RESEARCH ARTICLE

Diabetes Management

Self-reported frequency and impact of non-severe hypoglycemic events in insulin-treated diabetic patients in Denmark

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Practice points

Frequency of hypoglycemia

- Mean weekly non-severe hypoglycemic event (NSHE) frequencies were 1.9 (in Type 1 diabetes mellitus [T1DM]) and 0.5 (in Type 2 diabetes mellitus [T2DM]) per patient, and mean annual NSHE frequencies were 99 (in T1DM) and 27 (in T2DM) per patient.
- T1DM patients reported approximately 22 nocturnal NSHEs per year and T2DM patients reported 8 nocturnal NSHEs per year.

Awareness of hypoglycemia

- Impaired awareness/unawareness of hypoglycemia was reported by 61% of T1DM and 48% of T2DM patients.
- In T1DM patients, higher NSHE frequencies were observed in those who were unaware compared with those who were aware. This trend was reversed in T2DM patients, with statistically significantly lower NSHE frequencies observed in those who were unaware compared with those who were aware.

Communication regarding hypoglycemia with HCPs

- Overall, 64% of T1DM and 51% of T2DM patients rarely/never informed HCPs about NSHEs.
- In all patients, mean weekly NSHE frequencies were statistically significantly higher in those who rarely/never inform HCPs about NSHEs compared with those who always/usually report events.
- As awareness of hypoglycemia declined, communication with HCPs statistically significantly increased for all patients.

Patient impact & economic burden of hypoglycemic events

- After NSHEs, 59% of patients reported feeling tired/fatigued and 25% reported reduced alertness.
- Effects on patients' emotional wellbeing lasted for 5 h on average, with nocturnal events lasting 3–5 h longer than daytime events.
- In the week after a NSHE, blood glucose measurement increased by 8% (in T1DM) and 21% (in T2DM).
- In employed patients, 9% of NSHEs led to lost work time of 1.4 h (in T1DM) and 1.9 h (in T2DM) per event.

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Future Medicine part of fsg

Practice points (cont.)

Conclusion

- NSHEs are a common occurrence for insulin-treated T1DM and T2DM patients in Denmark.
- NSHEs are associated with a cost burden and a negative impact on patient wellbeing.
- Many patients are unable to recognize the symptoms of hypoglycemia.
- Patient communication with HCPs regarding hypoglycemia is limited and in need of improvement.
- The burden of hypoglycemia might be underestimated in Denmark.

SUMMARY **Aim:** Limited real-world hypoglycemia data exist. We investigated the self-reported frequency and impact of non-severe hypoglycemic events (NSHEs) in Denmark. **Patients & methods:** Patients with insulin-treated Type 1 (T1DM) or Type 2 (T2DM) diabetes completed four or fewer weekly questionnaires. NSHEs were defined as not requiring third-party assistance of their management. **Results:** From 601 patients, mean NSHEs/week were 1.9 for T1DM and 0.5 for T2DM. Less than half (45%) of all patients were fully aware of hypoglycemia. More than half of all patients (T1DM = 64%; T2DM = 51%) rarely/never reported NSHEs. These patients experienced more NSHEs ($p < 0.05$). In employed patients, 9% of NSHEs led to lost work time. **Conclusion:** NSHEs are common and associated with economic burden, but as many patients rarely/never discuss them, the burden may be underestimated.

KEYWORDS
• awareness • complications • diabetes • economic impact • hypoglycemia • insulin • non-severe hypoglycemic event

Hypoglycemia is the main side effect of insulin therapy and has a negative physical and emotional impact on patients. This results in distress and reduced quality of life [1]. Furthermore, fear of hypoglycemia may promote inappropriate avoidance behavior towards compliance with treatment regimens and prohibit glycemic control [2,3]. Thus, hypoglycemia represents an important barrier to optimal disease management.

A hypoglycemic event is defined as severe if third-party assistance is required to manage the event [4,5]. Non-severe hypoglycemic events (NSHEs), which account for 88–98% of all hypoglycemic events [6–8], do not require third-party assistance [4,5]. NSHEs have been shown to interrupt daily-life functioning [9] and to affect health-related quality of life [6–10], healthcare resource use [6] and work productivity [9]. However, data on the frequency of NSHEs outside of clinical trials are limited and varied [1,7,8,10].

In addition, diabetes patients may not communicate the frequency of their hypoglycemic events with healthcare professionals (HCPs), such as general practitioners and specialists. This has the potential to hinder education regarding the recognition and the treatment of hypoglycemia (the need for which is highlighted by the current European Association for the Study of Diabetes [EASD] and American Diabetes Association [ADA] consensus statement) [11]. It also has the potential to hinder rational revision of treatment in order to avoid future events.

Previous studies have reported real-world estimates on the frequency of hypoglycemia in Denmark [8,12–14] and other European countries [1,7,10]. However, results vary according to methods of data collection, sample selection, patients' diabetes type and treatment duration, as well as targets for glycemic control. Furthermore, the majority of the available literature focuses on the frequency of severe hypoglycemic events (SHEs) and therefore may not adequately reflect the overall burden of hypoglycemia. In addition, evidence is limited regarding communication between HCPs and diabetes patients about hypoglycemic events, the patient impact of hypoglycemia and the use of healthcare resources due to NSHEs.

