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REVIEW ARTICLES

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HYPERGLYCEMIA AS A RISK FACTOR FOR IN-HOSPITAL MORTALITY IN MYOCARDIAL INFARCTION

HIPERGLICEMIA COMO FACTOR DE RIESGO DE MORTALIDAD HOSPITALARIA EN INFARTO DE MIOCARDIO

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ABSTRACT

Introduction: Myocardial infarction continues with high mortality rates, from 4.6% to 13.1%. There are predictive risk stratification models, such as the Grace Score, which does not include glycemia as a variable. Patients hospitalized for myocardial infarction with hyperglycemia on admission may have higher mortality, in ST elevated and non-elevated infarcts. **Objectives:** The objective of this review is to identify and systematize the evidence on hyperglycemia on admission as a biomarker of mortality and heart failure in acute myocardial infarction. **Methods:** The search was carried out in the MEDLINE database including the MeSH terms hyperglycemia and hospital mortality or heart failure in myocardial infarction, selecting 12 articles. **Results:** Hospital mortality was calculated in 11 articles, in 9 of them a significant association was found between hyperglycemia and hospital mortality, both in the bivariate and multivariate analysis, and in 2 articles this association was not demonstrated. For in-hospital mortality, the results of 11 articles included in this review were synthesized. The frequency of occurrence of heart failure was determined in 11 articles, finding a higher frequency in 9 of them. For in-hospital mortality, the results of 11 articles included in this review were synthesized and analyzed, in 8 the analysis was performed in non-diabetics, obtaining OR: 4.15, IC 95% (2.853-6.035), in 3 for diabetics obtaining OR 2.365 IC 95% (1.778- 3,146) and in 6 for the total population finding OR 3,314 (2,910-3,774). **Conclusions:** Hyperglycemia on admission is associated with increased mortality and frequency of occurrence of heart failure during hospitalization for myocardial infarction, with evidence of moderate quality.

Keywords: Hyperglycemia; Hospital mortality; Myocardial infarction. (Source: MESH-NLM)

RESUMEN

Introducción: El infarto de miocardio continúa con altas tasas de mortalidad, desde 4.6 % hasta 13.1 %. Existen modelos predictivos de estratificación de riesgo, como el Score Grace, que no incluye la glicemia como variable. Los pacientes hospitalizados por infarto de miocardio con hiperglicemia al ingreso pueden tener mayor mortalidad, en infarto ST elevado y no elevado. **Objetivo:** Identificar y sistematizar la evidencia sobre hiperglicemia al ingreso como biomarcador de mortalidad y de insuficiencia cardiaca en infarto de miocardio. **Métodos:** La búsqueda se realizó en la base de datos Medline, se incluyeron los términos MeSH hiperglicemia y mortalidad hospitalaria o insuficiencia cardiaca en infarto de miocardio y se seleccionaron 12 artículos. **Resultados:** La mortalidad hospitalaria se calculó en 11 artículos; en 9 de ellos se encontró asociación significativa entre hiperglicemia y mortalidad hospitalaria; en el análisis bivariado y en el multivariado y en dos artículos, no se demostró dicha asociación. En 11, se determinó la frecuencia de aparición de insuficiencia cardiaca y se encontró mayor frecuencia en nueve de ellos. Para mortalidad hospitalaria, se sintetizaron y analizaron los resultados de 11 artículos incluidos en esta revisión; en ocho, se realizó el análisis en no diabéticos y se obtuvo OR: 4,15, IC 95 % (2,853-6,035); en tres, para diabéticos, OR 2,365 IC 95 % (1,778-3,146) y en 6, para población total, OR 3,314 (2,910-3,774). **Conclusiones:** Hiperglicemia al ingreso está asociada a mayor mortalidad y frecuencia de aparición de insuficiencia cardiaca durante la hospitalización por infarto de miocardio, con evidencia de moderada calidad.

Palabras clave: Hiperglicemia; Mortalidad hospitalaria; Infarto del miocardio. (Fuente: DeCS- BIREME)

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INTRODUCTION

Ischemic coronary heart disease is a prevalent condition worldwide, and acute myocardial infarction (MI) is one of its forms with high mortality rates. Over the years, with the aging of the global population, an increase in mortality due to ischemic diseases has been observed. According to the WHO, in 2000, there were 2 million deaths from ischemic heart disease, which increased to 8.9 million in 2019. In 2019, 16% of deaths worldwide were attributed to ischemic heart disease [1].

In Peru, cardiovascular disease mortality has increased to constitute 33% of the top 20 causes of mortality [2]. The mortality rate for myocardial infarction globally ranges from around 5-10%, with reports ranging from 4.6%[3] to 13.1%[4]. In Peru, studies have been published on hospital mortality in myocardial infarction, for both types of infarctions: ST-elevated and non-ST-elevated, with figures of 3.4%[5], 7.3% [6], and 4.9% [7], and specifically for ST-elevated myocardial infarction, 10.1% [8] and 8.5% [9]. These values remain high despite technological advances. Predictive risk stratification models, such as the Grace Score[10], exist; however, new predictive scales may be necessary to properly identify high-risk patients and attempt to reduce these mortality rates.

Hyperglycemia upon emergency admission is a prognostic marker for mortality and morbidity in hospitalized patients with any disease. In the case of MI, stress hyperglycemia is defined as elevated admission glucose levels, typically above 140 mg/dL[11]. However, the definition may vary among authors. A systematic review found hyperglycemia to be a predictor of in-hospital mortality for any cause. In MI, hyperglycemia upon admission is common, and several studies suggest that patients with hyperglycemia upon admission may have higher mortality rates, both in ST-elevation MI[13-15] and non-ST-elevation MI[16], although its value remains controversial. This association also extends to non-diabetic groups[16-18]. Furthermore, this association persists when evaluating the occurrence of complications such as pulmonary edema and cardiogenic shock [19]. However, admission glucose levels are not included in classic predictive models of in-hospital mortality for MI.

