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Hospital admissions trends for severe hypoglycemia in diabetes patients in Spain, 2005 to 2015

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A B S T R A C T

Aims: To analyze hospital admissions trends, inpatient mortality, and mean length of hospital stay due to hypoglycemia in patients with diabetes in Spain from 2005 to 2015.

Methods: National Institute of Statistics provided information on hospital discharge and mortality. Hospital admissions due to severe hypoglycemia were identified using ICD-9 codes. Age-adjusted admission and mortality rates were stratified by sex and year. Joinpoint regression models were used to estimate trends.

Results: Admissions rates per 100,000 population were higher for men than women in 2005 (30.2, 95%CI:29.3, 31.0 versus 21.5, 95%CI:20.9, 22.1) and 2015 (23.7, 95%CI:23.0, 24.4 versus 13.2, 95%CI:12.7, 13.6). Mortality per 100,000 population was also higher for men in both years (2005: 9.4, 95%CI:7.8, 11.0 versus 8.6, 95%CI:7.4, 9.8; 2015: 6.4, 95%CI:5.3, 7.6 versus 4.1, 95%CI:3.3, 4.8). Mortality dropped 5.2 percentage points annually (95%CI:−8.4, −1.9) in men and 7.0 percentage points annually (95%CI:−8.7, −5.2) in women from 2005 to 2015. Mean length of hospital stay changed only for women: 7.8 days (95%CI:7.5, 8.0) to 6.7 days (95%CI:6.4, 6.9).

Conclusions: Hospital admissions and inpatient mortality due to hypoglycemia in diabetes patients decreased from 2005 to 2015. This trend was more pronounced in women. Mean length of hospital stay decreased in women.

1. Introduction

People with diabetes mellitus (DM) may experience numerous chronic and severe complications, which can result from both the disease and its treatment. Severe hypoglycemia is the most common acute adverse effect of glucose-lowering therapy [1], and it is also one of the most feared for its healthcare, social, and economic impact [2]. This complication is

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associated with a 3.4-fold increased risk of death in patients with diabetes [3], who experience, on average, 19 episodes of mild hypoglycemia and one episode of severe hypoglycemia every year [4].

DM imposes a high cost for healthcare systems, as evidenced by the Hypoglycaemia Assessment Tool (HAT) study [5] estimating that the global healthcare cost was at least USD 612 billion in 2014. Hypoglycemia increases the use of healthcare resources, and consequently, contributes to an increased economic burden of diabetes management. In 2010, Spanish national data provided an estimated cost of approximately €3500 per severe hypoglycemia episode [6].

Previous studies reported decreased or increased trends in hospital admissions for hypoglycemia depending on the study period and the country [7–9]. Data from countries such as, the USA or England seem to indicate that there has been a stabilization, or even a decrease, in severe hypoglycemia events during the last decade. In Spain, hospital admission rates in patients with diabetes due to primary severe hypoglycemia (defined as such if it is the main reason for admission) remained stable from 1997 to 2007, standing at around 1.7% a year [10]. Recommendations about glycaemic control and prescribing practices of antidiabetic agents in patients with diabetes vary throughout the years. Several authors [11,12] think that the incidence of severe hypoglycemia increased due to the findings of the Diabetes Control and Complications Trial (DCCT) [13] in 1993, which suggested to intensify the hyperglycemia control. Later research did not support this recommendation because they identified a harmful effect of the use of intensive therapy [14].

It is important to know the effect of recommendations on clinical diabetes management. Thus, the main objective of this study was to analyze trends in hospital admissions and inpatient mortality due to hypoglycemia in patients with diabetes in Spain from 2005 to 2015.

