REVIEW

Epidemiological, Social and Economic Burden of Severe Hypoglycaemia in Patients with Diabetes Mellitus in Portugal: A Structured Literature Review

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ABSTRACT

Introduction: The aim of this review was to identify and review studies reporting on the epidemiological, social and economic impact associated with severe hypoglycaemia (SH) in people with diabetes mellitus (DM) in Portugal.

Methods: A structured literature search was carried out in PubMed and Embase using a predefined selection criterion. Studies published in either Portuguese or English, between January 2010 and February 2021 were deemed eligible for inclusion.

Results: Twelve studies including adults (aged ≥ 18 years) with type 1 and/or type 2 diabetes mellitus (T1DM/T2DM) were eligible for inclusion. Epidemiological estimates varied according to the setting and type of data source used. The proportion of patients who experienced ≥ 1 SH episode (SHE) in the previous 6–12 months varied from 3.1% in adults with T2DM to 36.8% in adults with T1DM. In adults

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with T2DM the prevalence in a community-based study was highest in the insulin and sec-retagogue combination treated group (9.1%), while in an emergency department setting prevalence was highest in the insulin-based therapy group and the oral hypoglycaemic agent without secretagogues group (32.0% and 20.0%, respectively). The prevalence of SH in other studies in patients with DM ranged from 0.1% (emergency department) to 18.1% (hospital ward). Patients treated with secretagogues had the highest rates of hospitalisations. In patients with T1DM, the annual rate of SHE was higher in those with impaired hypoglycaemia awareness than in those with intact awareness. Mean total cost (direct and indirect) per SHE ranged from €1493.00 in patients with T2DM treated in an emergency setting to €2608.51 in patients with T1DM who were hospitalised.

Conclusion: Hypoglycaemic events, especially SHE, have a significant effect on the life of persons living with DM and their caregivers. Studies show that the prevalence of this acute complication of diabetes is not negligible. In addition to the negative impact on the quality of life, the burden of SHE in Portugal translates into a significant impact on the global health expenditure.

Key Summary Points

This structured literature review analysed 12 studies to identify the epidemiological, social and economic impact of severe hypoglycaemia (SH) in people with diabetes mellitus in Portugal

The prevalence of SH ranged from 0.1% (emergency department) to 18.1% (hospital ward)

Hypoglycaemic events, especially SH events, have a huge effect on the life of persons living with diabetes mellitus and their caregivers

Mean total cost (direct and indirect) per SH episodes ranged from €1493.00 in patients with type 2 diabetes mellitus treated in an emergency setting to €2608.51 in patients with type 1 diabetes mellitus who were hospitalised

More prospective studies are warranted to identify the factors that influence the frequency of SH, its economic impact and its burden on patients' quality of life

INTRODUCTION

Diabetes mellitus (DM) is a group of metabolic diseases characterised by chronic hyperglycaemia that results from insufficient insulin secretion, insulin action or both [1]. The classical definition of DM is that type 1 diabetes mellitus (T1DM) is due to destruction of β cells of the pancreas, representing 5–10% of DM cases and that type 2 diabetes mellitus (T2DM) mainly results from insulin resistance, accounting for approximately 90–95% of all cases [1]. The goal of DM management is to optimise metabolic control through lifestyle intervention and pharmacological agents to prevent or delay the onset of late-stage DM complications while also avoiding the occurrence of acute complications [2, 3]. Regarding pharmacological agents, insulin is the standard treatment for people with T1DM, whereas people with T2DM are usually treated with other glucose-lowering agents and may have insulin introduced into their treatment regime at an advanced stage of the disease [4].

Over the past decades, the number of people with T2DM has grown because of the rising levels of obesity and an ageing population. The impact of ageing on the age structure of the Portuguese population (20–79 years) was reflected in an 1.9% increase in the prevalence of DM between 2009 and 2018, which corresponds to a

growth rate of 16.3% over a 10-year period [5]. In 2021, the International Diabetes Federation ranked Portugal fourth (9.1%) for the age-adjusted prevalence of people with diabetes (age 20–79 years) [6]. According to the latest national data, 13.6% (approximately 1 million cases) of the adult population in Portugal (aged 20–79 years) presented with DM in 2018; 5.9% of these of cases were undiagnosed [5]. Specific data on the number of people with T1DM or T2DM in Portugal are limited. However, Risso and Furtado [7] estimated that 894,637 people were electronically prescribed at least one antidiabetic medicine during 2016; of these, 5.8% were prescribed insulin only, 11.5% were prescribed insulin plus oral glucose-lowering agents, and 82.7% were prescribed oral glucose-lowering drugs alone [7]. Biguanides without sulfonylureas and dipeptidyl peptidase-4 inhibitors (DPP-4i) were the most commonly prescribed class of oral glucose-lowering drugs, followed by sulphonylureas and DPP-4i without sulphonylureas [7].

The economic impact of DM is also high and will continue to rise. In 2021, approximately US$ 966 billion global health expenditure was spent on DM for adults aged 20–79 years [6]. In Portugal, data show a similar trend in terms of Portuguese healthcare expenditure for the care of patients with DM. The Portuguese national health system (NHS) is funded by taxes, and every citizen has access to it. However, some specific subgroups of the populations have access to an additional health coverage funded and proportioned based on their income, while the third and last option of healthcare system is the private insurance [8]. In 2018, costs associated with DM represent 0.6–0.8% of the Portuguese gross domestic product and 7–8% of the total health expenditure [5]. Much of this burden can be attributed to acute and late-stage DM complications [9].

Hypoglycaemia is an acute complication of DM that negatively influences disease management, patients' quality of life (QoL) and associated costs. In addition, it is the most common and often limiting factor for effective metabolic control [9], particularly with insulin or sulphonylureas treatment [10]. At the moment of the literature review, Portugal does not have available records regarding the total cost/year that is specifically allocated to treatment of hypoglycemia. The available data is related with diabetes acute complications, including hypoglycemia, ketoacidosis, hyperosmolarity, diabetic coma and other complications, but it does not have specific information related to hypoglycemia. However, a study has been performed to study the prevalence of severe hypoglycemia requiring emergency room assistance in Portugal (Hypoglycemia In Portugal Observational Study–Emergency Room–Hypos-ER) that showed its magnitude in insulin and secretagogue-treated patients. Another study, HIPOS-WARD (Hypoglycemia In Portugal Observational Study-Ward), was performed with the aim to characterize ward admissions due to hypoglycemia episodes in patients with diabetes and assess their economic impact to the NHS. It has displayed the huge economic impact of hospitalization due to hypoglycemia in Portugal. Both studies have been included in this review and have been described in detail. Portugal has tried to contrast the incidence of hypoglycaemia by increasing the use of DPP-4i, sodium-glucose cotransporte-2 inhibitors (SGLT-2i) and glucagon-like peptide 1 receptor agonists (GLP-1 RAs), all associated with a lower risk of hypoglycaemia, and by decreasing the use of sulphonylurea. However, it is unclear whether this approach has influenced the number of hospital admissions due to hypoglycaemia [11].

This review has adopted the American Diabetes Association (ADA) classification of hypoglycaemia as follows: hypoglycaemia can be level 1 or level 2 (blood glucose level between < 70 mg/dl and $\geq$ 54 mg/dl and < 54 mg/dl, respectively, and the event can be resolved by the individual) or level 3 (if the event is severe and requires assistance by a third-party to recover) [12]. A severe hypoglycaemia episode (SHE) requires immediate medical intervention; otherwise, a seizure or even coma may occur [13]. In Portugal, medical assistance for an SHE can include calls for pre-hospital emergency services (i.e., an ambulance and/or an emergency and resuscitation medical vehicle unit), treatment in an emergency department (ED) and/or admission to a hospital

ward [12]. The risk of severe hypoglycaemia (SH) is particularly increased among those frail individuals, specifically those with cognitive damage and those with a longer duration of diabetes where counterregulatory response is impaired [14, 15].

Most people with DM who experience SHEs develop fear of hypoglycaemia and adopt changes in self-management of DM that may further compromise glycaemic control [16]. Ultimately, SH can negatively affect the QoL of people with DM [17]. Furthermore, evidence suggests that witnessing an SHE can have a negative emotional impact on caregivers of people with DM [18]. In addition to the individual impact of SHE, several European countries have highlighted the detrimental economic impact of SHE from both a healthcare and societal perspective [19, 20].