The primary aims of this study were to report the frequency of patient-reported NSHEs among insulin-treated diabetes patients (Type 1 and Type 2) in Denmark and to draw comparisons to Europe-wide data from a previously reported study with the same methodology [15]. The secondary aims were to investigate levels of awareness of hypoglycemia, communication of hypoglycemic events to HCPs and the health-related and economic impacts of NSHEs in Denmark. In order to achieve these aims, a

Table 1. Patient demographics.

Demographic	T1DM	T2DM
Number of patients, n (%)	258 (43)	343 (57)
Age, mean (SD)	49.2 (13.3)	60.3 (8.9)
Gender, female, n (%)	112 (43)	118 (34)
Marital status, n (%):		
– Single	74 (29)	100 (29)
– Married	149 (58)	209 (61)
– Partner	35 (14)	34 (10)
Living arrangements, n (%):		
– Alone	56 (22)	98 (29)
– With others	202 (78)	245 (71)
Employed, n (%)	173 (67)	149 (43)
Education, n (%):		
– Primary school	27 (10)	65 (19)
– High school	95 (37)	125 (36)
– University (plus PhD or higher)	109 (42)	104 (30)
–Other	27 (10)	49 (14)
BMI, mean (SD)	25.7 (4.3)	32.0 (7.1)
Diabetes duration, n (%)[†]:		
– Mean, years (SD)	22.2 (14.7)	12.3 (7.2)
– <2 years	2 (1)	10 (3)
– 2–5 years	34 (14)	55 (17)
– 5–9 years	18 (7)	57 (17)
– 10–14 years	28 (12)	97 (29)
– 15+ years	161 (66)	111 (34)
Insulin treatment type, n (%):		
– Basal-only therapy	11 (4)	137 (40)
– Basal bolus therapy	208 (81)	101 (29)
– Other insulin types	39 (15)	105 (31)
Duration of insulin treatment, n (%)[†]:		
– Mean, years (SD)	21.6 (14.7)	6.6 (5.4)
– <2 years	4 (2)	50 (15)
– 2–5 years	37 (15)	120 (36)
– 5–9 years	17 (7)	73 (22)
– 10+ years	185 (76)	87 (26)
Mean HbA_{1c} [‡]:		
– Mean mmol/mol (SD)	59.8 (12.1)	61.7 (17.8)
– NGSP % (SD)	7.6 (1.1)	7.8 (1.6)
Medical complications[§], none reported, n (%)	162 (63)	187 (55)

Unless stated otherwise, percentages of numbers represent proportions of the number of patients that participated in the study.
[†]Diabetes duration and duration of insulin treatment were based on responses from 243 T1DM and 330 T2DM patients.
[‡]Mean HbA_{1c} was based on responses from 213 T1DM and 249 T2DM patients.
[§]Response options to the question 'What medical complications do you have as a result of your diabetes?' included: none, eye problems, neuropathy, cardiovascular disease, renal disease, amputations and other.
NGSP: National Glycohemoglobin Standardization Program; SD: Standard deviation; T1DM: Type 1 diabetes mellitus; T2DM: Type 2 diabetes mellitus.

questionnaire-based survey of diabetes patients was conducted.

Patients & methods

The study was conducted in Denmark between November 2011 and March 2012, and the full study methodology has been previously reported [15,16]. Patients were primarily identified through large patient panels that were representative of the general diabetes population. Patients were also identified through advertising on diabetes-related websites (including those of patient associations), as well as through referral from family and friends.

Patients aged over 15 years with Type 1 diabetes mellitus (T1DM) or Type 2 diabetes mellitus (T2DM) and receiving insulin treatment were included in the study. T2DM patients were

categorized into subgroups based on the form of insulin that they were receiving: basal-only/long-acting only, basal bolus/long- and short-acting (T2BB) and other forms, such as premixed or bolus-only insulin (potentially administered using an insulin pump). Patients were anonymized in accordance with the regulations of the European Society for Opinion and Marketing Research (ESOMAR) [17] and the European Pharmaceutical Market Research Association (EphMRA) [18]. Upon completion of the study, patients were reimbursed €2–25 for their participation.

Patients were invited to complete four online questionnaires at 7-day intervals. Questionnaires were adapted from those used in a previous study [9] and were developed using insights from diabetes focus groups on the impact of hypoglycemia on patients [19]. Certain questions were repeated in all questionnaires (e.g., those relating to the frequency of NSHEs during the study recall period, as well as the impact of a patient's most recent NSHE on their use of healthcare resources). Other questions were only asked once: either in the first questionnaire (e.g., those relating to patient demographics, awareness of hypoglycemia, discussions with HCPs and the frequency of SHEs in the preceding year) or in any of the four questionnaires, depending on patients' previous responses (e.g., those relating to negative feelings and affected work productivity following a patient's most recent NSHE). For the subgroup analyses, patients were included if they reported a NSHE in the previous 7 days or in the initial 4-week recall period from the first questionnaire.

A NSHE was defined as symptoms of hypoglycemia (e.g., sweating, shaking and headache) with or without a blood glucose measurement (BGM) or a low BGM (≤3.1 mmol/l) in the absence of symptoms that did not require third-party assistance (e.g., a family member, friend or HCP, including emergency room visits and hospitalization) [15]. A SHE was defined as an event of low blood glucose where the patient required assistance from a third party. A nocturnal event was defined as one that occurred while the respondent was in bed or asleep (at night). The mean weekly NSHE frequency was calculated using data from patients that completed at least the first questionnaire, and multiplied by 52 to give the estimated annual NSHE frequency.

