ORIGINAL RESEARCH

Self-Reported Frequency and Impact of Hypoglycemic Events in Spain

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ABSTRACT

Introduction: Hypoglycemia is a common side effect of insulin therapy and has negative implications for quality of life and healthcare resources. The authors investigated the self-reported frequency of non-severe and severe hypoglycemic events (NSHEs and SHEs), hypoglycemia awareness, patient–physician communication, health-related effects and economic impact on people with insulin-treated diabetes (Type-1 and Type-2) in Spain.

Methods: People with Type-1 (T1DM) or insulin-treated Type-2 (T2DM) diabetes older

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than 15 years of age completed up to 4 questionnaires at weekly intervals. NSHE was an event which respondents could manage without assistance. SHE needed help from a third party to manage.

Results: In total, 630 respondents completed questionnaires covering 2,235 weeks. Mean self-reported NSHEs per respondent-week were 1.7 (T1DM) and 0.4–0.8 (T2DM). Impaired hypoglycemia awareness or unawareness was reported by 55% of T1DM and 39% of T2DM respondents. Overall, 31% of T1DM and 20% of T2DM respondents rarely/never informed their physician about NSHEs. Respondents reported feeling tired/fatigued after 67% of NSHE and less alert after 45% of NSHE. Over the week following an NSHE, blood glucose measurement test-strip use increased by 5.3 (mean). In employed respondents (43%), 18% of NSHEs were reported to lead to lost work time (mean 1.5 h per event). After an SHE, 49% of respondents required emergency visits and/or hospital admission.

Conclusion: NSHE are a common occurrence with T1DM and insulin-treated T2DM in Spain and are associated with a cost burden and negative impact on well-being. Patient–physician

communication is higher in Spain than Europe overall; however, many patients expressed reluctance to discuss their hypoglycemia.

Keywords: Diabetes; Economic impact; Endocrinology; Hypoglycemia awareness; Insulin therapy; Non-severe hypoglycemic event; Patient impact; Severe hypoglycemic event

INTRODUCTION

The prevalence of diabetes is increasing and according to the International Diabetes Federation (IDF), more than 3.8 million adult citizens currently live with diabetes in Spain, corresponding to a prevalence of 10.8% (2013 estimate) [1]. Other studies have estimated a slightly higher prevalence of diabetes (≤15%) [2], the most recent reporting a prevalence of 13.8% in a representative sample of the Spanish population [3].

Maintenance of normoglycemia, often through the use of insulin, is the cornerstone of optimal diabetes management. However, intensification of insulin therapy can lead to an increased incidence of hypoglycemia: the most common adverse event associated with insulin treatment [4]. Hypoglycemic episodes are defined as either severe or non-severe depending on whether assistance is required by another individual, or whether the person can manage the event alone, respectively [5, 6]. Non-severe hypoglycemic events (NSHEs) account for 88–98% of all events [7–9] and have been shown to impact the health-related quality of life of people with diabetes [7, 10]. Furthermore, the rise in the prevalence of diabetes may also create problems for healthcare systems as hypoglycemia can have a direct and indirect economic impact [11].

Hypoglycemia also represents a barrier to optimal diabetes management, as fear of hypoglycemic events can cause sub-optimal insulin therapy and poor glycemic control [12, 13]. Although international diabetes bodies (the European Association for the Study of Diabetes and the American Diabetes Association) highlight that education on the recognition and treatment of hypoglycemia is an important part of diabetes management, the real-world level of patient–physician communication regarding hypoglycemia is not known [14].

There are limited data on the frequency of hypoglycemia outside of clinical trial settings and, furthermore, there are few studies reporting data for NSHEs in people with Type 1 Diabetes Mellitus (T1DM) and Type 2 Diabetes Mellitus (T2DM) in Spain. Previous European studies have reported real-world estimates [8–10, 15]; however, results vary according to the definition of events used, methods of data collection, and country coverage. Moreover, limited data exist on the health-related impact and the use of healthcare resources due to NSHEs in Spain.

This paper reports the frequency of self-reported NSHEs and severe hypoglycemic events (SHEs) in people with T1DM and insulin-treated T2DM in Spain. Additionally, levels of impaired hypoglycemia awareness, patient–physician communication of hypoglycemic events and the health-related effects and economic impact of NSHEs are reported.

