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ORIGINAL ARTICLE

Risk factors for hypoglycaemia in non-critical hospitalised diabetic patients

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KEYWORDS
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Abstract
Objective: To determine the risk factors for hypoglycaemia in patients with diabetes on general hospital wards based on a systematic review of the literature since 2013 and meta-analysis.
Methods: Systematic review of the literature focused on the conceptual and methodological aspects of the PRISMA Declaration. The search carried out in Pub Med, Web of Science, Medline, Scielo, Lilacs, OVID, grey literature and Google Academic focused on risk factors for hypoglycaemia in patients with diabetes on general hospital wards. The CASPe (Critical Appraisal Skills Programme Spanish) tool was applied for quality control.
Results: From 805 references, 70 potentially eligible articles were identified for review of abstracts and full text. Finally, according to inclusion and exclusion criteria, seven studies with 554,601 patients of Asian, European and North American ethnicity were selected.

A meta-analysis performed using the random effects model found an association between the presence of hypoglycaemia and: the use of insulin (OR 2.89 [95% CI: 1.8—4.5]); the use of long-acting insulin (OR 2.27 [95% CI: 1.8—2.8]) or fast-acting insulin (OR 1.4 [95% CI: 1.18—1.85]); nasogastric tube feeding (OR 1.75 [95% CI: 1.33—2.3]); chronic kidney disease (OR 1.65 [95% CI: 1.14—2.38]); congestive heart failure (OR 1.36 [95% CI: 1.10—1.68]); and elevated levels of glycosylated haemoglobin (OR 1.59 [95% CI: 1.32—1.91]).
Conclusion: The factors associated with the risk of hypoglycaemia in non-critically ill hospitalised patients with type 2 diabetes were: use of any insulin; nasogastric tube feeding; elevated glycosylated haemoglobin levels; history of congestive heart failure; and chronic kidney disease.

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PALABRAS CLAVE
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Hospitalización

Factores de riesgo de hipoglicemia en pacientes diabéticos hospitalizados no críticos: revisión sistemática de la literatura y metaanálisis

Resumen

Objetivo: Determinar los factores de riesgo de hipoglicemia en pacientes diabéticos hospitalizados en servicio general a partir de una revisión sistemática de la literatura y metaanálisis, desde el 2013.

Métodos: Revisión sistemática de la literatura centrada en los aspectos conceptuales y metodológicos de la Declaración PRISMA. La búsqueda realizada en Pub Med, Web of Science, Medline, Scielo, Lilacs, OVID, literatura gris y Google académico se centró en factores de riesgo de hipoglicemia en pacientes diabéticos hospitalizados en servicio general. Se aplicó la herramienta CASPe (*Critical Appraisal Skills Programme* Español) para control de calidad.

Resultados: A partir de 805 referencias, se identificaron 70 artículos potencialmente elegibles para revisión de resúmenes y texto completo, finalmente de acuerdo a criterios de inclusión y exclusión se seleccionaron 7 estudios con 554.601 pacientes de etnia oriental, europea y norte americana.

Se realizo un meta-análisis usando el modelo de efectos aleatorios, donde se encontró una asociación entre la presencia de hipoglicemia y el uso de insulina (OR 2,89(IC 95%:1,8–4,5)); uso de insulina larga acción (OR 2,27(IC 95%:1,8–2,8)); o de acción rápida (OR 1,4 (IC 95%:1,18–1,85)); alimentación por sonda nasogástrica (OR 1,75(IC 95%:1,33–2,3)); la presencia de enfermedad renal crónica(OR 1,65(IC 95%:1,14–2,38)); Falla cardiaca congestiva (OR 1,36(IC 95%:1,10–1,68)); y los niveles elevados de Hemoglobina glicosilada (OR 1,59(IC 95%:1,32–1,91)).

Conclusión: Los factores asociados con riesgo de hipoglicemia en el paciente diabético tipo 2, hospitalizado no crítico, fueron: uso de cualquier insulina, alimentación por sonda nasogástrica, niveles elevados de hemoglobina glicosilada, antecedente de falla cardiaca congestiva o enfermedad renal crónica.