The objective of this review is to identify and systematize evidence regarding admission hyperglycemia as a biomarker for mortality and heart failure in acute MI.

METHODS

The study design is based on a literature review on hyperglycemia, hospital mortality, and heart failure in MI.

1. Eligibility Criteria

Inclusion criteria were as follows: Studies involving patients with MI who presented with hyperglycemia upon admission. The definition of MI used was the third [20] or fourth [21] definition of MI that was in effect at the time of the study. Hyperglycemia was defined at the discretion of the author. The study types included observational studies, systematic reviews, or clinical trials that corresponded to the PICO question. They were studies published in English or Spanish.

Exclusion criteria were based on study type: preclinical studies, case series, case reports, letters to the editor, editorials, comments, technical notes, and narrative reviews.

2. PICO Question

Is hyperglycemia a prognostic marker for in-hospital mortality and heart failure in MI? The population comprised hospitalized patients with MI. The exposure was hyperglycemia, and the comparator was normoglycemic. Outcomes were in-hospital mortality or heart failure.

3. Search Strategy

The search strategy was conducted in the Medline database through PubMed using MeSH terms related to the PICO question: Myocardial infarction, myocardial infarct, acute myocardial infarct, hyperglycemia, high blood sugar, in-hospital mortality, in-hospital mortalities, inhospital mortalities, inhospital mortality, acute heart failure, shock cardiogenic. Literature from 2013 to 2023 was reviewed in English and Spanish.

The search date was September 25, 2023. The search strategy is shown in Supplementary Figure 1.

Methodological shortcuts included using only one database (PubMed/Medline), excluding manual or grey literature searches, limiting the search to the last 10 years, including studies in English or Spanish, and filtering the search to cohort studies, systematic reviews, or clinical trials. Study selection and data extraction were not performed in duplicate. After the search, articles were imported, and the reference manager Zotero was used to remove duplicate articles.

4. Evidence Selection and Data Extraction

After an initial phase of title and abstract reading, potentially relevant articles underwent full-text reading, and data were extracted into an Excel template, including the following data: First author, article title, year of publication, journal, sample size, gender, age, exposure characteristics, comparator characteristics, study design, outcome variable, independent variables, statistical analysis, univariate results, measure of association, final outcome, and conclusion. This stage was performed by the authors.

5. Bias Risk or Evidence Quality

Given that these were cohort studies, the Newcastle-Ottawa Scale was used to assess bias risk or evidence quality. This evaluation was conducted by the authors. Low risk of bias (high quality) was defined as seven to nine stars, and high risk (low quality) was defined as six or fewer stars.

6. Synthesis and Analysis

Frequencies of in-hospital mortality and heart failure from each study were compared, as well as the odds ratio between hyperglycemia and in-hospital mortality for both bivariate and multivariate analyses in studies reporting such data.

Subsequently, data from the studies were analyzed and synthesized, and a meta-analysis was performed using Jamovi version 2.3.18 for the variables hyperglycemia and in-hospital mortality, using a random-effects model to mitigate the effect of clinical and methodological heterogeneity among studies. Studies were categorized into two groups: Hyperglycemia and normoglycemia, according to the definition used by each author; if more than two categories were reported, such as moderate or severe hyperglycemia, they were included as a single group. Studies were classified into three subgroups: non-diabetics, diabetics, and the general population. The p-value (< 0.1 indicates heterogeneity present), and $I^{(2)}$ were used to quantify heterogeneity (>50% indicates substantial heterogeneity).

RESULTS

A total of 301 bibliographic citations were identified. Following screening by titles and abstracts, 271 articles were excluded, leaving 30. Full-text reading was then conducted; 18 were excluded, and 12 were selected. The study selection flowchart is shown in Figure 1. The characteristics of the selected studies are presented in Table 1, and the reasons for exclusion are detailed in Supplementary Table 1.

REVIEW ARTICLE

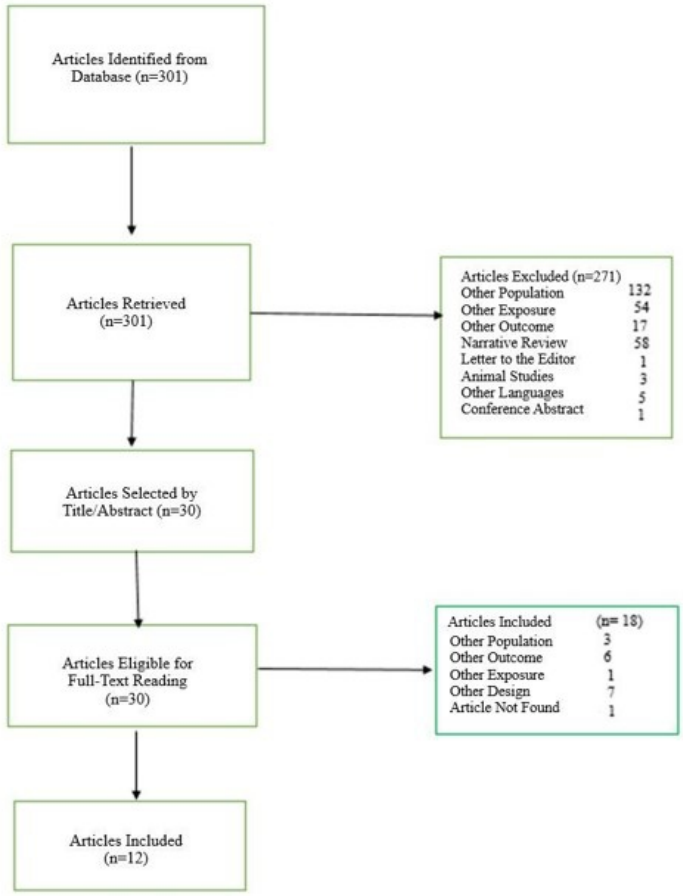

Figure 1. Study Selection Flowchart.