METHODS

Subjects

A full description of the methodology for this study has been previously reported by Östenson

et al. [16]. Respondents in Spain were recruited using existing large consumer panels that provided a representative sample of the general diabetes population. People over the age of 15 with a T1DM or T2DM diagnosis, receiving insulin, were included in the survey. Respondents with T2DM were divided into three subgroups based on regimen: long acting insulin only (basal only therapy; T2BOT), short and long acting insulin (basal bolus; T2BB) or other insulin regimens (e.g., premix; T2O).

A small incentive (5€) was offered for completion of the questionnaire, in line with current market research guidelines and to ensure that there was no undue incentive to participate. Questionnaires were completed anonymously in accordance with the regulations and practice of market research governing bodies European Society for Opinion and Marketing Research (ESOMAR) [17] and European Pharmaceutical Market Research Association (EphMRA) [18].

Materials: Online Questionnaires

Four waves of questionnaires were sent out over 4 weeks. The first questionnaire collected information on respondent demographics and patient awareness of hypoglycemia. It also collected the self-reported number of NSHEs in the preceding seven days and the number of SHEs in the past year. The subsequent three questionnaires recorded the frequency of NSHEs in the preceding seven days only. Data on the impact of hypoglycemia (particularly NSHE; based on a respondent's last NSHE within the 7-day recall period) on respondent well-being, work productivity and healthcare resource use were also collected. The questionnaire was based on one used in a previous study, [19] which was created using insights collected during focus groups on the self-reported

impacts of hypoglycemia [20]. Adaptations made to the questionnaire for this study included questions on frequency.

Definitions and Calculations

An NSHE was defined as symptoms of hypoglycemia (e.g., sweating, shaking, and headache) with or without a blood glucose measurement, or a low blood glucose measurement ($\leq$3.1 mmol/L) without symptoms, that the individual managed without assistance. An SHE was defined as an event of low blood glucose level ($\leq$3.1 mmol/L) needing help from a third party to manage (e.g., help from a family member or a health care professional, including emergency room visits and hospitalization).

Weekly NSHE frequencies were calculated using data from all respondents completing at least one questionnaire (wave) with annual frequency calculated using the mean weekly event frequency multiplied by 52. Standard descriptive methods (means/percentage and standard deviations) were used to report results for respondents.

The classification system for awareness of hypoglycemia was based on a prospectively validated study by Pedersen-Bjergaard et al. [21]. Any respondent who answered 'sometimes' or 'never' to the question "can you feel when your blood sugar is low?" was assigned as being unaware of hypoglycemia, those who answered 'usually' as having impaired awareness and those who answered 'always' deemed to be aware. Comparisons of NSHE frequencies according to respondent awareness were performed using t tests with an employed significance level of $p < 0.05$.

This was a non-interventional market research study. Questionnaires were completed anonymously in accordance with the

regulations and practice of market research governing bodies: European Society for Opinion and Marketing Research (ESOMAR) and European Pharmaceutical Market Research Association (EphMRA). The EphMRA Code of Conduct states that Market Research does not require Clinical Research Ethics Committee or Independent Review Board approval.

This article does not contain any new studies with human or animal subjects performed by any of the authors.

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

RESULTS

Subjects

The 630 patients entering the study completed in total 2,235 patient-week records with 90, 85 and 80% completing wave two (570 patients), wave three (534 patients) and wave four (506 patients), respectively. The frequency of NSHEs is based on 2,235 respondent-week records.

Demographics for respondents are shown in Table 1. In total, 47% of respondents had T1DM and 53% of respondents had T2DM.

Frequency of NSHEs

The mean self-reported NSHEs per week were 1.7 for T1DM, 0.4 for T2BOT, 0.8 for T2BB and 0.6 for T2O respondents. Annual calculated NSHE frequencies were 88.0, 18.3, 42.1 and 29.8 for T1DM, T2BOT, T2BB and T2O, respectively. The proportion of NSHE occurring at night was 26% in T1DM and 30–32% in T2DM respondents (depending on insulin treatment).

Self-reported mean annual SHE frequencies were 0.9 for T1DM, 0.3 for T2BOT, 0.3 for T2BB and 0.4 for T2O respondents.