Introduction

Hypoglycemia is one of the metabolic decompensations of diabetes mellitus, the severity of which, although sometimes unnoticed, can endanger patients' lives. Hypoglycemia in hospitalized diabetic patients is associated with increased hospital stay, anxiety, depression, and mortality.[1] The prevalence of hypoglycemia in hospitalized patients has been estimated at 10.1% at the intensive care unit (ICU) setting, and 3.5% outside the ICU. These data highlight the importance of developing strategies to identify patients at risk in the hospital setting and prevent the consequences of hypoglycemic events, thereby optimizing therapeutic regimens contributing to glycemic control. Different risk factors for hypoglycemia during hospitalization have been identified, including advanced age, low weight, high levels of glycosylated hemoglobin, low glomerular filtration rates, and type 2 diabetes mellitus.[2]

The objective of this study was to determine the risk factors for hypoglycemia in non-critically ill hospitalized patients with type 2 diabetes mellitus through a systematic literature review and meta-analysis.

Material and methods

Study design

Systematic literature review based on the conceptual and methodological aspects of the PRISMA statement.[3,4] According to the selection criteria, the studies corresponded to cohort, case-control, and cross-sectional studies conducted in adult patients with type 2 diabetes mellitus hospitalized in the last 10 years, published in English and Spanish; case reports, case series, systematic reviews, editorials, and letters to the editor were excluded. Additionally, the CASPe (Critical Appraisal Skills Programme *Español*) tool was used to check methodological quality, which was applied to all studies selected by two expert evaluators. The study was conducted with a defined protocol and registered in PROSPERO, an international database of systematic review registrations.[5]

Search strategy

The search strategy was conducted in PubMed, Web of Science, Medline, Scielo, Lilacs, OVID, as well as gray liter-

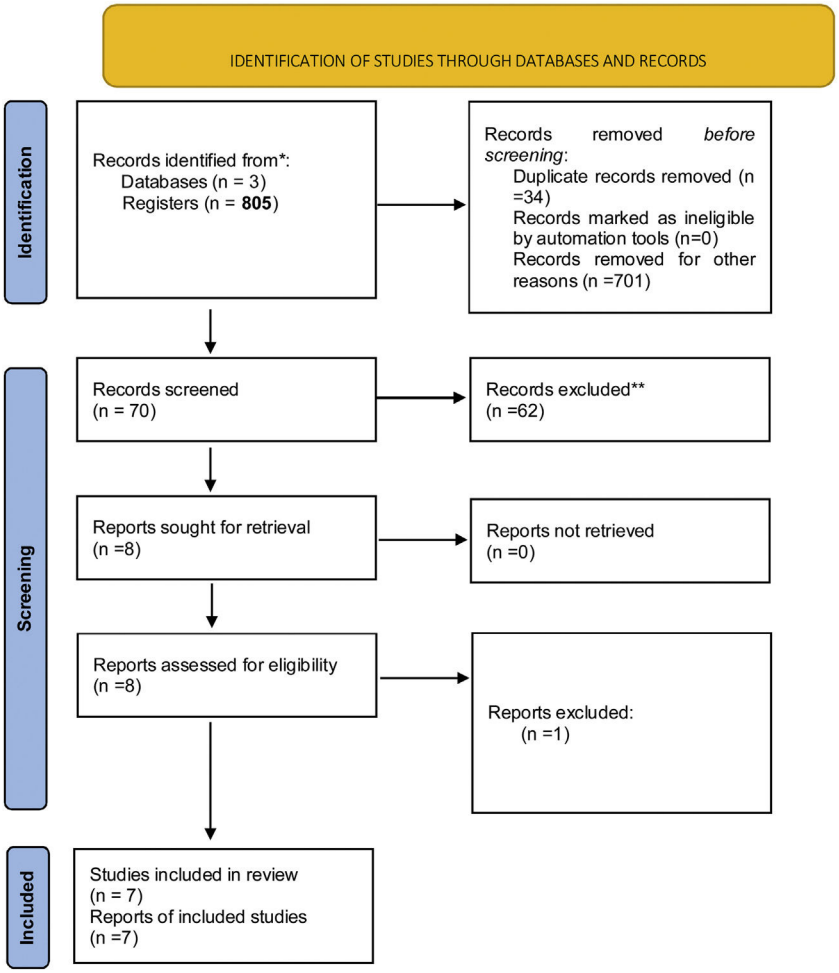

Figure 1 PRISMA 2020 flow diagram for new systematic reviews including searches of databases and registers only.
From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71.

