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Original Research

The Canadian Hypoglycemia Assessment Tool Program: Insights Into Rates and Implications of Hypoglycemia From an Observational Study

Ronnie Aronson MD [a,*], Ronald Goldenberg MD [a], Damir Boras MD [b], Rasmus Skovgaard MSc [c], Harpreet Bajaj MD, MPH [a,d]

[a] *LMC Diabetes & Endocrinology, Toronto, Ontario, Canada*
[b] *Novo Nordisk Canada Inc., Mississauga, Ontario, Canada*
[c] *Novo Nordisk A/S, Søborg, Denmark*
[d] *Leadership Sinai Centre for Diabetes, Mount Sinai Hospital, Toronto, Ontario, Canada*

Key Messages

- Randomized controlled trials may underestimate true hypoglycemia incidence. We found hypoglycemia rates of 127.6 per patient-year for type 1 diabetes patients and 37.3 per patient-year for insulin-using type 2 diabetes patients.
- Glycated hemoglobin was not a useful predictor of hypoglycemia incidence or severity.
- Health-care resources (hospital and outpatient) and workplace absenteeism/punctuality were all greatly impacted by even nonsevere hypoglycemia.

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ABSTRACT

Objective: The true prevalence of hypoglycemia in insulin-treated patients with diabetes and its impact on patients, employers and healthcare providers is poorly appreciated owing to a paucity of real-world data. The global Hypoglycemia Assessment Tool (HAT) study addressed this issue, and here we report data from the Canadian cohort of patients.
Methods: This noninterventional, 6-month retrospective and 4-week prospective study enrolled patients aged ≥18 years receiving insulin treatment for >12 months from community endocrinology practices. Data were collected using self-assessment questionnaires and patient diaries. The primary endpoint was the proportion of patients experiencing ≥1 hypoglycemic event during the 4-week prospective observational period.
Results: Four hundred ninety-eight patients with type 1 diabetes (n=183) and type 2 diabetes (n=315) were enrolled. The prevalence of hypoglycemia was similar in the retrospective (type 1 diabetes, 92.3%; type 2 diabetes, 63.5%) and prospective (type 1 diabetes, 95.2%; type 2 diabetes, 64.2%) periods. Prospective rates of any, nocturnal and severe hypoglycemia per patient-year (95% confidence interval) were 69.3 (66.4; 72.2), 14.2 (12.9; 15.6) and 1.8 [1.4; 2.4]. Higher rates were reported retrospectively, reaching significance for nocturnal hypoglycemia per patient-year (30.0 [28.1; 32.0] vs. 14.2 [12.9; 15.6]; p<0.001). Hypoglycemia led to increased healthcare utilization and absenteeism and was associated with potentially harmful self-care behaviours (e.g., reduced or skipped insulin doses) and increased blood glucose self-monitoring.
Conclusions: Prevalence and incidence of hypoglycemia were high among insulin-treated patients with diabetes in Canada, and some patients took harmful or costly actions when they experienced hypoglycemia. Identifying the insulin-treated patients who are at greatest risk may help to reduce the incidence of hypoglycemia.

* Address for correspondence: Ronnie Aronson, MD, LMC Diabetes & Endocrinology, 1929 Bayview Avenue, Suite 107, Toronto, Ontario M4G 3E8, Canada.
E-mail address: Ronnie.Aronson@LMC.CA

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RÉSUMÉ

Objectif : La prévalence réelle de l'hypoglycémie chez les patients diabétiques sous insuline et ses répercussions sur les patients, les employeurs et les fournisseurs de soins de santé sont mal caractérisées en raison d'un manque de données factuelles. L'étude HAT (*Hypoglycemia Assessment Tool*) a permis d'aborder cette question à l'échelle mondiale, et nous présentons ici les données issues de la cohorte de patients canadiens.

Méthodologie : Cette étude non interventionnelle, rétrospective durant 6 mois et prospective durant 4 semaines, a été menée chez des patients de 18 ans ou plus sous insuline depuis plus de 12 mois qui étaient traités par des endocrinologues communautaires. Les données ont été recueillies au moyen de questionnaires d'auto-évaluation et de journaux remplis par les patients. Le paramètre d'évaluation principal était la proportion de patients chez qui survenait au moins 1 épisode hypoglycémique pendant la période d'observation prospective de 4 semaines.