Self-Reported Hypoglycemia Awareness and Corresponding NSHE/SHE Frequency

In T1DM respondents who had previously experienced an NSHE (i.e., at any point in the past, and not just in the study recall period), 42% reported an impaired awareness of hypoglycemia. Impaired awareness was reported by 25% of T2DM respondents (Table 2). A further 13% of T1DM and 14% of T2DM respondents were classified as unaware.

Respondents with T2DM who had impaired awareness of hypoglycemia had a significantly ($p < 0.05$) higher NSHE frequency than those who were aware, driven by a significant difference in T2BOT respondents. A similar trend (although not significant) was seen in T2BB and T1DM respondents.

T2DM respondents with impaired awareness reported a significantly ($p < 0.05$) higher SHE frequency compared with respondents who were aware, driven by the trend in T2BB respondents.

Patient–Physician Communication Regarding Hypoglycemia

Overall, 31% of T1DM and 20% of T2DM respondents rarely or never informed their general practitioner (GP)/specialist about NSHEs (Table 3). The frequency of NSHE was significantly lower in T2BOT and T2BB respondents who rarely/never inform their GP/specialist about NSHEs. An opposing trend was seen in T1DM and T2O respondents, where the frequency of NSHEs was higher in respondents who rarely/never inform their GP/specialist, although this trend was not statistically significant (Table 3).

When respondents were asked about topics discussed during GP/specialist consultations,

Table 1 Respondent demographics

	Type 1	Type 2
Number of respondents, n (%)	294 (47%)	336 (53%)
Age, mean (SD)	39.9 (12.8)	63.5 (15.1)
Gender, female, n (%)	143 (49%)	150 (45%)
Marital status, n (%)		
Single	102 (35%)	79 (24%)
Married	145 (49%)	239 (71%)
Partner	47 (16%)	18 (5%)
Living arrangements, n (%)		
Alone	21 (7%)	33 (10%)
With others	273 (93%)	303 (90%)
Employed, n (%)	185 (63%)	89 (26%)
Education, n (%)		
Primary school	32 (11%)	165 (49%)
High school	132 (45%)	85 (25%)
University (plus PhD or higher)	129 (44%)	75 (22%)
Other	1 (0%)	11 (3%)
BMI, mean (SD)	25.5 (5.1)	29.0 (5.9)
Smoking, n (%)		
Smoker	111 (38%)	61 (18%)
Ex-smoker	57 (19%)	135 (40%)
Non-smoker	126 (43%)	140 (42%)
Diabetes duration, n (%)		
Average in years (SD)	18.5 (11.0)	20.0 (16.4)
<2 years	2 (1%)	5 (1%)
2–5 years	31 (11%)	45 (13%)
5–9 years	31 (11%)	43 (13%)
10–14 years	50 (17%)	67 (20%)
≥15 years	180 (61%)	176 (52%)
Insulin treatment type, n (%)		
Long acting insulin only	30 (10%)	179 (53%)
Both short and long acting insulin	211 (72%)	95 (28%)
Other insulin types	53 (18%)	62 (18%)
Duration of insulin treatment, n (%)		
Average in years (SD)	16.5 (10.5)	8.0 (8.3)
<2 years	7 (2%)	62 (18%)
2–5 years	44 (15%)	114 (34%)
5–9 years	26 (9%)	54 (16%)
≥10 years	217 (74%)	106 (32%)
Mean HbA1c		
Mean mmol/mol (SD);	61.6 (18.8)	78.8 (29.7)
NGSP %, (SD)	7.8 (1.7)	9.4 (2.7)

Table 1 continued

	Type 1	Type 2
Medical complications[a], none reported, n (%)	186 (63%)	157 (47%)

BMI body mass index, *HbA1c* hemoglobin A1c (glycosylated hemoglobin), *NGSP* National Glycohemoglobin Standardization Programme, *SD* standard deviation
[a] Questionnaire options for medical complications included: none, eye problems, neuropathy, cardiovascular disease, renal disease, amputations, other (please specify)

10% of T1DM and 13% of T2DM respondents reported that their GP/specialist did not ask about hypoglycemia during routine appointments (Table 3).

Economic Impact of NSHEs

NSHE resulted in increased use of healthcare resources (Table 4). Over the seven days following an NSHE, blood glucose measurement (BGM) test-strip use increased by a mean of 5.0 in T1DM and 5.9 in T2DM respondents. This equates to an estimated additional resource use of €1.3/event (cost/test-strip €0.25) [22, 23]. In respondents with T1DM, 8% of daytime and 12% of nocturnal NSHE during the study period led respondents to contact a healthcare professional (HCP) (Table 4). A fifth of NSHE (20%) in respondents with T2DM resulted in contact with a HCP, regardless of the time of day that the event occurred.