In a country with one of the highest rates of DM in Europe [21] and where approximately one-fifth of electronic prescriptions for antidiabetic medicines include insulin [7], surprisingly, up to now, no studies have collected integrated data related to the burden of SH to our knowledge. Therefore, the purpose of this review was carried out to identify and summarise studies reporting on the epidemiological, social and economic burden of SH in patients with DM in Portugal.

METHODS

Search Strategy

Both peer-reviewed journal articles and conference abstracts, published between January 2010 and February 2021, were considered in this review. A pragmatic, structured literature search was carried out in Embase and Medline via the OVID platform to identify relevant studies. Keywords for the search strategy were based on relevant components in the research question (hypoglycaemia and Portugal). Search strings were developed using both indexing terms and free-text words and were combined using the 'AND' or 'OR' operators. See Table S1 in the electronic supplementary material for the full database search strategy. An additional database

search was carried out via the Revista Portuguesa de Diabetes website (www.revportdiabetes.com); the keywords 'hypoglycemia' and 'hipoglicemia' were used to identify potentially relevant articles. Searches were carried out (by MT) in February 2021. The review protocol was not registered in a searchable database prior to the conduct of the review.

Study Selection and Data Extraction

After removing duplicates, citations were managed using a standard reference management software; full records were subsequently exported into a Microsoft Excel spreadsheet. Study selection followed a two-stage process using predetermined eligibility criteria. See Table S2 in the electronic supplementary material for details. In brief, studies were eligible for inclusion if they met the following criteria: (1) involved people aged ≥ 4 years of age with T1DM, T2DM or gestational DM and/or caregivers/family members/teachers of people with DM; (2) reported epidemiological, social or economic outcomes due to SH (defined as blood glucose value of < 54 mg/dl and/or hypoglycaemic event that required help/support from another person); (3) were conducted in Portugal; (4) were observational or economic studies or reported baseline data from interventional studies; (5) were written in English or Portuguese; (6) contained adequate information to be assessed for eligibility. Records were excluded if (1) there was not enough information to determine whether the hypoglycaemic episode was severe, (2) they reported outcomes due to SH in any other population and (3) were congress proceedings that had already been published as a full-text articles.

First, title and abstract screening was carried out by one author (MT) and validated by two authors (ARS and MC). Next, if available, full-text articles were retrieved for potentially eligible studies and were independently reviewed by MT, ARS and MC. Any inconsistencies between reviewers were resolved through consensus. If multiple records provided information on a single study, the record detailing the most comprehensive data was selected. Each stage of

the selection process was documented, including reasons for study exclusion at full-text review.

Data extraction was carried out using a structured form by one author (MT), with two authors (ARS and MC) undertaking a quality review of extracted information. Next, relevant data were summarised in Tables 1, 2, 3 and 4 and a narrative overview of key study characteristics and relevant outcomes was provided.

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

RESULTS

Study Selection

Results of the literature search and selection process are presented in Fig. 1. The database searches identified 217 records consisting of a combination of peer-reviewed publications from journals and abstracts from congress proceedings. After removal of duplicates ($n = 45$), 172 records were screened by title and abstract; of these, 100 were excluded. The remaining 72 records underwent further review; of these, 60 records were excluded for several reasons (see Fig. 1) and 12 peer-reviewed articles were deemed eligible for inclusion.

Characteristics of All Included Studies

Characteristics of included studies reporting on the epidemiological, social and economic burden associated with SH in patients with DM in Portugal are presented in Table 1, where it is specified if the study was conducted in a healthcare setting integrated in the NHS. Almost all records (11 out of 12) were published between 2016 and 2021 [11, 22–31]. Of the 12 studies included in this review, only 2 [26, 27] investigated SHEs in patients with T1DM. In the remaining studies, three focused on T2DM [24, 25] and seven reported data on both T1DM and T2DM [11, 23, 25, 28, 30–32].

Each study was conducted in a healthcare setting, although the type of setting varied between studies; emergency hospital setting was the most common [24, 25, 28, 30], followed by a hospital ward [11, 23, 29], emergency and resuscitation medical vehicle unit [31, 32], hospital-based diabetes clinic [26, 27] and community pharmacy [25]. Five studies were based on data collected across multiple centres [11, 23–25], with the number of centres ranging from EDs within 7 hospitals [24] to 233 community pharmacies [25]. Of all included studies, ten adopted an observational study design [11, 25–27, 29–33]. Azevedo et al. [27] and Pereira et al. [28] used a longitudinal approach to examine trends in SHEs over time. Two micro-costing studies [23, 24] that used data from Hypoglycemia In Portugal Observational Studies (HIPOS–Emergency Room [22] and HIPOS-WARD [11]) were identified in this review.

Studies adopted various entry criteria to identify or recruit participants. For example, five studies were open to any age groups; three studies restricted study entry to adults aged ≥ 18 years [11, 26, 29], whereas Azevedo et al. [27] limited study entry to those who started continuous subcutaneous insulin infusion (CSII) therapy aged ≥ 18 years. The three remaining studies restricted study entry to adults aged ≥ 40 years [22, 24, 25].

In terms of the characteristics of the study population, total sample size varied widely, from 20 adults with T1DM in a study examining the impact of CSII therapy [27] to 1890 adults with T2DM who participated in a nationwide study [25]. Though five studies did not restrict entry by age, none included children or adolescents with DM. Overall, the average age ranged between 38.2 [26] and 78.0 [25] years although those with T1DM had a younger average age profile than those with T2DM. In studies that stratified patients by DM classification [11, 23, 28–32], the proportion of patients with T2DM was higher than of those with T1DM across all studies. With respect to epidemiological, social and economic outcomes associated with the burden of SH, four studies reported data on more than one outcome [11, 26, 28, 30]. Epidemiological data related to the burden of SH were the most common
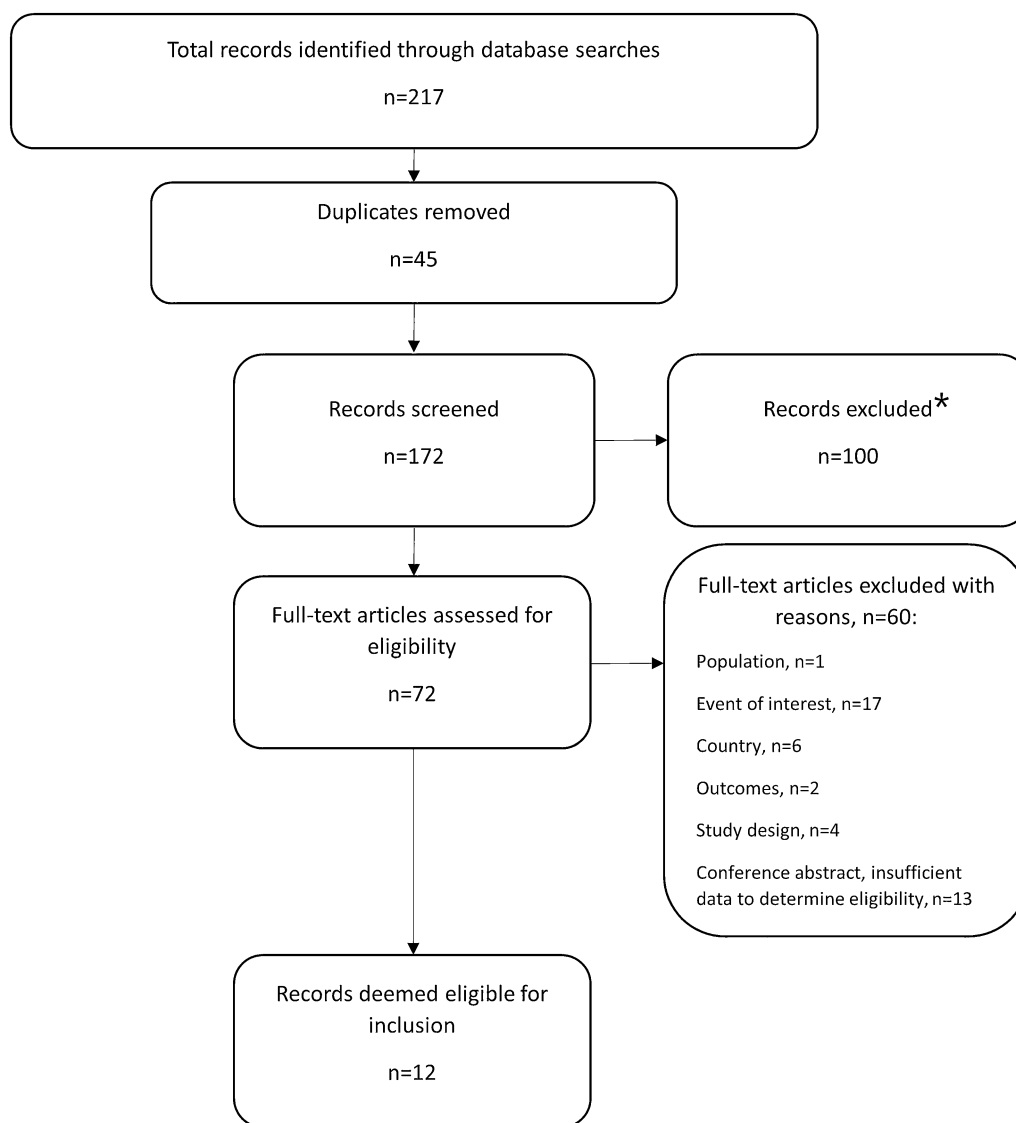
Fig. 1 Flow diagram illustrating results of search and selection process. *Records were excluded if (1) there was not enough information to determine whether the hypoglycaemic episode was severe, (2) they reported outcomes due to severe hypoglycaemia in any population other than people aged $\geq$ 4 years of age with type 1 diabetes mellitus, type 2 diabetes mellitus or gestational diabetes and/or caregivers/family members/teachers of people with diabetes mellitus and (3) were congress proceedings that had already been published as a full-text articles