2. Material and methods

We analyzed data from the National Hospital Morbidity Survey and the ongoing Population Census. The National Institute of Statistics (NIS) [15] provided access to these databases. These databases are public and freely accessible via NIS web, and all data are anonymized. Data from all national hospitals (private and public) were included. We used the ICD-9 (International Classification of Diseases, Ninth Revision) codes 251.0 (hypoglycemic coma), 251.1 (other specified hypoglycemia), 251.2 (hypoglycemia, unspecified) and 251.3 (Postsurgical hypoinsulinemia) to identify hospital admissions due to severe hypoglycemia (as primary cause of admission) [16]. The study period began in 2005, coinciding with the availability of the four ICD-9 codes, and it ended in 2015. We collected the following variables for the study period: admission year, sex, age, inpatient mortality, and length of hospital stay.

2.1. Statistical analysis

We calculated the absolute and relative frequency of hospital admissions and inpatient deaths, as well as mean length of hospital stay, with 95% confidence intervals (CIs) for each year. Age-adjusted admission rates (AAAR) and mortality rates (AAMR) were calculated by direct methods, taking the 2013 European population as the reference population for each year. To evaluate the change in admissions and mortality trends for the study period, joinpoint regression models were fitted, identifying the possible shift points of trends and calculating the annual percent change (APC) and 95% CIs of the AAAR within each segment [17]. All analyses were stratified by sex. The elevation factor deriving from the complex sample design was considered in the weighting of the analyses and adjusted for each survey in each year. SPSS v.18 statistical software was used to calculate the rates as well as the Joinpoint Regression Program v.4.6.0.0 software [17].

3. Results

There were a total of 4,678,130 hospital admissions in 2005 and 4,746,651 in 2015; 10,084 and 8331, respectively, were due to hypoglycemia, and of these patients, 340 and 244 died. In 2005, 0.24% (95% CI: 0.23, 0.25) of total admissions in men were due to hypoglycemia and 0.19% (95% CI: 0.18, 0.20) in women. In 2015, admissions for severe hypoglycemia represented 0.22% (95% CI: 0.21, 0.23) of total admissions in men and 0.14% (95% CI: 0.13, 0.15) in women, and patients had a mean age of 63.2 ± 23.7 years, and 53.7% were men. In 2005, 2.70% (95% CI: 2.24, 3.10) and 4.10% (95% CI: 3.59, 4.80) of patients admitted to the hospital with primary hypoglycemia died during the hospital stay, in men and women, respectively. In 2015, the inpatient mortality due to hypoglycemia was 2.50% (95% CI: 2.07, 3.00) in men and 3.50% (95% CI: 2.94, 4.20) in women. Length of hospital stay in men was higher than in women evey year Table 1 presents the number and percentage of hospital admissions, inpatient deaths and mean lengths of hospital stay, with 95% CIs, for each year.

Table 2 shows the AAAR and AAMR for each year. In 2005, there were 30.2 (95%CI: 29.3, 31.0) admissions per 100,000 population in men, which dropped to 23.7 (95%CI: 23.0, 24.4) admissions per 100,000 population in 2015. In women, these figures were 21.5 (95%CI: 20.9, 22.1) and 13.2 (95%CI: 12.7, 13.6), respectively. In-hospital mortality due to hypoglycemia decreased in both sexes: in men, from 9.4 (95%CI: 7.8, 11.0) to 6.4 (95%CI: 5.3, 7.6) per 100,000 population, and for women from 8.6 (95%CI: 7.4, 9.8) to 4.1 (95%CI: 3.3, 4.8) per 100,000 population.

Table 3 shows the change in hospital admissions and mortality trends for the study period, with the shift points, as well as the APC (95% CI) within each segment. Fig. 1 presents these trends visually. Throughout the study period, admissions in men decreased by an average APC of −3.3% (95% CI: −4.2, −2.4). From 2007 to 2015, admissions in women also dropped 7.2% per year (95% CI: −8.5, −5.8). In-hospital mortality fell by 5.2% (95% CI: −8.4, −1.9) per year for men and 7.0% (95% CI: −8.7, −5.2) per year for women.

4. Discussion

In Spain, between 2005 and 2015, both the age-adjusted admission and mortality rates due to hypoglycemia

Table 1 – Hospital admissions, inpatient mortality and lengths of stay due to hypoglycemia in Spain 2005–2015.