Among respondents who had experienced an SHE, 30% required emergency hospital visits following their last SHE and 19% were admitted to hospital. In employed T1DM respondents (n = 185), 18% of NSHE led to lost work time with approximately 1.5 h work time lost per event. In employed T2DM respondents (n = 89), 15% of NSHE led to lost work time, with approximately 1 h' work time lost per event (Table 4).

Table 2 Self-reported respondent awareness of hypoglycemia and corresponding frequency of NSHEs and SHEs

All respondents who have previously experienced an NSHE[a] (n = 517)	T1DM (n = 271)	T2DM			
		All T2DM (n = 246)	T2BOT (n = 114)	T2BB (n = 83)	T2O (n = 49)
Can you feel when your blood sugar is low? % (n)					
Always aware	45% (121)	61% (150)	61% (70)	53% (44)	73% (36)
Impaired awareness	42% (114)	25% (62)	23% (26)	35% (29)	14% (7)
Unaware	13% (36)	14% (34)	16% (18)	12% (10)	12% (6)
NSHE frequency per week stratified by respondents' awareness, mean (SD)					
Always aware	1.75 (2.43)	0.53 (1.42)	0.37 (1.08)	0.79 (2.05)	0.54 (0.95)
Impaired awareness	1.88 (2.42)	0.91 (1.81)*	0.78 (1.64)*	1.16 (2.08)	0.36 (0.58)
Unaware	1.63 (2.24)	0.77 (1.99)	0.47 (1.41)	0.62 (1.04)	2.00 (3.74)
SHE frequency in the past year stratified by respondents' awareness, mean (SD)					
Always aware	0.91 (2.71)	0.23 (1.31)	0.33 (1.86)	0.16 (0.53)	0.11 (0.40)
Impaired awareness	1.04 (3.20)	0.61 (1.25)*	0.65 (1.70)	0.62 (0.82)*	0.43 (0.79)
Unaware	1.31 (3.39)	0.79 (2.53)	0.39 (1.20)	0.20 (0.63)	3.00 (5.44)

NSHE non-severe hypoglycemic event, *SD* standard deviation, *SHE* severe hypoglycemic event, *T1DM* type 1 diabetes mellitus, *T2BB* type 2 diabetes mellitus respondents receiving basal bolus therapy/short and long acting insulin, *T2BOT* type 2 diabetes mellitus respondents receiving basal only therapy/long acting insulin only, *T2DM* type 2 diabetes mellitus, *T2O* type 2 diabetes mellitus respondents receiving other therapy (e.g., mixed insulin)

* Significant change versus always aware group or always/usually group (comparisons performed using *t* tests with an employed significance level of $p < 0.05$); however, the analysis of T2DM subgroups (T2BOT, T2BB, T2O) is inconclusive due to the small number of respondents who had impaired awareness in each group

[a] Base: All respondents that have previously experienced an NSHE at any point (not just in study recall period)

Patient Impact of NSHEs

Respondents reported negative health-related impacts following their last NSHE, including feeling tired/fatigued (following 70% and 63% of NSHE in T1DM and T2DM, respectively), less alert (48% and 42% of NSHE in T1DM and T2DM) and ill/uncomfortable (39% and 47% of NSHE in T1DM and T2DM). Respondents' emotional well-being was also affected, with NSHE resulting in feeling emotionally low (following 37% and 35% of NSHE in T1DM and T2DM, respectively), anxious/nervous (31% and 38% in T1DM and T2DM) and moody (30% and 26% in T1DM and T2DM).

Figure 1 shows the reported impact of NSHEs on daily routine for all respondents combined (i.e., T1DM and T2DM), according to if they were day or nighttime events. The specific impact of NSHEs relating to daily routine was similar, regardless of the time of day they occurred.

