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Insulin-induced Hypoglycemia after Implementing Hyperkalemia Protocol at Emergency Departments: An Updated Systematic Review

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Abstract

Background: Addressing the critical gap in managing hyperkalemia in emergency settings, emphasizing the balance between effective potassium reduction and hypoglycemia prevention. The findings highlight the need for standardized protocols and further research to enhance patient safety and treatment efficacy. This review aims to determine the optimal intravenous insulin dose, the necessary dextrose administration, and the appropriate timing for glucose-level monitoring to prevent hypoglycemia in adults undergoing hyperkalemia treatment in emergency departments.

Methods: A systematic review was conducted following PRISMA guidelines. Full-text articles published in English between 2016 and 2024, were selected from MEDLINE (PubMed), Science Direct, CINAHL, Cochrane Database, and Google Scholar. The inclusion criteria comprised studies involving adult patients treated for hyperkalemia in emergency departments, focusing on insulin and dextrose administration protocols. The review was registered on PROSPERO (***CRD42023399719***). Data extraction and synthesis involved assessing study quality, insulin doses, dextrose administration, and timing of glucose monitoring.

Results: The review included 16 studies, with 11 patients involving renal disease. Hyperkalemia was defined by 12 studies (75%) as a potassium level exceeding 5 mmol/L. The prevalence of hypoglycemia ranged from 15-20%. There was variability in the initial glucose monitoring time post-insulin administration, with 10 studies (63%) opting for a 6-hour mark. The most reported insulin dose to prevent hypoglycemia was 5-10 units. Additionally, 50% of the studies recommended administering 25 g of dextrose (D50%) to prevent hypoglycemia.

Conclusions: Although optimized insulin therapy regimens have shown promise in reducing hypoglycemia risk, effective management of potassium levels remains a challenge. Future research must inform treatment guidelines and clinical practice, ensuring safer and more effective care for hyperkalemia patients.

Keywords: Adult patients; Emergency Department; Glucose Level; Hyperkalemia; Hypoglycemia; Insulin.

1. INTRODUCTION

Hyperkalemia is a life-threatening electrolyte abnormality that can result in fatal cardiac arrest if not treated promptly [1, 2]. Hyperkalemia is defined as a high serum concentration of potassium in the blood where mild (>5.0-5.9 mmol/L), moderate (6.0 - 6.4 mmol/L), and severe (6.5 mmol/L) are common classifications [3].

Emergency treatment approaches that are used in hyperkalemia treatment include calcium to stabilize the cardiac membrane, insulin, and nebulized beta agonist to produce an intracellular shift of potassium, sodium bicarbonate, which also causes intracellular potassium shift through the hydrogen/potassium exchange, and loop diuretics, or hemodialysis to remove potassium from the body [4]. The insulin and dextrose combination are recommended as the primary treatment of hyperkalemia in the emergency department; it has been used since 1944 [5]. This treatment is considered effective in hyperkalemia treatment, but the primary adverse effect is hypoglycemia.

When treating hyperkalemia with insulin, close attention, and blood sugar monitoring must occur. Hypoglycemia (blood glucose less than 70mg/dl) has a critical impact on patients, not only leading to medical complications that put patients at risk of serious harm, such as neurologic symptoms like dizziness and convulsions [6], but also could lead to psychological symptoms such as anxiety or even coma and death [7, 8]. Moreover, hypoglycemia can give rise to non-medical complications, which could cause stress and increase healthcare costs and length of stay [7]. Cognitive impairment, peculiar behavior, seizures, and even death are also among the most severe hypoglycemia symptoms that patients could suffer [9, 10]. Following glucose and insulin administration to treat hyperkalemia, hypoglycemia is a frequent side effect [11-13]. In this environment, its incidence ranges from 8.7% to 75% [8, 14, 15]. However, there is disagreement regarding the optimum insulin dose is the safest way to treat hyperkalemia. Various guidelines have proposed using 5-10 units of regular insulin along with 25 grams of Dextrose infused over 5-30 minutes; however, studies have shown that these dosages can vary [16, 17].

Severe hypoglycemia (blood glucose concentration < 40 mg/dL) is independently associated with an increased risk of mortality in critically ill patients [18-20]. Due to severe illnesses and limited access to food, patients with chronic illnesses are probably at risk for inadequate calorie intake, which might raise the risk of hypoglycemia. This review attempts to provide appropriate treatment guidelines for effectively lowering potassium and minimizing the risk of hypoglycemia among adult patients treated for hyperkalemia in emergency departments.

Previous systematic reviews on insulin use in hyperkalemia management have been limited by narrow inclusion criteria, outdated data, and lack of quality appraisal [21-24]. This review aims to fill this gap by providing updated and comprehensive treatment guidelines for effectively lowering potassium and minimizing hypoglycemia risk among adult patients treated for hyperkalemia in emergency departments.

1.2 Research question

The Population, Issue of Interest, Comparison, Outcome, and time frame (PICOT) framework guided the research question. The research question for this systematic review is: What are the doses of insulin and Dextrose, and what is the timing for glucose-level checks associated with insulin-induced hypoglycemia following the

implementation of hyperkalemia treatment protocol among adults in Emergency Departments?

2. METHODS

2.1 Data Source and Research Strategy

The authors followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to conduct this study. A systematic review (Medline (PubMed), Science Direct, CINAHL Cochrane database, and Google Scholar) was performed to investigate the risk of developing insulin-induced hypoglycemia in patients with chronic illness (kidney or liver disease, uncontrolled diabetes mellitus) treated for hyperkalemia.

