Diabetes Ther (2019) 10:375–392
https://doi.org/10.1007/s13300-019-0563-0

REVIEW

Epidemiology, Quality of Life, and Costs Associated with Hypoglycemia in Patients with Diabetes in Spain: A Systematic Literature Review

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Received: November 6, 2018 / Published online: January 19, 2019

ABSTRACT

Objective: To assess the burden of hypoglycemia in patients with diabetes mellitus (DM) in Spain, including epidemiological data and information relating to healthcare resource utilization (HRU) and costs, and patients' quality of life (QoL).

Methods: A systematic literature review (SLR) was conducted to identify studies that included original information on epidemiology, HRU and costs, and/or QoL associated with hypoglycemia in patients with DM in Spain, published in either Spanish or English, between January 2007 and April 2017.

Results: Fifteen articles, involving 14 studies, were identified in the SLR and included in the analysis. The estimated rate of severe hypoglycemia (SH) events per patient per year ranged from 0.90 to 1.50 in patients with type 1 DM (T1DM) and from 0.30 to 0.63 in patients with type 2 DM (T2DM). The data on HRU differed extensively between studies, making it difficult to draw a conclusion. Total costs per SH event ranged from €409.97 in patients with T1DM to €713.10 in patients with DM. Work absence was reported in 11.80–18% of the working patients. Further, patients who experienced hypoglycemic events expressed a higher fear and had a poorer QoL than those who did not report these events.

Conclusion: Although the data included in the SLR were difficult to synthesize due to heterogeneity of the study designs and patient characteristics in the 14 studies, our search identified a high burden associated with hypoglycemic events in terms of HRU and costs, and patients' QoL. Further research is recommended to reach a consensus on hypoglycemia definition and study design to provide robust evidence on the burden of hypoglycemia and to accurately weigh the impact of this acute complication in Spain.

Funding: Eli Lilly and Company.

Keywords: Diabetes mellitus; Hypoglycemia; Observational studies; Spain; Systematic literature review

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INTRODUCTION

Diabetes mellitus (DM) is a group of metabolic disorders characterized by chronic hyperglycemia that develops because of insufficient

insulin secretion, reduced responsiveness to insulin, or both [1]. The eighth edition of the International Diabetes Federation (IDF) 2017 Diabetes Atlas, a global reference report, estimates that 424.90 million (8.80%) adults were affected by DM in 2017 globally. This number is estimated to increase to 628.60 million (9.90%) by 2045 [2]. A survey was conducted in 2009–2010 with the aim to quantify the prevalence of DM in Spain [3]; at that time it was estimated that DM affected 13.80% of the population and that these numbers would likely increase given estimated global figures [4]. In addition, global expenditure attributable to the care of DM patients has become an enormous economic burden on healthcare services, reaching US $727 billion in 2017 [2]. Projections in Spain reveal a comparable growth in upcoming years in the expenditure of the Spanish healthcare system for the care of DM patients [5–7]. Moreover, these predictions may worsen since the available estimations are usually described for patients who have been diagnosed with diabetes and do take into account the significant number of undiagnosed diabetic cases [8]. The most distressing consequence of DM appears to be its late complications. However, hypoglycemia, one of the acute complications of DM [9], also significantly impacts disease management, patients' quality of life (QoL), and costs [8, 10].

Insulin and a number of other glucose-lowering drugs may cause hypoglycemia. According to the recommendations of the International Hypoglycemia Study Group [11], a hypoglycemia alert value of $\leq$ 70 mg/dL (3.90 mmol/L) is often related to symptomatic hypoglycemia and can be an considered important value for therapeutic dose adjustment of glucose-lowering drugs for patients in clinical care. Further, a blood glucose level of $<$ 54 mg/dL (3.00 mmol/L) is considered sufficiently low to indicate clinically significant hypoglycemia. Severe hypoglycemia (SH) is defined as severe cognitive impairment requiring assistance from another person for recovery [11].

Symptoms attributed to hypoglycemia are categorized as neurogenic (autonomic) or neuroglycopenic [12]. Depending on its severity or duration, hypoglycemia can lead to seizure or coma, and ultimately death. Recent post hoc analyses of the ACCORD, ADVANCE and DEVOTE 3 trials, all of which examined the outcomes of intensive glycemic control, revealed a high association between SH and significantly higher rates of death [13–15]. For all of these reasons, these SH episodes are associated with considerable costs, both to the individual and to the healthcare system [16], and they also contribute to significant reductions in QoL in patients with DM and to a fear of hypoglycemia [17].

Despite the importance of being aware of this information for the correct management of hypoglycemia, none of the studies to date in the Spanish landscape have collected integrated data related to the burden of hypoglycemia. The aim of this systematic literature review (SLR) was to review available data in order to assess the burden of hypoglycemia in terms of its epidemiology, healthcare resource utilization (HRU), costs, and QoL in patients with DM in Spain.

METHODS

This SLR was planned, conducted, and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Two independent reviewers screened each retrieved record to identify potentially relevant articles for the full-publication review. A third senior researcher arbitrated in case of any doubt on eligibility or disagreement between the two primary reviewers.