These overall findings were reflected in the specific results for respondents with T1DM or T2DM. T1DM respondents reported having less energy than usual following 57% of daytime NSHE and 50% of nighttime NSHE, having a

Table 3 Communication of hypoglycemia

	T1DM (n = 271)	T2DM All T2DM (n = 246)	T2BOT (n = 114)	T2BB (n = 83)	T2O (n = 49)
All respondents who have previously experienced an NSHE[a] (n = 517)					
Proportion of respondents who rarely/never inform their GP/specialist about NSHEs, % (n)	31% (85)	20% (50)	22% (25)	19% (16)	18% (9)
Number of NSHE in those respondents communicating versus those who do not tell their GP specialist					
Always/usually	1.69 (2.15)	0.77 (1.44)	0.57 (1.13)	1.00 (1.62)	0.81 (1.67)
Rarely/never	2.18 (2.24)	0.4 (0.59)*	0.26 (0.47)*	0.38 (0.6)*	0.86 (0.70)
	T1DM (n = 294)	**All T2DM (n = 336)**	**T2BOT (n = 179)**	**T2BB (n = 95)**	**T2O (n = 62)**
Based on all respondents completing wave 1 (n = 630)[b]					
GP/specialist did not ask about hypoglycemia during routine appointments	10%	15%	16%	15%	13%

NSHE non-severe hypoglycemic event, *T1DM* type 1 diabetes mellitus, *T2BB* type 2 diabetes mellitus respondents receiving basal bolus therapy/short and long acting insulin, *T2BOT* type 2 diabetes mellitus respondents receiving basal only therapy/long acting insulin only, *T2DM* type 2 diabetes mellitus, *T20* type 2 diabetes mellitus respondents receiving other therapy (e.g., mixed insulin)

* Significant change versus always aware group or always/usually group (comparisons performed using *t* tests with an employed significance level of $p < 0.05$); however, the analysis of T2DM subgroups (T2BOT, T2BB, T2O) may be inconclusive due to the small number of respondents who rarely/never inform their GP/specialist about NSHEs

[a] Base: All respondents that have previously experienced an NSHE at any point (not just in study recall period) (n = 517)

[b] Base: All respondents completing wave 1 (n = 630)

headache following 32% (daytime) and 30% (nighttime) of NSHE, and requiring daytime sleeping following 35% (daytime) and 32% (nighttime) of NSHE. T2DM respondents reported similar trends with 54% of daytime and 43% of nighttime NSHE resulting in reduced energy levels, 27% (daytime) and 24% (nighttime) of NSHE resulting in headaches, and 36% (daytime) and 30% (nighttime) of NSHE leading to daytime sleeping. Respondents also changed their behavior relating to insulin administration, reducing their normal insulin

dose following 25% (T1DM) and 20% of NSHE (T2DM).

DISCUSSION

This study identifies the real-world frequency of NSHEs and SHEs both in people with T1DM and people with insulin-treated T2DM in Spain. Furthermore, it provides an insight into the negative impact of NSHEs on patient well-being and healthcare resource use specific to Spain.

Table 4 Economic impact of hypoglycemic events

	T1DM	T2DM	T2BOT	T2BB	T2O
Last NSHE across all respondents					
Percentage of daytime NSHE resulting in contact with HCP[a]	8%	20%	17%	20%	28%
Percentage of nocturnal NSHE resulting in contact with HCP[b]	12%	20%	30%	11%	22%
Mean increase BGM in the week following an NSHE[c]					
Overall	5.0	5.9	6.0	7.1	4.1
Daytime NSHE	4.5	5.5	5.1	7.1	4.1
Nighttime NSHE	6.5	7.0	10.3	6.9	4.1
Respondents experiencing SHE ($n = 235$)					
Percentage of respondents reporting an SHE who required emergency hospital visits	30%	30%	28%	23%	46%
NSHE from employed respondents ($n = 569$)					
Percentage of NSHE reported to lead to lost work time	18%	15%	12%	18%	9%
Average working time lost after NSHE (min)	90.4	64.1	159.5	28.8	67.5

HCP healthcare professional, *Mins* minutes, *NSHE* non-severe hypoglycemic event, *SHE* severe hypoglycemic event, *T1DM* Type 1 diabetes mellitus, *T2DM* Type 2 diabetes mellitus

[a] Base: Last daytime NSHE across all respondents ($n = 838$)
[b] Base: Last nocturnal NSHE across all respondents ($n = 240$)
[c] Base: Last NSHE across all respondents ($n = 993$)

