Self-reported hypoglycaemia: a global study of 24 countries with 27,585 insulin-treated patients with diabetes: Results from the German HAT population

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Introduction

- There is limited evidence from observational studies regarding rate of hypoglycaemia in clinical practice
  - International prospective studies have reported a hypoglycaemia frequency of 3.9–7.2 events/month for T1D[1–3] and 0.76–3.7 events/month for T2D[1–6]
  - The wide range of reported hypoglycaemia incidence in T2D highlights the need for additional data to determine factors associated with hypoglycaemia risk
- The global Hypoglycaemia Assessment Tool (HAT) study was designed to determine the extent of hypoglycaemia experienced in a global insulin-treated patient population; this analysis presents data from the German population. Predictive and continuous factors contributing to hypoglycaemia risk were also explored

Materials and methods

Study design

- Non-interventional, multicentre, 6-month retrospective and 1-month prospective study of hypoglycaemic events, conducted in 24 countries using self-assessment questionnaires (SAQs) and patient diaries (for the 28-day prospective period)

Study objectives

- Primary endpoint: percentage of patients experiencing at least one hypoglycaemic event during the observational period
- Secondary endpoints included:
  - Hypoglycaemia incidence rates
  - Relationship between hypoglycaemia and predictive or continuous factors such as age, gender, duration of insulin use or HbA_{1c}

Study population

- Consecutive eligible patients were enrolled during a routinely scheduled clinical consultation with their healthcare provider
- Inclusion criteria:
  - Patients with T1D or T2D treated with insulin for >12 months
  - Patients ≥18 years of age at the time of survey
  - Patients giving informed consent to participate in the survey

In Germany, 2430 (T1D 811; T2D 1619) patients at 176 sites participated in the study

Assessments

- Two-part SAQ
  - Part 1 (first visit): Baseline demographic and treatment information, knowledge, hypoglycaemia unawareness, perceptions of hypoglycaemia, history of severe hypoglycaemia over the previous 6 months, symptomatic hypoglycaemia over the previous 4 weeks
  - Part 2 (second visit): History of both severe and symptomatic hypoglycaemia over the 4 weeks following study entry, effect of hypoglycaemia on productivity, healthcare utilisation and productivity during this period
- Differences in reported hypoglycaemia in the retrospective and prospective periods were used to estimate under-reporting
- Hypoglycaemia unawareness was evaluated through the self-assessment question: 'Do you have symptoms when you have a low sugar level?', where the response, 'occasionally' denotes impaired awareness, and 'never' denotes severely impaired awareness
- A patient diary was used to assist recall and record hypoglycaemic events

Hypoglycaemia classification

- Hypoglycaemia was defined and classified as follows:
  - Severe hypoglycaemia was defined as per the American Diabetes Association (ADA) definition (requiring third party assistance)[7]
  - Any hypoglycaemia – the sum of severe and non-severe hypoglycaemia
  - Nocturnal hypoglycaemia – hypoglycaemia occurring between midnight and 06.00 h

Statistical analyses

- All statistical tests were two-sided and regarded as exploratory, with the criterion for statistical significance set at $p<0.05$. No adjustments were made for multiple comparisons
- The percentage of patients experiencing at least one hypoglycaemic event during the observation period was calculated together with the 95% confidence interval (CI) for this percentage, assuming a binomial distribution
- Negative binomial regression models stratified by country and specifying a log-transformed exposure time offset term were used to examine the relationship between various factors and the incidence of hypoglycaemia

Results

Patient characteristics

2056 patients in Germany completed the study. The patient characteristics for the population are summarised in Table 1.

Table 1 Characteristics of patient population

Characteristic	T1D (n=811)	T2D (n=1619)
Number of patients who completed part 2 SAQ, n (%)	641 (79.0)	1415 (87.4)
Number of patients who completed patient diary, n (%)	640 (78.9)	1404 (86.7)
Sex male/female, %	51/49	54/46
Mean age, years (SD)	47.8 (14.7)	66.3 (10.5)
Duration of diabetes, years (SD)	19.9 (12.8)	15.4 (8.8)
HbA_{1c}, mmol/mol (SD)	59.6 (13.8)	58.3 (13.6)
HbA_{1c}, %*	7.6	7.5
Method of diabetes treatment, n (%)		
Short-acting insulin	671 (82.9)	1237 (77.0)
Long-acting insulin	517 (63.9)	1348 (83.9)
Mixed insulin	7 (0.9)	129 (8.0)
Insulin pump	228 (28.2)	15 (0.9)
Oral antidiabetes treatments	17 (2.1)	449 (27.9)
Injectable antidiabetes treatments excluding insulin	0 (0.0)	27 (1.7)
Use of continuous glucose monitoring device, n (%)		
Yes	306 (38.3)	843 (52.4)
No	490 (61.3)	754 (46.9)
Not sure	4 (0.5)	12 (0.7)
Checks blood sugar levels, n (%)		
Yes	806 (99.4)	1597 (98.8)
No	5 (0.6)	20 (1.2)
Experienced hypoglycaemia, n (%)		
Yes	780 (97.1)	1224 (76.3)
No	13 (1.6)	322 (20.1)
Not sure	10 (1.2)	58 (3.6)