The SLR included observational studies conducted in Spain published between January 2007 and April 2017 that involved patients with any type of diabetes and which present original information on epidemiology, costs, HRU and/or QoL of patients with hypoglycemia. Both English and Spanish language publications were included in the search. Articles not presenting original data (such as SLR, reviews, letters to the editor, etc.), clinical trials, cost-effectiveness models, and abstracts or congress communications, and those studies that present

hypoglycemia data associated with a specific drug or intervention were not included in our SLR.

Articles that reported costs were actualized to the corresponding value in euros in 2016 using the CCEMG-EPPI-Centre Cost Converter tool in order to enable meaningful comparisons between costs [18].

A comprehensive search strategy was developed for the databases: Ovid (Embase + MEDLINE) and MEDES (Spanish bibliographic database). The corresponding search strategies used are presented as follows:

- MEDES (https://www.medes.com/Public/Home.aspx): (((hipoglucem*[título] OR hipoglucem*[resumen] OR hipoglucem*[palabras_clave]) AND ((epidemiologia[título] OR epidemiologia[resumen] OR epidemiologia[palabras_clave]) OR (incidencia[título] OR incidencia[resumen] OR incidencia[palabras_clave]) OR (prevalencia[título] OR prevalencia[resumen] OR prevalencia[palabras_clave]) OR (calidad[título] OR calidad[resumen] OR calidad[palabras_clave]) OR (vida[título] OR vida[resumen] OR vida[palabras_clave]) OR (carga[título] OR carga[resumen] OR carga[palabras_clave]) OR (coste*[título] OR coste*[resumen] OR coste*[palabras_clave]) OR (econom*[título] OR econom*[resumen] OR econom*[palabras_clave])))) AND (2007[año_publicación]: 2017[año_publicación])
- Ovid (http://link.am.lilly.com/sites/link/DataSources/Pages/EMBASE.aspx): Database: Embase <1974–2017 April 17> ; Ovid MEDLINE(R) <1946 to April Week 1 2017>.
  1. exp *nocturnal hypoglycemia/or exp *hypoglycemia/or exp *insulin hypoglycemia/(41,684)
  2. Item 1 or hypoglyc*.ti. (51,796)
  3. (spain OR espagne OR espana OR spain OR espagne OR espana OR osasunbide* OR osakidetza OR insalud OR sergas OR catalunya OR catalonia OR catalogne OR cataluna OR catala OR barcelon* OR tarragona OR lleida OR lerida OR girona OR gerona OR sabadell OR hospitalet OR l'hospitalet OR valencia* OR castello* OR alacant OR alicant* OR murcia* OR andalu* OR sevill* OR granad* OR huelva OR almeria OR cadiz OR jaen OR malaga OR [cORdoba not argentin*] OR extremadura OR caceres OR badajoz OR madrid OR castilla OR salamanca OR zamORa OR valladolid OR segovia OR sORia OR palencia OR avila OR burgos OR [leon not {france OR clermont OR rennes OR lyon OR USA OR mexic*}] OR galicia OR gallego OR compostela OR vigo OR cORuna OR ferrol OR ORense OR ourense OR pontevedra OR oviedo OR gijon OR asturia* OR cantabr* OR santander OR vasco OR euskadi OR basque OR bilbao OR bilbo OR donosti* OR san sebastian OR vizcaya OR biscaia OR guipuzcoa OR gipuzkoa OR alava OR araba OR vitORia OR gazteiz OR navarr* OR nafarrona OR pamplona OR iruna OR irunea OR aragon* OR zaragoza OR teruel OR huesca OR mancha OR ciudad real OR albacete OR cuenca OR [toledo not {ohio OR us OR usa OR OH}] OR (guadalajara not mexic*) OR balear* OR mallORca OR menORca OR ibiza OR eivissa OR palmas OR lanzarote OR canari* OR tenerife).mp. (223,672)
  4. Items 2 and 3 (140)
  5. Limit 4 to year = "2007–2017" (103)
  6. 5 not clinical trial/(93)
  7. Limit 6 to (conference abstract or conference paper or conference proceeding or "conference review" or editorial) [Limit not valid in Ovid MEDLINE(R); records were retained] (18)
  8. 6 not 7 (75)

The reviewers collected the following information from each article selected in the SLR.

1. Variables which described the main methodological characteristics, including the study design, information on follow-up and data collection, sample inclusion criteria, type of DM, number of patients in the study, mean age of the patients, mean duration of the DM, time frame to record hypoglycemia, severity of the hypoglycemic event reported, and healthcare system setting.
2. Epidemiology variables, comprising frequency of SH and non-severe hypoglycemia (NSH), hypoglycemic events per year for SH