Table 1. Characteristics of Selected Articles.

Author	Title	Year	Journal	Place	Study size (n patients)	Study type
Djordjevic-Radojkovic, Danijela; Koracevic, Goran; Stanojevic, Dragana; Damjanovic, Miodrag; Apostolovic, Svetlana; Pavlovic, Milan	Stress hyperglycemia in acute ST-segment elevation myocardial infarction is a marker of left ventricular remodeling	2013	Acute Cardiac Care	Serbia	275	Cohorte prospectiva

Zhang, Jian-Wei; Zhou, Yu-Jie; Cao, Shu-Jun; Yang, Qing; Yang, Shi-Wei; Nie, Bin	Impact of stress hyperglycemia on in-hospital stent thrombosis and prognosis in nondiabetic patients with ST-segment elevation myocardial infarction undergoing a primary percutaneous coronary intervention	2013	Coronary Artery Disease	Chi na	853	Cohorte retrospecti va
Chen, Pei-Chi; Chua, Su-Kiat; Hung, Huei-Fong; Huang, Chung-Yen; Lin, Chiu-Mei; Lai, Shih-Ming; Chen, Yen-Ling; Cheng, Jun-Jack; Chiu, Chiung-Zuan; Lee, Shih-Huang; Lo, Huey-Ming; Shyu, Kou-Gi	Admission hyperglycemia predicts poorer short- and long-term outcomes after primary percutaneous coronary intervention for ST-elevation myocardial infarction	2014	Journal of Diabetes Investigatio n	Chi na	959	Cohorte prospectiv a
Fujino, Masashi; Ishihara, Masaharu; Honda, Satoshi; Kawakami, Shoji; Yamane, Takafumi; Nagai, Toshiyuki; Nakao, Kazuhiro; Kanaya, Tomoaki; Kumasaka, Leon; Asaumi, Yasuhide; Arakawa, Tetsuo; Tahara, Yoshio; Nakanishi, Michio; Noguchi, Teruo; Kusano, Kengo; Anzai, Toshihisa; Goto, Yoichi; Yasuda, Satoshi; Ogawa, Hisao	Impact of acute and chronic hyperglycemia on in-hospital outcomes of patients with acute myocardial infarction	2014	The American Journal of Cardiology	Jap ón	696	Cohorte retrospecti va
Kim, Eun Jung; Jeong, Myung Ho; Kim, Ju Han; Ahn, Tae Hoon; Seung, Ki Bae; Oh, Dong Joo; Kim, Hyo-Soo; Gwon, Hyeon Cheol; Seong, In Whan; Hwang, Kyung Kuk; Chae, Shung Chull; Kim, Kwon-Bae; Kim, Young Jo; Cha, Kwang Soo; Oh, Seok Kyu; Chae, Jei Keon; investigators, KAMIR-NIH registry	Clinical impact of admission hyperglycemia on in-hospital mortality in acute myocardial infarction patients	2017	Internation al Journal of Cardiology	Cor ea	12625	Cohorte prospectiv a

Zhao, Shi; Murugiah, Karthik; Li, Na; Li, Xi; Xu, Zi-Hui; Li, Jing; Cheng, Chen; Mao, Hong; Downing, Nicholas S.; Krumholz, Harlan M.; Jiang, Li-Xin	Admission Glucose and In-hospital Mortality after Acute Myocardial Infarction in Patients with or without Diabetes: A Cross-sectional Study	2017	Chinese Medical Journal	China	10538	Cohorte retrospectiva
Ding, Xiao Song; Wu, Shan Shan; Chen, Hui; Zhao, Xue Qiao; Li, Hong Wei	High admission glucose levels predict worse short-term clinical outcome in non-diabetic patients with acute myocardial infraction: a retrospective observational study	2019	BMC cardiovascular disorders	China	1698	Cohorte retrospectiva
Paolisso, Pasquale; Foà, Alberto; Bergamaschi, Luca; Angeli, Francesco; Fabrizio, Michele; Donati, Francesco; Toniolo, Sebastiano; Chiti, Chiara; Rinaldi, Andrea; Stefanizzi, Andrea; Armillotta, Matteo; Sansonetti, Angelo; Magnani, Ilenia; Iannopollo, Gianmarco; Rucci, Paola; Casella, Gianni; Galiè, Nazzareno; Pizzi, Carmine	Impact of admission hyperglycemia on short and long-term prognosis in acute myocardial infarction: MINOCA versus MIOCA	2021	Cardiovascular Diabetology	Italia	1321	Cohorte prospectiva
Liu, Linlin; Qian, Jun; Yan, Wenwen; Liu, Xuebo; Zhao, Ya; Che, Lin	Relationship between hyperglycaemia at admission and prognosis in patients with acute myocardial infarction: a retrospective cohort study	2022	Postgraduate Medical Journal	USA	2027	Cohorte retrospectiva
Ekmekci, Ahmet; Cicek, Gokhan; Uluganyan, Mahmut; Gungor, Baris; Osman, Faizel; Ozcan, Kazim Serhan; Bozbay, Mehmet; Ertas, Gokhan; Zencirci, Aycan; Sayar, Nurten; Eren, Mehmet	Admission hyperglycemia predicts inhospital mortality and major adverse cardiac events after primary percutaneous coronary intervention in patients without diabetes mellitus	2014	Angiology	Turquia	503	Cohorte prospectiva
Jomaa, Walid; El Mhamdi, Sana; Ben Ali, Imen; Azaiez, Mohamed A.; El Hraiech, Aymen; Ben Hamda, Khaldoun; Maatouk, Faouzi	Prognostic value of hyperglycemia on-admission in diabetic versus non-diabetic patients presenting with ST-elevation myocardial infarction in Tunisia	2018	Indian Heart Journal	Tunez	1289	Cohorte retrospectiva
Khalfallah, Mohamed; Abdelmageed, Randa; Elgendy, Ehab; Hafez, Yasser Mostafa	Incidence, predictors and outcomes of stress hyperglycemia in patients with ST elevation myocardial infarction undergoing primary percutaneous coronary intervention	2020	Diabetes & Vascular Disease Research	Egipto	660	Cohorte prospectiva
				Total	33264	