To construct this systematic review, all databases were searched using the following terms in this review: "Hyperkalemia," "Insulin," "Hypoglycemia," and "Emergency Department." All possible keyword combinations were searched, and a manual literature search was also conducted. An example of a literature search query was: (hyperkalemia OR hyperkaliemia OR hyper potassium) AND (insulin) AND (hypoglycemia or hypoglycemia or low blood sugar or low blood glucose or low glucose levels) AND (Emergency department OR ED OR Emergency unit, Emergency Room, ER). Available full-text articles whether retrospective, prospective, and cohort studies were included in this study. However, articles were limited to English-language and those published between 2016-2024.

2.3 Ethical consideration

This literature review did not require approval from an institutional review board. The investigation follows the principles outlined in the Helsinki Declaration [25].

2.4 Study Selection and Eligibility

The (PICOT) framework guided the inclusion criteria. The following studies were considered for inclusion in the review: the population was adult patients (18 years or older); the intervention was receiving insulin for hyperkalemia at emergency departments; a control was not applicable to our study; and the outcome is hypoglycemia caused by insulin. Patients with mental illnesses, the pediatric population, and patients not treated in E.R. were excluded.

All relevant studies were selected based on inclusion and exclusion criteria; three reviewers recorded and reviewed them. To ensure study eligibility, the authors independently screened the titles and abstracts returned by the searches. If there were any disagreements among researchers about the titles of any study or the abstracts did not provide enough information, the full text (available and requested) was reviewed to determine whether the paper met the inclusion criteria. The full texts (available and requested) of all publications that were determined to potentially meet standards were then examined to determine the final inclusion. Any disagreements between reviewers were accepted through consensus or the decision of a third reviewer. Based on data abstraction, elements were summarized in numeric form. All data related to the dose of insulin, glucose level, incidence of hypoglycemia, or any other data related to understanding the factors associated with insulin-induced hypoglycemia during treatment were recorded. The author considered all studies that used a standardized protocol and prospective, retrospective, cohort studies, while systematic review and case reports were excluded in this review.

2.5 Data Extraction and Synthesis

This review was registered in the PROSPERO databases (***CRD42023399719***). Two reviewers scanned titles and abstracts for

initial selection. Selected articles were reviewed in full and were independently assessed for eligibility, and disagreements about data abstraction were resolved through consensus or by a third reviewer. A total of 18 articles were included in this review. Based on data abstraction elements, data were summarized in numeric form. The criteria for data extraction were limited to precise author details, study purpose, designs, sample size, results, and conclusion.

3. RESULTS

3.1 Study Selection

The study selection process adhered to the PRISMA guidelines. Initially, a comprehensive search was conducted across multiple databases, including PubMed (n=97), ScienceDirect (n=56), and additional records identified through Google Scholar (n=15), resulting in a total of 168 records. After removing 83 duplicates, 85 records were subjected to title and abstract screening, leading to the exclusion of 76 records for various reasons: 18 were irrelevant to our purpose, 9 were not written in English, and 49 were outside the specified timeframe. The remaining 51 full-text articles were assessed for eligibility based on predefined criteria, resulting in the exclusion of 35 articles that did not meet the eligibility criteria. Ultimately, 16 studies were included in the systematic review. Discrepancies during the selection process were resolved through discussion and consensus among the reviewers (**Figure 1**).