Frequency of Hypoglycemic Events

The self-reported frequencies of NSHEs and SHEs in Spain are similar to those seen in the overall European study using the same methodology, across all respondent subgroups [16]. In comparison to other previously conducted European studies, the frequency of NSHEs was similar for T1DM (1.7 in this study versus 1.8–2.2 in previous studies [9, 24, 25]), but differed for T2DM (0.4–0.8 in this study versus 0.3 in a previous study in Scotland [8]). This variation may be due to differences in the geographical region, T2DM treatment regimen, and study sample size, or how hypoglycemic events had been defined [8]. For example, the study in Scotland was substantially smaller (less than half the size of the Spanish study), with at least 70% of respondents with T2DM receiving premixed insulin (compared to fewer than 10% in this study). In addition, the definition of NSHE in the study in Scotland is narrower—all symptomatic NSHEs were recorded with a BGM, whereas this study included the detection of hypoglycemic symptoms with or without confirmation through a BGM [8].

The frequency of NSHE in T1DM respondents in this study is double the frequency of NSHE in T2DM respondents. It has been suggested that the risk of hypoglycemia in people with insulin-treated T2DM increases with longer diabetes duration, [8] and Henderson et al. [26] reported that NSHE frequency among people with T2DM only reached the same level as in people with T1DM after 10 years of insulin use in T2DM [26]. In the present study, only 32% of respondents with T2DM had received insulin for over 10 years,
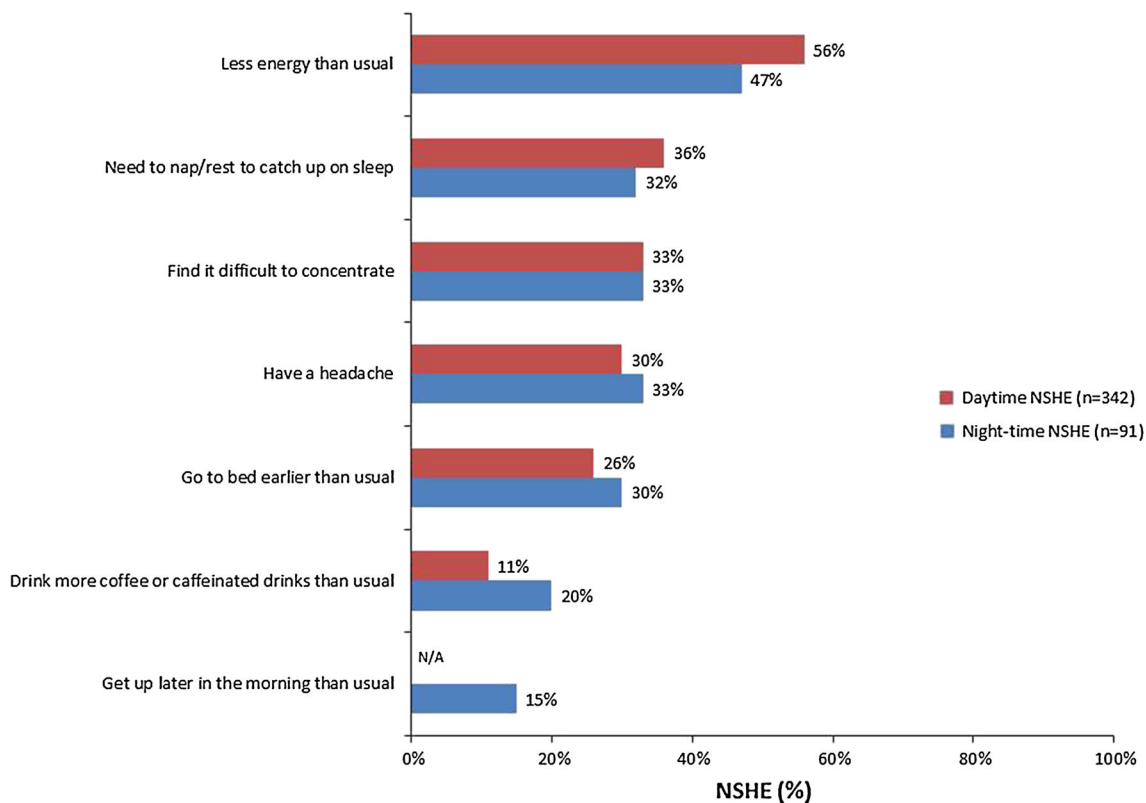
Fig. 1 The patient-reported impact of daytime and night-time non-severe hypoglycemic events in Type 1 Diabetes Mellitus and Type 2 Diabetes Mellitus patients combined. Base: All last events from respondents with at least one last event being a daytime ($n = 342$)/nighttime ($n = 91$) event in one of the waves. *N/A* not applicable, *NSHE* non-severe hypoglycemic event

which may partly explain the lower frequency of NSHEs. In T2DM, the frequency of NSHE also varies according to treatment regimen, although this is expected due to the different types of insulin coverage [14].

