabetes management. They refer to a mental process that involves discovering, analyzing, and solving problems. The problem-solving perception factor explained most of the variance between the seven factors. The problem-solving perception subscale consists of four reverse items: discouraged for failure to prevent hypoglycemia, feeling depressed or angry because of difficulties in preventing hypoglycemia, worrying about how to prevent hypoglycemia but have not taken any action, and reduced self-esteem. The intervention based on the HPSP effectively improved HbA1c levels and hypoglycemia problem-solving ability in individuals with hypoglycemia[46]. We should take into account an education program with an increased problem-solving ability of adults with T1D and IAH.

In conclusion, we identified protective factors in addition to risk factors for IAH in Japanese adults with T1D. This information may help manage problematic hypoglycemia. IAH has a complex pathophysiology and might lead to serious and potentially lethal consequences in patients with T1D[47]. A stepwise approach using diabetes-related technologies [48] was needed to educate and treat patients with T1D and IAH in the future.

Abbreviations

CGM: continuous glucose monitoring

CI: confidence interval

CSII: continuous subcutaneous insulin infusion

DCAN: diabetic cardiac autonomic neuropathy

DPN: diabetic peripheral neuropathy

HbA1c: hemoglobin A1c

IAH: impaired awareness of hypoglycemia

isCGM: intermittently scanned continuous glucose monitoring

MDI: multiple daily injection

rtCGM: real-time continuous glucose monitoring

T1D: type 1 diabetes

Declarations

Ethics approval and consent to participate

Approval of the research protocol: This study was approved by t the National Hospital Organization Central Review Board (NHOCRB/ R2-0117002 R3-0614027)

Informed consent or substitute for it was obtained from all patients for being included in the study.

Animal Studies N/A

Conflict of interest disclosures

None to be declared

Funding

The PR-IAH study with funding from the National Hospital Organization Clinical research (NHO) (Grant number: H31-NHO (Endocrinology and Nephrology)-01).

Authors' contributions

Authors’ contributions statement: NS conceived the ideas. MD analyzed the data. NS acquired the funding. SH, EN, RA,KK,MH,YM, YM, and KK collected the data. NS and AS written the original draft. TM, SS, FW reviewed and written the article.

Acknowledgments

The authors are grateful to the NHO Diabetology group.

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Tables

Table 1. Baseline characteristics of the study participants

Variables	Control group (n=233)	IAH group (n=55)	P-value
Age, years	49.9 (14.5)	52.8 (15.1)	0.179
Male sex, %	36.5	36.4	>0.999
Diabetes duration, years	17.6 (11.0)	17.6 (11.8)	0.998
BMI, kg/m^2	23.4 (3.5)	22.9 (4.4)	0.355
HbA1c, %	7.7 (0.9)	7.5 (1.0)	0.130
Diabetic complication			
Retinopathy, %			
NDR/SDR/PPDR/PDR	73.2/17.9/4.9/4.0	79.6/12.2/2.0/6.1	0.596
Photocoagulation	10.3	12.7	0.629
Nephropathy, %			
1st/2nd/3rd/4th/5th stage	81.0/13.4/3.4/0.4/1.7	85.2/14.8/0/0/0	0.673
Peripheral neuropathy, %	12.0	26.5	0.014*
Severe hypoglycemia, %	3.4	30.9	<0.001*
Treatment			
CSII, %	39.5	23.6	0.030*
CGM usage, %	56.2	56.4	>0.999
isCGM, %	32.2	36.4	0.633
rtCGM, %	24.0	20.0	0.597
TDD/BW, U/kg	0.6 (0.2)	0.6 (0.2)	0.090
Antihypertensive drug, %	23.2	20.0	0.721
Cholesterol-lowering drug, %	26.6	25.5	>0.999
Mecobalamin, %	2.6	9.1	0.039*
ECG			
QTc (Bazett's formula), ms	416.4 (27.8)	414.2 (23.1)	0.697
> 440 ms, %	14.3	14.3	>0.999
CV-RR, %	3.5 (1.7)	3.1 (1.4)	0.344
< 3%, %	48.6	50.0	>0.999

Mean (SD) or %. *P-value <0.05.

BMI, body mass index; HbA1c, glycated hemoglobin A1c; NDR, no diabetic retinopathy; SDR, simple diabetic retinopathy; PPDR, pre-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; CSII, continuous subcutaneous insulin infusion; isCGM, intermittently scanned continuous glucose monitoring; rtCGM, real-time CGM; TDD, total daily dose; BW, body weight; ECG, electrocardiogram; QTc, corrected QT interval; CV-RR, coefficient of variance of the heart rate variation.