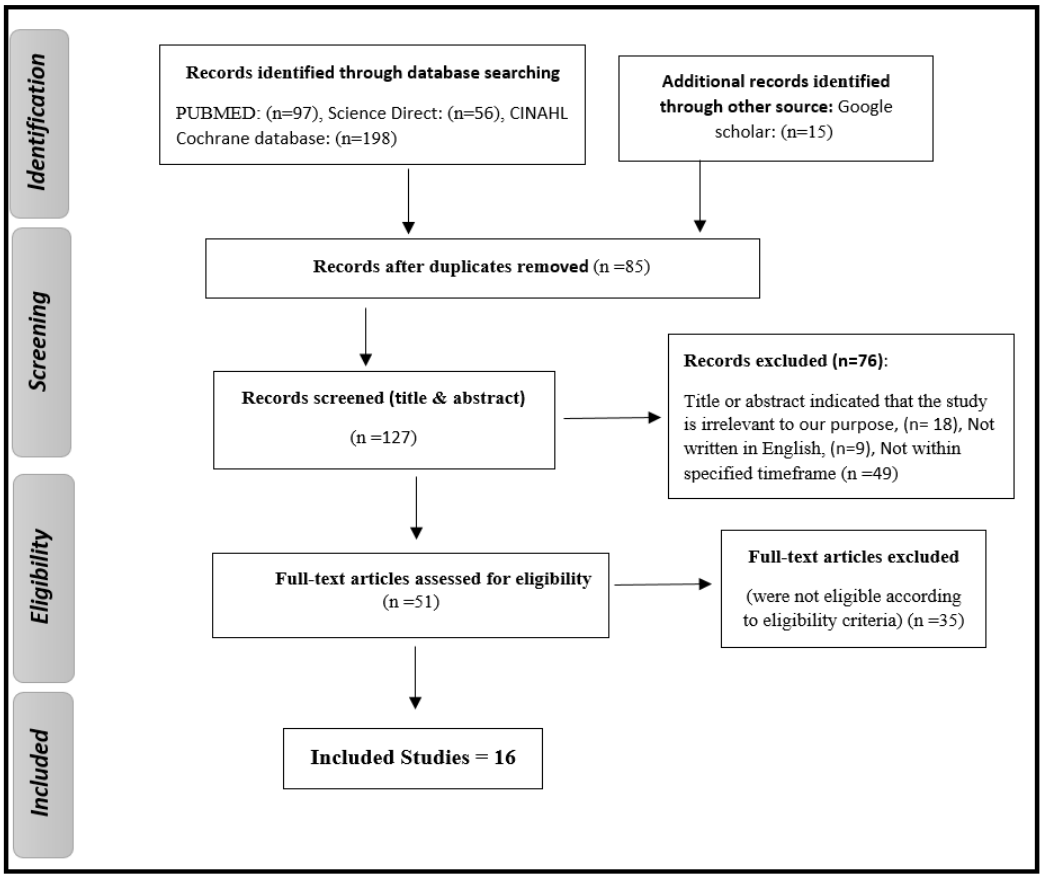

Figure. 1. PRISMA flowchart (flow diagram of the systematic search strategy).

3.2 Characteristics of included studies

The study exclusion process is shown in Figure 1. Our literature search yielded 265 abstracts, 85 of which were found eligible based on initial screening and, therefore, underwent full-text review. Of the 51 studies, 16 met the inclusion criteria and were included in the final evaluation. By analyzing the study characteristics, all studies were retrospective evidence (100%), and most were conducted among patients with renal disease (n=11, 68.8%). Most studies defined hypoglycemia as a glucose level less than or equal to 70 mg/dl (87.5%). Nine studies (56.2%) defined hyperkalemia as potassium of more than 5 mmol/L, while only five considered hyperkalemia if potassium was more than 6 mmol/L. 11 studies (68.8%) had a sample size of less than 500 participants and were mostly conducted between 2016 and 2019 (62.5%). Also, more than half of the studies were reported in the USA (56.2%) (**Table 1**).

Table 1. Studies Included and Summary

Author (Year)	Purpose	Design	Sample & setting	Results	Conclusion
Jacob et al. (2018)	To determine the incidence of hypoglycemia associated with insulin use during treatment of hyperkalemia among patients seen in the emergency department.	Retrospective	172 Patients ED	The incidence of hypoglycemia was 19.8% (n = 34). Severe Hypoglycemic patients had significantly lower median blood glucose at baseline compared to those who did not develop hypoglycemia (83.5 [72.0-112.0] mg/dL vs 123.0 [96.0-167.0] mg/dL. No difference was noted between groups in the average insulin dose administered (0.11 ± 0.04 units/kg vs 0.12 ± 0.05 units/kg, P = .6175)	There is a risk of hypoglycemia associated with insulin use during the treatment of hyperkalemia in the emergency department. Standard insulin doses may not be appropriate in some cases like patients with lower baseline blood glucose. Further research is warranted to develop safer hyperkalemia treatment protocols that mitigate this high risk of hypoglycemia associated with insulin use
Lui. (2019)	To decrease hypoglycemic episodes by 25% in patients treated for hyperkalemia using insulin and dextrose.	Retrospective	87 patients/ ED of Queen Medical Center	The five of 19 episodes that were not order set driven, resulted in an average time of 136 ± 102 minutes from insulin administration to hypoglycemia and 152 ± 152 minutes for the first glucose check after insulin administration	The average time from insulin administration and hypoglycemia was expected to decrease as glucose checks promoted efficient treatment for hypoglycemia
Brown et al. (2018)	Assessing the impact of an order panel utilizing weight-based insulin and standardized monitoring of blood glucose for	Retrospective	350 Patients/ Duke University hospital	Serum potassium lowering did not differ between groups and there was no relationship between the dose of insulin and the amount of potassium lowering. There was a difference in hypoglycemia rates between groups (P =	weight-based insulin dosing is equally effective for lowering serum potassium and may lower the risk of severe hypoglycemia