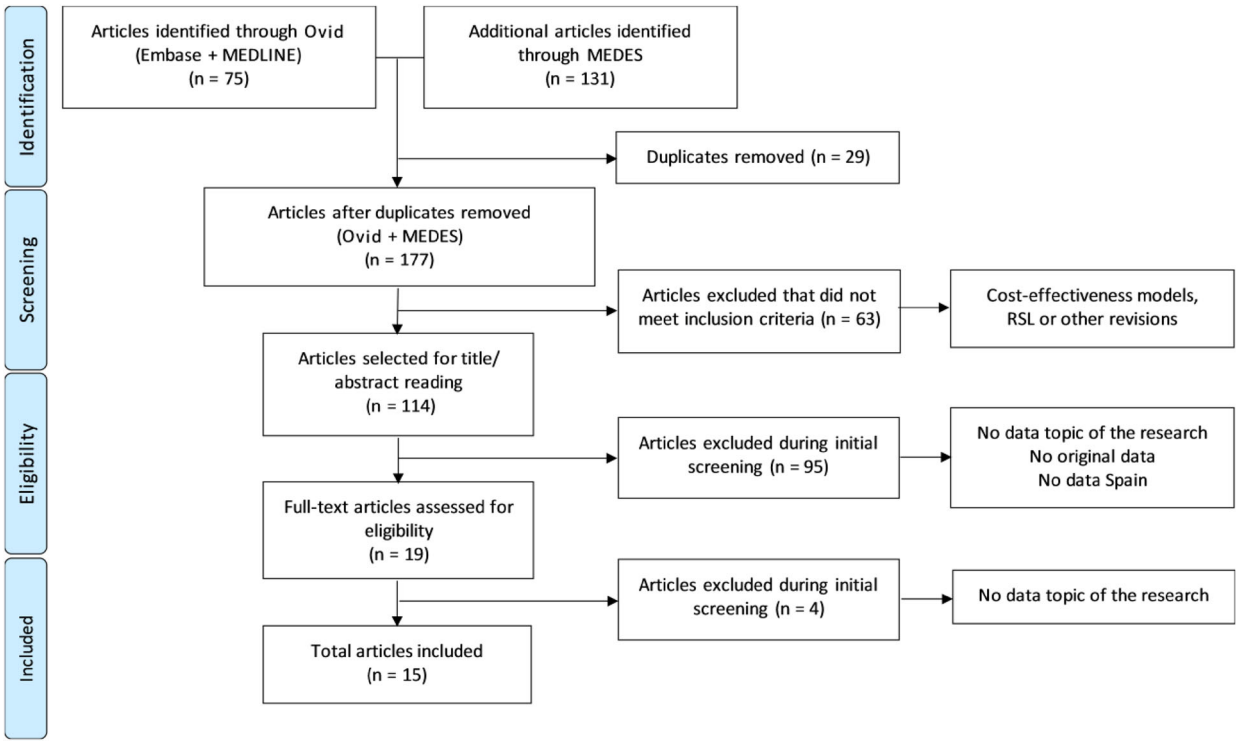

Fig. 1 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram

and NSH, and frequency of nocturnal hypoglycemia.
3. HRU and costs' variables, involving HRU per hypoglycemic event, costs related to hypoglycemia (direct and indirect costs), total costs, and information on impact at work.
4. QoL variables, including questionnaires used and main results, i.e., the scores for the hypoglycemic population versus the defined control population in each article and statistical significance of the comparison.

Ethical approval was not required since this article is based on previously conducted studies and did not involve experiments with animals or humans performed by any of the authors.

RESULTS

The search strategy identified 206 references (75 from Ovid and 131 from MEDES), of which 15 publications involving 14 studies were included in the analysis after the systematic review process (Fig. 1).

Description of the Selected Studies in the SLR

Of the 15 publications (14 studies) included in the SLR, six studies focused exclusively on data from patients with type 2 DM (T2DM) [19–24] and five studies reported combined data from patients with either type 1 DM (T1DM) or T2DM [25–30]. Only two studies highlighted data exclusively for patients with T1DM [31, 32], and one study reported neonatal hypoglycemia [33]. All of the studies collected data retrospectively employing a cross-sectional study design, with the exception of one study that used a longitudinal study design [22]. The majority of the studies reported the management of hypoglycemia events at either hospitals or a primary care setting; the exceptions were two studies that presented data from specialized care and emergency service settings [24, 29] and

two studies that did not report the study settings [26–28].

The number of patients in the studies ranged widely, from 100 in a study determining the costs of SH in patients with T1DM [31] to 5,447,725 clinical records from the basic minimum data set (BMDS) registry of the Spanish National Health System that includes general information on patients with DM [30]. The mean age of patients with T1DM ranged from 33.20 to 33.90 years, while studies reporting data for patients with T2DM included patient populations with a mean age ranging from 64 to 79.70 years. However, a wide-ranging mean age was observed in studies presenting data of patients with either T1DM or T2DM, from 39.90 to 70.20 years. The mean duration of the disease in patients with T1DM and T2DM ranged from 16.50 to 18.50 and from 8.40 to 20 years, respectively. One of the studies included in the SLR focused exclusively on neonatal hypoglycemia; the aim of this study was to determine whether an association exists between maternal pre-pregnancy body mass index category and the occurrence of neonatal hypoglycemia among infants born to women with gestational DM [33].

Epidemiology of Hypoglycemia

Table 1 presents the epidemiology data on hypoglycemia detailed in the studies selected for inclusion in this SLR (15 publications).

Type 1 Diabetes Mellitus

The average number of hypoglycemia episodes per patient was reported in three studies. Reviriego et al. recorded a mean of 2.99 SH events per patient per 2-year period, with a higher number of overall hypoglycemic episodes (54.40 events/patient/2 years) [31]. Orozco-Beltrán et al. reported an annual frequency of 0.90 events for SH and 1.70 NSH events per week, or an annual frequency of 88 NSH events [26]. Carral et al. reported a mean of 7.40 events (SH or NSH) per patient in 1 month [32].