Résultats : Au total, 498 patients atteints de diabète de type 1 (n=183) ou de type 2 (n=315) ont été admis à l'étude. La prévalence de l'hypoglycémie a été semblable au cours des périodes rétrospective (diabète de type 1 : 92,3 %; diabète de type 2 : 63,5 %) et prospective (diabète de type 1 : 95,2 %; diabète de type 2 : 64,2 %). Les taux prospectifs d'hypoglycémie tous types confondus, nocturne ou grave par année-patient (intervalle de confiance à 95 %) ont atteint 69,3 (66,4–72,2), 14,2 (12,9–15,6) et 1,8 (1,4-2,4). Les taux signalés rétrospectivement étaient plus élevés, et ils se sont révélés significatifs dans le cas de l'hypoglycémie nocturne par année-patient (30,0 [28,1–32,0] *vs* 14,2 [12,9–15,6]; $p<0,001$). L'hypoglycémie a entraîné une augmentation de l'utilisation des ressources de soins de santé et de l'absentéisme, en plus d'être associée à des comportements potentiellement dangereux en matière d'autosoins (p. ex. réduction ou omission de doses d'insuline) et à une autosurveillance glycémique accrue.

Conclusions : La prévalence et l'incidence de l'hypoglycémie étaient élevées chez les patients diabétiques sous insuline au Canada, et certains patients ont pris des mesures dangereuses ou coûteuses en présence d'hypoglycémie. Le repérage des patients sous insuline exposés à un risque plus élevé peut aider à réduire l'incidence de l'hypoglycémie.

Introduction

Insulin therapy is essential in the management of type 1 diabetes and is often required in type 2 diabetes to restore glycemic control and reduce the risks of comorbidities and mortality accompanying high blood glucose (BG). Hypoglycemia is common when insulin treatment is intensified and is a consideration when insulin strategies and glycemic targets are selected (1). Hypoglycemia is a major concern for patients living with diabetes (2), who may take actions to reduce the incidence of hypoglycemia (3), which has been associated with fear, anxiety and depression (4,5), reduced health-related quality of life, reduced productivity and increased healthcare costs (6–8).

Although the implications of hypoglycemia are understood, the scale of the problem remains unknown as there are few studies reporting rates of hypoglycemia in insulin-treated patients managed according to real-world clinical practice. Much of our hypoglycemia incidence data has emerged from clinical trials that enroll patients who are more motivated and health literate, exclude patients with comorbidities and history of frequent or severe hypoglycemia, randomize patients to compare different treatments or treatment algorithms, and titrate doses to achieve common treatment targets rather than individualized glycemic targets. One recent review in which real-world and clinical trial settings were compared revealed higher rates of hypoglycemia in real-world reports (9).

The global Hypoglycemia Assessment Tool (HAT) study was designed to collect information from 27,585 insulin-treated patients with type 1 or type 2 diabetes in real-world clinical practice in 24 countries and showed higher than expected rates of hypoglycemia with significant geographic variation (10). The aims of this analysis were to determine the real-world incidence and impact of hypoglycemia and to investigate predictors of hypoglycemia in Canadian patients with insulin-treated type 1 and type 2 diabetes.

Methods

Study design

The current analysis evaluates data from a Canadian cohort of insulin-treated patients enrolled in the global HAT study — a noninterventional, multicentre, retrospective and prospective survey of hypoglycemia in patients with type 1 and type 2 diabetes. The HAT study design and patient population have been described previously (10).

Study population

Patients were enrolled through consecutive sampling during routinely scheduled consultations with their healthcare providers (HCPs). Eligible patients were ≥18 years of age and had insulin-treated type 1 or type 2 diabetes for >12 months. Patients excluded were those who were nonambulatory or illiterate. Patients were not paid for their participation.

Assessments

The study comprised a 2-part self-assessment questionnaire (SAQ). Part 1 was a cross-sectional, retrospective assessment completed at baseline, recording demographic and treatment information, knowledge and perceptions of hypoglycemia, as well as history of nonsevere hypoglycemia and severe hypoglycemia over the previous 4 weeks and 6 months, respectively. Part 2 evaluated the occurrence of severe and nonsevere hypoglycemia over the 4 weeks after baseline. Patients were provided with a diary to record hypoglycemia during the 4-week prospective period. If hypoglycemic events were reported at a higher rate in the patient diary versus the SAQ, diary values were used to calculate hypoglycemia prevalence to compensate for potential recall bias. Data are presented from the full analysis set (Part 1) and completers' analysis set (Parts 1 and 2).

Study objectives

The primary objective was to evaluate the proportion of patients experiencing ≥1 hypoglycemic event during the 4-week prospective period. Secondary objectives included incidence of hypoglycemia (any, nocturnal, severe and nonsevere), relationship between glycated hemoglobin (A1C) and hypoglycemia (including proportion of patients with A1C <7.0% [53 mmol/mol], 7.0% to 9.0% and >9.0% [75 mmol/mol] in the 4 weeks after baseline). Response to hypoglycemia in the 4 weeks after baseline was measured by investigating the proportion of patients consulting their doctor/nurse, reducing exercise, reducing insulin dose, skipping insulin dose or increasing BG monitoring after an episode of hypoglycemia. The impact of hypoglycemia was assessed by calculating the proportion of patients with increased healthcare utilization and absenteeism after an occurrence of hypoglycemia.