Patients' awareness of hypoglycemia was assessed according to responses to the question 'Can you feel when your blood sugar is low?'. Patients who responded with 'sometimes' or 'never' were classed as being 'unaware', those who responded with 'usually' were classed as having 'impaired' awareness and those who responded with 'always' were classed as being 'aware'. This assessment was derived from a prospectively validated study by Pedersen-Bjergaard *et al.* [14].

In order to minimize erroneous reporting, upper and lower limits were applied to data entries. In addition, a logical consistency check was conducted to remove erroneous entries (e.g., instances in which a patient had reported receiving treatment for longer than the duration of their diabetes). Patients were excluded from the analysis if they did not know their diabetes type or if they erroneously reported any simple demographic characteristics (e.g., reporting a lower age than the duration of their diabetes).

Comparisons of NSHE frequencies according to patient communication with HCPs and patient awareness of hypoglycemia were performed using t-tests. The Cochran–Armitage trend test was used to assess potential trends between hypoglycemia awareness and patient communication with HCPs. All statistical analyses employed a 95% threshold for statistical significance.

Results

Patient demographics are outlined in **Table 1**. A total of 601 patients completed the first questionnaire. Of these, 84, 74 and 58% went on to complete questionnaires 2, 3 and 4, respectively. Collectively, this equates to a total of 1894 patient-weeks. Mean blood glucose levels were similar across T1DM and T2DM. The HbA_{1c} distributions for T1DM and T2DM patients are illustrated in **Figure 1**.

Frequencies of hypoglycemic events are outlined in **Table 2**. The mean weekly NSHE frequency was nearly fourfold higher in T1DM patients than in T2DM patients, but was similar across T2DM subgroups. Mean estimated annual NSHE frequencies were 99 in T1DM and 27 in T2DM patients (ranging from 23 in T2DM patients receiving basal-only therapy/long-acting insulin only to 39 in T2BB patients). When analyzing only the 412 patients that experienced a NSHE during the study recall period, annual NSHE frequencies were 106 in T1DM and 50 in T2DM patients (ranging from 41 in T2DM patients receiving other therapies to 63 in T2BB).

The proportion of NSHEs occurring at night was 22% for T1DM and 28% for T2DM patients, indicating that T1DM patients