Sex	Year	All-cause admissions	Admissions due to primary hypoglycemia		Hospital deaths due to primary hypoglycemia		Length of hospital stay(days)
		n	n	% (95% CI)	n	% (95% CI)	Mean (95% CI)
Men	2005	2,175,998	5288	0.24 (0.23, 0.25)	141	2.7 (2.24, 3.1)	8.6 (8.4, 8.9)
	2006	2,193,315	5474	0.25 (0.24, 0.26)	120	2.2 (1.82, 2.6)	8.2 (8.0, 8.5)
	2007	2,117,201	5723	0.27 (0.26, 0.28)	173	3.0 (2.59, 3.5)	8.2 (8.0, 8.4)
	2008	2,222,817	5505	0.25 (0.24, 0.26)	170	3.1 (2.64, 3.6)	8.3 (8.1, 8.6)
	2009	2,218,906	5513	0.25 (0.24, 0.26)	175	3.2 (2.72, 3.7)	8.2 (8.0, 8.4)
	2010	2,191,402	5426	0.25 (0.24, 0.26)	138	2.5 (2.14, 3.0)	8.2 (8.0, 8.4)
	2011	2,182,117	5328	0.24 (0.24, 0.25)	148	2.8 (2.35, 3.3)	8.2 (8.0, 8.4)
	2012	2,167,701	4777	0.22 (0.21, 0.23)	137	2.9 (2.41, 3.4)	8.3 (8.1, 8.6)
	2013	2,186,003	4706	0.22 (0.21, 0.22)	123	2.6 (2.17, 3.1)	8.4 (8.2, 8.7)
	2014	2,223,772	4664	0.21 (0.20, 0.22)	103	2.2 (1.80, 2.7)	8.4 (8.1, 8.6)
	2015	2,244,928	4884	0.22 (0.21, 0.23)	122	2.5 (2.07, 3.0)	8.8 (8.5, 9.1)
Women	2005	2,502,132	4796	0.19 (0.18, 0.20)	199	4.1 (3.59, 4.8)	7.8 (7.5, 8.0)
	2006	2,532,473	5206	0.21 (0.20, 0.21)	150	2.9 (2.44, 3.4)	7.3 (7.1, 7.5)
	2007	2,444,630	5346	0.22 (0.21, 0.23)	168	3.1 (2.69, 3.6)	7.0 (6.8, 7.2)
	2008	2,591,222	5152	0.20 (0.19, 0.21)	180	3.5 (3.00, 4.0)	7.0 (6.8, 7.2)
	2009	2,562,961	4859	0.19 (0.18, 0.20)	151	3.1 (2.63, 3.6)	6.9 (6.7, 7.1)
	2010	2,529,143	4813	0.19 (0.18, 0.20)	137	2.8 (2.39, 3.4)	6.9 (6.7, 7.1)
	2011	2,488,570	4614	0.19 (0.18, 0.19)	153	3.3 (2.81, 3.9)	6.7 (6.5, 6.9)
	2012	2,465,385	3923	0.16 (0.15, 0.17)	132	3.4 (2.82, 4.0)	6.2 (6.0, 6.5)
	2013	2,451,424	3755	0.15 (0.15, 0.16)	121	3.2 (2.67, 3.8)	6.6 (6.3, 6.8)
	2014	2,495,895	3533	0.14 (0.13, 0.15)	127	3.6 (3.00, 4.3)	6.6 (6.3, 6.8)
	2015	2,501,723	3447	0.14 (0.13, 0.15)	122	3.5 (2.94, 4.2)	6.7 (6.4, 6.9)

CI: confidence interval.

Table 2 – Admission rates and age-adjusted inpatient mortality rates due to hypoglycemia in Spain, 2005–2015.