Patient knowledge of hypoglycemia and the relationship between hypoglycemia and predictive variables were also assessed.

Hypoglycemia classification

Hypoglycemia was defined as an event resulting in a low BG measurement (3.1 mmol/L [<56 mg/dL]) or symptoms, and events were categorized as follows: an event managed by the patient alone (nonsevere); any event requiring assistance of another person to administer carbohydrate, glucagon or other resuscitative actions (11) (severe); and an event occurring between 12:01 to 5:59 am (nocturnal). A combined measure of any hypoglycemia was derived from the diary and SAQ entries.

Statistical analyses

Sample size was determined for the global HAT study (10), resulting in the enrolment of 27,585 patients in total, with 498 patients from Canada. Statistical tests were 2-sided and exploratory, with significance defined as $p<0.05$. Univariate negative binomial regression models based on the completers' analysis set, specifying a log–transformed exposure time offset term and adjusted for period and country, were used to examine the relationship between hypoglycemia and the continuous and predictor variables. Data are presented as means ± standard deviation.

The study was conducted in accordance with Good Clinical Practice, the International Conference on Harmonization (12) and the Declaration of Helsinki (13). An independent review board approved the protocol. Each patient gave written informed consent.

Results

Baseline characteristics

Baseline characteristics are reported for 498 patients with type 1 diabetes (183) and type 2 diabetes (315) in Table 1. Of these patients, 415 (147 with type 1 diabetes and 268 with type 2 diabetes) provided prospective data within their completed Part 2 SAQs and patient diaries. Mean duration of disease and insulin use were 20.4 and 20.0 years, respectively, in patients with type 1 diabetes and 15.1 and 6.7 years, respectively, in patients with type 2 diabetes. Both groups of insulin-treated patients largely used short-acting insulins, alongside basal insulin. Because this study reflects real-world clinical practice, reporting of patient data by insulin regimen (i.e., short-acting or long-acting basal insulin) will include a mixed population taking either human or analogue forms of insulin.

Table 1
Baseline characteristics

	Type 1 diabetes (n=183)	Type 2 diabetes (n=315)
Age (years)	44.3 (14.91)	60.3 (11.02)
Male/female (%)	47.5/52.5	59.7/40.3
Duration of diabetes (years)	20.4 (14.19)	15.1 (8.66)
Duration of insulin use (years)	20.0 (14.50)	6.7 (6.18)
A1C (mmol/mol)	63.1 (14.98)	65.7 (16.76)
A1C (%)*	7.9	8.2
Method of diabetes treatment [n (%)]		
Short-acting insulin	124 (67.8)	178 (56.5)
Long-acting insulin	74 (40.4)	248 (78.7)
Mixed insulin	3 (1.6)	61 (19.4)
Insulin pump	87 (47.5)	5 (1.6)
Oral antihyperglycemic agents	3 (1.6)	136 (43.2)
Injectable antidiabetes treatments excluding insulin	1 (0.5)	22 (7.0)

Note: Data are presented as means with standard deviation (SD) in parentheses, unless otherwise indicated; analyses are based on full analysis set; N is defined as total number of subjects participating from the country.
A1C, glycated hemoglobin; *SD,* standard deviation.
* Calculated, not measured.

Prevalence and annualized incidence of hypoglycemia

Over the prospective period, 95.2% of patients with type 1 diabetes and 64.2% of patients with type 2 diabetes experienced hypoglycemia, which is similar to the reported prevalence in the retrospective period (type 1 diabetes, 92.3%; type 2 diabetes, 63.5%). Annualized incidence rates were 127.6 events per patient-year (PPY) for patients with type 1 diabetes and 37.3 events PPY for patients with type 2 diabetes. Incidence rates for any, nocturnal and severe hypoglycemia are shown in Figure 1. Patients generally reported higher rates of hypoglycemia retrospectively than prospectively, reaching significance for nocturnal hypoglycemia for patients with type 1 diabetes (incidence rate ratio 0.39 [95% confidence interval: 0.17; 0.88] $p=0.023$) and patients with type 2 diabetes (incidence rate ratio 0.56 [95% confidence interval: 0.45; 0.69] $p<0.001$).