outcome reported, with ten studies providing relevant data [11, 25–32], followed by economic outcomes [23, 24, 29, 30] and social outcomes [11, 26, 28].

Epidemiology of SH in the Included Studies
Table 2 describes the epidemiological data related to hypoglycaemia in each included

study (10 publications). SH diagnostic criteria varied across studies and the follow-up period/ study duration ranged from 2 days [29] to 20 years [27].

Among the studies reporting separate outcomes for T1DM and T2DM [11, 28, 30–32], four of them [11, 28, 30, 31] collected data on the SHEs and then stratified the results by DM

Table 1 Characteristics of studies reporting the epidemiological, social and economic burden associated with severe hypoglycaemia among people with diabetes in Portugal

First author, publication year	Setting	Study design Year of data collection	Study population and study entry criteria	Characteristics of the study population Number of participants/SH cases Female (%) Age (years)	Outcome of interest
T1DM					
Azevedo et al., (2019) [27]	Outpatient clinic within a hospital in Portugal	Retrospective, longitudinal NR	Adults with T1DM, started CSII therapy ≥ 18 years old, previously on multiple daily injections with ≥ 10 years of follow-up	Total = 20 participants 65.0 Mean (SD), range: 44.3 (8.7), 31.0–61.0	Epidemiology
Sepulveda et al. (2020) [26]	Hospital-based diabetes clinic in Portugal	Cross-sectional Sept 2016–Dec 2018	Adults (≥ 18 years), with T1DM (≥ 12 months)	Total = 190 participants 51.58 Mean (SD): 38.24 (12.92)	Epidemiology Social
T2DM					
Conceição et al., (2018) [22]	EDs in 7 hospitals in Portugal	Multicentre, cross-sectional (HIPOS–ER) Jan 2013–Jan 2014	Adults (≥ 40 years old) with T2DM receiving treatment with a known antihyperglycaemic agent and admitted to the ED primarily because of a hypoglycaemic episode	Total = 238 participants 57.6 Median (range): 77.5 (45–97)	Epidemiology

Table 1 continued

First author, publication year	Setting	Study design Year of data collection	Study population and study entry criteria	Characteristics of the study population Number of participants/SH cases Female (%) Age (years)	Outcome of interest
Laires et al., (2016) [24]	EDs in 7 hospitals in Portugal	Micro-costing study based on (HIPOS-ER) [22] Jan 2013–Jan 2014	As above	Total = 238 participants 57.6 Mean (SD): 76.2 (10.4)	Economic
Torre et al., (2018) [25]	233 community pharmacies	Multicentre, cross-sectional (HIPOS-PHARMA) April 4–May 20 of 2016	Adults (≥ 40 years old) with T2DM receiving treatment with the same antihyperglycemic agent for ≥ 3 month	Total = 1890 participants 49.4 Mean (SD): 67.11 (9.98)	Epidemiology
T1DM and T2DM					
Alao et al., (2021) [11]	18 wards of 16 public hospitals integrated in the NHS	Multicentre, cross-sectional (HIPOS-WARD) Nov 2016–Aug 2018	Adults (≥ 18 years old) with DM receiving treatment with a known antihyperglycaemic agent, hospitalized in the ward due to a hypoglycaemia event or due to a hypoglycaemia episode in the nonhospitalized setting	T1DM = 18 cases 33.3 Median (range): 49.5 (28.0–74.0) T2DM = 152 cases 57.9 Median (range): 78.0 (35.0–98.0)	Epidemiology Social

Table 1 continued

First author, publication year	Setting	Study design Year of data collection	Study population and study entry criteria	Characteristics of the study population Number of participants/SH cases Female (%) Age (years)	Outcome of interest
Ferreira et al., (2020) [23]	18 wards of 16 public hospitals integrated in the NHS	Micro-costing study based on HIPOS-WARD[11] Nov 2016–Aug 2018	As above	T1DM = 18 cases NR NR T2DM = 152 cases NR NR	Economic
Pereira et al., (2020) [28]	ED of a tertiary hospital	Retrospective, observational, non-interventional 2012 and 2016	All DM-related hypoglycaemic episodes treated at the ED	Total = 676 cases in 597 patients with T1DM/ T2DM 59.0 Median (IQR): 71 (57–81)	Epidemiology Economic Social

Table 1 continued

First author, publication year	Setting	Study designYear of data collection	Study population and study entry criteria	Characteristics of the study populationNumber of participants/SH casesFemale (%)Age (years)	Outcome of interest
Esteves et al., (2018) [30]	Pre-hospital medical emergency unit and medical ED	Retrospective, cross-sectional 01 Jan–31 March 2010	All patients with DM examined due to hypoglycaemia	Prehospital medical emergency unit = 37 cases 72.3 (missing $n = 1$) Mean (SD): 60.7 (18.36); min–max 27–84 ED = 59 cases 52.5 Mean (SD): 68.0 (15.26); min–max: 23–93	Epidemiology Economic
Coelho et al., (2010) [32]	Emergency and resuscitation medical vehicle	Retrospective, observational, non-interventional Jan 2005–Dec 2009	Patients with T1DM and T2DM	Total = 595 cases T1DM = 41.1; T2DM = 59.3 NR	Epidemiology

Table 1 continued

First author, publication year	Setting	Study designYear of data collection	Study population and study entry criteria	Characteristics of the study populationNumber of participants/SH casesFemale (%)Age (years)	Outcome of interest
Marques et al., (2019) [31]	Emergency and resuscitation medical vehicle	Retrospective, observational, non-interventional Apr 2015 to Apr 2018	Patients with T1DM and T2DM	T1DM = 48 cases 54.2 Mean (SD): 44.8 ± 13.7 T2DM = 100 cases 60.0 Mean (SD): 73.8 ± 11.1	Epidemiology
Pereira et al., (2016) [29]	Wards of the Endocrinology and Internal Medicine services of a tertiary hospital	Retrospective, observational, non-interventional 2013 and 2014	All inpatients with DM	T1DM = 3 patients; T2DM = 88 patients; Probably DM = 25 57.8 Median (IQR): 75 (66–83)	Epidemiology

CSII continuous subcutaneous insulin infusion, *DM* diabetes mellitus, *ED* emergency department, *ER* emergency room, *IQR* interquartile range, *HIPOS-ER* Hypoglycaemia In Portugal Observational Study-Emergency Room, *HIPOS-PHARMA* Hypoglycaemia In Portugal Observational Study-Pharmacy, *HIPOS-WARD* Hypoglycaemia In Portugal Observational Study-Ward, *NHS* National Health Service, *NR* not reported, *SH* severe hypoglycaemia, *SD* standard deviation, *T1DM* type 1 diabetes mellitus, *T2DM* type 2 diabetes mellitus

type, while the remaining one [32] stratified all the SHEs by treatment and then stratified the insulin-based therapy group by DM type. The proportion of patients with T2DM was higher than of those with T1DM across all studies [11, 28, 30–32].