Type 2 Diabetes Mellitus

The frequency of hypoglycemic events was described in eight studies. An incidence of 1.82 episodes per 10,000 patients per year for SH was reported by Lindner et al. [25]. Orozco-Beltrán et al. reported an annual frequency of 0.30–0.40 events per year for SH, and 18.30–42.10 events per year for NSH [26]. Three studies described the incidence of SH as the percentage of patients who experienced an episode in 1 year, namely, 6.80% [20], 1.90% [21] and 0.56% [23], with the setting of the first two studies being primary care and that of the third study being the hospital.

In the study of Pérez et al., 93.20% of patients reported NSH or no hypoglycemia in a 1-year period [20], while Depablos-Velasco et al. reported that 9.60% of patients had NSH in the previous month [21]. A small number of studies did not differentiate between SH and NSH in these patients. Durán-Alonso et al. reported that 15.70% of patients in nursing homes experienced symptomatic hypoglycemia [19]. In a 2-year study by Sicras-Mainar et al., 37.70% of patients reported at least an episode of hypoglycemia [22], and Jódar-Gimeno et al. reported that 45% of patients experienced hypoglycemia in the previous 6 months [24].

Nocturnal Hypoglycemia

The epidemiologic data for nocturnal hypoglycemia were analyzed from three studies. Barranco et al. employed Public Company for Health Emergencies Service (EPES; Andalusian emergency service) data and noted that there were 2297 nocturnal SH episodes in a 1-year, which translated into 0.34 episodes per hour that required the assistance of emergency services [29]. Brod et al. explored the impact of nocturnal NSH events in similar patients who experienced an event in the past month and reported a mean of 21.60 nocturnal NSH events in 1 year [27]. In terms of nocturnal hypoglycemia according to the type of diabetes, the proportion of NSH events occurring at night was 26% in T1DM patients and 30–32% in T2DM patients recorded in the previous week [26].

Table 1 Summary of the epidemiology data reported in the studies included in the systematic literature review

Studies/references	Study design		Period to register hypoglycemia	Study entry criteria (cases)	Healthcare system setting	Number of patients	Mean age (years)[a]
	According to follow-up	According to data collection					
T1DM							
Reviriego et al. [31]	Retrospective	Cross-sectional	2 years	Patients who experienced at least one SH	Hospital	100	33.22 ± 12.17
Carral et al. [32]	Retrospective	Cross-sectional	1 month	16 to 60 year-old patients with T1DM (at least 12 months)	Hospital (endocrinologist)	130	33.90 ± 11.50
T2DM							
Durán Alonso et al. [19]	Retrospective	Cross-sectional	NA	Elderly patients with T2DM	PC (nursing homes)	312	79.70
Pérez et al. [20]	Retrospective	Cross-sectional	1 year	≥ 18 year-old patients with T2DM (at least 12 months)	PC	5382	66.70 ± 10.80
Depablos-Velasco et al. [21]	Retrospective	Cross-sectional	1 year	≥ 40 year-old patients with T2DM (at least 12 months)	PC	751	67.70 ± 9.90
Sicras-Mainar et al. [22]	Retrospective	Longitudinal	2 year	≥ 40 year-old patients with T2DM (at least 12 months)	PC and hospital	3760	67.80 ± 11.30
Alonso-Morán et al. [23]	Retrospective	Cross-sectional	1 year	Patients with T2DM or unspecified	Hospital	134,413	–
Jódar-Gimeno et al. [24]	Retrospective	Cross-sectional	6 months	≥ 18 year-old patients with DM (at least 12 months), receiving treatment	PC and specialized care	3812	64 ± 11
T1DM and T2DM							
Lindner et al. [25]	Retrospective	Cross-sectional	1 year	Hospitalizations due to SHE obtained from BMDS	Hospital	3,254,464	–
Orozco-Beltrán et al. [26]	Retrospective	Cross-sectional	7 previous days (NSHE) and 1 year (SHE)	> 15 year-old patients with DM, receiving insulin	–	630	T1DM: 39.90 ± 12.80 T2DM: 63.50 ± 15.10
DM							
Brod et al. [27]	Retrospective	Cross-sectional	1 month	≥ 18 year-old patients, with DM, who presented at least one episode of NSNHE the last month	–	242	42.20 ± 11.90
Brod et al. [28]	Retrospective	Cross-sectional	1 month	≥ 18 year-old patients, with DM, who presented at least one episode of NSNHE the last month	–	242	42.20 ± 11.90

Table 1 continued

Studies/references	Study design		Period to register hypoglycemia	Study entry criteria (cases)	Healthcare system setting	Number of patients	Mean age (years)[a]
	According to follow-up	According to data collection					
Barranco et al. [29]	Retrospective	Cross-sectional	1 year	All registered emergency calls in Andalusia	Emergency service	8683 emergency calls for hypoglycemic event	66 ± 20.20
Gómez-Huelgas et al. [30]	Retrospective	Cross-sectional	14 years	Discharges with diabetes obtained from BMDS	Hospital	5,447,725	70.20 ± 13.90
Neonatal							
García-Patterson et al. [33]	Retrospective	Cross-sectional	20 years	Pregnancies with GDM with a gestational age > 22 weeks	Hospital	2029 newborns	Maternal 33 (17–46)