Sex	Year	Admissions due to primary hypoglycemia		Hospital deaths due to hypoglycemia	
		n	AAAR (95% CI)	n	AAMR (95% CI)
Men	2005	5288	30.2 (29.3, 31.0)	141	9.4 (7.8, 11.0)
	2006	5474	30.5 (29.7, 31.4)	120	7.9 (6.4, 9.3)
	2007	5723	31.3 (30.4, 32.1)	173	11.2 (9.5, 12.9)
	2008	5505	29.6 (28.8, 30.4)	170	10.5 (8.8, 12.1)
	2009	5513	28.9 (28.1, 29.6)	175	10.5 (8.9, 12.1)
	2010	5426	27.9 (27.2, 28.7)	138	8.0 (6.7, 9.4)
	2011	5328	27.1 (26.3, 27.8)	148	8.3 (6.9, 9.6)
	2012	4777	24.0 (23.3, 24.7)	137	7.6 (6.3, 8.9)
	2013	4706	23.2 (22.5, 23.9)	123	6.8 (5.6, 8.0)
	2014	4664	22.9 (22.2, 23.6)	103	5.5 (4.4, 6.6)
	2015	4884	23.7 (23.0, 24.4)	122	6.4 (5.3, 7.6)
Women	2005	4796	21.5 (20.9, 22.1)	199	8.6 (7.4, 9.8)
	2006	5206	22.7 (22.1, 23.4)	150	6.3 (5.3, 7.3)
	2007	5346	22.9 (22.3, 23.5)	168	6.9 (5.8, 7.9)
	2008	5152	21.5 (20.9, 22.1)	180	7.0 (6.0, 8.1)
	2009	4859	19.9 (19.4, 20.5)	151	5.8 (4.9, 6.7)
	2010	4813	19.4 (18.8, 19.9)	137	5.1 (4.3, 6.0)
	2011	4614	18.3 (17.8, 18.9)	153	5.5 (4.6, 6.4)
	2012	3923	15.2 (14.7, 15.7)	132	4.6 (3.8, 5.4)
	2013	3755	14.5 (14.1, 15.0)	121	4.2 (3.5, 5.0)
	2014	3533	13.7 (13.2, 14.1)	127	4.2 (3.5, 5.0)
	2015	3447	13.2 (12.7, 13.6)	122	4.1 (3.3, 4.8)

AAAR: age-adjusted admission rate per 100,000 population, direct method (standard European population 2013).
AAMR: age-adjusted mortality rate per 100,000 population, direct method (standard European population 2013).
CI: confidence interval.

Table 3 – Hospital admissions and mortality trends in diabetes patients due to hypoglycemia, joinpoint regression (2005–2015).

	Trend segment 1			Trend segment 2		
	Period	APC (95% CI)	p-value	Period	APC (95% CI)	p-value
Hospital admissions						
Men	2005–2015	−3.3 (−4.2, −2.4)	<0.001			
Women	2005–2007	3.8 (−8.3, 14.5)	0.485	2007–2015	−7.2 (−8.5, −5.8)	<0.001
Hospital mortality						
Men	2005–2015	−5.2 (−8.4, −1.9)	0.006			
Women	2005–2015	−7.0 (−8.7, −5.2)	<0.001			

APC: annual percent change.
CI: confidence interval.

decreased significantly, and this trend was more pronounced in women. 2007 marked a significant change in the trend of hospital admissions for women, wherein the APC was negligible between 2005 and 2007 but showed a significant decline between 2007 and 2015. For all years in the study period, the percentage of admissions due to hypoglycemia was significantly higher in men than women. A remarkable difference was also found in AAAR and could be related to a higher prevalence of diabetes in men.