T1DM Of the seven studies describing epidemiological data in people with T1DM [11, 26–28, 30–32], two provided data on the average duration of DM [11, 26]. Sepulveda et al. [26] recorded a mean (standard deviation, SD) duration of 20.10 (11.28) years, whereas Alao et al. [11] recorded a slightly longer median (range) duration of 22 (4–52) years.

Coelho et al. [32] assessed the frequency of calls for emergency and resuscitation medical vehicles due to SHEs in patients with T1DM; this study reported an increase of 10.1 percentage points in calls over a 5-year period (41.8% in 2005 to 51.9% in 2009).

In other studies, the frequency and prevalence of SHEs differed across study settings and varied according to the type of data source used. Using medical records, Azevedo et al. [27] reported 2 SHEs over a 20-year period in 20 patients attending an outpatient clinic who had been CSII therapy for a mean duration (SD) of 13.2 (2.3) years prior to the study commencement. Using item 3 and/or 4 of the Minimally Modified Clarke Hypoglycemia Survey (MMCHS), Sepulveda et al. [26] reported that over a third of patients attending a diabetes clinic had experienced an SHE 6–12 months prior to the study commencement. Marques et al. [31] recorded 148 calls for emergency and resuscitation medical vehicles due to SHEs over a 5-year period; of these, less than a third were from people with T1DM. In reference to hospital ward admissions due to SH, Alao et al. [11] reported a total of 18 episodes over a 21-month period.

T2DM A total of seven out of ten studies reported data for people with T2DM [11, 25, 28, 30–32]; of these, two stratified outcomes by T2DM treatment regimen [22, 25]. In studies reporting the average duration of DM among people with T2DM, the average time ranged from 10 years [11] to 19 years [25].

Like T1DM data, estimates differed between settings and by the type of data source used. The proportion of patients who experienced a SHE in the previous 12 months was approximately 7.5 times lower in a community-based setting where estimates were based on self-report than in an ED setting where estimates were derived from medical records (3.1% [25] vs. 23.5% [25]).

T1DM and T2DM In the studies combining outcomes for T1DM and T2DM, the prevalence of SH over the study period varied depending on the type of setting.

Distribution of SHEs According to Various Treatment Regimens The community-based study by Torre et al. [25] in adults with T2DM showed that the prevalence of SHEs in the previous 12 months was highest in the insulin and secretagogue combination group (9.1%) and the lowest in the other antihyperglycaemic agent-based therapy group (1.9%). In an ED setting, Conceição et al. [22] showed that this prevalence in adults with T2DM, admitted primarily for a hypoglycaemic episode, was highest in the insulin-based therapy group (32.0%) followed by the oral hypoglycaemic agent without secretagogues group (20%). Alao et al. [11] reported a similar distribution in adults with T1DM and T2DM admitted to the hospital ward because of SH over a 21-month study period [11].

Regarding data for the regimens without insulins and/or secretagogues, estimates varied between studies. The highest proportion of SHEs occurred in the other antihyperglycaemic agent-based therapy group (35.6%) [25] followed by the non-secretagogue-based therapy group (9.7%) [11], with the lowest proportion occurring in the oral hypoglycaemic agent without secretagogues group (6.7%) [25].

Probable Cause of and Trigger for SHEs Four studies provided data on the probable cause of or trigger for the SHEs [25, 28, 30, 31]. Only one study [31] compared triggers between T1DM and T2DM, although no between-group differences were observed. Dietary-related factors were the most common probable cause or trigger reported, followed by illness and issues related to DM treatment. See Table S3 in the electronic supplementary material for more details.

Table 2 Epidemiology of severe hypoglycaemia among people with diabetes in Portugal

First author, publication year	Number of patients/SH cases DM duration (years)	Data source SH diagnostic criteria	Follow-up period/ Study duration	Outcome
T1DM				
Azevedo et al., (2019) [27]	20 patients DM duration up to CSII implementation- Mean (SD), range: 16.1 (7.9), 4.0–32.0	Medical records Characteristic symptoms of hypoglycaemia requiring assistance of another person to treat and confirmed blood glucose level < 50 mg/dl	20 years (follow-up at 6 months, Year 1, 5, 10, 15 and 20)	Frequency of SHEs over the study period, $n = 2$ (0.0095episodes/patient/year)
Sepulveda et al., (2020) [26]	190 patients Mean (SD): 20.10 (± 11.28)	Self-report Score of reduced awareness in either item 3[a] and/or item 4[b] of the MMCHS [34]	Sep 2016-Dec 2018	Prevalence of ≥ 1 SHE 6–12 months prior to the study, n/N (%):70/190 (36.8%)
T2DM				
Conceição et al., (2018) [22](HIPOS-ER)	238 cases Median, range: 19.0 (0.1–50.0)	Medical records Blood glucose level < 70 mg/dl and typical symptoms reversed by glucose or glucagon	12 months	Distribution of SHEs by AHA treatment group during the study period, n/N (%): Insulin based therapy: 131/238 (55.0) Secretagogue-based regimen: 75/238 (31.5) Oral hypoglycaemic agent without secretagogues: 16/238 (6.7) Insulin + secretagogues: 16/238 (6.7) Prevalence of SHEs during the study period: 74/100, 000 emergency admissions (0.07% [95% CI 0.07 to 0.08]) Prevalence of SHEs during the study period (per 100, 000 patients in the ED), by AHA treatment group, n (%): Insulin-based therapy: 31 (0.031%)

Table 2 continued

First author, publication year	Number of patients/SH cases DM duration (years)	Data source SH diagnostic criteria	Follow-up period/ Study duration	Outcome
				Secretagogue-based regimen: 18 (0.018%)
				Oral hypoglycaemic agent without secretagogues: 4 (0.004%)
				Insulin + secretagogues: 4 (0.004%)
				Prevalence of ≥ 1 similar SHE in the previous 12 months before current ED admission, n/N (%): 56 (23.5)
				by AHA treatment group, n (%):
				Insulin-based therapy: 41/131 (32.0)
				Secretagogue-based regimen: 10/75 (14.7)
				Oral hypoglycaemic agent without secretagogues: 3/16 (20.0)
				Insulin + secretagogues: 2/16 (15.4)
Torre et al., (2018) [25] (HIPOS-PHARMA)	1890 patients Mean (SD) (NR = 63): 11.80 (9.33)	Self-report Episode requiring assistance from medical personnel	7 weeks	Prevalence of SHEs in the 12 months prior to the study, n/N (%) (NR = 2): 59/1890 (3.1)
				by AHA treatment group, n/N (%):
				Insulin-based therapy: 14/222 (6.3)
				Secretagogue-based regimen: 10/418 (2.4)
				Other antihyperglycaemic agent-based therapy: 21/1096 (1.9)
				Insulin + secretagogues: 14/154 (9.1)
				Number of SHEs in the 12 months prior to the study, mean (SD): 2.51 (3.94)
				by AHA treatment group, mean (SD):
				Insulin-based therapy: 1.50 (0.76)
				Secretagogue-based regimen: 2.00 (2.49)
				Other antihyperglycaemic agents-based therapy: 2.81 (4.82)
				Insulin + secretagogues: 3.43 (5.11)