ature and freely accessible databases like Google Scholar. The included study types were analytical cohort, case-control, and cross-sectional studies of type 2 diabetes patients who during hospitalization in general wards experienced episodes of both symptomatic and asymptomatic hypoglycemia, published from 2013 onwards. MeSH (Medical Subject Headings terms) terms: ''diabetes mellitus type 2'', ''risk factors'', ''hospitalization'', ''hypoglycemia'' and equations were used (Fig. 1).

Criteria assessment and manuscript synthesis

The titles and abstracts of articles meeting the selection criteria were independently evaluated by two researchers to select articles of scientific quality. For the selected articles, the full text was independently reviewed to verify compliance with the inclusion criteria before entering the group of final article selection. Inter-reviewer disagreement was resolved by consensus and consulted with co-authors; any discrepancies were resolved by a third party.

Data mining

Data mining was performed independently by two reviewers using a predefined collection format. The following study characteristics were recorded: author, year, period, study type, quality, sex, ethnicity, age, and sample size; regarding variables, the following ones were included: type of hypoglycemia test, equipment used for measurement, insulin use, long-acting insulin use, rapid-acting insulin use, acute renal failure, nasogastric or gastrostomy feeding, vomiting as the cause for admission, chronic kidney disease, advanced age, current smoking, alcoholism, low body mass index, sedentary lifestyle, oral hypoglycemic agents without sulfonylurea, oral hypoglycemic agents with sulfonylurea, multiple oral hypoglycemic agents, hypertension, sepsis, congestive heart failure, elevated glycosylated hemoglobin, previous history of hypoglycemia, fasting, dysglycemia on admission, modified Charlson comorbidity index $\geq$ 6 points, 8–10 observation days, $\geq$11 observation days, presence of type 2 diabetes mellitus complications; insulin therapy + sulfonylurea. Both the evaluation and data mining were determined by inclusion and exclusion criteria,

Table 1 Characteristics of the studies.

Study	Year	Period	Study type	Quality	Male	Female	Ethnicity	Age (mean)	Sample size	Hypoglycemia test
Elbaz	2020	2017–2018	Cohort	10/11	260	214	Eastern (Israel)	74	474	NR
Mervyn	2021	2016	Cohort	10/11	341	253	Western	72	594	Peripheral glucose
Akirov	2018	2011–2013	Cohort	10/11	380	412	Eastern	73	792	NR
Alghamdi	2020	2016–2017	Case-control	10/11	189	137	Eastern	67	326	Peripheral glucose
Pilla	2021	2009–2019	Cohort	10/11	269,925	279,116	Western	61	549041	NR
Fu	2014	2007–2010	Cohort	10/11	887,182	887,182	Western (United States)		887182	NR
Borzi	2016	2011–2012	Cohort	8/11	1561	1605	Western Italy	75.2	3167	

NR, not reported.

disagreements were resolved by consensus between two reviewers.

Quality assessment

The methodological quality of the included studies was assessed by 2 medical specialist reviewers in internal medicine and 1 internist resident independently, using the CASPe tool.

Statistical analysis

Descriptive analysis of the included studies was performed with calculation of measures of central tendency. With the information obtained from the studies, a systematic review and subsequently a meta-analysis were developed. Heterogeneity or homogeneity among the selected studies for different risk factors was assessed using Dersomonian and Laird's Q heterogeneity test, at a significance level of 10% ($P < .10$). For risk factors showing heterogeneity in the studies, the random effects method was used ($P < .10$), and for factors with homogeneity, the fixed effects method was used ($P > .10$). Egger's test and Begg's test were used to identify publication bias at a significance level of 5% ($P < .05$), with $P > .05$ indicating no bias. Epidat 3.1 and 4.2 software from the Pan American Health Organization and the Galician Health Council, and the Comprehensive Meta-Analysis Software, were used.