Author (Year)	Purpose	Design	Sample & setting	Results	Conclusion
	hyperkalemia patients			.049), with fewer severe hypoglycemic events in the panel (2.56%) than in the non-panel group (10.14%)	
Aljabri et al. (2019)	To better characterize the changes in blood glucose and to identify patients who may have an increased response to insulin for hyperkalemia management	Retrospective	90 ED Patients Three hospitals in southwestern United States	Patients who developed hypoglycemia had a median baseline blood glucose of 110mg/dL (IQR 80 to 127mg/dL), which decreased to a median value of 52mg/dL (IQR 40 to 60mg/dL). Higher baseline blood glucose was significantly associated with greater blood glucose reduction (coefficient −0.36, 95%CI −0.55 to −0.18, p<0.001	The extent of blood glucose reduction is variable, and hypoglycemia is common. The high incidence of hypoglycemia highlights the importance of frequent blood glucose monitoring
Pearson et al. (2022)	To compare the prevalence of hypoglycemia between patients who received standard-dose VS. reduce-dose IV insulin in the treatment of hyperkalemia	Retrospective	710 patients/ ED Medical Center.	There was no statistically significant difference in the occurrence of hypoglycemia when comparing the pre-and post-implementation groups (36(17.7%) pt VS 34(18.7%) pt P=0.7924. The post-implementation group had a statistically significant lower reduction in potassium levels after treatment than the pre-implementation group (mean interquartile range), -0.9(-1.3, -20.5) meq/l vs-0.6(-1.2,-0.2) meq/l P=0.0095). Baseline potassium levels were similar between the groups.	Administration of reduced-dose IV insulin for the treatment of hyperkalemia was significantly less effective in lowering serum potassium levels and did not decrease the prevalence of hypoglycemia. When accounting for potential confounders the only variable that was associated with hypoglycemia was pretreatment glucose level.
Humphrey et al. (2022)	To describe emergency management of hyperkalemia in adults with insulin dextrose and to explore clinical outcomes associated with insulin-dextrose treatment	Retrospective .	542Pts. ER.	To describe the emergency management of hyperkalemia in adult to describe the emergency management of hyperkalemia in adults with insulin-dextrose and to explore clinical outcomes associated with insulin-dextrose treatment	This study provides novel insight into the emergency management of hyperkalemia in a large population, demonstrates the high risk of hypoglycemia and highlights the urgent need for an improved, evidence-based approach to the emergency management of hyperkalemia
Lim et al. (2023)	To describe the demographics of adult patients who were receiving	Retrospective	135 patients / ER	There were 31 hypoglycemia events in patients who received hyperkalemia protocol.	Implementing a standardized BGM protocol that ensures frequent monitoring of

Author (Year)	Purpose	Design	Sample & setting	Results	Conclusion
	hyperkalemia treatment at ED and examine the BGM regimen in relation to the outcomes of patient receiving.				the blood glucose is vital but most often underutilized practice toward preventing the incident of hypoglycemia
Wheeler et al. (2016)	To determine the impact of weight-based insulin dosing on potassium-lowering effects of therapy and to detect any risk factors for the development of hypoglycemia among this patient population	Retrospective	132 patients/ ED	Patients in the weight-based dosing group received between 4 and 9 u of insulin, depending on body weight. A reduction in the number of hypoglycemia episodes was detected in the weight-based dosing group of 56% within 24 hours from 18-8 events	Findings indicated that using a weight-based approach to insulin dosing when treating hyperkalemia may lead to a reduction in hypoglycemia without sacrificing the efficacy of potassium lowering. females and patients with glucose values< 140 mg/dl were at increased risk of hypoglycemia.
Kneeney et al. (2019)	To assess safety by evaluating the occurrence of iatrogenic hypoglycemia	Retrospective	1770 patients/ ED.	Compared to an IV dose of 10 units, a bolus IV dose of 5 units of insulin for the treatment of acute hyperkalemia resulted in a significantly lower occurrence of hypoglycemia, with no difference in serum potassium reduction. Hypoglycemia was more frequent in the high-dose insulin group compared to the low-dose group (15.6% versus 6.1%, p=0.004). Both high and low-dose insulin groups achieved similar potassium reductions from baseline.	The findings suggest that for patients with reduced renal function, as indicated by an eGFR<-45 ml/min/1.73, the utilization of a low-dose insulin regimen is equally efficacious and less likely to cause iatrogenic hypoglycemia when treating acute hyperkalemia
Larue et al. (2016)	To compare the efficacy of 5 units versus 10 units of insulin for the treatment of hyperkalemia in patients with renal insufficiency	Retrospective	675 Patients/ ED	Hypoglycemia occurred in 26 of 133 patients receiving 5 units of insulin (19.5%) and in 155 of 542 patients receiving 10 units (28.6%) Difference= -9.1%, 95% confidence interval (-16.8 to -1.3)	Patients with renal insufficiency and hyperkalemia 5 units of insulin reduced serum potassium to the same extent as 10 units of insulin, but with a lower rate of hypoglycemia. Hyperkalemia is a frequent and potentially life-threatening complication in patients presenting to the emergency department

Author (Year)	Purpose	Design	Sample & setting	Results	Conclusion
Gracia et al. (2018)	To compare the effectiveness of reduced and conventional doses of insulin for hyperkalemia treatment	Retrospective	82 Patients/ ED	Ninety-two administrations of reduced-dose insulin and 309 administrations of conventional-dose insulin were included. No significant difference was found in potassium reduction between the groups (-0.096mmol/l, P value=.2210). Post hoc subgroup analysis of patients with serum potassium>6mmol/l revealed a lower reduction in potassium in the reduced dose group compared to the conventional dose group (difference: -0.238mmol/l, p value=.018	Conventional dose insulin may be more effective than reduced dose regular insulin at baseline serum potassium levels>6 mmol/l in the treatment of hyperkalemia. frequent monitoring of serum potassium and glucose after administration of insulin is necessary to confirm adequate response and avoidance of hypoglycemia
Moussavi et al. (2020)	To evaluate the safety and efficacy of insulin dosing of less than 10 units versus 10 units in patients receiving hyperkalemia treatment	Retrospective	690 patients/ ED	Patients treated with less than 10 units of insulin had significantly lower initial serum glucose versus patients who received 10 units of insulin (114 [IQR, 92–171] vs 139 [IQR, 102–212] mg/dL; p = 0.0001 There were no other significant differences in demographics	Patients treated for hyperkalemia with insulin doses of less than 10 units had reduced frequency of hypoglycemia; however, potassium reduction post-treatment was more modest in these patients. These findings suggest providers choosing to administer 10 units IV insulin should ensure patients have adequate monitoring for hypoglycemia
Crnobrnja (2020)	To determine the factors associated with hypoglycemia (glucose < 3.9 mmol/L, or < 70 mg/dL) and the critical time window with the highest incidence	Retrospective	421 patients/ Medical ED	On average, the cohort comprised older male patients (mean age of 69.6 years, 62.2% male), with a high prevalence of diabetes (60.3%) and CKD with an eGFR < 60 ml/min/1.73 m2 (70.3%). This also included 26 of 421 (6.2%) of patients with kidney failure on chronic dialysis and approximately half of all patients experienced AKI. Around one-third of patients were treated with an ACE inhibitor or beta-blocker	The incidence of hypoglycemia remains relatively high with a standard IDT protocol of 25 g of glucose and 10 U of insulin. Increased vigilance is needed for patients with an eGFR < 60 ml/min/1.73 m2 or low BMI, and additional measures to avoid hypoglycemia may be considered.
McNichol et al.	To evaluate whether an educational effort	Retrospective	267Pts. ED	Treatments ordered using a protocol for hyperkalemia	Education on the use of a protocol for