General Characteristics of Included Studies

Twelve studies were identified. According to design, six were retrospective cohorts (4, 14, 16, 22–24) and six were prospective (25-30). The studies were conducted between 2013 and 2022; and the origins were Asia (6): China (4), Korea (1), Japan (1); Europe (3): Italy (1), Serbia (1), and Turkey (1); Africa (2): Tunisia (1), Egypt (1); and USA (1). Cohort sizes varied from 275 patients (25) or 503 patients (29) to 10,538 (4) and 12,625 patients (27), totaling 33,264 patients across the 12 studies.

Regarding pre-existing diabetes, in this review, it was found in between 15%[25] and 35% of the cohorts[27], and it has a direct relationship with the threshold used to determine hyperglycemia; higher thresholds were associated with higher frequencies of diabetes. However, in two of the studies, diabetes was not included in the subgroup analysis [23,26]. Electrocardiogram stratifies infarctions into 2 types: ST elevated and non-ST-elevated; in six articles, the type of infarction was not considered (4, 16, 23, 24, 27, 28), and in the other six, ST elevated infarctions were included (14, 22, 25, 26, 29, 30). No study evaluated non-ST-elevated infarction separately.

Regarding gender, males were the majority in all cohorts, ranging from 58% (4) to 90%[29]. This predominance was consistent across all studies, regardless of the hyperglycemia threshold used. All patients were adults with ages whose means or medians varied according to the hyperglycemia threshold used but were always higher in hyperglycemic than in normoglycemic individuals, with statistically significant differences. This relationship also held in subgroup analyses of diabetics and non-diabetics. If using glycemia >140 mg/dl: 73 years (63-81) and <140 mg/dl: 69 (58-78), p<0.001 (28); <180 mg/dl: 61.7+/-10.1; >180 mg/dl: 63.9+/-12.4; p=0.031 (22); for diabetics, glycemia <200 mg/dl or >200 mg/dl: 64.7+/-12.05 versus 66.1+/-11.2; p<0.001, in non-diabetics <200 mg/dl 63+/-13.01 versus >200 mg/dl 66+/-13.26; p<0.001[27].

Glycemia was measured in all studies upon emergency admission; nine studies were multicenter, so the same laboratory and methodology were not used; only three studies were single-center[16,23,30].

Specific Characteristics of Included Studies

In 11 studies, hospital mortality was analyzed as the primary outcome, and in 11, the presence of heart failure during hospitalization was determined. Only one article analyzed the composite outcome of hospital mortality, reinfarction, and revascularization of the culprit vessel [29].

In this latter case, patients were divided into three groups according to admission glycemia: <118, 118-145, and >145 mg/dl, and it was found that hospital mortality was directly related to admission glycemia. Hospital mortality was 0%, 1.1%, and 5.3%; p=0.01, in each of the groups. The presence of cardiogenic shock was related to the value of glycemia at admission: 0.6%, 4.1%, and 10%, respectively. In the bivariate analysis for the composite outcome, the OR was 1.01 (1.00-1.02; p<0.01), and in the multivariate analysis, the OR was 1.009 (1.003-1.015; p=0.01). Age, systolic blood pressure at admission, left ventricular ejection fraction, and creatinine were used as variables in the multivariate analysis[29]. In the remaining 11 articles, outcomes were evaluated separately: Hospital mortality and occurrence of heart failure.

Hospital Mortality

In nine articles, a significant association was found between hyperglycemia and hospital mortality (Table 2), and in two, no association was demonstrated (Table 3). In the group of hyperglycemic patients, hospital mortality is higher compared to normoglycemic patients, regardless of the threshold of hyperglycemia used, such as >140 (4, 16, 25, 26, 28–30), >180 (31), or >198-200 mg/dl [12,23,27]. Moreover, it was found that with a higher threshold for hyperglycemia, there is higher hospital mortality; if >140 mg/dl was used, mortality was 4.6% (28), > 180 mg/dl was found 5.2% (31), and

>200 mg/dl was 9.8% (23). For the subgroup of diabetics, this relationship also holds, with hospital mortality of 4.4% in hyperglycemics and 0% in normoglycemics, p=0.02 [28]. The OR of hyperglycemia and hospital mortality, for the bivariate analysis, was significant in nine studies, regardless of the threshold of hyperglycemia used, at >140 mg/dl: OR 2.72 (2.29-3.23; p<0.001) (4), >180 mg/dl: OR 3.873 (1.485-10.10; p=0.006) (16), or >190 mg/dl: OR 2.74 (1.4-5.5; p=0.004) (26). It also holds for the subgroup of diabetics: OR 2.19 (1.18-4.06; p=0.013) (24) and in non-diabetics: OR 2.63 (1.83-3.78; p<0.01) (24) or 6.37 (1.366-29.70, p=0.018) [25].

The same behavior was found in the multivariate analysis. One study found a significant association between hyperglycemia and hospital mortality OR 6.95 (2.29-18.9; p<0.001); the other variables used were: Age, gender, smoking, previous infarction, Killip class at admission, STEMI, primary PCI, reperfusion time[23]. In the subgroup analysis, another study demonstrated an association in non-diabetics with moderate hyperglycemia (140-198 mg/dl) or severe (>199 mg/dl); OR 2.34 (1.93-2.84; p<0.001) and 3.92 (3.04-5.04; p<0.001), respectively, and in diabetics with moderate or severe hyperglycemia: OR 1.175 (1.04-2.92; p=0.032) or 2.97 (1.87-4.71; p<0.001), respectively [4].