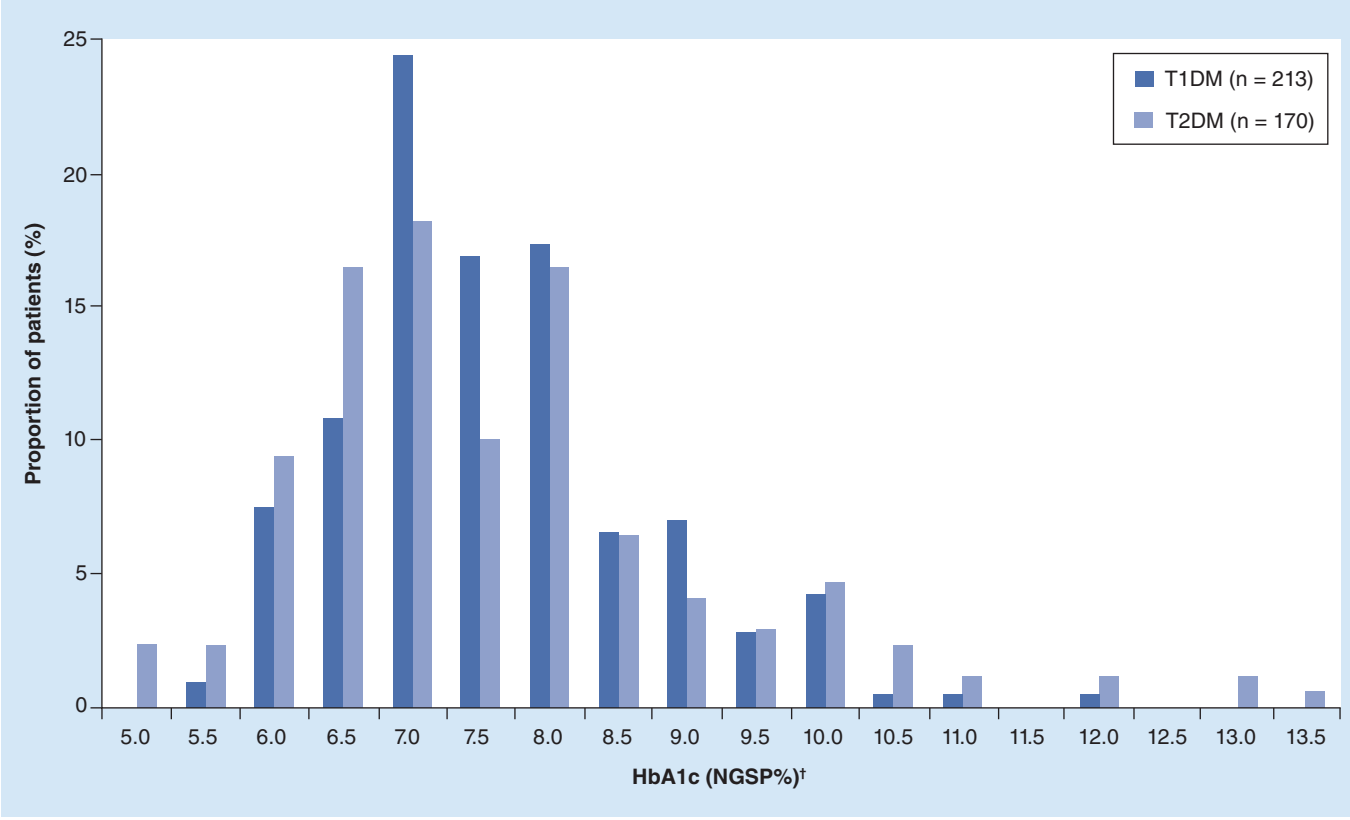

Figure 1. HbA_{1c} distribution in Type 1 and Type 2 diabetes mellitus patients.
†x-axis values are midpoints of 0.5% ranges (e.g., 5.0 represents an HbA_{1c} level of ≥4.75 and <5.25%).
NGSP: National Glycohemoglobin Standardization Program; T1DM: Type 1 diabetes mellitus; T2DM: Type 2 diabetes mellitus.

experience approximately 22 nocturnal NSHEs per year and that T2DM patients experience approximately eight nocturnal NSHEs per year. The mean annual SHE frequency was highest for T1DM patients and similar for all T2DM subgroups (**Table 2**).

A significantly greater proportion of patients who experienced a NSHE during the study recall period (n = 412) reported their HbA_{1c} level than those who did not (80 vs 70%, respectively; p = 0.0105). There was also a trend towards lower $HbA1_c$ levels in patients who experienced a NSHE during the study recall period versus those who did not (7.6 vs 7.9%, respectively). However, comparing the average number of NSHEs between these two groups showed no significant difference (p = 0.0618).

Patients' awareness of hypoglycemia and frequencies of hypoglycemic events are outlined in **Table 3**. Normal awareness of hypoglycemia was more common in T2DM patients than in T1DM patients. Notably, over half of all patients reported impaired awareness or unawareness. Mean weekly NSHE frequencies and annual SHE frequencies were highest for T1DM patients that were unaware of hypoglycemia, but this trend was not statistically significant due to one outlier patient with normal awareness reporting 30 SHEs per year. However, excluding this patient from the analysis reduced the yearly frequency of SHEs in aware respondents to 0.3 (standard deviation = 1.1), resulting in a significant difference for unaware versus aware patients (p = 0.01). A significant association between awareness and NSHE frequencies was observed in T2DM patients, with lower NSHE frequencies in patients who were unaware of hypoglycemia (p < 0.05 vs aware patients).

Data relating to patient communication of hypoglycemia with HCPs are outlined in **Table 4**. Over a quarter of all patients reported that their HCP does not ask about hypoglycemic events during routine appointments (this was more commonly reported by T2DM patients than T1DM patients). Over half of patients reported that they rarely/never inform HCPs about their NSHEs. This was more common for T1DM patients. For all patients, mean weekly NSHE

Table 2. Self-reported recalled frequencies of non-severe hypoglycemic events (1894 patient-weeks from 601 patients).

	T1DM	T2DM			
	(n = 258; 800 pw)	*All T2DM (n = 343; 1094 pw)*	*T2BOT (n = 137; 422 pw)*	*T2BB (n = 101; 327 pw)*	*T2O (n = 105; 345 pw)*
NSHEs/week, mean (median)	1.9 (1)	0.5 (0)	0.5 (0)	0.7 (0)	0.4 (0)
NSHEs/year, mean:	98.6	27.4	23.4	38.5	21.9
– Daytime NSHEs (%)	76.6 (78)	19.6 (72)	17.0 (73)	29.4 (76)	13.6 (62)
– Nocturnal NSHEs (%)	22.0 (22)	7.8 (28)	6.4 (27)	9.1 (24)	8.3 (38)
Patients that experienced ≥1 NSHE in the study recall period					
	T1DM	*T2DM*			
	(n = 236; 744 pw)	*All T2DM (n = 176; 601 pw)*	*T2BOT (n = 64; 215 pw)*	*T2BB (n = 58; 201 pw)*	*T2O (n = 54; 185 pw)*
NSHEs/week, mean (median)	2.0 (1)	1.0 (0)	0.9 (0)	1.2 (0)	0.8 (0)
NSHEs/year, mean:	106.0	49.9	46.0	62.6	40.8
– Daytime NSHEs (%)	82.3 (78)	35.7 (72)	33.4 (73)	47.9 (76)	25.3 (62)
– Nocturnal NSHEs (%)	23.7 (22)	14.2 (38)	12.6 (27)	14.7 (24)	15.5 (38)
Patients that experienced ≥1 nocturnal NSHE in the study recall period					
	T1DM	*T2DM*			
	(n = 154; 484 pw)	*T2DM (n = 84; 288 pw)*	*T2BOT (n = 32; 106 pw)*	*T2BB (n = 25; 87 pw)*	*T2O (n = 27; 95 pw)*
NSHEs/week, mean (median)	2.5 (2)	1.3 (1)	0.9 (0)	1.9 (1)	1.2 (1)
NSHEs/year, mean:	129.1	68.4	47.6	98.6	64.0
– Daytime NSHEs (%)	92.7 (72)	38.8 (57)	22.1 (46)	64.6 (65)	33.9 (53)
– Nocturnal NSHEs (%)	36.4 (28)	29.6 (43)	25.5 (54)	34.1 (35)	30.1 (47)

NSHE: Non-severe hypoglycemic event; pw: Patient-weeks; T1DM: Type 1 diabetes mellitus; T2BB: Type 2 diabetes mellitus patients receiving basal bolus therapy/short- and long-acting insulin; T2BOT: Type 2 diabetes mellitus patients receiving basal-only therapy/long-acting insulin only; T2DM: Type 2 diabetes mellius; T2O: Type 2 diabetes mellitus patients receiving other therapy (e.g., mixed insulin).

frequencies were significantly higher in those that rarely/never inform HCPs about NSHEs compared with those that always/usually report these events ($p < 0.05$). Descriptive analysis of patient demographics suggests that there were no major differences between patients that discuss their hypoglycemia regularly versus those that do not (data not shown).