Author (Year)	Purpose	Design	Sample & setting	Results	Conclusion
(2018)	to encourage the use of a protocol through CPOE that suggests the use of 5 units might be beneficial for CKD/ESRD patients			increased following the educational intervention58 of 78 patients [74%] vs. 62 of 99 patients [62%]), and the number of CKD/ESRD patients prescribed 5 units of insulin as per protocol increased (30 of 32 patients [93%] vs. 32 of 43 [75%], P = .03). Associated with this, the incidence of hypoglycemia associated with insulin treatment was lower (7of 63 patients [11%] vs. 22 of 76 patients [28%], P = .03), and there were no cases of severe hypoglycemia compared to the 3 cases before the intervention	hyperkalemia resulted in a reduction in the number of patients with severe hypoglycemia associated with insulin treatment
Kijprasert et al. (2018)	To develop a scoring model to predict hypoglycemia after the treatment of hyperkalemia	Retrospective	385 Patients/ Medical ED	Three hundred and eighty-five patients were included, with 97 post-treatment hypoglycemia (25.2%). The predictive model comprised the following three criteria: age > 60 years old, pretreatment blood glucose ≤ 100 mg/dL (≤ 5.6 mmol/L), and pretreatment potassium > 6 mmol/L. The AuROC of this model was 0.671 (95% confidence interval [CI] 0.608 to 0.735). The calibration plot demonstrated consistency with the original data. Hosmer–Lemeshow goodness-of-fit test showed no evidence of lack-of-fit (p 0.792); therefore, the model was also fit to the original data. Internal validation via bootstrap sampling showed a consistent AuROC of 0.670 (95% CI 0.660 to 0.670) with minimal model optimism. A high risk for post-treatment hypoglycemia was indicated if patient met at least one of those criteria. Sensitivity and specificity were 95.9% and 14.9%, respectively	High risk was indicated when at least one of the criteria was met: age > 60 years old, pretreatment blood glucose ≤ 100 mg/dL (≤ 5.6 mmol/L), and pretreatment potassium > 6 mmol/L. Blood glucose levels should frequently be checked in the high-risk group

Author (Year)	Purpose	Design	Sample & setting	Results	Conclusion
Scott et al. (2022)	To describe the rate of hypoglycemia following the administration of insulin for the treatment of hyperkalemia in the emergency setting and to examine independent the associations between key variables and the development of hypoglycemia.	Retrospective	914 patients/ ED	Lower glucose value before insulin, higher insulin dose administered, and lower D50 dose administered were significantly associated with increased odds of developing hypoglycemia	While intravenous insulin continues to be a critical therapy for ED patients with hyperkalemia, physicians should be aware of the frequency of adverse events associated with its use and adopt strategies to mitigate the risk involved. This work suggests that variables related to the treatment have a greater influence on the development of hypoglycemia than patient-specific characteristics.

3.2 Assessment of risk of bias

The current reviews used the Joanna Briggs Institute (JBI) critical appraisal tool for the included cross-sectional studies. This tool consists of eight questions that include four possible choices (yes, no, unclear, not applicable), and each question was concise and clearly defined. There was a low risk of selection bias; all included studies reported the inclusion criteria for participants and described the setting of the study adequately. Similarly, there was a low risk of detection bias as 80% of the studies used validated objective tools for outcome measurement. Two studies scored (100%) [11, 26] and 87% for all questions [11, 27]. In addition, six studies scored 75% [7, 28-32]; see Table 2. However, only 40% of studies reported the confounding variables and how to adjust them, suggesting a high risk of bias in their articles. Four studies scored 62% for overall questions [5, 33-35], while four scored 50% [6, 36-38]. Concerning selection and detection bias, the quality of evidence from the included studies was good overall (77%).