On the other hand, in two studies, a significant association could not be obtained; both included non-diabetics and ST elevation. In one of them, the results were not significant in the bivariate analysis for non-diabetics and ST elevation; OR 2.24 (0.947-5; p=0.066) was obtained (30). The other study found no association in the multivariate analysis, for the group of non-diabetics: OR 1.93 (0.97-3.86; p=0.06). In this case, the other variables used were: Age, anemia, heart rate at admission, and creatinine [14].

Table 2. Characteristics of studies demonstrating an association between hyperglycemia and hospital mortality.

Author	Study Size (n patients)	Study Type	Glucose Groups (mg/dl)	Age (years)	Male Sex (%)	Diabetic Subgroup	Hospital Mortality (%)	Bivariate	Multivariate
Djordjevic	275	Prospective Cohort	<144, >144, diabetics	54.2+/-11, 58.9 +/-10.6, 60.9+/-9 p<0.001	71.4, 76.4,65 p<0.001	Si	1.6, 9.3, 5 p<0.05	Only in non-diabetic group OR 6.378 (1.366-29.70, p=0.018)	
Zhang	853	Retrospective Cohort	<180, > 180	61.7+/-10.1, 63.9+/-12.4 p=0.031	70, 71.5 p=0.706	No	2.4, 5.2 p=0.045	No	OR 1.83(1.52-2.14,p=0.024)
Chen	959	Prospective Cohort	<100,100-139,140-189,190-245,>250	61.2+/-12.9,58+/-12.6,61+/-12.7, 62.2+/-12.2, 63+/-12 p<0.001	88.9,88.7, 83.1,78.9, 68.1 p<0.001	No	8.3, 2.9,5.1,9.6,21.5 p<0.001	Glucose > or equal to 190 mg/dl found OR 2.74 (1.4-5.5, p=0.014).	
Fujino	696	Retrospective Cohort	<200, >200	67.4+/-12.8, 68.7+/-11.9, p=0.268	72,72 p=0.921	No	9.8 y 1.6, p<0.001	OR 6.34 (2.8-15.3,p<0.001)	OR 6.35 (2.29-18.9 ,p<0.001)

Kim	12625	Prospective Cohort	Diabetics: >200, <200 Non-diabetics >200, <200	Diabetics: 64.7+/-12.05, 66.1+/-11.2 p<0.001 Non-diabetics 66.6+/-13.26, 63+/-13.01 p<0.001	Diabetics: 67.8,71.6 p=0.007, Non-diabetics 70.1,76.7 p<0.001	Yes	HG: Diabetics 7.2% and Non-diabetics 17.4% (p<0.001), NG: Diabetics 2.7 % and Non-Diabetics 2.2% (p=0.165)	Non-diabetics: HR 2.498 (1.259-4.958, p=0.009). Not calculated for the other groups	
Zhao	10538	Retrospective Cohort	<70,70-139,140-198,>199	67(57-74),66(56-74),67(58-75),68(58-75) p<0.001	67,75,66,58 p<0.001	Yes	No DM:9.9, 5.8, 14.4 y 29.4 DM:28.2, 5.9,9.5 y 17.3	No DM: HG moderate and severe OR 2.72 (2.29-3.23,p<0.001) and 6.72 (5.46-8.28,p<0.001) in DM: OR 1.67 (1.06-2.64,p=0.028) and 3.53 (2.23-4.97, p<0.001)	No DM: OR 2.34 1.93-2.84 p<0.001) y 3.92 3.04-5.04 p<0.001); DM:OR 1.175 1.04-2.92 p=0.032) y 2.97 1.87-4.71 p<0.001)
Ding	1698	Retrospective Cohort	<140,140-180,>180	63(55-76),64(57,76),66(57,73) p=0.022	76.5,72.7,76.8 p=0.32	Yes	NG vs Moderate HG: 2.8 vs 3.8 % p>0.05; NG vs HG severe: 2.8 vs 10.7% p<0.001	HG severe vs NG OR 4.5 (1.9-10.8,p<0.001) and between HG moderate vs HG severe OR 3.8 (1.48-10.1,p=0.006)	
Paolisso	1321	Retrospective Cohort	>140, <140	73(63-81), 69(58-78) p<0.001	70,74.2 p=0.037	Yes	HG 4.6, NG 0.8 p<0.001; in DM HG 4.4 NG 0 p=0.02	HR 4.22 (1.867-9.499, p=0.001), in DM HR 3.5 (1.532-8.215 p=0.03)	
Liu	2027	Retrospective Cohort	Alive, Deceased; Diabetics HG >224.5,NG<224.5, Non-diabetics HG>139.5,NG<139.5	66.9+/-13.8, 74+/-13.1 p<0.001	65.9,53.7 p<0.001	Yes	DM:NG 11.4% vs HG 26.6% p<0.001; no DM: NG 7.8%, HG 24.8%, p<0.001	DM with HG OR 2.19 (1.18-4.06,p=0.013); no DM with HG OR 2.63 (1.83-3.78,p<0.01).	

HG: Hyperglycemic
NG: Normoglycemic
DM: Diabetics
No DM: Non-diabetics

Table 3. Characteristics of studies not demonstrating association between hyperglycemia and hospital mortality.