Studies/references	Mean duration of diabetes (years)[a]	Hypoglycemia frequency		Total number of hypoglycemic events/year		Nocturnal hypoglycemia
		SHE	NSHE	SHE	NSHE	
T1DM						
Reviriego et al. [31]	16.90 ± 10.90	Mean: 2.99	events/patient/2 years (1.50 events/patient/year[b]) Median: 2/patient/2 years (1/patient/year[b])	–	–	
	Mean: 54.40 events/patient/2 years (27.20 events/patient/year[b]) Median: 24/patient/2 years (12/patient/year[b])	–				
Carral et al. [32]	16.50 ± 9.50	7.40 events/patient ± 5.80 in the last month		–		–
T2DM						
Durán Alonso et al. [19]	66.90% ≥ 10 years 25.40% ≥ 5 years 6.10% ≤ 5 years 1.60% ≤ 1 year	15.70% (symptomatic)		–		–
Pérez et al. [20]	8.80 ± 6.30	6.80%	93.20% (NSHE or not hypo)	–		–
Depablos-Velasco et al. [21]	8.40 ± 6.50	1.90% (≥ 1/year)	9.60% (> 1/month)	–	–	–
Sicras-Mainar et al. [22]	8.50 ± 3.50	37.70% (need medical attention)		–		–

Table 1 continued

Studies/ references	Mean duration of diabetes (years)[a]	Hypoglycemia frequency		Total number of hypoglycemic events/year		Nocturnal hypoglycemia
		SHE	NSHE	SHE	NSHE	
Alonso-Morán et al. [23]	–	0.56%	–	0.63		episodes/patient
–	–					
Jódar-Gimeno et al. [24]	10 ± 7	45%		–		
T1DM and T2DM						
Lindner et al. [25]	–	–	–	0.82% T2DM: 1.82 per 10,000	–	–
Orozco-Beltrán et al. [26]	T1DM: 18.50 ± 11 T2DM: 20 ± 16.40	–	T1DM: 1.70 events/week T2DM: 0.40-0.80 events/week	T1DM: 0.90 events/year T2DM: 0.30-0.40 events/year	T1DM: 88 events/year T2DM: 18.30-42.10 events/year	T1DM NSHE: 26% T2DM NSHE: 30–32%
DM						
Brod et al. [27]	10.20 ± 8.50	–	100%	–		100%
Brod et al. [28]	10.20 ± 8.50	–	100%	–		100% (21.60 events/year)
Barranco et al. [29]	–	–	–	General population: 10.34 episodes per 10,000 person/year DM patients: 80 (78-83) episodes per 10,000 person/year	–	No. of patients: 2297 Nocturnal SHEs: 0.34 episodes per hour of all urgencies registered
Gómez-Huelgas et al. [30]	–	1.70% discharges with primary	hypoglycemia 2.80% with secondary hypoglycemia	–	–	
–						

Table 1 continued

Studies/references	Mean duration of diabetes (years)[a]	Hypoglycemia frequency		Total number of hypoglycemic events/year		Nocturnal hypoglycemia
		SHE	NSHE	SHE	NSHE	
Neonatal						
García-Patterson et al. [33]	–	3%		–		–

BMDS Basic minimum data set, *DM* diabetes mellitus, *GDM* gestational diabetes mellitus, *NSHE* non-severe hypoglycemic event, *NSNHE* non-severe nocturnal hypoglycemic event, *PC* primary care, *SHE* severe hypoglycemic event, *T1DM* Type 1 DM, *T2DM* Type 2 DM

[a] Standard deviation

[b] Calculated

Resource Utilization and Costs

Table 2 summarizes information on HRU and costs associated with hypoglycemia obtained in the SLR (11 articles involving 10 studies) [20, 22–31].

Severe Hypoglycemia

Sicras-Mainar et al. reported that 0.50% of patients with T2DM needed to be hospitalized, among whom 1.00% had to be treated in the specialized care departments, and 34.10% attended medical visits in primary care settings over a period of 2 years [22]. Lindler et al. reported that 6.34% and 5.01% of the patients with T1DM and T2DM, respectively, required hospitalization [25]. Orozco-Beltrán et al. reported that among the respondents with either T1DM or T2DM, 30% required emergency hospital visits and 19% were admitted to hospital because of their hypoglycemia [26].

In terms of costs associated with patients with T1DM, Reviriego et al. reported an overall mean cost per episode of €409.97, of which 65.40% were direct costs and 34.60% were indirect costs [31]. These authors found that the highest costs were due to hospitalization (€204.98 per episode), representing 50% of the total costs [31]. Alonso-Morán et al. provided data on patients with T2DM [23]. These authors observed that the average overall cost per patient with T2DM was higher in a patient who had experienced one or more hypoglycemic episodes than in a patient who did not experience any such episode. The results presented by these authors were differentiated by gender and were specifically related to primary care, prescriptions, specialized care, emergencies and hospitalizations [23]. Barranco et al. recorded an estimated mean direct cost of €713.10 per episode in patients with either T1DM or T2DM. These costs increased if the hypoglycemia was nocturnal or if it required emergency hospital care or caused loss of consciousness [29].