Our study databases did not include information about type of diabetes. As the proportion of type 1 diabetes is less than 10% [18], we assumed that most of admissions due to hypoglycemia were in patients with type 2 diabetes. Thus, the decline in AAAR due to hypoglycemia may be due to several factors: it coincides with the approval for the Spanish market of the first glucagon-like peptide(GLP)-1 receptor agonist, exenatide, in 2007 and the first dipeptidyl peptidase (DPP)-4 inhibitor, sitagliptin, in 2008 [19]. Both of these drug classes are incretins, which have the advantage of not causing hypoglycemia or weight gain while at the same time delaying insulin therapy initiation or reducing insulin dose. Together with metformin, incretins have started to displace secretagogues (sulfonylureas and glinides) in clinical practice guidelines, as these older drugs can cause hypoglycemia and weight gain.

Sulfonylureas are still being used in some cases in combination with metformin due to their high effectiveness in reducing HbA1c and their low cost. However, in January 2009, a joint publication by the American Diabetes Association (ADA), the American College of Cardiology (ACC) and the American Heart Association (AHA) recommended relaxing the glycemic targets for diabetes control, based on the

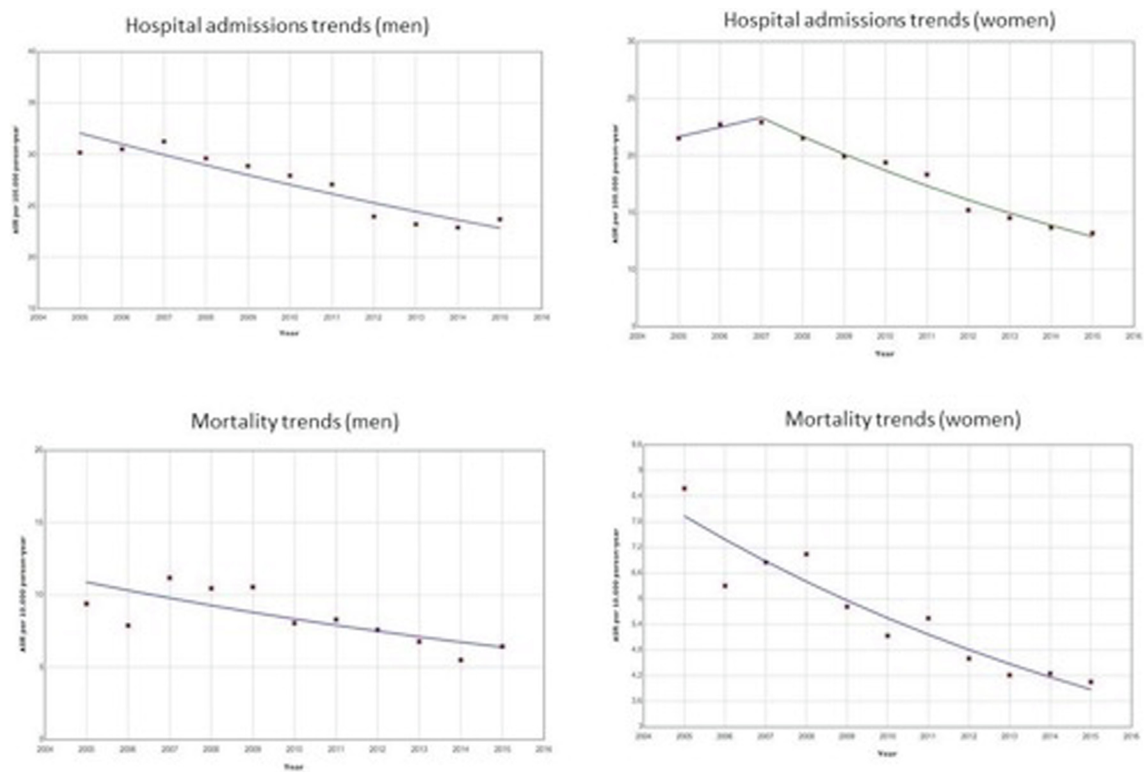

Fig. 1 – Hospital admissions and mortality trends due to hypoglycemia in men and women using joinpoint regression, Spain (2005–2015).

findings of the ACCORD, ADVANCE and VADT studies [14]. Furthermore, results showed the importance of reducing secondary control effects, specifically hypoglycemia, by adopting more lenient glycemic targets. The resulting changes to clinical practice could partially explain the decrease in AAAR. Another factor that may have had an influence is the gradual change from insulin scale charts for fast-acting insulin or premixed insulins to a basal-bolus regimen; different studies have associated both insulin scale charts [20] and premixed insulin [21] with high rates of hypoglycemia. The continuous glucose monitor (CGM) was introduced into the Spanish public health system in 2018. Further research is needed to assess if CGM reduces hypoglycemia events.