Author	Size (n patients)	Study Type	Glucose Groups (mg/dl)	Age (years)	Male Sex (%)	Diabetic Subgroup	Hospital Mortality (%)	Bivariate	Multivariate
Jomaa	1289	Retrospective cohort	>198, <198	60.39 +/-12.8	70.7, 81.3	Si	12.6, 4.5 p<0.001	No DM HG OR2.57 (1.39-4.74,p=0.002);, DM: OR 8.85 (2.11-37.12, p<0.001)	DM: OR 9.6 (2.18-42.22,p=0.003; no DM OR 1.93 (0.97-3.86, P=0.06) non-significant result
Khalfallah	660	Prospective cohort	>140, <140	56.8+/-10.18; 54.7+/-9.29 p=0.041	49.5,57	No DM	8.1,3.5 p= 0.027	OR 2.24 (0.947-5.31, p=0.066) non-significant	

HG: hyperglycemic
NG: normoglycemic
DM: diabetics
No DM: non-diabetics

Heart failure

Hyperglycemia upon admission is also related to the presence of heart failure in patients hospitalized for myocardial infarction. Eleven articles that calculated it were found; in nine, the frequency was higher (Table 4).

Heart failure is a complication of myocardial infarction; there is a clinical classification method called Killip, ranging from II to IV (cardiogenic shock); the latter being the most severe. The occurrence of heart failure is variable and appears more frequently in the

hyperglycemic group than in the normoglycemic group. In one study, hyperglycemic patients had heart failure in 35% versus 14% in normoglycemic patients, p <0.001[23]; in another 15.1% versus 9.1%; p=0.02[31]. Similarly, in the case of cardiogenic shock, another study found, according to the glycemic interval of 70-139 mg/dl: 2%, 140-198 mg/dl: 6%, and >198 mg/dl: 11%, p <0.001[4]. Only in two studies, there was no statistical difference between the hyperglycemia and normoglycemia groups regarding the presence of heart failure [25,30]. (Table 5). No measures of association between hyperglycemia and heart failure were reported in any study.

Table 4. Characteristics of Studies Demonstrating Higher Frequency of Heart Failure.

Author	Glycemia Groups mg/dl	Heart failure (%)
Chen	<100,100-139,140-189,190-245,>250	18.1,13.9,19,26.3,36.6 p<0.001
Zhao	<70,70-139,140-198,>199	9,2,6,11 p<0.001 (CS)
Paolisso	<140, >140	2.4, 13.3 p<0.001
Jomaa	>198, < 198	HF: 27,18.8 p<0.001; SC 3.5, 1.5 p=0.018
Ekmekci	<118,118-145,>145	0.6-4.1.10 p=0.01
Zhang	<180, >180	9.1,15.1 p=0.020 (CS)
Fujino	<200, >200	14,35 p<0.001
Kim	<200,>200	DM: 12.4,21.8 p<0.001, no DM: 8.2,38.6 <0.001
Ding	<140, >140	1.7,8.1 p<0.01 (CS)

HG: Hyperglycemic
NG: Normoglycemic
DM: Diabetic
No DM: Non-diabetic
HF: Heart Failure
CS: Cardiogenic Shock

Table 5. Characteristics of studies that did not find a higher frequency between hyperglycemia and the occurrence of heart failure.

Author	Glucose groups mg/dl	Heart failure %
Djordjevic	<144, >144, diabetics	1.6,4.8,2.6 p>0.05
Khalfallah	<140, > 140	8.6, 13.5 p=0.103

Evidence Quality of Studies

It was found that seven studies had a low risk of bias (4, 14, 16, 24, 28–30) and 5 had a high risk of bias (23, 25–27,31) (see supplementary table 2).

Analysis and Synthesis of Studies

Out of the 12 articles included in this review, analysis and synthesis were conducted for hospital mortality in 11 of them. Three subgroups were determined: Non-diabetics (eight articles), diabetics (three articles), and the general population (without distinguishing between diabetics and non-diabetics, six articles).

Non-Diabetic Patients

There were eight articles, with the study by Zhao et al. (4) from 2017 having the highest weight at 17.98%. When conducting meta-analysis for hyperglycemia and hospital mortality, an OR of 4.15 was obtained with a 95% CI (2.853-6.035), and the log OR was 1.42 with a 95% CI (1.049 - 1.798) and p <0.001. Heterogeneity was high, with p < 0.001 and I2 = 84.5% (see supplementary figure 2). The forest plot is presented in figure 2.

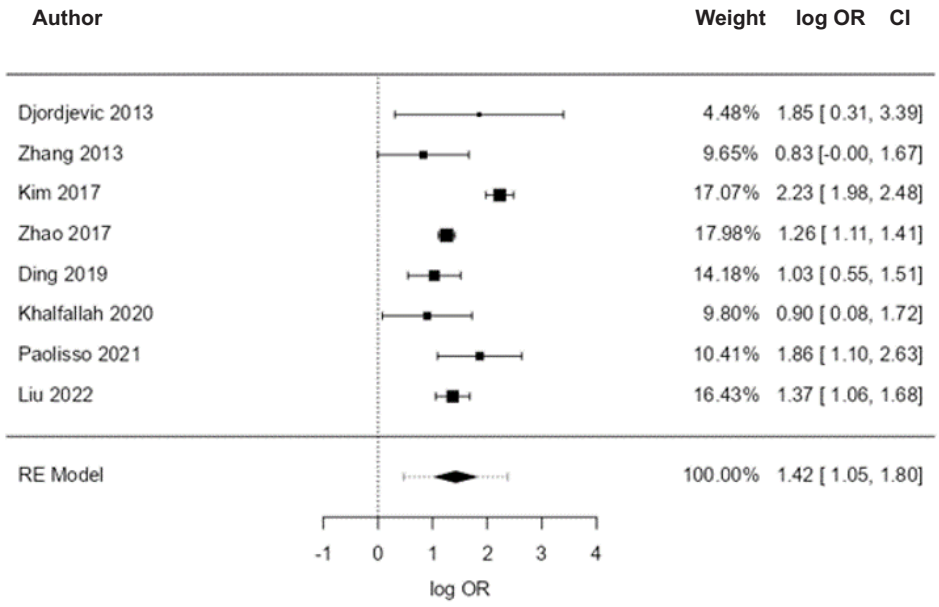

Figure 2. Forest Plot of Studies Showing Association Between Hyperglycemia and Hospital Mortality in Non-Diabetic Patients.