Self-Reported Hypoglycemia Awareness and Implications for SHEs

In the present study, the authors investigated levels of hypoglycemia awareness in Spain. Reports of unawareness were similar between T1DM (13%) and T2DM (14%) respondents, although impaired awareness was higher in T1DM respondents (42% versus 25%). This is consistent with the overall European findings [16]. Consideration should be given to respondent demographics when comparing awareness levels across respondent groups. For example, the prevalence of impaired awareness is reported to increase with diabetes duration in T1DM, [9] which may confound the results of this study. Further investigation with larger sample sizes is required to fully understand the complex relationship between diabetes duration, hypoglycemia awareness and NSHE frequency.

Impaired awareness has previously been reported as the most important risk factor for severe hypoglycemia [27]. The results of this study support this finding; T2DM respondents with impaired awareness reported significantly higher SHE frequencies ($p < 0.05$) than respondents who were aware of their hypoglycemia. This trend,

although not significant, was also seen for T1DM respondents. The statistical analysis of T2DM subgroups (T2BOT, T2BB, and T2O) may be inconclusive due to the small number of respondents with impaired awareness in each group. Further investigation with larger sample sizes is required to fully understand the trends for people receiving different insulin regimens.

Patient–Physician Communication Regarding Hypoglycemia and Corresponding NSHE Frequency

An interesting finding of this study is the higher patient–physician communication levels observed in Spain, compared to the overall European study [16]. The proportion of Spanish respondents who always/mostly inform their GP/specialist of a hypoglycemic event was nearly double that observed in the wider European study [16] (approximately 70–80% in Spain versus 35–50% in Europe). Furthermore, only a small proportion of respondents stated that their GP/specialist did not ask about hypoglycemia (10–16% in Spain, compared to 17–28% in Europe).

This study also analyzed trends in NSHE frequency according to patient communication of hypoglycemia. T2DM respondents who always/usually inform their GP/specialist about their hypoglycemia reported significantly ($p < 0.05$) higher NSHE frequencies than those who rarely/never inform their GP/specialist. Although causality cannot be established, these results suggest that patients who experience hypoglycemia more often are more likely to discuss their events with their physician (potentially in an attempt to improve their recognition and treatment of hypoglycemia; although this was not investigated as part of this study). Despite this, almost a third of patients surveyed in Spain

expressed reluctance to discuss their hypoglycemia, which may be due to wider factors such as concerns regarding driving privileges, [12] implications for employment, or fear that they may be perceived by their general practitioner/specialist to have poor control of their diabetes. Further research is needed to understand the reasoning behind why people may not actively be reporting their hypoglycemic events.

Patient-burden and Economic Impact of NSHEs

Unsurprisingly, NSHEs were shown to have a negative effect on respondent's physical and emotional well-being. The impact following a nighttime or a daytime NSHE was relatively similar across diabetes type. NSHE also altered a patient's daily routine, as a quarter of T1DM and a fifth of T2DM reduced their normal insulin dose following an NSHE. This is consistent with an average of 24.9% reported in a study by Brod et al. [19] in a study of 4 countries (USA, UK, Germany and France). Respondents may have altered their correct insulin dose following an NSHE in fear of a future hypoglycemic event, an avoidance behavior shown to be a substantial obstacle to appropriate diabetes management [28–30].

Another adaptive behavior demonstrated by diabetes patients, in this study and previous studies, is an increase in self-monitoring of glucose levels. Whilst this change in diabetes self-management behavior is an appropriate adaptive response which may help prevent new events in the short-term [12], it presents a direct cost burden through increased healthcare resource use (i.e., increase in BGM test-strip consumption). This burden could be alleviated if NSHE frequency was reduced through improved awareness and recognition of events.