Table 2 continued

First author, publication year	Number of patients/SH cases DM duration (years)	Data source SH diagnostic criteria	Follow-up period/ Study duration	Outcome
T1DM and T2DM				
Alao et al., (2021) [11] (HIPOS-WARD)	170 cases Median, range: T1DM: 22.0 (4.0–52.0); T2DM: 10.0 (0.0–51.0)	Medical records Diagnosed by ED physician based on signs and symptoms suggestive of hypoglycaemia that resolve with the administration of carbohydrates or glucagon and blood glucose level < 70 mg/dl	21 months	Frequency of SHEs during the study period, n (%): by DM classification: T1DM 18 (10.2); T2DM: 152 (86.4) by AHA treatment group: Insulin-based therapy: 82 (48.2) Secretagogue-based regimen: 53 (31.2) Non-secretagogue-based therapy: 17 (10.0) Insulin + secretagogues: 18 (10.6)
Pereira et al., (2020) [28]	676 cases (597 patients) NR	ED reports Confirmed hypoglycemia (capillary or venous plasma glucose level < 70 mg/dl)	5 years (2012–2016)	Frequency of SHEs treated in the ED during the study period by DM classification, n/N (%): T1DM 165/676 (24.4); T2DM 511/676 (75.6) Prevalence of SHEs in the ED during the study period, n/N (%): 676/604,318 (0.1) of ED episodes
Esteves et al., (2018) [30]	86 cases (84 patients) Prehospital medical emergency unit = 37 cases in 37 patients Mean (SD), range: 19.1 (8.37), 10–30 ED = 61 cases in 59 patients (49 not previously examined in the prehospital medical emergency unit) Mean (SD), range: 16.2 (10.25), 0–37	Medical records International Classification of Diseases, Ninth Revision (ICD-9) codes potentially associated with DM and its complications or hypoglycaemia	3 months (01 Jan–31 March 2010)	Frequency of SHEs during the study period by DM classification, n (%): Prehospital medical emergency unit: T1DM 11 (35.5); T2DM: 20 (64.5); Missing: 6 ED: T1DM 5 (8.5); T2DM: 48 (81.4); Other: 6 (10.2) Prevalence of SHEs evaluated in the prehospital medical emergency unit during the study period, n/N (%): 37/793 (4.7) emergency calls evaluated 13 SHEs (35.1%) occurred during the hours 24.00–08.00 Prevalence of SHEs in the ED during the study period, n/N (%): 61/54,366 (0.1) of ED episodes Patients with a history of SH: Prehospital medical emergency unit, n: 8 (missing: 29)[c] ED, n (%): 12 (20.3)

Table 2 continued

First author, publication year	Number of patients/SH casesDM duration (years)	Data sourceSH diagnostic criteria	Follow-up period/Study duration	Outcome
Coelho et al., (2010) [32]	595 cases NR	Medical records Blood glucose level < 70 mg/dl	Jan 2005–Dec 2009	Frequency of SHEs during the study period, %: by DM classification: T1DM 32.9; T2DM 67.1 ($p < .01$) by DM treatment: Insulin 72.8; OAD: 27.2 ($p < .01$) Frequency of SHEs in patients with T1DM since 2005, %: 41.8 in 2005 to 51.9 in 2009
Marques et al., (2019) [31]	148 cases NR	Form completed by the doctor responsible for the SHE	Apr 2015–Apr 2018	Frequency of SHEs by DM classification, %: T1DM 32.4; T2DM: 67.6 Prevalence of SHEs in emergency and resuscitation medical vehicles during the study period, n/N (%): 148/4723 (3.1%)
Pereira et al., (2016) [29]	116 patients NR	Medical records Blood glucose level ≤ 50 mg/dl	2 days (14 Nov 2013–2014)	Prevalence of SH in patients with DM during the study period, n/N (%): 21/116 (18.1)

[a]Item 3 of the MMCHS: In the past 6 months, how often have you had hypoglycemic episodes, where you might feel confused, disorientated or lethargic and were unable to treat yourself? [b]Item 4 of the MMCHS: In the past year, how often have you had hypoglycemic episodes where you were unconscious or had a seizure and needed glucagon or intravenous glucose? [c]% not reported

AHA antihyperglycaemic agent, *CSII* continuous subcutaneous insulin infusion, *DM* diabetes mellitus, *ED* emergency department, *ER* emergency room, *IQR* interquartile range, *HIPOS-ER* Hypoglycaemia In Portugal Observational Study–Emergency Room, *HIPOS-PHARMA* Hypoglycaemia In Portugal Observational Study–Pharmacy, *HIPOS-WARD* Hypoglycaemia In Portugal Observational Study–Ward, *NHS* National Health Service, *MMCHS* Minimally Modified Clarke Hypoglycemia Survey, *NR* not reported, *OAD* oral antidiabetics, *SH* severe hypoglycaemia, *SHE* severe hypoglycaemia episode, *SD* standard deviation, *T1DM* type 1 diabetes mellitus, *T2DM* type 2 diabetes mellitus

Table 3 Social burden of severe hypoglycaemia among people with diabetes in Portugal

First author	Number of patients/ SH cases	Outcome(s)	Description of instrument	Outcome- results
T1DM				
Sepulveda et al., (2020) [26]	190 patients	Hypoglycaemia awareness	Gold score [35] and the eight-item MMCHS [34] IAH defined as Gold/MMCHS score of ≥ 4	**Prevalence of IAH, %:** Gold score: 23.7 MMCHS: 14.3
T1DM and T2DM				
Alao et al., (2021) (HIPO-WARD)[11]	170 cases	Dependency on others	Medical records	**Diabetes management, n/N (%):** Solely managed by self: T1DM: 13/18 (72.2); T2DM: 58/152 (38.2) Solely managed by others: T1DM: 1/18 (5.6); T2DM: 50/152 (32.9) Occasional assistance: T1DM: 4/18 (22.2); T2DM: 44/152 (28.9)
Pereira et al., (2020) [28]	676 cases (597 patients)	Dependency on others	Extracted from ED reports	Dependent to some degree on other people for performing daily activities: 31.4% ($n/N = 204/650$) Close family member is responsible for administering DM medication: 31.9% ($n/N = 199/624$)

DM diabetes mellitus, *ED* emergency department, *HIPOS-WARD* Hypoglycaemia In Portugal Observational Study-Ward, *IAH* impaired awareness of hypoglycaemia, *MMCHS* Minimally Modified Clarke Hypoglycemia Survey, *SH* severe hypoglycaemia, *T1DM* type 1 diabetes mellitus, *T2DM* type 2 diabetes mellitus

Complications due to SHEs The only study describing complications due to SH, Conceição et al. [22], reported a prevalence of approximately 16%, with trauma being the most common complication recorded. See Table S3 in the electronic supplementary material for more details.

Social Burden of SH in the Included Studies
Only 3 of the 12 included publications described data on the social burden of SH in Portugal (Table 3). Literature concerning this outcome in the context of the population with DM in Portugal is limited; no studies reported the impact of SHEs on the QoL and emotional health of people with DM or the caregivers or acquaintances of people with DM.

Regarding hypoglycaemia literacy and awareness, Sepulveda et al. [26] used validated questionnaires to measure impaired awareness of hypoglycaemia (IHA). This study compared the prevalence of IHA in 190 patients with T1DM using two different instruments (Gold score [35] and MMCHS [34]). They found the prevalence of IAH was almost 10% higher when measured by the Gold score than when

measured by MMCHS [26]. Additionally, the study showed a higher annual rate of SH by the Gold score in those with IAH than in those with intact awareness [26]. Alao et al. [11] and Pereira et al. [28] highlight the role and the responsibility that family members have in the management of DM.

Economic Burden of SH in the Included Studies
Table 4 summarises data on healthcare resource use (HRU), work loss and costs associated with SH identified in the review (6 out of 12 publications); HIPOS-ER [24] and HIPOS-Ward [23] provided the most comprehensive overview of the economic burden of SH in Portugal.

HRU Five studies described information related to HRU [24, 28, 30–32]; data on pre-hospital emergency services, ED care and in-patient hospital care were available.

Laires et al. [24] showed a high proportion of ED admissions due to SH required prehospital attendance and transportation by ambulance. Marques et al. [31] reported that over a 5-year period, 3.1% ($n = 148$) of the total emergency and resuscitation medical vehicle use was attributed to SHEs; over half (56.1%) of these SH cases were transferred to the ED. Esteves et al. [30] reported that almost a third (32.4%) of prehospital medical emergency unit SH cases were referred to the ED. Coelho et al. [32] reported a higher proportion of people with T2DM than with T1DM were transferred to hospital after assistance by the emergency and resuscitation medical vehicles. In the same study, hospitalisation was more frequent in those taking oral antidiabetic drugs (OADs) than in those on insulin therapy [32].