Factors predictive of hypoglycemia

Very few variables were associated with rate of hypoglycemia (Table 2), namely female gender, type 1 diabetes and use of short-acting insulins compared with long-acting insulins. Unsurprisingly, an increased frequency of BG testing was strongly associated with each type of hypoglycemia. Younger age and longer duration of insulin therapy were each slightly, but significantly, associated with any hypoglycemia. Interestingly, fear of hypoglycemia was only linked to severe hypoglycemia.

No significant associations were found with A1C and, when stratified by A1C, there were no meaningful differences, other than in severe hypoglycemia, which was reported by fewer patients with a baseline A1C of <7.0% compared with 7.0% to 9.0% (Figure 2).

Impact of hypoglycemia

Fear of hypoglycemia

On a scale of 0 to 10, where 10 is "absolutely terrified," fear of hypoglycemia was reported an average of 4.5±3.0 times, with higher fear levels in patients with type 1 diabetes (5.1±2.59) than in those with type 2 diabetes (4.2±3.20) (Figure 3). Fear of hypoglycemia was associated with incidence of severe hypoglycemia (incidence rate ratio 1.2 [(95% confidence interval 1.06; 1.38, $p=0.004$]). Just over half (51.9%) of patients reported fear of hypoglycemia ≥5/10, with a fifth of patients reporting "terrified" (20.2%, ≥8/10) and 6% reporting at a level classified as "absolutely terrified." A greater proportion of patients with type 2 diabetes, compared with those with type 1 diabetes, rated their fear at either extreme (i.e., 0 to 2 and 9 to 10).

Patients' actions

Patients' actions after a hypoglycemic event were compared during the prospective period (Figure 4). The most common action

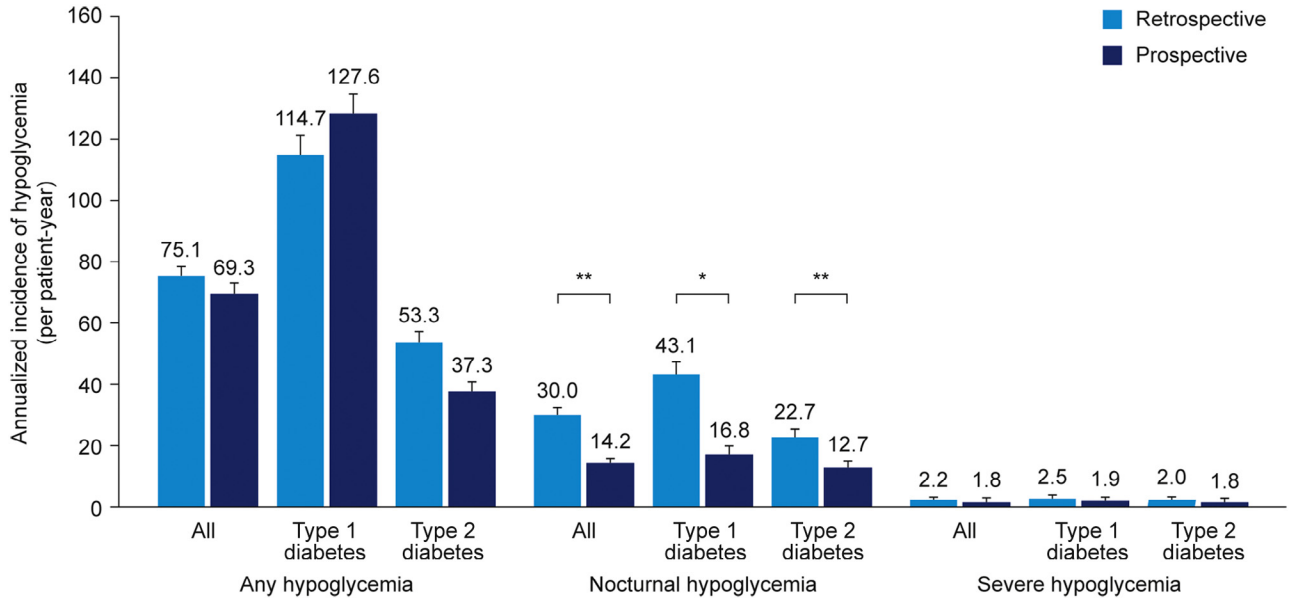

Figure 1. Annualized incidence of hypoglycemia. Estimated annual incidence rate (95% confidence interval). Completers' analysis set: All, n=415; type 1 diabetes, n=147; type 2 diabetes, n=268; *p=0.023, **p<0.001. Retrospective = 4 weeks before baseline; prospective = 4 weeks after baseline.