A significant association was also observed between communication and awareness; as awareness of hypoglycemia declined, communication with HCPs increased for all patients (p-values for this trend were $p = 0.0237$ in T1DM and $p = 0.0178$ in T2DM patients; **Figure 2**). T2DM patients who were aware or had impaired awareness were more likely to communicate with HCPs than their T1DM counterparts. The association that was observed between communication and awareness for T1DM patients appeared to be primarily attributed to the high level of communication among unaware TD1M patients.

Following the most recent NSHE, patients most commonly reported tiredness/fatigue and reduced alertness. Patients' emotional wellbeing was also affected, with NSHEs resulting in irritability and feeling emotionally low **(Figure 3)**. On average, these feelings lasted for 5 h, but their duration varied according to diabetes type as well as the time of the day that the event occurred (with nocturnal events lasting 3–5 h longer than daytime events on average).

NSHEs resulted in increased healthcare resource use **(Table 5)**. Overall, 3% of NSHEs during the study period led to contact with a HCP. Over the 7 days following a NSHE, BGM test-strip use increased by 8% in T1DM and 21% in T2DM patients.

The mean duration of work time lost by employed patients as a result of their most recent NSHE was highest for T2DM patients **(Table 6)**. In addition, T2DM patients were more likely to experience an inability to complete a work task in a timely manner following a NSHE than T1DM patients.

Discussion

This study has revealed that NSHEs are a common occurrence across insulin-treated T1DM and T2DM patients in Denmark. However, patients express a reluctance to discuss their

Table 3. Self-reported awareness of hypoglycemia and corresponding frequencies of hypoglycemic events.

Patients who had experienced a NSHE (not just in study recall period; n = 483)	Awareness	T1DM (n = 252)	T2DM (n = 231)
Awareness of hypoglycemia, n (%)	Aware	99 (39)	120 (52)
	Impaired	125 (50)	84 (36)
	Unaware	28 (11)	27 (12)
Weekly NSHE frequency stratified by awareness of hypoglycemia, mean (SD)	Aware	1.9 (2.4)	0.7 (1.5)
	Impaired	1.9 (2.1)	0.8 (1.4)
	Unaware	2.5 (3.2)	0.2 (0.7)*
Annual SHE frequency stratified by awareness of hypoglycemia, mean (SD)	Aware	0.6 (3.2)	0.1 (0.3)
	Impaired	0.4 (0.8)	0.3 (1.4)
	Unaware	1.8 (2.8)	0.2 (1.0)

*p < 0.05 versus aware patients.
NSHE: Non-severe hypoglycemic event; SD: Standard deviation; SHE: Severe hypoglycemic event; T1DM: Type 1 diabetes mellitus; T2DM: Type 2 diabetes mellitus.

hypoglycemia with HCPs, and over half of patients reported impaired or unawareness of hypoglycemia, which are associated with increased NSHE frequencies. This suggests that the burden of hypoglycemia might be underestimated and demonstrates a need for patient education regarding the management of hypoglycemia.

NSHEs were common in Denmark, and the self-reported frequency was similar to that observed in a wider European study (reported previously) [15]. We report a mean annual NSHE frequency of 99 (in T1DM) and 27 (in T2DM) in Denmark. The results of a subanalysis excluding patients who did not experience any NSHEs during the study recall periods revealed a higher annual NSHE frequency, suggesting that patients who have previously experienced NSHEs are more susceptible to further events. This uneven distribution, with some individuals prone to more frequent hypoglycemic events, has been observed in previous studies [7,20–25] and suggests that the real-world burden in those that have regular hypoglycemic events may be higher than previously reported. It is, however, important to consider that the current results only relate to a 4-week period, so further research is warranted in order to better understand this issue.

The majority of median weekly NSHE frequency values were zero. This is likely due to only a subgroup of patients having the majority of hypoglycemic events. This trend has also been reported previously for SHEs [26].

The NSHE frequency in T1DM patients was nearly four-times that of T2DM patients in Denmark. This may be explained by risk of hypoglycemia in insulin-treated T2DM patients reportedly increasing with diabetes duration (in our study, diabetes duration was shorter in T2DM compared with T1DM) [7]. Furthermore, it has been reported that the NSHE frequency among T2DM patients only reaches the same level as T1DM patients after 10 years of insulin

Table 4. Communication of hypoglycemia between patients and healthcare professionals.