Table 2. Critical appraisal of studies

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Total (%)
Jacob et al. (2018)	Y	Y	Y	Y	NA	NA	U	Y	62%
Lui. (2019)	Y	Y	Y	Y	NA	NA	Y	Y	75%
Brown et al. (2018)	Y	Y	Y	Y	Y	U	U	Y	75%
Aljabri et al. (2019)	Y	Y	Y	Y	Y	Y	Y	Y	100%
Scott et al. (2017)	Y	Y	Y	U	N	N	U	Y	50%
Moussavi et al. (2020)	Y	Y	Y	Y	Y	U	Y	Y	87%
Crnobrnja et al. (2020)	Y	Y	U	Y	Y	Y	U	Y	75%
McNicholas et al. (2018)	Y	Y	Y	Y	NA	NA	Y	Y	75%
Kijprasert et al. (2022)	Y	Y	Y	Y	U	U	Y	Y	75%

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Total (%)
Garcia et al. (2018)	Y	N	U	Y	Y	Y	Y	Y	75%
LaRue et al. (2016)	Y	Y	U	Y	Y	Y	Y	Y	87%
Keeney et al. (2019)	Y	U	Y	Y	U	U	Y	Y	62%
Wheeler et al. (2016)	Y	Y	U	N	U	U	Y	Y	50%
Lim et al. (2022)	Y	Y	U	U	N	N	Y	Y	50%
Pearson et al. (2021)	Y	Y	N	U	N	N	Y	Y	50%
Humphrey et al. (2021)	Y	Y	U	Y	N	N	Y	Y	62%
Note: Y: yes, N: no, NA: not applicable, U: unclear									

3.3 Prevalence of hypoglycemia after administration of insulin

Eight studies (42.1%) reported that the prevalence of hypoglycemia after insulin administration varied from 15% to 20%. In contrast, the remaining studies revealed a prevalence of less than 15% (n = 6, 31.6%) or more than 20% (n= 5, 26.3%). The articles that used two insulin doses (5 units vs. 10 units) reported a prevalence of hypoglycemia for each dose separately, see Table 3. In terms of hyperkalemia, no significant difference in lowering serum potassium was reported despite various insulin doses.

Table 3. Findings summary (N=16)

	N	%	Studies names
Prevalence of hypoglycemia[#]			
<15%	6	31.6%	[6, 26, 28, 30, 31, 33]
15%_20%	8	42.1%	[5, 11, 27, 33, 35-38]
>20%	5	26.3%	[7, 27, 29, 30, 32]
IV dextrose quantity			
25 gm D50%	9	56.2%	[7, 26, 27, 29-31, 35, 39, 40]
50 gm D50%	3	18.8%	[5, 36, 38]
Both	4	25%	[6, 28, 33]
Insulin dose			
10 unit	5	31.3%	[7, 26, 29, 32, 35]
0.1u/kg	2	12.5%	[31, 36]
5/10 unit	9	56.2%	[6, 11, 27, 28, 30, 33, 36-38]
Timing of hypoglycemia post insulin administration			
1 - 2 hrs	5	31.2%	[29, 31, 35, 36, 38]
>2 - 6 hrs	7	43.8%	[5, 7, 11, 15, 27, 30, 32]
Not reported	4	25%	[6, 28, 33, 37]

3.4 Dose of the administered insulin

Most studies (n=10, 55%) reported that the dose of administered insulin varied from 5 to 10 units among hyperkalemia patients in E.R. Six studies reported that patients received a fixed intravenous dose of 10 units of insulin (38%). However, only two studies (11%) used a weight-based approach (given a dose of insulin as (0.1u/kg)). Furthermore, 14 studies confirmed that the incidence of hypoglycemia

increased when 10 units of insulin or a low dose (25 ml) of Dextrose were used. Three studies found that 5 insulin units effectively lower potassium with a low risk of developing hypoglycemia.

3.5 Timing of hypoglycemia/ glucose monitoring post insulin administration

All studies reported that blood sugar monitoring or the time of developing hypoglycemia was different. In seven studies (43.8%), most patients developed hypoglycemia between 2-6 hours after administering the insulin intravenously, while five studies reported that the decrease in glucose level occurred during the first two hours of insulin administration (31.2%).

3.6 Volume of administered dextrose fluid

To avoid hypoglycemia, administering dextrose fluid volume is reported but debated in the included studies. A dextrose concentration of D50% was used in different amounts (25g / 50 gm). In more than half of the studies (56.2%), 25mg of Dextrose was used, and in three studies (18.8%), 50mg of Dextrose was used to manage hypoglycemia. In four studies (25%), both doses (25mg and 50 mg) were used to manage hypoglycemia.

4. DISCUSSION

In this systematic review, the main focus was on hypoglycemia as an adverse effect following administering insulin to treat hyperkalemia at emergency treatments. Hyperkalemia is one of the serious electrolyte imbalance complications that could lead to fatal heart dysrhythmias. Protecting the heart from dysrhythmias, moving K+ into cells, and improving K+ elimination are all parts of managing hyperkalemia. Insulin treatment is one of the most dependable and constant ways to transfer K+ into cells. This review aimed to determine the effective dose of intravenous insulin administration in the emergency department to treat hyperkalemia that could cause hypoglycemia. In this review, 16 research articles reported insulin-induced hypoglycemia between 2016-2022. All studies suggest a potential risk of hypoglycemia associated with the different doses of insulin therapy during the treatment of hyperkalemia.