Diabetic Patients

There were three articles; again, the study by Zhao (49) had the highest weight at 62.79%. In this group, a logOR of 0.861 was obtained with a 95% CI (0.575-1.146), p <0.001, and an OR of 2.365 with a 95% CI (1.778-3.146). Heterogeneity was low: p = 0.341 and $I^{(2)}$ = 3.18% (see supplementary figure 3). The forest plot is presented in figure 3.

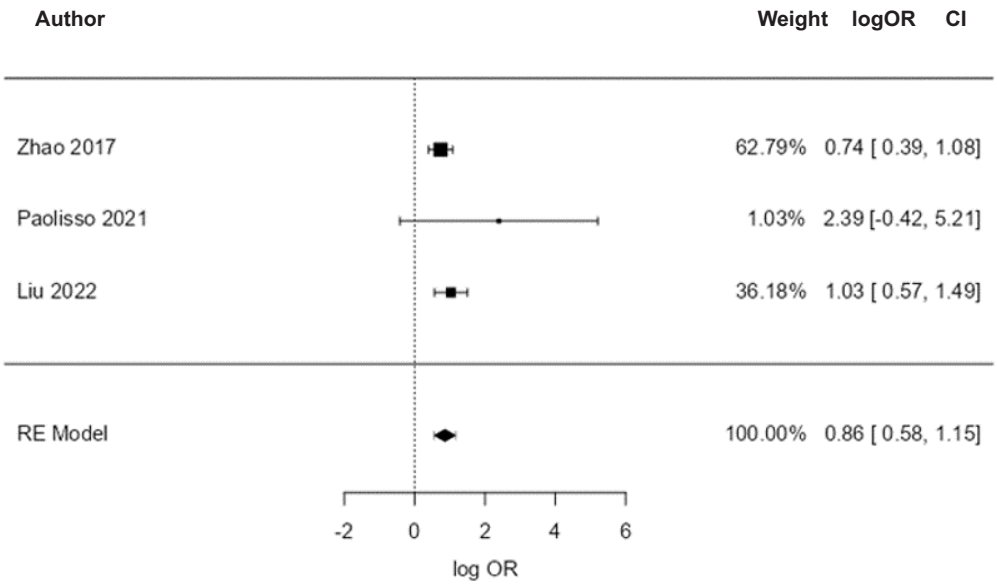

Figure 3. Forest Plot of Studies Showing Association Between Hyperglycemia and Hospital Mortality in Diabetic Patients.

General Population

There were six articles. The study by Zhao accounted for 58.34% of the weight [4]. The log OR was 1.20 with a 95% CI (1.068-1.328) and p <0.001, and the OR was 3.314 (2.910-3.774). Mild heterogeneity was found, with p = 0.188 and $(I2)$ = 9.12% (see supplementary figure 4). The forest plot is presented in figure 4.

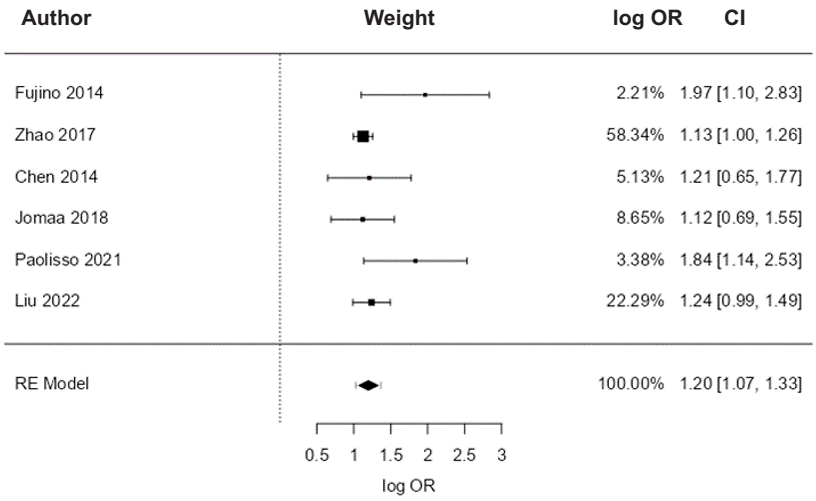

Figure 4. Forest Plot of Studies Showing Association Between Hyperglycemia and Hospital Mortality in the General Population.

DISCUSSION

Hyperglycemia upon admission is more frequently encountered in myocardial infarction complications such as mortality or heart failure. Observational studies in the literature attempt to determine this association. There are no recent systematic reviews or meta-analyses determining this association. Two meta-analyses found a significant association, but they used different outcomes: 30-day mortality[15] or the composite of in-hospital mortality and mortality at 30-90 days[32]. A systematic review from 2000 determined the relationship between hyperglycemia and in-hospital mortality in both diabetic and non-diabetic patients; it included studies conducted between 1985 and 1993[33].

The phenomena occurring during hyperglycemia are varied. Stress induces a hyperadrenergic state, leading to catecholamine release, induction of glycogenolysis, increased free fatty acids, insulin resistance, nitric oxide inactivation, and increased reactive oxygen species production, resulting in oxidative stress. Additionally, there is increased thrombin formation, platelet activation[34,35], and reduced coronary flow by interfering with nitric oxide-mediated vasodilation[36,37].

The quality of evidence in our review was moderate, with 58% of articles rated as good quality according to the Newcastle Ottawa Quality Assessment Scale. Singh reported 82% and Cheng reported 96% of articles as good quality. Compared to other reviews, the issues in ours included lack of comparability with other factors and problems with outcomes such as self-reporting or loss to follow-up (supplementary table 2). Although admission hyperglycemia has a poor prognosis, it is not included in risk scores for myocardial infarction. The GRACE score is widely used for mortality risk stratification in myocardial infarction; it could be improved by including an easily obtainable variable like admission glycemia.