Patients who had experienced a NSHE (not just in study recall period; n = 483)	T1DM (n = 252)	T2DM (n = 231)
Frequency that patients inform HCPs of NSHEs, n (%):		
– Always/usually	90 (36)	113 (49)
– Rarely/never	162 (64)	118 (51)
Weekly NSHE frequency, stratified by frequency that patients inform HCPs of hypoglycemic events, mean (SD):		
– Always/usually	1.6 (1.9)	0.5 (0.9)
– Rarely/never	2.3 (2.3)*	0.8 (1.4)*
Patients who completed the first questionnaire (n = 601)	**T1DM (n = 258)**	**T2DM (n = 343)**
HCPs do not ask about hypoglycemic events during appointments, n (%)	60 (23)	103 (30)

*p < 0.05 versus patients who always/usually inform HCPs of NSHEs.
HCP: Healthcare professional; NSHE: Non-severe hypoglycemic event; SD: Standard deviation; T1DM: Type 1 diabetes mellitus; T2DM: Type 2 diabetes mellitus.

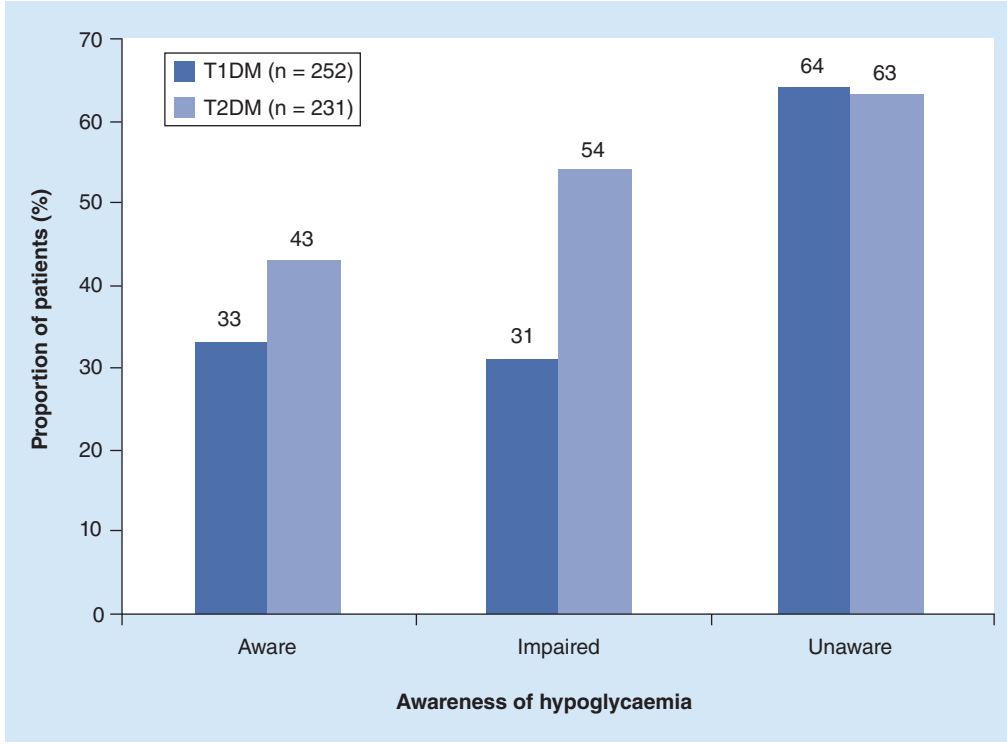

Figure 2. Proportion of patients who always/usually inform healthcare professionals of hypoglycemic events, stratified by awareness of hypoglycemia. Statistical significance was confirmed using a Cochran–Armitage trend test. The trend analysis was based on patients who had ever experienced a NSHE (not just in study recall period; n = 483). Patient numbers were as follows: T1DM 'always' (n = 99); T1DM 'impaired' (n = 125); T1DM 'unaware' (n = 28); T2DM 'always' (n = 120); T2DM 'impaired' (n = 84); and T2DM 'unaware' (n = 27).
NSHE: Non-severe hypoglycemic event; T1DM: Type 1 diabetes mellitus; T2DM: Type 2 diabetes mellitus.

use [27]. In this study, the majority of patients (74%) with T2DM had received insulin for less than 10 years, which might explain the lower frequency of NSHEs in these patients. The NSHE frequency also varies according to treatment regimen in T2DM patients, although this is expected, due to the different types of insulin coverage [11]. Although this study indicates that NSHEs are more common in T1DM than T2DM patients, the proportion of NSHEs occurring at night is higher in T2DM patients (28 vs 22% for T1DM patients). This supports previous findings by Henderson *et al.* [27].

Mean HbA_{1c} levels (7.6% for T1DM patients and 7.8% for T2DM patients) were higher than those recommended by the ADA and EASD (7%) [11,28], as well as the American Association of Clinical Endocrinologists (AACE; 6.5%) [29]. This finding may indicate that many diabetes patients are not achieving optimal glycemic control, which may be attributed to the high prevalence of hypoglycemia in this sample (91% of T1DM patients and 51% of T2DM patients experienced at least one NSHE during the study period). However, it should be noted that some participants may have had individual targets set by their physician that are higher than those recommended by the ADA, EASD and AACE, but HbA_{1c} target levels were not collected in this study.