In trend analysis, Pereira et al. [28] reported a decrease of 0.5 percentage points in ED admission rates due to hypoglycaemia in patients with DM was observed over the duration of the study (2012: 1.5%; 2016: 1.0%; $p < 0.001$). Overall, the average length of stay in the ED ranged from 8 h [28] to 17.2 h per SHE [30]. Pereira et al. [28] found that the median length of stay in the ED was higher for patients taking sulphonylureas than for those taking insulin (12 vs. 8 h).

The proportion of ED admissions requiring additional care in a hospital ward varied widely. In the study by Pereira et al. [28], 8.1% of SH episodes in the ED between 2012 and 2016 resulted in hospitalisation. Of these, the rate of hospitalisation was over five times higher for those taking sulphonylureas (22.7%) than for those taking insulin (4.2%). Of 238 ED admissions due to SH in people with T2DM, Laires et al. [24] found that 44.1% resulted in hospitalisation, with the highest proportion occurring in patients in the secretagogue group (70.7%), followed by those in the oral hypoglycaemic agent without secretagogue group (56.2%), the insulin with secretagogue group (31.2%) and the insulin-based therapy group (29.0%). In the study by Esteves et al. [30] over a third of SHE cases recorded in the ED were admitted to the ward for further observation. In studies reporting on HRU in a hospital ward, the average length of stay in hospital per SHE was similar (8.8 days [24] and 9 days [30]).

Impact on Work Data describing the impact of SH on work were limited. One study reported on the average time absent from work due to SH. This included 6.5 h due to an ED admission and 4 days due to hospitalization [24]. Like the social burden of SH, the impact of SH on family members and caregiver work circumstances was not represented in the literature.

Costs The two micro-costing studies based on HIPOS-ER [24] and HIPOS-Ward [23] presented the estimates of both direct and indirect costs per SHE in the ED care and hospital ward setting in Portugal, respectively.

In HIPOS-ER, the overall mean total cost per SHE in patients with T2DM was €1493, of which €1479 comprised direct costs and €15 comprised indirect costs. Hospitalisation was the most significant cost driver; the total cost per SHE was approximately 18 times higher in those who had been hospitalised than in those who had not been hospitalised. When stratified by antihyperglycaemic agent treatment group, the mean total cost per SHE was higher in patients being treated with a secretagogue-based regimen (€1880) than in those in other treatment groups [22].

Table 4 Economic impact of severe hypoglycaemia among people with diabetes in Portugal

First author, publication year	Number of patients/ SH cases Study duration	Outcome- resource use/productivity	Outcome- costs
T2DM			
Laires et al., (2016) [24] (HIPOS-ER)	238 cases 12 months	Proportion of SHEs requiring healthcare resources, n %:	Overall direct cost per SHE (€), mean (SD), range:
		Activation/transportation by an ambulance of the Medical Emergency National Institute: 214 (90.3%)	Total: 1479 (2947), 34–26,818
			Hospitalised: 3132 (3851), 230–26,818
		Activation/transportation by an emergency and resuscitation medical vehicle: 63 (26.6%)	Nonhospitalised: 173 (111), 34–621
		Administration of medications: 214 (89.9%)	by AHA treatment group:
		Laboratory analyses at the ED: 238 (100%)	Insulin-based therapy: 1299 (3332), 34–26,818
		Examinations/procedures at the ED: 213 (89.5%)	Secretagogue-based regimen: 1851(2394), 63–12,869
			Oral hypoglycaemic agent without secretagogues: 1348 (2437), 61–9862
		Hospitalisation: 105 (44.1%)	Insulin + secretagogues: 1330 (2401), 87–8937
		Intensive care unit: 6 (2.5%)	Indirect cost per SHE (€), mean (SD), range:
		Medical unit: 100 (42.0%)	Overall: 15 (120), 0–1579
		Surgery unit: 4 (1.7%)	Hospitalised: 31 (180) 0–1579
		Care time (minutes), mean (SD), range:	Nonhospitalised: 2 (8) 0–57
		Nursing: 71.2 (63.8), 5–480	by AHA treatment group:
		Medical: 84.5 (90.3), 10–600	Insulin-based therapy: 10 (70), 0–736
		Number of laboratory analyses and examinations/ procedures, mean (SD), range:	Secretagogue-based regimen: 29 (194), 0–1579
		Laboratory analyses: 16 (8.2), 2–53	Oral hypoglycaemic agent without secretagogues: 1 (5), 0–21
		Examinations/procedures: 2.8 (2.0), 0–14	Insulin + secretagogues: 0
		Length of hospitalisation (days), mean (SD), range: 8.8 (9.7), 1–62.3	Mean cost of productivity loss due to hypoglycaemia in the subgroup of active workers, mean (range): 248 (8–1579)
		Absenteeism due to SH in the subgroup of active workers:	Total cost (direct and indirect) per SHE (€), mean (SD), range:
		ED (hours), average: 6.5	Overall: 1493 (2962), 34–26,818
		Hospitalisation (days), average: 4	Hospitalised: 3163 (3866), 230–26,818

Table 4 continued

First author, publication year	Number of patients/ SH cases Study duration	Outcome- resource use/productivity	Outcome- costs
			Nonhospitalised: 175 (112), 34–621
			by AHA treatment group:
			Insulin-based therapy: 1309 (3339), 34–26,818
			Secretagogue-based regimen: 1880 (2435), 63–12,869
			Oral hypoglycaemic agent without secretagogues: 1350 (2436), 82–9862
			Insulin + secretagogues: 1330 (2401), 87–8937
T1DM and T2DM			
Pereira et al., (2020) [28]	676 cases (597 patients) 5 years	Trends in ED admissions for SH (SHEs as a proportion of all ED admissions): 1.5% in 2012 to 1.0% in 2016 (P < .001)	NR
		by DM classification, % (n/N):	
		T1DM: 15.9% (27/170) in 2012 to 24.0% (31/129) in 2016, P = 0.42	
		T2DM: 81.8% (139/170) in 2012 to 72.9% (94/129) in 2016; P = 0.44	
		Length of stay in the ED (hours), median (IQR):	
		Overall: 8 (5–14.5)	
		Patients taking sulphonylureas versus those taking insulin: 12 vs. 8 h, P < .001	
		ED SHEs admitted to hospital, % (n/N):	
		Overall (2012 to 2015): 8.1% (55/676)	
		Patients taking sulphonylureas versus those taking insulin (2012 to 2015): 22.7% (29/128) vs. 4.2% (21/496); P < .001[a]	
		Trends in hospital admission rates for SH, % (n/N): 11% (19/173) in 2012 to 4.3% (5/117) in 2015 and 5.4% (7/130) in 2016, P = .02	

Table 4 continued

First author, publication year	Number of patients/ SH casesStudy duration	Outcome- resource use/productivity	Outcome- costs
Ferreira et al., (2020) [23] (HIPOS-WARD)	170 cases 22 months	NR by DM classification	Direct costs per hospitalisation episode (€) from NHS perspective by diabetes classification, mean (SD):
			T1DM (n = 18): 1840.49 (2100.63)
			Medications: 15.19 (21.67)
			Laboratory analyses: 176.51 (121.51)
			Examinations: 79.74 (90.65)
			Physician attendance: 483.68 (1053.53)
			Nurse attendance: 474.78 (677.19)
			Standardised bed occupancy: 610.60 (524.81)
			T2DM (n = 152): 2051.29 (2154.69)
			Medications: 49.45 (80.72)
			Laboratory analyses: 219.21 (218.30)
			Examinations: 61.45 (72.30)
			Physician attendance: 246.22 (544.23)
			Nurse attendance: 693.06 (983.93)
			Standardised bed occupancy: 781.91 (876.59)
			Indirect costs due to absenteeism (€), mean (SD):
			T1DM: 768.02 (1488.13)
			T2DM: 39.05 (371.72)
			Total cost (direct and indirect) per hospitalisation SHE (€) by DM classification, mean direct + indirect cost:
			T1DM: 1840.49 + 768.02 = 2608.51
			T2DM: 2051.29 + 39.05 = 2090.34