Data from the present study showed that there was a significant total decline in the AAAR due to hypoglycemia (−33% in men and −57% in women) in Spain between 2005 and 2015. However, the prevalence of diabetes increased over the 10-year period. According to the Spanish National Health Survey, 6.03% of people older than 15 years reported having a diagnosis of diabetes in 2006, compared to 7.82% in 2017—a relative increase of 29.6% [22]. Moreover, hospitalizations in patients with diabetes more than doubled in Spain from 1997 to 2010 [23]. Heart failure and neoplasms saw the greatest annual increases and remained the primary causes of admission, while hospitalizations for coronary and cerebrovascular diseases increased more modestly, suggesting an improvement in cardiovascular care in diabetes in Spain.

Thus, these findings suggest that great advances in pharmacological therapies are enabling patients to control their diabetes better, with less incidence of hypoglycemia. An official report from the Spanish Ministry of Health [24] showed that the use of sulfonylureas per 1000 people decreased from 29.1 defined daily doses (DDD) in 2000 to 12.3 DDDs in 2014. In addition, the use of human insulin also decreased; by 2014, insulin analogues represented 89% of total insulin use.

In Germany, Holstein et al. [25] showed that the frequency of severe hypoglycemia among all emergency admissions increased considerably from 264 events in 1997–2000 to 495 events in 2007–2010. That study period pre-dated ours and probably corresponded to a different pattern of drug management, with higher use of sulfonylureas and human insulin, and more stringent HbA1c targets. Zaccardi et al. [8] analyzed hospital admissions for hypoglycemia between 2005 and 2014 and found that hospital admissions in England for hypoglycemia increased by 39% in absolute terms and by 14% considering the general increase in hospitalization; however, the number of admissions remained more stable from 2010. Zhong et al. [11] analyzed the period 1998–2013, also in England, showing an increased burden of hypoglycemia requiring hospitalization in adults with both type 1 and type 2 DM, with the exception of elderly adults with type 2 DM, whose admissions started to decline in 2009. In the USA, a retrospective observational study using data from Medicare fee-for-service beneficiaries (aged $\geq$ 65 years) from 1999 to 2011 [7] found that admissions for hypoglycemia have declined modestly since 2007. Also in the USA, Lipska et al. [26] used claims data from 1.66 million privately insured and Medicare Advantage patients with type 2 diabetes from 2006 to 2013 and found that despite dramatic changes in the use of glucose-lowering drugs, the overall rate of severe hypoglycemia remained largely unchanged. In Canada [27], a population-based cross-sectional analysis in older adults (mean age 75 years) treated for diabetes from 2002 to 2013 showed a decrease in the percentage of patients presenting to hospital for hypoglycemia.

It is difficult to explain our good results relative to those from other countries [7,8,11,25–27]. Spain has a national health system guaranteeing universal access to primary and specialized care. In the 1990 s, general practitioners (GPs) become the reference doctor for patients with diabetes. Each GP provides routine care to 100 to 150 type 2 diabetes patients [28]. A National Strategy for the Prevention, Diagnosis and Treatment of Diabetes dates back to 2006 [29], and new drugs associated with a lower risk of hypoglycemia are widely available. These factors could be at play in preventing hypoglycemia.