Table 2. Lifestyle factors in adults with T1D with or without IAH

Variables	Control group	IAH group	P-value
Lifestyle			
Skipping breakfast, %	10.0	9.1	>0.999
Fast eating, %	33.3	40.0	0.349
Late-night dinner eating, %	26.0	29.1	0.615
Snack and sweetened beverage, %	74.6	69.1	0.400
Fruits ≥ 1 intake per day, %	27.3	18.2	0.228
Milk ≥ 1 intake per day, %	57.6	54.5	0.762
Fish ≥ 1 intake per day, %	6.9	10.9	0.395
Vegetable ≥ 5 dishes intake per day, %	3.9	7.3	0.287
Exercise habit, %	31.2	34.5	0.632
Physical activity, %	54.5	53.7	>0.999
Fast walking, %	44.6	52.7	0.295
Overwork, %	20.8	18.5	0.852
Current smoking, %	17.3	21.8	0.440
Drinking everyday, %	15.6	21.8	0.315
Excessive drinking, %	9.1	10.9	0.617
Healthy lifestyle score, points	4.3 (1.4)	4.2 (1.5)	0.392
Sleep			
Average sleep time, min	395 (58)	391 (87)	0.704
Sleep time on a weekday, min	380 (61)	374 (90)	0.632
Sleep time on a weekend, min	433 (79)	432 (102)	0.955
Sleep debt, min	53 (74)	57 (78)	0.711
Nonrestorative sleep, %	39.0	40.0	0.879

Mean (SD) or %.

Table 3. Laboratory data of the study participants

Variables	Control group	IAH group	P-value
TP, g/dL	6.9 (0.4)	6.9 (0.4)	0.824
Alb, g/dL	4.2 (0.3)	4.1 (0.3)	0.547
AST, U/L	20.2 (7.4)	21.0 (7.4)	0.482
ALT, U/L	17.6 (11.2)	16.7 (8.1)	0.592
GGT, IU/L	21.4 (19.1)	22.1 (19.2)	0.806
BUN, mg/dL	15.5 (5.8)	14.3 (4.1)	0.155
Serum creatinine, mg/dL	0.9 (1.0)	0.8 (0.5)	0.530
eGFR	77.8 (22.2)	78.6 (14.5)	0.801
HbA1c, %	7.7 (0.9)	7.5 (1.0)	0.130
GA, %	22.0 (3.7)	21.7 (3.6)	0.591
GA/HbA1c ratio	2.9 (0.3)	2.9 (0.4)	0.520
LDL-C, mg/dL	113.0 (27.9)	107.0 (23.4)	0.143
HDL-C, mg/dL	79.2 (20.1)	77.6 (20.0)	0.605
TG, mg/dL	94.0 (54.8)	92.6 (73.9)	0.865

Mean (SD).

TP, total protein; Alb, albumin; ALT, alanine transaminase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase

BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; GA, glycated albumin.

LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride.

Table 4. Odds ratio of interest variables for IAH in adults with T1D

Variables	Odds ratio (95% CI)	P-value
Diabetic complications		
Diabetic peripheral neuropathy	2.63 (1.13–5.91)	0.014*
Retinopathy, NDR/SDR/PPDR vs. PDR	1.56 (0.26–6.55)	0.456
Nephropathy, 1st vs. 2nd/3rd/4th/5th stage	0.74 (0.28–1.74)	0.560
Diabetes treatment		
CGM usage	1.01 (0.53–1.91)	<0.999
CSII treatment	0.48 (0.22–0.96)	0.030*
Hypoglycemia problem-solving scale		
1. Problem-solving perception	0.54 (0.37–0.78)	0.001*
2. Detection control	0.95 (0.75–1.21)	0.690
3. Identifying problem attributes	1.09 (0.84–1.42)	0.503
4. Setting problem- solving goals	1.00 (0.77–1.32)	0.973
5. Seeking preventive strategies	0.98 (0.72–1.33)	0.886
6. Evaluating strategies	0.86 (0.63–1.17)	0.339
7. Immediate management	1.12 (0.83–1.51)	0.446

Odds ratio (95% CI). *P-value <0.05.

Table 5. Hypoglycemic symptoms in adults with T1D with or without IAH

Variables	Control group	IAH group	P-value
Autonomic, points			
Sweating	3.6 (1.9)	2.9 (1.9)	0.019*
Palpitations	3.5 (1.8)	3.1 (1.9)	0.122
Shaking	3.7 (1.8)	3.1 (1.8)	0.013*
Hunger	3.6 (1.9)	3.1 (1.8)	0.087
Neuroglycopenic, points			
Confusion	1.9 (1.5)	2.5 (2.0)	0.016*
Drowsiness	2.1 (1.5)	2.7 (1.8)	0.014*
Odd behavior	1.5 (1.1)	2.1 (1.6)	0.003*
Speech difficulty	1.7 (1.3)	2.6 (2.0)	<0.001*
Incoordination	2.5 (1.7)	3.1 (1.7)	0.010*
General malaise, points			
Headache	1.8 (1.4)	2.1 (1.7)	0.150
Nausea	1.6 (1.1)	1.9 (1.6)	0.059
Total score, points	26.8 (10.1)	28.4(12.5)	0.328
Psychological			
PAID, points	29.1 (19.4)	35.7 (18.4)	0.022*
PHQ-9, points	3.9 (4.2)	4.9 (4.1)	0.113
HFS-B, points	18.0 (6.3)	18.2 (6.8)	0.798
HFS-W, points	10.0 (9.1)	14.9 (10.5)	0.001*
EQ-5D utility index	0.91 (0.13)	0.86 (0.17)	0.015*

Mean (SD). *P-value <0.05