Table 4 continued

First author, publication year	Number of patients/ SH casesStudy duration	Outcome- resource use/productivity	Outcome- costs
Esteves et al., (2018) [30]	Prehospital medical emergency unit = 37 cases ED = 61 cases 3 months	Frequency of prehospital medical emergency unit cases referred to the ED, n/N (%): 17/37 (45.9) Length of ED stay (hours), mean (SD): 17.2 (1.27) Frequency of admission to the ward, n/N (%): 19/61 (31.1) Length of stay in the hospital ward (days), median (range): 9 (3–130)	NR
Coelho et al., (2010) [32]	595 5 years	Proportion of patients transferred to hospital after assistance by emergency and resuscitation medical vehicles (%): by DM classification: T1DM 26.8; T2DM: 63.7 ($p < .05$) by AHA treatment group: OAD 95.2; Insulin 26.8 ($p < .05$)	NR
Marques et al., (2019) [31]	148 cases NR	Emergency and resuscitation medical vehicle cases transferred to the ED, n/N (%): 83/148 (56.1)	NR

€ Euro, *AHA* antihyperglycaemic agent, *DM* diabetes mellitus, *ED* emergency department, *HIPOS-ER* Hypoglycaemia In Portugal Observational Study–Emergency Room, *HIPOS-WARD* Hypoglycaemia In Portugal Observational Study-Ward, *IQR* interquartile range, *NHS* National Health Service, *NR* not reported, *OAD* oral antidiabetic drug, *SH* severe hypoglycaemia, *SD* standard deviation, *T1DM* type 1 diabetes mellitus, *T2DM* type 2 diabetes mellitus

[a]Patients taking both sulphonylureas and insulin were excluded from this analysis

In HIPOS-WARD, the overall total average cost per SHE in patients with T1DM and T2DM was €2608.51 and €2090.34, respectively. In this study, the direct cost per hospitalisation for SHE was approximately €210 higher in patients with T2DM than in those with T1DM (T2DM: €2051.29 vs. T1DM: €1840.49), with physician and nurse attendance contributing to approximately a half of the direct costs in both groups (T2DM: €939.28; T1DM: €958.46) [11].

DISCUSSION

This structured review aimed to identify and summarise studies published between January 2010 and February 2021 reporting on the epidemiological, social and economic burden of SH in patients with DM in Portugal. Twelve studies conducted in healthcare settings were included; epidemiological data related to the burden of SH were the most commonly reported, followed by economic and social outcomes.

The authors acknowledge that estimates from healthcare setting are not representative of the true epidemiology of SH. However, the search did not identify any eligible article on the epidemiology of SH outside a healthcare setting. Similarly to some systematic reviews [36], this review found that comparability between studies was limited because of differences in research settings, study entry criteria, patient characteristics and SH diagnostic criteria. This wide heterogeneity led to variability in the results.

With respect to the epidemiology of SH, in contrast to other studies [37] and reviews of the literature [36, 38], this review found a higher frequency of SHEs in T2DM than in T1DM, based on the five studies [11, 28, 30–32] that presented separate outcomes for the above-mentioned subgroups. In Spain, Núñez et al. [36] reported that the rate of self-reported SH was higher in people with T1DM than in those with insulin-treated T2DM (0.82 and 0.33 episodes per week or 0.90 episodes per year vs. 0.40 per year) [37]. Similarly, a structured literature review conducted by Elliot et al. [38] showed that in people with T1DM in real-world settings; SH rates ranged from 0.70 to 1.59 episodes per

patient per year (PPY). In people with T2DM, SH rates were slightly higher in those on basal-bolus and premix insulin regimens (range 0.00 to 0.20 PPY) than in those on a basal-oral regimen (range 0.00 to 0.12 PPY) [38]. However, other studies observed that hypoglycaemia is an important risk associated with T2DM in patients treated with insulin, with reported rates of SH around 2.5 events per person per year [39]. In this review, evidence suggests that treatment regimens more related with SHEs are insulins and/or secretagogues; therefore, it is important to reflect on patient and physician education regarding strict glycaemic targets and, in general, the regimens that include therapies that increase the hypoglycaemia risk.

Higher rates of SHEs are observed in real-world settings than in randomised clinical trials (RCTs) [38], suggesting that RCT data cannot adequately reflect the burden of this treatment complication. Therefore, real-world evidence is crucial to understanding the true epidemiological burden of SH.

Regarding the causes of or triggers for SH, the top two precipitating factors for SHEs are neglecting to eat and taking the wrong insulin (rapid acting vs. long acting) [40]. Dietary-related factors were the most common probable cause or trigger reported, followed by illness and issues related to DM treatment. Findings from Sepulveda et al. [26] highlighted the importance of hypoglycaemia literacy and awareness in the prevention of SHE. Evidence indicates that participation in structured interventions, including patient education, can reduce the frequency of SH [41].

The International Hypoglycaemia Study Group provides several resources to assist healthcare professionals (HCP) in the understanding of hypoglycaemia causes and treatments [42]. The ADA recommends oral glucose as first-line treatment for hypoglycaemia for all the people with diabetes who are conscious and able to swallow [43].

The ADA recommends the use of glucagon for the individuals who lost consciousness and that cannot ingest oral glucose. Every person with diabetes who is prescribed glucagon should share the exact location of the medication, along with the instructions for using it,

with their daily contacts, e.g., relatives, friends, colleagues, etc. The use of glucagon does not require medical training and different formulations of this product are available: glucagon injection powder that requires reconstitution prior to injection, intranasal glucagon and ready-to-inject glucagon [12].

From a healthcare system perspective, an SHE may require emergency medical assistance and transportation to and medical care in the ED and hospitalisation. Therefore, it is not surprising that SH is a major contributing factor to the substantial healthcare costs of DM in Europe [44, 45]. However, between-country comparisons of the cost attributed to SH is challenging because of variations in diabetes treatment guidelines, care pathways and healthcare costs [44–46]. In this review, mean total cost (direct and indirect) per SHE ranged from €1493.00 in patients with T2DM treated in an emergency setting [24] to €2608.51 in patients with T1DM who were hospitalised [23]. Another review focusing on the burden of SH in Spain [36] reported that the total cost per SHE ranged from €409.97 in patients with T1DM to €713.10 in patients with DM, and this total cost increased to €1703.53 when emergency medical assistance was needed. Jakubczyk et al. [44] estimated the total annual, direct and indirect costs of SHEs in nine European countries. In this study, the cost per SHE treated in hospital ranged from €279.00 in Bulgaria to €1175.00 in Slovenia. The cost per SHE treated by a family member was remarkably lower, ranging from €0.06 in Hungary to €4.76 in Poland [44]. Another costing study conducted in three European countries also reported that, per SHE, hospitalisation was a major cost driver per SHE in Germany, Spain and the UK [45]. Therefore, prevention of SHEs, particularly those requiring hospitalisation, is key to reducing the economic burden of DM in any healthcare system [36]. Furthermore, physicians should be vigilant in preventing hypoglycaemia and should not aggressively attempt to achieve near-normal HbA1C levels in people in whom such targets cannot be safely and reasonably achieved. It was observed that Portuguese literature presented a big gap regarding collection of data related to awareness and social burden of hypoglycaemia.

This fact highlighted that there is still work to be done in terms of health education and/or support programs for physicians, patients and caregivers to minimise therapeutic inertia and the risk of SHE. Moreover, it is equally important to develop and improve data collection strategies and tools including QoL questionnaires.

Nevertheless, the epidemiological burden and economic impact for the National Healthcare System in Portugal are evident and in line with data coming from other countries.

The search strategy was robust and focused on collecting extensive and elaborate data. However, due to the observational, non-interventional nature and heterogeneity of the included studies, further high-quality prospective studies are necessary to accurately establish the burden of SH in patients with DM in Portugal.

CONCLUSIONS

The literature identified in this review reinforces the evidence of the high burden of SH on the life of patients with DM in Portugal and on the global health expenditure. However, existing data are too heterogeneous to provide solid understanding and characterisation of this important complication for patients with T1DM and T2DM. More prospective studies are warranted to identify which factors influencing the frequency of SH, its economic impact and its burden on patients' QoL.

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REFERENCES

1. Kharroubi AT, Darwish HM. Diabetes mellitus: the epidemic of the century. World J Diabetes. 2015;6(6):850–67.

2. Nathan DM, et al. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med. 1993;329(14):977–86.

3. Holman RR, et al. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med. 2008;359(15):1577–89.

4. Association AD. 9. Pharmacologic approaches to glycemic treatment: standards of medical care in diabetes—2021. Diabetes Care. 2021;44(1): 111–1124.