Some studies seek to evaluate the effect of glycemia on the GRACE score. Some small studies found no benefits [34,35]. Timóteo et al. developed a new model that added glycemia to the GRACE score and better classified low-risk patients as truly low-risk and high-risk patients similarly to the GRACE score, although the improvement was small. This could prevent unnecessary interventions that would increase costs and the risk of procedure-related adverse events[38].

In our review, age in all cohorts was higher in the hyperglycemic group compared to the normoglycemic group, except in the study by Fujino. This cohort had some particularities; it used higher thresholds for hyperglycemia (> 200 mg/dl), and the number of diabetics was higher than in other cohorts (69% in hyperglycemic versus 24% in normoglycemic)[23]. Diabetes, being a condition with a worse prognosis, should be analyzed separately. In this review, only three studies analyzed diabetic patients separately and found a significant odds ratio, albeit lower than in the non-diabetic group. The effect of hyperglycemia in diabetics is attenuated by various factors; it may be that they are receiving prior insulin, which prevents hyperglycemia-induced damage, or that chronic exposure to hyperglycemia produces antioxidant defenses that protect tissue from oxidative stress induced by hyperglycemia[39].

The threshold used for hyperglycemia may depend on the cohort's place of origin and be a source of different outcomes. Cohorts from Europe usually use 140-170 mg/dl, while those from Asia or Eastern Europe prefer >200 mg/dl. Cheng et al. [32], in their review, found a greater effect of hyperglycemia on mortality in cohorts from Asia (RR 3.04: 2.61-3.55) and Europe (RR 3.55: 2.6-4.85), and a lesser effect in those from Africa (RR 2.24: 1.04-4.83) and North America (OR 1.85: 1.59-2.16). In our review, in the non-diabetic group, a stronger association was found in cohorts from Eastern Europe[25] (OR 6.3: 1.36-29.7) and Asia (OR 6.72: 5.46-8.28; p<0.001) [4] than in those from North America (OR 2.63: 1.83-3.7;

p<0.01)[24].

The value of hyperglycemia as a prognostic factor for hospital mortality is better demonstrated in the subgroup of ST-elevation myocardial infarctions. Our rapid review and that of Singh included only ST-elevation cases; on the other hand, Cheng only included one article with non-ST-elevation cases. The reason may be that ST-elevation myocardial infarctions, having a greater extent of necrosis, represent a more severe disease and therefore raise blood glucose levels more and have a greater effect on mortality. Cheng et al., in their review, found that the association between hyperglycemia and mortality is strengthened when divided by subgroups, geographical regions, and types of infarctions, being greater in ST-elevation myocardial infarctions, followed by non-ST-elevation ones, and finally the group composed of both types of infarction [32].

In our review, most studies were in non-diabetic ST-elevation myocardial infarction cases; that is, they used a lower threshold for hyperglycemia. If only diabetic cases were studied, they would predominantly be non-ST-elevation cases, and it may be the case that no effect is found because lower thresholds for hyperglycemia would be used. In our rapid review, only in the study by Liu et al., were different thresholds used for diabetic and non-diabetic cases[24].

Regarding short and medium-term mortality, Cheng et al. found that hyperglycemia at admission was associated with mortality to a greater extent at 30-90 days (RR 2.66: 2.10-3.36) than in-hospital mortality (RR 2.43: 2.18-2.72) with moderate-quality evidence [32]. Mortality found by Cheng et al.[32] in the overall population was 2.12 times higher, 1.3 times higher in the diabetic subgroup, and 1.12 times higher in the non-diabetic subgroup; unlike Singh 15 and Capes 33, who found 3.3, 0.71, and 2.93 times, respectively. In our review, we found 2.31, 1.365, and 3.15 times, respectively. The association for the overall population was weaker in Cheng's review and ours; the reason could be that in more recent studies, modern treatments are more effective, and the impact of hyperglycemia would be attenuated. On the other hand, the cohorts of Singh and Capes were fundamentally from the West (USA, Western Europe), while those of Cheng and ours mostly came from the East: Asia, Eastern Europe, another reason for finding different results.

Another point to consider is the timing of blood sampling, fasting or at admission. Some studies have found that fasting blood glucose has better prognostic accuracy [40]. On the other hand, blood glucose, when taken fasting, is usually on the second day, after performing angioplasty. In older reviews, such as those by Capes and Singh, both revascularization methods, lysis, and angioplasty, were used, while in Cheng's and ours, predominantly angioplasty was used, which is more effective than lysis. This could be another reason for finding a weaker association in these latter studies.

The difference between our review and the others is that ours had more specific criteria; they were cohorts that analyzed admission blood glucose and in-hospital mortality. The other reviews grouped admission and fasting blood glucose, on the second day, and also took into account composite mortality or 30-90 days.

Limitations

Not all studies had the same definition of admission hyperglycemia. In this rapid review, only studies from the Medline database were included, reducing the possibility of literature from our region. The populations were predominantly Asian. An analysis and synthesis of observational study data were performed, which do not have the same level of evidence as meta-analyses; however, their effect may have a similar

direction. Glycosylated hemoglobin determination was not routinely performed, which would allow for determining whether we are dealing with a stress hyperglycemia phenomenon or an unrecognized diabetes, a situation that can lead to confusion.

CONCLUSIONS

The magnitude of the association between hyperglycemia and hospital mortality depends on the threshold used to define hyperglycemia, being greater if the threshold is higher, with moderate-quality evidence. Admission hyperglycemia is more frequently encountered in myocardial infarctions that presented heart failure during hospitalization.

Most studies demonstrated the association between hyperglycemia and hospital mortality in ST-elevation myocardial infarctions; there is little information for non-ST-elevation myocardial infarctions.

The value of hyperglycemia as a prognostic factor for hospital mortality is better demonstrated for the subgroup of non-diabetics, with moderate-quality evidence.

REVIEW ARTICLE

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