Results

Identified and selected studies

A total of 805 citations were obtained from the initial electronic search: 339 from PubMed, 358 from Web of Science, and 108 from Ovid. After removing duplicates, 70 articles potentially eligible for review of abstracts and full text were identified. Using inclusion and exclusion criteria, a total of 7 studies with 554 601 patients were selected, from which variables were extracted to answer the objectives of the present review and meta-analysis. Fig. 1 illustrates the flow diagram of the study inclusion, as well as the reasons for exclusion.

Study characteristics

The characteristics of the studies are observed in Table 1. A total of 86% (n = 6) of the studies were analytical cohort studies, while only 1 study was a case-control study.

The quality analysis of the studies was performed using the CASPe tool, which showed that all included studies had high quality and low risk of bias. A total of 57% of the 7 studies included (n = 4) were conducted in Western countries, according to the findings of both evaluators.

Patient characteristics

The studies included a total of 2,328,757 participants, 49.8% (n = 159,838) men and 50.2% (n = 1,168,919) women; the median age was 72.5 years (IQR, 68.2–75.2). Only 2 studies reported on the type of glycemia test used, and none on the equipment used for measurement.

The quality analysis of the studies was performed using the CASPe tool, showing that all included studies had high quality and low risk of bias, as agreed upon by the 2 investigators. A total of 57% (n = 4) of the 7 studies included were conducted in Western countries.

Risk factors for hypoglycemia

The risk factors for hypoglycemia in non-critically ill hospitalized patients with type 2 diabetes mellitus were different in each study, which limits analysis. Individual factors included: presence of acute renal failure, vomiting as a cause for admission, current smoking, alcoholism, low body mass index (BMI), sedentary lifestyle, use of oral hypoglycemic agents with sulfonylureas, multiple oral hypoglycemic agents, history of hypertension, diagnosis of sepsis, previous history of hypoglycemia, fasting, dysglycemia on

Table 2 Risk factors for hypoglycemia in non-critically ill hospitalized patients with type 2 DM.

Risk Factor	Number of Studies	OR	Heterogeneity (%)	*P*-value
Insulin	4	2.89 (1.8–4.5)	15	.002*
Long-acting insulin	2	2.27 (1.8–2.8)	0.4335	.510
Rapid-acting insulin	2	1.4 (1.18–1.85)	0.7531	.380
Nasogastric tube feeding	2	1.75 (1.33–2.3)	0.6	.430
Chronic kidney disease	4	1.65 (1.14–2.38)	38	<.001*
Advanced age	2	2.69 (0.88–8.15)	39.4	<.001*
Female sex	2	1.21 (0.9–1.62)	6.17	.013*
Oral hypoglycemic agents without sulfonylureas	2	1.32 (0.15–11.38)	95	<.001*
Congestive heart failure	3	1.36 (1.10–1.68)	0.98	.612
Elevated glycosylated hemoglobin	2	1.59 (1.32–1.91)	0.01	.911

* Random effects method.