The role of GPs in managing insulin in type 2 diabetes patients could also be an important issue. In a study involving 17,374 people from different countries (Canada, China, Germany, Israel, Italy, Poland, Portugal, Spain, Turkey and the UK), GPs and other specialists achieved comparable improvements in glycemic control following insulin initiation in patients with different characteristics [30]. Clinical inertia could be associated with lower hypoglycemia rates, as GPs (46%) showed more inertia compared to internists (43.2%) and endocrinologists (31.3%), waiting three to six months before starting insulin in poorly controlled patients [31].

Worse glycemic control might also result in reduced admissions for severe hypoglycemia; however, different publications have reported that a good proportion of Spanish patients achieve clinical targets. In one study, between 52.2% and 55.6% of patients reached an HbA1c of 7% or less from 2007 to 2013, while 72.8% to 75.7% met individualized targets [32]. In another report, 58% of elderly patients with diabetes (mean age 82.3 years) had an HbA1c below 7.0%, and in 36.8%, it was less than 6.5% [33].

Regarding mortality, our results show consistently higher rates in men for every year under study as well as a significant decrease over the period as a whole. These improvements can be attributed to advances in primary, secondary and tertiary prevention, including access to new drugs, which have enabled better supervision of patients and fewer complications, thus lower mortality rates. The reduction in mortality also coincided with the launch of the National Diabetes Strategy in 2006, which seems to have led to a decrease in all-cause (including hypoglycemic-related) mortality in patients with diabetes [29]. A recent study investigated the global differences and trends of hypoglycemia-related mortality in 109 countries, reporting that most countries in South America, Central America and the Caribbean showed the highest proportions of diabetes-related deaths attributable to hypoglycemia [34]. Countries with higher socioeconomic development had lower rates. However, between 2000 and 2014, rising trends were also observed in the USA and Japan.

Finally, the length of hospital stay due to hypoglycemia was significantly higher in men than in women for all years. In men, this indicator remained quite stable, oscillating between 8.2 and 8.6 days. In women, the length of stay decreased significantly, from 7.8 days in 2005 to 6.7 days in 2015. A high number of comorbidities or complications could be related to longer hospital stays in men, and overall life expectancy could also have an impact.

To our knowledge, this is the first study using national data that reports a significant reduction in hospital admissions and mortality due to severe hypoglycemia. However, there are several limitations to this study. Our data were obtained from official Spanish databases [15], guaranteeing their validity but the ICD-9 classification system is imperfect for case identification, as it was created for reimbursement rather than research purposes. This selection bias is common is this type of database analysis. We collected inpatient mortality of those patients who were admitted to the hospital due to severe hypoglycemia (as primary cause of admission) from the National Hospital Morbidity Survey. Data about the specific cause of death of these patients are not available and we supposed they were due to severe hypoglycemia. Therefore, our study results and conclusions are subjected to this limitation. The lack of information about patients' treatments, comorbidities, and other characteristics could limit advanced analyses, although this was not the aim of the study. Further research is needed to identify the characteristics of the Spanish healthcare system and the variables associated with these results that could inform policies in other healthcare systems.

In summary, hospital admissions and inpatient mortality adjusted for age due to hypoglycemia in patients with diabetes in Spain presented a reduction from 2005 to 2015 and this trend was more pronounced in women. The mean length of hospital stay in diabetes patients with hypoglycemia remained stable in men but decreased in women.

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Author contributions

D.O.B drafted the manuscript. D.O.B, A.G.M., AM.C.C., J.N.P., VF.G.G., JA.Q.R, FJ.P.G., A.L.P., C.C.M. contributed to the study concept and design. JA.Q.R. contributed to the data management and statistical analysis. D.O.B, A.G.M., AM.C.C., J.N.P., VF.G.G., JA.Q.R, FJ.P.G., A.L.P., C.C.M. contributed to the interpretation of the results and revision of the manuscript for important intellectual content. D.O.B., A.G.M., AM.C.C, J.N.P., VF.G.G., JA.Q.R., FJ.P.G., A.L.P., C.C.M. approved the final version of the manuscript. D.O.B. and A.G.M. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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