The use of insulin in managing hyperkalemia has been examined in four systematic reviews so far, each of which had its own limitations, not to mention that they were all outdated [21-24]. In the first research review, only randomized control trials were included [23], so the allocation of participants might have been predicted in one way or another, and that could have resulted in a selection bias as the study groups were unmasked; consequently, results might not have mimicked real-life treatment situations. In the other two reviews (the second and third ones) [21, 22], both reported broader inclusion criteria, and both reviews did not include a quality appraisal for the included studies, which constrained the generalizability of the findings. The last review (fourth one) by Harel was conducted seven years ago, which included individuals at a high risk of developing hyperkalemia and had criteria for prospective inclusion and evidence of case studies [24]. Conversely, our analysis included patients already treated for hyperkalemia in emergency departments and had wide criteria for inclusion to incorporate all relevant evidence (prospective and retrospective studies). Furthermore, our study scope expanded to include studies from existing literature.

Our study revealed that only six studies were substantial in size and examined administering 10 units of insulin and its impact on the serum K+ concentration. They recommended administering 10 units of insulin to patients with severe hyperkalemia;

however, an increased risk of hypoglycemia is reported.

In our review, 10 (55%) studies have compared insulin dosage strategies in patients with hyperkalemia (5 units vs. 10 units). According to the National Kidney Foundation report (2016), administering 10 units of regular IV insulin as an intervention for managing acute or chronic hyperkalemia is recommended. As well as other studies supported this finding [41, 42].

Administering either 5 or 10 units of intravenous insulin to treat hyperkalemia is still debated. An altered regimen of intravenous insulin from 10 to 5 units with a variation of Dextrose has shown effectiveness in lowering the risk of hypoglycemia [6]; since little evidence shows the difference in efficacy regarding the reduction of potassium with lower doses of insulin, it seems that lower doses of insulin should be considered to reduce episodes of hypoglycemia in hyperkalemia treatment [8, 11, 37]. In our review, 10 studies recommended infusing 5-10 units of insulin intravenously at different times. Some of these studies found that a decrease in potassium level (0.3 mmol/L) was evident after 15–30 minutes of administering the 5-10 units of intravenous insulin [43] and 0.48 mmol/L after one hour [44]. On the other hand, some studies recommended using a weight-based insulin dosing (0.1 U/kg) for acute hyperkalemia therapy, resulting in less risk of developing hypoglycemia; however, there was no significant impact on potassium level. One study that compared using weight-based insulin dose versus 10 units for treating hyperkalemia found that using 0.1 unit/kg as an approach to insulin dosage in hyperkalemia treatment led to less risk of hypoglycemia without affecting the efficacy of lowering the potassium compared with administering 10 units regular insulin [31, 36], that was evident among older adults who were treated for hyperkalemia [45].

In the protocol of hyperkalemia management, administering Dextrose congruent with insulin is clearly to avoid induced hypoglycemia. In the current review, nine studies (50%) found that dextrose 25gm with 10 units of insulin was adequate to avoid hypoglycemia for all patients receiving insulin for hyperkalemia. While three studies (16%) supported using higher doses of Dextrose (50gm) as the risk of hypoglycemia appears to be minimal and short when compared with lower doses (25gm) [5, 36]. Coca and his colleagues confirmed that the combination of 10 units of insulin and 50 gm glucose is effective in reducing serum K+ and lowering the risk of hypoglycemia[34]. Based on these findings, high insulin dosage or lower dextrose dosage were identified as significant factors that increased the risk of developing hypoglycemia, so the combination of lower insulin dose strategies with higher dextrose dose strategies would likely be the best approach in reducing hypoglycemia risk [6, 11, 38]. Moreover, Chothia et al. (2022) found that administering Dextrose as a continuous infusion was associated with a low risk for hypoglycemia compared with bolus administration [8].

The variation in blood glucose results and the high incidence of hypoglycemia entail frequent and longer duration of frequent glucose monitoring for hypoglycemia [6]. In this review, more than half of the studies recommended monitoring blood sugar every 6 hours after insulin administration. This is congruent with protocols that mention the need to monitor glucose levels beyond 4 hours, especially if the patient has significant renal disease or if no repeat doses of insulin or Dextrose are given to further decrease elevated potassium levels.

4.1 Limitations

This review possesses several limitations. A scant number of studies addressed the underestimated prevalence of hypoglycemia. All studies were retrospective studies, while the need for prospective studies or validation of quality improvement efforts can evaluate the success of treatment regimens in medical settings; thus, most clinicians will use a historical and common-sense approach when confronted with patients who have an immediate need to reduce potassium to normal level and avoid hypoglycemia. Most experiments did not delineate the amount of potassium lost or the duration involved. Original studies often lacked clear specifications of insulin or dextrose dosages. Also, this review did not address a failure to reduce potassium or the necessity of dialysis if patients were anuric and acidotic or could not tolerate fluid because of concomitant heart failure or other electrolyte abnormalities related to treating and reducing potassium in these complex patients. Finally, no studies mention patients who may have chronic liver disease with depleted reserves of glucose and who may also require Dextrose to prevent significant hypoglycemia.

4.2 Implication and Recommendation

This systematic review aims to identify the optimal intravenous insulin dose, the necessary dextrose administration, and the best timing for glucose-level checks to prevent hypoglycemia in patients undergoing hyperkalemia treatment. By examining studies conducted between 2016 and 2022, the review seeks to collate evidence that can inform treatment protocols and thus improve patient outcomes.