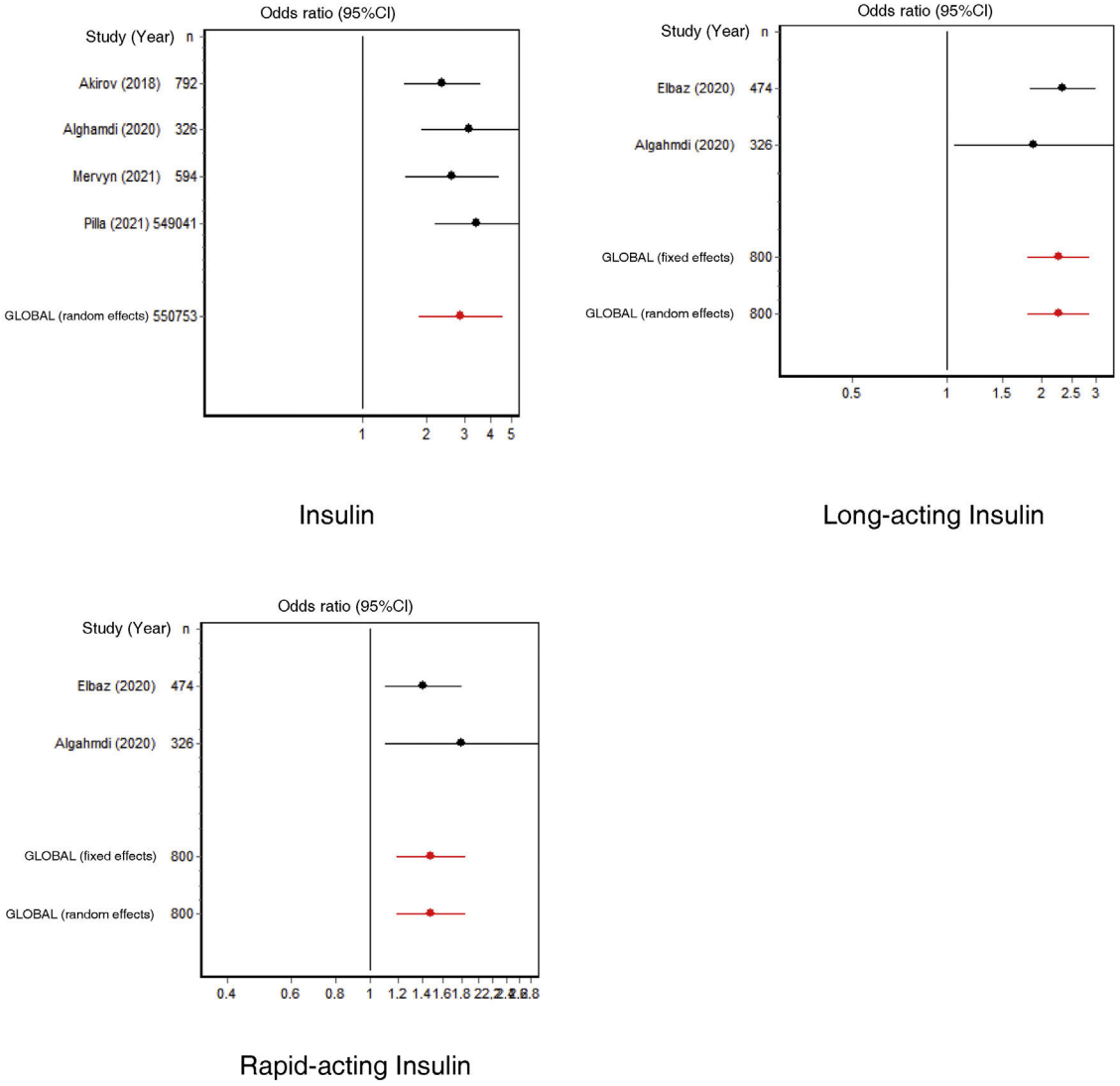

Figure 2 Forest plots of significant risk factors for hypoglycemia in non-critically ill hospitalized type 2 diabetic patients related to treatment.

admission, modified Charlson comorbidity index ≥ 6 points, 8–10 observation days between, ≥11 observation days, presence of type 2 diabetes mellitus complications, insulin therapy + sulfonylurea. The risk factors for hypoglycemia evaluated in more than one study and allowing for meta-analysis were: insulin use, long- and rapid-acting insulin use, nasogastric feeding, chronic kidney disease, advanced age, female sex, oral hypoglycemic agents without sulfonylureas,