Severe and Non-Severe Hypoglycemia

In the study by Pérez et al., a total of 6.80% of patients with T2DM required medical attention in the preceding year, of whom 0.50 and 4.60%

Table 2 Summary of the healthcare resource utilization and costs related to hypoglycemia events reported in the studies included in the systematic literature review

Studies/ references	Type of hypoglycemia	Follow-up period	Number of patients/cases	Healthcare resources utilization/ hypoglycemia	Costs related to hypoglycemia			Work impact
					Direct costs	Indirect costs	Total costs	
T1DM								
Reviriego et al. [31]	SHE	2 years	100		Cost per SHE: Hospitalization: €204.98 Diagnosis: €12.32 Medication: €5.60 Other: €45.93	Cost per SHE: €142.26	Cost per SHE: €409.97	
T2DM								
Pérez et al. [20]	SHE/NSHE	1 year	5382	Medical attention: 6.80% Hospitalization: 0.50% Outpatient care: 4.60% Unspecified: 1.70%				
Sicras-Mainar et al. [22]	SHE	2 years	3760	PC: 34.10% Hospitalization: 0.50% ED: 1%				
Alonso-Morán et al. [23]	SHE	1 year	134,413		Annual cost per patient who suffered ≥ 1 HE: PC: M: €1049.83 W: €1160.61 Prescriptions: M: €1419.76 W: €1570.18 Specialized care: M: €1268.34 W: €1513.26 ED: M: €432.94 W: €439.04 Hospitalization: M: €7085.61 W: €6076.43		Total healthcare annual cost per patient who suffered ≥ 1 HE, by sex: M: €11,257.50 W: €10,759.52 On average an SHE accounted for additional €2549.88 in annual healthcare costs	

Table 2 continued

Studies/ references	Type of hypoglycemia	Follow-up period	Number of patients/cases	Healthcare resources utilization/ hypoglycemia	Costs related to hypoglycemia			Work impact
					Direct costs	Indirect costs	Total costs	
Jódar-Gimeno et al. [24]	SHE/NSHE	6 months	3812	Hospitalization: 11% (mean: 1.63 visits) ED: 26% (mean: 1.86 visits)				Work absences: 14% of patients
T1DM and T2DM								
Lindner et al. [25]	SHE	1 year	3,254,464 hospitalizations due to SHE	Hospitalization: T1DM: 6.34% T2DM: 5.01%				
Orozco-Beltrán et al. [26]	SHE/NSHE	7 previous days (NSHE) and 1 year (SHE)	630	SHE: Hospitalization: 19% ED: 30% NSHE: PC: 8% daytime and 12% nocturnal (T1DM) PC: 20% (T2DM)	Test strips by event: €1.32			T1DM NSHE: 18% lost work time (mean: 1.50 h/event) T2DM NSHE: 15% lost work time (mean: 1 h/event)
DM								
Brod et al. [27]	NSNHE	1 month	242	HCP: 24%			–	
Brod et al. [28]	NSNHE	1 month	242	HCP: 24%	Yearly cost for fall: €686.83	Cost per NSHE: €357.45	Annual economic burden of the sample: €32810.65	11.80% patients missed a mean of 10.40 h of working time

Table 2 continued

Studies/ references	Type of hypoglycemia	Follow-up period	Number of patients/cases	Healthcare resources utilization/ hypoglycemia	Costs related to hypoglycemia			Work impact
					Direct costs	Indirect costs	Total costs	
Barranco et al. [29]	SHE	1 year	8683 emergency calls for HE	After emergency call: 13.83% events solved over the phone 85% required domiciliary assistance by emergency team After receiving domiciliary assistance: 21% of patients required hospital referral (24.10% M and 19.40% W)	Cost per SHE: Emergency care in place or residence: €471.34 ± 277.32 Transfer to hospital: €30.47 ± 74.15 Emergency hospital care (< 24 h): €211.29 ± 414.45 Cost per nocturnal SHE: Emergency care in place or residence: €481.50 ± 255.99 Transfer to hospital: €24.38 ± 69.08 Emergency hospital care (< 24 h): €172.69 ± 383.98 Cost per SHE requiring emergency hospital care: Emergency care in place or residence: €532.29 ± 315.92 Transfer to hospital: €145.26 ± 99.55 Emergency hospital care (< 24 h): €1025.98 ± 0 Cost per SHE causing loss of consciousness: Emergency care in place or residence: €656.22 ± 268.18 Transfer to hospital: €38.60 ± 76.19 Emergency hospital care (< 24 h): €333.19 ± 480.48		Cost per SHE, by type: SHE: €713.10 ± 573.94 Nocturnal: €678.57 ± 11.17 Requiring emergency care: €1703.53 ± 308.81 Loss of consciousness: €1028.01 ± 610.51	

Table 2 continued

Studies/references	Type of hypoglycemia	Follow-up period	Number of patients/cases	Healthcare resources utilization/hypoglycemia	Costs related to hypoglycemia			Work impact
					Direct costs	Indirect costs	Total costs	
Gómez-Huelgas et al. [30]	SHE/NSHE	14 years	5,447,725 discharges with a diagnosis of diabetes obtained from BMDS (1.70% primary hypoglycemia and 2.80% secondary hypoglycemia)	Mean of stay in hospital: Primary hypoglycemia: 9.01 (11.72) days Secondary hypoglycemia: 12.04 (13.40) days				

ED Emergency department, *HCP* healthcare professional, *M* men, *W* women
Where applicable, data are reported as the mean ± standard deviation

required hospitalization and outpatient care, respectively [20]. Jódar-Gimeno et al. reported that 11 and 26% of patients with T2DM required a mean of 1.63 ± 1.34 (± standard deviation) hospitalizations and 1.86 ± 1.32 emergency department visits in the preceding 6 months [24].