Many patients reported unawareness or impaired awareness of hypoglycemia (61% of T1DM and 48% of T2DM patients). This is an important finding as it has previously been reported that reduced awareness is a key risk factor for SHEs [12]. Our results support this with a threefold (sixfold following the removal of one outlying patient) higher annual SHE frequency reported by unaware T1DM patients compared with those who were aware. It is possible that the highly publicized implementation of stricter EU legislation on driver's licensing in Denmark in January 2012 may have led to patients being

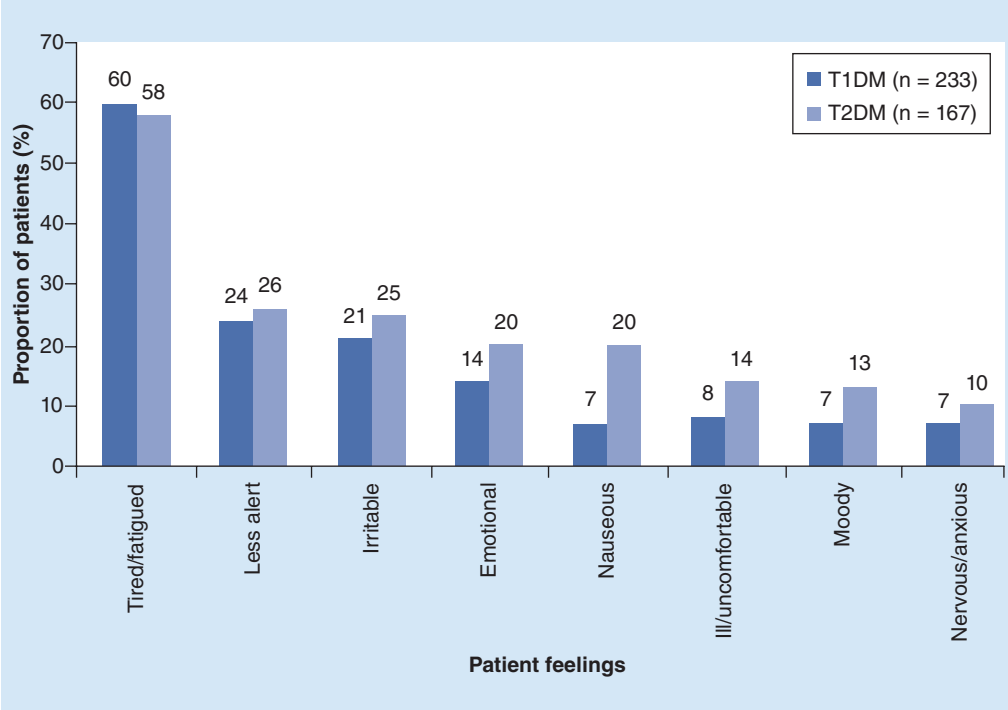

Figure 3. Patients' feelings following their most recent non-severe hypoglycemic event.
T1DM: Type 1 diabetes mellitus; T2DM: Type 2 diabetes mellitus.

more reluctant to report experiencing SHEs. This is supported by the findings of Pedersen-Bjergaard *et al.*, who observed a 50% decrease in patient-reported SHEs in 2012 compared with the preceding years [30]. However, this trend was not observed for T2DM patients.

The frequency of NSHEs was highest in unaware T1DM patients (2.5 NSHEs/week) and lowest in unaware T2DM patients (0.2 NSHEs/week). This difference could be partly attributed to the lower frequency of weekly BGM tests reported by T2DM patients (13.6 vs 25.1 for T1DM patients; **Table 5**), which may have also contributed to the lower frequency of hypoglycemia reported by these patients.

Over half of insulin-treated patients in Denmark rarely/never inform HCPs of NSHEs. This is similar to levels of patient–physician communication reported in a wider European study [15]. In addition, approximately a quarter of patients reported that HCPs do not ask about hypoglycemic events during appointments. In light of the statistically significant association between infrequent patient reporting of events

Table 5. Direct economic impacts of hypoglycemic events.

Most recent NSHE from all patients	T1DM	T2DM
NSHE resulting in contact with HCP, % (n)		
– Overall[†]	1 (4)	7 (22)
– Daytime NSHE[‡]	1 (4)	7 (15)
– Night-time NSHE[§]	0 (0)	8 (7)
Self-reported number of weekly BGM tests, mean	25.1	13.6
Mean increase in BGM test-strip use within 7 days of a NSHE[¶]		
– Overall	2.1	2.8
– Daytime NSHE	1.9	2.9
– Night-time NSHE	2.8	2.6

[†]Base: T1DM (n = 584), T2DM (n = 316).
[‡]Base: T1DM (n = 466), T2DM (n = 223).
[§]Base: T1DM (n = 118), T2DM (n = 93).
[¶]Base: T1DM (n = 498), T2DM (n = 302).
BGM: Blood glucose measurement; HCP: Healthcare professional; NSHE: Non-severe hypoglycemic event; T1DM: Type 1 diabetes mellitus; T2DM: Type 2 diabetes mellitus.

Table 6. Indirect economic impact of non-severe hypoglycemic events in employed patients.

Economic impact	T1DM	T2DM
NSHEs leading to lost work time, % (n)		
– Overall[†]	9 (34)	9 (12)
– Daytime NSHE[‡]	7 (22)	9 (9)
– Night-time NSHE[§]	16 (12)	8 (3)
Mean work time lost after a NSHE (in patients who lost work time), min		
– Overall	83.2	111.5
– Daytime NSHE	89.5	54.4
– Night-time NSHE	71.7	282.8
Employed patients who reported an inability to complete a work task in a timely manner following a NSHE, % (n)[¶]	48 (75)	58 (40)
Employed patients who reported difficulty concentrating at work following a NSHE, % (n)[¶]	24 (37)	20 (14)

[†]Base (NSHEs): T1DM (n = 392), T2DM (n = 137).
[‡]Base (NSHEs): T1DM (n = 315), T2DM (n = 98).
[§]Base (NSHEs): T1DM (n = 77), T2DM (n = 39).
[¶]Base (patients): T1DM (n = 157), T2DM (n = 69).
NSHE: Non-severe hypoglycemic event; T1DM: Type 1 diabetes mellitus; T2DM: Type 2 diabetes mellitus.

and increased NSHE frequencies (in both T1DM and T2DM), these results imply that the frequency of NSHEs might be under-reported and underestimated in clinical practice. Furthermore, a statistically significant inverse association was observed between patient communication and awareness for both T1DM and T2DM patients. As a result, HCPs may be at risk of underestimating the number of hypoglycemic events experienced by patients with a high level of awareness.