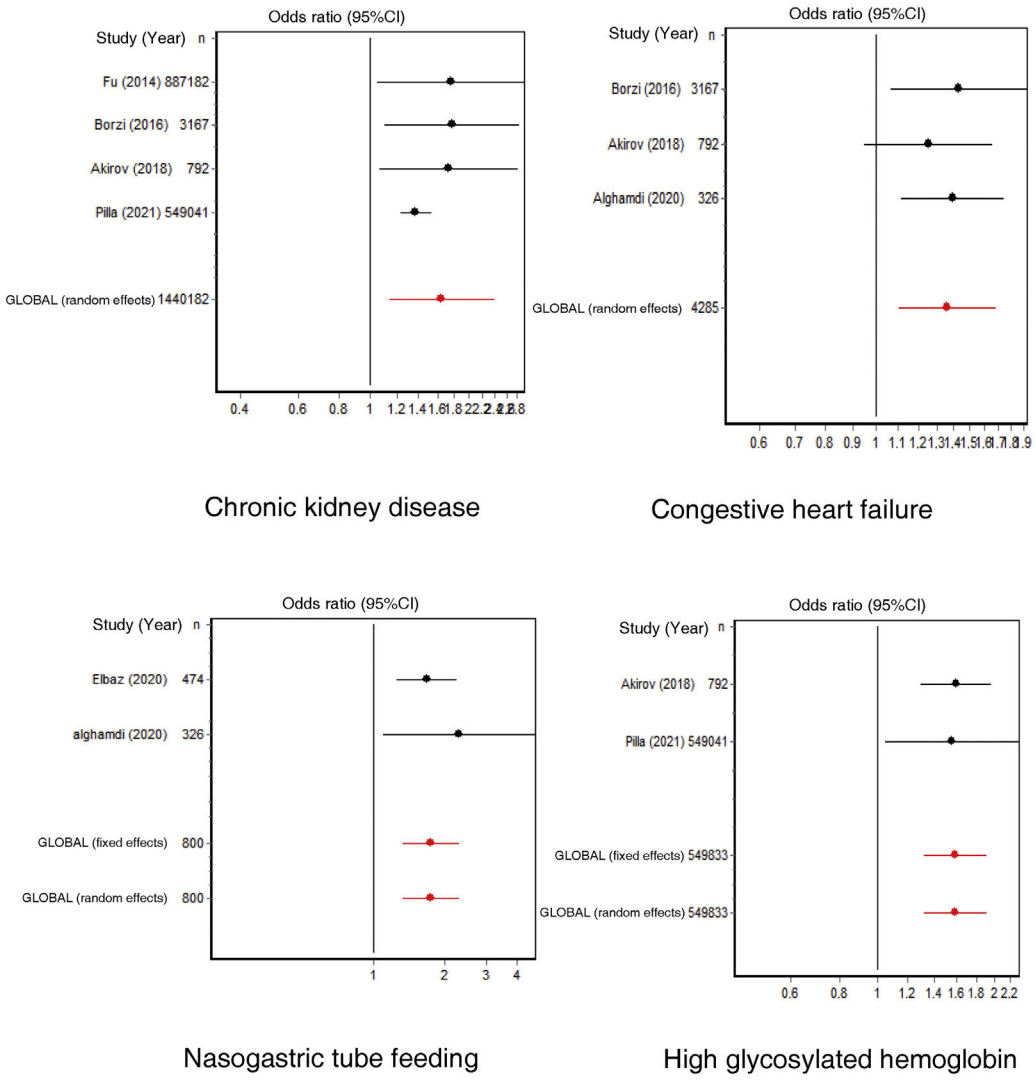

Figure 3 Forest plots of significant risk factors for hypoglycemia in non-critically ill hospitalized type 2 diabetic patients related to clinical history.

congestive heart failure, and glycosylated hemoglobin. Significant associations were found in the meta-analysis between hypoglycemia and the use of any insulin (OR, 2.89 [95%CI, 1.8—4.5]); long- (OR, 2.27 [95%CI, 1.8—2.8]) or rapid-acting insulin use (OR, 1.4 [95%CI, 1.18—1.85]); nasogastric feeding (OR, 1.75 [95%CI, 1.33—2.3]); presence of chronic kidney disease (CKD) (OR, 1.65 [95%CI, 1.14—2.38]); congestive heart failure (OR, 1.36 [95%CI, 1.10—1.68]) and elevated levels of glycosylated hemoglobin (OR, 1.59 [95%CI, 1.32—1.91]), while advanced age, female sex, and use of oral hypoglycemic agents without sulfonylureas were not significant (Table 2). Figs. 2 and 3 present the Forest plots of the risk factors for hypoglycemia in non-critically ill hospitalized type 2 diabetic patients, as evidenced in the meta-analysis (Table 2).