Impact at Work

Analysis of the data on amount of working time lost revealed that among employed respondents with T1DM, 18% of NSH events led to lost work time of approximately 1.50 h per event. In T2DM patients, 15% of NSH events led to lost work time of approximately 1 h per event [26]. Brod et al. showed that 11.80% of patients with DM experienced nocturnal NSH events that led to a mean of 10.40 h of lost work time per month [28].

Quality of Life

The QoL and fear of hypoglycemia data obtained in two studies [21, 24] through the use of validated questionnaires are shown in Table 3. The authors of these studies assessed data only from patients with T2DM who experienced both SH and NSH.

In a study by Depablos-Velasco et al., patients with at least one SH or more than one NSH per month in the past year had a poorer QoL than did patients with no such events, as concluded from the results obtained from the Audit of Diabetes-Dependent QoL (ADDQoL) questionnaire [21]. No statistical significance was reached in the treatment satisfaction results obtained from the Diabetes Treatment Satisfaction Questionnaire (DTSQ). However, a significantly greater fear of hypoglycemia was observed for both groups of patients, those with at least one SH and those with one or more than one NSH per month in the past year, than for patients with no such events (results from the Hypoglycemia Fear Survey [HFS-II]) [21]. Jódar-Gimeno et al. showed that patients with hypoglycemia expressed a higher fear for hypoglycemia than those who did not experience hypoglycemia; the difference was statistically significant (results from HFS-II), and the overall

Table 3 Summary of the quality of life data reported in the studies included in the systematic literature review

Studies/references	Type of diabetes	Number of patients	Health-related QoL questionnaires								
			ADDQoL[a]			DTSQ[b]			HFS-II[c]		
			Control population	Hypo population	*p* value	Control population	Hypo population	*p* value	Control population	Hypo population	*p* value
Depablos-Velasco et al. [21]	T2DM	751	< 1 SHE: − 1.80 (1.90)	≥ 1 SHE: − 2.80 (2.10)	0.049	< 1 SHE: 29.30 (6.00)	≥ 1 SHE: 26.90 (7.10)	0.157	< 1 SHE: 10.90 (14.40)	≥ 1 SHE: 24.10 (22.10)	0.003
			≤ 1 NSHE/month: − 1.80 (1.90)	> 1 NSHE/month: − 2.00 (1.80)	0.405	≤ 1 NSHE/month: 29.40 (6.10)	> 1 NSHE/month: 28.50 (5.30)	0.238	≤ 1 NSHE/month: 10.60 (14.50)	> 1 NSHE/month: 16.90 (14.50)	0.001
Jódar-Gimeno et al. [24]	T2DM	3812	Patients without hypoglycemia: − 1.64 (1.36)	Patients with hypoglycemia: − 2.48 (1.61)	< 0.001	–	–	–	Patients without hypoglycemia: 18.85 (16.03)	Patients with hypoglycemia:31.32 (15.71)	< 0.001

QoL Quality of Life, *SHE* severe hypoglycemia event (in past year)
[a] ADDQoL: The Audit Diabetes Dependent Quality of Life questionnaire. Mean score obtained from the 19 items, indicating the mean impact of diabetes on the patients' health-related QoL. Scores range from − 9 (maximum negative impact) to 3 (maximum positive impact)
[b] DTSQ: Diabetes Treatment Satisfaction Questionnaire. Scores range from 0 (very dissatisfied) to 36 (very satisfied)
[c] HFS-II: Hypoglycemia Fear Survey-II. Higher scores indicate increased fear

impact on their QoL was more negative in this population ($p < 0.001$ [results from the ADDQoL]) [24].

DISCUSSION

This SLR provides an overview of the burden of hypoglycemia in patients with DM in Spain based on data published in the literature in the last 10 years by reporting information on the rate of hypoglycemia and on its impact on HRU and costs, and patients' QoL. The search strategy was robust and focused on collecting extensive and elaborate data. However, due to the observational nature and heterogeneity of the included studies, further high-quality prospective studies are necessary to accurately establish the burden of hypoglycemia in patients with DM in Spain.

The quality of the studies was not evaluated because the majority of articles selected in the search were observational studies, with different designs and objectives, making it difficult to use any assessment tool. This difficulty is due to the fact that most questionnaires available in the literature have been designed for assessing the quality of observational studies, having been developed mainly for comparative research between specific types of design or different intervention arms, which was not the objective of this study [34–36].

The data collected in the search showed a wide heterogeneity, possibly due to the large variety in study design, participants' inclusion criteria, study period and strategy used to register hypoglycemia (such as percentage of the sample in a specific timeframe, rates of events per unit of time, etc.), in addition to a lack of consensus in the definition of hypoglycemia. This led to a large variation in the results that detailed the estimated burden and costs of hypoglycemia.

The data observed in our analysis seem to be comparable to the results of a recent structured literature review by Elliott et al. [37]. These authors identified hypoglycemic event rates in patients with T1DM and T2DM and categorized them according to the insulin regimen. In patients with T1DM, SH rates ranged from 0.70

to 1.59 episodes per patient per year, and NSH rates ranged from 91.00 to 136.80 episodes per patient per year. In patients with T2DM, SH rates ranged from 0 to 0.20 episodes per year; further, NSH ranged from 0.22 to 38.90 episodes per year depending on the insulin regimen [37]. Although these data cannot be directly compared with the results of our analysis, we did observe some degree of similarity in the numbers extracted in our search and global figures reported by Elliott et al. [37]. We postulate that standardizing the definition of hypoglycemic measures could help in the systematic collection of information, thereby enabling comparison of burden of this complication across countries [38].

