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

Introduction
- There is limited evidence from observational studies regarding the ‘true’ rate of hypoglycaemia for patients with diabetes in clinical practice.
  - International prospective studies have reported a hypoglycaemia frequency (any or severe) of 3.9–7.2 events/month for T1D and 0.76–3.7 events/month for T2D.
- The wide range of reported hypoglycaemia incidence for both T1D and 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 by patients in a global insulin-experienced patient 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 28 days).
- Study objectives
  - Primary endpoint: percentage of patients experiencing at least one hypoglycaemia event during the observational period.
  - Secondary endpoints included:
    - Hypoglycaemia incidence rates.
    - Relationship between hypoglycaemia and predictive factors including age, gender, disease duration, duration of insulin use or HbA1c.
- 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.

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.
- 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, ‘Usually’ denotes impaired awareness, and ‘Occasionally’ or ‘Never’ denotes severely impaired awareness (unawareness).
- 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).
  - 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

Table 1: Characteristics of patient population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>T1D</th>
<th>T2D</th>
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<tbody>
<tr>
<td>Number of patients who completed part 2 SAQ, n (%)</td>
<td>7073 (88.1)</td>
<td>18,435 (94.2)</td>
</tr>
<tr>
<td>Number of patients who completed patient diary, n (%)</td>
<td>6822 (85.0)</td>
<td>16,805 (85.9)</td>
</tr>
<tr>
<td>Sex (male/female), n (%)</td>
<td>4852/537</td>
<td>5352/4751</td>
</tr>
<tr>
<td>Mean age, years (SD)</td>
<td>42.1 (15.1)</td>
<td>60.8 (8.2)</td>
</tr>
<tr>
<td>Duration of diabetes, years (SD)</td>
<td>7.7 (4.6)</td>
<td>11.8 (7.2)</td>
</tr>
<tr>
<td>HbA1c (mmol/SD)</td>
<td>62.8 (16.2)</td>
<td>64.2 (16.3)</td>
</tr>
<tr>
<td>Duration of diabetes, years (SD)</td>
<td>7.7 (4.6)</td>
<td>11.8 (7.2)</td>
</tr>
<tr>
<td>HbA1c, %†</td>
<td>7.9</td>
<td>8.0</td>
</tr>
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Method of diabetes treatment, n (%)
- Short-acting insulin: 6508 (81.4) | 8472 (43.6) |
- Long-acting insulin: 5885 (73.6) | 12,412 (84.0) |
- Both short- and long-acting insulin: 5674 (70.7) | 7419 (37.9) |
- Mixed insulin: 516 (5.5) | 6563 (33.8) |
- Insulin pump: 1441 (18.0) | 229 (1.2) |
- Oral antidiabetes treatments: 240 (3.3) | 7514 (38.7) |
- Injectable antidiabetes treatments excluding insulin: 21 (0.3) | 538 (2.8) |

Checks blood sugar levels, n (%)
- Yes: 7688 (98.6) | 17,818 (91.6) |
- No: 110 (1.4) | 1635 (8.4) |

Experienced hypoglycaemia, n (%)
- Yes: 7759 (97.4) | 15,167 (78.0) |
- No: 159 (2.0) | 3372 (16.9) |

Not sure: 49 (0.6) | 940 (4.6) |

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

Hypoglycaemia type

Table 2: Hypoglycaemia incidence and prevalence in retrospective and prospective periods

<table>
<thead>
<tr>
<th>Hypoglycaemia type</th>
<th>T1D</th>
<th>T2D</th>
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<tbody>
<tr>
<td>Frequency, % of patients</td>
<td>83.4</td>
<td>50.6</td>
</tr>
<tr>
<td>Incidence, (per patient year)</td>
<td>46.8</td>
<td>23.5</td>
</tr>
<tr>
<td>Severity: 25.0</td>
<td>15.8</td>
<td></td>
</tr>
<tr>
<td>Hypoglycaemia, % of patients</td>
<td>16.2</td>
<td>3.7</td>
</tr>
<tr>
<td>Incidence, (per patient year)</td>
<td>16.2</td>
<td>3.7</td>
</tr>
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*Retrospective period: 6-month retrospective; Prospective period: 1-month prospective study.

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

Conclusions
- This large retrospective and prospective study using patient diaries determined the extent of hypoglycaemia experienced by patients in a global patient population.
- Estimated rates of hypoglycaemia were higher than previously reported.
- Duration of insulin therapy appeared to be a predictor of hypoglycaemia incidence.
- There was no correlation between HbA1c and hypoglycaemia.
- It is anticipated that these findings will assist clinicians in better tailoring insulin treatment for individual patients with diabetes.

References

The incidence rate ratio for any hypoglycaemia in the prospective/retrospective periods (calculated from complete population) was 1.47 (95% CI 1.41, 1.53) for T1D and 1.20 (95% CI 1.15, 1.24) for T2D.

44.6% of all patients identified hypoglycaemia by symptoms and blood glucose measurements (~18–0.0 mg/dl [95% CI <0.25; 9.0–6.3]).

Associations between hypoglycaemia and continuous or predictor variables
- Overall, fully-adjusted negative binomial modelling showed only a weak association between any hypoglycaemia and duration of insulin therapy (incidence rate ratio [IRR] 1.01; 95% CI 1.01, 1.02) (Figure 2a).

Figure 2 Estimated rate of hypoglycaemia by duration of insulin treatment in patients with (A) type 1 diabetes (T1D) and (B) type 2 diabetes (T2D)