Table 2
Association between predictor and continuous variables and rate of hypoglycemic events

Predictor variables	N	Nocturnal	p	Severe	p	Nonsevere	p
Female vs. male gender	498	2.52 [1.24; 5.13]	0.011	1.52 [0.77; 2.98]	0.226	1.44 [1.02; 2.03]	0.036
Type 2 diabetes vs. type 1 diabetes	498	0.62 [0.25; 1.52]	0.294	0.97 [0.46; 2.07]	0.939	0.37 [0.26; 0.53]	<0.001
Prospective vs. retrospective	498	0.53 [0.35; 0.78]	0.002	0.84 [0.45; 1.57]	0.581	1.01 [0.76; 1.36]	0.933
Knowledge of hypoglycemia	498	2.62 [1.06; 6.46]	0.036	1.49 [0.40; 5.50]	0.550	1.32 [0.47; 3.69]	0.599
Hypoglycemia unawareness	435	0.35 [0.15; 0.80]	0.013	0.58 [0.22; 1.57]	0.287	0.86 [0.43; 1.71]	0.663
Long-acting vs. short-acting insulin	498	0.39 [0.23; 0.67]	<0.001	0.48 [0.14; 1.73]	0.263	0.41 [0.19; 0.89]	0.025

Continuous variables	N	Any	p	Nocturnal	p	Severe	p	Nonsevere	p
Age	498	0.99 [0.97; 1.00]	0.029	0.99 [0.95; 1.03]	0.607	1.00 [0.98; 1.02]	0.731	0.99 [0.97; 1.00]	0.031
Duration of diabetes	498	1.01 [0.99; 1.02]	0.446	0.98 [0.96; 1.02]	0.333	1.01 [0.98; 1.04]	0.454	1.01 [0.99; 1.02]	0.473
Duration of insulin therapy	498	1.02 [1.01; 1.03]	<0.001	1.01 [0.99; 1.02]	0.252	1.01 [0.99; 1.03]	0.444	1.02 [1.01; 1.03]	<0.001
A1C	454	0.99 [0.97; 1.01]	0.435	1.01 [0.96; 1.07]	0.719	0.98 [0.97; 1.00]	0.088	0.99 [0.97; 1.01]	0.459
Frequency of BG testing	494	1.25 [1.17; 1.34]	<0.001	1.14 [1.03; 1.26]	0.012	1.14 [1.05; 1.24]	0.002	1.26 [1.17; 1.35]	<0.001
Fear of hypoglycemia	498	1.03 [0.97; 1.10]	0.286	0.97 [0.81; 1.15]	0.698	1.21 [1.06; 1.38]	0.004	1.03 [0.97; 1.09]	0.380

Note: Knowledge of hypoglycemia = did versus did not know what hypoglycemia was; Hypoglycemia unawareness = occasionally/never have symptoms with low blood glucose measurement versus always/usually have symptoms with low blood glucose measurement.
A1C, glycated hemoglobin; *BG,* blood glucose.

after hypoglycemia in patients with either type 1 or type 2 diabetes was increased BG monitoring, ranging from a mean of 5.2±7.3 to 1.9±4.1 additional tests for patients with type 1 diabetes and type 2 diabetes, respectively. Other common reactions included reduction in insulin dose, skipping of injections, avoiding physical activity and increasing calorie intake.

Healthcare resource utilization after hypoglycemia

Work absenteeism

The impact of hypoglycemia on absenteeism was investigated before baseline over the previous year. After a hypoglycemic event, 9.4% of patients took sick leave from work or study, with a mean of 9.8±36.3 reported days. A greater proportion of patients with type 1 diabetes than those with type 2 diabetes was absent from work. Punctuality was reduced by a single event of hypoglycemia with 13.8% of patients arriving late to work or study; 9.4% left early. Patients further reported late arrivals on 4.7±8.4 days and early departures on 2.3±1.2 days. These findings were also more common in patients with type 1 diabetes than in those with type 2 diabetes.

Healthcare utilization

In the prospective period, 2 patients in each cohort of type 1 diabetes and type 2 diabetes required hospital admission for treatment of hypoglycemia (1.0% overall). After a single hypoglycemic event, similar proportions of patients with type 1 and type 2 diabetes (23.4% and 21.8%) consulted a doctor or nurse or required some form of medical assistance (23.4% and 23.1%), including 1.3±1.0 additional clinic visits and 1.3±0.6 additional telephone contacts.