*Calculated, not measured
Full analysis set. SAQ, self-assessment questionnaire; SD, standard deviation; T1D, type 1 diabetes; T2D, type 2 diabetes

Overall hypoglycaemia frequency

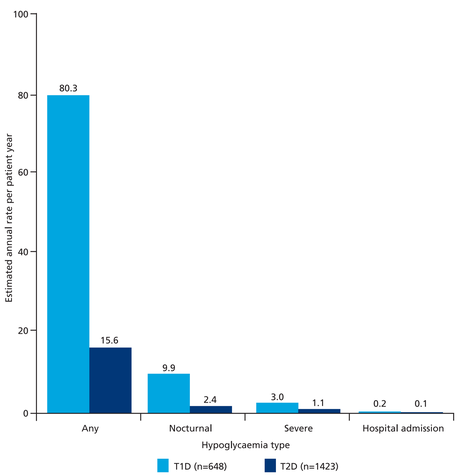
- Prospective and retrospective hypoglycaemia incidence and prevalence are shown in Table 2
  - Self-reported hypoglycaemia rates in T1D and T2D during the prospective period are shown in Figure 1

Table 2 Hypoglycaemia incidence and prevalence in retrospective and prospective periods

	Retrospective		Prospective	
	T1D	T2D	T1D	T2D
Hypoglycaemia prevalence, % of patients				
Any (4 weeks)	82.8	45.3	81.3	39.7
Nocturnal (4 weeks)	43.2	16.5	37.3	12.2
Severe	23.5*	9.9*	9.1†	5.4†
Hypoglycaemia incidence, events per patient year				
Any (4 weeks)	50.0	11.2	80.3	15.6
Nocturnal (4 weeks)	14.4	3.6	9.9	2.4
Severe	2.1*	0.4*	3.0†	1.1†

*6-month period, †4-week period
T1D, type 1 diabetes; T2D, type 2 diabetes
Incidence and prevalence calculated from full analysis set

Figure 1 Self-reported hypoglycaemia rates in the 4-week prospective period

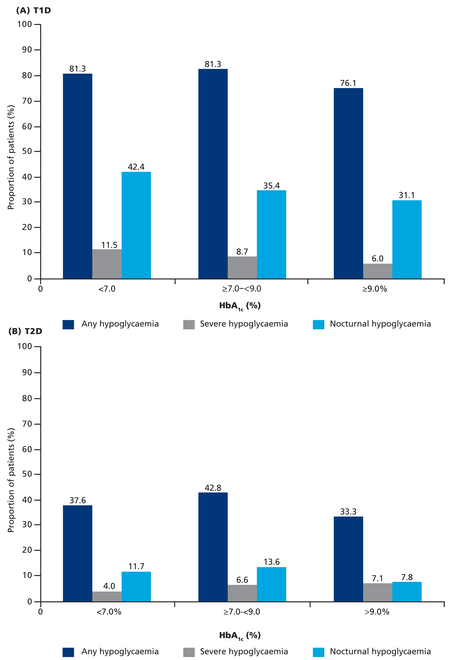


- The incidence rate ratio for any hypoglycaemia in the prospective/retrospective periods (calculated from completer population) was 1.62 (95% CI 1.42, 1.85) for T1D and 1.39 (95% CI 1.23, 1.56) for T2D
- 64.2% of all patients identified hypoglycaemia by symptoms and blood glucose measurements

Associations between hypoglycaemia and continuous or predictor variables

- Fully-adjusted negative binomial modelling showed only a weak association between any hypoglycaemia and HbA_{1c} levels (incidence rate ratio [IRR] 0.99; 95% CI 0.99, 0.99)
- The proportions of T1D and T2D patients with hypoglycaemia incidence by HbA_{1c} level is shown in Figure 2

Figure 2 Proportions of patients with hypoglycaemia by HbA_{1c} level in patients with (a) type 1 diabetes (T1D) and (b) type 2 diabetes (T2D)



- Age was weakly correlated with the rate of any hypoglycaemic events (IRR 0.98; 95% CI 0.98, 0.99)
- Females were more likely to report hypoglycaemia overall than males (IRR 1.30; 95% CI 1.15, 1.46)
- Patients with hypoglycaemia unawareness – specifically, those who occasionally/never have symptoms with low blood glucose measurement – were less likely to report incidence of any hypoglycaemic event (IRR 0.87; 95% CI 0.72, 1.05)

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Conclusions

- This large retrospective and prospective study determined the extent of hypoglycaemia experienced by insulin-treated T1D and T2D patients in the German population
- Estimated rates of overall, nocturnal and severe hypoglycaemia were higher than previously reported[1–6]
- An increased incidence of overall hypoglycaemia in the prospective study compared to the retrospective reports indicated under-reporting of hypoglycaemia
- There were no strong associations between hypoglycaemia and the predictor variables studied
- These findings highlight the need for clinicians to tailor insulin treatment to individual patients with diabetes

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