Reluctance to discuss hypoglycemia may be attributed to a range of factors, including fear of being perceived to have poor control of their disease and fear of driving restrictions [2]. Further research is needed in order to characterize the reasons for poor communication between patients and HCPs so as to enhance education regarding the recognition and treatment of hypoglycemia, in line with the current EASD and ADA consensus statement [11].

NSHEs affected patients' physical and emotional wellbeing. The patient-reported impacts of a NSHE were similar regardless of diabetes type; tiredness/fatigue, reduced alertness and irritability were the most commonly reported effects in both T1DM and T2DM patients. This supports a previous study in which patients reported that hypoglycemia was a source of anxiety and impacts on daily life [10]. The health-related impacts of hypoglycemia were further confirmed in a UK study: as the frequency and severity of hypoglycemia increased, quality of life (according to the SF-36 – a multipurpose, short-form health survey) and health-related utility (measured using the EQ-5D – a standardized instrument for use as a measure of health outcomes) decreased [6].

NSHEs also caused patients to measure their blood glucose more frequently. Although this adaptive response may help prevent NSHEs in the short term [2], it represents a direct cost burden due to increased use of BGM test-strips. This burden could potentially be alleviated by enhancing education about hypoglycemia and revision of treatment to prevent hypoglycemia.

In addition to the direct economic burden of hypoglycemic events, this study also reports an indirect cost burden in Denmark. As well as lost work time, patients reported reduced productivity at work after a NSHE (including difficulty concentrating and an inability to complete work tasks in a timely manner).

The percentage of NSHEs resulting in lost work time (9%) was half that reported by Brod *et al.* (18%) [9]. In addition, the mean amount of work time lost as a result of NSHEs was considerably lower (1.4–1.9 h) compared with Brod *et al.* (9.9 h) [9]. A potential explanation for this is that the Brod *et al.* study only included NSHEs that occurred during working hours [9], whereas this study also included NSHEs that occurred outside of work time. It may also be attributed to cultural differences in different countries (e.g., consequences of repeatedly reporting sick at work).

Study limitations have been reported previously [15,16]. A total of 601 patients participated in this study. With a larger sample, additional subgroup analyses could have been conducted (e.g., to investigate whether the frequency of

NSHEs in patients using premixed or bolus-only insulin differs from those receiving other forms of insulin). This study also involved self-reporting and data anonymization, both of which prevent data validation, and did not factor seasonal variation in hypoglycemia frequencies (this study was conducted from November to March).

According to recommendations from a workgroup of the ADA and The Endocrine Society, hypoglycemic events that are not confirmed by a plasma glucose measurement of ≤3.9 mmol/l are classed as 'probable' events (as opposed to 'documented' events) [31]. This study used a blood glucose level of ≤3.1 mmol/l as a threshold in the definition of asymptomatic NSHEs, as this level has been commonly used to define hypoglycemia in randomized clinical trials.

Patient recruitment was primarily achieved through online patient panels and required patients to have an email address. This may have introduced selection bias, although it should be noted that the patient panels were reflective of the general diabetes population, and the internet penetration rate in Denmark is high (90.0%) [32].

Patients were not informed that the survey was about hypoglycemia prior to enrolling. This excludes the possibility of a selection bias towards patients struggling with hypoglycemia. However, diminishing response rates (84, 74 and 58% of patients completed questionnaires two, three and four, respectively) may indicate that later questionnaires were completed by patients with greater experience of hypoglycemic events. A subsequent analysis comparing event frequencies for the different waves did not suggest any trends towards higher frequency in later waves.

Notably, 4% of patients with T1DM in Denmark reported receiving long-acting insulin only. Since long-acting insulin monotherapy should only be administered to manage T2DM, this may indicate incorrect reporting. If incorrect reporting had occurred on the part of T2DM patients, the study may underestimate the hypoglycemic event frequency in T1DM patients (since T2DM patients reported having fewer hypoglycemic events). Alternatively, the use of long-acting insulin in T1DM may represent patients with diabetes mellitus that is secondary to pancreatitis (as these patients are often treated with basal-only insulin) [33] or patients with poor compliance.

Conclusion

NSHEs are common among diabetes patients in Denmark. However, many patients are unable to recognize the symptoms of an event and rarely discuss them with their HCP. The importance of improving glycemic control is evidenced by the negative impact of non-severe events on patient wellbeing and healthcare resource use in Denmark.

Future perspective

Reducing the frequency of NSHEs experienced by insulin-treated diabetes patients will be essential for optimizing their glycemic control. This could potentially be achieved in the future by enhancing patient education regarding the management of hypoglycemia, increasing communication regarding hypoglycemia between patients and HCPs and revision of treatments to prevent hypoglycemia. New treatments that optimize glycemic control while reducing the risk of hypoglycemia may help reduce the overall burden of hypoglycemia.

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