Discussion

In this analysis of insulin-treated patients from the Canadian cohort of the global HAT study, almost all of those with type 1 diabetes and two-thirds of those with type 2 diabetes experienced ≥1 episode of hypoglycemia in the prospective period. Although the prevalence of hypoglycemia was similar in the retrospective and prospective periods, the rates of any, nocturnal and severe hypoglycemia were higher retrospectively versus prospectively, reaching statistical significance for nocturnal hypoglycemia. Significant

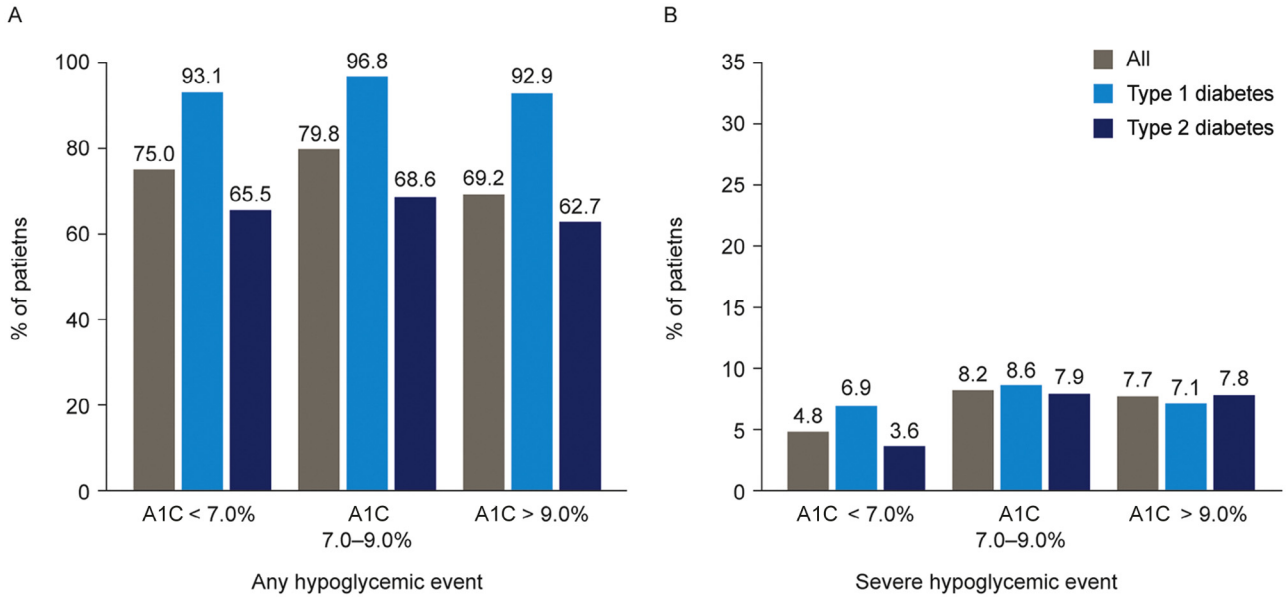

Figure 2. Hypoglycemic events (A) and severe hypoglycemic events (B) reported in the 4 weeks after baseline. Analyses are based on full analysis set; percentages are based on number of patients with evaluable data. *A1C,* glycated hemoglobin.

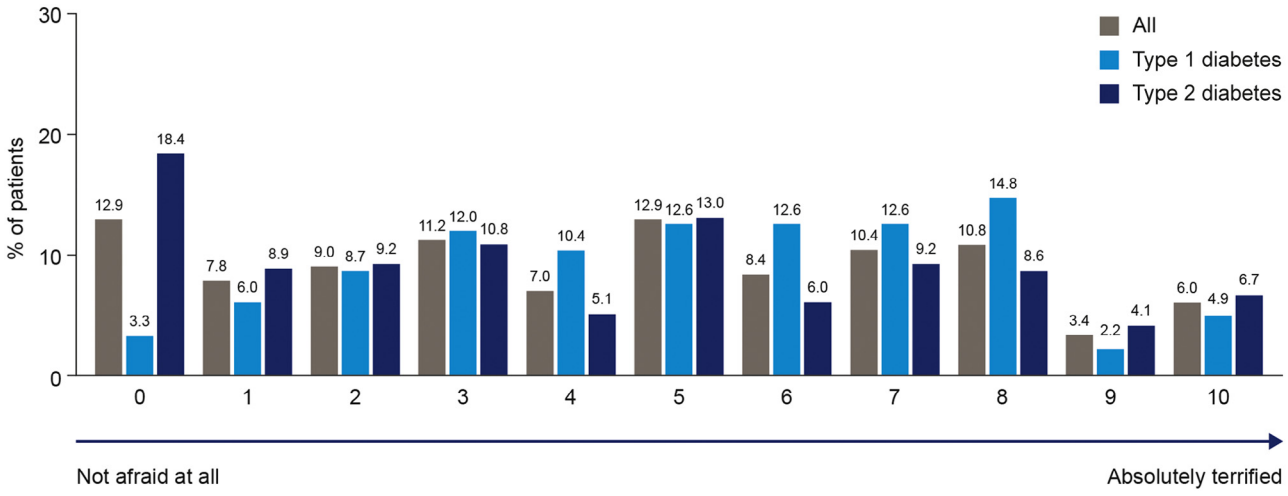

Figure 3. Fear of hypoglycemia at baseline. Percentages are based on the number of patients with evaluable data from the full analysis set.