The review found that while hypoglycemia is a common consequence of hyperkalemia treatment, it can potentially be avoided through careful adjustment of insulin therapy and dextrose administration. The studies analyzed varied in their protocols for monitoring blood sugar after insulin administration, with a majority (63%) performing checks after 6 hours. Half of the studies also reported administering dextrose fluid (D25%) as a preventative measure against hypoglycemia. However, there was no consensus on the best insulin regimen to minimize the risk of hypoglycemia while effectively managing potassium levels. The findings of this review can have significant implications for patient care in emergency departments. They underscore the importance of carefully titrating insulin doses and dextrose administration in hyperkalemia treatment to avoid the serious complications of hypoglycemia. Furthermore, they highlight the need for more research to develop standardized protocols for glucose-level checks, which can improve the safety and efficacy of hyperkalemia treatment. Ultimately, a more nuanced understanding of these dynamics can enhance patient outcomes and reduce the risk of adverse events during emergency care.

5. CONCLUSIONS

Conclusion: This systematic review identifies key strategies to mitigate the risk of hypoglycemia in insulin therapy, specifically administering an insulin dose of 5-10 units, delaying initial blood sugar monitoring until 6 hours post-insulin administration, and administering 25mg of Dextrose 50%. Hypoglycemia remains the most significant adverse effect of insulin therapy, but its incidence can be reduced by optimizing insulin and dextrose administration protocols. Although the majority of studies in this review were retrospective, the findings underscore the need for future prospective and randomized controlled trials to establish the

most effective insulin therapy regimen. Such trials should aim to balance the reduction of hypoglycemia risk with the maintenance of effective potassium-lowering outcomes. This evidence will be crucial in shaping treatment guidelines and improving clinical practice.

Declarations

Ethics approval and consent to participate: Not applicable.

Consent for publication: Not applicable.

Availability of data and materials: All data generated or analyzed during this study are included in this published article.

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Highlights

- Significant variability was found in the timing of glucose checks post-insulin administration in reviewed studies.
- This review emphasizes tailoring insulin doses and dextrose to prevent hypoglycemia in hyperkalemia treatment.
- Half of the reviewed studies used dextrose fluid as a preventative measure against hypoglycemia in hyperkalemia care.

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نقص السكر في الدم الناتج عن الأنسولين بعد تنفيذ بروتوكول فرط بوتاسيوم الدم في أقسام الطوارئ: مراجعة منهجية محدثة

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الملخص

الخلفية: يسعى هذا البحث إلى سد الفجوة الحرجة في إدارة فرط بوتاسيوم الدم في حالات الطوارئ، مع التركيز على التوازن بين تقليل البوتاسيوم بفعالية ومنع نقص السكر في الدم. تسلط النتائج الضوء على الحاجة إلى بروتوكولات موحدة وإجراء المزيد من الأبحاث لتعزيز سلامة المرضى وفعالية العلاج. تهدف هذه المراجعة إلى تحديد الجرعة المثلى من الأنسولين الوريدي، وكمية الجلوكوز اللازمة، وتوقيت مراقبة مستوى الجلوكوز المناسب لمنع نقص السكر في الدم لدى البالغين الذين يخضعون لعلاج فرط بوتاسيوم الدم في أقسام الطوارئ.

منهجية الدراسة : أُجريت مراجعة منهجية وفقًا لإرشادات PRISMA . تم اختيار المقالات النصية الكاملة المنشورة باللغة الإنجليزية بين 2016 و2024 من قواعد بيانات MEDLINE (PubMed) ، Science Direct، CINAHL، Cochrane، وGoogle Scholar. شملت معايير الاختيار الدراسات التي تضمنت مرضى بالغين يعالجون من فرط بوتاسيوم الدم في أقسام الطوارئ، مع التركيز على بروتوكولات إعطاء الأنسولين والجلوكوز. تم تسجيل المراجعة على PROSPERO (CRD42023399719). اشتمل استخراج البيانات والتحليل على تقييم جودة الدراسات، جرعات الأنسولين، إعطاء الجلوكوز، وتوقيت مراقبة مستويات الجلوكوز.

النتائج: شملت المراجعة 16 دراسة، 11 منها تتناول مرضى يعانون من أمراض الكلى. تم تعريف فرط بوتاسيوم الدم في 12 دراسة (75%) على أنه مستوى بوتاسيوم يزيد عن 5 ملمول/لتر. تراوحت نسبة حدوث نقص السكر في الدم بين 15–20%. كان هناك تفاوت في توقيت المراقبة الأولية للجلوكوز بعد إعطاء الأنسولين، حيث اختارت 10 دراسات (63%) توقيتاً بعد 6 ساعات. كانت جرعة الأنسولين الأكثر شيوعًا للوقاية من نقص السكر في الدم 5–10 وحدات. إضافة إلى ذلك، أوصت 50% من الدراسات بإعطاء 25 جرامًا من الجلوكوز (D50%) . للوقاية من نقص السكر في الدم

الاستنتاجات: على الرغم من أن نظم العلاج المحسّنة بالأنسولين أظهرت نجاحًا في تقليل خطر نقص السكر في الدم، فإن إدارة مستويات البوتاسيوم بشكل فعال لا تزال تشكل تحديًا. يجب على الأبحاث المستقبلية أن توجه إرشادات العلاج والممارسات السريرية لضمان رعاية أكثر أمانًا وفعالية لمرضى فرط بوتاسيوم الدم.

الكلمات الدالة: المرضى البالغين؛ قسم الطوارئ؛ مستوى الجلوكوز؛ فرط بوتاسيوم الدم؛ نقص السكر في الدم؛ الأنسولين.