5. Raposo JF. Diabetes: factos e Números 2016, 2017 e 2018. Revista Portuguesa de Diabetes. 2020;15(1): 19–27.

6. IDF. <IDF_Atlas_10th_Edition_2021.pdf>. 2021.

7. Risso T, Furtado C. Rational use of blood glucose test strips for self-monitoring in patients with diabetes mellitus: economic impact in the Portuguese healthcare system. Diabetes Res Clin Pract. 2017;134:161–7.

8. Tavares AI, Marques I. Multi-layer health insurance coverage, medical services use and health in a Universal National Health System, the case of Portugal. Eur J Health Econ. 2021;22(1):141–53.

9. Williams R, et al. Global and regional estimates and projections of diabetes-related health expenditure: results from the international diabetes federation diabetes atlas. Diabetes Res Clin Pract. 2020;162: 108072.

10. Wallia A, Molitch ME. Insulin therapy for type 2 diabetes mellitus. JAMA. 2014;311(22):2315–25.

11. Alao S, et al. Hypoglycemic episodes in hospitalized people with diabetes in Portugal: the HIPOS-WARD study. Clin Diabet Endocrinol. 2021;7(1):2.

12. American Diabetes Association Professional Practice. 6. Glycemic targets: standards of medical care in diabetes-2022. Diabetes Care. 2022;45(Suppl 1): S83–96.

13. Towler DA, et al. Mechanism of awareness of hypoglycemia. Perception of neurogenic (predominantly cholinergic) rather than neuroglycopenic symptoms. Diabetes. 1993;42(12):1791–8.

14. Silbert R, et al. Hypoglycemia among patients with type 2 diabetes: epidemiology, risk factors, and prevention strategies. Curr Diab Rep. 2018;18(8):53.

15. American Diabetes Association (ADA). 4. Comprehensive medical evaluation and assessment of comorbidities: standards of medical care in diabetes-2021. Diabetes Care. 2021;44(Suppl 1):S40-s52.

16. Dømgaard M, et al. Individual and societal consequences of hypoglycemia: a cross-sectional survey. Postgrad Med. 2015;127(5):438–45.

17. Rossi MC, et al. Impact of severe and symptomatic hypoglycemia on quality of life and fear of hypoglycemia in type 1 and type 2 diabetes. Results of the Hypos-1 observational study. Nutr Metab Cardiovasc Dis. 2019;29(7):736–43.

18. Ampudia-Blasco FJ, et al. Conversations and reactions around severe hypoglycaemia (CRASH): Spanish results of a global survey of people with type 1 diabetes or insulin-treated type 2 diabetes and caregivers. Endocrinol Diabetes Nutr. 2021;2:2.

19. Hoskins N, Tikkanen CK, Pedersen-Bjergaard U. The economic impact of insulin-related hypoglycemia in Denmark: an analysis using the local impact of hypoglycemia tool. J Med Econ. 2017;20(4):363–70.

20. Parekh W, et al. The economic burden of insulin-related hypoglycemia in adults with diabetes: an analysis from the perspective of the Italian healthcare system. Diabetes Ther. 2018;9(3):1037–47.

21. International Diabetes Federation (IDF). IDF Diabetes Atlas 2019, 9th edition. 2019.

22. Conceicao J, et al. Severe hypoglycaemia among patients with type 2 diabetes requiring emergency hospital admission: the hypoglycaemia in Portugal observational study-emergency room (HIPOS-ER). Diabetes Obes Metab. 2018;20(1):50–9.

23. Ferreira JP, et al. Hospitalization costs due to hypoglycemia in patients with diabetes: a micro-costing approach. Diabetes Therapy. 2020;11(10): 2237–55.

24. Laires PA, et al. The cost of managing severe hypoglycemic episodes in type 2 diabetic patients. Expert Rev Pharmacoecon Outcomes Res. 2016;16(2):315–25.

25. Torre C, et al. Real-world prevalence of mild to moderate hypoglycemic episodes in type 2 diabetes in Portugal: results from the HIPOS-PHARMA study. Prim Care Diabetes. 2018;12(6):537–46.

26. Sepulveda E, et al. Differentiating hypoglycemia awareness status from hypoglycemia experience in tools for measuring impaired awareness of hypoglycemia. Diabetes Technol Ther. 2020;22(7): 541–5.

27. Azevedo S, et al. The impact of prolonged use of continuous subcutaneous insulin infusion in the control of type-1 diabetes. Acta Med Port. 2022;32(1):17–24.

28. Pereira CA, Almeida R, Dores J. Characteristics of hypoglycaemic episodes in diabetic patients treated at the emergency room of a Portuguese tertiary centre, 2012–2016. Endocrinol Diabet Metab. 2020;3(3):e00150.

29. Pereira M, Tavares H, Carvalho AJ. O Impacto da Hipoglicemia no Resultado Clínico de Doentes

Diabéticos Não-críticos Internados em Serviços Médicos: Um Estudo de Caso-controlo. Revista Portuguesa de Diabetes. 2016;11(1):3–9.

30. Esteves C, et al. Severe hypoglycaemia in diabetic patients in pre-hospital and emergency department care: a cross-sectional survey. BMC Res Notes. 2018;11(1):249.

31. Marques A, et al. Estudo HiposRainha–Hipoglicémias Severas Numa Viatura Médica de Emergência e Reanimação. Revista Portuguesa de Diabetes. 2019;14(1):3–10.

32. Coelho JF, et al. Caracterização das hipoglicémias severas em doentes diabéticos assistidos por uma viatura médica de emergência e reanimação. Revista Portuguesa de Diabetes. 2010;5(3):100–5.

33. Pereira M, et al. Trends in prevalence of diabetes mellitus and mean fasting glucose in Portugal (1987–2009): a systematic review. Public Health. 2014;128(3):214–21.

34. Little S, et al. Comparison of optimised MDI versus pumps with or without sensors in severe hypoglycaemia (the hypo COMPaSS trial). BMC Endocr Disord. 2012;12(1):33.

35. Gold AE, Macleod KM, Frier BM. Frequency of severe hypoglycemia in patients with type I diabetes with impaired awareness of hypoglycemia. Diabetes Care. 1994;17(7):697–703.

36. Núñez M, et al. Epidemiology, quality of life, and costs associated with hypoglycemia in patients with diabetes in spain: a systematic literature review. Diabetes Therapy. 2019;10(2):375–92.

37. Donnelly LA, et al. Frequency and predictors of hypoglycaemia in type 1 and insulin-treated type 2 diabetes: a population-based study. Diabet Med. 2005;22(6):749–55.

38. Elliott L, et al. Hypoglycemia event rates: a comparison between real-world data and randomized controlled trial populations in insulin-treated diabetes. Diabetes Ther. 2016;7(1):45–60.

39. Khunti K, et al. Rates and predictors of hypoglycaemia in 27 585 people from 24 countries with insulin-treated type 1 and type 2 diabetes: the global HAT study. Diabetes Obes Metab. 2016;18(9):907–15.

40. Freeland B. Hypoglycemia in diabetes mellitus. Home Healthc Now. 2017;35(8):414–9.

41. Kloos C, et al. Reduction of severe hypoglycaemia in people with type 2 diabetes after a structured inpatient intervention. 2019.

42. International Hypoglycaemia Study Group. Practice tools for patients & care providers. [cited 2019 24 November]; Available from: https://ihsgonline.com/resources/tools-for-patients-and-care-providers/.

43. American Diabetes Association (ADA). 6. Glycemic targets: standards of medical care in diabetes-2021. Diabetes Care. 2021;44(Suppl 1):S73-s84.

44. Jakubczyk M, et al. Cost of severe hypoglycaemia in nine European countries. J Med Econ. 2016;19(10):973–82.

45. Hammer M, et al. Costs of managing severe hypoglycaemia in three European countries. J Med Econ. 2009;12(4):281–90.

46. Aazza S, et al. Antioxidant, anti-inflammatory and anti-hyperglycaemic activities of essential oils from thymbra capitata, thymus albicans, thymus caespititius, thymus carnosus, thymus lotocephalus and thymus mastichina from Portugal. Nat Prod Commun. 2022;11(7):1029–38.