The increase in BGM test-strip use in the week following an NSHE in this study (5.0–5.9) is comparable to that reported by Brod et al. in a study of 4 countries (5.6) [19]. The increase in BGMs following nighttime NSHEs in this study (6.5 in T1DM and 7.0 in T2DM) was similar to that reported by Spanish respondents in a study focusing on nighttime NSHE (6.8) [31]. An additional contributor to the direct cost burden of NSHEs in Spain is the resulting contact with HCPs.

Although direct costs associated with SHE are not reported in this study, the cost of an SHE to the Spanish healthcare system has previously been reported as €3,500 per event [11]. On average, 30% of respondents reported an emergency hospital visit following an SHE in this study, and 19% were admitted to hospital (16% T1, 25% T2). Considering the higher frequency of SHE reported in Spain compared to the European study, this could present a substantial burden on the Spanish healthcare system.

NSHE and SHE also present an indirect cost burden in Spain through lost work time. The percentage of NSHE reported to lead to lost work time in this study (18%) is the same as that reported by Brod et al. [19]. However, the amount of work time lost due to an NSHE was considerably lower in this study (1.5 h) compared to Brod et al. (9.9 h). This could be explained by this study encompassing NSHE which occurred outside work time, whereas Brod et al. [19] included only NSHE which occurred during working hours.

Comparison to Methodologies used in Other Publications

Methodological differences between this study and the UK Hypoglycemia Study Group study [15] relate to the recall period, patient subgroups, and the classification of hypoglycemia awareness. Patients in the UK Hypoglycemia Study recorded each hypoglycemic event as it occurred for 9–12 months [15], whereas this study used a 7-day recall period over 4 weeks. The recall period chosen for this study was supported by a previous study demonstrating that a respondent's ability to remember NSHE during the previous week was not significantly different from the prospective recording of events over 1 week [9]. Another study has shown that people with T1DM and people with T2DM are able to accurately recall severe hypoglycemic events within a 1-year period (corresponding with the recall period in the current study) [21]. In addition to collecting self-reported data, the UK Hypoglycemia Study recorded biochemical hypoglycemia through continuous glucose monitoring with a continuous glucose monitoring system (CGMS) [15]. Patient subgroups also varied— the UK study compared the frequency of hypoglycemic events on the basis of recent or prolonged duration of insulin therapy, plus use of sulfonylureas without insulin in T2DM respondents [15]. Finally, in the UK Hypoglycemia Study, patients rated their awareness of hypoglycemia symptoms on a scale from 1 to 7 (1 = full awareness, 7 = total unawareness) [15]. This study used three categories (unaware, impaired awareness, always aware), thereby enabling identification of the gradual loss of awareness, in contrast to the Clarke [32] and Gold [33] methods which use only two categories (aware/unaware). Whilst there is no consensus on how to classify awareness, the method used in this study is the only one proven to perform similarly across language barriers [34].

Study Limitations

The limitations of the study have been reported previously, by Östenson et al. [16]. A total of 10% of respondents with T1DM in Spain reported receiving long acting insulin only. Since long acting insulin as monotherapy should only be used in T2DM, this may indicate that some respondents with T2DM had incorrectly reported their condition as T1DM. If this is the case, the proposed study may underestimate the frequency of events in T1DM, since the respondents reported as having T2DM had fewer hypoglycemic events.

There is also the potential that the study duration may over- or underestimate the annual frequency of hypoglycemia, as seasonal variation is not considered (study conducted December to May). Self-reporting and anonymity also make validation of patient data impossible, and as the response rates for waves of the study diminished (90%, 84% and 80% of respondents completed wave two, three and four, respectively), the authors cannot rule out the possibility that later waves were completed by respondents who had more experience of hypoglycemic events.

CONCLUSION

This study shows that NSHEs are a common occurrence across people with T1DM and T2DM in Spain. Although communication levels between respondents and GP/specialists are higher than reported across Europe as a whole, respondents experience a similar frequency of NSHEs, demonstrating a need for patient education surrounding hypoglycemia management. The importance of improving glycemic control is evidenced by the negative impact on patient well-being and healthcare resource use in Spain that result from even non-severe events.

ACKNOWLEDGMENTS

Ethics Committee or Independent Review Board approval.

This article does not contain any new studies with human or animal subjects performed by any of the authors.

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

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