Discussion

This systematic literature review and meta-analysis allowed us to determine the risk factors for hypoglycemia in non-critically ill hospitalized patients with type 2 diabetes mellitus, such as the use of insulin, rapid- and long-acting insulin, history of CKD, congestive heart failure, nasogastric feeding, and elevated levels of glycosylated hemoglobin, across 7 studies.

Hypoglycemia, defined as glucose levels < 70 mg/dL,[6] is considered the major complication in the management of patients with diabetes mellitus and its incidence rate is 20%[7] in the hospital setting.[8,9] It occurs in different scenarios: outpatient, inpatient, and critical care, and in all settings. Hypoglycemia is considered as a factor that increases the risk of complications and morbidities, with a significant impact on the patients' cognitive function and mortality.[1,9–12] According to Gómez-Huelgas et al., hypoglycemia is associated with higher in-hospital mortality rates and long lengths of stay.[13] Therefore, the American Diabetes Association (ADA), through the ''Standards of medical care in diabetes,'' provides current clinical practice recommendations aimed at providing components of diabetes care, general treatment goals, and therapeutic guidelines

to avoid glycemic fluctuations and reduce associated risks of complications.[14] After analyzing glycemic control from the perspective of patient safety, Griffing proposes addressing hospitalized patients with type 2 diabetes from a preventive approach to hypoglycemia, leaving aside reactive management after the event, which impacts the control of associated risks of complications and mortality.[6]

Unlike the findings reported by Feng et al.,[12] female sex and advanced age were not shown to be risk factors for hypoglycemia, as reported by Huri et al. and Kagansky et al.[15]; the latter in a study conducted on 5404 patients older than 70 years.[16] Elderly patients are considered a high-risk group for hypoglycemia, especially when they have diabetes-related comorbidities and renal disease[17]; however, in this meta-analysis, significant results demonstrating that both advanced age and female sex are risk factors for hypoglycemia in the non-critically ill hospital setting were not obtained.

It is particularly common for hypoglycemia to occur in patients treated with hypoglycemic agents, such as insulin or sulfonylureas.[18] The use of sulfonylureas has been described as a factor associated with hypoglycemia[6,12]; however, in this review, the use of sulfonylureas as a risk factor for hypoglycemia was only analyzed in one study, which prevented its meta-analysis. Therefore, insulin therapy is necessary for glycemic control in most type 2 diabetic patients hospitalized with poor control.

The literature reports various factors associated with the presence of hypoglycemia in hospitalized patients, organ failure, such as heart failure and CKD. One of the risk factors determined in this meta-analysis was the history of CKD. In this regard, Gianchandani et al. conducted a study with patients with renal disease undergoing hemodialysis, in which high rates of hypoglycemia were found in more than 50% of patients, with over 35% experiencing more than 1 episode. These findings were associated with high total daily doses of insulin; therefore, they support lower doses of 0.23 units/kg/day.[19] Other authors also report CKD as a risk factor for hypoglycemia.[16,17]

Limitations

One limitation of this research was that individual studies evaluated different risk factors, preventing a meta-analysis of all factors; additionally, in the literature, many studies address patients in different contexts, such as critically ill patients, outpatients, or those admitted for hypoglycemia, while this research focused on non-critically ill hospitalized patients with hypoglycemic events during the standard of care.

Conclusions

The information analyzed in this systematic review with meta-analysis indicates that factors associated with the risk of hypoglycemia in hospitalized diabetic patients include insulin use, whether long- or rapid-acting, nasogastric feeding, elevated levels of glycosylated hemoglobin, and a past medical history of congestive heart failure or CKD.

The results of this meta-analysis could guide the creation of tools to predict the risk of hypoglycemia in non-critically ill hospitalized type 2 diabetic patients and thus direct specific surveillance strategies. More studies in this population are needed to support the evidence.

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Conflicts of interest

None declared.

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