Additionally, hypoglycemia has been considered to cause significant consequences that depend on the severity and duration of the episodes. Hypoglycemia has been shown to result in cardiovascular [39] and cognitive impairment, as well as falls, fall-related fractures, among other events, in certain populations, such as pediatric and elderly populations [40, 41]. Further, the cognitive impairment in these populations could worsen the development of functional cognition. On the other hand, cardiovascular impairment may worsen the morbidity associated with hypoglycemia and lead to increased mortality due to sudden death syndrome [30, 40]. Further, the importance of appropriately managing nocturnal hypoglycemia is well-known as poor management leads to increased costs and resources, fear, anxiety, poor QoL, and a number of potential clinical consequences, including convulsions and coma and even death [42]. It has been well documented that hypoglycemia may lead to emergencies and hospitalization, resulting in an increased economic burden on patients with DM. Differences in study designs, timeframe, health system setting, etc. have hampered the comparability of results between studies. We were unable to draw any meaningful comparisons in terms of hospitalization rate, direct and indirect costs in patients experiencing SH versus NSH due to the heterogeneity of the studies. However, these data are comparable with the results in the literature highlighting that the more severe the hypoglycemic events, the higher the associated costs and HRU and the worse the QoL. A recent study in Italy collected data on cases with an established diagnosis of hypoglycemia in emergency departments. The results demonstrated that SH in patients with DM contributes substantially to the economic burden on national healthcare systems [43]. Another study assessed the total annual, direct, and indirect cost of SH events in nine European countries, including Spain. This study, conducted in 2016, reported an annual total cost for single SH event of €1076.05, €209.28 and €0.46 for hospital-treated, medical professional-treated and family-treated SH events in Spain, which in terms of the whole population affected translates into €32,339,530.58, €19,513,354.64 and €94,856.70, respectively [44]. Taking these figures into consideration, the prevention of hypoglycemia is essential in DM management programs given its impact on patients and on healthcare systems. Failure to account for these costs may underestimate management strategies that minimize hypoglycemia.

With reference to the QoL information obtained from our literature search, none of the studies reported data on patients with T1DM. Further, only two articles assessed the health-related QoL and treatment satisfaction in patients with T2DM. We infer that the reason for this lack of data may not be a lack of interest to measure this outcome in patients with T1DM but, rather, because we excluded studies from our SLR that presented hypoglycemia data associated with a specific drug or intervention [45]. Patients with T2DM who experienced hypoglycemia had a poorer QoL versus patients with no such events. Further, patients with hypoglycemia expressed a higher fear of hypoglycemia, and the overall impact on their QoL was more negative as previously reported [38].

In summary, our analysis of studies included in our SLR reinforces the high burden of hypoglycemia on patients with DM. However, we consider that existing data are too heterogeneous to provide any consistent understanding of hypoglycemia episodes. Further, all included studies had retrospective data, implying that the development of the evidence are faster and generally less expensive than in prospective studies. Nonetheless, these data can lead to an

erroneous estimate of the real rate of hypoglycemic events due to a lack of systematic collection of events in medical records, with these events being more difficult to follow if they are NSH episodes. Another aspect to take into account is the definition of hypoglycemia in these articles, which varies across studies. The International Hypoglycemic Study Group has recently worked on the definition and classification of hypoglycemia and on the ways to attribute severity to an event. Such guidelines may help researchers to design future studies better [11].

To conclude, this study delineates hypoglycemia as a frequent acute complication of DM that presents a high clinical, personal and socioeconomic impact, and it provides information that could be useful to improve diabetes care in Spain. However, considering the heterogeneity of the methods used in the reviewed studies, we believe that in future studies and analyses there is a need to comprehend the evolution of hypoglycemia and to determine the factors that may influence and help focus the data obtained in this SLR in terms of epidemiology, HRU and patients' well-being in Spain.

ACKNOWLEDGEMENTS

Funding. Eli Lilly and Company sponsored this study and the publication of this article. All authors had full access to all of the data in this study and take complete responsibility for the integrity of the data and accuracy of the data analysis.

Medical Writing Assistance. Richi Taneja, an employee of Eli Lilly and Company, provided medical writing assistance in the preparation of this article.

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article. All take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Disclosures. Mercedes Núñez is an employee of Eli Lilly and company and has no other conflicts of interest. Silvia Díaz is an employee of Eli Lilly and company and has no other conflicts of interest. Tatiana Dilla is an employee of Eli Lilly and company and has no other conflicts of interest. Jesús Reviriego is an employee of Eli Lilly and company and has no other conflicts of interest. Antonio Pérez has participated as a consultant for or has received lecture fees or travel reimbursement from Sanofi-Aventis, Esteve, GSK, Almirall, Novo Nordisk, Eli Lilly, MSD, Boehringer Ingelheim, Novartis, Menarini, Janssen and AstraZeneca.

Compliance with Ethics Guidelines. Ethical approval was not required since this article is based on previously conducted studies and did not involve experiments with animals or humans performed by any of the authors.

Data Availability. Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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