associations were found between any hypoglycemia and younger age, female gender, type 1 diabetes, duration of insulin therapy, increased frequency of BG testing and treatment with short-acting insulins. In addition, fear of hypoglycemia was associated with severe hypoglycemia. The behavioural consequences of hypoglycemia included more frequent self-monitoring of BG, greater contact with HCPs and reduced attendance in the workplace, as well as potentially harmful self-care behaviours including reduction in or skipping of insulin doses, excess calorie intake and avoidance of physical activity.

The annualized rates reported herein of 127.6 PPY for patients with type 1 diabetes and 37.3 PPY for patients with type 2 diabetes are consistent with findings of the global HAT study (10) but are higher than rates typical of clinicians' experience and generally accepted hypoglycemia rates, classically derived from clinical trials. Indeed, a recent meta-analysis (9) has revealed higher rates of hypoglycemia in real-world practice than those reported in clinical trials. Further support for this conclusion has been provided by a recent meta-analysis of 46 real-world studies, which showed that among insulin users with type 2 diabetes, rates were 23 events PPY for any hypoglycemia and 1 event PPY for severe hypoglycemia (14). Likewise, in the DIALOG study, the authors reported that in a similar cohort of insulin-using patients, the rates for any hypoglycemia in patients with type 1 diabetes and type 2 diabetes, respectively, were 7.4 and 1.7 events per patient month, and the rates for severe hypoglycemia were 0.2 and 0.1 event per patient month (15). It appears that the design of clinical trials may provide an explanation for the differences with real-world studies; specifically, the selection of patients at study inclusion, the exclusion of patients with known hypoglycemia unawareness or recent severe hypoglycemia, the controlled nature of therapies and stipulated frequency of glucometer testing during the trial, and the use of standardized treatment targets in contrast to individualized goals.

As we observed in our study, nonsevere hypoglycemia may go unreported because many events may be asymptomatic and some patients may not report events to their HCP. In a recent European review of nonsevere hypoglycemia, investigators found that 65% of patients with type 1 diabetes and up to 59% of patients with type 2

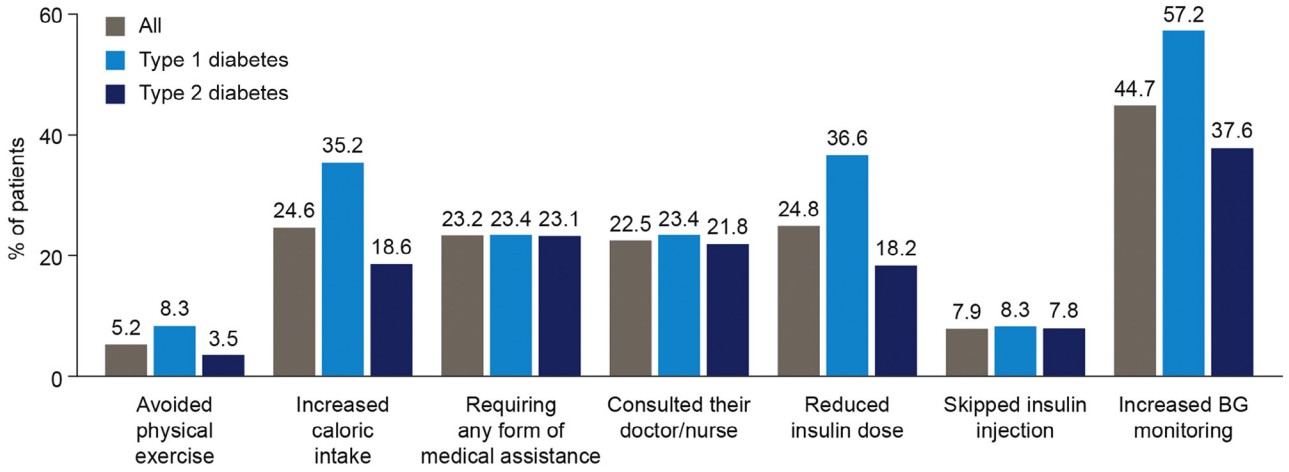

Figure 4. Patient actions resulting from hypoglycemia in the 4 weeks after baseline Percentages are based on the number of patients from the full analysis set with evaluable data for the 4 weeks after baseline. If a patient recorded more instances of "Consulted doctor/nurse" using the patient diary than in Part 2 of the self-assessment questionnaire, his or her patient diary was used to calculate incidence. *BG*, blood glucose.

diabetes either rarely or never reported their hypoglycemia (16). Additionally, and especially in the case of severe hypoglycemia, patient underreporting may be rooted in a reluctance to admit to less-than-ideal glycemic control, the fear of implications such as losing a job or having a driving licence suspended (17), or hypoglycemia unawareness (18).

Although fear of hypoglycemia generally mirrored the high prevalence of any hypoglycemia, severe levels of "absolutely terrified" were somewhat overrepresented (20.2%) in our study, considering the prevalent rate of severe (1.8%) and nocturnal (14.2%) hypoglycemia. Fear was closely associated with severe hypoglycemia, reflecting the significant impact of hypoglycemic events on patient well-being (19,20). Fear of hypoglycemia has generally been shown to have even higher predictive value for patient well-being and health status than hypoglycemia itself (19).

We further report on the extent of potentially unproductive reactive behaviours after a single episode of hypoglycemia. Common responses such as skipping or reducing an insulin dose and increasing calorie intake may add significant barriers to patients' ability to achieve their preferred diabetes care outcomes. Similarly, a recent survey (21) showed that in a given month, hypoglycemia was frequently the cause of dosing aberrations—including skipped doses (44%) and reduced doses (60%). In response to their last self-treated hypoglycemia event, patients intentionally missed (8%), mistimed (6%) or reduced (9%) their insulin dose, and 50% of patients increased their self-monitoring as a result of hypoglycemia.

Several findings imply a significant cost burden of hypoglycemia to the healthcare system derived from increased self-monitoring and HCP contacts, whether by telephone or in person. Perhaps even more underappreciated are the costs of lost productivity and potential career impairment caused by absenteeism. In addition to the 9.8 days of leave from work or study in the previous year, the significant impact on punctuality may also lead to reduced productivity and impaired employability. After an episode of hypoglycemia, 23.2% of patients experienced impaired punctuality or absenteeism, affecting 17.0 days of their previous work/study year. Similar findings have been reported in a previous Canadian survey (7), with up to 9% of patients missing work/study after an episode of hypoglycemia, and in a European survey in which 14.3% of patients reported losing a mean of 9.9 hours of work after an episode of hypoglycemia (22). In that study, a nocturnal hypoglycemic event was associated with an average loss of 14.7 working hours.

We found no significant associations of hypoglycemia frequency with A1C level among patients with type 1 diabetes or type 2 diabetes. This pattern has been recently substantiated by another large population study (23). Advances in insulin therapy strategies, availability of self-monitoring and the growing momentum for individualized treatment goals may be enabling optimal titration to an individual's limit of hypoglycemia. Alternatively, hypoglycemia may be more related to glycemic variability, which is not well reflected by A1C alone.

Strengths and limitations

The prospective design, use of patient diaries to collect information about hypoglycemia in a systematic fashion and the simplicity of the Part 2 SAQ are all strengths of this study. Limitations include the observational nature and the inclusion of symptomatic (unconfirmed) hypoglycemia in the reporting. This approach provided a real-world capture of the patient experience but may have resulted in overestimation of the incidence of hypoglycemia. Use of the highest rate reported in the patient diary versus Part 2 SAQ, while compensating for recall bias, may have also contributed to an overestimation. However, while the safety results from clinical trials are often reported with a hypoglycemia threshold of <3.9 mmol/L (<70 mg/dL), a threshold of <3.1 mmol/L (<56 mg/dL) was used in this study to ensure that rates of hypoglycemia were not overreported. This is supported by the recently published guidelines from The International Hypoglycaemia Study Group (24), which recommend that a threshold of 3.0 mmol/L (54 mg/dL) should be reported in clinical trials (and not higher thresholds, i.e., 3.9 mmol/L [70 mg/dL]), because this is considered sufficiently low to indicate serious, clinically important hypoglycemia. The simplicity of the SAQ contributed to the high completion rate but may have limited the information collected. Finally, despite efforts to enroll sequentially presenting eligible patients, there may also be some volunteer bias.

Conclusion

This analysis demonstrates a high prevalence and incidence of hypoglycemia among insulin-treated patients with diabetes in Canada, with an identifiable impact on patient health and healthcare resource utilization, implying a potential increase in economic burden on employers and HCPs. In addition, patient recall seemingly provides an inaccurate estimate of the frequency of hypoglycemic events, particularly nocturnal hypoglycemia. Further investment in patient and HCP education may help reduce the impact of

hypoglycemia on patient health and the healthcare system and allow patients to more effectively meet their treatment goals.

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